Obstetrics & Gynaecology
UNIVERSITY OF TORONTO



Obstetrics & Gynaecology Clerkship
OBS 310Y

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Notes:

1. The guidelines and recommendations found in this syllabus are current to the time of revision of each chapter of this book.
2. Video recordings of each seminar topic are available for viewing on Elentra.

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Obstetrics



Antepartum Care

Antepartum Care Objectives:

At the end of the seminar, students should be able to:

1. Discuss pre-conception counselling and planning
2. Describe methods to:
    - Assess physiologic changes of pregnancy
    - Diagnose pregnancy
    - Assess gestational age
    - Assess pregnancy risk
    - Assess fetal growth and well being
3. Be able to describe:
    - A template for routine prenatal care
    - Routine diagnostic studies
    - Options for genetic screening and diagnosis
4. Describe appropriate physical assessments during pregnancy:
    - prenatal exam (SFH, FHR, fetal lie, presentation, BP, weight)
      pelvic examination (speculum, Pap, cultures, GBS screen)
5. Counsel patients regarding:
    - Nutritional needs of the pregnant woman
    - Adverse effects of drugs, alcohol and nicotine
    - Environmental and occupational hazards
    - Sexual activity
    - Exercise
    - Immunizations
    - Mood disorders (depression)
    - Patient education programs (prenatal classes, lactation classes)
    - Expectations of early labour
6. Answer commonly asked questions regarding pregnancy, labour and delivery, including a management plan for nausea and vomiting of pregnancy

Last revised: July 2019

PRE-CONCEPTION ISSUES

Purpose:
To optimize maternal health prior to conception to result in the best possible pregnancy outcome

- Record the first day of menses and cycle length
- For those wishing to conceive, review time of ovulation and optimal timing of intercourse
- Discuss folic acid supplementation to reduce risk of open neural tube defects (by ~70%):
    - Timing - 3 months prior to conception
    - Eat folate-rich diet and take daily supplementation
    - Risk factors: woman or male partner with previously affected pregnancy, epilepsy, pre-gestational diabetes, increased BMI
    - Dosing:
        - Low risk- 0.4 mg po daily
        - Moderate risk- 1 mg po daily until 12 weeks, then 0.4-1.0 mg po daily
        - High risk- 4 mg po daily for 3 months prior until 12 weeks, then 0.4-1.0 mg daily

Targeted Review:

1. **Age:** decreased fertility, increased risk of spontaneous abortion, increased risk of chromosomal abnormality with advancing maternal age

2. **BMI**: If obese, may be possible to optimize weight prior to pregnancy

3. **Immunization Status**: Rubella and Varicella immunization may be administered if patient non-immune (remember only preconception, NOT in pregnancy)

4. **Genetic/Familial/Ethnic Risks**: Sickle cell anemia, thalassemia, cystic fibrosis, Ashkenazi Jewish panel, any family members with developmental delay or birth anomalies, consanguinity

5. **Medical Conditions:**
    - Maternal and fetal risks will be illness-specific
    - Consider impact of pregnancy on maternal medical condition and impact of condition on pregnancy, labour and delivery
    - Congenital malformations either due to illness itself or potential exposure to maternal medications
    - Minimize medications if possible or change to safer medications eg:
        - Hypertension - nifedipine, labetolol or methyldopa, instead of ACE inhibitors (associated with fetal anomalies)
        - Anticoagulation - consider heparin or low-molecular weight heparin instead of warfarin (warfarin embryopathy)
    - In most circumstances, single drug preferred to multiple drug regimens e.g. epilepsy, diabetes
    - Optimize disease control e.g. Diabetes: meticulous sugar control; Hgb A1c < 6.5 ideal, Metformin and insulin safe in pregnancy

6. **Obstetrical History:**
    - If three (3) or more consecutive early losses or any mid-trimester loss, consider:
        - Antiphospholipid antibody testing
        - Sonohysterogram to check for abnormalities of uterine cavity
        - Genetic Counselling +/- maternal and paternal karyotyping
        - Cervical cerclage at 13-14 weeks of pregnancy (for those with cervical insufficiency only)
        - Medications: low dose ASA (if previous pre-eclampsia/or high risk for pre-eclampsia), evidence of previous placental abruption/thrombosis - for more information please see 'Pregnancy and Hypertension' chapter
        - Progesterone supplementation (some evidence in luteal phase defects and prevention of preterm labour)

7. **Social History and Lifestyle:**
    - Smoking
    - Alcohol
    - Recreational drugs
    - Domestic violence
    - Exercise
    - Occupational hazards

PREGNANCY DIAGNOSIS AND ASSESSMENT

Physiologic changes of pregnancy

Gastro-intestinal:

- Progesterone acts as a smooth muscle relaxant resulting in:
    - Constipation - from decreased GI motility
    - Reflux - due to decreased gastroesophageal sphincter tone, delayed gastric emptying, and increased intra-abdominal pressure
    - Gallbladder stasis

Skin:

- Pigment changes: darkening of areola, linea nigra, chloasma
- Spider nevi
- Palmar erythema
- Changes in moles
- Proliferation of skin tags

Hematologic:

- ↑plasma volume
- ↑red blood cell mass - less than plasma → apparent decrease in Hb and HCT
- ↑WBC count

- ↑most coagulation proteins (fibrinogen, not factor XIII); important with respect to development of venous thromboembolism (DVT/PE)
- ↑transport proteins → increase in the total levels of those hormones and minerals they bind
- ↓total protein (largely dilutional)
- ↓serum albumin

Renal:

- Slight decrease in blood urea nitrogen (BUN) and creatinine
  ↑renal plasma flow
  ↑glomerular filtration rate
- Anatomic changes related to progesterone the effects → dilatation of the ureters and renal pelvis (R>L)
- Glycosuria - may be the result of these changes as the RPF increase exceeds that of the GFR preventing reabsorption as per the non-pregnant state
- Diagnosis of gestational diabetes mellitus should be made from blood studies not from glycosuria

Cardiovascular:

- ↑cardiac output
- ↑heart rate
- ↑blood volume
- ↓BP due to decreased total peripheral resistance from the progesterone effect on vascular smooth muscle
- ↓venous return due to:
  - large uterus compressing the inferior vena cava
  - (supine) hypotension
  - venous distention → lower extremity edema, varicosities, hemorrhoids and vulvar varicosities

Respiratory:

- Elevated diaphragms
- Progesterone increased CO2 sensitivity
- ↓total lung capacity
- ↓functional residual capacity
- ↓residual volume
- Vital capacity unchanged
- Increased minute ventilation

Endocrine:

- ↑size of thyroid gland
- ↑basal metabolic rate
- ↑total thyroid hormone (secondary to increased thyroid binding globulin)
  - free T4 and TSH as per non-pregnant state
- ↑total and free cortisol

- ↓total calcium secondary to decreased serum albumin
- ↓PTH:
  - ↑bone resorption
  - ↑gut absorption of calcium
  - unchanged free calcium
- ↑bone turnover with no loss of density - due to estrogen's inhibition of resorption
- Diabetogenic tendencies: ↑ serum cortisol and ↑ insulin resistance

Diagnosis of pregnancy

Presumptive Signs: (remember other possible diagnoses)

- Amenorrhea in a woman in the reproductive age group, with previously regular cycles
- Chadwick's sign: bluish discolouration of the walls of the vagina and cervix due to increased vascularity of the pelvis
- Breast changes: tenderness, darkening of the areolae, prominence of Montgomery's follicles (aka tubercles), prominent vascular patterns
- Subjective phenomena: fatigue, urinary frequency, digestive disturbances (nausea, vomiting, constipation, dyspepsia)
- Perception of fetal movement by the patient (quickening); expect by ~20 weeks gestation, earlier in multiparous women
- Localized changes in skin pigmentation (e.g. Chloasma or "mask" of pregnancy)
- Development of abdominal +/- breast striae

Probable Signs:

- Enlargement of the abdomen
- Enlargement of the uterus
- Hegar's sign: softening of the cervix

Positive Signs:

- Auscultation of the fetal heart
- Perception of fetal movement by an experienced examiner
- Demonstration of a fetus by transvaginal ultrasound:
  - 5 weeks - intrauterine sac
  - 6 weeks - fetal pole
  - 7-8 weeks - fetal cardiac activity
- Positive pregnancy test: presence of β-hCG
  - Peptide hormone produced by the placenta
  - Has alpha and beta subunits
  - Serum - is positive by 9 days post conception
  - Plasma levels double every 48 hours to a maximum at 8-10 weeks gestation when it plateaus
    - Abnormalities in how the β-hCG is rising: consider missed abortion or ectopic pregnancy
    - If β-hCG is higher than expected: consider twins or molar pregnancy
- Urine - detection 28 days after last menstrual period

Assessment of gestational age

- Calculated from last (normal) menstrual period (LNMP or LMP) by convention
- Average length of pregnancy:
    - 280 days or 10 lunar months
    - 40 weeks from LMP (38 weeks from ovulation/conception)
    - Estimated date of delivery (EDD) - determine using Naegele's rule:
        - EDD = LMP + 9 calendar months + 7 days; or
        - EDD = LMP – 3 calendar months + 7 days
        - Based on a 28-30 day menstrual cycle; adjust according to cycle length
        - Or by using a gestation wheel or gestational calculator applications for handheld devices
- Ultrasound accuracy:
    - First trimester - within 5 days
    - Second trimester - within 1-2 weeks
    - Third trimester - 2-3 weeks
    - (Source: SOGC Clinical Practice Guideline #303, Feb 2014)
- Uterine fundus location (via bimanual or abdominal examination):
    - 12 weeks - at symphysis (bimanual examination)
    - 16 weeks - between symphysis and umbilicus
    - 20 weeks - at umbilicus
    - Term - at xyphoid
- Symphysis-fundal height (SFH) measurement:
    - Between 20-36 weeks
    - Measure from symphysis pubis to top of the uterine fundus
    - Measurement (in centimetres) roughly equal to gestational age (in weeks) E.g. 25 cm = 25 weeks GA

Table 1: SFH Measurements

SFH Too Small	SFH Too Big

• Wrong measurement
• Wrong dates
• Oligohydramnios
• Fetal Growth Restriction
  • due to maternal disease/infection
  • due to abnormal genetics
  • due to placental insufficiency
• Constitutionally small
	• Wrong measurement
	• Wrong dates
	• Polyhydramnios
	• Fibroids
	• Macrosomia
	• Twins
	• Constitutionally large

PRENATAL CARE

The purpose of prenatal care is to:

- Educate regarding self-care, normal and abnormal symptoms
- Provide Psychosocial support

- Anticipate possible complications, manage and prepare for identified complications
- Intervention if maternal or fetal compromise (healthiest mother, healthiest baby possible)

THE ANTENATAL VISITS

First prenatal visit

- Standard records currently Ontario Ministry of Health Antenatal Records (see Appendix 12)
- Pregnancy considered in trimesters (three in total, each 12 to 14 weeks in length)
- Each pregnancy should be assigned a risk category (see reverse side of antenatal record forms) to ensure appropriate investigations, surveillance and management

History

1. **History of Present Pregnancy:**
    - First day of last normal period - consider cycle length, recent uncharacteristic vaginal bleeding, recent use of oral contraceptive pills
    - Determine EDD (estimated date of delivery)
    - Inquire about subjective symptoms of pregnancy
2. **Past Obstetrical History:**
    - Gravidity: total number of pregnancies including current
    - Parity: number of pregnancies carried to 20 weeks or more
        - Ob/Gyn history includes a summary of G and P
        - For more complicated patients, can further categorize into GTPAL:
            - G: any pregnancy (include losses, ectopic, mole, current)
            - T: term – infants delivered after 37 completed weeks
            - P: preterm – infants delivered 20 - 36+6 weeks
            - A: abortions – pregnancy loss prior to 20 weeks (whether spontaneous or termination)
            - L: live – number of currently living children
    - Documenting each previous pregnancy allows for risk assignment, awareness of complications that may occur, and consideration of management options
    - If pregnancy loss prior to 20 weeks, inquire:
        - How did loss happen (termination? bleeding and cramping? pressure or PPROM?)
        - Differentiate between causes such as therapeutic abortion, spontaneous abortion, fetal anomaly, maternal issues (incompetent cervix)
        - Was a surgical procedure such as a D & C (Dilatation and Curettage) or D & E (Dilatation and Evacuation) required?
        - Was medical intervention such as misoprostol (for missed abortion or blighted ovum) required?
    - If pregnancy loss after 20 weeks, inquire:
        - Date of delivery, location, sex, birth weight, gestational age at delivery, mode of delivery (vaginal – assisted or spontaneous; Caesarean – low segment or classical); were there any antepartum, intrapartum or postpartum complications and/or fetal anomalies

3. **Past Medical and Surgical History**
4. **Family History:** genetic diseases, congenital malformations, consanguinity
5. **Medications, Allergies**
6. **Social History:** smoking, alcohol, recreational drugs, home environment, occupational hazards
7. **Review of Systems**

Physical Examination

1. **General: Vital signs, Weight (calculate BMI)**
2. **Head and Neck:**
    - Thyroid exam
    - Chloasma
    - Gums/mucous membranes: hyperemic/swollen; epulis of pregnancy
3. **Chest:**
    - Consider anatomic and physiologic effects of pregnancy
    - Elevated diaphragm
4. **Heart:**
    - Increased heart rate
    - Murmurs: flow versus possible pathologic
    - If murmur is pathologic, consider maternal tolerance of pregnancy, ECG, echocardiogram, Cardiology referral, need for antibiotics for endocarditis prophylaxis during labour
5. **Breast:**
    - Leakage
    - Physiologic changes
6. **Abdomen:**
    - Striae
    - Linea nigra
    - Rectus diastasis
    - Uterus
7. **Pelvic Examination:**

See http://www.nejm.org/doi/full/10.1056/NEJMvcm061320 for a clinical exam video

- External Genitalia Inspection:
    - Lesions: condyloma, ulcers, varicosities
    - Previous surgeries: female genital mutilation
- Internal Genitalia:
    - Speculum Exam
        - Speculums come in various sizes
        - Disposable plastic and metal available
        - Exam is clean but not sterile (unless suspect rupture of membranes)
        - Advisable to warm speculum under tap for comfort - do not use gel as it will interfere with Pap/cultures

- Inspection:
    - Vagina:
        - Chadwick's sign (bluish discoloration)
        - Vaginitis (yeast is common)
    - Cervix:
        - Ectropion
        - Polyps
- Cultures:
    - Swab off excessive cervical mucus
    - Chlamydial culture is taken from just inside the external os
    - Gonorrheal culture from os/cervix
    - May also screen for Gonorrhea/Chlamydia in urine (PCR)
- Pap:
    - Recommended q3 years in women with three consecutive normal yearly Pap smears (https://www.cancercareontario.ca/en/system/files_force/derivative/OCSPScreeningGuidelines.pdf)
    - Do not use intracervical brush during pregnancy - spatula or external brush only
    - The cervix is soft and often friable during pregnancy and may bleed with the Pap - reassure patient spotting can occur when a Pap is done, but no risk to the pregnancy
- Bimanual Examination: (note widespread use of early ultrasound is impacting traditional clinical practice)
    - Non-latex glove
    - Lubricating gel
    - Two fingers are inserted into vagina and other hand is used to palpate externally:
        - Cervix
            - Hegar's sign (softening)
    - Uterus
        - Size (ensure it is consistent with dates)
        - Shape (expect it to be symmetrically enlarged)
        - Consistency (expect soft)
        - If the uterus is firm, smaller than expected, irregularly enlarged, then reconsider dates, viability, uterine anomaly, ectopic pregnancy
    - Adnexa
    - Consider any masses, their size, shape, consistency, mobility, tenderness

8. Extremities: check for edema and varicosities

Follow-up antenatal visits

- First visit ~ 8-12 weeks
- Every 4 weeks until 28 weeks gestation
- Every 2 weeks from 28-36 weeks gestation
- Every week from 36 weeks to delivery

Encourage both partners to attend if possible.

See diagram on next page for "My Pregnancy Timeline".

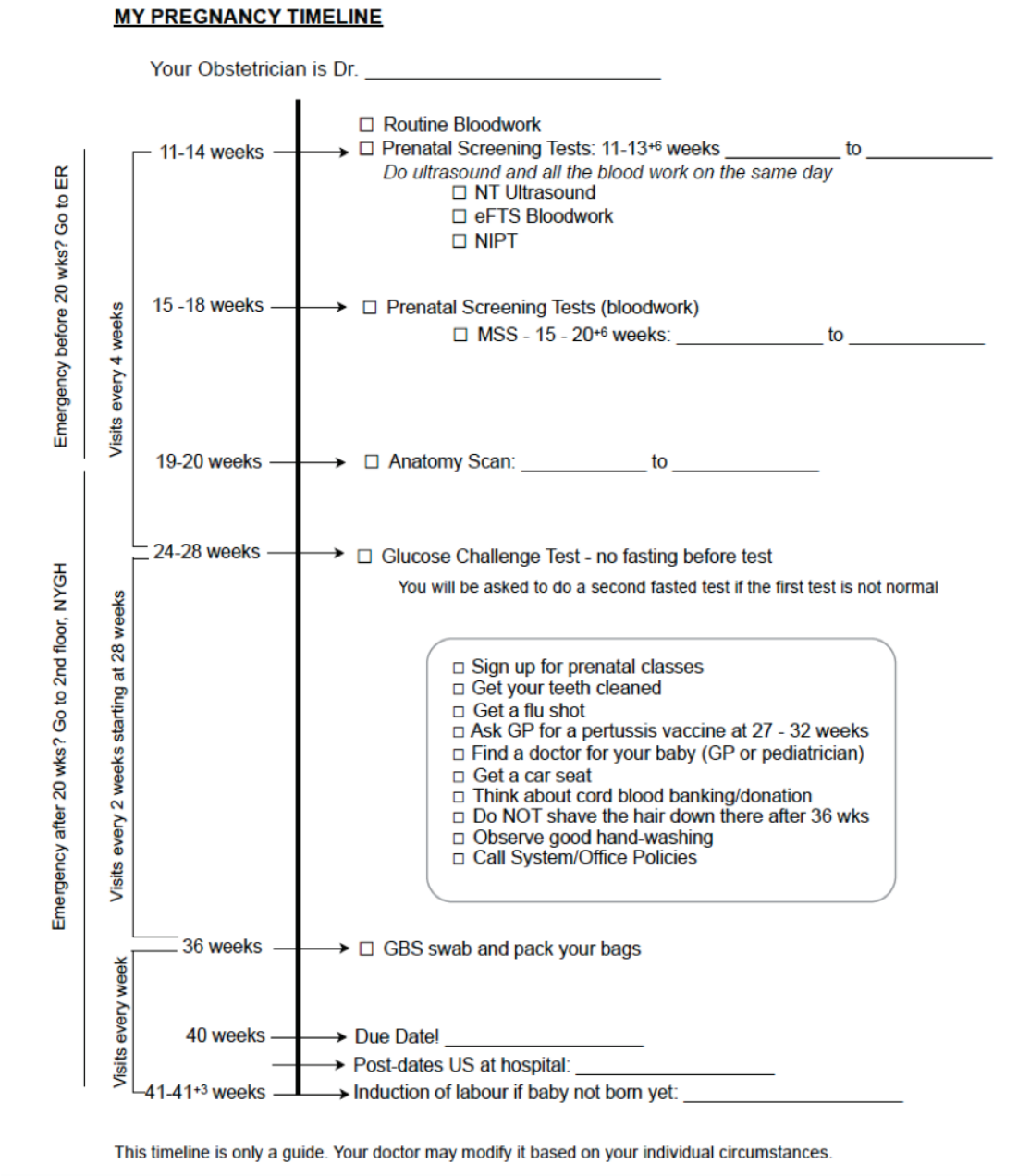
History:

- General well-being
- Specific concerns
- New developments
- Fetal activity

Physical:

- Weight
- Blood pressure
- Uterine size (symphysis-fundal height, is it compatible with dates, enlarging appropriately)
- Auscultate fetal heart (audible with handheld Doppler or "Doptone" from early second trimester (approximately 15-16 weeks)
- After 30-32 weeks - Leopold's maneuvers:
    - Presentation
    - Lie
    - Location of small fetal parts
    - Presence of engagement (in late third trimester primigravidae)

Figure 1: My Pregnancy Timeline (example courtesy of Dr. Karthika Devarajan at North York General Hospital)



Laboratory Investigations at First Visit (Standards of Care):

- CBC
- Rubella status
- Hepatitis B Surface Antigen
- VDRL (Syphilis)
- Blood Group and Rh status, Antibody Screen (to check for red blood cell antibodies)
- Sickle Cell/hemoglobinelectrophoresis - dependent on ethnic and racial background
- Urinalysis (Routine and Microscopic)
- Mid-Stream Urine (MSU) for culture and sensitivity (2-7% or women have asymptomatic bacteriuria)

- Pap smear, if due
- Gonorrhea and Chlamydia screen - cervical cultures or urine screen (PCR)

Consented Investigations:

Genetic Screening (discussed below):

- NIPT
- eFTS
- Quad Screen
- MSAFP (generally restricted to limited indications e.g. BMI >35, timely/quality ultrasound unavailable, family history of oNTD, valproate/carbamazepine medication use)

HIV:

- Test must be consented, with implications discussed and confidentiality assured
- Diagnosis of HIV+ status can impact current and previous partner(s), family, ability to obtain health and life insurance
- Long-term maternal outcomes are better if HIV+ status is known and treated
- Known HIV+ status allows people to practice safer sex and protect partners (if uninfected)
- Dramatically decreased risk of vertical transmission to fetus if optimally treated in pregnancy (from 25% to 2%)
- Breastfeeding contraindicated
- Most patients take more than one medication, optimal management continues to be revised

Subsequent Investigations and Management for All Women:

Gestational Diabetes Mellitus (GDM)

- Physiologic changes of pregnancy predisposing to glucose intolerance become evident at 24-29 weeks
- Anti-insulin factors produced by placenta and high serum cortisol lead to increased peripheral insulin resistance
- Current standard of care is to investigate all pregnancies with oral glucose challenge test
    - Glucose Challenge Test (GCT):
        - Generally done between 24 and 28 weeks
        - Can do earlier in certain situations (e.g. past history macrosomia, maternal obesity, previous GDM)
        - Can repeat if circumstances warrant
    - Process:
        - No preparation required, no fasting prior to test needed
        - 50 gram oral glucose load is given
        - One hour after drink (no eating or drinking during this time) blood drawn for glucose

        - Results interpretation - blood glucose levels:
            - <7.8 mmol/L - is a negative screen
            - 7.8-11.0 mmol/L - complete glucose tolerance test (see below)
            - >11.1 mmol/L - diagnosis of GDM
        - Glucose Tolerance Test (GTT):
            - Fasting blood sugar (FBS) drawn first
            - 75 gram oral glucose load is then given
            - Blood is drawn at 1 and 2 hours after the drink is completed
        - Abnormal for 75 gram 2-hour GTT (Source: CDA Clinical Practice Guideline 2013):
            - Fasting ≥ 5.3 mmol/L
            - 1-hour ≥ 10.6 mmol/L
            - 2-hour ≥ 9.0 mmol/L
        - One abnormal value = GDM
- Treatment
        - Dietary and lifestyle changes - may help to normalize blood sugar values
        - Metformin or insulin - if conservative measures not sufficient
- Multidisciplinary approach with endocrinologist, nutritionist, etc. is ideal – many units have a "Diabetes Clinic" or "Diabetes in Pregnancy" program
- Counseling:
        - Current pregnancy - implications on fetal growth and newborn wellbeing, pregnancy surveillance
        - High-risk of future Type 2 DM: good impetus to improve diet and lifestyle
- Postpartum follow-up: GTT between 6 weeks and 6 months postpartum, with appropriate follow-up (with endocrinology or family doctor)

Rh Immune Globulin (Rhogam, RhIG)

- Rhogam - IgG antibody, which prevents mother from mounting an immune response to any Rh positive fetal red blood cells in the maternal circulation during pregnancy
- Indicated if mother is Rh negative and has no Rh antibodies
- Given at 28 weeks or whenever there is possibility of fetomaternal hemorrhage (e.g. spontaneous abortion, termination, ectopic, chorionic villus sampling/amniocentesis, antepartum hemorrhage, postpartum)
- Protection lasts approximately 12 weeks - during this time, patient's antibody screen will be positive
- Consider testing the father:
        - If father Rh negative as well then baby must be Rh negative and Rhogam will not be required
        - Ensure patient understands the potential severity of alloimmunization - paternity must be certain if declining Rhogam (for more information, please refer to 'Fetal Complications Part II' chapter)
- Dose: 300 mcg given intramuscularly at 28 weeks' gestation: standard dose is sufficient to protect against approximately 15 mls of fetal RBC or 30 mls of fetal whole blood

- If suspect larger fetomaternal hemorrhage (FMH): Send Betke-Kleihauer test/flow cytometry to quantify degree of FMH and adjust dose (e.g. additional 10 mcg of RhIg for every 0.5 mls of fetal RBC)
- The blood group and antibody screen (BGAS) ordered at the first antenatal visit will identify if mother already has Rh antibodies - Rhogam not given to patients already alloimmunized

Other Serum Antibodies

- Many other red blood cell antibodies (outside the Rh group) exist
- If BGAS identifies other antibodies, establish whether these have been associated with fetal or neonatal anemia i.e. hemolytic disease of the fetus/newborn (e.g. antibodies in the Kell and Duffy group)
- If a potentially harmful antibody is identified, consider: paternal antigen status testing, referral to a high-risk clinic, potential for fetal status testing, serial antibody titres, ultrasound monitoring for fetal anemia with MCA peak systolic velocity/hydrops (for more information please see 'Fetal Complications Part II' chapter)

Serum Hemoglobin:

- Will likely drop from first trimester due to dilutional effect
- If severe drop, re-evaluate diet, supplements, maternal status
- Repeat at 25-28 weeks (Fe, B12, Folate as well if concerns)

Group B Streptococcus (GBS) status:

- Done at 35-37 weeks (earlier if threatened preterm labour/multiples)
- Single combined culture from vagina and anorectal area
- If positive, antibiotic prophylaxis given in labour to reduce risk of neonatal GBS infection
- If GBS bacteriuria at any time during pregnancy, treat as GBS positive (indicator of heavy colonization, no need to vaginal-rectal swab)
- This is NOT a maternal infection: about 10-30% of women are carriers of GBS; status can change over time
- Concern is neonatal infection, potential significant morbidity

Biophysical Profile (BPP) Assessment:

- Management of post-dates pregnancy: twice weekly in 41st week until delivery

Other investigations/Interventions depending on circumstance:

- Thyroid function/treatment
    - TSH often done, value of routine screening in doubt (2015 ACOG guideline)
- Hepatitis C
    - If positive for HIV, Hepatitis B or other risk factors (blood transfusion prior to 1984 and untested, current or previous partner with known infection, intravenous drug use, sex trade workers, extensive piercing or tattooing)

        - No vaccine but appropriate treatment and counselling can result in better outcomes
        - Vertical transmission rate low (5%)
    - Varicella zoster immunity with IgG titre (if no clear history of childhood infection)
    - Toxoplasmosis (house pets, gardeners)
    - Parvovirus B19 immunity (IgG) (primary school teachers, daycare workers)
    - Hemoglobin A1C (pre-gestational diabetic patients)
    - TB (family or household contact, symptoms, homeless)
    - Urinalysis - by dip stick if elevated BP
        - UTI, renal disease, proteinuria in the context of gestational hypertension
    - History of Herpes Simplex
        - Oral antiviral agent given from 36 weeks to minimize risk of active infection during labour and need for Caesarean delivery
    - Low Dose ASA (81 - 162 mg)
        - History of increased BP, placental issues
        - Best if started by late first trimester (ideally prior to 16 weeks gestation)
        - For more information please refer to 'Pregnancy and Hypertension' chapter

Identification of the at-risk pregnancy

- Assess risk based on history and physical
- Categorize the risk currently as per Ontario Ministry of Health Antenatal Record 1 and 2
- Additional work-up and discussion as indicated
- Reassess risk at each visit, high risk status may be identified at any point
- Pre-existing risk (identified at first visit):
    - underlying medical illness (hypertension, Type 1 DM, SLE)
    - anatomical issues: large fibroids, septate or bicornuate uterus
    - prior uterine surgery, cervical surgery or fibroid embolization
    - poor obstetrical history
    - late maternal age
    - social issues (abuse, substance dependency)
    - multiple pregnancy
- Subsequent visits - maternal issues:
    - gestational hypertension without proteinuria or with proteinuria ("pre-eclampsia")
    - gestational diabetes
    - rarer: intrahepatic cholestasis of pregnancy (ICP), pruritic urticarial plaques and papules of pregnancy (PUPPPS)
- Subsequent visits - fetal issues:
    - growth restriction or macrosomia
    - anomalies: chromosomal abnormalities, structural malformations
    - cardiac arrhythmias
    - hydrops (immune and non-immune)
    - malpresentation

- Subsequent visits - placental/obstetrical issues:
    - short cervix
    - uterine irritability/preterm labour
    - preterm prelabour rupture of membranes (PPROM)
    - abnormal placentation: placenta previa, accreta and percreta;"uteroplacental vascular insufficiency"; velamentous or marginal cord insertion
    - antepartum hemorrhage (preterm labour, abruption, chronic abruption, placenta previa)
    - polyhydramnios/oligohydramnios
    - post-term pregnancy

ASSESSMENT OF FETAL WELL-BEING

Fetal Growth:

- Assessed indirectly at each visit through symphysis fundal height (SFH)
- Can be assessed more accurately by ultrasound estimation of growth (accuracy of ultrasound assessment of growth declines in late pregnancy and with larger fetuses)

Fetal Kick Counts:

- Perception of fetal movement by mother
- Several acceptable protocols exist (ex. 6 kicks in 1 hour, 10 in 2 hours) usually dependable by approximately 30 weeks
- Failure to meet criteria ("decreased fetal movement") requires immediate assessment

Non Stress Test (NST):

See Table 1: Antepartum Classification: Non-Stress Test

- Continuous assessment of fetal heart rate using external Doppler for 20 minutes
- Consider gestational age, maternal medications, fetal sleep patterns (may decrease variability)
- Allows an extended evaluation of the fetal heart rate pattern and fetal status
- Can be done at any time from mid second trimester to delivery, for many different indications

Parameter	Normal NST (Previously "Reactive")	Atypical NST (Previously "Non-Reactive")	Abnormal NST (Previously "Non-Reactive")
Baseline	110–160 bpm	• 100–110 bpm • > 160 bpm < 30 min. • Rising baseline	• Bradycardia < 100 bpm • Tachycardia > 160 for > 30 min. • Erratic baseline
Variability	• 6–25 bpm (moderate) • ≤ 5 (absent or minimal) for < 40 min.	≤ 5 (absent or minimal) for 40–80 min.	• ≤ 5 for ≥ 80 min. • ≥ 25 bpm > 10 min. • Sinusoidal
Decelerations	None or occasional variable < 30 sec.	Variable decelerations 30–60 sec. duration	• Variable decelerations > 60 sec. duration • Late deceleration(s)
Accelerations Term Fetus	≥ 2 accelerations with acme of ≥ 15 bpm, lasting 15 sec. < 40 min. of testing	≤ 2 accelerations with acme of ≥ 15 bpm, lasting 15 sec. in 40–80 min.	• ≤ 2 accelerations with acme of ≥ 15 bpm, lasing 15 sec. in > 80 min.
Preterm Fetus (< 32 weeks)	≥ 2 accelerations with acme of ≥ 10 bpm, lasting 10 sec. < 40 min. of testing	≤ 2 accelerations of ≥ 10 bpm, lasting 10 sec. in 40-80 min.	≤ 2 accelerations of ≥ 10 bpm, lasting 10 sec. in > 80 min.
ACTION	FURTHER ASSESSMENT OPTIONAL, based on total clinical picture	FURTHER ASSESSMENT REQUIRED	URGENT ACTION REQUIRED An overall assessment of the situation and further investigation with U/S or BPP is required. Some situations will require delivery.

Table 2: Antepartum classification: non-stress test

Adapted from: SOGC Clinical Practice Guideline No. 197 (2007)

Ultrasound:

1. First Trimester Scan
    - Accurately establish dates, to determine viability, to rule out ectopic pregnancy, to determine number of fetuses, and in multiple pregnancy to establish chorionicity
    - 11-14 weeks: fetal nuchal translucency (NT) done as part of their prenatal genetic screening
2. Anatomy Scan (18-20 weeks)
    - Offered to all pregnant women as a screen for placental, fetal, and pregnancy problems
    - Ideally carried out between 18-20 weeks
    - Complete scan should establish:
        - Live, structurally normal intrauterine fetus
        - Normal amniotic fluid volume
        - Locate the placenta and establish it is clear of the internal os
        - Identify any uterine and adnexal abnormalities (fibroids, bands, septae, short cervix, ovarian masses)
    - Assess for neural tube defects (now replacing use of serum markers) and any other fetal structural anomaly
    - Complete scan requires visualization and documentation of specific anatomical structures of the fetus (in general detailed structures of brain, face, cardiac, thoracic, abdominal, kidneys, bladder, extremities, spine)
3. Growth
    - Healthy fetus should follow established growth curves which exist for estimated fetal weight (EFW), fetal abdominal circumference (AC), biparietal diameter (BPD), head circumference (HC), femur length (FL), etc.

- Ultrasounds for estimated fetal weight (EFW) should NOT be repeated more often than every 2 weeks for a reliable trend
- Growth below the 10th centile or falling off its growth curve may indicate fetal abnormality or compromise, requiring more intensive monitoring including early delivery
- Consider ethnic specific, twin specific growth curves if available

4. Biophysical Profile (BPP)
   - Ultrasound study of overall fetal wellbeing
   - Each factor given a score of 2 if present, 0 if not present or decreased
   - Satisfactory score is 8
   - Ultrasound parameters must be seen within a 30-minute study:
     1. **Gross Body Movement:** 3 discrete body or limb movements
     2. **Fetal Tone:** one episode of active extension with return to flexion of limb or trunk (hand opening and closing also acceptable)
     3. **Breathing Movements:** one 30-second episode of fetal breathing movement (fetal diaphragm or kidneys seen to move up and down, chest wall or abdomen in and out)
     4. **Amniotic Fluid (AF):** at least one pocket 2cm x 2cm adequate

5. Amniotic Fluid Index (AFI)
   - Measure of amniotic fluid volume
   - Addition of vertical measurement of fluid pocket in all four quadrants of the uterus (RUQ + RLQ + LUQ + LLQ)
   - 5-25 cm considered normal, varies with gestational age
   - May indicate oligohydramnios even with normal BPP

6. Doppler Flow Studies:
   - Ultrasound measurement of blood-flow velocity through fetal blood vessels

   Established vessels include:

   Umbilical Artery (UA):
   - Of value in assessment of growth-restricted fetuses
   - Pulsatility index (PI) most used in reporting (direct relationship between PI and resistance e.g. PI is an index reflecting resistance to flow)
   - Indicative of abnormal placentation
   - Important principle is end-diastolic flow should be maintained (e.g. placental flow should be low resistance circuit):
     - Low end-diastolic flow (high PI)- needs close monitoring,
     - Absent end-diastolic flow- likely needs admission +/- delivery
     - Reversed end-diastolic flow- needs delivery

Middle Cerebral Artery (MCA):

- Used clinically in different ways
- Typical indices measured include pulsatility index (measure of resistance to flow) and peak systolic velocity (predictive of fetal anemia)
    - Pulsatility index (PI)- most used for assessment in growth restricted fetuses
    - In growth restricted fetuses, MCA PI is measured to identify the "brain sparing" effect: when a fetus decreases resistance in its cerebral vasculature to protect its brain, the MCA waveform will reflect increased flow in diastole (decreased resistance to flow)
    - Peak systolic velocity (PSV)- used to identify fetal anemia (e.g. abnormally elevated PSV predictive of fetal anemia) in pregnancies at risk (e.g. Rh isoimmunization, infection such as Parvovirus)
    - An anemic fetus will become hyperdynamic with less viscous blood, and the PSV will increase

Uterine Arteries (UTA):

- Abnormal uterine artery waveforms at 20-22 weeks can identify women at risk for uteroplacental vascular insufficiency (potentially leading to intrauterine growth restriction IUGR and pre-eclampsia)

7. Third trimester scan
    - Some obstetricians order routine third trimester ultrasound around 32-34weeks
    - Cost/benefit is unproven
    - Specific indications include: decreased fetal movement, fetal growth, position, re-assessment of previously identified problems (placental site if marginal or previa at 20 weeks, fetal pelviectasis)

Prenatal genetic screening (PGS) and diagnosis (PGD)

Prenatal Genetic Screening:

- Non-invasive screening vs invasive diagnosis
- Non-invasive screening should be offered to every pregnant woman (SOGC, 2007)
- Informed consent is essential
- Non-invasive screening assigns a specific chromosomal abnormality risk, mainly for Down Syndrome - this is not diagnostic, but is rather a means of assessing risk - a low or high-risk result is then used to guide decision-making for diagnostic testing
- Some pregnancies achieved by IVF will have the embryo tested before being placed in uterus (preimplantation genetic diagnosis) and no further testing required

Non-Invasive Genetic Screening:

1. *NIPT (Non-Invasive Prenatal Testing):*
    - Offered in Canada since 2013
    - Peripheral blood test which analyzes cell-free fetal DNA in the maternal circulation
    - Screens for numerical abnormalities of chromosomes 21, 18, 13, X and Y; some methods also allow for screening for other genetic conditions
    - Very high detection rate for Down Syndrome (>99%), as well as Trisomy 18 and 13 when validated in high-risk pregnancies (93% detection rate)
    - Applicable for singleton and uncomplicated twin pregnancies from about 10 weeks
    - Cost approx. $500 - Ontario Ministry of Health will cover cost for women aged 40 and over, or with positive screening tests or other major risk factors

2. *eFTS:*
    - Enhanced First Trimester Screen
    - Done at 11+3 - 13+3 weeks or crown-rump length measurement via ultrasound of 44.9 – 84.1 mm
    - Includes: nuchal translucency (NT, ultrasound measurement) maternal serum PAPPA, HCG, AFP (or placental growth factor – PlGF – depending on testing site)
        - Note: enlarged NT can be associated with chromosomal anomalies, cardiac defects, genetic syndromes
    - Assigns risk to pregnancy for Down Syndrome and used in deciding on whether or not to proceed with NIPT or invasive testing

3. Integrated Prenatal Screening (IPS):
    - An older version of prenatal testing, still available in some centres
    - Integrates results from tests performed in first and second trimesters
    - Combines the following measurements to establish a risk assessment for Down's Syndrome:
        - NT Ultrasound: at 11-14 weeks
        - Lab tests: PAPP-A at 11-14 weeks
        - Repeat lab tests: AFP, uE3, hCG, Inhibin A from 15-18 weeks

4. *Quad Screen*
    - Similar to above, for patients who present later than 13+ weeks

5. *MS-AFP (maternal serum screen for Open neural tube defects)*
    - Limited indications (obesity BMI>35, inability to get timely/quality scan, family history open neural tube defects, use of antiepileptic medication such as valproic acid and carbamazepine)
    - Largely replaced by good quality anatomy ultrasound scan

Table 3: Current Options Prenatal Screening

	Detection Rate for Trisomy 21	False +ve Rate
Maternal Age (MA) >35	33%	>10%
MA + MSS	75%	7%
MA + FTS	85%	5%
IPS	89%	2.4%
NIPT	99%	0.1%

Invasive Diagnostic Testing:

1. *Chorionic Villus Sampling (CVS):*
    - 11-14 weeks
    - Placental biopsy via transcervical (using special forceps or flexible catheter) or transabdominal approach
    - Chorionic villi are aspirated and placed into culture media
    - Preliminary results for very high risk patients may be available in a few days [usually using QF-PCR (polymerase chain reaction)]; microarray may also be done
    - Early termination of affected pregnancies can be offered (psychological and physical advantages)
    - Procedure related pregnancy loss rate 1-2%
    - Rarely, inaccurate results due to placental mosaicism
    - Main advantage of CVS over amniocentesis: can be performed earlier in gestation (~11 weeks)

2. *Amniocentesis:*
    - 15-20 weeks - but in special circumstances may be done any time after 15 weeks
    - Collection of amniotic fluid transabdominally under ultrasound guidance
    - Karyotype of fetal cells obtained from amniotic fluid – QF-PCR analysis results in 2-3 days, microarray may also be done (in Toronto, microarray analysis done for all samples)
    - Pregnancy loss traditionally quoted as 1/200; FASTER study data suggests much lower
    - Failures may occur if inadequate sample or contamination of sample by maternal cells

QUESTIONS AND COUNSELLING

- For many concerns remember:
    - Re-enforce normalcy
    - Most are short lived
    - Empathy and understanding required
    - Severity determines if and what therapy is required

Nausea and vomiting of pregnancy (NVP)

- NVP affects 50-90% of pregnant women
- Most severe form (hyperemesis gravidarum) affects 1% (rule out twins or molar pregnancy)

- Persistent vomiting
- Loss of >5% of pre-pregnancy weight
- Electrolyte imbalance, ketonuria
- Etiology likely multifactorial
- Often limited to first trimester (T1) but may persist throughout pregnancy
- "Morning Sickness" may be a misnomer since some women have it all day

Management

- Rule out other possible causes of N&V
- Weigh frequently, assess level of hydration, test urine for ketones

Dietary and Lifestyle Changes

- Avoid mixing fluids and solids
- Frequent small meals
- Stop prenatal vitamin (but continue folic acid until >12 wks)
- Increase sleep/rest (fatigue may exacerbate NVP)

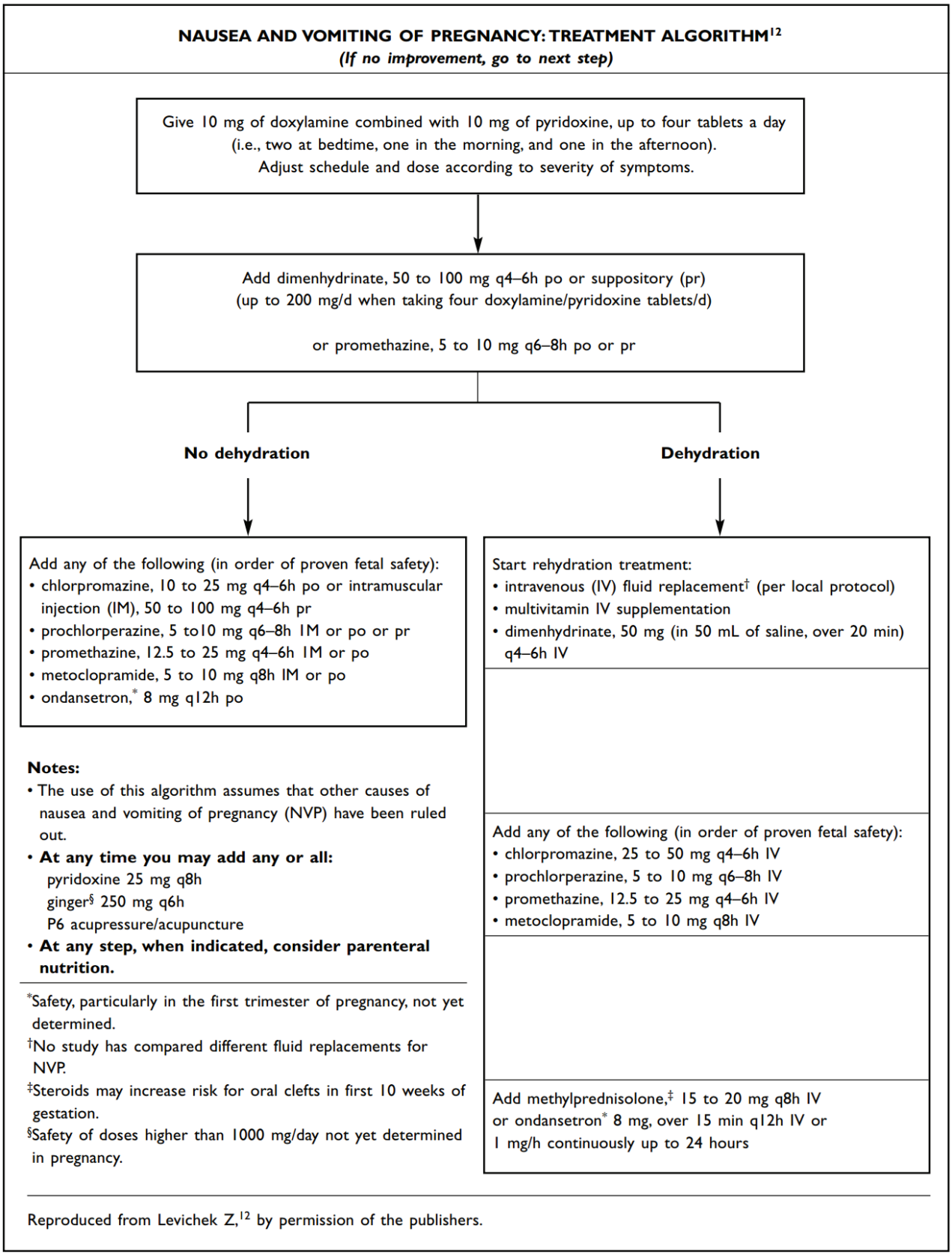
Pharmacologic Management

- Diclectin (doxylamine/pyridoxine) is standard of care, normally 2-4 tablets po daily but may increase to 8 tablets daily - this is a class "A" drug in pregnancy, no fetal risk; see algorithm for other options (Figure 2)
- Dimenhydrinate (Gravol)
- Metoclopramide (Maxeran)
- Ondansetron (Zofran)

Severe, Refractory NVP

- Consider Home Care to manage with IV fluids and parenteral anti-emetics
- Consider hospitalization
- Emotional support

Figure 2: Management of N&V (Adapted from SOGC Clinical Practice Guideline No. 120, 2002).



Nutrition

- Prenatal vitamin (PNV) supplementation recommended (Materna, PregVit)
- Supplementation not always essential as long as diet is meeting calcium, iron and folic acid needs
- Appropriate intake is recommended (not necessary to "eat for two")

Canada's Food Guide currently suggests the following:

- 3-4 servings of milk per day
- Increase intake by:
    - First trimester - 100kCal/day
    - Second/third trimester - 300 kCal/day
    - Breastfeeding - 450kCal/day
- Well balanced, include variety of food
- Special attention should be given to folate, calcium, vitamin D, iron and essential fatty acid intakes, because there is potential for inadequate intakes in some groups of women (vegetarian, lactose intolerant, low BMI, NVP, poor socio-economic status, teen pregnancy).

Canada's Food Guide and recommendations for nutrition in pregnancy are being reviewed and rewritten with new prenatal guidelines expected to be released in 2018-19.

Optimal weight gain in pregnancy:

- Inadequate maternal weight gain has been associated with growth restriction and prematurity
- Excessive maternal weight gain has been associated with development of GDM and large-for-gestational-age (LGA) babies
- It is NOT recommended to try to lose weight during pregnancy
- Rough guideline for appropriate weight gain: 1-3.5 kg (2-8 lbs) in the first trimester, then one pound per week to delivery.
- Current recommendations for optimal weight gain depend on maternal prepregnancy body mass index (BMI)

Table 4: Guidelines for gestational weight gain ranges.

BMI Category*	Recommended Total Gain	
	kg	lb
BMI <20	12.5 - 18.0	28 - 40
BMI 20 - 27	11.5 - 16.0	25 - 35
BMI >27	7.0 - 11.5	15 - 25

*Canadian BMI categories for Healthy Weights, established in 1988 by Health Canada, correspond closely although not exactly to the BMI categories used by the United States Institute of Medicine (IOM). IOM categories for BMI are: low: <19.8; normal/healthy: 19.8-26; high: >26-29. These guidelines do not apply to multiple gestations.

Drugs, alcohol and nicotine

- Offer support, assistance and referral to pregnant women with addictions
- Reinforce these are not advisable during pregnancy
- Substances and risks:
    - Heavy smoking - IUGR, preterm labour, smoking in the home associated with increase in SIDS
    - Cocaine - IUGR, abruption, fetal demise, fetal anomalies (vasoactive compound, can disrupt fetal development), neonatal withdrawal
    - EtOH - fetal alcohol spectrum disorders (IUGR, distinctive facies, developmental delay, behavioural problems); most common preventable cause of developmental delay

Environmental and occupational hazards

- Physical, biologic, chemical hazards may result in infertility, early pregnancy loss, IUGR, prematurity
- Employers' responsibility to make work environment safe and employees' responsibility to follow safety rules at work
- Stress and extreme physical activity may represent occupational risks
- Consider modification of work requirements as needed

Radiation (from medical diagnostic procedures)

- Generally, studies necessary for maternal well-being should be done
- Shield fetus with lead apron if possible (e.g. dental x-rays)
- Exposure prior to recognition of pregnancy: detrimental outcome is extremely unlikely - this is not an indication for termination
- Exposure to less than 5cGy (5 rads or 5000 millirems) has NOT been associated with an increase in fetal anomalies or pregnancy loss
- Most investigations involve minimal fetal radiation doses [estimated fetal radiation dose - CXR: 0.5 millirems, pelvic xray: 210 millirems (Source: Motherisk.org)]
- Radioactive isotopes of iodine are contraindicated during pregnancy
- There are no known adverse effects on pregnancy from ultrasound or MRI

Sexual activity

- Semen contains prostaglandins
- Female orgasm may be associated with uterine contractions
- Spotting often seen after intercourse usually due to friable cervix
- As long as comfortable and no bleeding or cramping, intercourse is safe in pregnancy
- Restrict intercourse with certain pregnancy complications such as PPROM, threatened preterm labour, uterine irritability, antepartum hemorrhage, placenta previa, history of preterm labour and birth

Exercise

- No documented increase in fetal or maternal risk in exercising pregnant women
- All women without contraindications should be encouraged to maintain a healthy active lifestyle
- Pregnancy is not the time to try to reach peak physical fitness or train for athletic competitions
- Exercising women should be aware of potential for light-headedness, loss of balance and falls; choose appropriate activities
- Reconsider abdominal exercises as pregnancy progresses: may aggravate diastasis and compromise utero-placental blood flow in the supine position
- Kegel exercises may decrease future urinary incontinence

Table 5: Contraindications to exercise in pregnancy.

CONTRAINDICATIONS TO EXERCISE IN PREGNANCY

Absolute Contraindications	Relative Contraindications
• Ruptured membranes	• Previous spontaneous abortion
• Preterm labour	• Previous preterm birth
• Hypertensive disorders of pregnancy	• Mild/moderate cardiovascular disorder
• Incompetent cervix	• Mild/moderate respiratory disorder
• Growth restricted fetus	• Anemia (Hb <100 g/L)
• High order multiple gestation (≥ triplets)	• Malnutrition or eating disorder
• Placenta previa after 28th week	• Twin pregnancy after 28th week
• Persistent 2nd or 3rd trimester bleeding	• Other significant medical conditions
• Uncontrolled type I diabetes, thyroid disease, or other serious cardiovascular, respiratory, or systemic disorder	

Reprinted and modified with permission from the Canadian Society for Exercise Physiology.[23]

Adapted from SOGC Clinical Practice Guideline No. 129 (2003).

Immunizations

- Inactivated vaccines generally considered safe
- Live attenuated vaccines best avoided
- Measles Mumps Rubella Vaccine (MMR)
    - Not given in pregnancy
    - If unexpected pregnancy occurs within 3 months of receiving an MMR vaccine, no evidence of complications has ever been documented
    - If a woman is rubella non-immune in pregnancy, give MMR vaccine immediately postpartum
- Flu vaccine recommended, safe at any stage of pregnancy
- Tdap vaccine for Newborn Pertussis protection recommended for all women
    - Canadian National Advisory Committee on Immunization (NACI) and the

Society of Obstetricians and Gynaecologists of Canada (SOGC) now recommend immunization with the Tdap vaccine (Tetanus Toxoid, Reduced Diphtheria Toxoid and Reduced Acellular Pertussis) in every pregnancy, regardless of previous immunization history

- Generally given in early third trimester, consider from 21-32 weeks gestation
- NACI recommends vaccination may be provided from 13 weeks up until delivery, but should ideally be provided between 27 and 32 weeks of gestational age because it strikes the best balance between safety and effectiveness data and optimal antibody transfer for babies born after 37 weeks

Table 6: Immunizations in pregnancy.

Considered safe if otherwise indicated	**Contraindicated during pregnancy or safety not established**	**Special recommendations pertain**
Tetanus and diphtheria toxoids (Td)	BCG*	Anthrax
Hepatitis B	Measles*	Hepatitis A
Influenza	Mumps*	Japanese encephalitis
Meningococcal	Rubella*	Pneumococcal
Rabies	Varicella*	Polio (IPV)
		Typhoid (parenteral and Ty21a*)
		Vaccinia*
		Yellow fever*

**—Live, attenuated vaccine.*

BCG = bacille Calmette-Guérin; IPV = inactivated polio virus.

Adapted from Guidelines for vaccinating pregnant women. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Atlanta, Ga.: Centers for Disease Control and Prevention, 2002.

Adapted from Vaccinations in Pregnancy. Am Fam Phys 2003; 68:E299-309.

Depression

- Affects 1/10 women during pregnancy or postpartum
- Risk is highest in women with previous history of major depressive disorder (MDD)
- SSRI use (USA data) in approximately 2-3% of pregnancies
- In women with history of major depressive disorder, 66% had relapse during/post pregnancy if stopped therapy vs. 26% if continued treatment
- Involve family physician, social work, psychiatry as needed
- Conflicting studies regarding a connection between SSRI use and some rare newborn anomalies:
    - Most consistent association has been with Neonatal Abstinence Syndrome ("withdrawal') and Persistent Pulmonary Hypertension of the Newborn (PPHN)
    - Absolute risk of PPHN still extremely small (6-12 cases per 1000 exposed)
- Paxil (Paroxetine) not currently recommended in pregnancy, suggest switch to another SSRI
- Each women's individual situation must be considered and risks of continuing therapy vs. risks of discontinuing therapy should be discussed

Prenatal and lactation classes

- Encourage attendance if interest or uncertainty expressed, may decrease anxiety
- Sibling, parenting, refresher classes all available as well
- General classes discuss labour coping mechanisms: breathing techniques, acupuncture, aromatherapy, role of support person and general questions about what to expect during labour experience: monitoring, assisted vaginal delivery, etc.
- Advise the woman the baby will need his/her own health care provider after delivery (may or may not differ from care provider for pregnancy).

Work

- Electronic equipment safe: computers, microwave, etc.
- Presence of symptoms of pregnancy may affect performance at least in the first trimester
- If uncomplicated pregnancy, expect reasonable performance to late third trimester
- Excessive work hours have been associated with premature labour
- Individualized: patients with NVP, carrying twins or large for gestational age fetus, or with other complications (antepartum hemorrhage, hypertensive disorders of pregnancy, threatened preterm labour) may benefit from reduced hours or home rest

Travel

- Travel generally safe
- Immunizations as needed
- Care with excessive heat/sun at vacation destinations
- Normal food precautions for travelers, may want to carry rehydration salts
- Consider medical insurance and availability of obstetric and newborn care in case of pregnancy complications
- Airline restrictions may be instituted in the third trimester - patient should check with airline
- Increased risk of venous thromboembolism with prolonged immobility (long drives or flights):
    - Move about during flight
    - Maintain good fluid intake
    - Avoid diuretics (caffeine)
    - Seek medical attention if leg swelling, pain, or chest pain/SOB after travel
    - Consider compression stockings

Early Vaginal Bleeding

- Not uncommon
- Ultrasound after 7-8 weeks generally reassuring of viability
- Avoid intercourse
- Consider re-adjustment of activities (bedrest not indicated)

Over-the-counter medications

- Consider use if "benefits outweigh risks"
- Very few drugs are known teratogens; conversely very few drugs have proven safety in pregnancy
- Commonly used medications (antihistamines, laxatives) are not known to be harmful to pregnancy
- Acetaminophen preferable to ibuprofen (e.g. Avoid NSAIDs in pregnancy)

Prescribed medications

- CONTRAINDICATED--Documented adverse effects:
    - ACE inhibitors: renal defects, IUGR, oligohydramnios
    - Tetracycline: stains teeth, may affect long bone development
    - Retinoids (Accutane): major human teratogen - craniofacial, cardiac, thymic, and CNS malformations
    - Diethylstilbesterol (DES): historical risk - female genital tract structural abnormalities, clear cell carcinoma
- CONSIDER OTHER MEDS, WEIGH RISKS AND BENEFITS—Documented adverse effects (though use in pregnancy may be necessary for management of maternal disorders):
    - Anticonvulsants: most proven associations are open neural tube defects, hydantoin syndrome (IUGR, mental retardation, facial and other anomalies), other associations: congenital cardiac defects, limb-reduction defects, and other skeletal anomalies
    - Lithium (Ebstein's anomaly)
    - Warfarin: pregnancy loss, warfarin embryopathy (nasal hypoplasia, epiphyseal stippling, optic atrophy, intra-cranial bleeds)
    - Prostaglandin inhibitors/NSAIDS: indomethacin, ibuprofen after 32 weeks associated with premature closure of the ductus arteriosus

Breastfeeding (BF)

- Encourage breast feeding for a minimum of 6 months
- HepB and HepC carriers okay to BF (newborns of HepB carriers are vaccinated)
- HIV positivity is a contraindication to BF - TERESA group provides free formula to Ontario HIV+ mothers for 1 year
- Anatomy may affect BF (inverted nipples, history of breast reduction or augmentation surgeries)
- Lactation consultants available, BF classes offered on many postpartum wards
- Dietary adequacy, continue pre-natal supplements
- Impact of maternal medications: may require pediatric consultation
    - Generally safe: penicillin, aminoglycosides, cephalosporins, Progesterone only BCP, combination OCP (may decrease milk supply), DepoProvera
    - Avoid: tetracycline, antineoplastics, some immunosuppressives, Accutane
- Nipple Care: breast milk left to dry on nipples after BF, Lansinoh (lanolin based nipple care cream), topical steroid if needed

- Newborn oral thrush can lead to painful candidal infections of nipple
- Breast engorgement: cool compresses or ice packs, manual expression, cabbage leaves
- Treat mastitis promptly (continue BF, cloxacillin)
- If milk supply inadequate can consider fenugreek, domperidone (used less often due to concerns around maternal adverse side effects)

Circumcision

- No clear medical benefit to male circumcision
- Personal choice, tradition, religious considerations are often the deciding factors
- Address with pediatrician

Psychosocial Issues

- Each pregnancy is unique
- Consider the couple's relationship, financial worries, family illness, siblings, child care, history of abuse, religious/ cultural factors, in home support during postpartum period, postpartum blues, occupational responsibilities
- Be aware of community resources (parenting groups, public health, etc.)
- Employ interpreters to ensure that information is understood
- Input from psychiatry, social work, cultural community and religious counselors may be appropriate
- Remember privacy with all discussion/contacts
- Consent for referrals
- Physician responsibility to contact CAS in cases where child suspected to be abused or at high risk for abuse

Constipation

- Dietary adjustments (adequate fluids, fibre)
- Reconsider/reduce prenatal vitamins (folate needs to be continued till >12 wks)
- Stool softeners/fibre supplement (Colace, Metamucil) PRN

Hemorrhoids

- Avoid straining
- Avoid constipation
- Cream or suppositories if symptomatic (Anusol) - available with topical steroid and with topical analgesic
- Sitz baths,Tucks pads

Vaginitis

- Yeast
    - Common due to high estrogen environment
    - Treat locally with antifungal agents if symptomatic (Monistat, Canesten - preferable not to use the plastic applicator, use finger)
    - May recur or require prolonged course of therapy
    - Oral fluconazole if all else fails (class C)

- Bacterial Vaginosis
    - Need to treat is controversial
    - Treat if previous preterm labour or risk factors for preterm labour
    - Treat with oral or vaginal flagyl, option of clindamycin orally

Urinary Frequency

- Common symptom throughout pregnancy
- Rule out urinary tract infection
- If culture is positive, treat with appropriate antibiotic compatible with pregnancy
- Reculture as indicated

Nose and gum bleeds

- Minor gum and nose bleeds are common
- Examine gums for gum disease – may require a dental visit
- If severe, repeated bleeds, investigate for bleeding disorder

Numbness of hands

- Carpal tunnel syndrome most common cause (compression of median nerve)
- Wrist splints or steroid injections may be of benefit
- Decrease aggravating factors (prolonged computer work)
- Most resolve after pregnancy - if not, surgery may be required

Sleep Disturbances

- Anxiety, abdominal pain, fetal movement, physical changes, abdominal enlargement, ligament laxity, urinary frequency, use of unnatural sleep positions all contribute
- Consider naps, sleep in chair, body pillows, modification of responsibilities
- Encourage sleeping on left side/uterine wedge to maximize uteroplacental blood flow
- Not generally recommended to treat with sleeping pills

Maternal anxiety

- Fear of unknown, pain, life changes, responsibility of parenting, normalcy of baby
- Allow to verbalize
- Encourage prenatal education/support group; explore support system

Edema

- Common normal experience
- Rule out pathology such as pre-eclampsia, deep venous thrombosis (DVT), congestive heart failure (peripartum cardiomyopathy)
- Consider compression stockings or support pantyhose
- Elevate lower extremities above level of heart
- Avoid standing for long periods

Headaches

- Common especially early to mid-second trimester
- Rule out pathology: check BP, blood sugar
- Use of analgesia as indicated, acetaminophen preferred
- Adequate rest
- Severe unremitting headaches need to be investigated as per non-pregnant (e.g. 'red flag' headaches)

Heartburn/GI Upset

- Antacids as indicated (extra perk is that TUMS have calcium)
- Small frequent meals
- Avoid aggravating foods
- Adjust meal times
- Sleep sitting up (or elevate head of bed)
- Rule out pathology: Preeclampsia/HELLP syndrome, gastroduodenal ulcer
- Ranitidine if severe

Fatigue

- Common in first trimester and late third trimester
- Modify activities
- Assistance in the home
- Consider time off work
- If sleep issues, consider naps, sleep in chair
- May be compounded by other symptoms of early pregnancy

Round Ligament Pain

- Condensed tissue in superior broad ligament extending from uterus to inguinal canal
- Soften and lengthen during pregnancy
- Often stretched during pregnancy as uterus grows and shifts, causing pain
- Commonly experienced in mid second trimester
- Pain generally felt in right or left lower aspect of uterus, radiating into the groin and aggravated by movement, shifting, walking, etc.
- No specific management: supportive care, rule out other etiologies for pain, adjust position, reassure

Lower Abdominal Pain/Pelvic Pressure

- Common increases with gestational age of pregnancy, maternal BMI and parity
- Consider pregnancy support belt

Vaginal Preparation for Labour

- Perineal Massage
- Graduated vaginal dilators

PRELABOUR COUNSELLING

Many women (and their partners) are anxious about various labour issues:

- Pain
- How they will cope
- Time involved
- Fear of the unknown
- Fear of loss of control
- Hospital phobia:
    - Often their first experience with hospitals
    - May have had previous bad or sad experience in hospital
- Possible complications
- Trust issues

Encourage prenatal classes and labour floor visit
Consider multi-disciplinary approach if needed to maximize preparation and comfort level: pediatrics, anesthesia

Signs and symptoms of labour
Labour is a process involving uterine activity that results in progressive dilatation and effacement of the cervix and descent of the presenting part of the fetus culminating in the expulsion of the fetus and placenta.

Divided into 3 stages:

First Stage: Onset of regular uterine activity to full dilatation

1. Often subdivided into latent stage and active stage
2. Latent phase: variable period of time of irregular uterine activity (of varying intensity not resulting in progressive changes in cervix)
3. Active phase: presence of strong, regular uterine contractions (associated with progressive/ predictable changes in the cervix and descent of the presenting part)

Second Stage: Full dilatation to delivery of the infant

Third Stage: Delivery of infant to delivery of placenta

Diagnosis of labour

- May be difficult to diagnose
- May require serial assessments to determine
- Expect irregular, not excessively painful contractions which become more frequent, regular and uncomfortable
- Generally require moderate to strong contractions every 2-3 minutes (start to start) lasting 45 to 60 seconds to result in expected cervical changes

- Often associated with small amount of vaginal loss of blood stained mucous, so called "bloody show"
- 30% of women rupture their membranes before the contractions starts (prelabour rupture of membranes or PROM)
- Ruptured membranes is identified by a gush of fluid and/or ongoing leakage - evidence:
    1. Speculum exam- pooling of fluid, leaking during cough
    2. Nitrazine - pH paper will turn dark blue when in contact with amniotic fluid
        - False positives: also turns blue in presence of semen, blood and vaginitis
    3. Ferning - place sample of the fluid on a glass slide, allowing it to air dry and then examining it under the microscope for the presence of a "fern-like" pattern
        - Positive test = diagnostic

When to go to the hospital

- Varies with gestational age and parity
- Earlier gestational ages and higher parity should go to hospital sooner
- Generally, go to the hospital if:
    1. Contractions- regular, painful, increasing in intensity and frequency
        - Counsel woman at prenatal visits about the latent phase of labour (may take several days and result in anxiety, fatigue, and dehydration)
        - 511 rule: contractions 5 minutes apart, lasting 1 minute long, for 1 hour
    2. Spontaneous rupture of membranes (SROM)
        - If preterm
        - If fluid looks green (meconium could indicate fetal stress)
        - If fluid is excessively bloody
        - If woman is GBS positive (antibiotics will be required)
        - If baby is not in vertex position
        - If fluid is clear and there are no problems and no contractions
            - Expect onset of labour within 24 hours in a majority of women
            - Present to hospital within 12 hours of SROM for induction of labour, since ROM >18 hours is associated with increased risk of infection
    3. Vaginal bleeding (not bloody show)
    4. Decreased fetal movements
    5. At any point if uncertain, better to attend hospital (advise women at prenatal visits that it is not uncommon to be assessed, counselled and sent home from labour and delivery unit)

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9. Breastfeeding Tips and Resources: www.breastfeedinginc.ca
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Appendix 1: Ontario Perinatal Record

Ontario

Ministry of Health and Long-Term Care

Ontario Perinatal Record 1

Last Name	First Name				
Address - street number, street name	Apt/Suite/Unit	Buzzer No			
City/Town	Province	Postal Code	Partner's First Name	Partner's Last Name	
Contact - Preferred	Leave Message ☐Y ☐N	Contact - Alternate/E-mail	Partner's Occupation	Partner's Education Level	Age
Date of Birth YYYY/MM/DD	Age at EDB	Language	Interpreter Required ☐Y ☐N	Occupation / Education Level	Relationship Status / Sexual Orientation
OHIP Number	Patient File Number	Disability Requiring Accommodation ☐Y ☐N	Planned Place of Birth	Planned Birth Attendant	
Newborn Care Provider In Hospital In Community			Family Physician/Primary Care Provider		
Allergies or Sensitivities (include reaction)			Medications (include Rx/OTC, complementary/alternative/vitamins and dosage)		

Pregnancy Summary

LMP YYYY/MM/DD Cycle q _____ Certain ☐Y ☐N Regular ☐Y ☐N

Planned Preg ☐Y ☐N Contraceptive Type Last Used YYYY/MM

Conception: Assisted ☐Y ☐N Details

EDB By LMP YYYY/MM/DD

Final EDB YYYY/MM/DD

Dating Method
☐T_1US ☐T_2US ☐LMP
☐IUI YYYY/MM/DD ☐Embryo Transfer YYYY/MM/DD
☐Other

Gravida	Term	Preterm	Abortus	Living Children	Stillbirth(s)	Neonatal / Child Death

Obstetrical History

Year/ Month	Place of Birth	Gest. (wks)	Labour Length	Type of Birth	Comments regarding abortus, pregnancy, birth, and newborn (e.g. GDM, HTN, IUGR, shoulder dystocia, PPH, OASIS, neonatal jaundice)	Sex M/F	Birth Weight	Breastfed / Duration	Child's Current Health

Medical History (provide details in comments)

Current Pregnancy
1 Bleeding ☐Y ☐N
2 Nausea/vomiting ☐Y ☐N
3 Rash/fever/illness ☐Y ☐N

Nutrition
4 Calcium adequate ☐Y ☐N
5 Vitamin D adequate ☐Y ☐N
6 Folic acid preconception ☐Y ☐N
7 Prenatal vitamin ☐Y ☐N
8 Food access/quality adequate ☐Y ☐N
9 Dietary restrictions ☐Y ☐N

Surgical History
10 Surgery ☐Y ☐N
11 Anaesthetic complications ☐Y ☐N

Medical History
12 Hypertension ☐Y ☐N
13 Cardiac / Pulmonary ☐Y ☐N
14 Endocrine ☐Y ☐N
15 GI / Liver ☐Y ☐N
16 Breast (incl. surgery) ☐Y ☐N
17 Gynecological (incl. surgery) ☐Y ☐N
18 Urinary tract ☐Y ☐N
19 MSK/Rheumatology ☐Y ☐N
20 Hematological ☐Y ☐N
21 Thromboembolic/coag ☐Y ☐N
22 Blood transfusion ☐Y ☐N
23 Neurological ☐Y ☐N
24 Other ☐Y ☐N

Family History
25 Medical Conditions ☐Y ☐N
(e.g. diabetes, thyroid, hypertension, thromboembolic, anaesthetic, mental health).

Genetic History of Gametes
26 Ethnic/racial background:
Egg _____ Age _____Yrs
Sperm _____
27 Carrier screening: at risk? ☐Y ☐N
• Hemoglobinopathy screening (Asian, African, Middle Eastern, Mediterranean, Hispanic, Caribbean) ☐Y ☐N
• Tay-Sachs disease screening (Ashkenazi Jewish, French Canadian, Acadian, Cajun) ☐Y ☐N
• Ashkenazi Jewish screening panel ☐Y ☐N
28 Genetic Family History
• Genetic conditions (e.g. CF, muscular dystrophy, chromosomal disorder) ☐Y ☐N
• Other (e.g. intellectual, birth defect, congenital heart, developmental delay, recurrent pregnancy loss, stillbirth) ☐Y ☐N
• Consanguinity ☐Y ☐N

Infectious Disease
29 Varicella disease ☐Y ☐N
30 Varicella vaccine ☐Y ☐N
31 HIV ☐Y ☐N
32 HSV Self ☐Y ☐N Partner ☐Y ☐N
33 STIs ☐Y ☐N
34 At risk population (Hep C, TB, Parvo, Toxo) ☐Y ☐N
35 Other ☐Y ☐N

Mental Health / Substance Use
36 Anxiety Past ☐Y ☐N Present ☐Y ☐N
GAD-2 Score _____
37 Depression Past ☐Y ☐N Present ☐Y ☐N
PHQ-2 Score _____
38 Eating disorder ☐Y ☐N
39 Bipolar ☐Y ☐N
40 Schizophrenia ☐Y ☐N
41 Other ☐Y ☐N
(e.g. PTSD, ADD, personality disorders)
42 Smoked cig within past 6 months ☐Y ☐N
Current smoking _____ cig/day
43 Alcohol: Ever drink alcohol? ☐Y ☐N
If Yes: Last drink: (when) _____
Current drinking _____ drinks/wk
T-ACE Score _____
44 Marijuana ☐Y ☐N
45 Non-prescribed substances/drugs ☐Y ☐N

Lifestyle/Social
46 Occupational risks ☐Y ☐N
47 Financial/housing issues ☐Y ☐N
48 Poor social support ☐Y ☐N
49 Beliefs/practices affecting care ☐Y ☐N
50 Relationship problems ☐Y ☐N
51 Intimate partner/family violence ☐Y ☐N
52 Parenting concerns ☐Y ☐N
(e.g. developmental disability, family trauma)
53 Other ☐Y ☐N

Comments

Completed By		Reviewed By	
Signature	Date	MRP Signature	Date

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Ontario

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Ontario Perinatal Record 2

Last Name	First Name
Planned Birth Attendant	
Newborn Care Provider In Hospital	In Community

G	T	P	A	L	S	Final EDB YYYY/MM/DD	Family Physician/Primary Care Provider

Physical Exam			
Ht _____ cm	Pre-pregnancy Wt ____ kg		
BP _____	Pre-pregnancy BMI ____		
Exam As Indicated			
Head and neck	N/Abn	MSK	N/Abn
Breast/nipples	N/Abn	Pelvic	N/Abn
Heart/lungs	N/Abn	Other	N/Abn
Abdomen	N/Abn		
Exam Comments			

Last Pap YYYY/MM/DD	Result

Initial Laboratory Investigations		Second and Third Trimester Lab Investigations	
Test	Result	Test	Result
Hb		Hb	
ABO/Rh(D)		Platelets	
MCV		ABO/Rh(D)	
Antibody screen		Repeat Antibodies	
Platelets		1hr GCT	
Rubella immune		2 hr GTT	
HBsAg			
Syphilis			
HIV			
GC			
Chlamydia			
Urine C&S			

Additional investigations as indicated	Test	Result	Test	Result
TSH, Diabetes screen, Hb Electrophoresis/ HPLC, Ferritin, B12, Infectious diseases (e.g. Hep C, Parvo B19, Varicella, Toxo, CMV), Drug screen, repeat STI screen.				

Prenatal Genetic Investigations

Screening Offered ☐Yes ☐No	Result		Result
☐FTS (between 11-13+6wks)		CVS/Amnio Offered ☐Y ☐N	
☐IPS Part 1(between 11-13+6wks) ☐Part 2(between 15-20+6wks)		Other genetic testing Offered ☐Y ☐N	
☐MSS (between 15-20+6wks) ☐AFP (between 15-20+6wks)		NT Risk Assessment 11-13+6wk (multiples)	
Cell-free fetal DNA (NIPT) Offered ☐Y ☐N		Abnormal Placental Biomarkers	

No Screening Tests

☐Counseled and declined	Date YYYY/MM/DD	☐Presentation > 20+6wk NIPT offered ☐Y ☐N	Date YYYY/MM/DD

Ultrasound

Date	GA	Result		
YYYY/MM/DD				
YYYY/MM/DD		NT Ultrasound (between 11-13+6 weeks)		
YYYY/MM/DD		Anatomy scan (between 18-22wks)	Placental Location	Soft Markers
YYYY/MM/DD				
YYYY/MM/DD				
YYYY/MM/DD				
YYYY/MM/DD				
YYYY/MM/DD				
YYYY/MM/DD				
YYYY/MM/DD				
YYYY/MM/DD				
YYYY/MM/DD			Genetic screening result reviewed with pt/client ☐	
YYYY/MM/DD			Approx 22 wks: Copy of OPR 1 & 2 to hospital ☐ and/or to pt/client ☐	

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Ontario

Ministry of Health and Long-Term Care

Ontario Perinatal Record 3

Last Name	First Name
Planned Birth Attendant	

Newborn Care Provider In Hospital In Community	Allergies or Sensitivities (include reaction)
Family Physician/Primary Care Provider	Medications (include Rx/OTC, complementary/alternative/vitamins, include dosage)

G	T	P	A	L	S	Final EDB YYYY/MM/DD

Issues (abnormal results, medical/social problems)	Plan of Management / Medication Change / Consultations

Special Circumstances	GBS
Low dose ASA indicated ☐ Progesterone indicated (PTB Prevention) ☐ HSV supression indicated ☐	Rectovaginal swab ☐pos ☐neg
Social (e.g. child protection, adoption, surrogacy)	Other indications for prophylaxis ☐Y ☐N

Recommended Immunoprophylaxis

Rh(D) neg ☐ Rh(D) IG given YYYY/MM/DD Additional dose given YYYY/MM/DD	Influenza Discussed ☐ ☐Received ☐Declined	Pertussis Discussed ☐ Up-to-date ☐Y ☐N Year _____ Received ☐ Declined ☐	Post-partum vaccines discussed ☐Rubella ☐Other _____	Newborn needs ☐Hep B prophylaxis ☐HIV prophylaxis

Pre-pregnancy Wt _____ kg BMI _____

Subsequent Visits

Date	GA (wks/days)	Weight (kg)	BP	Urine Prot.	SFH	Pres.	FHR	FM	Comments	Next Visit	Initial(s)
YYYY/MM/DD											
YYYY/MM/DD											
YYYY/MM/DD											
YYYY/MM/DD											
YYYY/MM/DD											
YYYY/MM/DD											
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YYYY/MM/DD											
YYYY/MM/DD											
YYYY/MM/DD											
YYYY/MM/DD											

Discussion Topics

1st Trimester	2nd Trimester	3rd Trimester
☐Nausea / Vomiting	☐Prenatal classes	☐Fetal movement ☐Work plan / Maternity leave
☐Routine prenatal care /Emergency contact /On call providers	☐Preterm labour	☐Birth plan: pain management, labour support
☐Safety: food, medication, environment, infections, pets	☐PROM	☐Type of birth, potential interventions, VBAC plan
☐Healthy weight gain ☐Breastfeeding	☐Bleeding	☐Admission timing ☐Mental health
☐Physical activity ☐Travel	☐Fetal movement	☐Breastfeeding and support ☐Contraception
☐Seatbelt use ☐Quality information sources	☐Mental health	☐Newborn care / Screening tests / Circumcision / Follow-up appt.
☐Sexual activity ☐VBAC counseling	☐VBAC consent	☐Discharge planning / Car seat safety ☐Postpartum care

Comments

Approx 36 wks: Copy of OPR 2 (updated) & OPR 3 to hospital ☐ and/or to pt/client ☐

1. Name / Initials	2. Name / Initials	3. Name / Initials	4. Name / Initials	5. Name / Initials

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Ontario
Ministry of Health and Long-Term Care
Resources

Last Name	First Name

Anxiety Screening

Generalized Anxiety Disorder scale (GAD-2) Date YYYY/MM/DD

Over the last 2 weeks, how often have you been bothered by the following problems:	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not been able to stop or control worrying	0	1	2	3

A total score of 3 or more warrants consideration of: Using the GAD-7 for further assessment or additional mental health follow-up.

Total Score ____

Depression Screening

The Patient Health Questionnaire-2 (PHQ-2) Date YYYY/MM/DD

Over the last 2 weeks, how often have you been bothered by the following problems:	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3

A total score of 3 or more warrants consideration of: Using the Edinburgh Postnatal Depression Scale (EPDS) or the Patient Health Questionnaire (PHQ) 9 for further assessment or additional mental health follow-up.

Total Score ____

T-ACE Screening Tool (Alcohol)

Response Key
1 Drink is equivalent to:
• 12 oz of beer • 12 oz of cooler • 5 oz of wine • 1.5 oz of hard liquor (mixed drink)

Date YYYY/MM/DD

	Response	
1. How many drinks does it take to make you feel high?	≤ 2 drinks = 0	> 2 drinks = 1
2. Have people annoyed you by criticizing your drinking?	No = 0	Yes = 1
3. Have you felt you ought to cut down on your drinking?	No = 0	Yes = 1
4. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover?	No = 0	Yes = 1

A total score of 2 or greater indicates potential prenatal risk and need for follow-up.

Total Score ____

Edinburgh Perinatal / Postnatal Depression Scale (EPDS) Cox, Holden, Sagovsky, (1987).

In the past 7 days: Date YYYY/MM/DD

1. I have been able to laugh and see the funny side of things	☐ As much as I always could = 0 ☐ Not quite so much now = 1	☐ Definitely not so much now = 2 ☐ Not at all = 3
2. I have looked forward with enjoyment to things	☐ As much as I ever did = 0 ☐ Rather less than I used to = 1	☐ Definitely less than I used to = 2 ☐ Hardly at all = 3
3. I have blamed myself unnecessarily when things went wrong	☐ No, never = 0 ☐ No, not very often = 1	☐ Yes, some of the time = 2 ☐ Yes, most of the time = 3
4. I have been anxious or worried for no good reason	☐ No, not at all = 0 ☐ Hardly ever = 1	☐ Yes, sometimes = 2 ☐ Yes, very often = 3
5. I have felt scared or panicky for no very good reason	☐ No, not at all = 0 ☐ No, not much = 1	☐ Yes, sometimes = 2 ☐ Yes, quite a lot = 3
6. Things have been getting on top of me	☐ No, I have been coping as well as ever = 0 ☐ No, most of the time I have coped well = 1	☐ Yes, sometimes I haven't been coping as well as usual = 2 ☐ Yes, most of the time I haven't been able to cope = 3
7. I have been so unhappy that I have had difficulty sleeping	☐ No, not much = 0 ☐ Not very often = 1	☐ Yes, sometimes = 2 ☐ Yes, most of the time = 3
8. I have felt sad or miserable	☐ No, not much = 0 ☐ Not very often = 1	☐ Yes, quite often = 2 ☐ Yes, most of the time = 3
9. I have been so unhappy that I have been crying	☐ No, never = 0 ☐ Only occasionally = 1	☐ Yes, quite often = 2 ☐ Yes, most of the time = 3
10. The thought of harming myself has occurred to me	☐ No, never = 0 ☐ Only occasionally = 1	☐ Yes, quite often = 2 ☐ Yes, most of the time = 3

Total Score ____

Score of 1-3 on item 10 indicates a risk of self-harm. Patient requires immediate mental health assessment and intervention as appropriate.
Score > 9 Monitor, support, and offer education
Score > 12 Follow up with comprehensive bio-psychosocial diagnostic assessment for depression.

Institute of Medicine Weight Gain Recommendations for Pregnancy (2009)

Prepregnancy Weight Category	Body Mass Index	Recommended range of Total Weight in kg (lb)	Rates of Weight Gain in Second and Third Trimesters	
			kg/wk	lb/wk (mean range)
Underweight	Less than 18.5	12.5-18 kg (28-40)	0.5	1 (1-1.3)
Normal Weight	18.5-24.9	11.5-16 kg (25-35)	0.4	1 (0.8-1)
Overweight	25-29.9	7-11.5 kg (15-25)	0.3	0.6 (0.5-0.7)
Obese (includes all classes)	30 and greater	5-9 kg (11-20)	0.2	0.5 (0.4-0.6)

†Calculations assume a 0.5 to 2 kg (1.1-4.4 lb) weight gain in the first trimester.

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Ontario

Ministry of Health and Long-Term Care

Ontario Perinatal Record
Postnatal Visit

Last Name	First Name			
Date of visit YYYY/MM/DD	Date of Delivery YYYY/MM/DD	Number of weeks postpartum	GA at Birth	Primary Care Provider

History

Review of birth	Vaginal:	☐Spontaneous	☐Vacuum	☐Forceps	☐VBAC	☐Episiotomy / Lacerations	☐OASIS	
	Caesarean:	☐Planned	☐Unplanned					

Details	Birth Attendant

Pregnancy/birth issues requiring follow-up (e.g. diabetes, hypertension, thyroid)

Baby's Name	Baby's Care Provider

Birth Weight (g)	Baby's Health/Concerns

Infant feeding ☐Breast milk only ☐Combination of breast milk and breast milk substitute ☐Breast milk substitute only

Feeding concerns

Current Medications

Bladder function	Emotional wellbeing
Bowel function	Relationship
Sexual function	Postpartum Depression Screen (EPDS or other)
Lochia / Menses	Family Support / Community Resources
Perineum / Incision	
Smoking ☐No ☐Yes_____ cig/day	Alcohol ☐No ☐Yes If yes: Drinks/wk _____ and If yes: T-ACE score _____

Non-prescribed substances / drugs (e.g. opioids, cocaine, marijuana, party drugs, other) ☐No ☐Yes

Rubella Immune ☐Yes ☐No ☐Discussed ☐Declined ☐Received	Influenza ☐Discussed ☐Declined ☐Received YYYY/MM/DD
Pertussis (TdAP) Up-to-date ☐Yes ☐No ☐Discussed ☐Declined ☐Received	Other Immunizations
Last Pap YYYY/MM/DD Result	

Physical Exam As Indicated

Weight Today kg	Pre-Delivery Weight kg	Pre-Pregnancy Weight kg	BP mm Hg

Affect	N/Abn	Abdomen	N/Abn	Comments
Thyroid	N/Abn	Perineum	N/Abn	
Breasts	N/Abn	Pelvic	N/Abn	

Discussion Topics	Comments
☐Transition to parenthood/partner's adjustment	
☐Family violence and safety	
☐Nutrition/physical activity/healthy weight	
☐Plan for management of alcohol / tobacco / substance use	
☐Contraception	
☐Pelvic floor exercises	
☐Community resources (e.g. Healthy Babies Healthy Children)	
☐Advice regarding future pregnancies and risks	
☐Preconception planning (e.g. folic acid,medications)	
☐If CS, future mode of birth and pregnancy spacing	
☐Other comments / concerns	

Signature of healthcare provider

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Intrapartum Care

Intrapartum Care Objectives:

At the end of the seminar, students should be able to:

1. Describe the initial assessment of the labouring patient
2. Describe the characteristics of false labour
3. Describe the stages and mechanisms of normal labour and delivery
4. Describe techniques to evaluate the progress of labour
5. Describe pain management in labour
6. Describe methods of monitoring the mother and fetus
7. Describe the management of normal delivery
8. Describe the management of the third stage of labour
9. Describe classification of vaginal tears, their repair and how to avoid them
10. List the indications for episiotomy
11. Discuss the principles of family-centered care
12. List the indications for consultation during labour and delivery

Last revised: June 2019

DEFINITIONS OF LABOUR

Labour

- Onset of regular painful uterine contractions of sufficient and progressive intensity, frequency, and duration to lead to progressive cervical effacement and dilation, and descent of the presenting part

False Labour (Braxton-Hicks Contractions)

- Irregular uterine contractions of unchanged intensity and duration with no cervical dilation or effacement over time

Table 1: True and False Labour

	TRUE LABOUR	FALSE LABOUR
Pattern	Regular	Irregular
Frequency	Incresing to q2-3min	Unchanged, variable
Strength	Painful; uterine wall cannot be idented with palpation	Discomfort; uterine wall may be indented with palpation
Duration	45-60s	Variable
Location	Abdomen, back	Confined to lower abdomen
Alleviating Factors	None	Rest, hydration, sedation (e.g. morphone, dimenhydrinate)

Dilation

- Open diameter of the cervix (measured in centimeters)

Effacement

- Thinness of the cervix (starts at 4cm long and decreases to paper thin)

Station

- Distance between bony presenting part of the fetal head and maternal ischial spines, measured in centimeters and used as a measure of fetal descent (spines(sp) -5 considered floating; sp 0 considered engaged; sp +5 considered crowning)

STAGES OF NORMAL LABOUR

Much of our understanding around the progress of human labour and rate of cervical dilation is based on a series of papers published by Dr. Emmanuel Friedman in the 1950s. His definitions and threshold values for the stages of labour have served as the basis of obstetrical management for decades, and should be the focus of your learning.

However, from 2000-2010, several investigators started to question the validity of Friedman's definitions among more contemporary cohorts of women. Their studies take into account variables such as maternal age, parity, BMI, use of oxytocin, use of regional anaesthesia, and type of labour (e.g. spontaneous, induced). A contemporary labour curve based on a study of ~62,000 women by Zhang et al. is highlighted below.

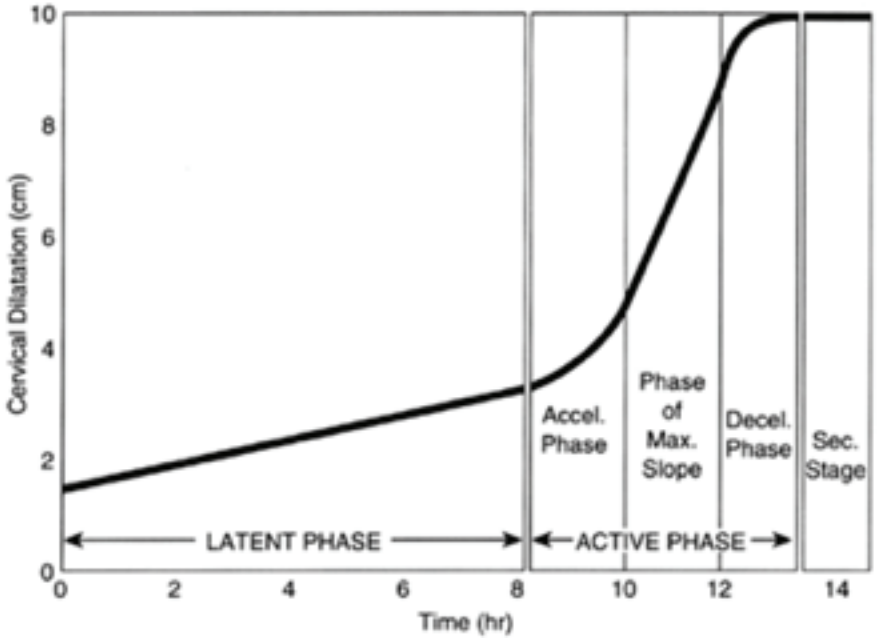
FRIEDMAN STAGES OF LABOUR (Table 2)

STAGE	PHASE	DEFINITION	DESCRIPTION	MANAGEMENT
1st	Latent	Maternal perception of contractions to 4cm	- Uterine contractions only - Dilation, effacement, fetal descent - Normal if: <20 hours for nulliparous, <14 hours for multiparous	- Serial pelvic examinations - Address labour dystocia if arises (see below)
1st	Active	4cm to 10cm	- Uterine contractions only - Dilation, effacement, fetal descent - Normal if: >1.2cm/hour for nulliparous, >1.5cm/hour for multiparous	- Serial pelvic examinations - Address labour dystocia if arises
2nd	N/A	Full dilation to delivery of fetus	- Uterine contractions + maternal pushing - Continued decent of presenting part - Expect delivery by 1-2-2-3 rule: <1 hour for multiparous (–) epidural <2 hours for multiparous (+) epidural <2 hours for nulliparous (–) epidural <3 hours for nulliparous (+) epidural	- Serial pelvic examinations - Address labour dystocia if arises
3rd	N/A	Delivery of fetus to delivery of placenta	- Placental separation (signs: fundus becomes firm/globular, fresh show of blood, uterus rises in abdomen, lengthening of umbilical cord) - Normal if: <30 minutes	- Administration of oxytocin - Controlled cord traction to assist placental delivery

STAGE	PHASE	DEFINITION	DESCRIPTION	MANAGEMENT
4th	N/A	1 hour after delivery	- Highest risk period for serious postpartum complications, especially postpartum hemorrhage	- Monitor maternal vitals, uterine tone, and bleeding - Repair perineal lacerations - Inspect placenta for completeness and 3 vessels (2 arteries, 1 vein)

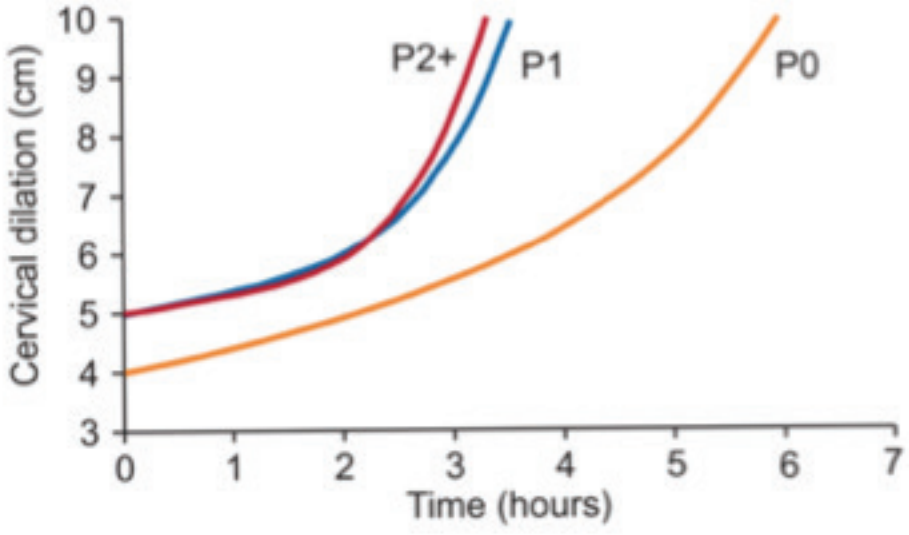
FRIEDMAN LABOUR CURVE (Figure 1)

- Latent phase: Slow rate of dilation until 4cm
- Active phase: Abrupt acceleration in the rate of dilation (acceleration phase + phase of maximum slope), followed by a deceleration at 9cm (deceleration phase)



ZHANG LABOUR CURVE (Figure 2)

- Gradual increase in the rate of dilation as labour progresses
- Nulliparous patients (P0) have no clear inflection point between latent and active labour
- Multiparous patients (P1, P2+) enter the active phase at 6cm (not at 4cm)
- No deceleration phase at the end of the 1st stage of labour



FETAL POSITIONING

- Successful vaginal delivery depends on: (1) fetal positioning (lie, presentation, position, and attitude); (2) fetal size, and (3) maternal pelvic architecture.
- The relationships between these factors will determine the movements required to negotiate the birth canal successfully for a spontaneous vaginal delivery, or will result in a need for operative vaginal delivery or caesarean delivery.

FETAL LIE

- Definition = Relationship of the long axis of the fetus to that of the mother/uterus
- Classification = Longitudinal, transverse, oblique
- Ascertainment = Leopold's second manoeuvre

FETAL PRESENTATION

- Definition = Portion of the fetal body which is foremost within the birth canal, directly over the internal os of the cervix, and felt through the cervix on vaginal exam
- Classification = Fetal presentation (i.e. cephalic, breech, shoulder/arm, compound) or non-fetal presentation (i.e. placenta, umbilical cord)
- Ascertainment = Leopold's 1st and 3rd manoeuvres, vaginal examination

Table 3: Fetal Presentation

Cephalic	• Vertex/occipital: Occipital fontanelle is presenting part (full flexion) • Sinciput: Anterior fontanelle is presenting part (partial flexion) • Brow: Brow is presenting part (partial extension) • Face: Face is presenting part (full extension)
Breech	• Frank: Hips flexed and knees extended so feet adjacent to fetal head • Complete/full: Both hips and knees are completely flexed • Incomplete/footling: One or both hips are not completely flexed (thus one or both feet may be presenting)
Shoulder/arm	• Occur in labour with oblique or transverse lie
Compound	• More than one fetal part (e.g. head/hand)
Non-fetal	• Placenta (major placenta previa), umbilical cord (cord presentation)

FETAL POSITION

- Definition = Relationship between the reference bony point of the presenting fetal pole (occiput for vertex presentations, sacrum for breech presentations, mentum/chin for face presentations) and the maternal pelvis
- Classification = Direct/left/right anterior; left/right transverse; direct/left/right posterior
    - Optimal position for vertex delivery is occiput anterior
    - Optimal position for breech delivery is sacrum anterior
    - Face delivery can only occur in mentum anterior position
- Ascertainment = Vaginal examination

FETAL ATTITUDE

- Definition = Fetal posture
- Classification = Flexion, extension
    - Normal attitude at later gestational age: Back convex, head flexed so chin in contact with chest, thighs flexed over abdomen, legs bent at knees
    - Abnormal attitude: Back concave, head extended

CARDINAL MOVEMENTS OF LABOUR (Table 4)

- Positional changes in the fetal presenting part required to navigate the birth canal
- Remember: "**E**very **D**andy **F**ellow **I**n **E**gypt **E**ats **R**aw **E**ggs"

Engagement	Biparietal diameter (greatest transverse diameter of the fetal head) passes through the pelvic inlet, usually in a transverse or oblique position • Nulliparous: Occurs in the last few weeks of pregnancy • Multiparous: Occurs at the start of labour

Descent	Ongoing downward movement of the fetal through the birth canal due to contractions, gravity, maternal positioning, or pushing efforts • Nulliparous: Occurs in the second stage • Multiparous: Occurs with engagement
Flexion	Flexion of fetal head with descent • As the descending head meets resistance from maternal tissues (i.e. cervix, bony pelvis, etc.), the head is flexed and the chin is brought into contact with chest, resulting in a smaller diameter of the presenting part for easier passage
Internal Rotation	Rotation of the fetal head from the initial transverse or oblique position to an occiput anterior (more likely) or occiput posterior (less likely) position • Essential for delivery unless fetus is very small
Extension	Extension of fetal head in direction of vulvar opening for delivery • Without extension, flexed head would tear through perineum
Restitution (external rotation)	Once delivered, the fetal head "restitutes" or returns to its original transverse position – this brings the head in line with the shoulders, which are now pointing in an anterior/posterior position • If occiput initially left: Rotates to left ischial tuberosity • If occiput initially right: Rotates to right ischial tuberosity
Expulsion	Anterior shoulder of the fetus delivers beneath the maternal public symphysis, followed by posterior shoulder and then the rest of the body

INITIAL ASSESSMENT OF LABOUR

- **ID:** Age, GP status, gestational age, GBS status
- **HPI:**
  - Contractions: When? How frequent? How often? How strong?
  - Rupture of membranes: When? Colour of fluid?
  - Vaginal bleeding: When? How much?
  - Fetal movements
- **ROS:** As required
- **PObHx:**
  - Current pregnancy: Antenatal screening, ultrasounds (last U/S results and indication), GDM, HTN, infections, GBS status
  - Previous pregnancies: Complications and outcomes (e.g. spontaneous abortion, therapeutic abortion, preterm/term birth, vaginal delivery, operative delivery, C/S)
- **PMHx, Meds, Allergies**
- **Physical Exam:**
  - Vital Signs: Maternal, fetal HR
  - Inspection: Degree of maternal distress
  - Abdomen Exam: Leopold's for fetal lie/presentation

    - Vaginal Exam: Presence of bloody show; sterile speculum exam if indicated to assess status of membranes (nitrazine, ferning); vaginal exam for cervical dilation, effacement, station, position, membrane status, and fetal presentation
    - Non-Stress Test: Fetal HR, strength/timing/duration of contractions by tocometer
- **Investigations:**
    - Blood group & screen
    - May require additional bloodwork/urinalysis if other conditions suspected
- **Assessment/Plan:**
    - Discharge if early labour
    - Admission if active labour for +/- antibiotics, epidural, AROM, oxytocin
    - Admission if condition warranting inpatient observation (e.g. antepartum hemorrhage, pre-eclampsia)

MONITORING OF FETAL HEALTH

Monitoring Fetal Health in Labour

- Indirect Monitoring:
    - Meconium or blood in amniotic fluid
    - Maternal temperature (sign of intrauterine infection)
- Direct Monitoring:
    - Fetal heart rate monitoring: May be intermittent or continuous (see below)
    - Fetal scalp/capillary blood sampling: Entails assessment of fetal pH or lactate, depending on equipment available at the particular unit
        - Indicated if other surveillance modes suggest fetal compromise, the cervix is adequately dilated, and the equipment is available and calibrated
        - If pH: <7.2 deliver; 7.2-7.25 repeat in 30min; >7.25 continue labour

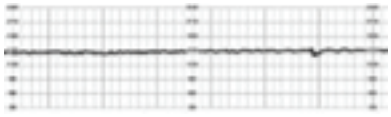
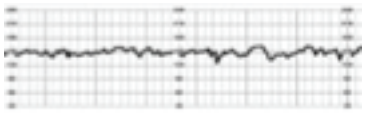
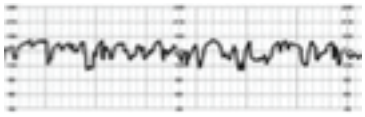
Options for Fetal Heart Rate Monitoring (Table 5)

	Intermittent auscultation with Doppler	**Electronic fetal heart rate monitoring**
Indications	• Healthy women without risk factors for adverse outcomes	• Maternal or fetal risk factors • Abnormal intermittent auscultation
Frequency	• Latent 1st stage: q1h • Active 1st stage: q15-30min • Second stage: q5min	• Continuous

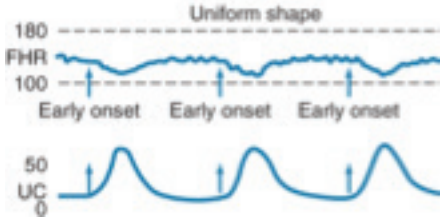
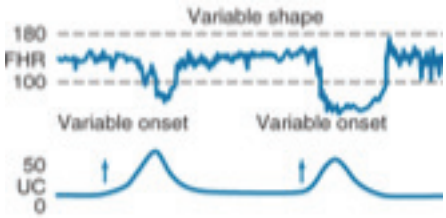
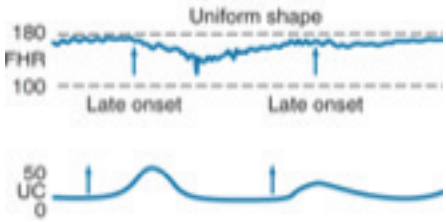
Steps to Assessing a FHR Tracing (Table 6)

1. Uterine activity pattern	Frequency, duration, intensity, uterine resting tone
2. Assess baseline	Approximate mean FHR rounded to increments of 5bpm • Normal: 110-160bpm • Bradycardia: <110bpm for >10 minutes • Tachycardia: >160bpm for >10 minutes
3. Assess variability	Fluctuations in baseline: Difference between highest and lowest FHR in a 10min segment free of accelerations or decelerations • Absent: No variability • Minimal: <5bpm • Moderate: 6-25bpm • Marked: >25bpm
4. Assess accelerations	Visually apparent abrupt increase in FHR above baseline • >32 weeks: >15bpm x >15s, return to baseline <2min • <32 weeks: >10bpm x >10s, return to baseline <2min • Prolonged acceleration: 2-10min • Change in baseline: >10min
5. Assess decelerations	Visually apparent abrupt decrease in FHR below baseline • Early, variable, or late (see below)

Etiology of FHR Variability (Table 7)

Minimal	Moderate	Marked
		
Sleep cycle Fetal acidosis Drugs (e.g. benzodiazepines, MgSO4, narcotics) Prematurity	Normal	Mild hypoxemia Fetal stimulation Drugs (e.g. cocaine, nicotine, methamphetamine)

Etiology of FHR Decelerations (Table 8)

TYPE	DESCRIPTION	APPEARANCE	ETIOLOGY
Early	Gradual decrease (>30s to nadir) and return to baseline that **mirrors** contraction		- Benign - Normal physiologic response to fetal head compression
Variable	Abrupt decrease (<30s to nadir) and return to baseline Variable in shape and timing		- Cord compression - If complicated features (ex. <70bpm for >60s, slow return to baseline, biphasic, associated with loss of variability or fetal tachycardia/bradycardia), then may be indicative of fetal hypoxia
Late	Graduate decrease (>30s to nadir) and return to baseline that occurs after contraction		- Pathologic - Sign of uteroplacental insufficiency & hypoxia

LABOUR DYSTOCIA (Table 9)

- Labour dystocia = Labour that is abnormally long or not progressing, as per Friedman curve/ thresholds
- Etiology = 4Ps = Power (expulsive forces), passenger (maternal pelvis), passage (fetus), psyche (maternal psyche)

Stage	Diagnostic Criteria		Power	Passenger	Passage	Management
	Nulliparous	Multiparous				
1st Latent	>20 hours	>14 hours	- Dysfunctional contractions (should be 45s, q2-3min, palpably strong)	May foreshadow abnormal fetal presentation or ensuing cephalopelvic disproportion (CPD)		- Reassure, explain, empathize, encourage - Discharge home - Encourage nutrition, ambulation, hydration - Offer analgesia or anti-emetics
1st Active	<1.2cm/hr	<1.5cm/hr	- Dysfunctional contractions	- Presentation: Compound - Position: OT, OP - Attitude: Deflexed - Macrosomia or fetal anomalies (e.g. hydrocephalus, soft tissue tumours)	- Non-gynecoid maternal pelvis - Maternal obesity - Obstructing lesions (e.g. full bladder, uterine fibroids, pelvic tumours)	- Labour augmentation (e.g. AROM, oxytocin) - Adequate pain control (e.g. epidural) - Optimize position (e.g. manual rotation to OA) - Empty bladder - Caesarean section
2nd –Epidural +Epidural	 >2hr >3hrs	 >1hrs >2hrs	- Dysfunctional contractions - Ineffective maternal pushing - Maternal fatigue	- As above	- As above - Bony pelvis (flat sacrum or coccyx, prominent ischial spines, narrow pubic arch)	- Labour augmentation (e.g. AROM, oxytocin) - Coaching/support for maternal pushing - Optimize position (e.g. manual or forceps rotation to OA) - Empty bladder - Operative delivery with vacuum/forceps - Caesarean section

PERINEAL LACERATIONS

Classification

- 1st Degree: Involves vaginal mucosa and/or perineal skin (not underlying fascia/muscles)
- 2nd Degree: Additionally involves the fascia/muscles of the perineal body
- 3rd Degree: Additionally involves the anal sphincter
- 4th Degree: Involves rectal mucosa

Principles of Repair

- Recognition of the type of tear by careful (often bimanual) examination
- Good positioning, lighting, and assistance
- Restore anatomy & ensure hemostasis
- Use appropriate absorbable sutures
- Ensure adequate analgesia during and after repair
- Note: If a 3rd or 4th degree tear is not properly repaired, patients can later develop anal incontinence or a rectovaginal fistula

OBSTETRIC ANALGESIA/ANAESTHESIA

- Always remember: Two (or more) patients
- Issues to remember: Effectiveness, t ½, S/E's, allergies, contraindications

Innervation

- 1st Stage: Uterine contractions:
  - pain - T11 - T12
  - motor - T7 - T8
- 2nd Stage: Vaginal/perineal pain
  - Pain: S2-S4 (via pudendal nerve)

Methods of anaesthesia

Comfort Measures

- Changes in maternal position
- Massage or counter-pressure on lower back
- Aqua therapy (shower, Jacuzzi)
- Breathing techniques
- Supportive care

General anaesthesia (GA)

- *Narcotic analgesia:*
  - IM/IV (e.g. patient controlled analgesia)
  - Can be used early in 1st stage alone or as an adjunct to other means of pain relief
  - May be associated with nausea and can be given with antiemetic
  - Can cause maternal sedation and newborn respiratory depression, so try to avoid administration <4 hours prior to delivery
- *Inhalation analgesia:*
  - Can be self-administered thereby maintaining patient control
  - May be used as an adjunct to local/pudendal
  - Does not diminish uterine activity, motor control or ability to push
  - Typically used in multiparous patient during late 1st or 2nd stage of labour
  - Usually a mix of nitrous oxide and oxygen

- *General anaesthetic:*
  - In emergency situations and, rarely, for elective Caesarean section where regional anaesthesia is contraindicated, not available or unsuccessful.
  - Have to be aware of risk of aspiration, delayed gastric emptying, difficult intubation, high intra-abdominal pressure, and anaesthetic agents crossing the placenta.
  - Must consider complications of pregnancy that may impact on GA such as gestational hypertension, placental abruption, coagulopathy etc.

Local Anaesthesia

- *Local Anaesthetic:*
    - Good for repair of lacerations/episiotomies
    - For example, 1% lidocaine (Xylocaine) with or without epinephrine
    - Aspirate while injecting to avoid intravascular administration.
- *Pudendal Block:*
    - Transvaginal application through sacrospinous ligament 1cm medial and inferior to ischial spine: 10 ml of 1% lidocaine each side
    - Effective within 5 minutes and good for operative vaginal deliveries (forceps, vacuum, assisted breech)
- *Paracervical Block:*
    - Rarely performed, but effect short-acting block
    - Inject 5-10ml local anaesthetic at 3-4 o'clock & 8-9 o'clock positions of cervix, aspirating intermittently
    - More often used for dilatation & curettage than during labour
    - Concern for fetal bradycardia and compromise

Regional Anaesthesia:

- *Epidural:*
    - Local anaesthetic +/- narcotic injected into potential space between ligamentum flavum and dura at L3-L4 or L4-L5 interspace; requires larger dose/volume than spinal & takes 10-15 minutes to take effect and reveal side effects
    - Allow for patient control (PCEA) by metered dose pump
    - IV fluid preloading of mother required to avoid maternal hypotension and fetal bradycardia, and placement of indwelling catheter afterwards
    - "Walking epidural" refers to reduced motor blockade through use of narcotic, but has significant degree of generalized pruritus associated with it
- *Spinal:*
    - Technically easier, using finer needle, smaller dose (and volume) of hyperbaric local anaesthetic solution injected into subarachnoid space to emphasize effect in dependent areas of the body with rapid effect (2-5 min)
    - Risk of: (1) spinal fluid leakage and subsequent headache, or (2) spread upwards and higher blockade
    - Used most often for elective Caesarean section with dose of spinal/epidural narcotic for long-acting pain relief
- Note: A combination of these may be utilized by the anaesthesiologist

INDICATIONS FOR CONSULTATIONS

- Each labour floor will have specific required consultations for family physicians and midwives outlined in their policies and procedures.
- As the situation becomes more high risk at any point in pregnancy care, from antepartum through labour to the postpartum period, there will be times where a formal obstetrical consultation is indicated.

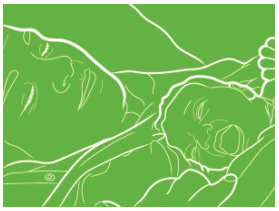
The following would be common examples:

- Gestational diabetes requiring insulin treatment
- Trial of labour after Caesarean Section (TOLAC)
- Hypertensive disorders
- Active antepartum hemorrhage
- Preterm labour or rupture of membranes <36 weeks
- Multiple gestation
- Malpresentations (e.g. breech)
- Operative vaginal deliveries – usually consultation is required if more than outlet forceps/vacuum is needed
- Failure to progress/descend
- Induction/augmentation with oxytocic agents may require consultation if higher risk factor is involved (e.g. TOLAC, intrauterine growth restriction, etc.)
- Perineal lacerations: 3rd and 4th degree tears require obstetrical consult
- Retained placenta

A vitally important medicolegal concept is one of "most responsible physician" whereby at any point in a patient's care there is one readily identifiable physician who is named on the hospital record as the individual who assumes responsibility and coordination for the care of that patient. With this in mind, some of the above consultations may require transfer of care to the Obstetrician.

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Postpartum Care

Postpartum Care Objectives:

At the end of the seminar, students should be able to:

Postpartum Care

1. Describe the maternal physiologic changes of the postpartum period.
2. Describe normal postpartum care (following Caesarean/vaginal delivery).
3. Describe the assessment and management of postpartum pain and/or fever.
4. Counsel patients appropriately regarding sexual activity, family planning, emotional and social support, depression, and common concerns of the postpartum period.
5. List the symptoms, signs, predisposing factors, appropriate investigations and management of the following postpartum complications:
    - Endometritis
    - Pelvic abscess
    - Infected episiotomy
    - Mastitis
    - Galactocele
    - Thromboembolic disease
    - Postpartum hemorrhage – early and delayed

Lactation

1. List the normal physiologic changes and anatomic changes of the breast during pregnancy and the postpartum period.
2. Recognize and treat common postpartum abnormalities of the breast.
3. Recognize the benefits of breast feeding.
4. Recognize commonly used medications which are appropriate and inappropriate to use while breast feeding.
5. Counsel the lactating patient about commonly asked questions such as frequency, duration, inadequate production of milk.

Mood Changes and Disorders

1. Define postpartum blues, depression and psychosis.
2. List risk factors for postpartum blues, depression and psychosis.
3. Describe the management of postpartum blues, depression and psychosis.

Postpartum Thyroiditis

1. Pathogenesis
2. Clinical Features
3. Laboratory Findings
4. Treatment

Last revised: July 2019

The **postpartum period,** also known as the puerperium, is the period that extends from after the birth of the baby to six weeks. Rapid physiological changes occur in the first 24 hours and may persist beyond 6 weeks as pregnancy related changes return to the nonpregnant state.

MATERNAL PHYSIOLOGICAL CHANGES IN THE POSTPARTUM PERIOD

Uterus

- In the pregnant state, uterine blood flow is increased (the uteroplacental blood flow is 450 to 600mL/min). The existing veins and arteries increase in size and new ones are formed.
- In the postpartum period, the arteries and veins decrease in size almost to the pre-pregnancy state.
- The external os of the cervix is usually lacerated laterally, giving the appearance of a parous os. This change becomes permanent in the postpartum period and thereafter.
- The muscle mass of the uterus increases in pregnancy. The uterus weighs 70g pre-pregnancy and has a volume of 10mls. In the immediate postpartum period the uterus weighs about 1100g, with a capacity of 5L. Muscle cells decrease in size as the uterus involutes. By the end of the second week the uterus weighs 300g and less than 100g thereafter.

Uterine "After Pains"

- The uterus contracts tonically causing "after pains". More pronounced as parity increases.
- Worse during breast feeding (due to oxytocin release)
- Tends to subside by the third postpartum day

Lochia

- The lochia refers to the sloughing of the uterine decidual tissue
- Occurs in the early postpartum period
- Quantity and color progressively changes as the puerperium progresses
    - Red in the first few days and called lochia rubra.
    - After 3 to 4 days, it becomes pale and watery – lochia serosa.
    - By the 10th day, it becomes whitish or yellow – lochia alba.
    - The lochia may persist for up to 4 - 6 weeks and in some cases beyond.
- The superficial layer of the endometrium becomes necrotic and replaced by the newly regenerated layer from the basal layer.
- The basal layer is never shed and remains intact.

Involution of the Uterus

- The process where the pregnant uterus returns to its pre-pregnancy size.
- The uterus contracts after the expulsion of the placenta.
- The previously hypertrophied muscle cells shrink, rather than reduce in number.
- The fundus remains below the umbilicus within 24 hours of delivery, midway between the pubic symphysis and the umbilicus within 1 week postpartum, impalpable per abdomen by 2 weeks and returns to normal size by 6 weeks postpartum.
- Constriction of the intramyometrial vessels by uterine contraction immediately after delivery, is the major mechanism preventing hemorrhage. Inadequate myometrial contraction post-delivery results in uterine atony. By week 4, the uterus weighs about 100g (pregnancy 1100g).

Sub-involution

- The delay in the normal postpartum changes in the uterus results in delayed involution where the uterus fails to go back to its normal size.
- The two most common causes are retained products of conception and pelvic infection.
- Presents as persistent vaginal discharge, mild or profuse bleeding.
- Treatment depends on the etiology.
- Retained products of conception may respond to misoprostol (to aid uterine contraction) or surgical intervention (evacuation of the uterus typically via dilatation and curettage).
- Pelvic infection (endometritis) responds to antibiotic therapy.

Delayed postpartum hemorrhage

- Bleeding occurring 24 hours to 12 weeks after delivery.
- May result from retained products of conception or abnormal placental site involution.
- The retained piece of the placental tissue may become calcified forming a placental polyp.
- Treatment with ergometrine, misoprostol and prostaglandin is conservative and preserves the uterus. Antibiotics are added if infection is suspected.
- Surgical treatment with gentle dilatation and curettage is reserved for severe bleeding or if medical treatment fails. Beware of overzealous curettage as this may lead uterine synechiae (Asherman's syndrome).

Urinary tract changes

- During pregnancy, there is physiological retention of water and dilation of the collecting system.
- Water diuresis occurs after delivery due to the loss of the elevated venous pressure and the loss of the hyperestrogenemia of pregnancy.
- Bladder distension can occur from regional anaesthesia.
- Incomplete emptying, bladder distension, and excessive urine residual occur frequently and may predispose to urinary tract infection.
- Stress or urge urinary incontinence is common; more so if there was an instrumental delivery or a prolonged second stage.

Relaxation of the vaginal outlet and prolapse of the uterus

- After delivery the capacity of the vagina increases but diminishes subsequently, but not to the nulliparous size.
- The hymen becomes replaced by tags called myrtiform caruncles.
- There is a predisposition to pelvic floor prolapse.

Peritoneum and abdominal wall

- The gravid uterus causes the stretching of the anterior abdominal wall.
- Postpartum, the abdominal wall becomes flabby; with exercise returns to normal.
- Post Caesaren delivery, recommend start exercise after 6 weeks to allow fascia to heal. There is separation of the rectus muscle 'diastasis recti'.
- The silvery striae (stretch marks) fail to disappear completely.

Blood and fluid changes

- In the puerperium, there is leukocytosis, thrombocytosis, lymphopenia and eosinopenia.
- Cardiac volume elevated for the first 48 hrs.
- Elevation of plasma fibrinogen.
- ESR remains elevated.
- Increased risk of DVT and PE due to hypercoagulability up to 12 weeks postpartum.

NORMAL POSTPARTUM CARE

Following Spontaneous Vaginal Delivery (SVD) and Caesarean Section:

- The risk of significant PPH is greatest immediately postpartum. Close observation required with frequent assessments of vital signs, monitor amount of bleeding, ensure fundus is well contracted. Blood can accumulate in the uterus without external bleeding. Managed by uterine fundal massage and uterotonics as needed.
- Commence regular diet as soon as possible, as long as there is no contraindication to doing so. It is no longer mandatory to wait until the return of bowel sounds before resuming regular diet after Caesarean section.
- Resume activity as tolerated. Early ambulation reduces the risk of bladder complications, constipation and VTE.
- Regular perineal cleansing 2 to 3 times daily or following bowel movements and urination.
- Ice packs to perineum if painful.
- Sitz bath with warm water if perineal laceration or episiotomy.
- Treat symptomatic hemorrhoids with warm soaks, topical anesthetics, topical steroids and stool softeners.
- Regular analgesia. Alternating acetaminophen and Ibuprofen recommended. Avoid use of codeine.
- Urinary retention and bladder overdistention are common postpartum due to decrease bladder sensation and muscle tone. Contributing factors include induction anaesthesia, trauma from delivery especially if prolonged second stage, operative delivery, iv fluid and oxytocin infusion. Close observation after delivery is required.
- Give Rhogam if Rhesus negative and unsensitized with Rhesus positive infant (see 'Fetal Complications Part II' chapter for information regarding prevention of Rh isoimmunization)
- Support and encourage skin to skin contact with newborn and exclusive breastfeeding. For women who decide against breastfeeding, avoid breast stimulation and use a breast binder, tight-fitting bra or sports bra.
- Rooming in with baby improves successful breastfeeding. Provide breastfeeding support at home if difficulty with breastfeeding.
- Give MMR to women who are not immune to rubella (instruct patient to avoid getting pregnant for 3 months).
- Discuss contraception ideally upon discharge home and be prepared to discuss it again at the six week postpartum check.
- Emotional and social support: immediate postpartum period can be overwhelming. Encourage patients to have adequate rest, spousal time off/paternal leave; discuss signs and symptoms of postpartum mood changes.

POSTPARTUM PAIN AND FEVER

Postpartum fever is the presence of fever =/>38 degrees Celsius.

Causes:

- "After pains"
    - Common the first 3 days, due to uterine contractions. Common during breastfeeding. Usually resolve spontaneously within 3 – 7 days.
    - Encourage simple analgesia: acetaminophen, NSAIDS. Avoid opioids.

Etiology of fever postpartum:

- Think of the B-5W (Toronto Notes 2013)
    - Wind (atelectasis, pneumonia)
    - Water (UTI) (cystitis, pyelonephritis)
    - Wound (Gram positive/negative aerobes or anaerobes) check CS site and episiotomy site
    - Walking (DVT, Pelvic Thrombophlebitis)
    - Womb (endometritis)
    - Breast (engorgement, mastitis)

Wound infection: check episiotomy and perineal sites for erythema, swelling, purulent exudate and breakdown. Infected episiotomy- keep open, frequent sitz bath, keep dry, consider oral antibiotics if cellulitis, indurated, painful with purulent discharge. Avoid re-suturing, as healing is by secondary intention.

Abdominal wound infection: generally occurs after 4 – 7 days. If superficial, treat with oral antibiotics; if deep, may need to admit, open the incision and treat as appropriate.

Approach:

- Detailed history and physical examination:
- Order tests depending on the etiology – CBC, Blood and urine cultures, imaging.
- Treatment depends on the etiology – for infection, start appropriate antibiotics; change when sensitivity becomes available.
    - Endometritis: clindamycin + gentamicin IV
    - Mastitis: generally caused by Staph Aureus. Treat with Penicillins (cloxacillin) or first generation Cephalosporins (cephalexin, cephazolin). If MRSA, treat with clindamycin or trimethoprim + sulfamethoxazole (Septra)
    - DVT: Anticoagulants
    - UTI: treat with appropriate antibiotics
    - Wound infection: Penicillins or Cephalosporins (same antibiotics as mastitis)

SEXUAL ACTIVITY

- Can be resumed within 4-6 weeks of childbirth.
- 50-80% resumes sex by 6 weeks, 90% by 12 weeks.
- Counselling regarding possible perineal discomfort from vaginal dryness, repair of episiotomy or laceration or vaginal atrophy from breastfeeding.
- Dyspareunia can be treated with lubricants or topical estrogens.

CONTRACEPTION

- Ovulation can occur within 4 to 6 weeks of delivery in women who are not breastfeeding.
- Barrier contraception is safe but there is an increased risk of failure if condom accident.
- Hormonal preparation are safe in women breastfeeding (secretion in breast milk is minimal).
- Milk production can be affected in the early postpartum period with the use of combined contraceptive pill.
- Progesterone only pill (POP)/Progesterone or depot medroxyprogesterone acetate (depo provera) i.m. injections, can be started within 2 weeks of delivery.
- The combined oral contraceptive pill or POP can be commenced within 1-2 weeks in women who are not breastfeeding.
- Depo-Provera 150mg IM can be started after delivery.
- The intrauterine device (progesterone or copper IUD) can be inserted immediately (within 10 minutes) after the delivery of the placenta. Because of the high risk of expulsion, it is typically inserted after 6 weeks or after 3 months if Caesarean delivery.
- Tubal sterilization can be performed during Caesarean section, immediately postpartum after a vaginal delivery or as an interval procedure should the patient desire a permanent method of contraception.

POSTPARTUM COMPLICATIONS

Endometritis

- Infection of the uterine myometrium and parametrium.
- A common cause of postpartum febrile morbidity.
- Uncommon in uncomplicated vaginal deliveries.
- Signs and symptoms: fever +/- chills, tachycardia, abdominal pain, uterine tenderness, abnormal bleeding or foul smelling lochia.
- Examination revealed a tender abdomen and uterus, offensive discharge.
- Predisposing factors: prolonged rupture of membranes and labour, multiple vaginal examinations, use of internal fetal monitoring, intrapartum chorioamnionitis, caesarean section.
- Single dose preoperative intravenous antibiotic prophylaxis significantly reduces the risk of post Caesarean delivery infections. It is recommended for all women undergoing CS delivery.
- Bacteriology: Polymicrobial- aerobes and anaerobes colonizing the lower genital tract (normal commensals), low virulent organisms. Other common pathogens include Group B strep, Mycoplasma/ureaplasma species, Chlamydia and Neisseria gonorrhoea.
- Investigations: complete blood count—may show neutrophilia, blood and urine cultures.
- Management will depend on the severity of infection.
- Mild endometritis: Patients who are well can be treated with oral antibiotics on an outpatient basis.
- Severe endometritis: Sick patients, post abdominal deliveries, treat with intravenous therapy- Clindamycin IV 900mg every 8 hours + Gentamicin IV 1.5mg/kg every 8 hours or extended interval dosing of Gentamicin 5mg/kg every 24 hours. The extended dosing is convenient and does not require Gentamicin levels.
- Ampicillin IV 2g start and 1g every 6 hours can be added to Clindamycin and Gentamicin, to cover for enterococci if there is no response by 48 to 72 hours.

- Other modalities of treatment for severe endometritis- Cefotetan, Cefoxitin, Piperacillin +/- Tazobactam, Metronidazole can be used in addition to Ampicillin and Gentamicin (Metronidazole is not a preferred option in the presence of other options in breastfeeding patients).
- Duration of treatment: IV antibiotics should be continued until the patient is clinically improved and afebrile for 24- 48 hours.
- Follow-up treatment: Follow-up antibiotics treatment is not necessary unless the patient was bacteremic by positive blood cultures; in this case step down to oral antibiotics for a total of 7 days.
- Persistent postpartum fever: Refers to a lack of improvement or deterioration in clinical status after 48 hours of treatment. Re-evaluate the patient, perform a full physical exam and consider imaging like ultrasound to exclude retained products of conception (RPOC), consult infectious disease team (ID team).
- Consider other causes like infected hematoma, pelvic abscess, pelvic cellulitis, wound infection, septic pelvic thrombophlebitis, and ovarian vein thrombosis.
- Treatment: consider antibiotics changes (consult ID team); consider gentle curettage if there is RPOC to remove necrotic tissue. "Gentle" to prevent uterine scarring/ Asherman's syndrome.

Postpartum hemorrhage

Please refer to the chapter on PPH in the syllabus

Definition and Classification:

- Blood loss of > 500mL following vaginal delivery and > 1000mL after CS
- Can be classified as early (within 24 hours of delivery) and late (after 24 hours but before 6 weeks).

Postpartum Mood Disorders

Pregnancy is a major life stressor. Risks for mental illness are increased. Up to 15% of women develop a non-psychotic postpartum depressive disorder within 6 months of delivery. This may be an exacerbation of a pre-existing psychiatric disorder, a recurrence, or onset of a new condition

Stressors of pregnancy include:

- Concerns regarding fetal health
- Childcare
- Lifestyle changes
- Fear of pain during childbirth

Etiology:

- Unknown
- Biological factors: Inconsistencies in many studies regarding its true etiology. Some studies have implicated hormonal changes occurring following delivery.
- Psychological
- Occurs in all cultures
- Obstetrical complications have been implicated such as preterm birth or delivery, fetus at risk for congenital malformations, medical complications of pregnancy such as preeclampsia or growth restriction

- Prior history of mood disorders
- Familial predisposition

Impact of postpartum mood disorders:

- Increased risk of depression later in life
- Disorders of mother-fetal attachment
- Interference with social and cognitive development in the infant
- Impact on marital relationship and mental health of the partner

Postpartum mood disorders are characterized by:

- Mood lability - from elation to sadness - happiness alternating with tearfulness
- Irritability
- Low spirit (rather than sadness)
- Anxiety
- Depression
- Feeling overwhelmed
- Decreased concentration
- Insomnia

Risk factors:

- History of depression
- Antepartum history of depression: prior or current medical treatment, current symptoms
- Family history of depression
- Premenstrual or oral contraceptive associated mood changes
- Psychological impairment around work, relationships, and leisure activities
- History of sexual, physical or verbal abuse, nicotine dependence or substance abuse

Perinatal Evaluation and Screening

- Universal screening is recommended during the first Prenatal visit and the Postpartum visit
- The Edinburgh Perinatal/Postnatal Depression Scale (EPDS) is included in The Ontario Perinatal Record (see Appendix 12 in Antepartum Care chapter)
- Women at risk for depression are counselled and referred to the appropriate resources

Postpartum Blues

- Common experienced by 30 to 75% of new mothers
- Self-limiting mood disorder
- A normal reaction to physiological changes occurring after delivery
- Symptoms begin 3-4 days postpartum, peaks on the 5th day, lasts 10 days

Treatment:

- Self-limiting, resolves with conservative management
- Reassurance
- Family support

- Ensuring adequate sleep
- Limited use of benzodiazepine for insomnia (risks of addiction and crosses breast milk)
- Further evaluation if symptoms persist (increased risk of postpartum depression)

Postpartum Depression

This is a major depressive illness. It is the most common. It begins in or extends to the postpartum period (may start in the prenatal period). There is a threefold increase in the onset of depression during the postpartum period. It affects 10 to 25% of women. There is no difference in cultural and social status. Postpartum depression has long-term consequences on the patient and her family. Early recognition will optimize the care of the woman and her infant.

Clinical Features (DSM-IV criteria for Major Depression):

- The presence of 5 or more of the following symptoms for a period of two weeks or more:
    - Depressed mood
    - Diminished interest in activities once pleasurable
    - Loss of concentration
    - Loss of appetite
    - Feeling of worthlessness, helplessness
    - Excessive guilt
    - Loss of energy, fatigue
    - Significant weight loss or gain
    - Psychomotor retardation or agitation
    - Recurrent thoughts of suicide or death

Etiology: Unknown; the rapid decline in estrogen and progesterone levels following delivery has been implicated.

Risk Factors:

- Depression during pregnancy
- Anxiety during pregnancy
- Low levels of social support
- Previous history of depression (up to 70% of women with a previous history of postpartum depression will have a subsequent episode)
- Infant temperament
- Poor marital adjustment
- Low self esteem
- Postpartum blues
- Unplanned/unwanted pregnancy
- Abuse of the mother
- History of psychiatric disorder in the mother

Treatment of postpartum depression is similar to that in the non-pregnant woman.

Non-pharmacological treatment:

- Psychotherapy on its own may be adequate for treating mild to moderate depression. Whereas in severe cases, psychotherapy is combined with pharmacotherapy.
- Interpersonal psychotherapy is more effective in decreasing depressive symptoms than no treatment at all.
- Cognitive behavioural therapy has been shown to improve functioning in women with postpartum depression
- Group therapy provides social and emotional support from other women who have been affected

Pharmacological treatment:

- Antidepressants - SSRIs Sertraline (Zoloft), Fluoxetine (Prozac) Citalopram (Celexa) and Paroxetine (Paxil)
- Tricyclic Antidepressants - Amitriptyline (Elavil) and Imipramine (Tofranil)
- Antidepressants may take up to 4-6 weeks before a therapeutic level is reached
- The risk of suicide may theoretically increase at the initial period of treatment, therefore close follow up is necessary
- Women on antidepressants prior to pregnancy may require increased dose due to the pharmacological changes during pregnancy
- Continue treatment for 1 year after full remission, to minimize the risk of relapse
- Slow tapering of medication preferred than abrupt taper
- NB: SSRI use during pregnancy must be weighed against marginally increased neonatal risk

Antidepressants and breastfeeding:

- Secreted in low concentration but safe.
- Sertraline and Paroxetine are well researched.
- Watch for effects on the neonate: sedation, irritability, agitation, poor feeding and gastrointestinal distress.

Electroconvulsive therapy (ECT):

- Is effective, with little or no side effects on the mother and has no side effects on breastfeeding. It is useful where:
    - Rapid response is necessary in severely depressed women unresponsive to pharmacotherapy
    - There are psychotic symptoms in addition to severe depression
    - The woman is at risk of infanticide or suicide

Hormonal therapy:

- Limited data
- No role in the use of progestins in the prevention and treatment of postnatal depression
- The use of transdermal estrogen has shown improvements in depressive symptoms compared to placebo
- The optimal dose is unknown
- It is not recommended as a standard therapy

Postpartum Psychosis

This is an acute psychotic episode triggered by the complex psychosocial stressors and hormonally related changes that occur following childbirth. Incidence is 1-2 cases/1000 births. The symptoms usually occur within the first 2 weeks of childbirth but remain high for months after delivery. There is a 50% risk of recurrence in the next pregnancy.

Clinical features:

- Loss of touch with reality
- Alternating lucidity and psychosis
- Impairment of functioning
- Delusions
- Hallucinations
- Symptoms of depression: low mood, feeling of worthlessness and guilt
- Manic symptoms: mood elation, distractibility and increased activity

Risk factors:

- Background history of depression, mania, schizophrenic or schizoaffective disorder
- Most important risk factor is a history of bipolar disease
- More common in nulliparous with obstetrical complications
- Severe life event in the preceding year
- Pre-existing psychotic illness Young age
- Family history of psychiatric illness

Treatment:

- A psychiatric emergency. These women may commit infanticide
- Usually requires hospitalization, pharmacological treatment and long-term psychiatric care
- Mood stabilizers + antipsychotics (relationship between psychosis and bipolar disorder)
- Lithium – teratogenic concerns for cardiac defects, excreted in breast milk, toxicity has been reported in breastfed infants
- Clozapine – an atypical antipsychotic can be used
- ECT – can be effective

Postpartum Thyroiditis

- A destructive thyroiditis induced by an autoimmune mechanism within one year after parturition.
- Incidence varies from 1 to 15%
- There is a sequence of hyperthyroidism followed by a period of hypothyroidism then recovery.
- The symptoms of postpartum thyroiditis may go unrecognized because the symptoms may be attributed to breastfeeding or stresses related to parturition or postpartum mood disorders.
- Diagnosis is by clinical features of hyper- and hypothyroidism, in addition to laboratory tests.
- The symptoms and signs of hyperthyroidism can be mild and consists of fatigue, weight loss, palpitations, heat intolerance, anxiety, irritability, tremor etc.
- The symptoms and signs of hypothyroidism is usually mild, lack of energy, constipation, weight gain, cold intolerance, dry skin and sluggishness.

- There may be elevated or high normal level of T3 and T4, low TSH in the hyperthyroid state. The TSH is high in the hypothyroid state.
- Treatment in asymptomatic women: observation and monitoring of thyroid function tests (TFT) every 4 to 8 weeks until resolution or progression to permanent hypothyroidism.
- In symptomatic hyperthyroidism: treat with propranolol or atenolol until TFT become normal.
- In symptomatic hypothyroidism of TSH >10mU/L, treat with Levothyroxine 50-100mcg/day.
- Most women recover after 12 months postpartum. 30% never recover from the initial hypothyroid state and develop permanent hypothyroidism.
- Risk Factors:
    - History of autoimmune disorder such as Type I diabetes,
    - High concentrations of anti-thyroid antibodies,
    - Personal or family history of thyroid problems.

LACTATION

Anatomy:

- The mammary glands arise from the ectodermal layer.
- There are multiple pairs of breast buds that disappear with only 1 pair remaining.
- Residual mammary glands can persist along the milk lines.
- At puberty, there is rapid growth of the breasts.
- The breast is under the influence of estrogen and progesterone.
- Effects of estrogen: breast growth, development of mammary glands, increased fat deposition.
- Progesterone effects: development of alveoli for future lactation.

In pregnancy:

- The breast responds to hormonal changes:
    - Increase growth of the breast
    - Increase in the number of the alveoli
    - Infiltration of the interstitial tissue with lymphocytes, plasma cells and eosinophils
    - The stroma, adipose tissue and connective tissue are decreased

Postpartum:

- The sudden decline in progesterone level appears to be the initial stimulus to milk production
- Prolactin is necessary for milk production
- Estrogen inhibits milk production
- Progesterone has no effect on the production and composition of milk production
- Suckling stimulates both the production of oxytocin and prolactin (milk let down)
- Oxytocin causes the contraction of the myoepithelial cells surrounding the alveoli
- Prolactin is responsible for milk production

COMMON POSTPARTUM LACTATIONAL PROBLEMS

Breast Engorgement

- Breast engorgement results from congestion and increased vascularity of the breasts, causing breast fullness, firmness, pain and tenderness or a transient fever.

- Usually occurs within 24 hours of birth.
- Breast engorgement results in difficulty with latching and worsening of engorgement.
- Treatment: exclude other causes of fever; treat with analgesia (e.g. acetaminophen, breast support, ice packs
- Manual expression or breast massage may be necessary to relieve the engorgement; frequent breastfeeding is crucial to minimize engorgement

Mastitis

- Inflammation of the mammary glands
- Usually occurs when breastfeeding is well established, weeks and months after delivery
- Rare before the end of the first week, almost always unilateral
- It is preceded by breast engorgement, followed by fever, chills, rigors and tachycardia
- The breast is hard, red, fluctuant and painful; abscess may form
- The commonest organism is Staphylococcus aureus arising from the infant's throat and nose

Treatment of Mastitis

- Culture breast milk can be considered in refractory cases, but rarely indicated
- Commence antibiotic therapy as soon as possible before abscess formation
- Staphylococcus aureus is sensitive to Penicillin and Cephalosporin (e.g. cloxacillin, cephalexin)
- Use erythromycin if Penicillin allergic
- Vancomycin, Clindamycin or Septra, if methicillin-resistant staphylococcus (MRSA)
- Encourage continuing breast feeding to minimize the risk of abscess formation
- Breast pumping if unable to breast feed
- Continue treatment for 10 - 14 days

Breast Abscess

- May necessitate drainage under general anesthesia
- Ultrasound may be helpful in diagnosis
- Consider ultrasound guided needle aspiration with local anesthetic

Galactocele

- Results from clogging of a duct. May form a palpable mass
- Alternative positions of breast feeding may help spontaneous resolution
- Uncommonly requires aspiration

Nipple abnormality and injury

- The nipple may be flat or depressed, making latching difficult or impossible
- Inverted nipples can be drawn out by the use of the breast pump
- Nipple soreness can be relieved by the use on nipple ointment (over the counter)
- Nipple injury (bruising, cracking and bleeding) can result in persistent pain of the nipple. It is due to incorrect breastfeeding technique. Treatment - proper latching technique, breast pump, nipple shield, topical lanolin, avoidance of excessive moisture.
- Proper latching technique: nipple and areola are both taken in (not only the nipple)
- Refer lactation consultant. Exclude an oral cavity abnormality in the baby.

- Cracked/abraded nipple – use topical antibiotics or APNO (all-purpose nipple ointment).
- Accessory breasts (polymastia); enlargement during pregnancy or engorgement postpartum may cause discomfort and anxiety

Advantages of breast milk

- Provides ideal nutrition for baby
- Cheap and easily available
- No preparation or sterilization needed
- Colostrum: secretion from the breasts immediately after delivery. It is yellow in colour and contains carotenoids, minerals and protein, IgA and growth factors
- The presence of antibodies: IgA protects against enteric coated pathogens
- Other immunoglobulins include complements, macrophages, lactoferrin
- Contains all vitamins except Vitamin K
- Contains less Fe – supplements required after 6 months
- Contains more protein and fatty acids: alpha-lactalbumin, beta-lactoglobulin and casein+
- Easily digestible by the infant
- Breast milk composition is stable even if the mother has a poor diet
- Decreased postpartum weight retention, lower risk of breast and reproductive cancers
- Higher IQ in breastfed children. Lower incidence of SIDS
- Breastfeeding may suppress the release of gonadotropins and luteinizing hormone, therefore potentially suppressing ovulation (remember however that breastfeeding is not a reliable means of contraception).
- The Baby Friendly Hospital Initiative: is an international program (WHO based) - promotes breastfeeding exclusively for 6 months.

FREQUENTLY ASKED QUESTIONS BY BREAST FEEDING MOTHERS

Is my baby getting enough milk?

- This question is frequently asked as the mother has no way of measuring how much she has fed her baby. However, signs that the baby is getting enough include:
    - The baby latches on well and continues to move their jaw, stopping/pausing in between suckling movements
    - Wet Diapers: soaking about six diapers/day
    - Bowel movements: by day 3 should have 2 to 3 stools per day

What if I'm not producing very much milk?

- Domperidone (Motillium) is commonly used to increase milk quantity in cases when mothers are pumping for a sick infant, feeding an adopted child, or trying to wean an infant off supplements. This medication works by blocking the effect of dopamine (an inhibitor of prolactin secretion), which has a net effect of increasing prolactin secretion. It is important to exclude other causes of decreased production before prescribing Domperidone. Dosing is 30mg po TID.

- Discussion re: risks and benefits must take place. Canadian Boxed Warning – domperidone may be associated with an increased risk of ventricular arrhythmias or sudden cardiac death, particularly in doses >30 mg per day. Use the lowest possible dose for the shortest duration necessary

DRUGS AND LACTATION

- Most drugs are secreted in breast milk, but in small concentration. For most drugs, the milk to plasma ratio (the ratio of the drug concentration in breast milk to those in maternal plasma) is less than 1.

Acceptable drugs during breastfeeding:

- Analgesics: acetaminophen, non-steroidal anti-inflammatory (NSAIDs),
- Migraine Headaches: sumatriptan (Imitrex)
- Anticoagulants: acenocoumarol, heparin
- Antidepressants: Sertraline, Fluoxetine
- Antiepileptics: phenytoin, carbamazepine, valproic acid
- Antihistamines
- Antimicrobials
- Beta adrenergics: propranolol, labetalol
- Insulin
- Steroids

Medications contraindicated in breastfeeding:

- Bromocriptine: causes milk suppression
- Cyclophosphamide: suppresses immune system
- Cocaine: intoxication
- Lithium, phenindione, radioactive iodine, methotrexate, cyclosporine, retinoids, amiodarone, gold salts. Tetracycline may cause staining of dental enamel
- Avoid recreational drugs such as marijuana and alcohol

Other contraindications to breastfeeding:

- Women who abuse drugs and alcohol
- Infant with galactosemia
- HIV infection
- Untreated tuberculosis
- Hepatitis B not contraindicated, as long as the baby is given the hepatitis B immune globulin (HBIG) within 12 hrs of birth. The first dose of the Hepatitis B vaccine is initiated simultaneously and again at 1 and 6 months of life.
- Cytomegalovirus is transmitted in breast milk. However, the colonization does not lead to actual disease because of IgG transfer via the placenta during the pregnancy.
- Mothers with active Herpes Simplex lesions may breastfeed if there are no breast lesions. Frequent hand washing is recommended.



Pregnancy and Hypertension

Pregnancy and Hypertension Objectives:

At the end of the seminar, students should be able to:

1. Define and classify hypertensive disorders in pregnancy
2. Describe the pathophysiology of pre-eclampsia-eclampsia syndrome
3. Describe the symptoms, physical findings and diagnostic methods for pre-eclampsia-eclampsia syndrome (including HELLP and acute fatty liver)
4. Describe an approach to the management and follow-up of a patient with pre-eclampsia-eclampsia syndrome
5. Describe an effective plan of management of hypertension in pregnancy
6. Describe the maternal and fetal complications related to hypertensive disorders of pregnancy
7. List medications indicated and contraindicated in the management of hypertension in pregnancy
8. Discuss strategies for the prevention hypertensive disorders of pregnancy

Last revised: July 2019

DIAGNOSIS, EVALUATION, MANAGEMENT OF HYPERTENSIVE DISORDERS OF PREGNANCY

Objectives: Students should demonstrate competence in:

- Classification of hypertensive disorders of pregnancy (HDP)
- Diagnosis of HDP
- Workup of woman with HDP
- Understanding treatment modalities for HDP
- Understanding effective strategies for prevention of HDP in low- and high-risk women

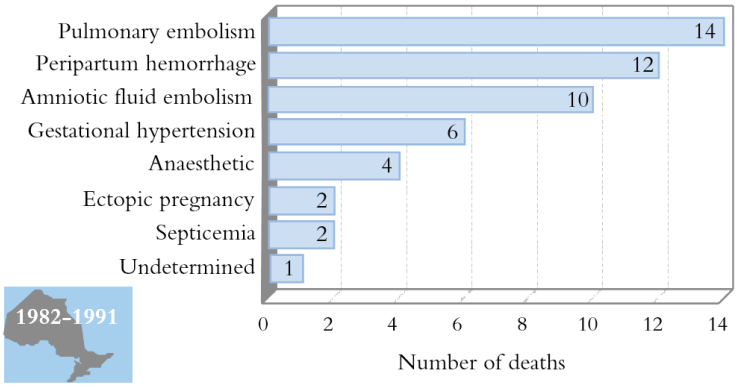
Significance of Hypertensive Disorders of Pregnancy

Table 1: Incidence of hypertensive disorders in pregnancy.

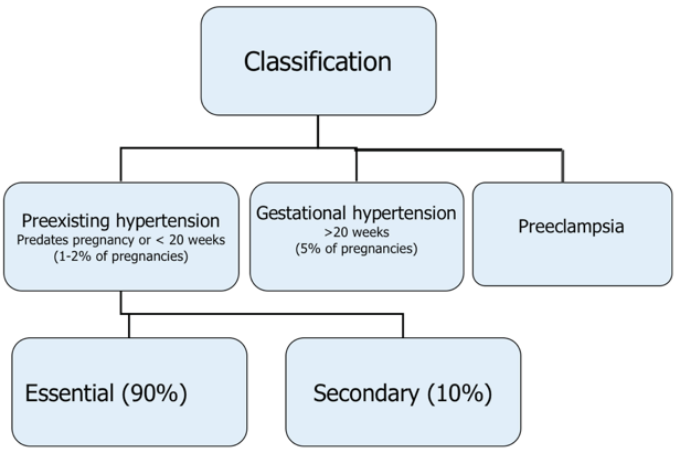
Condition	Incidence
Pre-existing hypertension	1-2%
Gestational hypertension	5%
Pre-eclampsia (severe <34 wks)	1-2%

- Risk of pre-eclampsia with chronic hypertension is 10-20%
- Risk of pre-eclampsia increases if BP increases <34 wks (35%)
- "White coat" hypertension is common (30%), and increases risk of gestational hypertension (40%), pre-eclampsia (8%) and severe complications compared to normotension at booking visit.

Figure 1: Causes of Direct Obstetrical Deaths.



Classification and Definitions (Figure 2)



Modified from JOGC: No. 2016 March 2008

Hypertensive disorders of pregnancy classified as:

1. *Pre-existing hypertension (pre-dates pregnancy or occurs <20 weeks) or*
2. *Gestational hypertension (onset >20 weeks) or*
3. *Pre-eclampsia*

- Pre-eclampsia can occur de novo, or can develop superimposed upon pre-existing or gestational hypertension
- Hypertension is defined as systolic BP >140 mm Hg and/or diastolic BP >90 mm Hg based on average of at least 2 measurements in-hospital or in-office, taken at least 15 minutes apart, using the same arm
- Systolic BP not as useful as it is:
    - More variable;
    - In general accompanied by increased dBP; and
    - Associated with more false positive diagnoses
- Systolic BP should still be followed closely
- Severe hypertension is sBP of ≥160 or dBP ≥110

PRE-ECLAMPSIA

Pre-eclampsia can arise de novo, in the context of pre-existing or gestational hypertension, and is important to diagnose because of its association with more adverse maternal and perinatal outcomes.

Pre-eclampsia can arise de novo. Pre-eclampsia is defined as gestational hypertension with one of more of the following:

- New proteinuria or
- One or more adverse conditions★ or
- One or more severe complications★★

Pre-existing hypertension with evidence of pre-eclampsia is defined as:

- New-onset or worsening proteinuria or
- One or more adverse conditions* or
- One or more severe complications** or
- Resistant hypertension (defined as the need for **3 or more** antihypertensive medications for BP control)

Gestational hypertension with evidence of pre-eclampsia is defined as:

- New-onset or worsening proteinuria or
- One or more adverse conditions* or
- One or more severe complications**

Additional Classification and Definitions

Severe pre-eclampsia: pre-eclampsia with one or more severe complications** as per SOGC Guidelines. Please note that International Society for the Study of Hypertension in Pregnancy (ISSHP) recommends against using the diagnosis of mild or severe preeclampsia as the clinical course can often change quickly and become more emergent at any time.

Eclampsia: seizures that cannot be attributed to another cause in a woman with pre-eclampsia

***ADVERSE CLINICAL CONDITIONS:**

Maternal

- Headache, visual disturbance
- Abdominal/epigastric or RUQ pain
- Chest pain, dyspnea
- Nausea, vomiting
- Eclampsia
- Abruption
- Abnormal lab values

Fetal

- Oligohydramnios
- IUGR
- Fetal demise
- Absent or reversed umbilical artery Doppler, re-distribution of middle cerebral artery flow, ductus venosus abnormalities

****SEVERE COMPLICATIONS:**

Maternal

- Eclampsia
- Posterior reversible leukoencephalopathy syndrome
- Cortical blindness or retinal detachment
- Glasgow coma scale <13
- Stroke, TIA
- Uncontrolled severe hypertension (not controlled with medication or requiring greater or equal to 3 antihypertensive medications to control)
- Oxygen desaturation, pulmonary edema
- Myocardial infarction/ischemia

- Platelet count <50 x 10^9/L
- Transfusion of any blood product
- New indication for dialysis
- Hepatic haematoma or rupture
- Hepatic dysfunction (INR >2 in absence of DIC or warfarin)
- Acute kidney injury (creatinine > 150 umol/L with no prior renal disease)

Fetal

- Abruption with evidence of maternal or fetal compromise
- Stillbirth
- Reversed ductus venosus A wave
- Absent or reversed end diastolic flow in the umbilical artery Doppler waveform
- Intrauterine growth restriction (Up to 30% of pregnancies affected by pre-eclampsia are complicated by intrauterine growth restriction, usually asymmetrical, although growth can be symmetrically reduced with severe placental disease. It may occur with, precede, or occur without maternal disease)

Measurement of blood pressure (BP)

1. BP measured in sitting position with the arm at the level of the heart
2. An appropriately sized cuff (i.e. length of 1.5 times the circumference of the arm) should be used
3. Korotkoff phase V used to designate diastolic BP
4. If BP is consistently higher in one arm, arm with higher values used for all BP measurements
5. BP measured with mercury sphygmomanometer, calibrated device, or automated aneroid BP device validated for use in pre-eclampsia
6. Automated BP machines may underestimate or overestimate BP in women with pre-eclampsia. Comparison with mercury sphygmomanometry or aneroid device is recommended
7. Ambulatory BP monitoring (by 24-hour or home measurement) may be useful to detect isolated office (white coat) hypertension
8. Patients should be instructed on proper BP measurement technique if performing home BP monitoring and BP machine must be calibrated

Assessment of Proteinuria

- All pregnant women should be assessed for proteinuria
- Urinary dipstick testing may be used for screening for proteinruai when suspicion of preeclampsia is low (visual or automated testing)
- Significant proteinuria should be suspected when urinary dipstick is 1+ or greater
- Significant proteinuria is defined as 0.3g/d in a 24-hour urine collection or >30 mg/mmol urinary protein to creatinine ratio in a spot (random) urine sample (spot UPCR)
- Insufficient information to make a recommendation about the accuracy of the urinary albumin/creatinine ratio in pregnancy

- Although the gold standard is a 24 hour urine protein >300 mg per day in practice these collections take time and may be inaccurate due to incomplete collection. Spot UPCR samples offer a means to a faster result and thus helps speed up decision making
- 24 hour urine collection still indicated in preeclampsia to confirm nephrotic syndrome which has implications for thromboprophylaxis.
- Severe/heavy proteinuria = 3 to 5 g/day

Symptoms of Pre-eclampsia

- Visual scintillations/scotomata = occipital cortical ischemia
- Persistent headache = cerebral ischemia and/or edema
- Epigastric/right upper quadrant pain = hepatic capsular irritation; hepatic necrosis/hematoma
- Dyspnea and/or chest pain = non-cardiogenic pulmonary edema
- None of these are specific to pre-eclampsia

Co-morbid Conditions

- Conditions that are part of classification of hypertensive disorders of pregnancy
- Conditions such as those that are associated with significant cardiovascular risk:
    - Diabetes Mellitus (not GDM)
    - Cerebrovascular Disease
    - Renal Parenchymal or Vascular Disease

Clinical Points Regarding Pre-eclampsia

- Stroke can occur at a systolic BP of 160 mmHg or more (this is the reason to treat hypertension)
- Stroke and, to a lesser extent, pulmonary edema are the leading causes of maternal death
- in pre-eclampsia
- The sensitivity/specificity of clonus or hyperreflexia for complications is unknown
- Seizures of eclampsia usually isolated; imaging before and after eclampsia with CT or MRI studies have usually shown ischemia followed by edema

Investigations to Diagnose or Monitor Maternal and Fetal Status in HDP

Table 2: Maternal and fetal diagnosis and monitoring in pre-eclampsia.

Investigations for diagnosis	Investigations for prognosis	Description in women with preeclampsia
	Maternal	
Hemoglobin	Hemoglobin	Higher (due to hemoconcentration) unless there is microangiopathic hemolytic anemia[89-92]
WBC and differential	WBC and differential	Higher (largely due to exaggerated neutrophilia)[89,93]
Platelet count	Platelet count	Lower
Blood film		Microangiopathy with RBC fragments[94,95]
INR and aPTT	*INR and aPTT**	Higher with DIC
Fibrinogen	*Fibrinogen**	Lower
Serum creatinine	Serum creatinine	Higher (due to hemoconcentration and/or renal failure)
Serum uric acid	Serum uric acid	Higher[96]
Glucose		Low in acute fatty liver of pregnancy
AST	AST	Higher
ALT	ALT	Higher
LDH	LDH	Higher
Albumin	Albumin	Lower
Bilirubin	Bilirubin	Higher (unconjugated from hemolysis or conjugated from liver dysfunction)
Urinalysis (routine and microscopy)		
Proteinuria (assessed by urinary protein dipstick, spot or 24 hr)	Proteinuria	Higher (discussed elsewhere)
	Fetal	
Fetal movement count	Fetal movement count	Decreased
Non-stress test	Non-stress test	Non-reassuring FHR
Biophysical profile	Biophysical profile	Lower score (associated with adverse perinatal outcomes, but due to deepest amniotic fluid pocket)[97,98]
Deepest amniotic fluid pocket	Deepest amniotic fluid pocket	Lower
Ultrasonographic assessment of fetal growth	Ultrasonographic assessment of fetal growth	Usually asymmetrical intrauterine fetal growth
Umbilical artery Doppler	Umbilical artery Doppler	Increased resistance, absent or reversed end-diastolic flow

* Tests of coagulation are recommended if there is thrombocytopenia or placental abruption. APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; ALT: alanine aminotransferase; DIC: disseminated intravascular coagulation; INR: international normalized ratio; LDH: lactate dehydrogenase; RBC: red blood cells; WBC: white blood cell.

Adapted from SOGC Clinical Practice Guideline No. 206 (2008).

Risk Factors for Pre-eclampsia

Table 3: Risk factors for development of pre-eclampsia.

First trimester markers			Second or third trimester markers
Demographics	Past history	Current pregnancy	
	Previous preeclampsia	**Multiple pregnancy**	
	Anti-phospholipid antibodies		
	Pre-existing medical condition(s)		
	Pre-existing hypertension or booking diastolic BP ≥ 90 mmHg		
	Pre-existing renal disease or booking proteinuria		
	Pre-existing diabetes mellitus		
Maternal age ≥ 40 years	Obesity (BMI ≥ 35 kg/m^2)	First ongoing pregnancy	
	Family history of preeclampsia (mother or sister)	Inter-pregnancy interval ≥ 10 years	
		Booking sBP ≥ 130 mmHg, or booking dBP ≥ 80 mmHg	
Ethnicity: *Nordic, Black, South Asian or Pacific Island*	Non-smoking	Inter-pregnancy interval < 2 years	Elevated BP†
Lower socioeconomic status	Heritable thrombophilias‡[103-106]	Reproductive technologies§	Abnormal MSS‖
	Increased pre-pregnancy triglycerides	New partner	Abnormal uterine artery Doppler velocimetry¶
	Family history of early-onset cardiovascular disease[107]	Gestational trophoblastic disease	Cardiac output > 7.4L/min
	Cocaine and metamphetamine use	Excessive weight gain in pregnancy	Elevated uric acid
		Infection during pregnancy (e.g., UTI, periodontal disease)	Investigational laboratory markers#

Hints that hypertension is chronic:

- Retinal changes on fundoscopic examination
- Cardiac enlargement on chest radiograph and ECG
- Compromised renal function or associated renal disease
- Medical disorders known to lead to hypertension
- Previous history of hypertensive pregnancies
- Persistent hypertension beyond the 42nd day postpartum

Etiology of Pre-eclampsia:

- Abnormal trophoblast invasion
- Uteroplacental mismatch
- Vascular endothelial damage
- Endothelial cell activation
- Cardiovascular maladaptation
- Coagulation abnormalities
- Immunologic phenomena
- Genetic predisposition
- Dietary deficiencies or excesses

Prevention of pre-eclampsia in **LOW-RISK** women

- Calcium supplementation (1.2-2.5g/day, orally) recommended for women with low dietary intake of calcium (< 600 mg/d)
- Recommended for other established beneficial effects in pregnancy:
    - Abstention from alcohol
    - Exercise for maintenance of fitness
    - Periconceptual folate-containing multivitamin for prevention of neural tube defects
    - Smoking cessation for prevention of low birthweight and preterm birth
- The following measures are NOT recommended for pre-eclampsia prevention, but may be useful for prevention of other pregnancy complications:
    - Prostaglandin precursors (fish oil)
    - Mg or Zn supplementation
- The following measures are NOT recommended for pre-eclampsia prevention:
    - Dietary salt restriction during pregnancy
    - Calorie restriction during pregnancy for overweight women
    - Low-dose aspirin
    - Vit C and E are not recommended and may be detrimental, thiazide diuretics

Prevention of pre-eclampsia in **HIGH-RISK** women

- Calcium supplementation (1.2-2.5 g/d) recommended for women with low calcium intake
- Low-dose aspirin (75–150 mg/d - In Canada recommend 81-162 mg/d) qhs, starting ideally before 16 weeks' gestation, generally discontinued at approximately 35-36 weeks or earlier depending on anticipated timing of delivery (there is some evidence for benefit if started up to 22 wks)
- May be useful:
    - Avoidance of inter pregnancy weight gain;
    - Increased rest at home in third trimester; and
    - Reduction of workload or stress
- The following measures are NOT recommended:
    - Calorie restriction in overweight women
    - Weight maintenance in obese women
    - Antihypertensive therapy specifically to prevent pre-eclampsia
    - Vitamins C and E
- The following measures have INSUFFICIENT evidence to be recommended
    - Heart-healthy diet, exercise
    - Heparin, even among women with thrombophilia and/or previous pre-eclampsia (based on current evidence)
    - Selenium
    - Garlic, zinc, pyridoxine, iron (with or without folate)
    - Multivitamins with/without micronutrients
- *Anti-hypertensive therapy:*
    - Does NOT prevent pre-eclampsia (RR 0.99; 95% CI 0.84–1.18) or associated adverse perinatal outcomes

- Does decrease the incidence of severe hypertension among women with mild hypertension (RR 0.52; 95% CI 0.41–0.64) and decreases risk of stroke in women with severe hypertension

TREATMENT OF HYPERTENSIVE DISORDERS OF PREGNANCY

- In-patient care for women with severe hypertension or severe pre-eclampsia
- For outpatient treatment, reduced activity may be helpful for gestational hypertension
- Care through hospital day units or home care considered for women with non-severe pre-eclampsia or non-severe (pre-existing or gestational) hypertension.
- Women prefer day unit/home care if possible
- Dietary changes not useful
- Exercise/workload reduction not studied enough
- For hospitalized women, bedrest is NOT helpful, many recommend quiet activity

Anti-hypertensive Therapy

For Severe Hypertension (sBP of >160 or dBP >110 mmHg)

- BP should be lowered to <160 mmHg systolic and <110 mmHg diastolic
- Initial antihypertensive therapy should be with labetalol, nifedipine capsules, nifedipine PA tablets, or hydralazine
- $MgSO_4$ is not recommended as an antihypertensive agent but is used for seizure prophylaxis
- Continuous FHR monitoring is advised until BP is stable
- Nifedipine and $MgSO_4$ can be used contemporaneously

Table 4: Commonly used agents for the treatment of severe hypertension.

Agent	Dosage	Comments
Labetalol	Start with 20 mg IV; repeat 20–80 mg IV q 30min, or 1–2 mg/min, max 300 mg (then switch to oral)	Best avoided in women with asthma or heart failure. Neonatology should be informed, as parenteral labetalol may cause neonatal bradycardia
Nifedipine	5–10 mg capsule to be bitten and swallowed, or just swallowed, every 30 min 10 mg PA tablet every 45 min to a maximum of 80 mg/d	There are three types of nifedipine preparations (i.e., capsules, intermediate-release tablets [PA], and slow-release tablets [SL]) with which all staff must be familiar
Hydralazine	Start with 5 mg IV; repeat 5–10 mg IV every 30 min, or 0.5–10mg/hr IV, to a maximum of 20mg IV (or 30 mg IM)	May increase the risk of maternal hypotension

Adapted from SOGC Guideline No. 206 (2008).

For Non-Severe Hypertension (140/90 to 160/110)

- Without comorbid conditions, antihypertensive therapy to keep sBP at 130–155 mmHg and dBP at 80–105 mmHg
- With comorbid conditions, antihypertensive therapy to keep sBP at 110-140 mmHg and dBP at 80–85 mmHg
- The CHIPS trial enrolled mostly chronic hypertensive women and advocated tighter control targeting a dBP of 85 and found reduced chance of developing severe hypertension with no adverse outcome for babies

- Initial therapy with:
  - Methyldopa;
  - Labetalol or other beta-blockers (acebutolol, metoprolol, pindolol, and propranolol);
  - Calcium channel blockers (nifedipine)

Table 5: Antihypertensive medications for non-severe hypertension.

Agent	Dosage	Comments
Methyldopa	250–500mg po bid-qid (max 2g/d)	There is no evidence to support a loading dose of methyldopa.
Labetalol	100–400mg po bid-tid (max 1200 mg/d)	Some experts recommend a starting dose of 200 mg po bid.
Nifedipine	PA tablets (10–20 mg po bid-tid, max 180 mg/d) or XL preparation (20–60 mg po OD, max 120 mg/d)	Caution should be exercised in ensuring that the correct form of nifedipine has been prescribed.

Adapted from SOGC Guideline No. 206 (2008). Target BP is debatable and treatment of BP 140-160/90-110 not proven to have overall benefit when matched against risk of growth restriction with antihypertensive Rx.

Treatment aims:

- With pre-eclampsia, the goal of antihypertensive therapy is to prevent severe hypertension, sBP >160 and dBP > 110. As per the CHIPS trial tighter control is appropriate to prevent severe hypertension which is associated with more adverse fetal outcomes (IUGR, prematurity, NICU stay) and maternal complications (thrombocytopenia, stroke, longer hospital stay)
- Labetalol and methyldopa most frequently used
- Thiazides not totally contraindicated after 1st trimester
- Atenolol NOT recommended
- ACE inhibitors CONTRAINDICATED

Corticosteroids for acceleration of fetal pulmonary maturity

- Considered for pre-eclampsia <34 weeks' gestation
- Considered at <34 weeks with gestational hypertension (without proteinuria or adverse conditions) if delivery contemplated within the next 7 days
- N.B. Corticosteroids may result in decrease in fetal heart rate variability for up to 4 days after administration and may increase maternal glucose levels – relevant if DM or GDM

Method/Mode of delivery

- Per obstetric indications and individualized according to each patient
- Gestational age
- Degree of illness
- Degree of cervical ripening
- Epidural helpful for BP control
- Ergometrine for management of postpartum hemorrhage is CONTRAINDICATED with hypertension (vasoconstriction)

Labour and delivery considerations

- Regional analgesia/anaesthesia generally appropriate in women with platelet count >75 x10^9 /L, unless there is coagulopathy or falling platelets
- Regional anaesthesia is appropriate with low-dose ASA in absence of coagulopathy with adequate platelet count
- Regional anaesthesia appropriate for women on LMWH 12 hours after a prophylactic dose, or 24 hours after a therapeutic dose
- Early epidural (in the absence of contraindications) recommended for pain control
- A fixed intravenous fluid bolus should NOT be administered prior to regional analgesia and/or anaesthesia
- IV and PO fluid intake should be minimized in women with pre-eclampsia, to avoid pulmonary edema
- Fluid administration NOT routinely given for oliguria (<15 mL/hr)
- For persistent oliguria, neither dopamine nor furosemide is recommended

Other Treatments for Symptoms of Pre-eclampsia

- *Nausea and vomiting*
    - Antiemetic
- *RUQ / Epigastric pain*
    - Morphine 2 - 4 mg IV
    - Antacid
    - Minimize palpation
- *Seizure prophylaxis*
    - Difficult to predict who will seize; not directly related to degree of hypertension or level of proteinuria
    - $MgSO_4$ is recommended for first-line treatment of eclampsia
    - $MgSO_4$ is recommended prophylaxis against eclampsia in women with severe pre-eclampsia
    - $MgSO_4$ may be considered as seizure prophylaxis for women with non-severe pre-eclampsia
    - $MgSO_4$ dose is 4 gram IV load, followed by 1-2 grams per hour IV infusion, to continue for 24 hours postpartum due to ongoing risk of seizures during this immediate postpartum period
- *Magnesium sulphate overdose*
    - Close observation for toxicity:
        - Weakness, respiratory paralysis, somnolence, heart block
    - High risk – renal failure, oliguria or use of Calcium Channel Blockers
    - *Antidote:* stop magnesium infusion, and initiate 10% Calcium gluconate 10 mL IV over 3 minutes

Treatment of Eclampsia

- Do not shorten/abolish initial convulsion
- Prevent maternal injury during convulsion
- Maintain adequate oxygenation
- Minimize risk of aspiration
- Avoid polypharmacy

Therapies for HELLP Syndrome

- Platelet transfusion not recommended, even prior to Caesarean section if platelet count is >50 x 10^9/L and there is no excessive bleeding or platelet dysfunction
- Consideration given to ordering blood products, including platelets for platelet count <50 x 10^9/L, or if falling rapidly, and/or if there is coagulopathy
- Platelet transfusion strongly considered prior to vaginal delivery when platelet count <20 x 10^9/L
- Platelet transfusion recommended prior to Caesarean section if platelet count is <20 x 10^9/L
- Corticosteroids considered for women with platelet count <50 x 10^9/L

Transfer of Women for Treatment of Pre-eclampsia

- Consideration if resources limited and maternal/fetal condition permits
    - Maternal BP and symptoms stable
    - Fetal status reassuring
- Discuss with receiving centre and patient/family
- Anti-hypertensive agents if indicated
- $MgSO_4$ if indicated for seizure prophylaxis and also consider for fetal neuroprotection if preterm delivery considered necessary

Cure for Hypertensive Diseases of Pregnancy

- Timely delivery minimizes morbidity and mortality
- Stabilize mother before delivery
- Delay delivery to gain fetal maturity and to allow transfer only when maternal and fetal condition allows
- Gestational hypertension is a progressive disease
- Expectant management is potentially harmful in presence of severe disease or suspected fetal compromise

Expectant Management in Pre-eclampsia

- For women <34 weeks, expectant management of pre-eclampsia considered, but only in perinatal centres capable of caring for very preterm infants
- For women 34–36 weeks with non-severe pre-eclampsia, there is insufficient evidence to make a recommendation about the benefits or risks of expectant management
- For women >37 weeks with pre-eclampsia (severe or non-severe), immediate delivery should be considered

POSTPARTUM MANAGEMENT

- BP may continue to increase and typically peaks days 3 to 6 after delivery
- Antihypertensive therapy may be restarted postpartum, particularly in women with severe pre-eclampsia and those who have delivered preterm
- Eclamptic seizures may occur for the first time in the early postpartum period thus Magnesium sulphate should be continued for 24h postpartum
- Severe postpartum hypertension treated with antihypertensive therapy, to keep sBP <160 mmHg and diastolic BP <110 mmHg
- Antihypertensive therapy used to treat non-severe postpartum hypertension, particularly in women with comorbidities
- Antihypertensive agents acceptable for use in breastfeeding include the following:
    - nifedipine XL, labetalol, methyldopa, captopril, and enalapril
- There should be confirmation that end-organ dysfunction of pre-eclampsia has resolved
- Non-steroidal anti-inflammatory drugs (NSAIDs) for postpartum analgesia should be avoided in women with pre-eclampsia, unless other analgesia not effective. This is especially important if renal disease or pre-eclampsia associated with placental abruption, postpartum hemorrhage, acute kidney injury.

PRE-CONCEPTION COUNSELLING IN PATIENT WITH HYPERTENSION

- Pre-conception counselling re: optimizing weight and general health
- Ensure anti-hypertensives regimen compatible with pregnancy
- Methyldopa, Labetalol and Calcium Channel Blockers (e.g. Nifedipine) safe for use in the first trimester
- May not need to replace antihypertensive therapy (physiological changes in pregnancy)

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Medical Disorders of Pregnancy

Medical Disorders of Pregnancy Objectives:

At the end of the seminar, students should be able to:

Pregnancy and Diabetes

- Describe the alterations in maternal carbohydrate metabolism in pregnancy
- Describe the maternal and fetal/neonatal consequences of uncontrolled pre-existing or gestational diabetes, including:
    - Congenital anomalies
    - Macrosomia
    - Hydramnios
    - Preterm labour
    - Fetal/neonatal and maternal trauma
    - Delayed fetal lung maturity
    - Neonatal hypoglycemia and hypocalcemia
- Outline the protocols for routine screening of pregnant women for carbohydrate intolerance and the rationale for such screening
- List the risk factors for gestational diabetes and the diagnostic test for the disease
- Outline the principles of management including diet, blood sugar monitoring and insulin therapy
- Describe the methods of surveillance of the fetus in pregnancies complicated by diabetes
- Describe the obstetrical management of the patient with diabetes in pregnancy

Cardiovascular Disease in Pregnancy

- Outline the physiologic cardiac changes in pregnancy
- Understand the classification of cardiac disease
- Describe the risks of maternal mortality caused by various heart problems
- List the predictors of primary cardiac events in pregnancy
- Understand the general management of the pregnant woman with heart disease

Renal Disease in Pregnancy

- Outline the physiologic renal changes in pregnancy
- Describe the management of 2 of the most common urinary tract problems in pregnancy: urinary tract infection and nephrolithiasis

Thyroid Disease in Pregnancy

- Discuss the diagnosis, management and adverse effects of hyperthyroidism in pregnancy
- Discuss the diagnosis, management and adverse effects of hypothyroidism in pregnancy

Last revised: July 2019

PRE-GESTATIONAL DIABETES

Introduction

- Prevalence of diabetes complicating pregnancy ~1% of pregnancies; although likely to rise with increasing rates of obesity
- **Type I** – Result of an inflammatory isletitis, presumably triggered by a viral infection or environmental insult in a genetically susceptible person, causing the development of auto-antibodies to pancreatic β-cells causing destruction and the development of diabetes due to lack of insulin
- **Type II** – Insulin resistance of target tissue causing abnormal insulin secretion, and hyperinsulinemia; patients may be insulin-dependent

Normal Glucose and Insulin Physiology in Pregnancy

- **First Trimester:** insulin secretion is increased and its anabolic actions are potentiated, decreasing fasting maternal glucose levels and promoting maternal energy storage
- **Second & Third Trimester:** insulin resistance develops due to increasing levels of human placental lactogen, cortisol, prolactin, placental growth hormone, estrogen and progesterone which results in higher fasting glucose and enhanced lipolysis (increased free fatty acids, triglycerides, lipids, ketones) to supply energy for fetal growth

Pregnancy in patients with pre-existing diabetes is a risky business!

Maternal Risks

- **Spontaneous Abortion:** Increased risk if poor glycemic control in first trimester
- **Difficult glucose control** with episodes of hypoglycemia (usually first trimester) and hyperglycemia
- **Anemia** due to Erythropoietin deficiency
- **Infection**: occurs at least once in 80% of diabetic pregnancies
    - Examples: Candida, urinary tract infection, pyelo (4%), upper respiratory tract infection
- **Diabetic Ketoacidosis** – rare
    - Can occur in hyperemesis, infection, Celestone (betamethasone) use; fetal loss is ~10%
    - *Typical symptoms:* abdominal pain, nausea, vomiting, altered sensorium
    - *Labs*: low pH, low bicarbonate, high anion gap, positive serum ketones, fetal heart rate abnormalities
    - *Treatment*
        - IV insulin infusion (loading dose 0.2-0.4 U/kg, then 2-10U/h maintain)
        - Fluids: Replace 4-6L in 12 hrs with NS; 1L in 1st hr, then 500cc-1L/h for 2-4h, then 250cc/hr
        - Glucose: begin 5% dextrose in NS when plasma level reaches (14mmol/L)
        - Potassium: if N or low, 15-20mEq/h; if high, replace when in normal range
        - Bicarbonate: Add one amp to 1L of 0.45NS if pH <7.0
        - Labs: ABGs, glucose, ketones, electrolytes q1-2h

Intrapartum and Postpartum

- Higher risk of operative or Caesarean delivery
- Genital tract trauma
- Postpartum hemorrhage
- Postpartum soft tissue infection

During Pregnancy: Aggravation of End-Organ Damage

- **Diabetic Nephropathy** (5-10% of pregnancies); leading cause of end stage renal disease (ESRD); incidence is 30% in type I DM, and 4-20% in type II; Begins with microalbuminuria (30-300mg/24hrs), this increases to overt proteinuria, then hypertension, and ESRD
- **Diabetic Retinopathy** – risk of developing diabetic retinopathy increases with duration of diabetes
    - Background retinopathy – retinal microaneurysm, dot-blot hemorrhage
    - Proliferative retinopathy – with neovascularization
    - Risk factors for the progression of diabetic retinopathy in pregnancy are severity of retinopathy at conception, adequacy of treatment, duration of diabetes, metabolic control before pregnancy, and the presence of additional vascular damage (i.e. pre-existing or concomitant hypertension)
    - Laser photocoagulation is recommended
    - Generally recommended that pregnant women with diabetes have ophthalmologic examination before conception and then again during the first trimester, followed by assessment approximately q3 months until delivery
- **Diabetic autonomic neuropathy:** may present as gastroparesis and intractable nausea and vomiting, or orthostatic hypotension
- **Cardiovascular Disease**
    - *Symptomatic coronary artery disease* may be a contraindication to pregnancy
    - *Chronic pre-pregnancy hypertension* seen in 5-10% - with this, increased risk of pre-eclampsia, stillbirth, growth restriction, placental insufficiency
    - Chronic hypertension and nephropathy increases risk of preeclampsia to 60%, iatrogenic preterm delivery, uteroplacental insufficiency
    - Risk of pre-eclampsia is 15-20% if no nephropathy

Fetal Risks

- **Congenital Anomalies** – incidence of 3-5% (10-20% if HbA1C >10%)
    - Of the anomalies, ~1/3 are cardiac, ~10% are neural tube defects, and the rest are musculoskeletal (e.g. caudal regression), renal, situs inversus
- **Preterm Birth** – both spontaneous and for medical/obstetrical indications
- **Birth Trauma**
- **Disorders of Amniotic Fluid**
    - *Polyhydramnios* – may be due to fetal polyuria secondary to fetal hyperglycemia
    - *Oligohydramnios* – due to placental insufficiency
- **Growth Disorders**
    - *Macrosomia*
    - *Intrauterine Growth Restriction:* especially if pre-existing hypertension ± renal disease

- **Stillbirths** – Incidence ~1%; usually >35 wks, large for gestational age, no obvious cause
    - Hypothesis: maternal high glucose with chronic transplacental passage of O_2 and metabolites causes fetal acidemia
- **Perinatal Mortality** – 2-4% (50% due to congenital anomalies)

Neonatal Risks

- Respiratory Distress Syndrome (hyperinsulinemia due to maternal diabetes can delay surfactant production)
- Hypoglycemia
- Hypocalcemia and other electrolyte disturbances
- Hyperbilirubinemia
- Hypertrophic cardiomyopathy – usually resolves by 6 months

Childhood Risks

- Insulin resistance
- Impaired glucose tolerance
- Obesity
- Type I DM - Inheritance ~1-3% risk if overt maternal Type I DM
- Type II DM

MANAGEMENT

Pre-Conception Care

- Most important time in the management of a pre-gestational diabetic; unfortunately many pregnancies are unplanned and therefore obstetrical care-providers do not have the opportunity to educate patients
- The etiology of diabetic embryopathy is multifactorial; largely related to poor glycemic control
- The incidence of congenital anomalies increases above the baseline of 3% as the HbA1C rises to ≥8%; it reaches 20-35% as HbA1C increases beyond 10%
- Questions to be addressed:
    - What is the effect of diabetes on pregnancy?
    - What effect will the pregnancy have on the disease especially if end-organ damage is present?
- **Pre-pregnancy investigations** (not all need to be done in each patient, tailor to symptoms and pre-existing complications)
    - Cardiovascular:
        - Physical Examination: Pulses, BP
        - ECG ± Echocardiogram
        - Perfusion studies
    - *Eyes:* Retinal examination – fundoscopy + visual acuity; then at least one per trimester
    - *Renal:* Electrolytes, BUN, creatinine, urinalysis, urine culture, 24 hr urine collection for protein and creatinine clearance
    - *Neurologic:* Peripheral nerve assessment
    - *Other endocrine:* TSH (40% have thyroid disease)

- **Goals prior to conception:**
    - Folic Acid up to 4-5mg po od – (SOGC 2015 guideline places pre-conception diabetes in a MODERATE risk category and recommends 1mg folic acid + a folic acid rich diet)
    - Achieve normoglycemia: HbA1C < 6.5% remain steady x 3months prior to conception (ideally <6% if possible)
    - Evaluation for the presence of diabetes related complications
    - Evaluation for the presence of concomitant disease
    - Assessment of medications and advice surrounding teratogenicity: ACE-inhibitors and Angiotensin Receptor Blockers need to be STOPPED after conception
    - Discussion of antenatal management
    - Effective contraception until goals are reached

First Trimester:

- Multi-disciplinary approach may include all or some of the following: Obstetrician or Maternal-Fetal Medicine Specialist, Endocrinologist, Diabetes Educator, Nutritionist, Registered Nurse, Social Worker
- Dating Ultrasound
- Routine prenatal screening options (e.g. eFTS)
- Attempt to maintain HbA1C ~6% through pregnancy
- Continue Folic Acid up to 4-5 mg po od in first trimester (SOGC 2015 guideline places pre-conception diabetes in a MODERATE risk category and recommends 1mg folic acid + a folic acid rich diet until 12 weeks and then 0.4-1mg /day for remainder of pregnancy)
- Careful glucose monitoring – high estrogen levels enhance insulin sensitivity and with nausea and vomiting, increase the risk for maternal hypoglycemia
- Increase antenatal visits for first trimester
- Total caloric intake 30-35kCal/kg/day
- Insulin requirements unstable in the first trimester (usually low, so watch for hypoglycemia)
- Glucose checks:
    - Fasting (goal <5.5-5.8 mmol/L), pre- and 1-hr post-prandial (goal <6.7 mmol/L), and qhs, as well as any time hypo- or hyperglycemia is suspected
- Check urine ketones if glucose >11.1mmol/L

Second Trimester:

- Antenatal visits approximately q 2 weeks
- Level II Ultrasound (18-20 weeks), Fetal Echocardiogram (20-22 weeks)

Third Trimester:

- Weekly visits – monitor glucose and evaluate for preeclampsia
- Antepartum fetal monitoring – begin at 26-32 weeks depending on risk
- Non-Stress Test (NST) approximately twice weekly from 30 weeks (depending on clinical situation)
- Biophysical Profile (BPP) assessment approximately weekly from 30 weeks (depending on clinical situation)

- Serial ultrasound (every 2-4 weeks) for growth and amniotic fluid assessment, umbilical artery/ middle cerebral artery (MCA) Doppler assessment if IUGR
- Hospitalization for poor control or hypertension
- Decreasing insulin requirements may indicate uteroplacental insufficiency, especially if requirements decrease by >50%

Delivery

- Planned >38 weeks, consider C/S if EFW >4500g
- Start insulin infusion in labour; glucose level q1h

Postpartum

- Insulin requirements drop after delivery, may not require insulin for 24 hrs
- If breastfeeding, need extra 500 kCal/d
- Contraception – can use combined oral contraceptive pills if no vasculopathy and non-smoker; other options include progestin only pill, intrauterine contraceptive device, tubal ligation

GESTATIONAL DIABETES MELLITUS (GDM)

- *Prevalence:* 2-5% (5-10% in Toronto)
- *Definition:* carbohydrate intolerance of variable severity, first recognized in pregnancy
- 50% of patients with GDM develop Type II DM within 20 years, possible increased rates of obesity and diabetes in their offspring
- Insulin resistance (greatest in third trimester) is due to human placental lactogen, progesterone, prolactin, placental growth hormone, cortisol, estrogen and progesterone
- No RCTs conclusively show that diagnosis and treatment of GDM leads to a reduction in the immediate and long-term effects of GDM on mother and child (e.g. perinatal mortality, macrosomia, shoulder dystocia, birth trauma, Caesarean section, preeclampsia, neonatal metabolic complications)

Screening Options (Table 1)

1. **No Screening**
2. **Risk Factor-Based Screening**

Low Risk	*High Risk*
• Age <25 years • Member of an ethnic group with low prevalence of diabetes • Normal pre-pregnancy BMI ≤27 • No history of abnormal glucose metabolism • No history of poor OB outcome • No diabetes in 1st degree relative	• Previous history of GDM or impaired glucose tolerance • Family history of diabetes • Previous infant >4000g • Previous unexplained stillbirth • Previous neonatal hypoglycemia, • Hypocalcemia, hyperbilirubinemia, • Advanced maternal age • Obesity • Repeated glycosuria in pregnancy • Polyhydramnios • Suspected macrosomia

3. **Universal screening at 24-28 weeks**
    - A screening test threshold of 7.8mmol/l has 10% less sensitivity than a threshold of 7.2 mmol/L– but fewer false positives; either is acceptable
    - 50g Glucose Challenge Test GCT (threshold: normal if less than7.8 mmol/L, diagnostic if ≥11.1 mmol/L; if between 7.8 and 11 mmol/L need to perform 75g OGTT see below)
    - – plasma glucose level 1 hour post
    - Diagnostic test:
        - 75g Oral Glucose Tolerance Test OGTT (need one abnormal value to diagnose GDM) – fasting, 1h and 2h labs are drawn
    - Exception to routine screening is if all low risk criteria are met
    - If high risk perform screen ASAP; if negative, repeat at 24-28 weeks ; can also screen with HbA1C
    - Post-prandial glucose values seem to be most effective at determining the likelihood of macrosomia or other adverse pregnancy outcome in GDM

Complications Associated with GDM

1. **Maternal Complications**
    - Gestational hypertension, Preeclampsia
    - Operative delivery – no evidence that treatment decreases this
    - Postpartum hemorrhage
2. **Fetal Complications**
    - Pre-existing Type II DM leads to 6-fold increase in *perinatal mortality*
    - *Stillbirth:* only at risk if fasting hyperglycemia (risk is at >32 wks)
    - *Macrosomia* (incidence 10-25%)
        - Increased fat on shoulder and trunk – fetus hyperinsulinemic due to maternal hyperglycemia, and this stimulates somatic growth

        - Incidence of shoulder dystocia is ~3%; incidence of permanent birth injury after shoulder dystocia ~1.6%)
        - Fairly good evidence that recognizing and treating GDM reduces macrosomia, but not birth trauma
        - Maternal obesity (esp. truncal) is an independent risk factor for macrosomia
    - *Neonatal hypoglycemia:* 4% of infants require IV glucose therapy
    - *Neonatal hyperbilirubinemia*

Management

- Diet: goals to prevent starvation ketoacidosis, provide necessary nutrients
    - Dietician
    - Average 30kcal/kg/d based on pre-pregnant weight (if normal)
    - Caloric restriction of 30% in obese women
    - Aim for diet: fasting <5.3, 1hr post prandial <7.8, 2 hr post prandial <6.7
- Timing of initiation of insulin is controversial – some studies say insulin reduces macrosomia
- Add insulin if fasting glucose >5.3, or 1 hr post-prandial >7.1-7.8 or 2 hr post-prandial >7 or both
- Glyburide may be safe in pregnancy, but no data for others, therefore avoid
- Metformin is increasingly being used instead of or in conjunction with insulin depending on glycemic control
- No evidence to show that either intervention results in improved perinatal outcome – goal of treatment is to lower macrosomia rate and its consequences
- Antepartum testing: no consensus; some regimens include:
    - NST twice weekly + assessment of fetal well-being (BPP, amniotic volume assessment)
    - If GDM not well controlled, insulin requiring, or other risks like hypertension, then manage the same as pre-existing diabetes

Delivery

- No data to support routine delivery at <40 weeks gestation
- Elective induction based on ultrasound evidence of macrosomia is controversial
- Reasonable to perform elective Caesarean Section if EFW >4500g

Postpartum

1. Recommend 75g OGTT 6-12 weeks postpartum
2. Insulin-requiring GDM at <24 weeks is a powerful predictor of postpartum diabetes
3. High risk of recurrence in subsequent pregnancy

CARDIOVASCULAR DISEASE IN PREGNANCY

- Incidence: 1% of pregnancies; 50% due to Congenital Heart Disease (CHD)
- 3-10% incidence of congenital heart disease in offspring if mother has CHD

Physiologic Cardiac Changes in Pregnancy

- **Cardiac output:** increases by 30-50%, max effect at 20 weeks, remains elevated through the third trimester and in the postpartum period

- Blood volume increases by 40%; maximum hypervolemia at 28 weeks; classically congestive heart failure presents at this time, but majority present postpartum
- Decrease in maternal heart rate by 10 bpm, increase in stroke volume, decrease in peripheral vascular resistance, decrease in blood pressure
  ↑ HR (~10bpm), ↑ SV, ↓ PVR, ↓ BP
- **Normal changes in physical examination:**
  - Exaggerated split S1
  - Loud, easy to hear S3
  - Systolic ejection murmur in 90%, Diastolic murmur 20%, continuous murmur from breast vasculature 10%
  - ↑ risk of arrhythmia due to: hormones, change in autonomic tone, hemodynamic shifts, mild ↓ K^+, underlying cardiac disease
- **Symptoms common in pregnancy as well as heart disease:**
  - Dyspnea, orthopnea, edema, palpitations, nocturnal cough, chest pain, syncope
- **Investigations:**
  - *ECG:* 15 degree left axis deviation, mild ST changes inferior leads, PAC, PVC
  - *Echo:* normal changes are tricuspid regurgitation, increase in size of left atrium

Clinical Classification of Cardiac Disease (New York Heart Association (NYHA) Classification)

- **Class I – Uncompromised:** no limitation of physical activity, no symptoms of cardiac insufficiency, no anginal chest pain *(10% risk CHF in pregnancy)*
- **Class II – Slightly compromised:** slight limitation of activity, comfortable at rest, but in ordinary physical activity they experience discomfort in the form of excessive fatigue, palpitation, dyspnea or angina *(10% risk CHF in pregnancy)*
- **Class III – Markedly compromised:** marked limitation of physical activity; comfortable at rest, less than ordinary activity causes excessive fatigue, palpitation, dyspnea or anginal chest pain
- **Class IV – Severely compromised:** inability to perform any physical activity without discomfort – symptoms of cardiac insufficiency or angina may develop at rest, at with any activity, discomfort increases

Risks of Maternal Mortality caused by various Heart Diseases

- **Group I – Minimal Risk (0-1%)**
  - ASD,VSD, PDA, pulmonic or tricuspid disease, corrected tetralogy of Fallot, bioprosthetic valve, mitral stenosis NYHA class I & II
- **Group II – Moderate Risk (5-15%)**
  - 2A: Mitral stenosis – NYHA class III & IV, aortic stenosis, aortic coarctation without valvular involvement, Uncorrected Tetralogy of Fallot, previous MI, Marfan syndrome – normal aorta
  - 2B: Mitral stenosis with atrial fibrillation, artificial valve
- **Group 3 – Major Risk (25-50%) – Consider TA:**
  - Pulmonary hypertension – either primary or secondary to Eisenmenger's syndrome
  - Cardiomyopathy with pre-existing heart failure
  - Marfan syndrome with aortic root dilatation (>40mm)

- Aortic coarctation with valvular involvement
- Maternal mortality: pulmonary hypertension, endocarditis, coronary artery disease, cardiac arrhythmia, cardiomyopathy

Predictors of Primary Cardiac Events in Pregnancy

Source: Siu et al, 2001

- Prior Cardiac Event (Heart Failure, TIA, Stroke)
- Arrhythmia
- NYHA Class >II or cyanosis
- Left heart obstruction (eg. mitral area <2cm^2, aortic area < 1.5cm^2, peak left ventricular outflow tract gradient >30mmHg by echo, ejection fraction <40%)

Each of these predictors is scored as 1 'point'; risk of a primary cardiac event (e.g. pulmonary edema, arrhythmia, stroke, death) during pregnancy is:

- 0 points – 5%
- 1 point – 27%
- >1 point – 75%

General Management

- Four concepts that affect management are emphasized by American College of Obstetricians and Gynecologists (ACOG):
  - 50% increase in blood volume and cardiac output by 28 weeks
  - Further fluctuations in volume and cardiac output in the peripartum period
  - A decline in systemic vascular resistance, reaching nadir at 20 weeks and rising to 20% below normal by late pregnancy
  - Hypercoagulability – especially if require anticoagulation prior to pregnancy
- *Class I & II:* No smoking; 1st sign CHF is nocturnal cough and basilar crackles
  - Pneumococcal, influenza vaccine
  - L&D: Attempt SVD; Minimize hypotension with epidural especially with lesions that depend on preload (aortic stenosis, pulm HTN); frequent vitals, treat intrapartum heart failure based on hemodynamic status
- *Class III & IV:* Pre-pregnancy consult – need to understand risks

RENAL DISEASE IN PREGNANCY

- Incidence of pre-pregnancy renal disease ~0.03%
- Low incidence because women are either beyond child bearing age or infertile, also incomplete reporting

Normal Physiology:

- Increase in glomerular filtration rate and renal plasma flow of ~50% which leads to:
- Higher creatinine clearance (110-150 mL/min)
- Lower serum creatinine (~45 – 70 umol/L) and serum BUN (9-12 mg/dL)
- Increase in kidney size, marked dilation of the renal pelvis, calyces and ureters

- To compensate for the 10mm reduction in PCO2 (28-30 mmHg), kidneys excrete more HCO_3 which results in 4-5mEq/L decrease in serum bicarb (~20-22 mEq/L). Serum osmolality also decreases by ~10 mOsm/L (serum sodium 5mEq/L).

Common Problems:

1. **Urinary tract infections:**
    - *Asymptomatic bacteruria (2-7%):* infection if colony count $>10^6$/mL; if untreated, then 25% risk symptoms will develop; Treatment: Amoxicillin/Nitrofurantoin for 3-7 day course; 30% recurrence; for chronic infection – Nitrofurantoin x 21 days
    - *Cystitis:* frequency/urgency/dysuria, 3-7 day course of antibiotics, if symptoms persist and negative urine culture, then screen for chlamydia
    - *Pyelonephritis:* 2% of pregnancies, most common, serious medical condition
        - Unilateral and Right sided in >1/2 of cases, thermoregulatory instability is common – clinical findings caused by endotoxemia
        - E. Coli 77%, Klebsiella 11%, Enterobacter 4%, Proteus 4%
        - 15% with acute pyelo have bacteremia, 1-2% have respiratory insufficiency
        - Treatment: IV hydration, IV broad spectrum antibiotics (Amp/Gent, Ceftriaxone/Ancef) – continue therapy x7-10 days, symptoms resolve in 2 days – if not then renal ultrasound looking for obstruction, discharge home after afebrile x 24 hours with po antibiotics x 7-10 days; urine culture and sensitivities 1-2 weeks post antibiotic therapy
2. **Nephrolithiasis**
    - 80% are calcium stones; need to exclude hyperparathyroidism
    - 1/2000 pregnancies; no adverse pregnancy outcomes treatment: hydration, analgesia, antibiotics if infected (present in 50%)
    - 75% pass stone with conservative management

Most Common Causes of Chronic Renal Disease

- Type I DM
- Glomerulonephritis
- Hypertension
- Lupus nephritis
- IgA nephropathy
- Polycystic Kidney Disease (PCKD)

Diabetic Nephropathy

- Optimize renal function with ACE-Inhibitor in the pre-pregnancy period – contraindicated once pregnant thus must be continued in pre-conception period or as soon as conception occurs
- Modulates smooth muscle cells and mesangial cells – effect lasts through pregnancy (i.e. after nephropathy optimized, lasts 2 years)
- Treat x 6 months – ***must be discontinued*** at conception - no ACE-inhibitors in pregnancy
- Increased frequency of infections, edema, pre-eclampsia

In general, adverse maternal and fetal outcomes include:

- Superimposed hypertension/pre-eclampsia – 6-64%
- Perinatal mortality – 0-11%
- Preterm delivery – 37-58%
- Intrauterine growth restriction – 8-37%
- Increased risk in pregnancy for: renal insufficiency, uncontrolled hypertension, worsening proteinuria

Prognosis depends on:

- Pre-pregnancy renal function
- Presence or absence of hypertension
- Women with minimal renal dysfunction and normal BP have a 90% chance of good outcome, and pregnancy is unlikely to affect renal function
- No consensus as to whether pregnancy adversely affects specific renal diseases
- Poor prognostic indicator for progressive renal failure are:
    - Hypertension >140/90
    - Nephrotic range proteinuria (>1g/day)
    - Pre-existing significant compromise in kidney function prior to pregnancy
    - Significant sclerosis on pre-pregnancy biopsy

Table 2: Grading of severity of renal dysfunction in pregnancy

Grading of severity of renal dysfunction in pregnancy			
	Serum creatinine (umol/L)	CrCl (mL/min)	Risk of progression to ESRD
Mild	<125	>70	
Moderate	125-220	40-70	1 in 6 (15%)
Severe	>220	<40	1 in 3 (33%)

Pre-Pregnancy Counselling

- Minimize risks with education
- Treat disease prior to conception: ACE-I, glycemic control, immunosuppression
- Review compatibility of medications with pregnancy
- Fertility is dependent on degree of renal insufficiency
- Pregnancy outcome is dependent on:
    - Degree of renal insufficiency
        - Renal disease may progress in pregnancy, especially in those with moderate to severe disease
        - Most pregnancies with moderate to severe will result in preterm birth
        - Women with creatinine > 180 umol/L have a 1/3 chance of progressing to end stage renal disease within 1 year postpartum
        - Pregnant women requiring dialysis are at even higher risk of complications and adverse pregnancy outcomes

- Pregnancy outcome is also related to degree of hypertension, effectiveness of anti-hypertensive therapy, degree of proteinuria, and presence or absence of new or worsening hypertension/pre-eclampsia
    - Maintain diastolic BP <90mmHg

Pregnancy Management

- Based on retrospective and observational series and opinions
- Multidisciplinary team at a tertiary care centre with Maternal Fetal Medicine and Nephrology
- Antenatal visits q2 weeks until 30-32 weeks, then weekly
- Fetal surveillance with ultrasound ~ 30-32 weeks (BPP), assessment of fetal growth
- Baseline renal function should be assessed at booking, then approximately 4-6 weeks
    - Serum creatinine, BUN, electrolytes
    - Albumin
    - CBC
    - Urinalysis and urine culture, 24 urine collection for protein and creatinine clearance
    - Urine microalbumin to creatinine ratio

THYROID DISEASE IN PREGNANCY

Labs in Pregnancy:

- Thyroid Binding Globulin increases (hepatic clearance decreases, estrogen stimulation of TBG synthesis)
- Increase in size of gland (by 18%, don't investigate)
- Decrease in iodine (due to fetal use and increase in renal clearance)
- TSH, free T4 remain overall unchanged

Transport across the placenta:

- *Cross the placenta:* TRH, iodine, PTU, methimazole and TSH receptor Ig's (Thyroid stimulating Ig (TSI) and Thyroid stimulating hormone binding inhibitory Ig (TBII)
- *Doesn't cross placenta:* TSH, T4, T3 (only small amount of T4 and T3 cross)
- **Fetal Thyroid:** controlled by fetal TSH at 20 weeks, adult levels at 36 wks

Hyperemesis: biochemical hyperthyroidism due to cross-reactivity of high hCG and TSH (same α-subunit) – does not need treatment unless other clinical signs of hyperthyroidism; do not routinely screen TSH with hyperemesis

Hyperthyroidism

- Affects 0.2% of pregnancies, or 1/2000
- Diagnosis: TSH decreased, fT4 increased
- Differential Diagnosis:
    - Graves' Disease (95% of cases) – autoimmune: presence of TSI and TBII
    - Excess TSH production
    - Gestational trophoblastic neoplasia (GTN)

- Toxic nodular goiter
- Subacute thyroiditis
- Extra-thyroid source of thyroid hormone
- Hyperfunctioning thyroid adenoma
- Follicular cancer
- Primary hyperthyroidism (TRH adenoma)
- Struma ovarii

Table 3:

Symptoms	Signs
• Frequent BM • Heat Intolerance • Irritability/nervousness • Palpitations • Tachycardia • Tremor • Weight Loss	• Pretibial myxedema • Lid lag • Non-tender goiter • Onycholysis • Palmar erythema • Proptosis • Staring gaze • Thick skin

Table 4:

If untreated, increased risk of:	If inadequately treated, increased risk of:
• Spontaneous Abortion • Preterm delivery • Severe gestational hypertension • Heart Failure (cardiomyopathy or hyperdynamic cardiovascular state)	• Preterm delivery (32%) • Intrauterine growth restriction (17%) • Stillbirth (18%); perinatal mortality 8% • Anomalies ↑6% if no Rx

Treatment:

Goal of management is to get to a high normal fT4; monitor level q2-4wks until stable.

Medications:

- *Propylthiouracil (PTU):* (dose 300-450mg po od) also blocks peripheral conversion of T4 to T3
- *Methimazole:* (10-40mg) can be used in pregnancy (previously thought to have risk of fetal aplasia cutis)
    - Mechanism: both drugs block organification of iodine; can breastfeed, can use both in pregnancy
    - I^{131}*:* contraindicated in pregnancy, effective cure in 80%; delay pregnancy until 4 months post treatment, avoid breastfeeding for 3 months post treatment; if given in pregnancy, then <10wks likely ok, if >10 wks may have ablated fetal thyroid – consider termination
- *Propranolol:* symptom relief

Side Effects of Thionamides (PTU, Methimazole):

- **Major:** agranulocytosis (0.1-0.4%); present with fever and sore throat, thrombocytopenia, hepatitis, vasculitis; all <1%
- **Minor:** rash, nausea, anorexia, fever, loss of taste/smell; all ~5%; 10% have transient leukopenia
- **Neonatal effects:**
    - In pregnancy monitor fetus for hyperthyroidism: tachycardia, IUGR, Oligo, goitre, hypervascular thyroid on ultrasound
    - Any patient with Graves' disease has a risk of fetal ↓↑thyroid because TSI and TBII can cross placenta; 1-5% of neonates have hyperthyroidism or Graves due to transplacental crossing (low incidence because balance of stimulating and inhibiting antibodies)
- **Thyroid Storm:**
    - *PTU:* 600-800mg po stat, then 150-200mg po q4-6h (can use methimazole po)
    - 1-2hrs post PTU, give KI 2-5 drops po q8h, or NaI 0.5-1.0mg IV q8h, or Lugol's 8 drops q6h, or Lithium carbonate 300mg po q6h; all block release of thyroid hormone from gland
    - *Dexamethasone:* 2mg IV/IM q6h x 4 doses; decrease thyroid hormone release and peripheral conversion of T4 to T3
    - *Propranolol:* 20-80mg po q4-6h or 1-2mg IV q5min to total 6mg, then 1-10mg IV q4h; if hx of bronchospasm can use reserpine, guanethidine or diltiazem
    - *Phenobarbital:* 30-60mg po q6-8h prn for restlessness
    - General supportive measures and assessment of fetal well-being

Hypothyroidism

- 5-8% incidence if hx of Type I DM; 25% risk of PP thyroid dysfunction
- Insufficient data to recommend routine screening of TSH (incidence ~1%)
- Annually screen: Pregnant women with DM, Turner's, Down's, Amiodarone, Lithium
- T3 is the primary physiologically active hormone

Differential Diagnosis

- Hashimoto's Thyroiditis (most common cause in North America) – autoimmune destruction of gland by anti-thyroid Ab's: i.e. anti-microsomal Ab's, anti-thyroglobulin Ab's
- Subacute thyroiditis
- Thyroidectomy
- Radioactive I^{131} treatment
- Iodine deficiency (most common worldwide cause of hypothyroidism)
- Anti-thyroid meds
- Surgery

Symptoms: cold, constipated, carpal tunnel, dry skin, fatigue, hair loss, weight gain
If untreated, risk of:

- Gestational hypertension, abruption, fetal distress in labour, heart failure
- Low birth weight, stillbirth
- If iodine deficiency, then: cretinism: growth failure, mental retardation, neuropsych deficits

Subclinical Hypothyroidism: High TSH, normal fT4 – incidence 5%; 10-20% progress to overt hypothyroidism in 1-4 years; risk in pregnancy is unclear, but may have increase gestational hypertension and preterm delivery

Risk of congenital hypothyroidism: 1/4000; DDx: thyroid agenesis, thyroid dyshormonogenesis, transient hypothyroidism (i.e. premature – don't need to treat)

Treatment

- Dose: 1.5mcg/lb – work up to this (i.e. start 0.88mcg)
- Takes ~4wks for TSH to normalize after starting L-thyroxine
- Data indicate increased maternal thyroid hormone requirements in pre-pregnancy hypothyroid pts; mean increase from 0.1mcg/day to 0.148mcg/day
- Check TSH each trimester in stable patients

Postpartum Thyroiditis

- Postpartum hypothyroidism or thyrotoxicosis occurs in 5-10% of women without history of thyroid disease
- Postpartum thyroiditis has a 70% risk of recurrence
- 25% of women with Type I DM develop postpartum thyroid dysfunction
- Pathogenesis: thought to be initiating inflammatory event followed by specific autoreaction from immune system
- Histology: destructive lymphocytic thyroiditis; many have anti-thyroid antibodies
- 7-10% of women have anti-microsomal antibodies – at high risk for postpartum thyroiditis

2 recognized clinical phases (Table 5):

	1-4 months Postpartum	**4-8 months Postpartum**
Condition	Thyrotoxicosis	Hypothyroidism
Incidence	4%	2-5%
Mechanism	Destruction induced hormone release	Thyroid failure
Symptoms	Small, painless goitre, fatigue, palpitations	Goitre, fatigue, inability to concentrate
Treatment	β-blockers for symptoms	Thyroxine 6-12 months
Sequlae	2/3 become euthyroid 1/3 develop hypothyroidism	1/3 permanently hypothyroid

Thyroid Nodule or Thyroid Cancer in Pregnancy

- 40% of nodules are malignant
- Pregnancy does not alter the course of thyroid cancer
- General treatment is thyroidectomy (can be done in second trimester) and radiation – individualize treatment to patient's gestational age

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Antepartum and Postpartum Hemorrhage

Antepartum and Postpartum Hemorrhage Objectives:

At the end of the seminar, students should be able to:

Antepartum Hemorrhage:

1. List a differential diagnosis for antepartum hemorrhage
2. Describe the approach to managing a patient presenting with antepartum hemorrhage
3. Compare symptoms, physical findings, and diagnostic methods that differentiate patients with placenta previa, placental abruption and other causes of antepartum hemorrhage.
4. Describe the complications (fetal and maternal) of placenta previa and placental abruption.
5. Describe the immediate management of shock secondary to antepartum hemorrhage.
6. List the indications and potential complications of blood products.

Postpartum Hemorrhage:

1. Define postpartum hemorrhage (PPH)
2. List the causes of PPH
3. Describe the predisposing factors for PPH
4. Outline the immediate management of a patient with PPH, including:
    - Inspection for lacerations
    - Use of uterotonic agents
    - Management of volume loss
    - Management of coagulopathy

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ANTEPARTUM HAEMORRAGE

Antepartum hemorrhage refers to bleeding from the genital tract after 20 weeks of gestation and complicates 4 to 5% of pregnancies.

Differential Diagnosis:

- Abruptio placenta 30-40%
- Placental previa 20-30%
- Unclassified 35%
- "Show" Associated with preterm/term labour
- Lower genital tract lesion 5%
- Uterine rupture – rare
- Vasa previa – rare

In the cases where the etiology of the antepartum bleeding is unclear (unclassified) and cannot be determined, the bleeding is usually attributed to a marginal separation of the placenta. An anatomical approach (from outer vulva into vagina to cervix to uterus) can also be made.

Significance of Antepartum Bleeding

In the non-pregnant state, the uterus receives 1% of the cardiac output but by the third trimester of pregnancy, it receives about 20% approximately 1L/minute. Bleeding in the second or third trimester of pregnancy can result in massive hemorrhage, leading to a hemodynamically unstable patient. Placenta previa and abruption placenta account for more than half of the cases of antepartum hemorrhage and are the leading causes of perinatal mortality and morbidity in the third trimester.

Management

Whenever a patient presents with an antepartum hemorrhage, it is important to first establish the maternal hemodynamic status, the severity of the bleeding and the status of the fetus. If the *maternal status is unstable and/or the fetal well-being is in jeopardy,* prompt action by the health care team to stabilize the mother and deliver the fetus may be essential and life-saving.

If both *mother and fetus are stable,* after initial assessment of maternal vital signs and fetal heart rate, then proceed with a complete history and physical examination. The history should concentrate on the onset, duration, amount, and quality of bleeding in addition to any other associated factors such as pain, contractions, loss of vaginal fluid, and absence of or decrease in fetal movements. The general maternal obstetrical, gynecological, medical and surgical history should be reviewed searching for possible risk factors associated with antenatal hemorrhage. Prenatal records and any previous ultrasound reports should be reviewed, if available.

External continuous fetal monitoring should be initiated. Physical examination should include maternal vital signs, fetal heart rate, uterine palpation for tenderness, tone, contractions, and fetal presentation. Check the external genitalia for the quantity of blood. *A digital cervical examination must be avoided until an ultrasound scan excludes the diagnosis of placenta previa*. Even a speculum examination should be avoided until an ultrasound examination is done, to search for placenta previa, although there is controversy

surrounding this issue. A speculum exam should be eventually done to assess the cervix for dilatation or any lesions.

Blood work should be sent for CBC, coagulation screen, blood group and screen and possibly a Betke-Kleihauer test in an Rhesus negative mother to help quantify the amount of Rh-immunoglobulin required. Additional tests may be indicated depending on the patient's history and examination.

Further management will depend on the clinical findings and assessment of the patient and fetus (see below). However, if the bleeding subsides, mother and fetus are stable, and blood work is normal, most patients who have had a significant amount of bleeding would be admitted for monitoring of maternal vitals, fetal well-being and any further bleeding for at least 48 hours.

PLACENTA PREVIA

Placenta previa refers to the localization of the placenta near, partially or completely over the cervical os. A complete previa covers the internal os. A COMPLETE placenta previa occurs when the internal os is approximately equidistant from the anterior and posterior placental edges. A PARTIAL placenta previa partially covers a portion of the internal os. A MARGINAL previa is where distal edge of placenta lies immediately adjacent to the cervical os without actually covering it. LOW LYING placenta represents a situation where the leading edge of the placenta is within 2 cms from the internal os, however does not cover the os, as measured by transvaginal ultrasound. All of these abnormalities of placental location are associated with a significantly increased risk of hemorrhage, particularly during the effacement and dilatation of the cervix which accompanies the onset of labour.

Ultrasonography:

Transvaginal sonography is the preferred technique for diagnosis of placenta previa because it provides a clearer image of the relationship of the edge of the placenta to the internal cervical os than transabdominal ultrasound and determines cervical length. The procedure can be performed safely since the optimal position of the vaginal probe for visualization of the internal os is 2 to 3 cms away from the cervix and the angle between the cervix and probe is sufficient to prevent the probe from slipping into the cervix.

The term low-lying placenta is used loosely to describe (1) a placenta which lies in the lower uterine segment but the exact relationship of the placenta to the internal os has not determined or (2) a placental edge that lies within 2 cms of the internal os. For clarity, it is best to describe the placental location in terms of sonographically estimated distance in centimeters between the inferior edge of the placenta and the internal os.

The incidence of placenta previa is 0.5-0.8% of all pregnancies. About 30% of patients will be found to have a "low-lying placenta" (see above) on sonography early on in their pregnancy but only 0.5% will persist as a placenta previa in the third trimester. Continued development of the lower uterine segment, as the pregnancy advances, relocates the stationary lower edge of a marginal or low-lying placenta progressively away from the internal os.

Invasive Placenta:

In 5-10% of cases of placenta previa, there is an associated placenta accreta, in which the anchoring placental villi are abnormally attached to the myometrium rather than being contained by the decidual cells, resulting in a placenta severely adherent to the uterus. The main risk factor is previous Caesarean delivery. Ultrasonography may help to recognize placenta accreta, if the normally present hypoechoic myometrium between the bladder and the placenta is absent and the placenta appears contiguous with the bladder wall.

Predisposing Factors:

- Prior placenta previa
- First pregnancy following any uterine surgery
- Multiple gestation
- Multiparity
- Previous Caesarean section/s
- Advanced maternal age

Asymptomatic Placenta Previa

Placenta previa may be first diagnosed incidentally on a routine ultrasound examination, typically at the anatomy scan done at around 18-20 weeks' gestation. If the leading edge of the placenta is demonstrated to be less than 2 cms from the internal os, it is recommended that a repeat scan be performed at 32-34 weeks' gestation to reassess the placental localization. In cases where the diagnosis of complete or marginal placenta previa or low lying placenta is confirmed on ultrasound, it is recommended that patients avoid intercourse and exercise and seek immediate attention if contractions or vaginal bleeding occur. Patients may be managed on an outpatient basis (unless bleeding occurs) and scheduled for a Caesarean delivery at term, usually between 37-38 weeks' gestation. As a precaution, blood should be cross-matched and typed at the time of the operative delivery. IV tranexamic acid at surgery reduces blood loss. A Cell Saver can return blood back to the patient intra-operatively.

Symptomatic Placenta Previa

The characteristic clinical presentation in 70-80% of women with symptomatic placenta previa is painless vaginal bleeding after 20 weeks' gestation. An additional 10-20% of women present with uterine contractions associated with bleeding and fewer than 10% are incidentally detected by ultrasound examination and remain asymptomatic.

Placenta previa must be suspected in any woman in the second half of pregnancy who presents with vaginal bleeding and a digital cervical examination must be avoided until such a diagnosis can be excluded by ultrasound scan.

Management

1. Admit and initiate maternal and fetal monitoring
2. Establish intravenous access and administer crystalloids
3. Take bloods – CBC, coagulation screen, blood group and screen, Cross match and type 4 units of packed red blood cells
4. Administer oxygen and monitor pulse oximetry

5. Unstable maternal/fetal condition
    - Stabilize
    - Begin transfusion, watch for DIC
    - Call for help (anaesthesia, pediatrics, RT, nursing, other OB)
    - Immediate delivery by CS
6. Stable maternal/fetal condition
    - *Mature fetus:* deliver by CS
    - *Immature fetus:* consider steroids, transfusion, transfer, monitor; discharge after bleeding stopped for minimum of 48 hours; continue inpatient / outpatient monitoring; schedule for CS at later date; return to hospital if any further bleeding
7. Rh(D)-immune globulin for Rh negative women

Complications (Table 1):

Maternal	**Fetal**
• Hemorrhage • DIC • Placental Accreta • Caesarean hysterectomy • Increase recurrence rate 4-8%	• Prematurity • Malpresentation • Fetal growth restriction • Vasa previa • Congenital anomalies

ABRUPTIO PLACENTA

Abruptio placenta is the premature separation of a normally implanted placenta from the uterine wall. The incidence of abruption is 1-2% of all pregnancies, with the risk significantly rising to 5-16% in a patient with a previous history of abruption. The immediate cause of the separation is rupture of defective maternal vessels in the decidua basalis, where it interfaces with the placental anchoring villi.

The majority of cases of abruption involve a chronic pathologic vascular process at the maternal-placental interface as demonstrated by the presence of spiral artery vasculopathy, spiral artery thromboses and failed physiologic transformation of uteroplacental vessels. In some cases, there is a single acute precipitating event, such as catastrophic trauma or preterm rupture of membranes.

Risk Factors:

- Previous abruption
- Trauma
- Rupture of membranes
- Uterine fibroids
- Uterine or placental anomalies
- Maternal hypertension
- Cigarette smoking
- Increasing parity
- Increasing age
- Cocaine use
- Inherited thrombophilias
- Multifetal gestation
- Polyhydramnios

Clinical Manifestations:

The classic symptoms and signs of acute abruption are vaginal bleeding (80% of patients), abdominal pain (50% of patients), uterine contractions, uterine tenderness, nonreassuring fetal heart rate tracing and/or fetal demise. Abruption in a posteriorly implanted placenta may cause back pain. When the classic signs and symptoms of abruption occur without vaginal bleeding, a severe concealed hemorrhage (blood that is retained between the placenta and uterus without vaginal bleeding) may be present. The blood may also infiltrate the myometrium to the serosal surface of the uterus (Couvelaire uterus) and become extremely atonic after delivery of the fetus. Therefore, the amount of bleeding does not always correlate well with the extent of maternal hemorrhage and cannot be used to gauge the severity of abruption.

The diagnosis of placental abruption is primarily clinical although laboratory and ultrasound findings may help. An abruption may only be seen on ultrasound in the most severe cases or when the placenta has completely separated from the uterus with resultant fetal demise. Thus, a normal ultrasound does not rule out an abruption. The presence of a coagulopathy on laboratory studies supports the diagnosis of a severe abruption particularly with hypofibrinoginemia and thrombocytopenia. Examination of the placenta after delivery often reveals a clot on the maternal surface.

Complications (Table 2)

Maternal	**Fetal**
• Hemorrhage • Transfusion • DIC • Postpartum hemorrhage (Couvelaire uterus) • Hysterectomy	• Prematurity • Hypoxic encephalopathy • Death

Management

1. Determine maternal hemodynamic stability and fetal status immediately
2. Establish intravenous access (2 large bore IVs, if needed) and administer crystalloids
3. Take blood – CBC, coagulation screen, blood group and screen, Cross and Type
4. Continuous monitoring of maternal and fetal well being
5. Administer oxygen and monitor pulse oximetry
6. Unstable patient/fetus
    - Call for help
    - Resuscitate and stabilize
    - Deliver - vaginal or Caesarean section depending on progress, circumstances
    - Watch for DIC
7. Stable patient/fetus
    - Live Fetus
    - Mature: vaginal delivery or CS
    - Immature: consider steroids, transfusion, transfer, admission, surveillance, consider inducing when term
8. Dead Fetus: Induce labour for vaginal delivery if not already in labour, watch for DIC

9. Rh(D) – immune globulin for Rh negative women; Betke-Kleihauer test/flow cytometry quantify amount of fetomaternal hemorrhage thus helping to confirm amount of immune globulin required.

VASA PREVIA

Vasa previa refers to fetal vessels that traverse the membranes located in the lower uterine segment in advance of the fetal presenting part. It is usually associated with velamentous insertion of the cord where the vessels of the cord insert directly into the membrane prior to reaching the placental body. These vessels are surrounded by fetal membrane only and without the protective effect of Wharton's jelly. Rupture of these vessels, usually at the time of rupture of the membranes, will lead to a nonreassuring heart rate pattern, (sinusoidal pattern of fetal anemia) due to fetal hypotension, accompanied by mild vaginal bleeding. The risk of fetal exsanguination and death is extremely high with a mortality rate of 50-70%. Confirmation that the vaginal blood is fetal may be done via the Apt test but there is usually not time to wait for test results before performing an emergency Caesarean delivery.

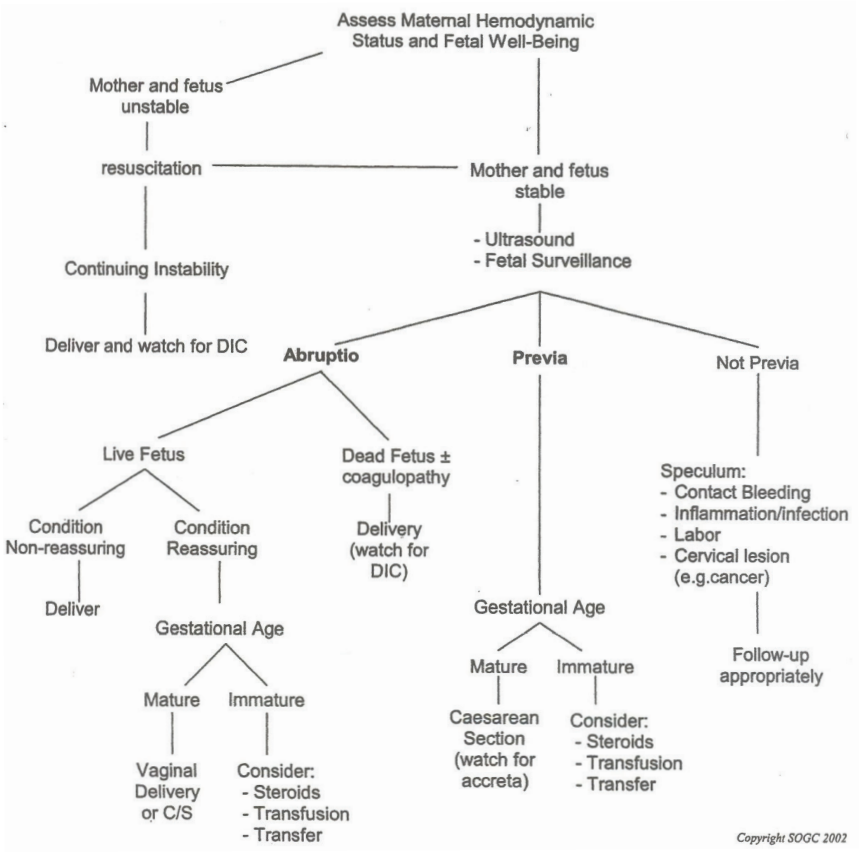
The frequency of vasa previa is approximately 1 in 3000 pregnancies. Occasionally, the fetal vessels may be felt on digital exam prior to rupture of the membranes or recognized on antenatal sonographic examination. If recognized antenatally, then appropriate serial surveillance of the fetus (and cervical length) can be initiated and plans may be made for delivery by elective Caesarean section when fetal maturity is reached.

Table 3:

	Abruptio Placenta	**Placenta Previa**
Associated Factors	Hypertension Trauma/Fall Uterus overdistended Substance abuse: cocaine, smoking Advanced maternal age	Previous C-section Previous uterine surgery (myomectomy, D+C, Ashermans, septoplasty) Multiparity, Multifetal preg Advanced maternal age
Pain	Abdominal pain Backache	Painless (unless in labour)
Uterine Tone	Increased, constant	Uterus soft
Uterine Tenderness	Tender	Non-tender
Contractions	Present Uterine Irritability	Absent
Presentation	Cephalic	Malpresentation
Fetal well-being	Absent Fetal Heart Rate Nonreassuring tracing Late decelerations	Reassuring tracing
Ultrasound	Usually not helpful (unless severe)	Confirms diagnosis

Blood work	CBC, G+S, Rh, BK Disseminated intravascular coagulation (DIC)	CBC, G+S, Rh

Figure 1: Antepartum Hemorrhage Decision Tree



POSTPARTUM Hemorrhage (PPH)

Traditionally, the definition of **postpartum hemorrhage (PPH)** has been blood loss in excess of 500 cc in vaginal deliveries and in excess of 1000 cc in abdominal deliveries. For clinical purposes, any blood loss that has the potential to produce hemodynamic instability will depend on the pre-existing condition of the woman. Hemodynamic instability is more likely to occur in conditions such as anemia (e.g. Iron deficiency, thalassemia) or volume contracted states (dehydration, gestational hypertension with proteinuria).

- **Immediate PPH:** in the first 24 hours postpartum
- **Delayed PPH:** after 24 hours and up to 6 weeks postpartum

Causes of PPH: Think of the 4 T's

1. **Tone (uterine atony)**
    - Overdistended uterus:
        - Polyhydramnios
        - Multiple gestations
        - Macrosomia

- Uterine muscle exhaustion:
    - Rapid labour
    - Prolonged labour
    - High parity
    - Oxytocin use
    - General anaesthetic
- Intra-amniotic infection:
    - Fever
    - Prolonged ROM
- Functional/anatomic distortion of uterus:
    - Fibroid uterus
    - Placental previa

2. **Trauma**
    - Uterine, cervical, or vaginal injury
    - Uterine rupture or inversion

3. **Tissue (retained products)**
    - Abnormal placentation
    - Retained cotyledon or succenturiate lobe
    - Retained blood clots lead to atonic uterus

4. **Thrombin**
    - Pre-existing or acquired coagulopathy
        - Hemophilia A
        - Von Willebrand's disease
    - Acquired in pregnancy
        - ITP
        - Thrombocytopenia with pre-eclampsia
        - DIC
    - Anticoagulation medication

The most common and important cause of PPH is uterine atony. The primary mechanism of immediate hemostasis following delivery is myometrial contraction causing occlusion of uterine blood vessels.

Table 4: Risk Factors for Postpartum Hemorrhage

Etiologic category and process	Clinical risk factors
Tone: abnormalities of uterine contraction	
Overdistension of uterus	Polyhydramnios Multiple gestation Macrosomia
Uterine muscle exhaustion	Rapid labour Prolonged labour High parity Oxytocin use
Intra-amniotic infection	Fever Prolonged rupture of membranes
Functional/anatomic distortion of uterus	Fibroids Placenta previa Uterine anomalies
Uterine-relaxing medications	Halogenated anesthetics Nitroglycerin
Bladder distension, which may prevent uterine contraction [4]	
Tissue: retained	
Retained products of conception	Incomplete placenta at delivery Previous uterine surgery High parity
Abnormal placentation	Abnormal placenta seen on ultrasonography
Retained cotyledon or succenturiate lobe	
Retained blood clots	Atonic uterus
Trauma: of the genital tract	
Lacerations of the cervix, vagina, or perineum	Precipitous delivery Operative delivery
Extensions, lacerations at cesarean section	Malposition Deep engagement
Uterine rupture	Previous uterine surgery
Uterine inversion	High parity Fundal placenta Excessive cord traction
Thrombin: abnormalities of coagulation	
Pre-existing states	History of hereditary coagulopathies or liver disease
Hemophilia A	
Von Willebrand's disease	
History of previous PPH	
Acquired in pregnancy	
Idiopathic thrombocytopenic purpura	Bruising, elevated blood pressure
Thrombocytopenia with preeclampsia	
Disseminated intravascular coagulation	
Gestational hypertensive disorder of pregnancy with adverse conditions	Elevated blood pressure
a) Dead fetus in utero	Fetal demise
b) Severe infection	Fever, neutrophilia/neutropenia
c) Abruption	Antepartum hemorrhage
d) Amniotic fluid embolus	Sudden collapse
Therapeutic anticoagulation	History of thrombotic disease

Adapted from SOGC Clinical Practice Guideline, No. 235 October 2009.

Prevention of PPH

1. Administer oxytocin routinely after delivery (with anterior shoulder)
2. Clamp and cut cord when baby delivered (delay clamping by 60 sec if <37wks GA)
3. Palpate uterine fundus and confirm that uterus is contracting
4. Keep tension on cord pulling gently while applying suprapubic counter-traction on uterus with other hand. Digital exam along the cord to determine whether the placenta is at the cervix. Pulling hard on cord may cause cord to avulse. Gentle traction with a relaxed uterus can cause uterine inversion.
5. If placenta not delivered in 15 minutes, use oxytocin infusion
6. Once placenta delivered, assess fundus to ensure it is well contracted
7. Inspect placenta and membranes for completeness
8. Examine external genitalia and internal genital tract for lacerations, hematomas.

Management of PPH

1. ABCs
    - Talk to and observe your patient
    - Monitor vital signs
    - Commence at least one large bore IV (16 gauge or larger)
    - Run IV crystalloid solution wide open
    - Obtain a CBC, cross-match and do coagulation studies
2. Get Help
    - Get additional personnel to manage resuscitation
    - Notify lab of potential need for massive transfusion
3. Assess fundus: if boggy, do bimanual massage: uterus massaged between a hand in vagina against the cervix and a hand on the fundus. Explore uterine cavity at this time to rule out retained products, uterine inversion or uterine rupture if analgesia allows.
4. Examine the genital tract for injury, placenta for completeness, and do manual uterine exploration to rule out retained products
5. Empty bladder: may insert Foley catheter to keep bladder empty (which helps keep uterus contracted) and monitor urine output
6. Drug therapy
    - Oxytocin
        - 5 units IV bolus
        - 20-40 units/250mL in crystalloid
        - 10 units IM if cardiovascular collapse or no IV access
    - Carbetocin (long-acting oxytocin)
        - 100ug IV/IM
    - Hemabate (Carboprost/15-Methyl Prostaglandin F2 alpha)
        - 250 ug IM or intramyometrial; repeat every 15 min as needed
        - Maximum cumulative dose 2 mg (8 doses)
        - Asthma is a relative contraindication

- Methylergonovine maleate
    - 0.25 mg IM/0.125 mg IV
    - Repeat every 5 mins as needed
    - Maximum 5 doses
    - Hypertension and some medications (eg proteases) are a contraindication
- Misoprostol (off-label use)
    - 600-800 ug po/sl (faster onset) or per rectum/per vagina
    - Side effect: Pyrexia if >600ug given; diarrhea; flushing
- Tranexamic Acid (cyklokapron)—antifibrinolytic
    - 1g IV

7. Consider alternative procedures
    - Intra-uterine balloon (Bakri balloon)
    - Uterine vessel ligation
    - Internal iliac artery ligation
    - Uterine suturing techniques
    - Hysterectomy
    - Bilateral uterine/internal iliac artery ligation
8. If coagulopathy
    - FFP
    - Cryoprecipitate
    - Platelets
    - Packed red blood cells

Figure 2: A Stepwise Approach to the Management of Postpartum Hemorrhage

Adapted from SOGC Clinical Practice Guideline, No. 88 April 2000.

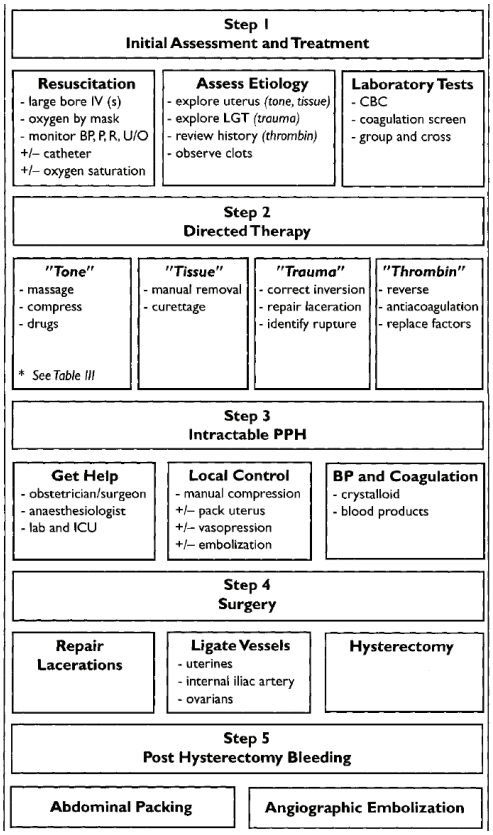


Table 5: Treatment of Postpartum Hemorrhage.

Initial assessment and treatment for primary PPH		Assess etiology	Directed therapy	If bleeding continues	If bleeding continues	If bleeding continues
Call for help Resuscitation • Assess the "ABC" • Oxygen by mask • IV line • Crystalloid, isotonic fluid replacement • Monitor BP, P, R • Empty bladder, monitor urine output Laboratory tests • Complete blood count • Coagulation screen • Blood grouping and cross	Uterus soft and relaxed	Uterine atony	Uterine massage Uterotonic drugs	Nonsurgical uterine compression • Bimanual uterine compression • External aortic compression • Uterine packing • Balloon (condom) tamponade	Compression sutures • B-Lynch • Vertical compression • Cho square Uterine artery embolization	Artery ligation (uterine, hypogastric) Hysterectomy (subtotal or total)
	Placenta not separated or partially separated (with or without hemorrhage)	Retained placenta	Whole placenta in uterus • Uterotonics • Controlled cord traction • Intraumbilical vein injection	Placenta still retained Manual removal	Placenta still retained (placenta accreta) Partial or complete removal of placenta through laparotomy Hysterectomy	
			Incomplete separation • Manual vacuum aspiration • Manual exploration • Gentle curettage		Hysterectomy	
	Excess bleeding or shock shortly after birth, uterus contracted	Low genital tract trauma	→ Repair tears in perineum, vagina and cervix			
		Uterine rupture	→ Laparotomy: • Primary repair • Hysterectomy			
	Uterine fundus not felt abdominally OR visible vaginally	Uterine inversion	→ Correct inversion in theatre under general anaesthesia	If nonsurgical correction fails, ensure that uterus remains contracted by continued oxytocin infusion	Surgery Correction via laparotomy Hysterectomy	
		Clotting	Clotting disorder • Treat accordingly with blood products			

Adapted with permission of the World Health Organization from Postpartum Hemorrhage Technical Consultation Meeting Document[55]

Adapted from SOGC Clinical Practice Guideline, No. 235 October 2009.

Uterine Inversion

- Often iatrogenic
- More common in grand multiparous women with fundal placenta
- Placenta appears at introitus with a mass attached
- Patient may experience shock due to bradycardia caused by increased vagal tone
- Replacement of uterus should be promptly performed without removing placenta
- Uterine relaxation may help replace uterus (nitroglycerin)
- May need laparotomy if all else fails

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Abnormal Labour and Delivery & Obstetrical Complications - Part I

Abnormal Labour and Delivery & Obstetrical Complications I Objectives:

At the end of the seminar, students should be able to:

Dystocia:

1. Recognize abnormal patterns of labour and classify them as to whether they are protraction or arrest disorders, in descent or dilatation, and in the latent, or active phase of labour.
2. List the causes of abnormal labour.
3. List methods in the prevention of dystocia.
4. Describe the factors important in the evaluation of the patient with abnormal labour.
5. List the indications and contraindications of oxytocin administration.
6. List the indications for operative vaginal delivery and the prerequisites for the application of forceps or a vacuum extractor.
7. List the indications for Caesarean Section (CS).
8. Discuss the use of analgesic and anaesthetic techniques in cases of abnormal labour or operative delivery.

Trial of Labour After CS (TOLAC) and Uterine Rupture:

1. Recognize that pregnant women with a previous CS require consultation with an obstetrician.
2. Describe the patients who are appropriate for trial of labour after Caesarean Section (TOLAC) and compare the advantages and risks of repeat Caesarean section (elective and after trial of labour) with TOLAC.
3. List the absolute contraindications to trial of labour after Caesarean Section.

Induction of Labour and Postterm Pregnancy:

1. List indications for induction of labour.
2. Outline options for induction of labour.
3. Discuss the risks and benefits of labour induction.
4. Define postterm pregnancy.
5. Describe the accuracy of methods for gestation dating, using available clinical data, physical examination and ancillary tools.
6. Outline the options for management of the post-term pregnancy.

Last revised: July 2019

DYSTOCIA

Dystocia is a Greek word signifying abnormal labour or difficult childbirth. Currently, dystocia is given a more practical and functional definition to describe abnormal progression of cervical dilatation and/or fetal descent during labour. Other terms have been used such as cephalopelvic disproportion which came to use prior to the 20th century to describe obstructed labour due to disparity between size of fetal head and maternal pelvis at a time when the main indication for CS was pelvic contracture due to rickets. Failure to progress has become more popular and refers to ineffectual labour. Neither of these terms is considered precise and thus dystocia, with the definition presented below, is more appropriate.

Definition of Dystocia

- In the active phase of the first stage: traditionally >4 hours of < 0.5cm/hour cervical dilatation, although recently can define dystocia as no progress in 4 hours of adequate contractions
- In the second stage: >1 hour with no fetal descent during active pushing

Labour is defined as the presence of uterine activity resulting in progressive effacement and dilatation of the cervix and descent of the fetus. The onset of labour usually begins with the latent phase and its onset is often difficult to define. Traditionally, the latent phase is complete and the active phase begins when a primiparous woman reaches 3-4 cms and a multiparous woman reaches 4-5 cms. Recently, in accordance with recommendations in the literature to safely prevent the primary CS, many obstetricians are now using 6 cm dilated as the definition of active phase labour. A diagnosis of dystocia should not be made in the latent phase of labour. In fact, investigators have found that 75% of women progress at >1 cm/hr after 3 cm dilatation and after 5 cm of dilatation, 90% of women progress at >1 cm/hr. Based on these findings, it is recommended not to make a diagnosis of dystocia when cervical dilatation is less than 6 cm.

The other important point regarding dystocia is that a certain amount of time must elapse before you should make this diagnosis. At least 4 hours between cervical examinations is required to confirm that progress is non-existent or less than 0.5cm/hr.

Abnormal Labour Patterns

1. **Primary abnormal progression in labour** – protraction
2. **Secondary arrest in dilatation** – adequate progress of labour followed by an arrest of dilatation in the first stage of labour; may be associated with occiput posterior position
3. **Secondary arrest in descent** – second stage of labour as fetus fails to descend particularly with maternal expulsive effort.

Etiology of Dystocia: The 4 P's

1. **Power**
    - Contractions may be hypotonic or incoordinate
    - Maternal expulsive efforts may be inadequate
2. **Passenger**
    - Fetal position

- Fetal attitude
- Fetal size
- Fetal anomalies (hydrocephalus)

3. **Passage**
    - Pelvic structure
    - Soft tissue obstruction (tumors, full bladder/full rectum, vaginal septum)
4. **Psyche**
    - Anxiety
    - Stress
    - Pain

Methods of Prevention of Dystocia

- Ensure adequate patient education about labour
- Use strict criteria for diagnosis of labour and non-progressive labour
- Pregnant women should not be admitted until active labour established, or at least 3-4 cm for a primip and 4-5 cm for a multip
- Have a plan to deal with the needs of women with a prolonged latent phase who are in pain but not in active labour
- Provide a supportive companion during labour, which results in faster progress of labour
- Have one-to-one nurse during labour
- Maintain ambulation and upright position in labour as much as possible
- Maintain adequate hydration
- Manage non-progressive active labour with rupture of membranes and oxytocin

Important Factors in the Evaluation of the Patient with Abnormal Labour

1. **Review the labour record**
2. **Assess maternal status**
    - Vitals
    - Pain management
    - Contraction pattern
    - Membranes: intact vs ruptured
    - Cervical dilatation and effacement
    - Pelvic architecture
3. **Assess fetal status**
    - Fetal heart
    - Fetal station
    - Fetal presentation and position
4. **Determine best course of action**
    - If membranes are not ruptured then perform Artificial Rupture of Membranes (ARM)
    - Offer pain relief: endogenous catecholamines can inhibit uterine contractility
    - Ensure adequate hydration
    - Oxytocin infusion to improve uterine contractility
    - If all the above tried consider operative delivery (i.e. CS or assisted vaginal birth if fully dilated)

Indications and Contraindications of Oxytocin Administration

Oxytocin is used to improve inadequate contractions when dystocia is diagnosed or to initiate contractions when labour induction is required.

Contraindications:

- Severe vaginal bleeding
- Placenta previa
- Hypotension
- Abnormal lie (transverse, footling breech)
- Prior classical or inverted-T uterine incision
- Pelvic structural deformities which would lead to obstructed labour

Adverse Effects:

- Fetal compromise from uterine hyperstimulation caused by hypertonic contractions (lasting > 2 min) or tachysystolic contractions (>5 contractions/10 min)
- Uterine rupture (especially with history of previous CS, hyperstimulation)
- Water intoxication (dilutional hyponatremia caused by its anti-diuretic hormone effects)
- Hypotension (vasodilatation)

Example of protocol for use of oxytocin for augmentation of labour (different protocols may be used):

- Initial dose: 1 – 2 mU/min
- Increase Interval: every 30 min
- Dosage Increment: 1 – 2 mU/min
- Average Dose for adequate labour: 6 mU/min, but may vary

ASSISTED VAGINAL BIRTH AND OPERATIVE DELIVERY

Indications for Assisted Vaginal Birth (Forceps or Vacuum Extractor) (Table 1):

Fetal	Maternal
• Evidence of fetal compromise requiring immediate delivery	• Failure to deliver spontaneously in the second stage • Conditions which require a shortened second stage • Conditions which contraindicate pushing • Inefficient maternal effort

Note: Whatever the indication, it is important that the indication is clear, well understood by the woman (and partner), and fully documented. The indications for forceps and vacuum are similar but forceps are more useful in correcting a sub-optimal attitude or position of the fetal head and can be used to apply rotational forces (ex. rotate the head from LOP to LOA). The vacuum extractor should not be regarded as an easier alternative to forceps, or for use by less skilled operators. The vacuum extractor is designed to produce traction upon the fetal scalp in order to assist maternal expulsive effort. It is not device for applying rotational forces nor is it likely to succeed in the absence of maternal expulsive effort. The vacuum may be used judiciously to correct attitude (deflexion) if it is properly applied and if traction is correctly utilized.

Contraindications for operative delivery (forceps or vacuum):

- Non-cephalic presentation, face or brow
- Unengaged head (above spines 0)
- Incompletely dilated cervix
- Low probability of success

Contraindications specific to cacuum:

- <34 weeks' gestation
- Deflexed attitude of fetal head
- Need for rotation
- Fetal conditions (bleeding disorder, demineralization disorder)

Prerequisites for application of vacuum extractor or forceps:

- Informed consent
- Vertex presentation
- Vertex engaged
- Term or near term fetus
- Cervix fully dilated
- Membranes ruptured
- Adequate anesthesia
- Adequate maternal pelvis by clinical assessment
- Care provider aware of fetal station and position
- Maternal bladder empty
- Backup plan (if forceps or vacuum not successful may need CS)
- Ongoing fetal and maternal assessment

Risks of Assisted Vaginal Birth:

- Maternal soft tissue trauma
- Fetal scalp trauma (hemorrhage, laceration)
- Increased risk of intraventricular hemorrhage with multiple procedures
- Fetal subgaleal or subaponeurotic hemorrhage with vacuum

Note: The suture lines of the skull do not limit hemorrhage into the subaponeurotic (subgaleal) space as they do in cephalohematoma. As a result, subgaleal hemorrhages can extend from the brow ridge to the nuchal ridge, and from ear to ear, covering the entire calvarium, with a potential volume of several hundred milliliters. This volume loss can produce profound, irreversible hypovolemic damage to the neonate and can be lethal. Subgaleal hemorrhage occurs in approximately 4 in 10,000 normal spontaneous deliveries and in 59 in 10,000 vacuum extractions. After every vacuum delivery, there should be surveillance of the neonate to ensure that the expected swelling on the head does not enlarge significantly and that there is no evidence of developing hypovolemia. Also, the widely accepted practice of using the vacuum extractor to move the fetal vertex from the mid-pelvis to the low pelvis and then applying forceps to complete the delivery if the vacuum is unsuccessful, must be re-evaluated. Any combination of forceps, vacuum and CS increases the risk of intraventricular hemorrhage.

Caesarean Delivery

Caesarean delivery (CS) refers to birth of the fetus from the uterine and abdominal wall.

Most Common Indications:

- Repeat Caesarean Section
- Dystocia
- Breech presentation and other malpresentations
- Non-reassuring fetal status

Absolute Indications:

- Placenta Previa
- Cord Prolapse
- Previous Uterine Surgery
- Previous Classical CS
- Previous Uterine Rupture
- Malpresentation (breech, transverse, brow)
- Obstructed pelvis (mass, contracted)

Relative Indications:

- Failed Induction
- Abnormal progression in labour
- Pre-eclampsia/eclampsia
- Diabetes
- Cardiac disease
- Placental abruption
- Multiple Pregnancy

Types of Incisions on Uterus

- Transverse lower uterine segment incision
- Classical vertical uterine incision
- Combination of above (inverted T incision)

Risks of CS

- Infection (wound, uterine, sepsis, urinary)
- Hemorrhage
- Atelectasis
- Injury to bowel or bladder or ureter
- Deep venous thrombosis
- Pulmonary embolus
- Longer recovery time
- Uterine rupture in future pregnancy

Most of these risks increase if the CS follows a trial of labour which was unsuccessful.

Analgesic and Anesthetic Techniques in Labour and Birth

Patients who reach the limit of their pain tolerance during labour may either request and/or be offered both nonpharmocologic and pharmacologic pain relief. Patients experiencing excessive pain or anxiety can develop high levels of endogenous catecholamines which have a direct inhibitory effect on uterine contractility and may lead to poor progress of labour. In some cases, a vicious circle develops of poor uterine progress leading to increased anxiety leading to increased catecholamines leading to further impairment of progress. The relief of pain by effective analgesia may allow endogenous catecholamine levels to decrease and improve uterine contractility. However, it is important to note that not all women will want or request pain control during labour.

Successful control of pain in labour does not just involve administering the best anesthetic agent available in a timely fashion. Pain management should begin with appropriate prenatal education and counselling. Measures to enhance comfort and reduce apprehension are required for the care of all women in labour.

I. Non-pharmacologic Pain Relief Techniques:

1. *Reduction of painful stimuli:*
    - Maternal movement and position change
    - Counter-pressure
    - Abdominal decompression
2. *Activation of peripheral sensory receptors*
    - Superficial heat and cold
    - Immersion in water during labour
    - Touch and massage
    - Acupuncture and acupressure
    - Transcutaneous electrical nerve stimulation (TENS)
    - Intradermal injection of sterile water
    - Aromatherapy
3. *Enhancement of descending inhibitory pathways:*
    - Attention focusing and distraction
    - Hypnosis and self-hypnosis
    - Music and audio analgesia
    - Biofeedback

II. Pharmacologic Methods of Pain Relief:

1. *Nitrous Oxide*
    - Entonox is self-administered. Deep inhalation begins as the woman is aware of the onset of a contraction. Useful in latter part of first stage of labour. Patient must self-administer via mask so that if a decrease level of consciousness occurs, the mask will naturally be dropped by the patient and control against overdose.
2. *Narcotics*
    - Can be given intravenously and with PCA pumps
    - Usually combined with anti-emetic
    - Decrease fetal heart rate variability
    - Cause neonatal respiratory depression (reverse with naloxone given to newborn)
3. *Peripheral Nerve Blocks – Pudendal Nerve Block*
    - Used for analgesia of perineum in second stage
    - Useful when other regional analgesia is not available or ineffective
4. *Perineal Infiltration* – especially for repair of perineal and vaginal tears
5. *Regional Anaesthesia* – Epidural Block

Epidural block can provide effective pain relief throughout all stages of labour and delivery. Effective pain relief decreases endogenous catecholamines and lowers epinephrine concentrations resulting in improved uterine contractions and possibly placental perfusion. Epidural analgesia can be beneficial to women with dystocia secondary to hypotonic contractions whose labour will require augmentation with oxytocin. Provision of more effective pain relief facilitates the use of the most appropriate oxytocin dosage to improve labour progress.

Epidural has been reported in some studies to have a negative effect on labour progress and to increase operative delivery rates but confounders which bias these studies exist. High dose motor block epidurals may lead to prolongation of the second stage due to: (1) blockage of natural increase in oxytocin in the second stage leading to infrequent and ineffectual contractions, and (2) paralysis of pelvic floor musculature resulting in persistent fetal head malposition. Discontinuing an epidural in the second stage to allow effective pushing is disadvantageous. The sudden return of pain may cause distress and distract the woman, possibly leading to ineffective pushing.

A pudendal nerve block or epidural block is necessary for adequate analgesia at the time of a vacuum or forceps assisted birth. A spinal block, epidural block or general anaesthetic is necessary for adequate analgesia during a Caesarean delivery. Regional methods are preferred over a general anaesthetic for Caesarean delivery since general anaesthesia presents more risks for the pregnant woman (aspiration).

TRIAL OF LABOUR AFTER CAESAREAN SECTION (TOLAC) AND UTERINE RUPTURE

All pregnant women who have had a previous CS require a consultation with an obstetrician, preferably in the late second or early third trimester. Most women will be appropriate for a trial of labour after Caesarean Section and usually are counseled against it if there are any absolute contraindications as listed below. The most severe complication of a trial of labour after CS is uterine rupture due to separation of the previous uterine scar during labour. Uterine rupture can have disastrous consequences including need for hysterectomy, fetal asphyxia, fetal death, maternal hemorrhage and maternal death.

Absolute Contraindications to a trial of labour after CS

- Previous classical, inverted-T, or unknown incision with high likelihood of classical or inverted-T incision (e.g severely preterm CS)
- Other uterine surgeries entering the uterine cavity (e.g. myomectomy)
- Previous history of uterine rupture
- Opinion of previous surgeon (important to get CS operative note)
- Woman desires a repeat CS
- Absolute contraindications to vaginal delivery in general (e.g. placenta previa)

Relative Contraindications to a trial of labour after CS

- Unknown incision, but reasonable to assume a transverse lower uterine segment incision was used
- If induction required (increases risks of uterine rupture)
- Two or more previous lower segment CS scars
- Multiple pregnancy
- Breech presentation
- Previous poor obstetrical history
- Patient desires a tubal sterilization

It is important to start discussion early with the patient about the options for delivery and the risks and benefits of a TOLAC versus elective repeat CS.

Risks of Trial of Labour after Caesarean Section

- Prolonged labour
- Maternal fever and infection
- Failed trial necessitating a repeat CS: risks of a CS done after a failed trial of labour of CS are higher when compared with an elective CS including infection, bleeding, trauma etc.
- Uterine rupture: with increased risk of maternal hemorrhage, fetal morbidity and mortality, possible need for Caesarean hysterectomy and ultimate loss of fertility

Benefit of successful Vaginal Birth after C-Section (VBAC)

- Reduced intervention and their risks (overall less morbidity and mortality for mother and baby)
- Faster recovery

Risks of elective repeat CS

- Increased risk (compared with primary CS) of injury to bowel, bladder, ureter due to scarring from previous surgery
- Increased risk of hemorrhage due to scarring
- All other risks as previously listed

Uterine Rupture

The risk of **uterine rupture** during a trial of labour after CS is about 1-9 cases per 1,000. The risk increases considerably when induction of labour is required and with high dose oxytocin. Usually one of the first signs of uterine rupture is a profound fetal bradycardia with no recovery and constant lower abdominal pain in the mother.

If the woman has an epidural for pain relief, the pain may not be experienced. Other signs and symptoms include: cessation of uterine contractions, vaginal bleeding, recession of the presenting part on vaginal examination (fetus may be extruded into the peritoneal cavity through the uterine incision), palpation of fetal parts by abdominal exam, a surgical abdomen, and hypovolemic shock.

Although a previous uterine scar is the most common reason for uterine rupture in our society, there are other causes.

Causes of Uterine Rupture

- Uterine Scar: CS, myomectomy, previous uterine perforation during D&C, salpingectomy with cornual resection
- Excessive Uterine Action: Oxytocin, prostaglandins, neglected obstructed labour
- Trauma: External cephalic version, forceps, manual removal of placenta, trauma (motor vehicle, accident, assault)
- Miscellaneous: multiparity, uterine anomalies, placenta accreta

Management of Uterine Rupture:

- Stabilize mother and treat hypovolemia
- Call for assistance – nursing, pediatrician, anaesthesia, respiratory therapist.
- Emergency laparotomy to deliver fetus, placenta and repair uterus.

INDUCTION OF LABOUR AND POST-TERM PREGNANCY

Induction of labour is the initiation of contractions in a pregnant woman who is not in labour.

Indications for Induction of Labour (Table 2):

Emergent	Urgent	Non-urgent:
• Severe gestational hypertension/pre-eclampsia • Suspected fetal compromise • Severe intra-uterine growth restriction • Maternal disease • Significant antepartum hemorrhage • Chorioamnionitis	• Prelabour rupture of membranes (PROM) • Intrauterine growth restriction with no acute compromise • Poorly controlled diabetes • Isoimmunization	• Prolonged pregnancy • Well controlled diabetes • Prior intrauterine death • Logistical problems (previous rapid labour, lives in remote area)

Contraindications to Induction

- Placenta previa, vasa previa, cord presentation
- Abnormal fetal lie
- Prior classical CS scar or inverted T incision
- Uterine surgery
- Active genital herpes
- Pelvic structural deformities
- Invasive cervical cancer

Risks of Induction

- Failure to achieve labour
- Failure to achieve a vaginal birth
- Cord prolapse with ARM
- Uterine hyperstimulation with fetal compromise
- Uterine hyperstimulation with uterine rupture
- Inadvertent delivery of preterm infant in the case of inaccurate dating assessment
- Maternal side-effects to medications

Note: whatever the indication, ensure that the risk of continuing the pregnancy exceeds the risk associated with induction of labour.

Phases of Induction of labour

1. Cervical Ripening
    - A method to make the cervix more "receptive" to induction, and therefore decrease the risk of failure and need for CS
    - Required when the Bishop score is < 6

Table 3:

	SCORE			
	0	1	2	3
Position	Posterior	Middle	Anterior	
Consistency	Firm	Medium	Soft	
Effacement	0-30%	40-50%	60-70%	80-100%
Dilation	Closed	1-2 cm	3-4 cm	5-6 cm
Station	-3 or higher	-2	-1 to 0	+1 to +2

    - Techniques:
        - Mechanical
            - Intrauterine Foley Catheter
            - Intracervical Dilators (laminaria, dilapan)
        - Medical
            - Prostaglandins (Prostin gel, Cervidil vaginal insert)
2. Induction
    - Once the cervix is favourable (Bishop score > 6) ARM and consider oxytocin

POSTTERM PREGNANCY (PROLONGED PREGNANCY)

A pregnancy has traditionally been considered **post-term** at >42+0 weeks gestation, as it was at this gestational age that the risk of adverse fetal and neonatal outcome, especially risk of perinatal death, increased.

Incidence of pregnancies completing:

- 41 weeks: 27%
- 42 weeks: 4-14%
- 43 weeks: 2-7%

Significance

Postterm pregnancies are at higher risk than term pregnancies of perinatal death (antepartum, intrapartum, and postpartum) due to anomalies (e.g. anencephaly), intrauterine infection, placental dysfunction and asphyxia with and without meconium. Post term pregnancies are also at a higher risk of neonatal morbidity (e.g. macrosomia, shoulder dystocia, meconium aspiration syndrome, admission to NICU, need for oxygen, intubation, pneumonia, and seizures). Postterm pregnancies are more likely to have a higher rate of induced labour, fetal non-reassuring tracing in labour, meconium staining of the amniotic fluid, and operative delivery than term pregnancies.

Do not confuse postterm with post-mature (refers to appearance of neonate: wrinkled patchy peeling skin, long thin body, alert, wisened, worried look, long nails, wrinkled palms and soles) or postdates (>41+0 weeks gestation). The goal of postdates induction of labour is the prevention of post-term pregnancy with its associated increased perinatal morbidity, mortality and operative delivery rates.

Management

1. Ensure that accurate gestational age is established (make sure to do early ultrasound)
2. No evidence for routinely initiating serial fetal monitoring prior to 41 weeks
3. After 41 weeks gestation, offer women either induction of labour or serial fetal monitoring
4. If induction selected, follow protocol above for induction of labour

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5. American College of Obstetricians and Gynecologists; Society for Maternal-Fetal Medicine. Obstetric care consensus no. 1: safe prevention of the primary cesarean delivery. Obstet Gynecol. 2014 Mar;123(3):693-711.



Abnormal Labour and Delivery & Obstetrical Complications - Part II

Abnormal Labour and Delivery & Obstetrical Complications II Objectives:

At the end of the seminar, students should be able to:

Breech Presentation:

1. Understand the etiology of breech presentation.
2. Understand the current options for management of breech presentation.
3. Discuss the risks and benefits of these options.

Shoulder Dystocia:

1. Describe the risk factors for and clinical presentation of shoulder dystocia and list the maneuvers needed for successful delivery in cases of shoulder dystocia.
2. List the maternal and fetal risks of shoulder dystocia.
3. Discuss the options for managing future pregnancies in a woman with previous shoulder dystocia.

Abnormal Fetal Status:

1. Identify the pregnancies where acute or chronic fetal distress is more likely to occur.
2. Describe the features of the biophysical profile score, which would indicate chronic hypoxia.
3. Describe the cord blood gas pattern in an asphyxiated fetus, both respiratory and metabolic.
4. Define abnormal variability and deceleration patterns in the fetal heart tracing.
5. Outline management of a patient with a fetus with an abnormal tracing.
6. Discuss the significance of meconium stained amniotic fluid.

Cord Prolapse:

1. Describe the risk factors and clinical presentation of cord prolapse.
2. Outline the management of a patient with recognized cord prolapse.

Last revised: July 2019

BREECH PRESENTATION

Etiology of Breech Presentation

Breech presentation occurs in 3 to 4% of all pregnant women reaching term. Factors, which appear to predispose to breech presentation, include uterine relaxation associated with great parity, multiple fetuses, polyhydramnios, oligohydramnios, hydrocephalus, anencephalus, previous breech delivery, uterine anomalies, and pelvic tumours such as fibroids.

There are different categories of breech presentation depending on whether or not the hips and knees are flexed. With a frank breech, the hips are flexed and the knees are extended so that the buttocks present at the cervix and the feet are near the head. With a complete breech, both the knees and hips are flexed. With an incomplete breech, one or both hips are not flexed, so that one or both feet or knees lie below the buttocks (i.e. feet or knee presents - footling breech, kneeling breech). It was generally felt that frank breeches had the best chance of delivering vaginally safely with incomplete breeches being more likely to experience birth trauma and death from the head not delivering.

Significance of Breech Presentation

In the presence of breech presentation, an increased frequency of the following complications can be anticipated when compared with a cephalic presentation:

1. Perinatal morbidity and mortality from birth trauma/asphyxia (related to head entrapment)
2. Low birth weight from preterm delivery and/or growth restriction
3. Prolapsed cord
4. Placenta previa
5. Fetal, neonatal, and infant anomalies
6. Uterine anomalies and tumours
7. Multiple fetuses
8. Operative intervention, especially Caesarean delivery

Rationale for head entrapment in breech presentation:

When the fetus is presenting in the cephalic, molding, shaping, and overlapping of the sutures of the fetal head occurs gradually over several hours during the labour process potentially allowing for a better fit through the maternal pelvic canal. After delivery of the head, the fetal body and buttocks usually follow quite easily as these body parts are smaller and softer. When the fetus is presenting breech, the fetal buttocks lead the way and tend to be less effective in making room in the pelvic canal for the relatively larger and harder head. With the buttocks coming first, the head has little opportunity to mold and shape to the maternal pelvis. Despite this situation, many breech babies have been born safely by the vaginal route. Frank breeches are better dilators of the cervix and expanders of the birth canal whereas, incomplete breeches, presenting with the feet and/or knees are less able to provide room for the after-coming head.

Management of Breech Presentation

It is important to recognize and confirm breech presentation at 35-36 weeks' gestation so that there is adequate time to have a discussion about the options for management and be able to offer these options in a timely fashion.

One option is to offer the woman an **External Cephalic Version (ECV)**, a procedure in which a fetus is turned in-utero from non-cephalic to cephalic presentation. This is ideally after 36 weeks' gestation because spontaneous version often occurs by 36 weeks, and after ECV, it is uncommon to turn back to breech after 36 weeks. Additionally, if there is a complication requiring immediate delivery, timing of ECV at 36 weeks will prevent too premature of a delivery. Risks of ECV include intrauterine death secondary to a cord accident, feto-maternal hemorrhage (rare), abruption, rupture of membranes, labour, fetal bradycardia necessitating immediate Caesarean delivery (< 1% risk), and alloimmunization (if mother Rh negative, Rhogam will be required when ECV done). Absolute contraindications to ECV include antepartum hemorrhage within 7 days, major uterine anomaly, non-reassuring fetal status, ruptured membranes, and any other contraindications for a vaginal delivery. Relative contraindications include oligohydramnios, major fetal anomalies, intrauterine growth restriction with abnormal Doppler assessment.

Another option for delivery is a planned lower segment Caesarean Section in the event of an unsuccessful ECV, and/or when contraindications to a trial of vaginal breech birth are present. This option became very popular when the results of the Term Breech Trial were published (a multi-centered RCT which compared outcomes in planned vaginal breech delivery versus planned Caesarean Section). The interim analysis of the results showed a significant difference in adverse neonatal outcomes in the planned vaginal delivery arm of the trial (5%) compared to those for planned CS (1.6%). As a result, the trial was terminated (The Lancet, Vol. 356, October 21, 2000). This trial had a dramatic change in practice such that many obstetricians in Canada (possibly North America) abandoned the option of trial of vaginal birth and recommended a planned Caesarean delivery in all cases of breech presentation.

A publication of SOGC Clinical Practice Guidelines in the JOGC, 2009, 31(6):557-66 stirred up the controversy once again between elective CS and trial of vaginal birth for breech presentation, encouraging intrapartum maternity care providers to offer a trial of vaginal breech birth to women with breech presentation. Based on a Medline search for RCTs, prospective cohort studies and selected retrospective cohort studies comparing planned CS with a planned trial of labour, the authors conclude the following:

1. Vaginal breech birth can be associated with a higher risk of perinatal mortality and short-term neonatal morbidity (such as seizures) than elective CS but long-term neurological infant outcomes do not differ by planned mode of delivery even in the presence of serious short-term morbidity.
2. Careful selection and labour management in a modern obstetrical setting may achieve a level of safety in vaginal breech birth similar to elective CS
3. With careful case selection and labour management, perinatal mortality occurs in approximately 2 per 1000 births and serious short-term neonatal morbidity in approximately 2% of breech infants born vaginally.

Labour Selection Criteria for Breech Presentation

All options available for management of a breech baby near term are best discussed with the mother prior to the onset of labour. Make a point of clearly establishing the fetal presentation by 35-36 weeks' gestation so that no breech baby goes unrecognized. If in doubt, send the woman for an ultrasound scan. Recognizing a breech presentation by this stage allows the health care provider and pregnant woman to calmly and thoroughly discuss all options, risks and benefits and develop a plan should the fetus remain in the breech presentation.

1. Do a pre- or early labour ultrasound to assess type of breech presentation, estimated fetal weight (EFW), attitude of fetal head (flexion preferred). Do CS if ultrasound not available.
2. Labour is contraindicated if:
    - Cord presentation
    - Fetal growth restriction
    - Macrosomia
    - Any presentation *other than* frank or complete
    - Inadequate maternal pelvis
    - Fetal anomaly incompatible with vaginal delivery (e.g. hydrocephalus)
    - Pregnant woman refuses a trial of vaginal breech birth (you may not find this criteria in the literature)
3. Vaginal breech delivery can be offered when the EFW is between 2500 g and 4000 g.
4. Labour management:
    - Check maternal pelvis for any abnormal pelvic contraction
    - Good labour progress is best indicator that there is adequate room for fetus
    - Continuous fetal monitoring preferred
    - Check for prolapsed cord when membranes ruptured
    - CS advised if labour progress is inadequate
    - Induction of labour not recommended
    - Oxytocin augmentation of labour is acceptable if contractions are infrequent or weak
    - Active second stage (i.e. patient pushing) should be done near an operating room with equipment and personnel ready to perform a CS
    - Health care provider for the planned vaginal breech birth needs to possess the requisite skills and experience
    - A health care professional skilled in neonatal resuscitation should be in attendance for delivery and should have a rehearsed plan of action should the after-coming head be trapped or nuchal arms are irreducible (fetal arms stuck behind the head)
    - Once active pushing occurs, if delivery is not imminent after 60 min, a CS is recommended

Whichever option a woman chooses in consultation with her health care provider, she must be fully informed of the risks and benefits of all options: ECV, Trial of Vaginal Birth, Planned CS.

SHOULDER DYSTOCIA

Shoulder dystocia: impaction of anterior shoulder above symphysis in the antero-posterior diameter, so that the remainder of the body cannot be delivered in the usual manner. The head may be tight against the maternal buttocks, known as the "Turtle Sign".

Incidence

1/1000 in babies < 3500 g
16/1000 in babies > 4000 g

Risk Factors for Shoulder Dystocia

- Post-term pregnancy
- Maternal obesity
- Fetal macrosomia
- Previous shoulder dystocia
- Operative vaginal delivery
- Prolonged labour
- Poorly controlled diabetes

Complications (Table 1)

Maternal	Fetal
• Postpartum hemorrhage • Uterine atony • Maternal lacerations • Uterine rupture	• Birth Injuries: • Fractures – clavicle, humerus • Brachial plexus palsy (extreme lateral traction on head, C5, C6 level; forearm flexors and supinators affected; therefore arm will be extended and pronated – Erb's palsy) • Hypoxic ischemic encephalopathy (HIE) and other sequelae • Death

Maneuvers for a Successful Delivery

Use the ALARMER pneumonic:

A Ask for help
L Lift/Hyperflex legs (McRobert's)
A Anterior shoulder dis-impaction:
Suprapubic pressure: Mazzanti
Vaginal shoulder pressure: Rubin
R Rotation of the posterior shoulder (Woods' corkscrew maneuver
M Manual removal/delivery of posterior arm
E Episiotomy
R Roll over on all fours

If none of this has resulted in delivery of the fetus, other suggestions:

- Deliberate fracture of clavicle
- Symphysiotomy
- Zavanelli maneuver (replace fetus in uterus and proceed to CS)

DO NOT:

- Pull (on the head)
- Push (on the fundus)
- Panic
- Pivot (severely angulate the head using coccyx as a fulcrum)

Note: Always document the severity of the shoulder dystocia, the maneuvers necessary to deliver fetus, and whether or not you would recommend a future vaginal delivery.

Management of Future Pregnancies

Discuss options with patient. Review notes from previous delivery. If previous delivery resulted in a severely affected infant, chances are an elective CS would probably be best decision. Risks and benefits of either a trial of vaginal birth or elective CS should be discussed.

ASSESSMENT OF FETAL WELL BEING IN LABOUR

Uterine contractions during labour decrease utero-placental blood flow, which results in reduced oxygen delivery to the fetus. Most fetuses tolerate this reduction of flow and have no adverse effect and a review of a fetal tracing will demonstrate a normal baseline, adequate variability, accelerations and no decelerations.

The distribution of oxygen to the fetus depends on the delivery of oxygen from maternal lungs to the uterus and placenta, diffusion from the placenta to fetal blood and distribution of fetal blood to various fetal tissues through fetal cardiovascular activities. Disturbances in any of these 3 steps will reduce availability of oxygen to the fetus and may result in an *abnormal* fetal tracing (previously "non-reassuring" – you may still hear this term being used as it is difficult to unlearn old nomenclature).

Maternal factors:

1. Decreased maternal oxygen carrying capability:
    - Significant anemia
    - Carboxyhemoglobin (smokers)
2. Decreased uterine blood flow:
    - Hypotension
    - Regional anesthesia
    - Maternal positioning
3. Chronic maternal conditions
    - Vasculopathies (SLE, Type 1 Diabetes Mellitus, chronic hypertension)
    - Antiphospholipid antibody syndrome

Utero-placental factors:

1. Uterine hypertonus
    - Hyperstimulation due to oxytocin, prostaglandins, normal labour
    - Placental abruption
2. Uteroplacental dysfunction
    - Placental abruption
    - Placental infarction/dysfunction marked by oligohydramnios or abnormal Doppler studies
    - Chorioamnionitis

Fetal factors:

- Cord compression
- Oligohydramnios
- Cord prolapse or entanglement
- Decreased fetal oxygen carrying capability
- Significant anemia (isoimmunization, fetomaternal bleed)
- Carboxyhemoglobin

When the fetus is recognized to have an abnormal fetal tracing, it is not appropriate to declare that the fetus is in "distress" (another outdated word) as the fetal condition cannot be completely assessed until birth. Fetal asphyxia, which correlates with permanent sequelae, must have all the components as listed below.

Definition of the Intrapartum Fetal Asphyxia (all must be present)

- Apgar score 0 to 3 for > 5 minutes
- Neonatal neurologic sequelae (hypotonia, seizures, coma)
- Evidence of multi-organ system dysfunction in the immediate neonatal period
- Umbilical cord arterial pH < 7.0 and base deficit > 16 mmol/L

Note: A low umbilical artery pH by itself does not define asphyxia. All the criteria above should be present to correlate birth hypoxia and adverse neurologic outcome.

Interpretation of Results

Respiratory and metabolic acidosis have different pathogenesis and clinical significance. Respiratory acidosis develops rapidly and disappears following the first neonatal breaths. It is considered part of a normal delivery. Respiratory acidosis occurs in blood vessels and develops when interruption of blood flow occurs (e.g. cord compression) causing a decrease in CO_2 transport from the fetus to the placenta. Carbon dioxide accumulates and after reacting with water produces hydrogen ions and bicarbonate. When the hydrogen ions exceed the buffer capacity of the blood, they accumulate in the vessel causing decrease in pH.

Metabolic acidosis develops as a result of fetal hypoxia that causes the fetus to shift to anaerobic metabolism to maintain positive energy balance. Lactic acid is produced in the tissue and is dissociated to lactate and hydrogen ions. Some of the latter find their way to blood vessels, reducing the pH value.

Metabolic acidosis is generated in hypoxic tissues, takes longer to develop and disappear, and has the potential to cause significant fetal damage.

Types of Acidosis (decreased pH)

1. **Respiratory:** Increased PCO_2 and normal base deficit
2. **Metabolic:** Normal PCO_2 and decreased base deficit
3. **Mixed:** Increased PCO_2 and decreased base deficit

Abnormal Fetal Heart Rate Patterns

1. **Bradycardia (FHR < 110 bpm)**
    - Maternal hypotension
    - Drug effects
    - Maternal position
    - Umbilical cord occlusion
    - Fetal hypoxia
    - Fetal vagal stimulation (head compression)
    - Fetal hypothermia
    - Fetal acidosis
    - Fetal cardiac conduction or structural defect
2. **Tachycardia (FHR > 160 bpm)**
    - Maternal: fever, infection, dehydration, hyperthyroidism, anxiety, drugs, anemia
    - Fetal: infection, prolonged fetal activity, chronic hypoxemia, cardiac abnormality, congenital anomalies, anemia
3. **Early decelerations**
    - Gradual decrease and return to baseline in FHR
    - Nadir of deceleration occurs at same time as peak of the contraction
    - Reflex vagal response due to head compression; not normally associated with fetal acidemia
4. **Variable decelerations**
    - Abrupt decrease in FHR > 15 bpm below baseline for at least 15 sec but < 2 min
    - Abnormal variable decelerations if: <70 bpm, >60 sec, prolonged return to baseline, loss of variability in baseline FHR
    - Associated with vagal stimulation due to cord compression or head compression in 2nd stage
    - If abnormal variable decels, may be associated with fetal acidemia
5. **Late decelerations**
    - Gradual decrease and return to baseline FHR in association with uterine contraction
    - Onset, nadir, and recovery of the deceleration occurs after the beginning, peak and end of the contraction
    - Can occur with: altered maternal blood flow to placenta (maternal hypotension); reduced maternal oxygen saturation; placental insufficiency; uterine hypertonus; fetal acidemia

6. Abnormal Variability

- Baseline fetal heart rate variability is an important index of cardiovascular function and appears to be regulated by the autonomic nervous system. The baseline rate normally exhibits an oscillating form, reflective of beat-to-beat changes in rate which gives it varying degrees of irregularity when printed on graph paper. The beat-to-beat variability can be affected by a variety of physiologic mechanisms and the lack of it has considerably different meaning depending on the clinical setting.
- Usually proper assessment of variability requires fetal heart rate monitoring by internal scalp electrode. Decreased beat-to-beat variability is diagnosed when the fetal heart rate baseline is flat or nearly flat. Although decreased variability can be an ominous sign indicating a seriously compromised fetus, decreased variability in the absence of fetal decelerations is unlikely due to fetal hypoxia. Maternal acidemia (diabetic ketoacidosis) and analgesic drugs during labour can decrease variability. Variability tends to decrease with increasing fetal tachycardia.

Table 2: Classification of intrapartum EFM tracings.

	Normal Tracing Previously "Reassuring"	Atypical Tracing Previously "Non-reassuring"	Abnormal Tracing Previously "Non-reassuring"
Baseline	110–160 bpm	Bradycardia 100–110 bpm Tachycardia > 160 for > 30 min to < 80 min. Rising baseline	Bradycardia < 100 bpm Tachycardia > 160 for > 80 min. Erratic baseline
Variability	6–25 bpm ≤ 5 bpm for < 40 min.	≤ 5 bpm for 40–80 min.	≤ 5 bpm for > 80 min. ≥ 25 bpm for > 10 min. Sinusoidal
Decelerations	None or occasional uncomplicated variables or early decelerations	Repetitive (≥ 3) uncomplicated variable decelerations Occasional late decelerations Single prolonged deceleration > 2 min. but < 3 min.	Repetitive (≥ 3) complicated variables: deceleration to < 70 bpm for > 60 secs. loss of variability in trough or in baseline biphasic decelerations overshoots slow return to baseline baseline lower after deceleration baseline tachycardia or bradycardia Late decelerations > 50% of contractions Single prolonged deceleration > 3 min. but < 10 min.
Accelerations	Spontaneous accelerations present (FHR increases >15 bpm lasting > 15 seconds (< 32 weeks' gestation increase in the FHR > 10 bpm lasting >10 seconds) Accelerations present with fetal scalp stimulation	Absence of acceleration with fetal scalp stimulation	Usually absent*
ACTION	EFM may be interrupted for periods up to 30 min. if maternal-fetal condition stable and/or oxytocin infusion rate stable.	Further vigilant assessment required, especially when combined features present.	ACTION REQUIRED Review overall clinical situation, obtain scalp pH if appropriate/prepare for delivery.

*Usually absent, but if accelerations are present, this does not change the classification of tracing.

Adapted from SOGC Clinical Practice Guideline No. 197, September 2007.

The classification of electronic fetal monitoring tracings has been revised so that now the tracing is classified as **normal** (previously reassuring, atypical (previously non-reassuring), and **abnormal** (previously non-reassuring). A distinction is now being made between tracings which have some concerning changes but not requiring immediate action (**atypical**) versus tracings that have major concerns and require an immediate intervention **(abnormal)**.

General Principles of Managing an Abnormal Fetal Tracing

1. Reposition patient to increase uteroplacental perfusion or alleviate cord compression
2. Check maternal vitals
3. Correct maternal hypovolemia, if present, by increasing IV fluids
4. Stop oxytocin if applicable
5. Administer oxygen at 8 to 10 L/min
6. Rule out fever, dehydration, drug effect, prematurity
7. Initiate continuous fetal heart rate monitoring to clarify and document components of FHR
8. If external monitor already in place, consider applying an internal fetal scalp electrode
9. Consider fetal scalp sampling if appropriate
10. If abnormal findings persist despite corrective measures and other tests are not available (like fetal scalp pH) or desirable, the delivery should be considered

Fetal scalp blood sampling (FBS) - pH

Done in patients with abnormal FHR patterns (see Table 3)

If pH ≥ 7.25	• Continue with labour • FBS should be repeated if abnormality persists
If pH 7.21 – 7.24	• Continue with labour • Repeat FBS in 30 minutes or consider delivery if rapid fall since last sample
If pH ≤ 7.20	• Delivery is indicated

Fetal scalp blood sampling (FBS) – Lactate

In situations where intrapartum fetal monitoring is abnormal, fetal lactate levels can also be used to establish the fetal condition. Fetal scalp lactate level correlates well with umbilical artery lactate level.

Assessment of fetal lactate levels via fetal scalp sampling is becoming increasingly available.

Cut –off levels are as follows:

- Lactate <4.1 mmol/L normal
- Lactate 4.2 – 4.8 mmol/L preacidotic range – consider repeat within 30 minutes or delivery if significant deterioration
- Lactate >4.8 mmol/L acidosis – arrange of immediate emergent delivery

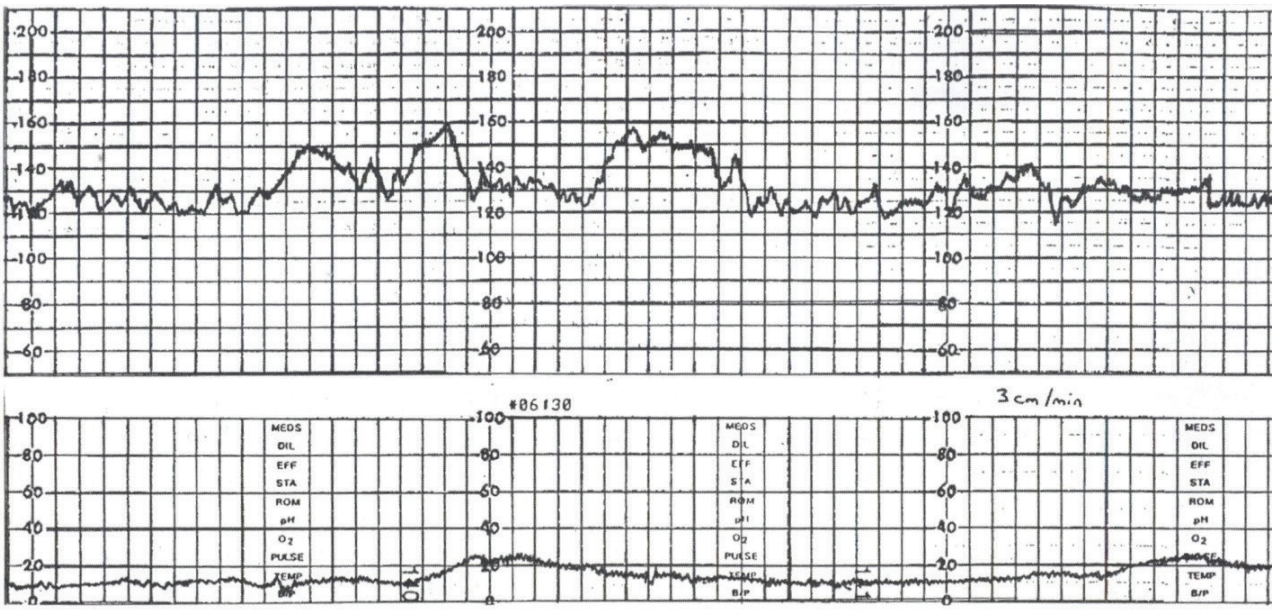
Steps in Interpreting a Fetal Tracing

When interpreting a tracing, consider the following:

1. What is the uterine contraction frequency? (check the paper speed)
2. What is the baseline fetal heart rate?

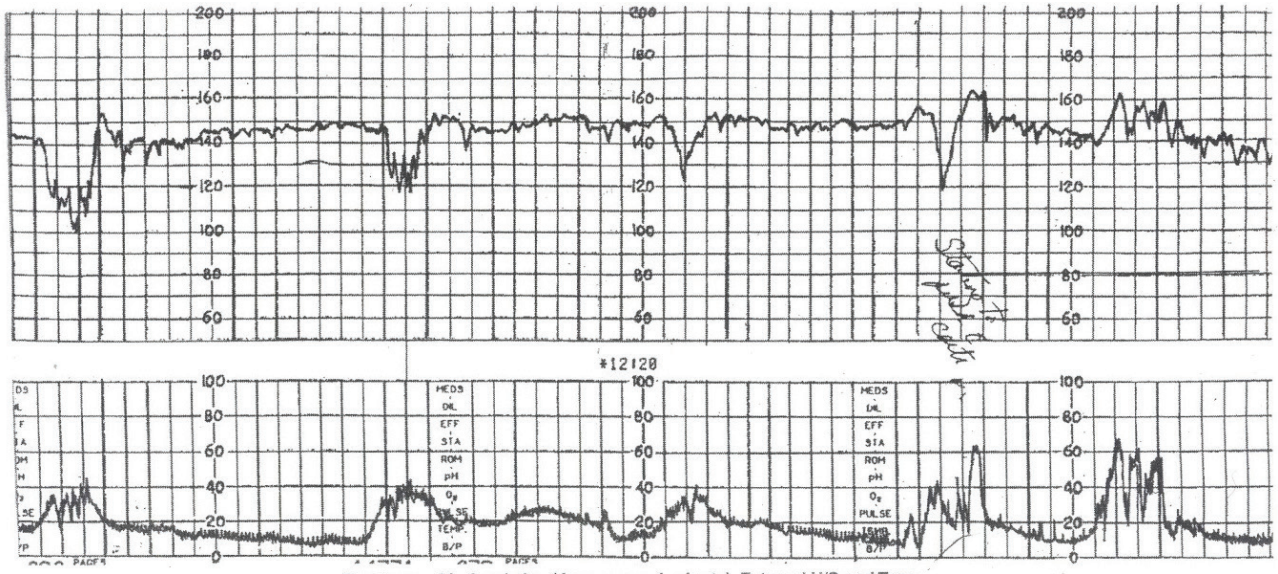
3. What is the baseline variability?
    - Absent
    - Minimal
    - Moderate/average
    - Excessive
4. Periodic changes noted on this tracing are:
    - Accelerations
    - Early decelerations
    - Late decelerations
    - Variable decelerations
5. This tracing is classified as:
    - Normal
    - Atypical
    - Abnormal
6. What would be your management?

Figure 1: Normal Fetal Heart Rate Tracing.



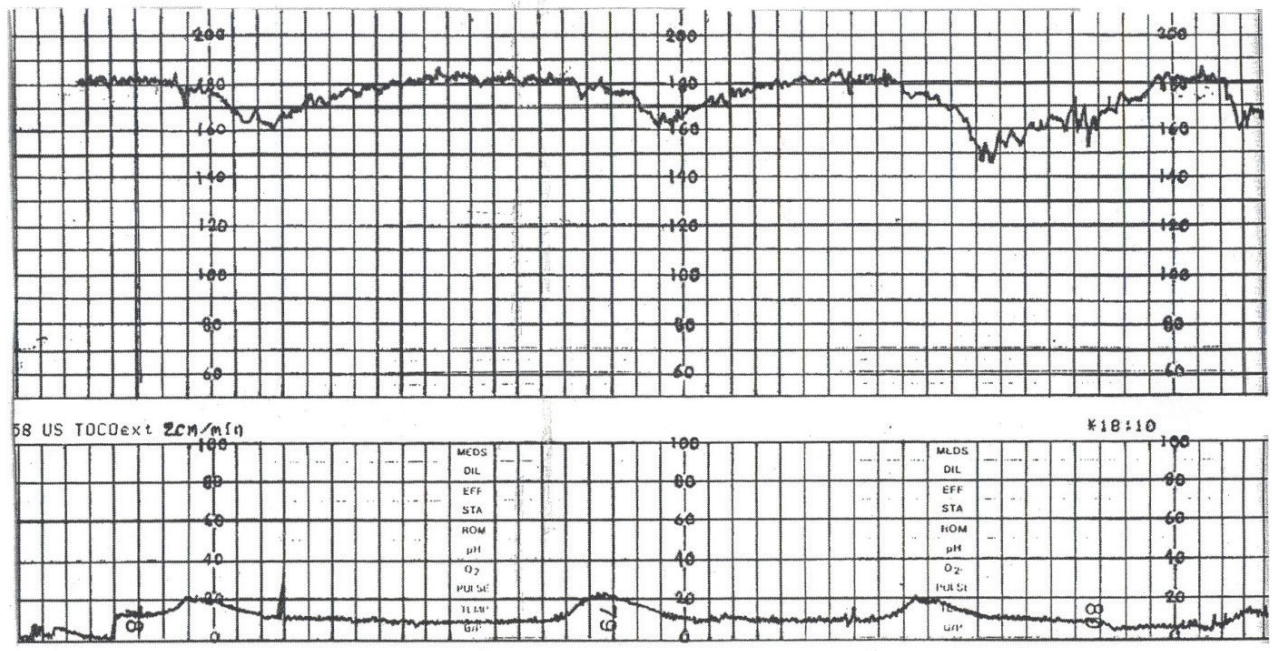
Paper speed is 3cm/min. (6 squares = 1 minute). External U/S and Toco.

Figure 2: Early Decelerations.



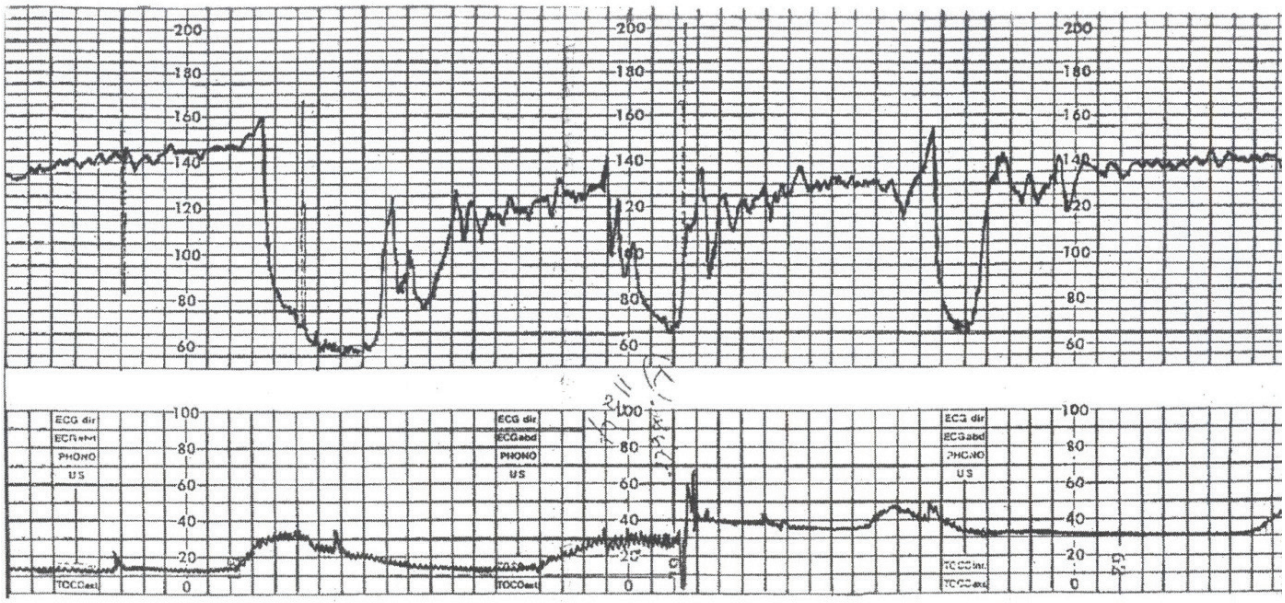
Paper speed is 2cm/min. (4 squares = 1 minute). External U/S and Toco.

Figure 3: Late Decelerations.



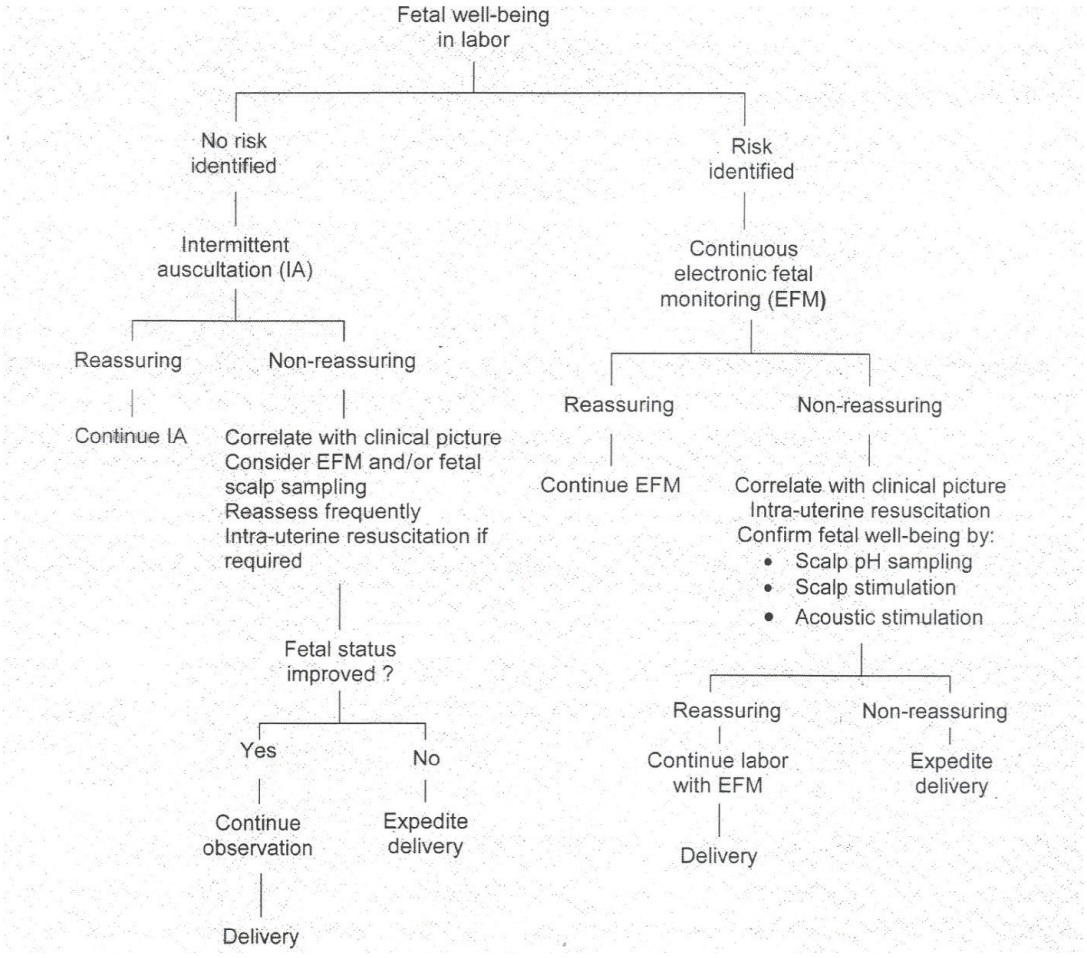
Paper speed is 2 cm/min. (4 squares = 1 minute). External U/S and Toco

Figure 4: Variable Decelerations.



Paper speed is 3 cm/min (6 squares = 1 min). External U/S and Toco.1.

Figure 5: Fetal Well-Being Decision Tree.



Adapted from MORE[OB].

Significance of Meconium Staining of Amniotic Fluid

Three theories have been suggested to explain fetal passage of meconium:

1. Pathologic: fetus passes meconium in response to hypoxia and signals fetal compromise
2. Normal gastrointestinal tract maturation under neural control
3. Vagal stimulation from common but transient umbilical cord compression and resultant increased peristalsis

Research evidence points to the likelihood that the high incidence of meconium observed in the amniotic fluid of women during labour often represents fetal passage of gastrointestinal contents in conjunction with normal physiological processes. Such meconium, however, can become an environmental hazard when fetal acidemia supervenes. Fetal acidemia occurs acutely and therefore, meconium aspiration is unpredictable and likely unpreventable.

Meconium Aspiration

The aspiration of some amniotic fluid before the onset of labour is a physiologic event. In about 20% of pregnancies, the fluid is contaminated by the passage of fetal meconium. Meconium aspiration may cause both mechanical obstruction of the airways and chemical pneumonitis, in addition to severe pulmonary hypertension. Free fatty acids in the meconium may strip away alveolar surfactant.

Meconium aspiration syndrome may follow delivery in otherwise normal labour. However, it is more likely to occur in post-term pregnancy and in pregnancies complicated by intrauterine growth restriction

If infant is vigorous and crying immediately after birth, suctioning the mouth and nares is not necessarily recommended in the presence of meconium. If infant is depressed at birth, tracheal intubation and suctioning of meconium from the lower airway should be done.

CORD PROLAPSE

Cord prolapse occurs when part of the umbilical cord falls in front of the presenting part. The frequency is about 1 in 200 to 1 in 400 deliveries.

Predisposing factors

- Malpresentation
- Prematurity
- Abnormal fetus
- Multiple pregnancy
- Polyhydramnios
- Premature rupture of membranes
- Artificial rupture of membranes
- Placenta previa
- High presenting part
- Obstetric procedures (ECV)

Clinical Presentation

Can be very dramatic with the sudden appearance of a loop of cord at the introitus, usually after rupture of membranes. More often, there is a sudden fetal bradycardia or deep variable decelerations and on vaginal examination, the cord is felt presenting at the cervix. The perinatal mortality associated with cord prolapse is at least 20-30% and is related to the detection-delivery interval. Rapid, decisive action is essential.

Management

1. **Assess fetal viability**
    - Check for cord pulsations
    - If fetus is already dead, too immature to survive, or has a lethal anomaly, intervention for fetal reasons are inappropriate
    - In above case allow labour to continue and fetus will deliver vaginally
    - If fetus in non-viable, but there is a contraindication to vaginal delivery (transverse lie) a Caesarean delivery may be necessary

2. **Relieve cord compression**
    - If cord outside introitus, gently replace in vagina
    - With hand in vagina, cradle cord in the palm and use tips of fingers to elevate the presenting part off of the cord
    - Adjust maternal position to Trendelenburg or knee-chest

3. **Method of delivery**
    - If cervix fully dilated and presenting part low do an assisted vaginal delivery
    - If cervix not fully dilated or vaginal delivery would be dangerous do an immediate CS

REFERENCES

1. Williams Obstetrics 20th Edition, 1997
2. MORE-OB Manual published by SOGC
3. Essential Management of Obstetric Emergencies by Thomas Baskett
4. SOGC Clinical Practice Guidelines – see website www.sogc.org



Preterm Labour and PPROM

Preterm Labour and Preterm Premature Rupture of Membranes (PPROM) Objectives:

At the end of the seminar, students should be able to:

Preterm Labour:

1. Define preterm labour.
2. Describe the biomolecular basis of preterm labour.
3. List the risk factors for preterm labour.
4. List the criteria necessary to make a diagnosis of preterm labour.
5. List a differential diagnosis for premature uterine contractions.
6. Describe available methods to identify women at high risk for preterm delivery.
7. Describe methods which may prevent preterm delivery in women at risk.
8. Outline the management of preterm labour, including:
    - Tocolytics
    - Steroids
    - Antibiotics
    - Fetal neuroprotection
9. Counsel the patient who has experienced prior preterm birth.

Premature Rupture of Membranes (PROM):

1. Describe the methods available to confirm the diagnosis of premature rupture of the membranes, including:
    - History
    - Physical findings
    - Diagnostic methods to confirm ROM
2. List the factors predisposing to PROM
3. Describe the risks and benefits of expectant management versus immediate delivery.
4. Describe the management regarding group B hemolytic streptococcus maternal colonization and the prevention of neonatal infection.
5. Describe methods to monitor maternal and fetal status during expectant management.

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PRETERM LABOUR

Preterm labour is defined as:

- Presence of uterine contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix prior to term gestation (between 20 and 37 weeks)
- Preterm labour precedes almost half of preterm births and preterm birth occurs in approximately 12% of pregnancies
- Preterm labour is leading cause of neonatal mortality in the United States.
- Preterm birth accounts for 70% of neonatal morbidity, mortality, and health care dollars spent on the neonate, largely due to the 2% of American women delivering very premature infants (<32 weeks)
- Preterm infants also at increased risk for cerebral palsy, cognitive impairment, blindness, deafness, respiratory illness, complications of neonatal intensive care, educational disadvantages and neurosensory impairments.

Goals of obstetric patient management of preterm labour should include:

1. Early identification of risk factors associated with preterm birth
2. Timely diagnosis of preterm labour
3. Identifying the etiology of preterm labour
4. Evaluating fetal well-being
5. Providing prophylactic pharmacologic therapy to prolong gestation and reduce the incidence of respiratory distress syndrome (RDS) and intra-amniotic infection (IAI)
6. Initiating tocolytic therapy when indicated
7. Establishing a plan of maternal and fetal surveillance with patient/provider education to improve neonatal outcome.

Mechanism(s) of preterm labour are largely unknown and involve the activation of a common final pathway.
Proposed mechanisms include:

1. Decidual hemorrhage, (e.g., abruption)
2. Mechanical factors such as uterine overdistension from multiple gestation or polyhydramnios
3. Cervical incompetence (e.g., trauma, cone biopsy)
4. Uterine distortion (e.g., Müllerian duct abnormalities, fibroid uterus)
5. Cervical inflammation (e.g., resulting from bacterial vaginosis [BV], trichomonas), maternal inflammation/fever (e.g., urinary tract infection)
6. Environmental exposure (e.g., drug abuse, smoking, alcohol consumption)
7. Uteroplacental insufficiency (e.g., all conditions that lead to impaired placentation including chronic hypertension, antiphospholipid antibody syndrome etc).
8. Fetal role: fetus plays a role in the initiation of labour. (e.g. the fetus recognizes a hostile intrauterine environment and precipitates labour by premature activation of a fetal-placental parturition pathway)

These diverse etiologies have led to the coining of the phrase *Preterm Parturition Syndrome.*

Risk Factors

- Previous preterm birth
- Non-white race
- Extremes of maternal age (<17 y or >35 y)
- Low socioeconomic status
- Low pre-pregnancy weight
- *The most significant single clinical risk factor is previous history of preterm birth*. Given a baseline risk of 10-12%, the risk of recurrent preterm birth after 1,2, and 3 consecutive preterm births may be increased to approximately 15%, 30%, and 45% respectively

PRECONCEPTUAL EVALUATION

- While the risk for preterm birth in nulliparous patients is hard to determine, past obstetric experience and personal behavior may provide significant insight into future pregnancy outcome in multiparous women
- Identifying at-risk patients preconceptually may allow additional treatment options

The presence of the following risk factors should be addressed prior to pregnancy:

Cervical trauma

- History of multiple first-trimester elective terminations or one or more second-trimester elective abortions may be at increased risk for preterm delivery
    - Cervical dilatation with laminaria or cervical ripening agents, such as misoprostol, appears to be less traumatizing to the cervix than mechanical dilation.
- Increased risks of preterm birth after preconceptual surgical treatment (e.g. cold knife cone, cryoconization, laser cone, LEEP) of cervical intraepithelial neoplasia (CIN)
    - The risk of subsequent preterm delivery may be proportional to the amount of cervical tissue removed during surgery

Genital tract infection

- Bacterial vaginosis (BV) is a vaginal syndrome associated with an alteration of the normal vaginal flora and has been linked to a 40% increase in risk of preterm delivery
- Antibiotic treatment of BV has not been shown to decrease the incidence for preterm birth thus treatment is currently reserved for symptomatic patients.
- Chlamydia, gonorrhea, trichomoniasis not conclusively associated with increased risk of preterm birth

Preterm labour/birth history

- Past obstetric history may be one of the strongest predictors of recurrent preterm birth.
- Given a baseline risk of 10-12%, the risk of recurrent preterm birth after 1, 2, and 3 consecutive preterm births may be increased to approximately 15%, 30%, and 45%, respectively.
- Preconceptual counselling should help patients to make informed decisions concerning future pregnancy in light of prematurity risk in the presence of previous preterm delivery

- Often the best time to counsel the patient is at her 4- to 6-week postpartum check after a preterm delivery.

Midtrimester loss

Midtrimester loss has many etiologies, including infection (e.g. Listeria), antiphospholipid syndrome, diabetes, substance abuse, genetic disorders, congenital Müllerian abnormalities, cervical trauma, and cervical incompetence. Many midtrimester losses remain unexplained.

A complete workup can include:

1. Detailed history
2. Immunological assessment: antiphospholipid antibodies
3. Anatomic assessment: Hegar test, hysterosalpingogram/sonohysterogram, MRI
4. Vaginal swabs (BV)
5. Placental pathology and autopsy reports.

Assessment of Risk during Pregnancy

Assessment during the first prenatal exam should include the patient's obstetric history, infection risk, and the presence of cervical or uterine abnormalities.

1. Should review details of previous preterm deliveries, including autopsy reports, placental histology and medical records
2. Integrity of the cervix and the extent of any prior injury to the cervix may be assessed by speculum and digital examination.
3. Presence of asymptomatic bacteriuria, sexually transmitted infections, and symptomatic BV may be investigated.
4. Assessment of placentation might be useful in risk stratification.
5. In some patients, formal cervical length assessment may be of use in risk assessment

Cervical length:

- At 24-28 weeks' gestation, measurement of cervical length has been demonstrated to be the most sensitive prenatal predictor of preterm birth between both high- and low-risk women
- In a mixed high- and low-risk population of singleton pregnancies, transvaginal ultrasound-measured cervical length at 24 weeks highly correlated with the risk of spontaneous preterm delivery before 35 weeks
- Relative risk of preterm delivery among women with a cervix 25 mm or shorter at 24 weeks was 6.2
- At 28 weeks, a short cervix (≤25 mm) was associated with a 9.6 relative risk of preterm delivery
- Cervical length 25 mm or shorter at 28 weeks had a 49% sensitivity for prediction of preterm delivery at less than 35 weeks
- A recent randomized controlled trial failed to demonstrate a benefit for rescue cerclage for cervical shortening < 15mm during a routine 18-22 week anatomy scan
- However there might be a specific benefit to cerclage in subgroups of women with short cervix and a history of preterm birth [Obstet Gynecol. 2011 Mar;117(3):663-71]
- Recently a randomised controlled trial that included 385 pregnant women with a short cervix of 25 mm or less between 18 to 22 weeks of gestation demonstrated that the use of a cervical

pessary was associated with a statistically significantly decrease in the incidence of spontaneous preterm birth less than 37 weeks' gestation compared with expectant management (22% versus 59 %; respectively, risk ratio (RR) 0.36, 95% confidence interval (CI) 0.27 to 0.49). REF: [Lancet. 2012 May 12;379(9828):1790]

- Since then, several other RCTs have been performed with contradictory results (N Engl J Med 2016; 374:1044-1052; JAMA. 2017;318(23):2317- 2324) thus the use of pessary for prevention of preterm birth remains largely confined to experimental trials
- In multiple gestations the use of a pessary for a short cervix has shown similar benefits in reduction of preterm birth < 34 weeks (relative risk, 0.41; 95% confidence interval, 0.22-0.76) in one trial but no difference in composite neonatal morbidity [Am J Obstet Gynecol. 2016 Feb;214(2):145-52]
- Prophylactic use of pessary in all multiple gestations does not lead to a reduction in preterm birth or adverse neonatal outcome [The Lancet Volume 382, No. 9901, p1341–1349, 19 October 2013]
- In patients with risk factors, the data is inconclusive whether a policy of prophylactic cerclage is superior to cervical surveillance and rescue cerclage when shortening/funneling is identified; thus, both treatment options can be offered

The use of progesterone therapy to prevent preterm birth

- Recent studies support use of progesterone supplementation to reduce preterm birth in patients at high risk for recurrent preterm delivery
- Weekly injections of 17 alpha-hydroxyprogesterone caproate or intravaginal administration of micronized progesterone 100 – 200 mg per day resulted in a substantial reduction in rate of recurrent preterm delivery among women who were at high risk for preterm delivery and reduced the likelihood of several complications in their infants
- In 2011, the US Food and Drug Administration (FDA) approved 17-hydroxyprogesterone (Makena) to reduce risk of preterm delivery before 37 weeks' gestation in women with singleton pregnancy and a history of at least one spontaneous preterm birth
- Currently not available for use in Canada
- A randomized controlled trial of intravaginal progesterone supplementation for asymptomatic women with an incidentally identified very short cervical length (< 15 mm) demonstrated a reduction in the risk of preterm birth
- In contradiction to this data are the results of a recently published RCT (Norman et al, Lancet May 2016) that vaginal progesterone was not associated with reduced risk of preterm birth or composite neonatal adverse outcomes
- An updated meta-analysis of patient level data from RCTs has reaffirmed the benefit of vaginal progesterone in the management of short cervix in singleton pregnancies [Ultrasound Obstet Gynecol. 2016 Sep; 48(3): 308–317]

MANAGEMENT OF PRETERM LABOUR (WITHOUT PPROM)

Diagnosis

- Contractions of sufficient frequency and intensity to affect progressive effacement and dilation of the cervix at 24-37 weeks' gestation are indicative of active preterm labour.
- If diagnosis suspected, but not confirmed and the gestational age is < 34 weeks gestation, it may be prudent to first obtain a vaginal fetal fibronectin (FFN) sample before pelvic cervical examination.
- If diagnosis of preterm labour becomes obvious after the pelvic examination, the FFN specimen can be subsequently discarded. However, if diagnosis remains in doubt, FFN specimen can be sent to the lab for analysis.
    - Fetal fibronectin is a glycoprotein produced by the chorionic membranes
    - Localized to the decidua basalis adjacent to the intervillous space.
    - Its primary purpose appears to be that of an adhesion molecule which helps bind the chorionic membranes to the underlying maternal decidua.
    - Remember FFN has a very high negative predictive value (e.g. if FFN negative, there is a >95% chance the woman will not deliver within the next 14 days), but low positive predictive value (i.e. most women with positive FFN will not deliver within 1 week of test)

Treatment

Preterm labour may be difficult to diagnose and a potential exists for overtreatment of uterine irritability. Tocolytic agents, while generally safe in appropriate dosages with proper clinical monitoring, have potential morbidity and should only be used after consideration of the risks and benefits of such use.

Between 24 and 33 weeks' gestation, benefits of tocolytic therapy are generally accepted to outweigh the risk of maternal and/or fetal complications and these agents should be initiated provided no contraindications exist.

The following table (Table 1) depicts survival, major short-term morbidity, and intact long- term survival by gestational age.

TABLE 3
Frequency of death and major, intermediate, and minor morbidity

		Delivery gestational age, wk														
Outcome	All, n = 8334	23, n = 43	24, n = 114	25, n = 124	26, n = 169	27, n = 159	28, n = 196	29, n = 213	30, n = 262	31, n = 312	32, n = 451	33, n = 639	34, n = 1058	35, n = 1477	36, n = 3117	*P* for trend
Death	119 (1.4)	19 (44.2)	36 (31.6)	15 (12.1)	19 (11.2)	13 (8.2)	4 (2.0)	4 (1.9)	4 (1.5)	3 (1.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	<.001
Major morbidity[a]	657 (7.9)	19 (44.2)	60 (52.6)	68 (54.8)	88 (52.1)	64 (40.3)	43 (21.9)	48 (22.5)	36 (13.7)	22 (7.1)	39 (8.7)	27 (4.2)	46 (4.4)	42 (2.8)	55 (1.8)	<.001
Minor morbidity[b]	3136 (37.6)	4 (9.3)	18 (15.8)	39 (31.5)	59 (34.9)	77 (48.4)	144 (73.5)	147 (69.0)	206 (78.6)	255 (81.7)	344 (76.3)	406 (63.5)	540 (51.0)	402 (27.2)	495 (15.9)	<.001
Survival without any of above morbidities	4422 (53.1)	1 (2.3)	0 (0.0)	2 (1.6)	3 (1.8)	5 (3.1)	5 (2.6)	14 (6.6)	16 (6.1)	32 (10.3)	67 (14.9)	205 (32.1)	472 (44.6)	1033 (69.9)	2567 (82.4)	

Data are n (%).

[a] Includes persistent pulmonary hypertension, intraventricular hemorrhage grade III/IV, seizures, hypoxic-ischemic encephalopathy, necrotizing enterocolitis stage II/III, bronchopulmonary dysplasia; [b] Includes intraventricular hemorrhage grade I/II, necrotizing enterocolitis stage I, respiratory distress syndrome, hyperbilirubinemia requiring treatment, hypotension requiring treatment.

Manuck et al. Preterm neonatal morbidity and mortality. Am J Obstet Gynecol 2016.

Criteria that indicate consideration of tocolytic therapy include more than 6 contractions per hour resulting in cervical change (transvaginal cervical length <2.5 cm, >80% cervical effacement, or cervical dilation >1 cm). If contractions are present without cervical change, management options include continued observation or non-specific analgesia (morphine sulphate 10-15 mg subcutaneous). If the FFN is negative and the contractions abate, the patient may be sent home with appropriate follow-up evaluation.

Tocolytic agents have not proven to be efficacious in preventing preterm birth or reducing neonatal mortality or morbidity. The primary purpose of tocolytic therapy is to delay delivery for 48 hours to allow the maximum benefit of glucocorticoids to decrease the incidence of RDS.

While tocolytics can be successful for 48 hours when membranes are intact, some clinical studies suggest that the effectiveness of tocolytics is only slightly better than partial bedrest and hydration, both of which have fewer adverse effects than tocolytic therapy.

Assessment

- Confirm gestational age.
- Rule out intra-amniotic infection/abruption
- Assessment of fetal wellbeing (is prolongation of pregnancy indicated?)
- Confirm diagnosis of preterm labour (serial vaginal exam, consider transvaginal ultrasound assessment of cervical length, tocodynamometer, FFN etc.)
- Vaginal swabs (Group B Streptococcus, bacterial vaginosis)
- Urine culture and sensitivity
- Assess for medical contraindications to tocolysis

Fetal therapy

The administration of glucocorticoids is recommended in the absence of clinical infection whenever the gestational age is between 24 and 34 weeks. An attempt should be made to delay delivery for 48 hours to obtain the maximum benefits of antenatal steroids.

The recommended dosage of glucocorticoids consists of two 12 mg doses of Betamethasone 24 hours apart or four doses of 6 mg of dexamethasone administered intramuscularly at 6-hour intervals.

Group B streptococci (GBS) prophylaxis

- All patients in preterm labour should be considered at high risk for neonatal GBS sepsis.
- Patients in preterm labour with the potential to deliver should receive prophylactic antibiotics against GBS, unless GBS culture is negative.
- Prophylactic antibiotics should be administered when the diagnosis of preterm labour is made and should be continued until delivery or for a minimum of 48 hours if undelivered.
- Patients should be re-treated if preterm labour recurs or when the patient enters labour at term depending upon culture results.

Tocolytic Agents

- The most common tocolytic agents used for the treatment of preterm labour are magnesium sulphate (MgSO4), indomethacin, transdermal nitrates and nifedipine.
- In the past, beta-mimetic agents, such as terbutaline or ritodrine, were the agents of choice, but in recent years their use has been significantly curtailed due to maternal and fetal side effects.
- Atosiban is a parenterally administered oxytocin receptor antagonist that is used in Europe but not available for use in North America.

1. Magnesium sulphate

Tocolysis:

- Magnesium sulphate is used in some countries as a tocolytic however generally not used in Canada.
- In 2014, a systematic review of randomized trials comparing magnesium sulphate with no treatment or placebo control, administration of magnesium sulphate did not result in a statistical
- Reduction in birth <48 hours or improvement in neonatal and maternal outcomes (Crowther CA et al. Cochrane Database Syst Rev 2014).
- Common maternal side effects include flushing, nausea, headache, drowsiness, and blurred vision.
- The mother should be monitored for toxic effects, such as respiratory depression or even cardiac arrest that can occur at supratherapeutic levels.
- When acute mild toxicity exists in the presence of normal urine output, magnesium sulphate should be temporarily discontinued until the serum magnesium level and deep tendon reflexes return to normal.
- If the toxicity symptoms are life threatening, administering 1 g of calcium gluconate by slow intravenous push and strongly considering not reinstituting magnesium sulphate despite the return to normal levels is recommended.

Neuroprotection:

- Several randomized controlled trials have demonstrated that administration of magnesium sulphate prior to preterm delivery < 32 weeks significantly reduces the risk of cerebral palsy in the newborn.
- Recent SOGC guidelines have recommended that magnesium sulphate be administered between 24 and 31+6 weeks when preterm delivery is inevitable.
- The protocol includes a 4g IV loading dose, over 30 minutes, followed by a 1g/hr IV maintenance infusion until birth.

2. Indomethacin

- Indomethacin is an appropriate first-line tocolytic for the pregnant patient in early preterm labour (<30 wk) or preterm labour associated with polyhydramnios.
- A more significant inflammatory response in the membranes and decidua is observed at gestational ages less than 30 weeks compared with 30-36 weeks.
- Indomethacin reduces prostaglandin synthesis from decidual macrophages.
- Prostaglandin synthetase inhibitors, such as indomethacin, readily cross the placenta and can cause oligohydramnios due to a decrease in fetal renal blood flow if used for more than 48 hours.

- During treatment, urine output, maternal temperature, and amniotic fluid index (AFI) should be evaluated periodically.
- The initial recommended dose is 100 mg PR followed by 50 mg PO every 6 hours for 48 hours.
- Indomethacin can also cause premature closure or constriction of the ductus arteriosus. Since this effect is more common after 32 weeks' gestation, indomethacin therapy is not usually recommended after 32 weeks, and is generally not administered for >48 hours.

3. Nifedipine

- Nifedipine, a calcium channel blocker, is commonly used to treat high blood pressure and heart disease because of its ability to inhibit contractility in smooth muscle cells by reducing calcium influx into cells.
- Consequently, nifedipine has emerged as an effective and safe alternative tocolytic agent for the management of preterm labour.
- Despite its off-label status, several randomized studies have shown that the use of nifedipine in comparison with other tocolytics is associated with a more frequent successful prolongation of pregnancy, resulting in significantly fewer admissions of newborns to the neonatal intensive care unit, and may be associated with a lower incidence of respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage.
- Contraindications to nifedipine therapy include allergy to nifedipine, hypotension, hepatic dysfunction, concurrent use of beta-mimetics or magnesium sulphate (relative contraindication), transdermal nitrates, or other antihypertensive medication.

Follow-up Care

Once the episode of preterm labour has been arrested, a gradual return to limited activity should be encouraged prior to hospital discharge. Bed rest should be discouraged given lack of evidence for its efficacy along with potential risks. The following factors may influence the decision to discharge the patient:

- Cervical dilation
- Fetal presentation
- Number of fetuses
- Gestational age
- Access to the hospital
- Social support at home (transportation at all times, telephone)
- Good patient compliance

PRETERM PREMATURE RUPTURE OF THE MEMBRANES (PPROM)

Preterm premature rupture of the membranes (PPROM), defined as rupture of membranes prior to the onset of labour, occurring prior to 37 weeks' gestation is far more difficult to manage than premature rupture of the membranes (PROM) at term.

Several issues need to be considered in formulating a plan of management. Prematurity is the principal risk to the fetus, while infection morbidity and its complications are the primary maternal risks. All plans

for management of PPROM remote from term should include the family and the medical team caring for the pregnancy, including the neonatal and maternal medical team.
Remote from term, PPROM should only be cared for in facilities where a NICU is available and capable of caring for the neonate. Because most PPROM pregnancies deliver within a week of membrane rupture, transfer of the pregnant mother to a qualified facility is urgent and should be facilitated immediately upon diagnoses.

The vast majority of women proceed to active labour and deliver soon after PPROM. With appropriate therapy and conservative management, approximately 50% of all remaining pregnancies deliver each subsequent week after PPROM. Thus, very few women remain pregnant more than 3-4 weeks after PPROM. This is important information to give the woman considering expectant management remote from viability.

Spontaneous sealing of the membranes does occur occasionally (<10% of all cases), mostly after PPROM that has occurred iatrogenically subsequent to amniocentesis; however, this is the exception rather than the rule.

Several areas of controversies exist regarding the best medical approach or management of PROM remote from term. Expectant management and immediate delivery are potential options in these patients, and each has its own advantages and disadvantages. With appropriate care, the maternal risks of expectant management are generally accepted to be minimal and a clear neonatal advantage exists by reducing risks of prematurity.

Diagnosis

- The initial evaluation of PPROM should include a thorough history and physical exam consisting of a sterile speculum examination to document ROM.
- Routine evaluation should include cervical
- inspection, nitrazine test, ferning and ultrasound to assess amniotic fluid index, fetal biometry and fetal position.
- Cervical cultures including Chlamydia trachomatis and Neisseria gonorrhoeae (if not obtained previously) and anovaginal cultures for Streptococcus agalactiae (Group B) should be obtained.
- Maternal vital signs should be documented as well as continuous fetal monitoring initially to establish fetal status.
- Digital examination should be avoided.
- When PPROM is diagnosed one needs to determine whether immediate delivery is indicated. Circumstances suggesting that immediate delivery of the fetus is indicated include chorioamnionitis, advanced labour, fetal distress, and placental abruption with non-reassuring fetal surveillance.
- If fetal lung maturity has been documented by either amniocentesis or collection of vaginal fluid, delivery should be facilitated.
- In a non-cephalic fetus with advanced cervical dilatation, the risk of cord prolapse may also outweigh the benefits of expectant management and delivery should be considered.

- Closer to term, between 34-37 weeks of gestation, the advantage of expectant management is decreased and delivery can be considered although a recent RCT [Lancet. Jan 2016; 387(10017):444-52] has shown no increase in neonatal sepsis with expectant management and a reduction in neonatal respiratory morbidity and length of stay.

Expectant management

After an initial period of continuous monitoring of fetal heart rate and uterine contractions (24- 48 h), if findings are suggestive of reassuring surveillance, then the patient would be a candidate for expectant management. The patient should be placed on the antenatal/obstetric floor for antenatal surveillance.

The goal of this surveillance is to identify the need for immediate delivery for either maternal or fetal indications and will include:

- Monitoring for signs of clinical chorioamnionitis (fever, tachycardia, leukocytosis, uterine tenderness, fetal tachycardia, foul smelling discharge)
- Monitoring of fetal wellbeing (NST/BPP)
- Monitoring for placental abruption (increased in PPROM)

The use of corticosteroids to accelerate lung maturity should be considered in all patients with PPROM with a risk of infant prematurity from 24-34 weeks' gestation. Most patients with PPROM remain pregnant at 48 hours and thus will benefit from corticosteroid therapy.

Data indicate that the use of corticosteroids reduces neonatal morbidity and mortality. The rates of respiratory distress syndrome (RDS), necrotizing enterocolitis, and intraventricular hemorrhage were all lower when either 12 mg of betamethasone IM was given g24h for two doses, or dexamethasone 6 mg q12h was given for 4 doses.

Once the decision to manage a patient expectantly has been made, the institution of broad-spectrum antibiotics should be considered. Multiple trials have examined the advantages and disadvantages of using antibiotics and the choice of antibiotics. In most studies, use of antibiotics has been associated with prolongation of pregnancy and reduction in infant and maternal morbidity.

Based on current evidence, 7 days of antibiotics should be used in patients with PPROM who are being managed expectantly. Therapy longer than 7 days should be avoided; it has not been shown to be more effective and may promote the emergence of resistance organisms.

PPROM prior to viability (<23 weeks) has a dismal prognosis mostly due to the potential for pulmonary hypoplasia and the decreased probability of delivering after 26-28 weeks' gestation. Expectant management *may be* appropriate in select patients who are well informed and educated about the potential maternal risks and the complications of extreme prematurity.

Delivery is also appropriate when the mother is concerned about her own risks, especially when PPROM has occurred prior to 20 weeks' gestation. Survival varies with gestational age at diagnosis (from 12% when diagnosed at 16-19 wk, to as much as 60% when diagnosed at 25-26 wk). Until viability, maternal safety should be the primary concern.

Tocolytics in the setting of PPROM

The most common cause of labour in the setting of PPROM is underlying chorioamnionitis. The use of tocolysis in that setting is thus not justified (e.g. attempting to stop contractions when signs of active infection is not justified). No data indicate that administering tocolysis in the background of PPROM benefits the neonate.

In one study, prophylactic tocolysis was found to briefly prolong latency. In another study by Jazayeri et al, latency was shorter when magnesium sulphate was given. The use of tocolysis, unlike corticosteroids and antibiotics, should be considered only when a clear clinical benefit exists, such as in transport of the mother to a tertiary institution with a NICU, and should not be used routinely in the setting of PPROM.

Summary of PPROM

In general, the following guidelines should be followed:

- Diagnosis of rupture of membranes needs to be confirmed.
- Digital vaginal examinations should be avoided.
- Ultrasonography should be performed to confirm gestational age, estimated fetal weight, presentation, amniotic fluid index, and fetal anatomy if not already fully evaluated.
- Antibiotics need to be given based on present evidence.
- Corticosteroids should be given to accelerate lung maturity between 24 and 34 weeks.
- Informed consent should be obtained for expectant management versus delivery with careful documentation in the chart
- In PPROM, the rule should be hospitalization after viability in an institution where care for a premature neonate can be provided.
- Maternal health is the primary indicator for the need to deliver. Any evidence of infection or maternal instability due to complications of PPROM, such as bleeding, requires careful evaluation and determination of the appropriateness of expectant management.
- Fetal monitoring should be performed at least daily until delivery, and fetal wellbeing and growth should be evaluated periodically with ultrasonography.
- After 32 weeks and certainly after 34 weeks' gestation, the appropriateness of expectant management of PPROM should be re-evaluated individually for each case.



Fetal Complications – Part I

Fetal Complications I Objectives:

At the end of the seminar, students should be able to:

Intrauterine growth restriction (IUGR)

1. Define intrauterine growth restriction and small for gestational age.
2. Describe the use of the menstrual history and ultrasound to determine the gestational age.
3. List the known etiological factors associated with intrauterine growth restriction.
4. Describe the fetal risks associated with intrauterine growth restriction.
5. List the appropriate ancillary diagnostic tests.
6. Describe the surveillance of fetal growth and wellbeing.
7. Describe how you can recognize the difference between symmetrical and asymmetrical types of growth restriction and explain the significance of this distinction.
8. Be aware of the differences between early- vs. late-onset fetal growth restriction
9. Describe the management of the pregnancy associated with intrauterine growth restriction.
10. Predict the outcome for future pregnancies for specific cases of intrauterine growth restriction.

Congenital Anomalies

1. List the risk factors in the history and physical examination of the pregnant patient at her initial visit, which may increase her chances of having a baby with a congenital anomaly.
2. Describe the basic principles of pre-pregnancy counselling, including the options available to a couple after completion of the Counselling.
3. List environmental factors in the antepartum period, which could have teratogenic effects on the fetus (maternal disease, substance abuse, infections, drugs, and radiation).
4. Describe the methods of investigation for prenatal detection of congenital anomalies (details can be found also in Antepartum Care Chapter of this Syllabus).
5. Discuss the significance of polyhydramnios and oligohydramnios associated with congenital anomalies.

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INTRAUTERINE GROWTH RESTRICTION

Abnormal intrauterine growth has been recognized for over 25 years, and continues to be among the common fetal complications. Intrauterine growth restriction (IUGR) carries a significantly increased risk of perinatal morbidity and mortality.

Definition and Incidence

IUGR is defined as a failure of a fetus to meet its growth potential due to pathological factors, most commonly placental insufficiency, putting the fetus/newborn at increased risk for perinatal morbidity and mortality. Small for gestational age (SGA) is a descriptive term that refers to infants with a birth weight below the 10th percentile for gestational age, irrespective of whether this is due to pathological factors or simply due to low growth potential (referred to as constitutional SGA).

In clinical practice, IUGR and SGA are often used interchangeably, so that IUGR is commonly suspected when the sonographic estimated fetal weight or birth weight are below the 10th percentile for gestational age. However, this approach is likely to result in over-diagnosis of IUGR as about 70% of infants with a birth weight below the 10th percentile are healthy constitutional SGA infants.

The use of birth weight percentile implies a comparison with a population having normal growth and requires the development of a standard growth curve for that population. There are discrepancies between different reported growth standards. The populations studied are discordant with respect to altitude, parity, sex, race, socioeconomic status and the gestational age calculation. The standard growth curve used for the diagnosis of IUGR should be appropriate for the study population. Some advocate for the use of 'customized growth standard' which individualize the growth standard to factors such as ethnic origin, maternal height and weight, parity and fetal sex.

Using the common definition for IUGR of birth weight less than the 10th percentile (i.e. encompassing both pathological IUGR and constitutional SGA babies), the incidence of IUGR per definition should be approximately 10 percent.

Classification and Etiology

Winich suggested three consecutive but overlapping phases for fetal growth. The first phase, cellular hyperplasia, encompasses the first 16 weeks of gestation, during which rapid increase in cell number occurs. In the second phase, hyperplasia and hypertrophy (increase in cell number and size) occurs between the 16th and 32nd weeks. In the third phase, cellular hypertrophy occurs with a rapid increase in cell size, between the 32nd weeks to term.

Traditionally, IUGR has been classified as either symmetrical (30%) or asymmetrical (70%) based on the relationship between fetal head and fetal abdominal circumference, since the growth pattern has been suggested to be associated with the underlying etiology and timing of onset of IUGR. In the symmetrically growth restricted fetus, the growth of both fetal head and abdomen are decreased. This pattern has been associated with early insults e.g. genetic disorders and intrauterine infection that interferes with cellular hyperplasia, causing a proportionate decrease in the size of all fetal organs. In asymmetrical IUGR, there is a disproportionate decrease in fetal abdominal size with respect to fetal

head. This may be caused by a later insult e.g. placental insufficiency that impairs cellular hypertrophy. However, there is a considerable overlap between fetuses with symmetrical and asymmetrical growth restriction with regard to the underlying etiology

Many conditions are associated with IUGR. These can be classified as fetal, maternal or placental (Table 1). In almost 50% of cases of IUGR, the etiology is unknown. The single most important risk factor is previous history of IUGR.

Fetal Factors

Fetal chromosomal abnormalities and congenital malformations are associated with 10% of cases of IUGR. The most common chromosomal abnormalities encountered are autosomal trisomies, which are associated with a 50% incidence of IUGR

Fetal infections account for less than 5% of IUGR. Pathogens that are known to cause IUGR include cytomegalovirus (CMV), rubella, toxoplasmosis, herpes, varicella and syphilis (designated by the acronym TORCH).

Placental Factors

A decrease in villous and capillary surface area may reduce the amount of nutrients available to the fetus thereby causing IUGR. Thus, placental infarction, placenta previa, circumvallate placenta, prolonged pregnancy and placenta accreta are associated with IUGR.

In twin pregnancies there is a relative decrease in placental mass compared to fetal mass. The incidence of IUGR in twins is 15 to 20%. The pathogenesis of IUGR in twin pregnancies is not well understood. The growth curve of twins usually starts to fall and deviate from singletons after 28-32 weeks.

Maternal Factors

The fetus depends on an adequate maternal nutritional supply and the ability of the maternal vascular system to deliver it to the fetoplacental unit. Maternal vascular disease with the associated decrease in uteroplacental perfusion is responsible for the majority of clinically recognized IUGR (30%). Pre-eclampsia, chronic hypertension or diabetes with vascular complications may cause placental microvascular changes that leads to decreased placental blood flow and IUGR. Diseases that cause maternal hypoxemia such as cyanotic heart disease and obstructive lung disease may also result in IUGR.

The birth weight relates to the preconceptual nutritional status. Extreme caloric restriction during pregnancy is not common in the developed world. It could be seen in women with sever gastrointestinal disease resulting in IUGR.

Factors present in the maternal environment can influence the rate of fetal growth. Cigarette smoking reduces birth weight by approximately 200gm per pack/day and produces symmetrical IUGR. If smoking is stopped before the third trimester, its adverse effect on birth weight ceases. The mechanism by which smoking results in IUGR is not clear.

Possible mechanisms include:

- Increased concentration of carboxyhemoglobin leading to a left shift of the oxyhemoglobin dissociation curve causing a decrease in oxygen delivery to the fetus, and nicotine-induced appetite suppression and a catecholamine-dependent vasoconstriction of uterine vessels.
- The consumption of alcohol, the use of coumarin or hydantoin derivatives can produce a fetus with IUGR and dysmorphic features.
- Women with a history of previous IUGR have a 25% chance of delivering a second infant with IUGR.

Perinatal Mortality and Morbidity

IUGR is associated with increased risk of perinatal mortality and morbidity compared with normally grown infants. Fetuses with IUGR are at increased risk of antenatal and intrapartum asphyxia due to diminished placental reserve and cord compression secondary to oligohydramnios.

Hypoglycemia, secondary to decreased glycogen reserves and to altered gluconeogenesis is a common metabolic problem in IUGR infants. Hypocalcemia may be secondary to hypoparathyroidism, a result of intrauterine asphyxia and acidosis. Hyperphosphatemia may develop due to tissue breakdown. Hyponatremia from compromised renal function is frequent. In these infants hyponatremia may also be secondary to asphyxia and the development of inappropriate antidiuretic hormone secretion. Polycythemia, secondary to intrauterine hypoxia is observed more frequently in IUGR infants. Polycythemia leads to increased red blood cell destruction causing an increased incidence of hyperbilirubinemia.

The long term neurologic outcomes for IUGR infants remains unresolved and depends on the timing of the insult, the plasticity of the brain, and particularly on environmental factors. More recent evidence suggests that IUGR due to placental insufficiency may result in 'fetal programming' by means of epigenetic modifications that may predispose the fetus to the metabolic syndrome later in life including childhood obesity, hypertension, diabetes and cardiovascular disease. These observations are in line with the newly emerging Developmental Origins of Health and Disease (DOHaD) hypothesis.

Diagnosis

The diagnosis of IUGR requires an accurate estimation of gestational date (dating of pregnancy). Estimating gestational age based on the last menstrual period (LMP) has been shown to have poor accuracy. Even with a "perfect" LMP, 14% delivered more than 14 days outside of the predicted date. Also, when gestational age was based on LMP, the incidence of suspected IUGR was 20% versus 5% when based on ultrasound dates. Another approach to date pregnancy is by means of the symphysis to fundal height; however, the sensitivity and positive predictive value of this approach to diagnose IUGR is 27% and 18% respectively. Thus, measurement of symphysis to fundal height should be used as a screening test for IUGR only, prompting further investigation such as ultrasound. The date of quickening (maternal perception of fetal movement) and the date of auscultation of the fetal heart are so variable as to be of little clinical value.

Ultrasound is the preferred method to estimate gestational age and date the pregnancy as well as to diagnose IUGR. The accuracy of estimation of gestational age by ultrasound has been shown to be comparable to the use of the LMP but when used appropriately yields more accurate results. Generally, with a first trimester dating ultrasound, if dating via measurement of crown-rump length (CRL) is discrepant from LMP dating, the dates can be adjusted to reflect ultrasound dating. Ultrasound offers other advantages including determination of internal fetal growth, estimation of fetal weight, detection of fetal structural abnormalities, and fetal functional assessment through the biophysical profile.

When multiple ultrasound fetal measurements were used, IUGR was recognized in 75 to 80 percent of cases. Serial biparietal diameter (BPD) measurements alone fail to detect most cases of asymmetrical IUGR. By using the head circumference (HC) to abdominal circumference (AC) ratio most of the growth restricted fetuses can be detected. In typically developing fetuses, the HC/AC ratio is greater than 1 up to 32 weeks' gestation, becomes equal to 1 between 32 to 34 weeks and less than 1 after 34 weeks' gestation. In fetuses with asymmetrical IUGR, the HC remains larger than the AC (brain sparing), resulting in a higher than average HC/AC ratio.

Femur length (FL) measurement is relatively spared in asymmetrical IUGR. It can be useful in cases where HC is difficult to assess because of fetal position. FL/AC ratio is 22 from 21 weeks' gestation to term. An FL/AC ratio greater than 23.5 suggests IUGR.

Decreased amniotic fluid volume is associated with IUGR and may precede the lag in fetal growth. Decreased amniotic fluid volume is described as no vertical fluid pocket measuring 2cm or greater on ultrasound. This finding is associated with a 20 to 39 percentincidence of IUGR. Measurement of amniotic fluid pockets and the FL/AC ratio does not rely on knowledge of the gestational age. These measurements can be useful in patients with unreliable dates who present late in pregnancy.

Various equations that use different fetal measurements have been used to estimate fetal weight. Estimates of fetal weight that include BPD, AC and FL correlate best with birth weight with 75% of the estimates lying within 10% of the actual birth weight. However estimated birth weight should not be used to diagnose IUGR as it can lead to considerable diagnostic error. On the other hand, serial assessment of fetal biometric parameters are extremely valuable in establishing the diagnosis of IUGR.

Management

The crux of the management of IUGR is to establish accurate dates and to balance between the hazards of prematurity and intrauterine demise. Delivery is recommended when IUGR infants demonstrate abnormal function tests, absence of growth or severe oligohydramnios.

Once IUGR is suspected, the clinician should seek possible etiological or associated factors contributing to growth restriction. Women should be counseled to stop smoking, ingesting alcohol and other harmful lifestyle habits. Treatment for maternal medical problems such as chronic hypertension, asthma and inflammatory bowel disease should be started. Non-specific therapies including bed rest and adequate dietary supplementation may be helpful.

Ultrasound is used to establish normal morphology and to detect congenital anomalies. In cases of symmetrical IUGR, amniocentesis, cord blood sampling or placental biopsy should be considered to rule out chromosomal abnormalities. When the diagnosis of a lethal congenital anomaly is confirmed, an unnecessary Caesarean section for fetal distress can be avoided.

In the case of IUGR, regular antepartum fetal assessments are indicated. There is no consensus as to which test accurately evaluates the IUGR fetus and when to use it. Current guidelines recommend measuring fetal growth by ultrasound every 2-3 weeks for IUGR fetuses with no major congenital anomaly. In addition to measuring fetal growth, a biophysical profile (BPP) with Doppler velocimetry of the umbilical artery can be done on ultrasound to identify fetuses at greatest risk for morbidity and mortality.

Experience with the non-stress test (NST) daily or twice weekly in IUGR fetuses has confirmed that a normal NST correlates with a fetus with no immediate danger of intrauterine demise. The appearance of spontaneous decelerations during the NST may reflect oligohydramnios and cord compression and associated with a high perinatal mortality rate. A 20-40 minute NST has a high false positive rate (80%). Prolonging the duration of the test up to 120 minutes reduces this false positive rate.

Patients with unknown LMP dates represent a diagnostic problem. If on repeated assessment of fetal growth parameters, functional signs remain normal, the fetus most probably is not growth restricted. However, when the growth rate is below the lower limit (5th percentile) the diagnosis of IUGR is established and efforts are then directed towards determining the cause, severity and prognosis.

Intrapartum management demands continuous fetal heart rate monitoring. Fetal scalp blood pH/lactate testing is utilized when uninterpretable fetal heart rate patterns occur. Caesarean delivery of the IUGR fetus should be considered when antepartum tests indicate deterioration of the fetal condition and the cervix is unfavorable for induction.

Table 1: Factors Associated with IUGR

Fetal	• Chromosomal abnormalities
	  • Autosomal trisomies (21,18,13)
	  • Monosomy deletion
	• Malformation
	• Fetal infection
	  • Cytomegalovirus
	  • Rubella

Placental	• Abruptio infarction • Placenta previa • Placenta accreta • Abnormal cord insertion • Circumvallate placenta • Chorioangioma • Twins • Prolonged gestation • Placental trisomies

Maternal	• Decreased nutrient availability
	  • Ileojejuneal bypass
	  • Inflammatory bowel disease
	  • Starvation
	• Decreased oxygen availability
	  • Hypertension
	  • Maternal vascular disease
	  • Smoking
	  • Cyanotic heart disease
	  • Obstructive lung disease
	  • High altitude
	• Drug ingestion and lifestyle habits
	  • Ethanol
	  • Narcotics
	• Previous IUGR

CONGENITAL ANOMALIES

About 3% of pregnancies will be complicated by major congenital malformation. Causes of developmental malformation are:

- Genetic: 20%
- Chromosomal: 5%
- Drugs/chemicals: 4-6%
- Infection/radiation: 1-2%
- Unknown: 65-70%

Screening for congenital anomaly

The first step in screening for congenital anomaly is an informed patient history. Identified risk factors on history, as described below, are indicators for initiation of prenatal counselling and potentially prenatal diagnosis procedures.

1. **History**
    - Maternal age: there is an association between advanced maternal age and aneuploidy. This is the most common indication for invasive prenatal diagnosis
    - Ethnic screening: A number of autosomal recessive genetic disorders occur more frequently in certain ethnic groups:
        - Carrier frequency of Tay-Sachs disease in Ashkenazi Jews is 1/31 (vs 1/277 in non-Ashkenazi subjects). Tay Sachs is also found at increased frequency in French Canadians or Cajun descent.
        - Carrier frequency of Cystic Fibrosis in North American Whites is 1/25
        - Hemoglobinopathies: Alpha thalassemia is common in individuals
        - of southeast and southwest Asia and African descent (5%). Beta thalassemia is common in Mediterranean and South East Asian populations (5-10%). Sickle cell disease carrier frequency in African-American population is 8%
    - Previous pregnancy with birth defect, chromosomal abnormalities or known genetic disorder
    - Parental carrier of balanced rearrangements
    - Multiple fetal losses, giving birth to a child with undiagnosed mental retardation
    - Consanguinity

    Additionally, prenatal counselling and potential prenatal diagnostic testing should be initiated if any of the following are found in the current pregnancy:
    - Fetus with suspected ultrasound abnormality
    - Abnormal serum marker screening
    - Exposure to a teratogen

Counselling

Ideally prenatal risk assessment is completed prior to pregnancy to allow time for medical review, testing and counselling. Usually the patient is asked to complete a self- administered questionnaire, followed by 3- generation pedigree. The findings are then reviewed by a physician using a non- directive approach. Often the issues raised involve complex social and ethical questions.

The first principle of counselling is to use terms readily comprehensible to patients. Written information can serve as a couple permanent records, alleviating misunderstanding. Counselling should include a confirmation of the diagnosis that was suspected at the time of referral to counselling. Counselling should be non-directive (i.e. the physician should not sway the patient toward a particular course of action. Couples experiencing abnormal pregnancy outcome show similar grief reaction that occur after

loss of loved one; denial, anger, guilt, bargaining and resolution. The understanding of psychological defenses described above helps to understand the failure of some intelligent couple to comprehend genetic information.

Prenatal Detection of Malformations and Prenatal Genetic Screening/Diagnosis

Please see Antepartum Care Chapter in this Syllabus for details regarding prenatal genetic screening options, diagnostic testing strategies, nuchal translucency ultrasound, and detailed anatomy ultrasound scan (18-20 week ultrasound).

Abnormalities of Amniotic Fluid Volume

Polyhydramnios: defined as amniotic fluid index ≥25cm or maximum vertical pocket ≥8cm. Causes of polyhydramnios in fetuses with structural malformation include anencephaly, absent stomach, esophageal and duodenal atresia (later is common in Down's syndrome), tracheoesophogeal fistula and neuromuscular disease. However, these conditions are mainly associated with severe polyhydramnios.

Oligohydramnios, defined as amniotic fluid index ≤5cm or maximum vertical pocket ≤2cm, may be associated with fetal anomalies including IUGR, renal agenesis, bladder neck obstruction, fetal chromosomal anomalies.

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2. SOGC Consensus Statements: Management of Twin Pregnancies (Part 1; No. 91, July 2000; Part 2; No. 92, August 2000)
3. SOCG Clinical Practice Guideline. Prenatal Screening for and Diagnosis of Aneuploidy in Twin Pregnancies. No. 262. July 2011.



Fetal Complications - Part II

Fetal Complications II Objectives:

At the end of the seminar, students should be able to:

Intrauterine Fetal Demise

1. Describe the common causes of fetal demise in each trimester
2. Describe the symptoms, physical findings, and diagnostic methods to confirm the diagnosis
3. Describe the management of a patient with fetal demise
4. Discuss the possible emotional reactions of the parents and their effect on management
5. Know of hospital and community resources to assist grieving parents
6. Discuss potential prevention of future fetal demise where possible
7. List the maternal complications associated with fetal demise including disseminated intravascular coagulopathy
8. Describe the methods for pregnancy termination, including their complications

Maternal and Newborn Mortality

1. Define the following terms, their causes, and epidemiologic rates:
    - Maternal death rate
    - Fetal death rate
    - Neonatal death rate
    - Perinatal death rate

Isoimmunization

1. Describe the pathophysiology of isoimmunization
2. List the indications for immunoprophylaxis
3. Describe the clinical circumstances under which isoimmunization is likely to occur
4. Describe the mechanisms of action of immunoprophylaxis
5. Describe the methods used to determine maternal isoimmunization and severity of fetal involvement

Multiple Pregnancy

1. Describe the etiology of monozygotic, dizygotic and multizygotic gestation
2. Describe the altered physiologic states of multifetal gestation
3. Describe the symptoms, physical findings and diagnostic methods
4. Describe the approach to antepartum, intrapartum and postpartum management

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INTRAUTERINE FETAL DEMISE

There is great sadness when a fetus dies. It triggers a change in management and in the patient's psychosocial needs. Almost 1% of women entering the second half of pregnancy will suffer the loss of their baby.

Diagnosis

The diagnosis is confirmed by the absence of fetal heart sounds detected by a Doppler device or by an ultrasound examination. Doppler is useful in picking up fetal heart sounds, but care should be taken to avoid mistaking transmitted maternal pulsation. The diagnosis is suspected when the mother lacks the appreciation of fetal movements and notices regression of uterine size.

Ultrasound will show the absence of fetal cardiac activity, potential skull collapse, poorly visualized midline falx, retraction of brain tissue, empty fetal bladder and a non-filled aorta. It may be helpful to show the women the findings as some women may report movement's hours or even days after the diagnosis is made.

Plain radiological signs:

- overlapping of the fetal skull bones (Spalding's Sign) or
- gas in the fetal circulation (Robert's Sign). Robert's sign is pathognomonic.

Attempts should always be made to elucidate the cause.

Management

It is essential that the cause of death be determined whenever possible by evaluating both the fetus and mother. Understanding the actual cause of death will help counsel the family regarding recurrence rate, prevention strategies, and often helps in the parental grieving process.

A thorough maternal past/present medical history and physical examination should be obtained. Possible causes and risk factors for fetal demise are in Table 1 (next page).

Table 1: Causes of Fetal Death

Maternal Systemic diseases	• Diabetes Mellitus • Hypertension, including preeclampsia • Any septicemia
Fetal	• Malformation: structural and chromosomal • Infection: bacterial, viral, protozoan • Fetal immune hemolytic disease • Cord accident: prolapse, amniotic band strangulation, cord compression • Metabolic disorders
Placental	• Dysfunctional: intrauterine growth restriction, postmaturity • Placental abruption • Placenta previa and vasa previa • Twin-to-twin transfusion syndrome • Maternal-fetal haemorrhage

Unless the history and physical examination lead to a cause, a basic laboratory test panel should be performed (see Table 2). If delivery is not likely to occur in near the future, amniocentesis may be performed to look for fetal infection and chromosomal anomalies. Placental pathology and fetal postmortem exam will also yield valuable information and should always be offered.

Table 2: Laboratory evaluation and follow-up of fetal death

On detection	
Maternal	• Fasting blood glucose, HbA1c • Platelet count, fibrinogen, indirect Coombs • CBC, antibody screen • Specific serology for targeted common infection (TORCH) • Betke Kleihauer test • Antiphospholipid antibodies, ANA, thrombophilia work-up
Fetal	• Karyotype analysis/microarray • Amniotic fluid culture for Cytomegalovirus, Parvovirus B19, herpes, aerobic and anaerobic bacterial culture
At follow-up	
Maternal	• Weekly fibrinogen level and platelets counts if fetal death > 4 weeks duration until delivery
Fetal (at delivery)	• Repeat infection work-up • Karyotype if not done prenatally • Total body X-ray • Postmortem examination including placental pathology

Delivery

Prior to 15 weeks, a D&C (dilatation and curettage) should be performed. Between 16 –20 weeks, one may consider a D&E (dilatation and evacuation) procedure or to induce labour using the prostaglandin derivative misoprostol. Most women (90%) will labour spontaneously within 3 weeks of detection of fetal death.

Maternal coagulopathy can occur after 20 weeks' gestation in 25% of cases, if undelivered for 4 or more weeks. Fibrinogen falls at a rate of 50 mg/dL per week, but is unlikely to cause a bleeding tendency until its level has fallen below 100mg/dL. This is also associated with a rise fibrin degradation products and a fall in platelets. The coagulopathy is thought to be a result of fibrinogen consumption following the release of thromboplastin from the retained products.

Parental psychological care

Most hospitals offer grieving support. Where appropriate, pastoral care may be helpful. Encourage the partner to stay and provide support. Parent(s) should be asked to view and hold the newborn and be informed that bruising and facial marks may be present. Neonatal footprints are made and the parent(s) are encouraged to name the child and provide a photograph of the child. The parent(s) are given an early follow up appointment (within 2 weeks) to discuss preliminary results and to assess mental wellbeing. A comprehensive discussion should take place within 3 months to discuss final investigation and postmortem results and make plans for future pregnancy.

MATERNAL AND NEWBORN MORTALITY

The field of obstetrics is concerned with all the physiological, psychological and social factors that influence the quantity and quality of human reproduction.

The field of obstetrics strives to minimize the number of women and infants who die as a result of the reproductive process. Vital statistics are important societal indicators for health and are collected re: maternal, perinatal, and neonatal events.

Vital statistics

- **Maternal death rate (maternal mortality rate)**
  - number of maternal deaths that result from the reproductive process per 100,000 live births
- **Fetal death rate (stillbirth rate)**
  - number of stillborn infants per 1,000 infants born
- **Neonatal death rate (neonatal mortality rate)**
  - number of neonatal deaths per 1,000 live births
- **Neonatal death**
  - *Early neonatal death* refers to death of a liveborn infant during the first 7 days after birth.
  - *Late neonatal death* refers to death after 7 but before 29 days.
- **Perinatal death rate (perinatal mortality rate)**
  - number of stillbirths plus neonatal deaths per 1,000 total births.

The *maternal mortality rate* in Canada has declined in the past 50 years. Currently it is 7.8/100,000. The main causes are: thromboembolism (20%), hypertensive disease (17%), haemorrhage (13%), ectopic pregnancy (10%), infection (8%), abortion related (6%), anesthetic complications (4%) and stroke (4%).

Perinatal mortality rate has fallen in the past 25 years. Currently perinatal death rate is 14.7 (7.8 fetal and 7.0 neonatal).

Neonatal death is caused primarily by prematurity followed by hypoxic injury to the brain and congenital anomalies.

The commonest cause of fetal death in the first trimester is **chromosomal abnormality**. In the third trimester, fetal death usually results from placental dysfunction (placental abruption, post-maturity), fetal prematurity, structural malformation, and maternal illness (diabetes mellitus, hypertension).

ISOIMMUNIZATION

The most important blood group system that may cause hemolytic disease of the fetus and newborn (HDFN) is the Rhesus system (though other RBC antigens, such as Kell, can be associated with HDFN). The Rh system is a complex one consists of various antigens.

Rh Blood Group System

Controversy exists regarding its nomenclature and genetics. The *hypothesis presented by Race and Fisher* is simple and practical. Fisher suggested the Rh antigens are grouped in 3 pairs: Dd, Cc, and Ee. The antigens are inherited in two sets of three, one set being contributed by each parent. The presence of D antigen determines whether the individual is Rh positive. The reciprocal of D, (d), has never been found, therefore, it is the absence of D (not the presence of d) that determines that a person is Rh(D)- negative. It is the production of antibodies in Rh(D)-negative women, a response to exposure to Rh(D)-positive blood, usually from a fetus, that creates the possibility of developing HDFN of a Rh(D)- positive fetus.

About 45% of Rh-positive individuals are homozygous for D and the other 55% are heterozygous, having inherited a D-containing set from one parent and a non-D containing set from the other parent. The genotype for D of the Rh-positive father, where the mother is Rh-negative, is important. If the father is homozygous, all of his children will be Rh-positive.

The incidence Rh-negative status in Caucasian is 15%, 30 – 35%, in the Basque population, 4 – 8% in Black Africans and 1 – 2% in North American Indigenous or Inuit populations.

Pathogenesis of Hemolytic Disease of the Fetus and Newborn

The Rh(D) antigen is confined to the red blood cell (RBC) membrane. *A primary Rh immune response develops in Rh(D)-negative mother exposed to Rh(D)-positive RBC.* The usual primary immune response is weak and slow (8 –9 weeks before response is detected after exposure) and consists mostly of gamma M immunoglobulin (IgM). IgM anti-D has a large molecular weight of 900 000 cannot cross the placenta, therefore, cannot cause fetal RBC hemolysis. Rh-immunized women quickly convert to production of IgG anti-D (molecular weight 160 000), which readily crosses the placenta and causes fetal RBC

hemolysis. Following primary immune response, a second exposure to Rh-positive RBC produces a rapid and strong immune response *(secondary immune response)*.

The basic pathogenesis is the destruction of Rh-positive fetal RBC's by maternal Rh antibodies (IgG anti-D). Red blood cell destruction produces fetal anemia. When the capacity of bone marrow red blood cell production cannot keep up with RBC destruction, extramedullary sites (liver, spleen) produce RBC causing hepatosplenomegaly. Fetal anemia will develop when RBC's production falls behind RBC's destruction leading to the development of hyperdynamic state and fetal hydrops.

The mechanism of RBC destruction by anti-D (IgG or IgM) is different than ABO system which is complement mediated. Anti-D attaches to Rh antigen in RBC cell membrane increasing chemotaxis (attraction of phagocytes to the RBCs). Adherence and rosette formation occur in the spleen allowing the macrophage to attach themselves to the antibody-coated RBC causing destruction of part of cell membrane which later heals. Loss of membrane substance produces a fragile RBC, which is susceptible to lysis. Phagocytosis of entire antibody-coated RBC does occur, but has a small role in Rh hemolysis.

Table 3: Classification of Severity of Rh Hemolytic Disease

		Incidence
Mild	Indirect bilirubin 16-20 mg/dL, no anemia, no treatment needed	45-50%
Moderate	No fetal hydrops, moderate anemia; Severe jaundice with risk of kernicterus	25 -30%
Severe	Fetal hydrops in utero Before 34 weeks After 34 weeks	20 - 25% 10 - 12% 10 - 12%

Incidence of Rh Immunization

ABO incompatibility between Rh-positive fetus and its Rh-negative mother offers protection against Rh immunization. The risk of first Rh-positive, ABO- compatible baby is 16% and for ABO-incompatible baby is 2%. The incidence is 2% after spontaneous abortion and 5% after therapeutic abortion at 20 weeks.

Isoimmunization Prophylaxis

It has been demonstrated in animal and clinical research that administration of Rh antibody prevents Rh immunization. Rh immune globulin (RhIG) has been used in North America for over 35 years, the standard dose is 300 mcg, given intramuscularly. In order to prevent Rh immunization, RhIG should be administered:

1. Before Rh immunization has developed.
2. In adequate dosage.

The exact mechanism by which Rh antibody prevents Rh immunization is unknown.

Recommendations for the use of RhIG for prevention of Rh isoimmunization

1. Every Rh-negative, unimmunized women who delivers an Rh-positive baby.
2. Every Rh-negative, unimmunized women after abortion (spontaneous, therapeutic or ectopic)
3. Every Rh-negative, unimmunized women, following amniocentesis or chorionic villus sampling.
4. Every Rh-negative, unimmunized women at 28 weeks' gestation or experienced vaginal bleeding prior to 28 weeks, unless the father is Rh – negative and paternity is certain.
5. After massive transplacental hemorrhage of Rh-positive fetus into an Rh-negative mother. In general, 300 mcg of RhIG should cover approximately 15 mL of fetal RBC or 30 mL of fetal whole blood; 120 mcg of RhIg should cover approximately 6 mL of fetal RBC. In cases of events potentially associated with fetomaternal hemorrhage (FMH) e.g. placental abruption, blunt trauma to the abdomen etc., quantitative testing for FMH may be considered , If FMH is in excess of the amount covered by the dose given, 10 mcg additional RhIg should be given for every additional 0.5 mL of fetal red blood cells.

Management of Pregnancy

Mother's ABO group and, where paternity is known and confirmed, father's Rh status and ABO group should be determined. If the father is Rh-positive, the overall risk is determined using ABO group (16% risk for compatible vs 2% for incompatible ABO group).

For women not Rh-isoimmunized, repeat antibody testing after initial first trimester test may be done at 28 weeks' gestation. Administer RhIG as under prevention above provided the antibody testing remains negative.

During labour, manual removal of the placenta and Caesarean section may increase the risk and volume of fetomaternal haemorrhage.

After delivery, cord blood is obtained for ABO group, Rh type and direct *antiglobulin test (Coombs)*. Maternal blood is tested for Rh antibody and to determine the amount of fetal cells in maternal circulation (*Betke Kleihauer and flow cytometry*) in order to determine the accurate dose of RhIG required postpartum.

For isoimmunized women the following will predict the severity of Rh hemolytic disease:

1. **History of fetus or infant with Rh disease**
   For women with one hydropic birth, the likelihood to have another hydropic fetus in future pregnancy is 90% and generally occur, in the later fetus, at the same time or earlier in gestation.

2. **Maternal Rh antibody titre**
   Titres are described as the highest dilution where the antibody is still able to cause agglutination of the antigen. The titre level determines if the fetus is at risk, but cannot predict severity of disease accurately. Each laboratory should determine the level of antibody at which there is

significant risk of fetal hydrops (critical titre). In some laboratories, this risk has been determined using the albumin Rh antibody titer as follow: 1:16 risk is 10%, 1:32 (25%), 1:64, (50%), 1:128 (75%). Rh antibody titre and maternal history are insufficient to allow proper management.

3. **Amniotic fluid optical density measurement**
   Serial determination of bilirubin in amniotic fluid, using amniocentesis, correlates with the degree of fetal hemolysis/ hemoglobin. The overall accuracy of prediction of severity of hemolytic disease using amniotic fluid optical density is 95%. This technique was historically used however has largely been replaced with the development of non-invasive fetal middle cerebral artery Doppler (peak systolic velocity) testing for prediction of fetal anemia.

4. **Ultrasound examination**
   Ultrasound is used frequently to determine fetal wellbeing and to assess for the risk of fetal anemia or hydrops. Doppler measurement of the middle cerebral artery peak systolic velocity (PSV) is useful in predicting fetal anemia. Ultrasound can also look at the liver, spleen, placental size, assess for fetal ascites, pleural and pericardiac effusion; all of which can be used to predict and/or diagnose fetal hydrops. Based on the above predictors and especially the MCA PSV, intrauterine fetal transfusion can be started when risk of hydrops is great (severe anemia) or hydrops has developed.

5. **Timing and location of delivery**
   When history and fetal MCA Doppler determines a mild or unaffected fetus, delivery can proceed to term in a well-equipped regional hospital. For fetuses requiring multiple intrauterine transfusions, delivery is accomplished once fetal lung maturity is established or at 36 –38 weeks in a tertiary care hospital. The baby will require intensive photo therapy and may need exchange blood transfusion. All infants born to isoimmunized mothers should be followed for the development of jaundice.

MULTIPLE PREGNANCY

The incidence of twin gestations across Canada has increased by 15% over the years 1993-1997 and this has been the major contributing factor to the rising incidence of preterm birth.

Etiology of multiple gestation

Multiple gestation may be defined as any pregnancy in which two or more embryos or fetuses exist simultaneously. Multiple gestation may occur as the result of the division of a fertilized egg, fertilization of more than one egg by more than one sperm, or a combination of the two processes. The former process results in monozygotic (identical) twins, whereas the latter results in dizygotic (fraternal) twins. Because dizygotic twins arise from two fertilized eggs, they will always have two amnions (diamniotic) and two chorions (dichorionic); the placentas may be either separate or fused, and the sexes may be different. With dizygotic twinning, the eggs may not be fertilized at the same time. Superfecundation may occur, in which two ova are fertilized within a short period of time but not at the same coitus.

Monozygotic twins may arise from cleavage of a fertilized egg at various stages during embryogenesis, and the relationship of the fetal membranes depends on the time at which the embryo divides.
If time of cleavage is within:

- **0 to 72 hours of fertilization:** dichorionic, diamnionic, monozygous twins
- **4 to 8 days of fertilization:** monochorionic, diamnionic, monozygous twins
- **9 to 12 days of fertilization:** monochorionic, monoamnionic, monozygous twins
- **>13 days of fertilization:** conjoined twins

Of all monozygotic twins, 70% are monochorionic and of these, almost all are diamnionic. Chorionicity does have important clinical relevance, in that monochorionic twins have a higher incidence of complications than dichorionic twins.

The optimal time for determining chorionicity by ultrasound is between 10-14 weeks' gestational age. Ultrasonography can determine chorionicity by examining the appearance of the membranes between the fetuses. The lambda sign is seen with dichorionic twins and the T-sign is seen with monochorionic twins. This ultrasound clue is not clearly seen in the second and third trimester, so it is important that the ultrasonographer recognize and document this finding on the first trimester scan report.

The frequency of multiple gestation varies throughout the world. Dizygotic twinning increases with a maternal history of twinning, increasing maternal age, and increasing maternal parity. The incidence of monozygotic twinning, 1 in 250 births, is constant throughout the world. In North America, twinning occurs in about 1 in 90 gestations. One third of these twin gestations are monozygotic and two thirds are dizygotic. Twinning in western Nigeria is 1 in 22 due to a higher incidence of multiple ovulation and higher rates of dyzygotic twinning. The incididence of twins increases with artificial reproductive technologies. The incidence of multiple gestation with the use of clomiphene is about 10% versus 30% following gonadotropin therapy.

Figure 1: Diagrammatic representation of the major types of twin placentas found within monozygotic twins

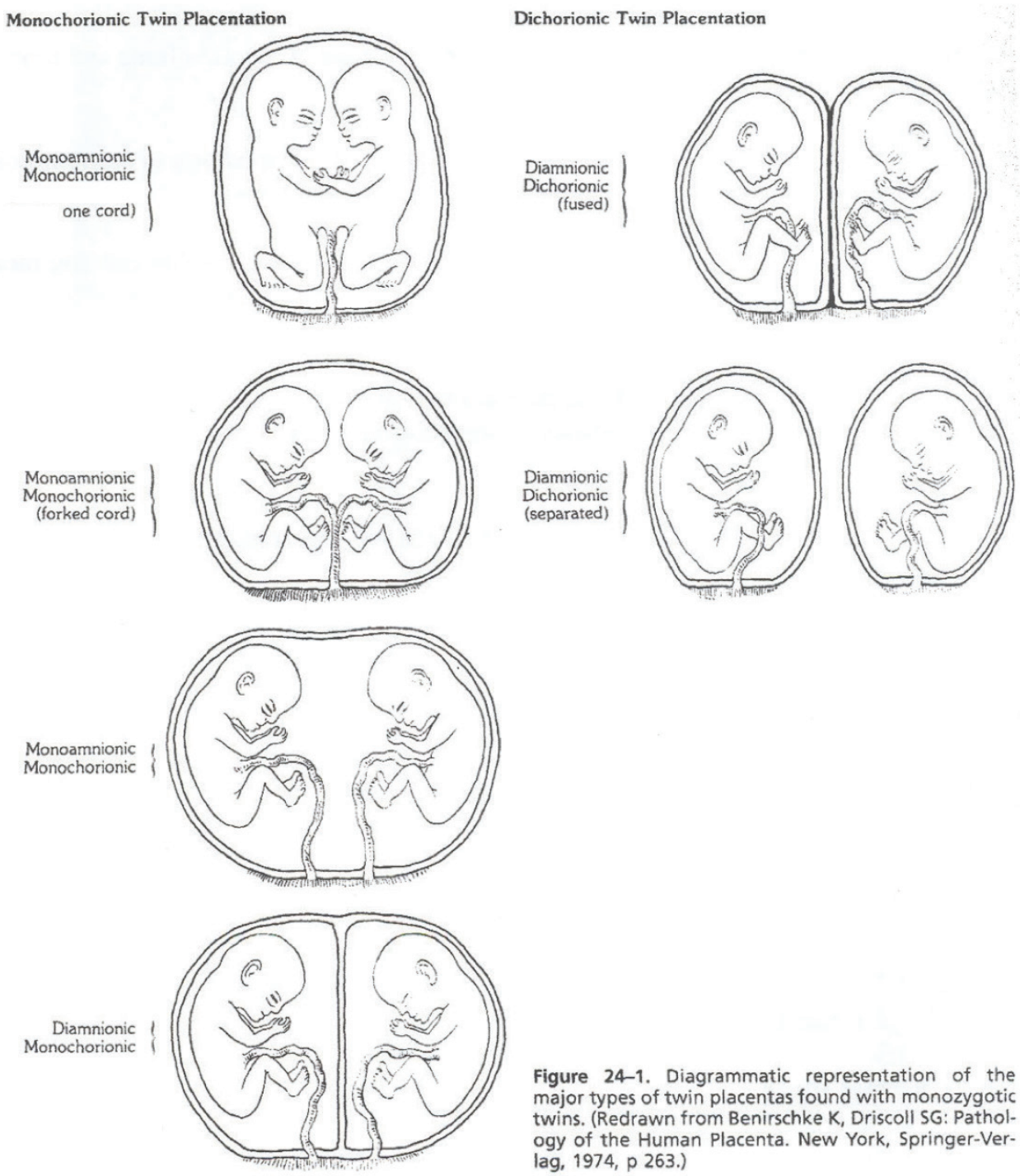


Figure 24–1. Diagrammatic representation of the major types of twin placentas found with monozygotic twins. (Redrawn from Benirschke K, Driscoll SG: Pathology of the Human Placenta. New York, Springer-Verlag, 1974, p 263.)

Maternal Physiologic changes associated with multiple pregnancies

A number of normal maternal physiologic responses to pregnancy are exaggerated with multiple fetuses:

- Blood volume: increases 500 ml or more over that of a singleton pregnancy
- Increased requirements for iron and folic acid
- Anemia: greater predisposition because of greater increase in blood volume and more need for iron and folic acid

- Increased respiratory difficulty: increased size of uterus, predisposition to hydramnios, overdistension of uterus causes greater elevation of the diaphragms
- Increased compression of great vessels: again by the overdistended uterus, causing more pronounced decrease in uterine blood flow due to aortic compression, and/or supine hypotension.
- More pronounced ureteral dilatation: greater compression of the ureters by the overdistended uterus can lead to obstructive uropathy and renal failure.

Risks for the mother and fetuses associated with multiple gestation

Increased Maternal Risks

- Anemia
- Polyhydramnios
- Ureteral dilatation and obstruction (rare)
- Gestational hypertension, pre-eclampsia
- Gestational diabetes
- Preterm labour and delivery
- Postpartum uterine atony
- Postpartum hemorrhage
- Instrumental vaginal delivery
- Caesarean delivery
- Genital tract trauma
- Increased incidence VTE

Increased Fetal Risks

- Spontaneous abortion
- Malpresentation
- Placenta previa
- Premature rupture of membranes
- Preterm labour and delivery
- Umbilical cord prolapse
- Intrauterine growth restriction
- Discordant growth between twins
- Congenital anomalies
- Conjoined twins
- Twin-twin transfusion syndrome in monochorionic twins
- Increased perinatal morbidity and mortality: respiratory distress syndrome, birth trauma, cerebral hemorrhage, birth asphyxia, birth anoxia, congenital anomalies, stillbirths, prematurity

Placental Vascular Anastomoses

Occur almost exclusively in monochorionic twins. The most common type is arterial-arterial, followed by arterial-venous and then venous-venous. Vascular communications between the two fetuses via the placenta may give rise to a number of problems, including abortion, poly hydramnios, twin-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS), and fetal malformations. The incidence of both minor and major congenital anomalies in twins is twice that in singletons, the majority of malformations occurring in monochorionic twins.

Twin-Twin Transfusion Syndrome

- Occurs in approximately 10% of monochorionic twins
- Due to presence of arteriovenous anastomoses in the placenta
- Arterial blood from donor twin enters placenta through cotyledon shared by twins
- Blood then empties into vein of recipient twin

- Results in chronic shunting of blood from donor twin to recipient twin
- Donor twin develops hypovolemia, hypotension, anemia, growth restriction and oligohydramnios
- Recipient twin develops hypervolemia, hyperviscosity, thrombosis, hypertension, cardiomegaly, polycythemia, edema, congestive heart failure, and polyhydramnios
- Recipient twin is at risk for developing kernicterus in neonatal period due to the polycythemia and hyperbilirubinemia

Fetal Malformations

- Arterial-arterial placental anastomoses may result in fetal malformations
- Arterial blood from donor twin enters arterial circulation in placenta of recipient twin
- Blood flow may become reversed in recipient twin such that it is perfused with relatively poorly oxygenated blood leading to poor fetal development-embolization can occur in recipient twin due to trophoblastic tissue entering its circulation

Umbilical Cord Abnormalities

- Occurs in higher frequency, particularly in monochorionic twins
- Absence of one umbilical artery occurs in about 3-4% of twins (0.5-1% In singletons)
- 30% of cases associated with other problems (such as renal agenesis)
- Other abnormalities include velamentous umbilical cord insertion

Management during the antepartum course, labour and postpartum period

Antepartum Management

- More frequent visits (q2weeks from mid second trimester, q1week from third trimester onward)
- Increased need for calories, iron, calcium and folic acid
- Earlier check for gestational diabetes
- First trimester ultrasound to determine chorionicity: monochorionic twins are at higher risk and will require greater surveillance and consideration of transfer to high risk centre antenatally

Discussion About Genetic Screening/Diagnosis

- Biochemical screening for aneuploidy is possible in twins
- First trimester serum screening combined with nuchal translucency (NT) may be considered in twin pregnancies as it has lower false-positive rates compared to screen by nt and maternal age only
- Maternal serum alpha fetoprotein is useful for detection of open neural tube defects though in recent years we have discontinued routine AFP testing and rely on the anatomy scan to detect for open neural tube defects, except for in cases where imaging can be difficult (e.g. elevated BMI).
- Amniocentesis comes with increased risk – need to check both twins in dizygotic pregnancies
- NIPT is possible in twins
- Women carrying a twin pregnancy should be offered genetic counselling and consideration for invasive testing

Labour

- Consider delivery in hospital
- Large bore intravenous access
- Continuous fetal monitoring
- Anaesthesia to be immediately available
- Recommend epidural analgesia
- Ultrasound availability to determine fetal presentations, lie etc during labour
- Adequate obstetrics, paediatrics, respiratory therapists to deliver and look after multiple neonates
- Appropriate number of nurses available
- Delivery to occur in Caesarean section room with "double set up" i.e. Everything is ready for a possible Caesarean delivery in case of complications

Vertex (Twin A)/Vertex (Twin B):

- Expect to have vaginal delivery for both twins
- After delivery of first twin (Twin A), clamp and cut cord
- Do vaginal exam to assess presentation and station of second twin, use US if needed to determine presentation and to assess for FHR
- Allow labour to continue if second twin is vertex
- Continuously monitor second twin
- If contractions decrease, use oxytocin to improve the contractions
- When head low enough, rupture membranes, wait for cervix to fully dilate again and anticipate a spontaneous vaginal delivery
- Optimal time interval between delivery of twins is controversial
- A longer interval may be allowed if the second twin exhibits a reassuring fetal pattern and there is no excessive bleeding

Vertex (Twin A)/Breech (Twin B) or Vertex (Twin A)/Transverse (Twin B):

- First twin may be delivered vaginally (spontaneously) and the second twin may be delivered vaginally by breech extraction

Twin A is Breech:

- Deliver by Caesarean section

Postpartum:

- After delivery of second fetus, the cord blood samples are obtained and placentas are delivered
- Oxytocin should be given to reduce risk of uterine atony and postpartum hemorrhage

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Gynaecology



Vulvar and Vaginal Disease and Lower Genital Tract Sexually Transmitted Infections (STIs)

Vulvar and Vaginal Disease and Lower Genital Tract STIs Objectives:

At the end of the seminar, students should be able to:

1. Understand the normal vulvar appearance and anatomy.
2. Understand the normal vaginal appearance and physiologic variations in secretions.
3. Describe the common clinical presentation, evaluation and management of common vulvar problems including:
    - Condyloma (HPV)
    - Herpes genitalis (herpes simplex virus)
    - Primary syphilis
    - Dermatologic conditions
    - Bartholin's gland disease
4. Describe the common clinical presentation, evaluation and management of common vaginal problems including:
    - Yeast vaginitis
    - Bacterial vaginosis
    - Trichomonas vaginitis
    - Foreign body
    - Atrophy
5. Describe the common clinical presentation, evaluation and management of prepubertal vulvovaginitis.
6. Describe the common clinical presentation, evaluation and management of vulvodynia.

Last revised: July 2019

VULVA

Normal Anatomy

- **Labia Majora:**
    - Comprised of hair-bearing skin containing eccrine and apocrine glands
- **Labia Minora:**
    - Contains sebaceous glands, but no sweat glands or hair follicles
    - "Fordyce" spots are tiny, raised, yellow lesions that are normal variant
- **Vestibule:**
    - The collision area between vagina and vulva
    - Non-keratinized, non-pigmented area containing minor vestibular glands as well as Skene's and Bartholin's glands
    - Skin is very sensitive to moisture and as a result, can form papillae that may easily be mistaken for viral disease
    - Openings of the minor vestibular glands are often erythematous on close inspection, appearing as infective lesions

Vulvar Problems

Human Papillomavirus (HPV)

- **Virology and Epidemiology**
    - Double-stranded DNA virus with over 200 subtypes
    - 40 subtypes can infect anogenital epithelium
    - Most common STI worldwide; most common viral STI in Canada
    - >80% of women have an HPV infection at some time during life (lifetime prevalence)
    - >80% of HPV infections clear spontaneously
- **Clinical Presentation**

  3 clinical outcomes following HPV infection:
    - Asymptomatic/subclinical (majority)
    - Anogenital warts (1% of adults infected with HPV; 90% of warts caused by HPV types 6, 11)
    - Genital tract neoplasia (caused by HPV types 16, 18, 45, 31, and others)
- **Investigations**
    - Diagnosis of genital warts is usually visual - can biopsy if unsure
    - HPV DNA testing now available, use increasing as a way to triage abnormal Paps
    - Pap smears, colposcopy and biopsy can also demonstrate HPV cellular changes
- **Treatment**
    - Choice of treatment guided by patient preference, physician experience, & resources
    - All treatment modalities have very similar efficacy and recurrence rates

    - Patient-applied
        - Imiquimod 5% cream (Aldara) - an immune modulator, applied at bedtime 3 times per week for up to 16 weeks, most common side effect is local skin irritation
        - Podofilox 5% solution - applied twice daily for 3 consecutive days in one week and then repeated for up to 4 weeks
    - Provider-administered
        - Podophyllin (contraindicated in pregnancy)
        - Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80-90% (safe in pregnancy)
        - Cryotherapy with liquid nitrogen or cryoprobe
        - Surgical removal (excision, cautery, laser)
- **Prevention**
    - HPV vaccines
        - Bivalent (HPV 16 & 18)
        - Quadrivalent (HPV 6, 11, 16, 18)
        - 9-valent (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58)
        - Other vaccines are in development

Herpes Simplex Virus (HSV)

- **Virology and Epidemiology**
    - One of the most common sexually transmitted infections in North America and worldwide
    - Most common cause of vulvar ulcers
    - HSV-2 seroprevalence in general population is ~20%
- **Investigations**
    - Viral culture (sensitivity declines as lesion heals)
    - HSV DNA PCR
    - Serologic type-specific tests for antibodies to HSV-1 & HSV-2
- **Treatment**
    - Treatment is with antiviral medications and dosing regimens listed below are suggestions/recommendations. If these regimens aren't effective, then may need to consult with expert.
    - First Episode Genital Herpes
        - Acyclovir 200 mg po 5 times daily (or 400 mg po tid) OR famciclovir 250 mg po tid OR valacyclovir 1g po bid, all for 5-10 days
    - Recurrent Genital Herpes - Episodic Therapy
        - Acyclovir 200 mg po 5 times daily for 5 days (or 800 mg po tid x 2 days) OR famciclovir 125 mg po bid for 5 days OR valacyclovir 500 mg po bid (or 1g po daily) for 3 days
    - Recurrent Genital Herpes - Daily Suppressive Therapy to Prevent Outbreaks and decrease viral shedding
        - Consider for patients with frequent (≥6) recurrences per year or if outbreaks very bothersome

        - Acyclovir 200 mg po tid (or 400 mg po bid) OR famciclovir 250 mg po bid OR valacyclovir 500 mg po daily (or 1g po daily)
    - Recurrent Genital Herpes - Daily Suppressive Therapy to Prevent Sexual Transmission to Partners
        - Valacyclovir 500 mg po daily

Syphilis (Treponema Pallidum)

- **Epidemiology**
    - Rates increasing over past 10-15 years
    - Rates in Toronto have increased by 200-300%
- **Clinical Presentation**
    - Primary Syphilis - local infection, painless chancre (ulcer), heals in 3-6 weeks
    - Secondary Syphilis - systemic infection, flu-like illness with rash (palms & soles)
    - Latent Syphilis - no clinically active disease, can last for many years, many patients stay in this stage and never progress beyond
    - Tertiary/Late Syphilis - end organ disease, neurosyphilis, CV disease, gummas
- **Investigations**
    - Darkfield Examination
        - Most sensitive & specific diagnostic test for syphilis
        - A positive test shows spirochetes in serous fluid scraped from lesion
    - Non-treponemal tests (VDRL, RPR)
        - Screening tests (multiple causes of false positive tests)
        - Detect antigens not specific to treponemes
        - Reported as titers, with titer level corresponding to disease activity
        - 4-fold change in titer represents a significant change
        - In most patients these tests will eventually become nonreactive after treatment
    - Specific Anti-treponemal Antibody Tests (FTA-ABS, MHA-TP, TP-PA, EIA)
        - Confirmatory tests (fewer causes of false positive tests, but still possible)
        - Will remain reactive for life, even after adequate treatment
        - Many public health units (including Toronto Public Health) use a specific test as first line, and if positive then follow that with a non-treponemal test and another specific test to confirm whether a recent or remote infection
- **Treatment**
    - For primary, secondary, and latent <1 year duration: benzathine penicillin G 2.4 million U IM in a single dose (or doxycycline 100 mg po bid for 14 days if penicillin allergic)
    - For latent >1 year duration and tertiary: benzathine penicillin G 2.4 million U IM weekly for 3 successive weeks
    - For neurosyphilis: aqueous crystalline penicillin G 3-4 million U IV q4 hours for 10-14 days
    - Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin

Lichen Sclerosus

- **Clinical Presentation**
    - Intense vulvar itching and burning
    - On exam - whitish figure of 8 distribution around vulva and anus
    - If patient has scratched skin, may see purpura, skin hemorrhage and ulceration
- **Investigations**
    - Diagnosis is usually visual, but may consider biopsy
- **Treatment**
    - High potency local steroid cream (clobetasol) is first line treatment
    - Testosterone cream, progesterone cream, and low dose steroid cream less effective
    - Treatment is long-term, with recurrence possible if/when treatment stopped

Lichen Simplex Chronicus

- **Clinical Presentation**
    - Itching and burning, especially at night, leading to chronic irritation
    - On exam - leathery skin appearance, especially on labia majora
    - Also known as squamous cell hyperplasia
- **Investigations**
    - Diagnosis is usually visual, but may consider biopsy
- **Treatment**
    - Short course (2-3 weeks) high or medium potency local steroid cream
    - Antihistamines may be helpful for itching especially at night

Lichen Planus

- **Clinical Presentation**
    - Plaques on genital skin with erosion of vestibule and extension into vagina
    - Loss of normal vaginal structure and erosion of vaginal walls (desquamative vaginitis)
    - Patients also may have oral lesions (lacy, white, web-like)
- **Investigations**
    - Diagnosis is usually visual but may consider biopsy
- **Treatment**
    - Local steroid creams or foams intravaginally
    - Anti-immune therapies such as cyclosporine may also be used

Bartholin's Gland Disease

- **Clinical Presentation**
    - Cysts result from obstruction of the Bartholin's duct in the posterior third of the vestibule
    - Cysts can become infected resulting in a painful swelling (abscess)
    - Located with centre at labia minora, partly extending into and partly outside the vagina

- **Investigations**
    - Diagnosis is usually visual
- **Treatment**
    - Incision and drainage through the vestibular area not the skin surface followed by insertion of a Word catheter (to keep cyst cavity open while healing)
    - Marsupialization- surgical procedure to open the cavity and suture it to remain open while healing

Vulvodynia

- **Clinical Presentation**
    - Painful vulvar area (common symptoms are pain, burning, discomfort) with no visible lesions or evident cause
    - Manifests as generalized vulvar discomfort
- **Investigations**
    - Usually a diagnosis of exclusion
- **Treatment**
    - Patient support very important
    - Local moisturizers and barrier creams
    - Cold compresses
    - Xylocaine jelly
    - Systemic nerve blocking with medications such as Amitriptyline 30-75 mg qhs or Neurontin 1000-2000 mg daily
    - Biofeedback
    - Pelvic floor physiotherapy

VAGINA

Physiologic Causes of Vaginal Discharge

- Not all vaginal discharge is infectious
- Up to 40% of cases are physiologic or have a mixed etiology:
    - Excessive physiologic secretions
    - Hypersensitivity- can be caused by latex condoms, spermicides, vaginal douches, soaps, bath oils, genital preparations
    - Dermatologic conditions- eczema, lichen sclerosus, lichen planus, psoriasis
    - Hormone-related- cyclic, menarche, menopause, pregnancy, exogenous (OCP, HRT)
    - Genital atrophy
    - Foreign body
    - Trauma
    - Lack of proper lubrication during intercourse

Important Points on History

1. Duration of symptoms
2. Presence or absence of vaginal discharge
    - Colour
    - Amount
    - Nature- thin/thick, runny, watery, clumpy, frothy
3. Presence or absence of odour
4. Irritative symptoms- itching/pruritis, burning, pain
5. Dysuria, dyspareunia
6. Any associated skin changes or lesions- erythema, vesicles, ulcers, bleeding points
7. Are symptoms temporally associated with menstrual cycle, intercourse?
8. Product use in vaginal/vulvar area- soaps, detergents, douches, tampons/pads
9. Is patient sexually active & any symptoms in sexual partners
10. Past history of vaginal infections (culture proven?) & treatments used (effective or not?)
11. Current medications

Important Points on Physical Examination

1. Inspection of external genitalia
    - Skin colour & texture, erythema, excoriations, vesicles, ulcers
2. Inspection of vagina and cervix
    - Discharge, edema, colour, lesions
3. pH test of vaginal secretions
4. Wet mount slide with normal saline and potassium hydroxide (10% KOH)
5. KOH whiff test
6. Bimanual examination
    - Cervical motion tenderness, uterine size/shape/orientation/tenderness/mobility, adnexal masses/tenderness/mobility

pH Test of Vaginal Secretions

- Performed by applying small amount of vaginal fluid/secretions collected from lateral vaginal wall to pH paper
- Vaginal pH correlates with the bacterial balance
- Normal vaginal pH is acidic, ≤4.5 (usually 3.8-4.2)
- Vaginal pH with yeast infection ≤4.5
- Vaginal pH with bacterial vaginosis or Trichomonas vaginalis >4.5
- pH measurement unreliable in presence of blood or semen

Wet Mount

- Microscopic examination of vaginal fluid/secretions mixed with normal saline & 10% KOH
- Should be performed under low (10x) and high (40x) powers
- Normal saline slide useful for assessment of vaginal flora, bacteria, inflammatory cells (WBCs), epithelial cells & clue cells, motile trichomonads
- KOH destroys (lyses) most of the epithelial cells & WBCs, allowing assessment of yeast (budding yeast, hyphae, pseudohyphae)

KOH Whiff Test

- Performed by passing swab of vaginal fluid/secretions mixed with 10% KOH under nose for quick whiff
- In the presence of bacterial vaginosis (and sometimes T. vaginalis) there will be a strong, fishy odour
- This occurs because the alkaline KOH liberalizes the amines produced by bacterial vaginosis or T. vaginalis

Differential Diagnosis of Vaginal Secretions (Table 1)

Diagnostic Criteria	Syndrome			
	Normal	**Bacterial Vaginosis**	**Trichomonas Vaginitis**	**Candida Vulvovaginitis**
Vaginal pH	3.8-4.2	>4.5	>4.5	≤4.5 (usually)
Discharge	White, clear, flocculent	Thin, homogenous, white, grey, adherent, often increased	Yellow-green, frothy, adherent, increased	White, curdy, 'cottage cheese-like', sometimes increased
Amine Odour (KOH Whiff Test)	Absent	Present (fishy)	May be present (fishy)	Absent
Primary Symptoms	None	Discharge, bad odour (possibly worse after intercourse)	Frothy discharge, bad odour, vulvar pruritis, dysuria Frothy discharge, bad odour, vulvar pruritis, dysuria	Itching/burning, discharge
Microscopy	Lactobacilli, epithelial cells	Clue cells with adherent coccoid bacteria, paucity of lactobacilli, no WBCs	Trichomonads, WBCs>10/hpf	Budding yeast, hyphae, pseudohyphae

Vaginal Discharge

- **Investigations**
    - pH test, wet mount, KOH whiff test
    - Gram stain
    - Culture
        - Although bacterial vaginosis is best diagnosed with wet mount, wet mounts are only 50-60% sensitive for T. vaginalis & yeast, so culture can be useful

- Also useful for identifying specific species of yeast (not all vaginal yeast is Candida albicans)

- **Treatment**
  1. *Bacterial Vaginosis*
     - Preferred treatment is metronidazole 500 mg po bid for 7 days
     - Alternatives are metronidazole 2g po in a single dose, metronidazole gel 0.75%, clindamycin cream, clindamycin orally
     - No treatment required for male sexual partner
  2. *Trichomonas vaginitis*
     - Preferred treatment is metronidazole 2g orally in a single dose
     - Male sexual partner should also be treated
  3. *Yeast vaginitis*
     - Multiple intravaginal over the counter preparations are available, including ovules & creams for 1, 3, or 7 days
     - Topically applied azole drugs (eg. miconazole, clotrimazole, etc.) are more effective than nystatin
     - Oral therapy also available (fluconazole 150 mg po in a single dose) and equally effective
     - Vaginal boric acid suppositories effective and especially useful for recurrent yeast
     - No role for treatment of male sexual partner unless yeast balanitis is present

Atrophic Vaginitis

- **Investigations**
  - Diagnosis of atrophy is usually visual, with thinning of the tissues, erythema, petechiae, bleeding points, and dryness
- **Treatment**
  - Estrogen vaginal cream (most common is Premarin)
  - Vaginal estrogen tablets (vagifem) or ring (estring)
  - Consider oral estrogen
  - Water-based lubricants and moisturizers can also be helpful (Replens, Astroglide) to relieve symptoms of dryness and to provide lubrication for intercourse

Prepubertal Vulvovaginitis

Multiple causes, including infectious agents, foreign body (most common), trauma.

- **Investigations**
  - Avoid speculum examination unless there is unexplained bleeding
  - Exclude the presence of a foreign body
  - If excluded, obtain vaginal swabs (not cervical) for Gram stain, cultures, wet mount
- **Treatment**
  - Depends on initiating cause

CERVIX

Mucopurulent Cervicitis

- Defined as the presence of a mucopurulent discharge from the endocervix, and erythema, edema, and friability of the cervix
- Grossly purulent cervical mucus indicates a high concentration of WBCs
- The 2 major causes are Neisseria gonorrhoeae & Chlamydia trachomatis; there may also be a role of the genital mycoplasmas (Mycoplasma hominis, Ureaplasma urealyticum), but this is more controversial
- In many cases, no organism can be isolated

Diagnosis

- Endocervical swabs to diagnose Neisseria gonorrhoeae & Chlamydia trachomatis
- N. gonorrhoeae can be demonstrated on Gram stain (Gram-negative diplococci), culture on enriched bacteriologic medium (most common is Thayer-Martin), or nonculture assays (nonamplified DNA probe tests & nucleic acid amplification techniques such as LCR or PCR)
- C. trachomatis can be demonstrated using cell culture, and nonculture assays. The most sensitive & specific tests are nucleic acid amplification tests (LCR, PCR)
- Some clinical settings now use a single nucleic acid amplification swab which tests for both organisms
- Increasing use of first void urine to test for GC and chlamydia in asymptomatic individuals for screening

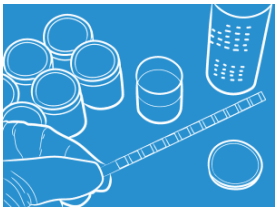
Treatment of N. gonorrhoeae

- Patients should be co-treated for Chlamydia unless it has been ruled out, because of high rate of coinfection
- Recommended treatment options include: ceftriaxone 250 mg IM OR cefixime 800 mg po in a single dose
- Ceftriaxone is now the recommended first choice in Canada due to higher bioavailability, with cefixime as an alternate choice
- Quinolones are not recommended if the case or contact are from an area with rates of quinolone resistance >3%-5% (most of Canada)
- In cases of cephalosporin allergy, alternative treatment is with azithromycin 2g po PLUS gentamycin 240 mg IM in 2 separate 3 mL injections of 40 mg/mL solution
- Spectinomycin is no longer available in Canada
- Directly observed therapy is preferred
- Test of cure not routinely necessary
- In pregnancy, should use cephalosporin (avoid quinolones)
- Sexual partners should be tested, & treated if appropriate
- Follow up re-screen should occur 6 months after treatment

Treatment of C. trachomatis

- Recommended treatment options include: azithromycin 1g po in a single dose OR doxycycline 100 mg po bid for 7 days

- These 2 regimens are equally effective & well-tolerated
- Alternative regimens include: ofloxacin 300 mg po bid for 7 days OR erythromycin 2g/day po in divided doses for 7 days OR erythromycin 1g/day po in divided doses for 14 days
- Test of cure not necessary, but is required in pregnant women 3 weeks after therapy
- In pregnancy, recommended regimes are: azithromycin 1g po in a single dose OR amoxicillin 500 mg po tid for 7 days OR erythromycin 2g/day po in divided doses for 7 days OR erythromycin 1g/day po in divided doses for 14 days
- Sexual partners should be tested, & treated if appropriate
- Follow up re-screen should occur 6 months after treatment



Upper Genital Tract STIs and Acute Pelvic Pain

Upper Genital Tract STIs and Acute Pelvic Pain Objectives:

At the end of the seminar, students should be able to:

Upper Genital Tract STIs

1. List the causes of a mucopurulent discharge of the cervix.
2. Describe the methods of obtaining appropriate cultures of the cervix.
3. Outline the symptoms, physical findings, evaluation and management of:
    - Chlamydia
    - Gonorrhea
4. Counsel patients on public health concerns including:
    - Screening programs
    - Prevention
    - Requirement for reporting
    - Partner evaluation and treatment
    - Psychosocial impact on woman and her partner

Acute Pelvic Pain and Pelvic Inflammatory Disease

1. List the causes of acute pelvic pain.
2. Describe the evaluation and management of a patient with acute pelvic pain.
3. For acute pelvic inflammatory disease, describe:
    - Pathogenesis
    - Common organisms
    - Signs and symptoms
    - Methods of diagnosis
    - Treatment
    - Sequelae including:
        - tubo-ovarian abscess
        - chronic salpingitis
        - ectopic pregnancy
        - infertility
4. Differentiate between the various causes of acute pelvic pain through the interpretation of:
    - Critical clinical findings (symptoms and signs)
    - Key laboratory findings
    - Diagnostic imaging and procedures
5. Provide patient education regarding prevention of salpingitis

Last revised: July 2019

UPPER GENITAL TRACT SEXUALLY TRANSMITTED INFECTIONS (PELVIC INFLAMMATORY DISEASE) & ACUTE PELVIC PAIN

Introduction

Approximately 100,000 cases of symptomatic pelvic inflammatory disease (PID) are diagnosed each year in Canada. In the United States, nearly 1 million women are diagnosed with PID. There appears to be a general decline in the rate of PID, however, major short-term and long-term morbidity remains. More importantly the reproductive complications such as infertility, ectopic pregnancy and chronic pelvic pain can be reduced significantly with improved recognition and treatment of acute upper genital tract infection.

Table 1: Epidemiology of STIs in Canada.

Infection	How common in clinical practice?	Trends in incidence	Most affected
Chlamydia	• Most commonly diagnosed and reported bacterial STI • Cases reported in Canada in 2002: 56,241 • Cases reported in Canada 2006: 65,000 (preliminary data)*	• Steadily increasing in Canada since 1997	• Young women aged 15–24 • Young men aged 20–29
Gonorrhea	• Second most commonly diagnosed and reported bacterial STI • Cases reported in Canada in 2002: 7,367 • Cases reported in Canada 2006: 10,808 (preliminary data)*	• From 1997-2004 (preliminary data)*, rate has increased by approximately 94% • Quinolone resistance has increased from <1% in the early 1990s to 15.7% in 2005 (national rate)†	• Males account for ⅔ of reported cases • Increase in MSM • Young men aged 20–29 • Young women aged 15–24
Infectious syphilis	• Previously rare in Canada • Cases reported in Canada in 2002: 463 • Cases reported in Canada 2006: 1,493 (preliminary data)*:	• Dramatic national increases noted since 1997 related to regional outbreaks across Canada	• MSM (HIV positive and negative) aged 30–39 • Sex workers and their clients • Acquisition in endemic regions

Continued on next page…

Infection	How common in clinical practice?	Trends in incidence	Most affected
Human papilloma virus	• Very common: 70% of the adult population will have had at least one genital HPV infection over their lifetime	• True incidence not known, as HPV is not a reportable disease	• Adolescent and young adult women and men (but affects women and men of all ages)
Genital herpes (HSV-1 and -2)	• Common	• True incidence not known, as HSV is not a reportable disease • Seroprevalence studies indicate rates of at least 20%	• Very common in both adolescent and adult men and women • Women are more affected than men
HIV	• Rare in general practice • 2,529 cases reported in Canada in 2004	• 20% rise in number of HIV+ test reports in Canada (2000–2004)	• MSM • Acquisition in endemic regions • Injection drug users • Young women aged 15–19
Hepatitis B	• Low to moderate in general practice and varies in different populations • Approximately 700 acute cases per year in Canada	• Acute hepatitis B is twice as high for men than for women • Peak incidence rates are found in the 30–39 age group	• Infants born to HbsAg+ mothers • Injection drug users who share equipment • Persons with multiple sexual partners • Acquisition in endemic regions • Sexual and household contacts of an acute or chronic carrier

MUCOPURULENT CERVICAL DISCHARGE

As clinicians, we often employ a syndromic approach to patients presenting with possible sexually transmitted infections. Waiting for lab tests and investigations would lead to delays that may harm the patient. One common complaint is that of vaginal discharge from the cervix. The goal of this chapter is to understand upper genital tract disease and thus does not encompass the broader area of vaginitis and vaginal infections (previously described).

To fully understand upper genital tract infection, one must begin with the cervix. Upper genital tract disease is defined as infection above the level of the cervix. [1] The cervix is composed of two different epithelium, squamous epithelium and glandular epithelium. Squamous epithelium is located on the ectocervix and can become inflamed by the same organisms that cause vaginitis (Candida, trichomonas, and herpes simplex virus). Glandular epithelium is located on the endocervix and can be infected by Chlamydia (C. trachomatis) and Gonorrhea (N. gonorrhoeae) [2]. Thus, all the organisms listed above can cause cervicitis or inflammation of the cervix, however, Chlamydia and Gonorrhea are responsible for the ascending infection in the upper genital tract.

The causes, tests, and considerations are listed in the table below (Table 2). Treatment regimens will be reviewed later in this chapter [3].

Table 2: Syndromic Approach to the Management of Sexually Transmitted Infections

Syndrome	Signs and symptoms	Etiology	Specimens and testing	Microscopy results and clinical findings	Next steps/special considerations
Cervicitis (females)	Mucopurulent cervical discharge Cervical friability Vaginal discharge Strawberry cervix	**Possible causes:** *N. gonorrhoeae* *C. trachomatis* *Trichomonas vaginalis* HSV	Cervical swab for Gramstain, *N. gonorrhoeae* culture and *C. trachomatis* (NAAT or culture)	On Gram-stain presence of ≥20 PMNs per HPF with mucopurulent discharge and/or cervical friability	See *Chlamydial Infections* chapter for treatment recommendations unless gonorrhea is suspected; then, see *Gonococcal Infections* chapter. **Note:** Although not a sensitive test, Gram stain may be helpful in diagnosing mucopurulent cervicitis and gonorrhea in symptomatic females.
			Swab of cervical lesions for HSV		If HSV is suspected or detected see *Genital Herpes simplex Virus Infections* chapter for treatment recommendations.
			Vaginal swab for wet mount	Trichomonads	See *Vaginal Discharge* chapter for treatment recommendations
				Where microscopy results are not immediately available	Treat for *N. gonorrhoeae* and *C. trachomatis* if partner is infected with gonorrhea or if follow-up is not assured. **OR** Treat for *C. trachomatis* and consider treating for *N. gonorrhoeae* if local prevalence is high or sexual contact occurred in a region with high prevalence.

HPF = high-power field; HSV = herpes simplex virus; IDU = injection drug use; NAAT = nucleic acid amplification test; PMN = polymorphonuclear leukocytes; STI = sexually transmitted infection

Methods of Obtaining Cervical Cultures

1. After inserting the speculum to view the cervix, remove overlying vaginal secretions and cervical exudates.
2. Insert a sterile swab 1-2cm into the endocervical canal, rotate 180 degrees and withdraw for collection of columnar cells for diagnosis of Chlamydia and Gonorrhea
3. C. trachomatis is detected by nucleic acid amplification testing (i.e. Nucleic acid amplification tests (NAATs) / polymerase chain reaction [PCR]) and is intra-cellular in location. N. Gonorrhea can also be tested by nucleic acid amplification but is commonly assessed by gram stain and culture in most centres.
4. Exocervical samples are better for Herpes Simplex Virus and Human Papilloma virus.
5. Cervical specimens should not be taken from pre-pubertal girls, since STIs in this age group involve the vagina, not the cervix.
6. Obtaining several specimens from the cervix does not usually produce discomfort and may be required to perform various tests.
7. In women who have had a hysterectomy collect first void urine or vaginal swab for NAAT. Although some NAATs have not been approved in Canada for use with vaginal specimens, recent data show that women infected with C. trachomatis, N. gonorrhoeae or Trichomonas vaginalis may be identified more often using vaginal swabs than cervical swabs, urethral swabs or urine.

Methods of Obtaining Vaginal Cultures

1. Collect pooled vaginal secretions, if present.
2. When no vaginal secretions are present, swab the vaginal wall in the posterior fornix to prepare a smear, or place the swab in a transport medium.
3. Wet-mount and Gram-stain smears are useful in the diagnosis of microbial vulvovaginitis, candidiasis, bacterial vaginosis, trichomoniasis or desquamative inflammatory vaginitis.
4. Collection of vaginal specimens from youth and adults is usually done as part of a speculum examination.

Cervical and Vaginal Cultures

Chlamydia trachomatis

- Results are highly dependent on the type of test available, appropriate specimen collection, storage, transport and laboratory expertise.
- Contact the laboratory for specific instructions before submitting specimens, and read and follow test-kit instructions regarding specimen collection, storage and transport.
- NAATs are the most sensitive and specific and should be used whenever possible for urine, urethral, and cervical specimens; blood and mucous can affect NAAT performance.
- Non-invasive specimens such as urine can be used in NAATs, making testing more acceptable to patients.
- Both C. trachomatis and N. gonorrhoeae can be detected from a single specimen in some NAATs.
- Because successful treatment rates are high, a test of cure is not usually performed.
- Other assays, such as nucleic acid hybridization and antigen detection, may be used, but they are less sensitive and specific, and positives may need to be confirmed. [12]
- Serology is not useful for the diagnosis of acute genital chlamydial infections (non-LGV only).

Neisseria gonorrhoeae

- The presence of Gram-negative diplococci inside polymorphonuclear leukocytes (PMNs) is highly predictive for the direct microscopic examination of smears; their presence outside PMNs is not, and confirmation by culture is required.
- The sensitivity and specificity of the Gram stain depends on the type of specimen.
- Urethral specimens from young adult males have a sensitivity and specificity of 95%; endocervical specimens from adult females have a sensitivity of 45–65% and 90% specificity
- Culture for N. gonorrhoeae is required for the determination of antimicrobial susceptibility in cases of sexual abuse/assault, as well as in cases of treatment failure.
- Successful culture of specimens requires proper collection and transportation of appropriate specimens or immediate inoculation of medium. Consult with your laboratory.
- NAATs are approved for cervical and urethral swabs and urine; some NAATs are also approved for vaginal swabs. Urine and vaginal swabs are convenient specimens for women without a cervix, and urine may be most convenient for those who may not readily submit to a pelvic examination.
- Serology is not available.

Trichomonas vaginalis

- The vaginal pH is >4.5, and the whiff test is usually negative (the withdrawn speculum does not have an abnormal odour)
- Because of the low sensitivity of direct microscopy, culture may be used, where available, to isolate the agent from urethral swabs, urine sediments, prostate fluid and vaginal specimens.

Candida albicans

- The vaginal pH is normal (<4.5), and the whiff test is negative [34].
- Wet-mount preparation with 10% KOH shows budding yeast and/or branching pseudohyphae.

Bacterial vaginosis

- The vaginal pH is >4.5, and the whiff test is positive [35].
- Gram stain demonstrates a shift in vaginal flora, with a decrease in large Gram-positive rods (lactobacilli) and an increase in small Gram-variable coccobacilli and clue cells (vaginal epithelial cells covered with numerous coccobacilli).

ACUTE PELVIC INFLAMMATORY DISEASE (PID) OR UPPER GENITAL TRACT SEXUALLY TRANSMITTED INFECTIONS

P**elvic inflammatory disease (PID)** is an infection of the upper female genital tract involving any combination of the endometrium fallopian tubes, pelvic peritoneum and adjacent structures [4].

PID is caused by micro-organisms colonizing the endocervix ascending to the endometrium (endometritis) and fallopian tubes (salpingitis). The inflammation may be at any point along the continuum that includes endometrium, fallopian tubes, and the peritoneum.

Common Organisms

PID is a polymicrobial infection. Pathogens can be sexually transmitted or endogenous and include:

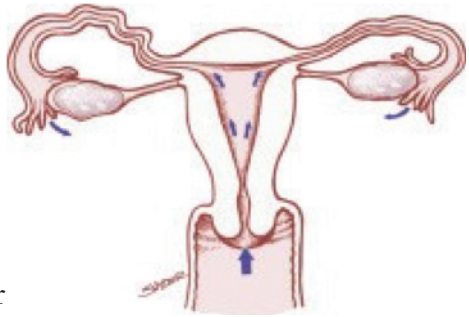
- Sexually Transmitted Infections
    - C. trachomatis
    - N. gonorrhoeae
- Endogenous Organisms
    - Genital mycloplasmas (Ureaplasma urealyticum, mycoplasma genitalium and hominis)
- Anaerobic Bacteria
    - Bacteroides
    - Peptostreptococcus
    - Prevotella
- Facultative (Aerobic) Bacteria
    - Escherichia coli
    - Gardnerella vaginalis
    - Streptococcus species
    - Haemophilus influenza

Signs and Symptoms

Traditionally, the diagnosis of PID has been based on the classic triad of fever, pelvic pain, cervical motion tenderness or adnexal tenderness. There is no single clinical history, physical finding, or laboratory finding that is both specific and sensitive for PID. [5] Only one-third (1/3) of women with PID have a temperature above 38.0°C [6].

Diagnostic criteria may be stratified as follows: [4]

1. **Minimum Diagnostic Criteria**
    - Lower abdominal tenderness
    - Adnexal tenderness
    - Cervical motion tenderness
2. **Additional Diagnostic Criteria**
    - Oral temperature >38.3°C
    - Leukocytosis
    - Presence of WBC on saline microscopy of vaginal wet mount
    - Elevated ESR
    - Elevated C-Reactive protein
    - Laboratory documentation of cervical infection with Neisseria gonorrhoeae or Chlamydia trachomatis
3. **Definitive Diagnostic Criteria (Figure 1)**
    - Endometrial biopsy with histopathologic evidence of endometritis
    - Transvaginal ultrasound showing thickened fluid–filled fallopian tubes with or without free pelvic fluid or tubo-ovarian complex
    - Gold standard: laparoscopy demonstrating abnormalities consistent with PID (i.e. fallopian tube erythema and/or mucopurulent exudates.



Treatment

Treatment as inpatient or outpatient is valid and data suggest that there are no significant differences in receiving parenteral versus oral therapy. Patients, however, must be followed carefully in an outpatient setting to ensure compliance and response to the treatment initiated. (I.e. re-evaluation at 72h post initiation of treatment). If no clinical improvement has occurred, hospital admission with parenteral therapy is indicated and there should be consideration of transvaginal ultrasound +/- diagnostic laparoscopy. Historically criteria for hospital admission and parenteral therapy have not been validated but consensus still supports its use [7].

They include:

1. **Criteria for Hospital Admission**
    - Inability to exclude alternate surgical emergencies (i.e. appendicitis)
    - Pregnancy
    - Failure of outpatient management
    - Inability to tolerate or follow an oral regimen

- Severe illness, vomiting or high fever
- Presence of a tubo-ovarian abscess (TOA)
- Inability to follow-up up after a 72h trial of outpatient therapy
- Adolescence (particularly if compliance is an issue)
- Co-existing HIV infection/Immunocompromised condition

2. Treatment Goals

- Control the acute infection
- Prevent long-term sequelae such as infertility, ectopic pregnancy, and chronic pelvic pain
- Regimens should provide empiric broad-spectrum coverage
- Parenteral therapy may be discontinued if improvement occurs after 24 hours of treatment
- Oral step-down therapy should begin and continued for a total of 14 days of therapy
- If improvement does not occur, laparoscopy and alternate diagnoses should be evaluated

3. Pharmacotherapy

- *Outpatient treatments [4] (Table 3)*

Regimen A[15] *[A-II]*	For each of three treatment options listed below, many experts recommend the addition of **metronidazole** 500 mg PO bid for 14 days to this regimen for additional anaerobic coverage and the treatment of bacterial vaginosis ‡ [B-III]. • **Ceftriaxone** 250 mg IM in a single dose§ ‖ PLUS **doxycycline** 100 mg PO bid for 14 days **OR** • **Cefoxitin** 2 g IM PLUS **probenecid** 1 g PO in a single dose concurrently once PLUS **doxycycline** 100 mg PO bid for 14 days **OR** • Other parenteral third-generation cephalosporin (e.g., **ceftizoxime** or **cefotaxime**) PLUS **doxycycline** 100 mg PO bid for 14 days
Regimen B[16] *[A-II]*	• **Ofloxacin** 400 mg PO bid for 14 days† PLUS/MINUS **metronidazole** 500 mg PO bid for 14 days‡ *[A-I]* **OR** • **Levofloxacin** 500 mg PO qd† PLUS/MINUS **metronidazole** 500 mg PO bid for 14 days‡ *[B-II]* – Metronidazole is added to provide anaerobic coverage‡ – Preliminary data suggest that oral levofloxacin is as effective as oral ofloxacin, with the advantage of once-daily dosing[9]

- Patients should not drink alcohol during and for 24 hours following treatment with oral metronidazole because of a possible disulfiram (antabuse) reaction.
- The use of ofloxacin, ciprofloxacin, levofloxacin, and doxycycline is contraindicated for pregnant and lactating women.
- Pregnant women should not be treated with quinolones or tetracyclines.
- Due to the rapid increase in quinolone resistant Neisseria gonorrhoea, quinolones such as ciprofloxacin and ofloxacin are no longer preferred drugs for the treatment of gonococcal infections in Canada.
    - Quinolones may be considered as an alternative treatment option ONLY IF:
        - antimicrobial susceptibility testing is available and quinolone susceptibility is demonstrated; OR
        - where antimicrobial testing is not available, a test of cure is essential.

- *Inpatient treatments [4] (Table 4)*

Regimen A[13] *[A-I]*	• **Cefoxitin** 2 g IV every 6 hours PLUS **doxycycline** 100 mg IV or PO every 12 hours – Parenteral therapy may be discontinued 24 hours after a patient improves clinically, and oral therapy with **doxycycline** (100 mg bid) should continue for a total of 14 days – Most authorities recommend administering doxycycline in oral form even in hospitalized patients, because IV administration is painful and more costly, and because oral and IV administration provide similar bioavailability
Regimen B *[A-I]*	• **Clindamycin** 900 mg IV every 8 hours PLUS **gentamicin*** loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Once-daily dosing may be substituted (5mg/kg of body weight IV every 24h) – Parenteral therapy may be discontinued 24 hours after a patient improves clinically, and oral therapy with **doxycycline** (100 mg bid) or **clindamycin** (450 mg PO qid) should continue for a total of 14 days
Alternative regimens[14] *[A-II]*	• **Ofloxacin** 400 mg IV every 12 hours† PLUS/MINUS **metronidazole** 500 mg IV every 8 hours‡ **OR** • **Levofloxacin** 500 mg IV once daily† PLUS/MINUS **metronidazole** 500 mg IV every 8 hours‡ **OR** • **Ampicillin/sulbactam** 3 g IV every 6 hours PLUS **doxycycline** 100 mg IV or PO every 12 hours **OR** • **Ciprofloxacin** 200 mg IV every 12 hours† PLUS **doxycycline** 100 mg IV or PO every 12 hours PLUS/MINUS **metronidazole** 500 mg IV every 8 hours‡ – Because ciprofloxacin has poor coverage against *C trachomatis*, it is recommended that doxycycline be added routinely – Because of concerns regarding the anaerobic coverage of quinolones, metronidazole should be included with each regimen‡

- Due to the rapid increase in quinolone resistant Neisseria gonorrhoeae, quinolones such as ciprofloxacin and ofloxacin are no longer preferred drugs for the treatment of gonococcal infections in Canada.
- These recommendations apply for those patients with normal renal function; gentamicin dosage to be adjusted for renal impairment. Renal function and gentamicin levels should be monitored during treatment.
- Quinolones may be considered as an alternative treatment option ONLY IF:
  - antimicrobial susceptibility testing is available and quinolone susceptibility is demonstrated; OR
  - where antimicrobial testing is not available, a test of cure is essential.

CHLAMYDIAL INFECTION

Etiology

- Chlamydia trachomatis serovars D to K

Symptoms and Physical Findings

- Often asymptomatic (30-50%)
- Vaginal discharge
- Dysuria
- Lower abdominal pain
- Abnormal vaginal bleeding
- Dyspareunia
- Conjunctivitis
- Proctitis

Evaluation

- Nucleic acid amplification testing (i.e. NAAT) is more sensitive than culture, immunoassay or direct fluorescent antibody assay
- Urine-based screening is ideal for asymptomatic patients where a pelvic examination is not warranted.
- Culture has been the preferred method for medico-legal purposes (i.e. sexual assault kit)
- Serology is not useful for acute genital chlamydial infections
- Evaluation should be appropriate for the presenting symptoms, signs and sexual history

Management

- Treatment for Chlamydia is indicated for the following:
    - A positive Chlamydia test
    - Diagnosis of a syndrome compatible with a chlamydial infection without waiting for the test results
    - Diagnosis of chlamydial infection in a sexual partner
- Empirical co-treatment when a diagnosis of N gonorrhoeae is made without waiting for test results of C. trachomatis due to significant probability of co-infection (20-42%) and possibility of false-negative results
- Test of cure at 3-4 weeks is no longer recommended routinely if the recommended treatment is taken AND symptoms and signs disappear AND there is no re-exposure to an untreated partner
- Test of Cure is indicated if compliance is suboptimal, an alternative treatment regimen has been used, pre-pubertal children and all pregnant women.
- Repeat testing is recommended at 6 months as reinfection risk is high
- This is a reportable disease and sexual partner(s) should be treated

Treatment Regimes

Cervicitis (adult non-pregnant/non-breastfeeding) (Table 5)

Preferred	Alternative
• **Doxycycline** 100 mg PO bid for 7 days *[A-I]* **OR** • **Azithromycin** 1 g PO in a single dose if poor compliance is expected* *[A-I]*	• **Ofloxacin** 300 mg PO bid for 7 days *[B-II]* **OR** • **Erythromycin** 2 g/day PO in divided doses for 7 days† *[B-II]* **OR** • **Erythromycin** 1g/day PO in divided doses for 14 days† *[B-I]*

*If vomiting occurs more than 1 hour post-administration, a repeat dose is not required.

Cervicitis (adult – pregnant or nursing) (Figure 2)

- **Amoxicillin** 500 mg PO tid for 7 days* *[A-I]*

OR

- **Erythromycin** 2 g/day PO in divided doses for 7 days*† *[B-I]*

OR

- **Erythromycin** 1g/day PO in divided doses for 14 days*† *[B-I]*

OR

- **Azithromycin** 1 g PO in a single dose, if poor compliance is expected‡ *[B-I]*

*If erythromycin or amoxicillin has been used for treatment in nursing mothers, test of cure should be performed 3-4 weeks after the completion of treatment.
† Gastrointestinal side effects are more severe with erythromycin than amoxicillin.
‡ If vomiting occurs more than 1 hour post-administration, a repeat dose is not required.

Upper Genital Tract Infection

- PID, see above section

GONOCOCCAL INFECTION

Etiology

- Caused by Neisseria gonorrhoeae

Symptoms and Physical Findings

- Vaginal discharge
- Dysuria
- Abnormal vaginal bleeding
- Lower abdominal pain
- Rectal pain and discharge with proctitis
- Deep dyspareunia

Evaluation

- Cultures obtained <48hours after exposure may be negative
- Culture is recommended method because it allows for antimicrobial susceptibility testing.
- In some settings, nucleic acid amplification testing may only be available
- Gram stain and culture of cervix and vagina and/or rectum/pharynx/conjunctiva

Treatment

- Due to rapid increases of quinolone-resistant N. gonororrhoeae *in Canada*, quinolones such as ofloxacin and ciprofloxacin are no longer preferred for the treatment of gonococcal infections
- All patients treated for gonorrhea should also be treated for chlamydial infection and unless Chlamydia test is available and negative
- Directly observed therapy with single dose is desirable if poor compliance is expected.
- If PID, see above section

- **For Urethral, Endocervical, Rectal or Pharyngeal Infection (non-pregnant or non-nursing women):**
    - Ceftriaxone 250mg IM, cefixime 800mg PO
- **Pregnant or Nursing Women**
    - Ceftriaxone 250mg IM, cefixime 800mg PO

Reporting and Follow-up (Chlamydia and Gonorrhea)

- Both gonococcal and chlamydial infections are reportable in all provinces and territories in Canada.
- Positive tests must be reported to the local public health authorities
- All partners who have had sexual contact with the index case within at least the 60 days prior to symptom onset or date of diagnosis (whichever is first) must be located, clinically evaluated and treated.
- Since co-infections are common, persons treated for gonococcal infections should also be treated for C. trachomatis unless concurrent tests for Chlamydia are negative.
- Repeat screening for individuals with gonorrhea **after 6 months** is recommended.
- Test of cure for C. trachomatis is not routinely indicated if a recommended treatment is taken and symptoms/signs disappear AND there is no re-exposure to an untreated partner except:
    - Where compliance is suboptimal
    - If an alternative regimen has been used
    - In all pre-pubertal children
    - In all pregnant women
- If a test of cure is performed, it should be performed **3-4 weeks after** completion of effective treatments to avoid a false-positive result **repeat testing is recommended 6 months post-treatment** as re-infection risk is high.

Prevention

Effective prevention and management of STIs requires the following elements:
Assessing the reason for consultation

- Knowing about the STI risk factors and epidemiology
- Performing a brief patient history and STI risk assessment
- Providing patient-centered education and counselling
- Performing a physical examination
- Selecting appropriate screening/testing
- Diagnosing by syndrome or organism and post-test counselling
- Treating appropriately
- Reporting to public health and partner notification
- Managing co-morbidity and associated risks
- Following up

Table 6: Partner notification reference chart.

Infection/syndrome	Reportable	Trace-back period*	Who to notify/ evaluate	Special considerations
Chlamydia (LGV and non LGV serovars)	Yes	60 days	SP/NB	• If no sexual partner(s) in the last 60 days, trace back to last sexual partner • Partner notification is not required in most provinces and territories as a public health measure but is highly recommended for NGU, MPC, PID and epididymitis
Gonorrhea	Yes	60 days	SP/NB	
Chancroid	Yes	14 days	SP	
Non-gonococcal urethritis	No	60 days	SP	
Mucopurulent cervicitis	No	60 days	SP	
Pelvic inflammatory disease	No	60 days	SP	
Epididymitis	No	60 days	SP	
Primary syphilis	Yes	3 months	SP/NB	
Secondary syphilis	Yes	6 months	SP/NB	
Early latent syphilis	Yes	1 year	SP/NB	
Late latent syphilis/ stage undetermined	Yes	Variable	SP/NB/ CMC	
Genital herpes	In some jurisdictions	Current/ future	SP/NB	• Partner notification is not required as a public health measure but is highly recommended
Trichomoniasis	In some jurisdictions	Current	SP	No need to test partners; treat as for index case
Human papilloma virus	No	Current/ future	SP	Partner notification is not required as a public health measure. Patients should be encouraged to notify their sexual partners, but there is no proof that this will lower the risk to the partner
Acute hepatitis B	Yes	Variable	SP/NSP/ HC/NB/ CMC	All unvaccinated/non-immune contacts should be notified. May benefit from PEP[13] Newborns must receive HBIG and vaccine post-natally[13]
Chronic hepatitis B	Yes	Variable	SP/NSP/ HC/NB/ CMC	All unvaccinated/non-immune contacts should be notified. May benefit from PEP[13] Newborns must receive HBIG and vaccine post-natally[13]
HIV/AIDS	Yes	Variable	SP/NSP/ NB/CMC	Start with recent sexual and needle-sharing partners; outer limit is onset of risk behaviour or to last known negative test Post-exposure prophylaxis may be considered by health care providers for individuals who have been in contact with HIV and appropriately timed initiation of antiretroviral therapy is associated with a better prognosis and is a prerequisite to prevention of further transmission of disease. Please consult with an expert in HIV

Adapted from Syndromic Management of Sexually Transmitted Infections. Canadian Guidelines on Sexually Transmitted Diseases 2010 Edition. Public Health Agency of Canada.

ACUTE PELVIC PAIN

The differential diagnosis for acute pelvic pain is numerous. Because of the proximity of both genitourinary and gastrointestinal systems, the differential diagnosis in women presenting with pelvic pain must include potential disorders affecting these systems. An excellent framework for approach to this patient is as follows (Figure 3).

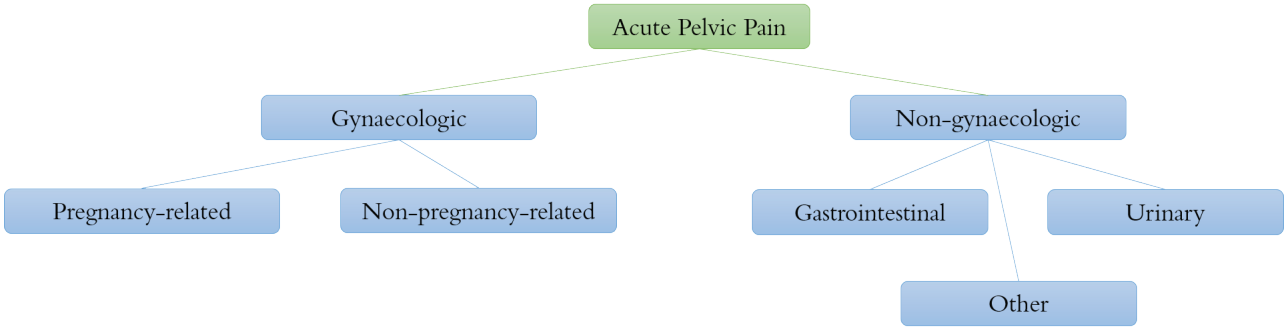


Table 7: Differential Diagnosis of Acute Pelvic Pain.

1. PREGNANCY RELATED
   - Spontaneous abortion
     - Threatened
     - Complete
     - Incomplete
     - Septic
   - Ectopic pregnancy

2.GYNAECOLOGIC: INFECTIOUS
   - Endometritis
   - PID/salpingitis
   - TOA

3.GYNECOLOGIC: NONINFECTIOUS
   - Dsymenorrhea
   - Uterine fibroids
   - Endometriosis
   - Mittelschmerz (midcycle ovulatory pain)
   - Ovarian cysts
     - Rupture
     - Hemorrhage
     - Torsion
   - Ovarian cancer/tumor
   - Ovarian hyperstimulation syndrome

4. NONGYNECOLOGIC
   - Gastrointestinal
     - Appendicitis
     - Gastroenteritis
     - Diverticulitis
     - Inflammatory bowel disease
     - Irritable bowel syndrome
     - Bowel obstruction
     - Mesenteric lymphadenitis
     - Constipation
     - Abdominopelvic adhesions
   - Urinary tract
     - Lower urinary tract infection/cystitis
     - Interstitial cystitis
     - Pyelonephritis
     - Nephrolithiasis
   - Musculoskeletal
     - Strained tendons/muscles
     - Joint infection/inflammation
     - Hernia
   - Other
     - Aortic aneurysm
     - Aortic dissection
     - Porphyria

PID = pelvic inflammatory disease; TOA= tubo-ovarian abscess

Adapted from Yudin MH and Wiesenfeld HC. Acute Pelvic Pain. In: Zenilman JM, Shahmanesh M, eds. Sexually transmitted infections: diagnosis, management, and treatment. London, United Kingdom 2012.

Table 8: Historic Data Useful in the Differential Diagnosis of Acute Pelvic Pain.

1. PATIENT AGE

2. PAIN CHARACTERISTICS
   - Onset
   - Position
   - Quality
   - Radiation
   - Severity
   - Aggravating/allevating factors
   - Associated symptoms
   - Urinary symptoms
   - Gastrointestinal symptoms
   - Fever/chills
   - Vaginal bleeding
   - Vaginal discharge
   - Treatment tried

3. OBSTETRICAL AND GYNECOLOGIC HISTORY
   - LMP
   - STI's/PID
   - Ectopic pregnancy
   - Uterine fibroids/ovarian cysts
   - Menstrual history
   - Contraception history
   - Sexual history

4. MEDICAL/SURGICAL HISTORY

5. SOCIAL HISTORY
   - Marital Status

LMP = last mestrual period; STI = sexually transmitted infection;
PID = pelvic inflammatory disease

Adapted from Yudin MH and Wiesenfeld HC. Acute Pelvic Pain. In: Zenilman JM, Shahmanesh M, eds. Sexually transmitted infections: diagnosis, management, and treatment. London, United Kingdom 2012.

Table 9: Differential Diagnosis Grouped by the Time of Onset.

1. ACUTE ONSET (SECONDS-MINUTES)
   - Ovarian cysts
   - Rupture
   - Hemorrhage
   - Torsion
   - TOA
   - Abdominal aortic aneurysm
   - Ectopic pregnancy
   - Aortic dissection
   - Nephrolithiasis

2. GRADUAL ONSET (HOURS-DAYS)
   - Appendicitis
   - Diverticulitis
   - Herpes zoster
   - Gastroenteritis
   - Mittelschmerz
   - Primary dysmenorrheal
   - Abortion

3. SLOW ONSET (DAYS-WEEKS)
   - Neoplasms
   - Cystitis
   - Pyelonephritis
   - Ectopic pregnancy
   - PID
   - Diverticulitis
   - Abortion
   - Abdominal aortic aneurysm

4. CHRONIC ONSET (WEEKS-MONTHS)
   - Neoplasms
   - Endometriosis
   - Uterine fibroids
   - Chronic pelvic pain
   - Domestic violence/sexual abuse
   - Diverticular disease
   - Irritable bowel syndrome
   - Inflammatory bowel disease

TOA = tubo-ovarian abscess; PID = pelvic inflammatory disease

Adapted from Yudin MH and Wiesenfeld HC. Acute Pelvic Pain. In: Zenilman JM, Shahmanesh M, eds. Sexually transmitted infections: diagnosis, management, and treatment. London, United Kingdom 2012.

Physical Exam

- General inspection: comfortable, writhing, moaning?
- Abdominal examination:
    - Inspection: distention, masses, scars, ecchymosis, hernias
    - Palpation: masses, areas of tenderness, peritoneal signs
    - Auscultation: bowel sounds, bruits

- Pelvic examination:
    - Examine external genitalia: masses, rashes, discolouration
    - Speculum exam:
        - Vagina: Discharge? Laceration? Foreign body?
        - Cervix: Abnormal discharge? Ulcers? Lacerations? Polyps? Masses? Infection?
        - Do vaginal and cervical swabs
    - Bimanual exam:
        - Palpate introitus and pelvic floor for trigger points
        - Uterus: Masses? Size? Symmetry?
            - Regular enlargement suggests pregnancy
            - Irregular enlargement could be fibroids or adherent bowel
            - Uterus is not usually tender. Pain suggests degenerating fibroid.
        - Cervix: cervical motion tenderness often a sign of PID, ectopic or appendicitis
        - Adnexae: masses, tenderness
            - A fixed tender mass suggestive of endometrioma or TOA
        - Consider rectovaginal exam: tender nodules suggestive of endometriosis

Laboratory

- Bhcg for all women of reproductive age
- Rh if pregnant
- CBC
- Urinalysis
- Cervical and vaginal swabs
- Remainder of testing guided by what is high on your differential

Imaging

- Ultrasound is effective, cheap, available and does not have any radiation
- CT may be required in some cases
- X-rays rarely helpful
- MRI may be required in some special cases
    - MRI preferred over CT in pregnant women

Laparoscopy

- Consider laparoscopy for diagnostic purposes if diagnosis not clear and differential includes serious pathology such as appendicitis, PID or ovarian torsion

Treatment

- Treatment depends on the cause

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Chronic Pelvic Pain

Chronic Pelvic Pain Objectives:

At the end of the seminar, students should be able to:

1. Define chronic pelvic pain
2. Cite the incidence of chronic pelvic pain
3. List the etiologies of chronic pelvic pain
4. Describe the clinical manifestations of chronic pelvic pain
5. Describe the evaluation and management of patients with chronic pelvic pain
6. With respect to dysmenorrhea:
    - Define primary and secondary dysmenorrhea
    - List the causes for secondary dysmenorrhea
    - Explain the pathophysiology for primary and secondary dysmenorrhea
    - Outline the investigation and management for primary and secondary dysmenorrhea
7. With reference to endometriosis:
    - Describe the symptoms and physical findings
    - List the theories of pathogenesis of endometriosis
    - List the common sites of endometrial implants
    - Describe the diagnostic methods
    - Discuss non-surgical and surgical management
    - Describe the natural history
8. With reference to adenomyosis:
    - Describe the symptoms and signs suggestive of adenomyosis.
    - Describe the pathologic features of adenomyosis.
    - Outline the methods of management of adenomyosis.

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Introduction

Pelvic pain is a condition commonly encountered in gynaecology. Determining the etiology of the pain and the appropriate management course is challenging. Pelvic pain may be classified as acute, cyclical (i.e. associated with the menstrual calendar) or chronic. There is no generally accepted definition of **chronic pelvic pain (CPP)** however most experts define it to be non-menstrual pelvic pain (below the umbilicus) that is persistent for greater than 6 months.

Dysmenorrhea is defined as recurrent, severe, painful abdominal cramping that occurs immediately prior to or during menses. It may be associated with systemic symptoms such as sweating, tachycardia, headaches, nausea, vomiting, diarrhea, and tremulousness. Dysmenorrhea has been classified in two categories: primary and secondary. In primary dysmenorrhea, no pelvic pathology is found. It is postulated that primary dysmenorrhea is caused by an increased in endometrial prostaglandin production. Secondary dysmenorrhea is associated with various pelvic conditions including endometriosis, adenomyosis, chronic pelvic inflammatory disease and cervical stenosis.

It is estimated that 12-15% of women in the United States suffer from CPP and approximately 75% of women experience dysmenorrhea. It is the most commonly reported gynecological complaint. These conditions may have significant consequences on women's personal and professional lives, thereby negatively impacting on their quality of life. We will review conditions associated with CPP and dysmenorrhea and provide an approach for managing these patients.

Etiology of Chronic Pelvic Pain and Dysmenorrhea

There are numerous etiologies of CPP. CPP is often due to an aggregation of causes which each contribute to the pain to varying degrees. A common approach to chronic pelvic pain is to first contemplate the gynecological causes, then rule out the possible non-gynecological etiologies.

I. Gynaecologic Causes

1. **Endometriosis:** Endometriosis is the most common cause of secondary dysmenorrhea. It occurs when endometrial tissue is found outside of the uterus. With menses, this endometrial tissue sheds and bleeds causing pain. Four main theories have been suggested to explain the histogenesis of endometriosis: retrograde menstruation, coelomic metaplasia, immunologic changes and hematogenous or lymphatic spread. It remains unclear as to why endometriosis develops in some patients and not others. A genetic predisposition for endometriosis has been suggested. In patients undergoing laparoscopy for CPP, endometriosis is the most commonly made diagnosis. Pelvic pain in patients with endometriosis may be continuous and/or have premenstrual exacerbations. It may also be associated with dysmenorrhea, dyspareunia, and dyschezia.
2. **Chronic pelvic inflammatory disease (PID):** Acute pelvic inflammatory disease (PID) is caused by an infection in the upper genital tract, most commonly *N. gonorrhoea* and *C. trachomatis*. 18-35% of women diagnosed with PID will eventually develop CPP. Specific risk factors for developing CPP in women with PID have not been identified.
3. **Adhesions:** The association between pelvic adhesions and chronic pelvic pain is controversial.

4. **Adenomyosis:** Adenomyosis is defined as the presence of endometrial tissue within the myometrium. It often coexists with endometriosis and uterine fibroids. Many patients with adenomyosis are asymptomatic. Typical symptoms of adenomyosis are heavy and/or prolonged menstrual bleeding and dysmenorrhea in a woman over the age of 40.

II. Non-Gynaecologic Causes

1. **Gastrointestinal:** Irritable bowel syndrome (IBS): IBS is a functional bowel disorder of unknown etiology. Approximately 50-80% of women with CPP will have symptoms suggestive of IBS such as pain that is relieved with defecation and a change in stool frequency and form.
2. **Genitourinary:** Interstitial cystitis: Interstitial cystitis is a chronic inflammatory condition of the bladder. It may present with pelvic pain, urinary urgency and frequency. Diagnosis is made using a potassium sensitivity test and at cystoscopy.
3. **Musculoskeletal and neurological:** Possible causes include nerve entrapment, myofascial pain and low back pain.
4. **Psychological:** Psychological conditions such as depression, anxiety, personality disorders and psychosomatic disorders may cause or exacerbate pelvic pain. However, one should always rule out all other causes of pain, as these psychological conditions may in fact be secondary to the chronic pain that these women experience.

Management Approach

History

As in any gynaecological patient assessment, history taking begins by gathering pertinent past medical, surgical, obstetrical and gynecological history. Obtaining a menstrual history which enquires about onset of menses, intensity and impact of dysmenorrhea and menorrhagia is important. A list of medications, including those previously tried in the management of the pain should be sought. A thorough pain history should then be gathered including the location, intensity, quality, duration, temporal pattern, precipitating factors, relationship to urination and defecation, and patterns of radiation. A mnemonic frequently used for obtaining a clear description of the pain is **PQRST**: **P**alliative factors, **Q**uality, **R**egion, **S**everity and **T**iming.

A review of symptoms should then be sought to rule in/out non-gynaecological causes, with particular focus on the gastrointestinal, genitourinary, and musculoskeletal systems. Screening questions for depression should be asked and a sexual history including physical, sexual or psychological abuse should be elicited as it is common in women who present with CPP. Finally, an inquiry should be made as to the use of prescription and/or illicit drugs.

Physical Exam

A thorough physical exam should be performed. Particular attention is directed to the abdominal, pelvic, vulvar, vaginal and rectovaginal exam. Nodularity of the uterosacral ligaments with a fixed, retroverted uterus or ovarian enlargement may be noted in patients with endometriosis. A diffusely enlarged uterus is suggestive of adenomyosis. Speculum examination with cervical cultures for gonorrhea and chlamydia should be considered. It is important to remember that a lack of physical findings does not signify that the patient is not experiencing pain. Findings may only be evident at laparoscopy or there may be no demonstrable pelvic disease.

Diagnosis and treatment

Individualized approach

The diagnostic tests required depend on the patient's symptoms. Abdominopelvic ultrasound or magnetic resonance imaging may be helpful in diagnosing gynecological conditions (particularly ovarian masses and adenomyosis) and gastrointestinal conditions. However, it is important to understand the limitations of radiological investigations. Although findings such as a cyst with the appearance of an endometrioma may be suggestive of endometriosis, the diagnosis can only be firmly made with either a response to medical therapy directed at endometriosis or at laparoscopy. Furthermore, in adenomyosis imaging may be normal and the only method of definitive diagnosis is on pathology at the time of a hysterectomy.

Cervical and vaginal cultures should be performed if the patient has any risk factors for sexually transmitted infections. If the patient has urinary symptoms a urinalysis should be performed. Distressing urinary symptoms and chronic pelvic pain with a normal urinalysis warrants evaluation by an urologist. In the context of primarily gastrointestinal symptoms, referral to a gastroenterologist is recommended.

Laparoscopy is helpful in establishing a diagnosis of endometriosis and in identifying other pelvic pathology. Characteristic findings of endometriosis at laparoscopy are "powder-burn" lesions (black, brown or bluish nodules), red implants, vesicles or white plaques on the peritoneum and adhesions. The majority of these implants are located in the dependent portions of the pelvis, the primary site being the ovaries. Other common sites of implants include the pelvic peritoneum over the uterus, the anterior and posterior cul-de-sac, and the uterosacral, round and broad ligaments. Not all patients with CPP require laparoscopy. In a patient with CPP and clinical findings suggestive of endometriosis, many gynaecologists will propose beginning empirical therapy (non-steroidal anti-inflammatory agents and hormonal contraceptives) and consider proceeding with laparoscopy only if this treatment option fails. Progestin regimens and GnRH- analogues are often prescribed in patients with endometriosis who fail first line medical therapy or in whom estrogen therapy is contraindicated

In women with CPP, at laparoscopy one can expect that 35% of women will have no visible pathology, 33% endometriosis, 24% adhesions, 5% chronic PID, and 3% ovarian cysts. As these statistics suggest, in one third of cases of CPP, despite a complete evaluation, the cause of the pain remains unclear. It is important to counsel women about this fact prior to any surgical intervention and explain that a normal laparoscopy does not mean that there is no physical basis for the pain.

For patients with primary dysmenorrhea, nonsteroidal anti-inflammatory agents (NSAIDs) and hormonal contraceptives are the mainstay of treatment. NSAIDs should be taken continuously beginning in the premenstrual phase until the second or third day of menses. Hormonal contraceptives may be used jointly with NSAIDs in either a cyclical or continuous fashion. An intrauterine system that releases levonorgestrel (e.g. Mirena intrauterine system IUS) may also be inserted for the management of dysmenorrhea. Progesterone therapy (oral or intramuscular injection) may also be considered.

As previously stated, the clinical diagnosis of adenomyosis is inaccurate and a definitive diagnosis of adenomyosis may be made on histological examination of the uterus after a hysterectomy. In women with dysmenorrhea between the age of 35 and 50 years with diffuse uterine enlargement and a negative

pregnancy test a presumptive diagnosis of adenomyosis may be made. Adenomyosis may be initially managed with NSAIDs, hormonal contraceptives, or a Levonorgestrel-releasing IUS. Complete relief of symptoms is often only with a hysterectomy.

Multidisciplinary approach

Due to the complexity of managing women with CPP, a multidisciplinary approach is advantageous. Pelvic pain clinics may include many specialists including gynaecologists, urologists, gastroenterologists, neurologists, anesthesiologists, psychological counselors, and pelvic physiotherapists to provide women with CPP the comprehensive care they require.

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Early Pregnancy Complications

Early Pregnancy Complications Objectives:

At the end of the seminar, students should be able to:

Spontaneous Abortion:

1. Develop a differential diagnosis for first trimester bleeding.
2. Define the types of spontaneous abortion including recurrent abortion.
3. Distinguish between the types of spontaneous abortion according to clinical presentation and diagnostic testing.
4. Describe the principles and options for management of spontaneous abortion
5. List the complications of spontaneous abortion.
6. Counsel a patient following a spontaneous abortion taking into consideration the emotional impact of pregnancy loss and relationship to future pregnancy.

Ectopic Pregnancy:

1. Develop a differential diagnosis for bleeding and abdominal pain in the first trimester.
2. Identify risk factors for ectopic pregnancy.
3. Describe symptoms and physical findings suggestive of ectopic pregnancy
4. Understand methods and tests used to investigate pregnancies of unknown location.
5. Describe treatment options for patients with ectopic pregnancy.

Gestational Trophoblastic Disease (GTD):

1. List the symptoms and physical findings of a patient with GTD.
2. Describe the diagnostic methods for a patient with GTD.
3. Describe the appropriate management of GTD.

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COMPLICATIONS IN EARLY PREGNANCY (FIRST TRIMESTER BLEEDING)

Bleeding during the first trimester of pregnancy is common (incidence: 20-25%). The amount of bleeding can vary from light spotting to hemorrhage. The amount and/or duration of bleeding does not necessarily predict cause or prognosis. Vaginal bleeding may be seen in normal early gestation, early pregnancy loss, ectopic pregnancy and gestational trophoblastic disease.

Differential for Bleeding in the 1st Trimester (Table 1):

NORMAL EARLY GESTATION	ECTOPIC PREGNANCY (2%)
• Cervical erosion or ectropion • Endocervical polyp • Cervical dysplasia/neoplasia • Vaginal abrasion/laceration • "Implantation bleeding" or subchorionic hemorrhage • Indeterminate or unknown	• Tubal ectopic • Cornual or interstitial ectopic • C-section scar ectopic • Cervical ectopic • Other ectopic – ovarian or abdominal pregnancy
EARLY PREGNANCY LOSS	**ABNORMAL PREGNANCY(<1%)**

• Rate increases with maternal age
  • 15% at 20 yrs old
  • 40% at 40 yrs old
  • 80% at 45 yrs old
	• Molar pregnancy
	• Partial molar pregnancy

EARLY PREGNANCY LOSS

Early Pregnancy Loss is defined as a non-viable intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus with no fetal heart activity. Early pregnancy loss is synonymous with miscarriage or spontaneous abortion. There is no consensus on terminology in the literature and these terms are often used interchangeably.

Classification of Early Pregnancy Loss:

- *Missed Abortion:* Non-viable pregnancy on ultrasound, without signs/symptoms of abortion.
- *Threatened:* Live intrauterine pregnancy with cramping and/or vaginal bleeding but closed cervix.
- *Inevitable:* Open cervix with cramping and/or bleeding, expulsion of tissue in progress
- *Incomplete:* Retained products of conception in uterus after some tissue has been passed, often with ongoing vaginal bleeding
- *Complete:* No remaining products of conception in uterus, pregnancy completely expelled.
- *Septic:* Any of the above in the presence of signs/symptoms of infection (most often incomplete)
- *Recurrent:* 3 consecutive early pregnancy losses

Etiology of Early Pregnancy Loss:

- Aneuploidy (most common cause)
  - Autosomal trisomy
  - Unbalanced translocation
  - Turner's Syndrome - XO (60%)
  - Triploidy
- Chronic Maternal Illness
  - Diabetes Mellitus
  - Renal Failure
  - Autoimmune Disorders
  - Hypothyroidism
- Substances and Toxins
  - Alcohol or drug misuse
  - Smoking
  - Lead toxicity
- Maternal Factors
  - Advanced maternal age
  - Increasing gravidity
  - History of previous pregnancy loss
  - Uterine septum or malformation
  - Intrauterine contraceptive device (IUD)
  - Progesterone deficiency
  - Infection
  - Thrombophilia
- Trauma
- Unknown

The majority of early pregnancy losses have no determinable etiology.

Initial Assessment of First Trimester Complications:

Common symptoms of early pregnancy loss, including vaginal bleeding, cramping, pelvic pressure and back pain are also common in normal early pregnancy, ectopic pregnancy and gestational trophoblastic disease. Prior to making any treatment decisions, it is important to distinguish early pregnancy loss from other early pregnancy complications. Initiating treatment prior to confirming the diagnosis can have negative consequences for the patient and pregnancy including interruption of a normally developing early pregnancy, pregnancy complications or birth defects and potential maternal morbidity or mortality.

First Steps in Assessment of the Patient with First trimester bleeding:

- **Initial Assessment** - identify the unstable patient needing resuscitation
  - Quantify the amount of bleeding, rule out acute hemorrhage
  - Look for signs of hypovolemia – pallor, postural hypotension/tachycardia
  - Assess for peritoneal signs due to intra-peritoneal bleeding (ruptured ectopic)
  - Identify signs of sepsis – fever, rigor, hypotension
- **Assess Pregnancy and Dating**
  - Determine Expected gestational age based on (in order of accuracy when available) IVF transfer date, previous dating ultrasound, current ultrasound measurements, last menstrual period date if known and cycles regular.
  - Assess uterine size, position and tenderness
  - Assess cervix – open vs. closed, look for partially expelled tissue stuck at cervical os.

Initial Workup:

1. CBC - expect a delay in hematocrit or hemoglobin drop with acute bleeding, serves as baseline
2. Group and Screen - may need blood products, determine if RhIG needed to prevent isoimmunization
3. β-hCG – Quantitative – may be useful as a baseline for serial measurement comparison however, there is wide variation in 'normal' Bhcg levels between pregnancies.

***Important Note: There is no 'cut-off' for Bhcg that can determine a viable from non-viable, intrauterine from ectopic or normal from abnormal pregnancy. Bhcg should approximately* **DOUBLE q48h** *in a typically developing pregnancy until it peaks at approximately 100,000 at 8-10 weeks gestation. However, a normally doubling Bhcg does not confirm viability or rule out ectopic. In early pregnancy loss, Bhcg may be expected to decline by exponential decay at a rate of at least 15% per day when tissue has been expelled.* **A plateaued or fluctuating Bhcg level on repeat testing should prompt high suspicion for an ectopic pregnancy.** *A single measurement is useful only as a baseline to compare subsequent values to and is not in itself particularly useful as the range of expected values is wide. Serial Bhcg measurements should be done in the same lab to enable accurate comparisons.*

Ultrasound Findings in Early Pregnancy

Transvaginal ultrasound is the preferred modality to assess early pregnancy and should be performed in **all women** presenting with early pregnancy complications **regardless of suspected gestational age quantitative Bhcg level**. Non-diagnostic ultrasound in which either no pregnancy is seen or the viability of a visualized pregnancy is uncertain should be repeated in 7-10 days to assess for ongoing development if the patient is stable and the pregnancy is wanted.

Ultrasound Findings in Normal Early Pregnancy (Table 2)

Approximate Gestational Age	Ultrasound Finding
24 days post-conception (BhCG ~1500)	Gestational sac visible, grows ~1 mm/day
5.5 weeks (gestational sac >8 mm)	Yolk sac
6.0 weeks (gestational sac 16 mm)	Small embryo ~3 mm
6.5 weeks (Crown Rump Length > 5.3 mm)	Fetal heart rate detected, may be < 100 BPM
8.0 weeks (Crown Rump Length 16 mm)	Embryo body movements visible, FHR ~175 BPM

Ultrasound Findings in Early Pregnancy Loss (Table 3)

Findings *suspicious* for pregnancy failure but *non-diagnostic*	**Ultrasound Findings *Diagnostic* of Pregnancy Failure (Non-Viable)**
Crown Rump Length (CRL) 5-7 mm with no FHR. Fetal Bradycardia (<100 BPM) at > 7 weeks Absence of an embryo at >6 weeks from LMP or with sac size of 16-24 mm Small sac size relative to the embryo (difference of < 5 mm between sac and CRL measurement) Enlarged (>7mm) or abnormally shaped (crenelated) yolk sac	No fetal heart rate when CRL > 7 mm (100% specific) No embryo or yolk sac in gestational sac > 25 mm in diameter (100% specific) Absence of an embryo with heart rate 11 days after a scan showing a yolk sac or 2 weeks after a scan without a yolk sac

Management of Early Pregnancy Loss:

1. **Always** ensure patient is hemodynamically stable first
2. **Always** rule out ectopic pregnancy
3. **Always** check Rh status before discharge and administer RhIg as indicated
4. There is **NO intervention** to prevent early pregnancy loss or 'save' a pregnancy with first trimester complications. There is no evidence of objective benefit from bedrest, exercise or work restriction in cases of threatened abortion. However, these restrictions may provide peace of mind and emotional comfort for an anxious patient with a wanted pregnancy.
5. In cases where the viability of the pregnancy is uncertain, the patient is stable, and the pregnancy is desired, a period of expectant management with close follow up using serial Bhcg and repeat ultrasound may be useful to reach a definitive diagnosis.

Options for the Management of a Confirmed Non-Viable Intrauterine Pregnancy in the First Trimester:

There are three options for the management of non-viable first trimester pregnancy in a stable patient without medical complications. Accepted management includes expectant management, medical treatment or surgical evacuation of the uterus. All have been shown to be reasonably effective and well accepted by patients. There is no evidence that any approach results in different long-term outcomes. All three approaches typically result in complete evacuation of the uterus and serious complications are rare. All three have similar risks of heavy bleeding or infection. In general, patient preference and local resources should guide management decisions.

Expectant Management:

- Considered to be generally safe in the first trimester but should not be attempted at higher gestational ages – usually restricted to pregnancy < 8 weeks size (CRL < 2 cm) by convention.
- Success rate of approximately 80% with enough time (up to 8 weeks) and may be more effective in women that are symptomatic (incomplete or inevitable abortion) than asymptomatic (missed abortion)
- Patients may experience moderate or heavy vaginal bleeding and cramping and should be provided with clear instructions on what is excessive bleeding (>2 pad per hour x 2 hrs) and how to seek urgent care.
- If expectant management fails, may require surgical evacuation of the uterus

Medical Treatment:

- Can be considered in women without evidence of infection, hemorrhage, severe anemia or history of bleeding disorders or significant medical co-morbidities.
- Shortens the time to complete expulsion and decreases the rate of retained tissue requiring surgical evacuation compared to expectant management. Success rate of 81% (missed abortion) to 93% (incomplete or inevitable abortion)
- Usually limited to a maximum gestational size of approximately 8 weeks by convention. Use of outpatient misoprostol at higher gestational ages may result in heavy bleeding, severe pain, emotional distress and higher chance of needing emergency care or surgical evacuation to achieve completion.
- Typical protocol:
    - Misoprostol 800 mcg x 2 doses given q24 hours either PV or SL. May be given PO but has greater chance of side effects (diarrhea)
    - The addition of Mifepristone 200 mg PO 24 hours prior to misoprostol has been shown in an RCT to increase the rate of complete expulsion and should be considered where available.
    - Patients should be provided with pain medication – NSAID's and sometimes a small number of narcotics to manage cramping at home.
- Patient should be counselled to expect bleeding heavier than typical menses with cramping and passage of tissue and clots. Bleeding should then decrease but may continue for up to 2 weeks. Patients should be counselled on excessive bleeding (> 2 soaked pads x 2 consecutive hours) and advised how to seek urgent care.
- Failure of medical treatment may require surgical evacuation.

Surgical Management (D&C – Dilatation and Curettage)

- Surgical evacuation of the uterus is successful in 99% of cases.
- Should be the management of choice for women presenting with hemorrhage, hemodynamic instability or signs of infection, failure of expectant or medical management, medical comorbidities or pregnancies of more advanced size (>8.5 weeks gestational size on ultrasound) or if pathologic evaluation of products of conception are needed or desired (suspected molar pregnancy, recurrent pregnancy loss).

- Many women prefer the immediacy of surgical evacuation but practical availability of the procedure is often limited by OR resources, especially in stable patients with non-urgent indications. D&C may also be completed in an office setting with local anesthesia +/- conscious sedation where resources permit.
- Suction evacuation of the uterus is preferred and there is no benefit to the addition of sharp curettage.
- Serious complications are rare (0.4-0.7%) and include:
    - Uterine perforation ± visceral injury
    - Intrauterine Synechiae/ Scarring of the endometrium (Asherman Syndrome)
    - Cervical injury and/or subsequent cervical incompetence

Counselling Patients with Early Pregnancy Loss:

Each woman responds differently to pregnancy loss and can exhibit all stages of grief. It is appropriate to acknowledge these feelings and emphasize that support from family and external groups (e.g. Bereaved Families of Ontario, PAIL – Pregnancy and Infant Loss Network) should be sought as needed. Many women may experience feelings of guilt or question why their miscarriage happened. There is very little evidence to suggest any link between things the patient has control over (e.g. diet, exercise, etc.) and miscarriage. Miscarriage in the absence of complications does not have any impact on future risk of miscarriage. Patients may 'try again' when they feel emotionally ready and after having one normal menstrual period.

ECTOPIC PREGNANCY

An **ectopic pregnancy** is defined as any pregnancy with implantation outside of the endometrial cavity.

Epidemiology:

Incidence of approximately 2% of all pregnancies. It is the *leading cause of maternal mortality in the first half of pregnancy* and accounted for 2.7% of all pregnancy related deaths in 2011-13. Overall rupture rate approximately 30% with highest risk of rupture in the first 48h after onset of symptoms. Prevalence of ectopic in pregnant women presenting to an ER with vaginal bleeding, abdominal pain or both is approximately 18%. Heterotopic pregnancy (co-existing ectopic and intrauterine pregnancy) occurs 1 in 4000 to 1 in 30,000 natural conceptions but can be as high as 1 in 100 for IVF pregnancies. Missed diagnosis and/or improper treatment and follow up of ectopic pregnancy remains an important cause of maternal mortality.

Risk Factors:

- **50% of women with ectopic pregnancy have no identifiable risk factor**
- Tubal Damage or partial obstruction:
    - Previous tubal surgery
    - Previous sterilization
    - Previous ectopic pregnancy (10% recurrence with one previous, 25% recurrence if 2+)
    - History of PID or pelvic infection (includes peritonitis of any etiology, eg: ruptured appendix)
    - Endometriosis

- Contraceptive Failure
    - Copper IUD failure – up to 53% of pregnancies occurring with IUD in situ are ectopic (IUD very effectively prevents intrauterine pregnancies but has limited effect in preventing pregnancy outside uterus)
- Infertility
    - History of infertility, even if current pregnancy naturally conceived
    - Infertility treatment - IVF treatment has 7% ectopic rate
- Maternal Factors
    - Smoking tobacco
    - Advanced maternal age (>35 yrs)

Pathophysiology:

- Altered tubal transport secondary to anatomic obstruction, abnormal cilia function, possibly delayed fertilization and/or abnormal embryo results in implantation outside the uterus
- Sites of ectopic pregnancy implantation:
    - Tubal >90% (ampulla, isthmus, interstitial),
    - Abdominal 1%, ovarian 1-3%, c-section scar 1-3%, cervical <1%

Presenting Symptoms:

- May have none.
- Period of amenorrhea (90-100%)
- Vaginal bleeding (60-80%)
- Abdominal pain (any pattern) (95%)
- Shoulder tip pain (15%)
- Dizziness/light-headedness (58%)
- Molimina (variable)
- GI symptoms – nausea, vomiting, diarrhea (80%)

Patient presentation varies greatly. A high index of suspicion is necessary to avoid serious morbidity and mortality from missed diagnosis and/or improper treatment/follow up.

Physical Signs:

Signs of acute intraperitoneal bleeding:

- Abdominal pain (75%)
- Peritoneal irritation, rebound, guarding, cervical motion tenderness (75%)
- Hemodynamic instability (1-50%)
- 'Boggy' abdomen (rare)
- Cullen's sign (rare)

Pelvic Examination:

- Palpable adnexal mass
- Cervical motion tenderness
- Adnexal tenderness

Differential for Pain in Early Pregnancy:

- Rupture of ovarian cyst (corpus luteum)
- Threatened abortion
- Acute salpingitis / infection
- Endometriosis
- Ovarian Torsion
- Appendicitis
- Irritable Bowel / Constipation
- Other non-gynaecological causes

Investigations:

Initial Investigations:

1. **CBC** - expect a delay in hemoglobin drop with acute bleeding, useful as a baseline
2. **Group and Screen -** may need blood products, may need prophylaxis against Rh isoimmunization
3. **β-hCG -** Quantitative to serve as baseline measurement for future comparisons. There is wide variability in Bhcg levels between pregnancies and a single quantitative value is of limited utility. There is no 'cut off' that will distinguish an ectopic from IUP or a viable from non-viable pregnancy, however in general, Bhcg levels are lower in ectopic pregnancies than in intrauterine pregnancies of the same gestational age. A Bhcg that doubles within 48h does not rule out an ectopic and a repeat Bhcg level that is plateaued or fluctuates over several repeats (some up, some down) should prompt high suspicion of ectopic pregnancy.
4. **Transvaginal high resolution ultrasound -** should be done in ALL women presenting with bleeding and/or pain in early pregnancy regardless of Bhcg level or suspected gestational age.

Table 4:

DIAGNOSTIC of ectopic pregnancy	SUGGESTIVE of ectopic pregnancy	NOT SUGGESTIVE of ectopic pregnancy
Extra-uterine yolk sac or fetal pole +/- FHR (PPV 100%)	Adnexal mass, separate from the ovary with no IUP (PPV 80-90%) Large volume of echogenic free fluid (blood) in cul-de-sac	Simple cyst in the adnexa Complex cyst in the ovary (most likely a corpus luteum)

Ultrasound Findings in Ectopic Pregnancy:

Non-diagnostic Ultrasound – Pregnancy of Unknown Location – a woman without a definitive finding of either an intrauterine or ectopic pregnancy on ultrasound has a "pregnancy of unknown location". A pregnancy of unknown location is NOT a diagnosis and should be considered a *transient state requiring very close follow up until a final diagnosis is reached*. Follow up to determine a diagnosis is recommended prior to initiating treatment to avoid unnecessary exposure to medications (with potential side effects) and the possibility of interruption or teratogenicity in a desired pregnancy.

Management of Pregnancy of Unknown Location:

- **Clinically stable patient with desire to continue the pregnancy**: Should be followed with serial repeat Bhcg q48h until a clear pattern emerges or the clinical status of the patient changes (i.e. increased pain, bleeding, no longer stable). A pattern is usually apparent within 1-2 repeated values and there is no utility in continuing serial Bhcg beyond this point.
    - *Bhcg increasing at a rate consistent with intrauterine pregnancy* (at least 50% increase in 48 hours): repeat ultrasound to assess pregnancy location and if confirmed IUP then q7-10 days until viability of pregnancy is determined.
    - *Bhcg decreasing at a rate of at least 15-20% from baseline*: consistent with failing pregnancy that is self-resolving. In stable patient, continue to follow Bhcg levels weekly to non-pregnant levels. Unlikely to require any intervention to achieve spontaneous resolution.
    - *Bhcg level is plateaued (less than 10-15% change either up or down)* or fluctuating: Pregnancy is NOT developing normally and will not progress to a 'take home baby' (100% specificity). There is a high risk of ectopic pregnancy (50%). In a stable patient that remains asymptomatic, repeat ultrasound to assess for pregnancy location. If location of pregnancy is still unclear (no IUP, no visualized ectopic) may consider uterine aspiration to assess for presence of chorionic villi. If chorionic villi identified, failed intrauterine pregnancy is confirmed. If no chorionic villi identified and no significant drop in Bhcg post-aspiration, highly suggestive of ectopic pregnancy and should be treated. If uterine aspiration not available or not acceptable to patient, may consider presumptive treatment for ectopic pregnancy although controversial as diagnosis has not been confirmed.

- **Clinically stable patient that does NOT desire to continue pregnancy:** pregnancy termination using medical or surgical approach. Close follow up of Bhcg for appropriate decrease. If no decrease post-treatment, strongly consider further work-up/treatment as an ectopic pregnancy.

Management:

Management of patients with either confirmed or highly suspected ectopic pregnancy is determined based on patient factors and local resources. Improperly managed ectopic pregnancy remains a significant cause of maternal morbidity and mortality in North America.

Priorities for Management:

Stabilization of the hemodynamically or potentially hemodynamically unstable patient – venous access, crystalloids +/- blood products, Trendelenburg position, foley catheter and emergent surgery for the patient presenting in hypovolemic shock or with signs of acute intraperitoneal bleeding. Surgery should also be the treatment of choice for patients that have absolute or relative contraindications to medical management (see table below) even if currently well.

Surgical management - if feasible the surgery should be laparoscopic and as minimally invasive as possible. Salpingostomy (incise the tube and leave to heal rather than suture closed) may be considered if the tube appears salvageable and the patient desires future fertility. Salpingectomy (removal of the tube) should be considered if the tube appears significantly damaged/ ruptured or the ectopic pregnancy is an ipsilateral

recurrence. Surgical management of non-tubal ectopic pregnancies (cervical, ovarian, c-section scar, cornual) requires an individualized approach and may be influenced by both patient (age, parity, surgical history, desire for future fertility) and surgeon (experience, resources, available skilled assistant) factors.

Medical management – may be considered in stable, patients without contraindications. There are several different published protocols for Methotrexate treatment of ectopic pregnancy. The most commonly used gives a single dose of Methotrexate 50mg/m2 IM on Day 1. Bhcg levels must be rechecked on Day 4 and Day 7 post-methotrexate and should decrease by at least 15% in this interval. Bhcg is then followed weekly until negative. Side effects include GI upset, stomatitis, hepatic dysfunction, renal toxicity and marrow suppression. Incidence of side effects at this dose are low, however baseline liver function tests, creatinine and CBC are required pre-treatment. In appropriately chosen patients, success rate for methotrexate treatment is 88-90% with resolution of Bhcg to negative in an average of 22 days.

Absolute Contraindications to Methotrexate	Relative Contraindications to Methotrexate
Hemodynamically Unstable	Gestational sac > 3.5 cm
Severe abdominal pain	Initial Bhcg > 5000
IUP or heterotopic pregnancy	Presence of +FHR
Immunodeficiency	Previous ipsilateral ectopic
Alcoholism or liver dysfunction	Refusal of blood transfusion
Blood dyscrasias or bone marrow dysfunction	Breastfeeding (no good evidence for safety)
Active pulmonary fibrosis	Non-tubal ectopic pregnancy (cervical, ovarian, etc)
Renal dysfunction	
Unable to complete follow up	

Expectant management is very seldom employed and is appropriate in very few patients. It may considered in the truly asymptomatic patient particularly if the gestational sac is very small, the beta hCG is low (<1000) and already spontaneously dropping and/or the implantation site is seen in the distal tube. Very close follow up with serial β-hCG monitoring is required. Patients must be counselled on and accepting of the risk of tubal rupture, intraperitoneal hemorrhage and the potential for emergency surgery and *must be able to access emergency care quickly*. In patients managed expectantly, Bhcg should be repeated in 48 h. If <20% drop in Bhcg, strongly consider an alternative treatment strategy to minimize the risk of complications.

Complications of Ectopic Pregnancy:

1. Treatment failure – with potential tubal rupture and acute intraperitoneal bleeding.
2. Persistence - low incidence after surgery, higher risk after medical management. May be managed medically with repeat doses of methotrexate or with surgery
3. Infertility – future fertility is compromised in patients with a history of an ectopic pregnancy. Only 60% will have a subsequent pregnancy. Future fertility rates are the same regardless of medical or surgical management.
4. Recurrence - 10% recurrence following one previous ectopic, 25% following two previous. Patients with previous ectopic should have an early dating ultrasound to confirm an IUP in subsequent pregnancies.

GESTATIONAL TROPHOBLASTIC DISEASE (GTD)

Gestational trophoblastic disease is a group of rare tumors that involve abnormal growth of cells within the uterine cavity. The origin of the abnormal cells is the trophoblast layer of an embryo. In a normal pregnancy the trophoblast layer forms finger-like projections called villi that grow into the lining of the uterus (endometrium) to form the developing placenta. The terms gestational trophoblastic disease, gestational trophoblastic tumor or gestational trophoblastic neoplasia may be used interchangeably in the literature. The majority of GTDs are benign and do not invade deeply into normal tissue or spread to distant areas of the body. Some GTD are malignant and capable of distant metastasis (usually liver, brain, lung). Most GTD occurs due to an abnormal pregnancy, however, GTD can also sometimes follow completion of a normal pregnancy and rarely occurs many years later. GTD is highly treatable and almost universally curable but may result in long-term morbidity or mortality if not diagnosed and managed appropriately.

Types of Gestational Trophoblastic Disease:

- **Hydatiform Mole – Partial or Complete**
  - The most common form of GTD, also known as a molar pregnancy
  - Abnormal villi are hydropic and fluid filled resembling clusters of grapes
  - Benign but may progress to invasive GTD without adequate treatment
- **May be either complete or partial:**
  - **Complete Mole**: typically 46XX but both chromosome sets are of paternal origin (no maternal DNA present). May result from fertilization of an 'empty' egg by 1 or 2 normal sperm or from errors in early cell division in which maternal nuclear material is lost. No fetal parts are formed and hydropic villi typically fill the uterus.
  - **Partial Mole**: is often triploid (69 chromosomes) with either a double maternal or double paternal set. Abnormal villi are present as in complete mole but usually some fetal tissue is also found (may be a complete fetus although with multiple anomalies). Fetus is non-viable and usually spontaneously demises in early pregnancy

- **Invasive Mole** - abnormal villi from either a complete or partial mole that have invaded beyond the endometrium into the muscular layer of the uterus. More common with a complete mole, women > 40 yrs old or with a long lag time between LMP and treatment (>4 months). Still benign but may become malignant if untreated.

- **Choriocarcinoma** – is a malignant form of GTD that grows quickly and can spread to distant organs. 50% of choriocarcinomas follow a molar pregnancy, 25% follow a spontaneous abortion, 25% follow a normal pregnancy and delivery.

- **Placental Site Trophoblastic Tumor** - a very rare type of malignant GTD that most commonly follows a normal pregnancy. May present at a time remote from the antecedent pregnancy (months to years)

Symptoms of GTD:

- Abnormal vaginal bleeding
- Passage of fluid filled vesicles vaginally (may appear like 'bunches of grapes')
- Symptoms secondary to high Bhcg levels (may be > 1 million)
    - Hyperemesis gravidarum
    - Early onset of pre-eclampsia
    - Hyperthyroidism
- Symptoms secondary to metastatic lesions
    - Hemoptysis
    - Severe headache/neurologic symptoms
    - Liver dysfunction

Signs of GTD:

- Uterine size may be outside of expected for gestational age – typically larger than expected for gestational age but may also be smaller or appropriate for GA.
- Vesicles may be seen in the vagina or prolapsing through the cervix
- Enlarged ovaries
- Signs of hyperthyroidism
- Hypertension
- Proteinuria

Investigations:

- CBC
- Group and Screen
- Quantitative Bhcg
- TSH
- Liver Function Tests
- Chest x-ray
- Transvaginal U/S – shows typical features of 'snow storm' pattern in complete mole or thick abnormal placenta +/- anomalous fetus in partial mole.

Treatment of GTD:

- **Requires surgical treatment:** Dilation and curettage (D&C) is usual first line but often requires the use of oxytocin or other uterotonics to prevent hemorrhage. If patient is not interested in future fertility, may consider hysterectomy.
- Screen for metastasis (CXR, LFTs, consider CT Head)
- Serial BhCG weekly until negative then monthly for 6-12 months.
- Defer pregnancy for 6-12 months (i.e. reliable contraception, OCPs are safe) to enable serial monitoring of Bhcg for signs of persistent or recurrent disease.
- If Bhcg does not become negative, or increases during surveillance period or there is evidence of any metastatic disease – refer to gyne oncology for adjuvant treatment (usually chemotherapy – regimen depends on risk factors)



Infertility and Recurrent Pregnancy Loss

Infertility and Recurrent Pregnancy Loss Objectives:

At the end of the seminar, students should be able to:
Infertility:

1. Define primary and secondary infertility.
2. Obtain a relevant history from a couple presenting with infertility.
3. List causes of male and female infertility.
4. Outline a plan of evaluation and management in a couple with infertility.
5. Describe the psychosocial issues associated with infertility.
6. Describe the new reproductive technologies such as IVF, ICSI, their applications, limitations, and complications.

Recurrent Pregnancy Loss:

1. Define recurrent pregnancy loss.
2. Describe the etiology of recurrent pregnancy loss.
3. Outline the evaluation of a couple with recurrent pregnancy loss.
4. Describe the management of a patient with recurrent pregnancy loss.
5. Describe the psychosocial issues associated with recurrent pregnancy loss.

Last revised: July 2019

INFERTILITY

Infertility is classically defined as the inability to conceive after 1 year of unprotected intercourse.

- 1 in 6 of all couples (overall).
- Percentage of infertility differs with age.
- *Primary:* infertility with no history of prior conception
- *Secondary:* infertility with history of prior conception (regardless of whether it resulted in delivery)

Relevant History Information

The evaluation of an infertile couple requires a detailed medical, sexual, and reproductive history.

Specific elements to evaluate include:

1. Length of time that the couple has been attempting to conceive
2. Prior reproductive performance of each partner
3. Menstrual cyclicity
4. Symptoms suggestive of pelvic inflammatory disease or endometriosis
5. Coital technique (timing and frequency)
6. Use of medications
7. Previous pelvic or abdominal surgery in the female
8. Urologic disorders of the male

Causes of Male and Female Infertility

- **Female infertility** accounts for ~ 50% of cases:
  - Ovulation disorders (25%)
  - Peritoneal (endometriosis/adhesive disease) and tubal disease (25%)
  - Cervical and uterine factors (10%)
  - Obesity
- **Male factor infertility** is the primary diagnosis in approximately 25% of cases and contributes an additional 15% to 25% of the remaining cases (total of 40-50% couples).
- **Unexplained infertility.** Infertility remains *unexplained in approximately 15%* of cases because numerous reproductive defects are undetectable with current diagnostic methods.

Standard Infertility Evaluation

A standard infertility evaluation is warranted for couples who have not been able to conceive despite 12 months of unprotected intercourse (if of advanced maternal age >35, 6 months is sufficient for initiation of evaluation).

The standard infertility work-up should include the following:

- **Ovulatory and luteal function** (day 3 FSH, luteal serum progesterone level (day 21) urinary LH kit)
- **Cervical factor** (post-coital test (PCT))
- **Uterine factor** (hysterosalpingogram/sonohysterogram and/or hysteroscopy; ultrasound)
- **Tubal factor** (hysterosalpingogram/sonohysterogram and laparoscopy)
- **Endometriosis or other pelvic pathology** (laparoscopy)
- **Male factor evaluation** (semen analysis)

Approach to work-up:

Female Partner:

1. Egg quality problem: female age
2. Egg quantity problem:
   - Day 3 FSH with Estradiol
   - Antral follicle count
   - AMH (can be done any day)
3. Ovulation defect (check progesterone in luteal phase)/cycle monitoring
4. Disorders of the hypothalamic-pituitary-ovarian axis
5. Anatomical problem: uterus and tubes

Male Partner:

- Gamete Issue
- Impotency

Couple:

- Intercourse Timing

Egg Quality Evaluation:

- Egg quality decreases with age (beginning after age 35, significantly after age 40)
- No testing available

Egg Quantity Evaluation:

- Follicle stimulating hormone (FSH) on cycle day (CD) #3 is gold standard (normal:< 10 mIU/L)
  - Make sure Estradiol is checked because if elevated due to presence of ovarian cyst(s), FSH can be falsely low due to negative feedback of Estradiol on the HPO axis
- Antral follicle counts (CDs 3-6): Total should be greater than 9 follicles
- AMH (anti-mullerian hormone): concentrations decrease over time before other markers of ovarian ageing/reduced baseline levels correlate with a poor response to ovarian stimulation for IVF

Ovulation Defect:

- Menstrual history - regular cycles can range anywhere from 24-35d
- Molimina - breast tenderness, bloating, moodiness (effects of progesterone)
- Basal body temperature (BBT) - requires special thermometer and same time of day measurement. Limit prolonged use.
- Serum progesterone - used to monitor ovulation induction
- Urinary LH kits - useful for timing intercourse/insemination

Disorders of the hypothalamic-pituitary-ovarian axis:

- Polycystic ovary syndrome - elevated androgens, acanthosis nigricans, cystic ovaries and anovulation
- Extremes of weight - obesity and anorexia

- Hypothalamic amenorrhea - organic vs. functional causes
- Prolactinoma - prolactin
- Ovarian failure - CD #3 FSH
- Thyroid dysfunction - TSH, free T3 and free T4

Obesity (Belan et al. CMAJ. 2018)

- The risk of infertility is increased by 78% and 27% in women of childbearing age with obesity and overweight, respectively.
- Obesity can negatively affect women's fertility via menstrual and ovulatory disorders.
- In women with no apparent ovulatory or menstrual dysfunctions, negative effects on reproductive health are observed: a linear decline of 4% in the chances of a spontaneous pregnancy for each increase of one point in the BMI score in obese women.

Figure 1: Extremes of Weight Affecting Ovulation.



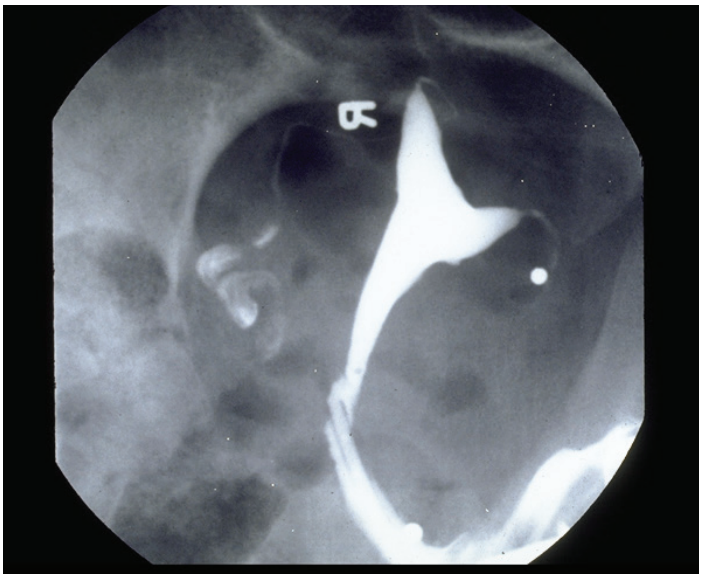
Figure 2: Evidence of Hirsutism and Acanthosis Nigricans Associated with PCOS.



Anatomical Problem

- Hysterosalpingogram (HSG): assess tubal patency and contour of uterine cavity
- Sonohysterogram (SHG): assess contour of uterine cavity (superior to HSG) and tubal patency
- Hysteroscopy
- Laparoscopy and dye study

Figure 3: Hysterosalpingogram Demonstrating Patent Tubes and Slightly Arcuate Cavity.



Male Gamete Issue

- Makes the male partner a full participant in the process
- Limited initial evaluation
- Semen analysis
- Focused history (ie. genital trauma, undescended testis, mumps orhitis, excessive alcohol use, smoking) and physical exam
- If oligospermia: serum androgens, LH, FSH, TSH

Impotency

- Important to ask about impotency; often not volunteered
- Medication history crucial (i.e. calcium channel blockers, anticholinergics and antidepressants)
- Past medical history: rule out vascular disease related to diabetes, hypertension
- Social history: smoking history

Intercourse Timing

- Frequency: 2-3 times per week
- Timing: mid-cycle using cycle averaging technique
- Avoid lubricants and post-coital douches. Many are spermicidal and package labeling is not always accurate (egg white, water based lubricants, vegetable/canola oil OK)

Therapies for Infertile Couples

Most of those who conceive do so with **basic treatments:**

- Counselling
- Medications
    - i.e. ovulation induction (letrozole vs. gonadotropins), thyroid meds, bromocriptine for excess prolactin
    - clomiphene citrate is discontinued in Canada (only available now through compounding pharmacy)

- Surgery – laparoscopy, hysteroscopy
- Intrauterine insemination (IUI) with partner's sperm

Advanced Fertility Therapies

- In Vitro Fertilization (IVF)
- IVF with Intracytoplasmic sperm injection (ICSI)
- Third party ART
    - Oocyte Donation
    - Sperm Donation
    - Embryo Donation
    - Gestational Surrogacy
- Preimplantation Genetic Testing for Aneuploidies (PGT-A)
- Preimplantation Genetic Diagnosis (PGD)

IVF and ICSI

Indications:

- *IVF:* blocked tubes, endometriosis, sperm problems, fertilization problem, egg donation, surrogacy, unexplained Infertility
- *ICSI*: male factor infertility

Technique:

- Literal translation of IVF: "fertilization in glass"
- Multiple oocytes simultaneously stimulated using gonadotropins (FSH and/or LH)
- Once follicles reach a critical diameter (18mm), hCG is given to induce ovulation and oocytes are retrieved ~ 35hrs later.
- Oocyte retrieval is performed using vaginal ultrasound to guide a needle into the ovaries via the cul-de-sac
- Each follicle is drained successively and aspirated into a test tube. The oocyte is then extracted by the embryologist
- Each egg is then incubated with approximately 50 000-100 000 capacitated sperm (yes, sperm is inefficient), placed in an incubator and examined 18 hours later for fertilization

For ICSI

- Only mature oocytes can be used
- A single spermatozoan is injected directly into the cytoplasm of the egg
- Oocytes are inseminated 4 hours following retrieval

Oocyte Donation

- Known vs. anonymous donation
- Full medical and psychosocial screening
- Age of recipient becomes irrelevant (all is based on genetics of donor)
- Indications: cancer treatment (chemo or radiation), early menopause (POF), etc.
- Highest success rate of all assisted reproduction procedures (50-60% per cycle)

- Ethical and legal issues regarding reimbursement of expenses or compensation for the donor.
- Bill C-6: in Canada donors cannot be reimbursed other than costs directly and indirectly related to the IVF cycle

Sperm Donation

- Known vs. anonymous donation (sperm bank)
- Full medical and psychosocial history screening
- Ethical and legal issues regarding reimbursement of expenses or compensation for the donor (Bill C-6)

Embryo Donation

- Patients often left with excess frozen embryos
- Donated anonymously, with medical history of each contributor to the embryo's genetics
- Age of recipient irrelevant (the uterus acts as an incubator)
- Success rate lower, since frozen embryos (in the order of 30-40%/cycle)
- Not allowed to purchase (Bill C-6)

Gestational Surrogacy

1. *Traditional or True Surrogate*
    - Ovum is from the carrier herself
    - The carrier is genetically the mother
    - No assisted reproduction required, self-insemination is the usual route ("turkey baster")
2. *Gestational Surrogate (Carrier)*
    - Ovum is from the intended parent or a donor
    - The carrier has no genetic link to the baby
    - Assisted reproduction required – IVF with transfer of embryos to the carrier
    - Ethical issues - legal contract needed

Preimplantation Genetic Testing for Aneuploidies (PGT-A)

- Tests for structural chromosomal anomalies prior to IVF transfer
- Aids in differentiating normal from abnormal embryos
- Not detrimental to embryo growth
- Risks: increased rate of monozygotic twinning and possible damage to embryo.

Preimplantation Genetic Diagnosis (PGD)

- Identifies hereditary genetic condition (single-gene disorders) prior to IVF transfer
- Employed when there is a known genetic disease predisposition
- Aids in differentiating normal from abnormal embryos
- Often done in combination with PGT-A
- Same risks as PGT-A

RECURRENT EARLY PREGNANCY LOSS

Recurrent early pregnancy loss (RPL) is classically defined as 3 pregnancy losses prior to 20 weeks. However, the practical definition has recently changed and now most clinicians investigate RPL after 2 losses.

- **Early**- before 12 weeks
- **Late**- between 12 and 20 weeks
- **Primary**- No previous live-born child
- **Secondary**- Previous live-born child
- **Incidence**: Occurs about 1 in 100 to 200 patients (0.5- 1.0%)

Table 1. Incidence of Recurrent Pregnancy Loss (RPL) at Parkland Memorial Hospital.

Year	#RPL[a]	# Deliveries[b]	%RPL
1988	82	14,533	0.56
1989	104	14,643	0.71
1990	86	14,883	0.58
1991	153	15,183	1.00

[a]new cases of RPL identified in the indicated year
[b]total women delivered of infants ≥500g

Recurrent early pregnancy loss most commonly occurs around 7 weeks when U/S or β-hCG is used for diagnosis.

Normal Loss Rate: normal loss rate depends on how aggressively you look for early miscarriage.

- If serum β-hCG is used for diagnosis, loss rate is as high as ~50%.
- Clinically recognized pregnancy loss is probably 15-30%.
- In 1980 Miller et al, measured β-hCG levels from 200 ovulating women starting 3 weeks after the last menstrual period in 623 cycles. Of 152 positive values, 50 of 152 (33%) pregnancies were lost preclinically, and 14 additional patients had clinically recognized losses. This resulted in a 43% loss rate overall.
- In 1988 Wilcox and colleagues found a 22% preclinical loss rate and a 12% clinical loss rate, for a total pregnancy loss rate of 31%.

Risk of occurrence is also related to maternal and paternal age, as shown in Table 2 (next page).

Table 2: Relation of Abortion Frequency to Maternal and Paternal Age at Conception.

Maternal Age (years)	Percent abortion	Paternal Age (years)	Percent abortion
<20	12.2	<20	12.0
20-24	14.3	20-24	11.8
25-29	13.7	25-29	15.7
30-34	15.5	30-34	13.1
35-39	16.7	35-39	15.8
40-44	33.8	40-44	19.5
>44	53.2	-	-

From Warburton and Fraser, 1961, with permission.

Risk of Recurrence

Risk of repeated loss depends on number of previous losses and number of previous successful pregnancies. Remember that clinically recognized pregnancy loss occurs in about 10-15% of all pregnancies. This must be considered when looking at the figure below.

- Note that if a couple had at least one normal pregnancy previously they have a 70-75% chance of eventually achieving a normal pregnancy after 2 or more miscarriages.
- If a couple has never had a previous liveborn pregnancy, the recurrence risk is significantly higher after each # of miscarriages (as compared to couples with a previous liveborn pregnancy). Once these couples meet the classical criteria for RPL (3 miscarriages) they have a 50% recurrence rate.
- Since women are having pregnancies later in their reproductive life, estimates of recurrent loss (RPL) are now between 1 and 2% (previously estimated at 0.5-1.0%).

Considering the fact that clinical miscarriage occurs 15% of the time, then by chance alone 2 miscarriages would occur in 2.3% of the population and three losses would occur 0.34% of the time. If you look hard enough 50-60% of couples with recurrent pregnancy loss will have an attributable cause.

Table 3: Recurrence Risk Relative to Prior Gestational Events.

Outcome	Prior Losses	Recurrence, %
Liveborn	0	12
	1	24
	2	26
	3	32
	4	26
Miscarriage	1	19
	2	35
	3	47
	4	54

Data from Poland and cc leagues, 1977, Warburton and Fraser, 1964.

Table 4: Diagnosis in Couples with Viable Pregnancies, and Single and Recurrent Pregnancy Loss.

Diagnosis	Viable Pregnancies	Single Loss	Recurrent Loss
Mullerian anomalies	1-3%	2-5%	10-15%
Cervical incompetence	1-2%	6-10%	8-15%
Leiomyomata	15%	15%	15-20%
Asherman's syndrome	<1%	<1%	5%
Luteal phase defect	8%	8-12%	10-15%
Autoimmune	1%	2%	15%
Chromosomal			
Parental	0.2%	N/A	2-5%
Fetal	0.5%	55%	20%

Etiologies of Recurrent Pregnancy Loss:

- Advanced maternal age (see Table 2)
- Genetic
- Endocrinologic
- Anatomical
- Immunological
- Infections
- Thrombophilias
- Environmental

Genetic Factors

The vast majority (~60%) of early (<12 wks) single abortions are due to chromosomal abnormalities in the fetus. Karyotyping couples will reveal that 3-8% have some abnormality, most frequently a balanced chromosomal rearrangement. With most parental karyotypic abnormalities there is a 50% chance the next pregnancy will be normal. Although nothing can be done to avoid the problem (except donor sperm or oocytes), IVF with PGT-A, CVS or amnio can be offered.

Genetic Factors:

- Chromosome anomalies are more common the earlier the loss.
- Parental aneuploidy is 3x more common in the mother than the father.
- Frequency of abnormal parental chromosomes in couples with RPL was 2.3% (Kutteh and Pasquarette, 1995).
- Trisomies are the most common group (50% genetic anomalies). Trisomy 16 is the most common trisomy (~1/3 of trisomies).
- Monosomy X is the next most common group (20% of anomalies), but when discussing a single chromosomal abnormality Monosomy X is most frequent, followed by Trisomy 16.
- Triploidy (3n=69) and tetraploidy (4n=92) account for 15% and 5% of anomalies, respectively
- Translocations are most often of the reciprocal type and the Robertsonian variety constitutes 4% of the anomalies

Endocrinological Factors

- **Poorly controlled Diabetes Mellitus**
  - Diabetics with a normal HbA1C do not have increased risk of miscarriage or anomalies.
- **Thyroid disorders**
  - Must be clinically evident thyroid disorder in order to contribute to RPL.
- **Luteal Phase Deficiency (LPD)/Endometrial Receptivity**
  - A condition whereby endogenous progesterone in not enough to maintain a functional secretory endometrium to allow normal embryo implantation and growth.
  - There is currently no standard characterization of progesterone secretion during the luteal phase in normal fertile women.
  - Some define LPD as < 13 days from uLH surge to onset menses.
  - No testing is recommended at this time: BBT, urinary LH detection kits, luteal progesterone testing, endometrial biopsy.
  - Abnormal ovarian function with decreased progesterone-P4 production by the corpus luteum (C.L.). Probably not that simple as the C.L. makes many hormones other than P4 that may play a part in LPD (relaxin, inhibin, estradiol-E2).
  - May be caused by excessive exercise, hyperprolactinemia, hypothyroidism, uncontrolled diabetes, and occasionally all normal women will have a cycle with LPD due to unknown reasons.
  - During the follicular phase of the cycle decreased FSH stimulation leads to inadequate E2 production, and a decrease in the activity of Granulosa cells. Endometrial maturation is delayed, the embryo has difficulty implanting or implants late. HCG production is inadequate or delayed, leading to early loss.

Polycystic Ovarian Syndrome (PCOS)

- Miscarriage rate in women with polycystic ovary syndrome (PCOS) may be as high as 20 to 40 percent
- The sex hormone abnormalities in women with PCOS may cause premature or delayed ovulation, poor endometrial receptivity, and disturbances in prostaglandins and ovarian growth factors
- From Metanalyses: No increase in risk of miscarriage.

Decreased ovarian reserve

- Women with unexplained RPL have a higher likelihood of elevated cycle day 3 serum follicle stimulating hormone (FSH) and estradiol (E2) levels. As the day 3 serum FSH level increases, the quality and quantity of oocytes decrease.
- This is particularly true in the cases of women of advanced maternal age, with high CD#3 FSHs and repeated losses
- Controversial

Treatment of endocrine factors:

1. Progesterone supplementation
2. Supplemental hCG
3. Gonadotropins
4. Thyroxine/Bromocriptine where applicable

Anatomical Factors

- **Congenital**
  - Mullerian Fusion Defects
    - Dx: MRI, Sonohysterogram, or laparoscopy.
    - Occurrence is 2-6% in women with normal reproductive histories. In women with RPL it is found in 10-15%. Usually a second trimester loss.
    - Unclear whether empiric treatment improves outcomes in any of the Mullerian anomalies. No R.C.T.'s to help us. Exception is probably a uterine septum, as it can be removed with little morbidity or mortality using the hysteroscope. Once RPL has occurred, cerclage may be indicated depending on the extent of the septum.
  - DES Exposure - cerclage indicated if T-shaped uterus
- **Acquired**
  - Asherman's
  - Leiomyoma
  - Polyps
  - Incompetent Cervix
    - Second trimester loss resulting from painless dilatation
    - Usually associated with previous cervical trauma (can be due to congenital defects of the cervix and DES exposure)
- **Obesity**
  - Women who are overweight or obese have a significantly higher rate of miscarriage of genetically normal pregnancies when compared with lean women. (Tremellen et al. RBM Online. 2017)
  - Even with IVF, the proportion of pregnancies that failed by 8wk ultrasound increased from 14.2% in lean group, 29.1% in the overweight group, and 41.9% in the obese groups.

Immunological Factors

Autoimmunity - 15% of RPL patients have autoimmune factors (Kutteh and Pasquarrette, 1995), compared to 1-3% of the normal obstetrical population. The most significant antibodies are the antiphospholipid antibodies: lupus anticoagulant and anticardiolipin Ab (LAC and ACA). These are also known as '**Acquired Thrombophilia**'. Some argue that beta 2 glycoprotein 1 and phosphatidyl serine are also important to consider. Of women with RPL, having ACA is more common than LAC (17% vs. 7%).

- **Antiphospholipid Antibodies (APA)** - are acquired antibodies that can be IgG, IgA, or IgM. They are targeted against a phospholipid in cell membranes of various tissues. These antibodies result in placental thrombosis and infarction through an uncertain pathway. One hypothesis is that

prostacyclin release is inhibited. Since prostacyclin is a potent vasodilator and inhibitor of platelet aggregation, vasoconstriction, platelet aggregation and thrombosis occurs. APA have also been shown to inhibit Protein C activation leading to clotting.

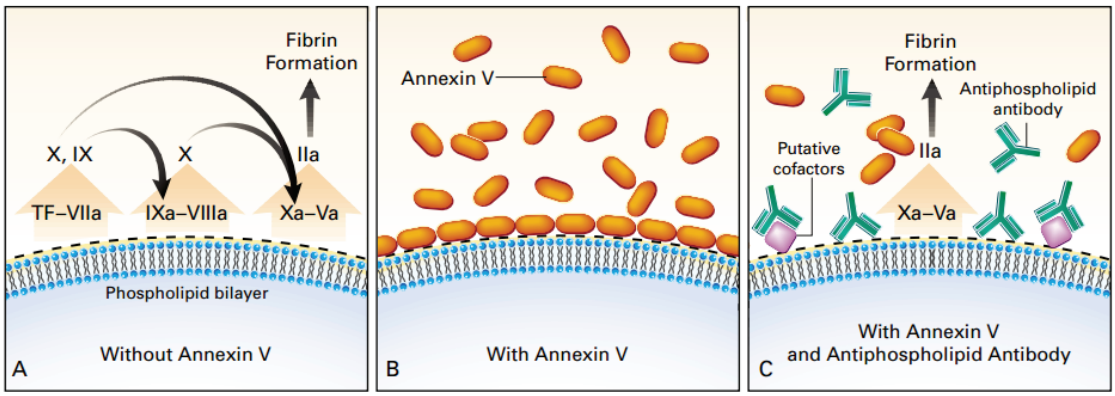
- **LAC** - an immunoglobulin (IgG, IgM, or both) that interferes with one or more of the phospholipid-dependent tests of in-vitro coagulation. The term is a misnomer in two ways. 1. It is not an anticoagulant, but rather is associated with increase thrombosis. 2. It is not usually associated with lupus erythematosus. Diagnosis of LAC activity: 1. aPTT 2. Kaolin clot time, 3. dilute Russell viper venom time (dRVVT), and 4. plasma clot time(PCT). aPTT is the most common test but is insensitive and cannot be used during pregnancy.
- **Cardiolipin (aCL) -** a phospholipid that is found in the inner mitochondrial membrane. ACL IgM and IgG are most important (IgA less important). The VDRL is a test to screen for syphilis that uses beef cardiolipin and results in false positive tests in patients with the ACA.
- **Beta 2-glycoprotein 1** - believed to act as a natural anticoagulant in human plasma and neutralization of its effect by aCL antibodies (or other antiphospholipid antibodies) may predispose to thrombosis. In vivo antiphospholipid antigen is formed from a complex between beta 2-glycoprotein 1 and phospholipids.

Hypothesized mechanisms of antiphospholipid syndrome (APS) pathogenesis

- Antiphospholipid antibodies predispose to thrombosis by inhibiting normal prostaglandin production producing clotting (see figure above).
- Decreased annexin V on placental villi leads to activation of the clotting cascade (see below).
- Antitrophoblast antibodies (McCrae et al. Blood, 1993).
- Beta 2-glycoprotein 1, mechanism described earlier.

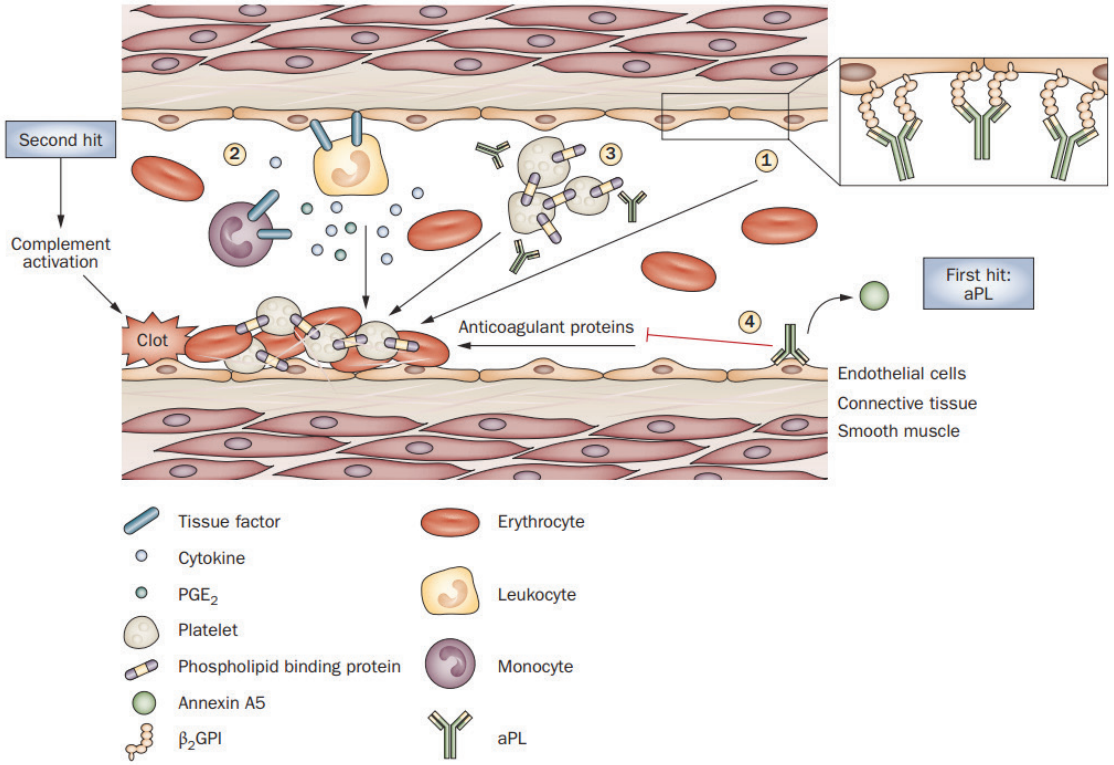
Annexin V is an important protein to understand. Rand et al, (NEJM 1997; 337(18):1327) discovered a possible underlying mechanism for the antiphospholipid antibody syndrome. Annexin V is a phospholipid binding protein with potent anticoagulant activity. It is thought to form a shield over cell surfaces blocking coagulation. This protein is markedly reduced in placental villi taken from women with RPL. See figure below that illustrates/describes the pathogenesis in detail.

Figure 4: Mechanisms of the Reduction of Annexin V Levels and the Acceleration of Coagulation Associated with Antiphospholipid Antibodies.



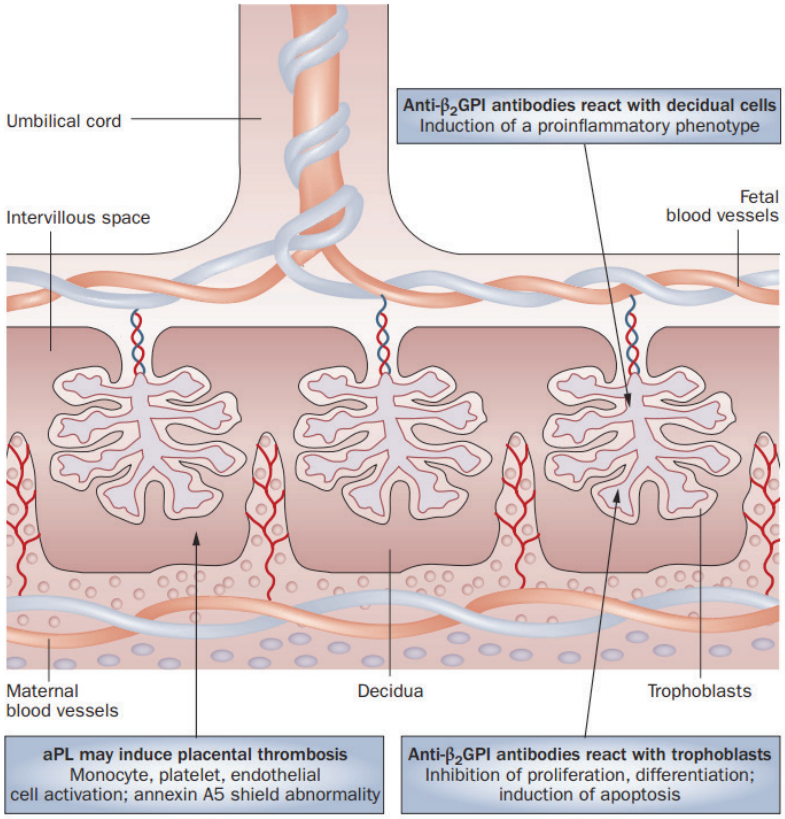
Adapted from Rand et al, (NEJM 1997; 337(18):1327).

Figure 5: Pathogenic Clotting Mechanisms Mediated by Anti-Phospholipid Antibodies.



Adapted from Meroni PL et al, Nat Rev Rheumatol 2011;7:330.

Figure 6: Main Effects of Anti-Phospholipid Antibodies on Placenta.



Adapted from Meroni PL et al, Nat Rev Rheumatol 2011;7:330.

Treatment

1. **Heparin** - not a benign treatment, 75% success rate. Recent case report of death due to intracranial hemorrhage.
2. **Heparin + ASA** - Kutteh, 1995, Heparin + ASA vs. ASA alone. Heparin + ASA had 80% success, whereas ASA alone had 44% success. Probably the best therapy at the present time.
3. **Prednisone** - Cowchock et al AJOG,1992- Heparin vs. Prednisone. Heparin is superior.
4. **Intravenous Immunoglobulins** - IVIG + Heparin/ASA vs. Heparin/ASA. No significant difference but a trend toward better fetal outcomes. Only currently recommended as part of research protocols.

Infections

- **Bacterial** - listeria, toxoplasma, chlamydia
- **Other** - mycoplasma, Ureaplasma

Diagnosis: endometrial biopsy, culture from endometrial biopsy tissue, cervical culture
Treatment: empiric antibiotics

Thrombophilias

- Factor V Leiden
- Prothrombin gene mutation
- Antithrombin III deficiency
- Protein C deficiency
- Protein S deficiency

Diagnosis: hematological testing (altered when pregnant so not reliable to test if positive β-HCG)
Treatment: low molecular weight heparin to be administered 2500IU SC daily throughout pregnancy

Environmental Factors

- Anaesthetics - nitrous oxide
- Medications - colchicine, isotretinoin, methotrexate
- Social habits - tobacco, ethanol, excessive caffeine intake
- Radiation

Table 5: Diagnosis and Management of Recurrent Pregnancy Loss.

Etiology	Diagnostic Evaluation	Therapy
Genetic	Karyotype partner	Genetic counselling Donor gametes
Anatomical	Hysterosalpingography Hysteroscopy	Septum transection Remove polyp Treat Asherman's Syndrome
Endocrinological	Endometrial biopsy Midluteal progesterone Thyrotropin Prolactin	Progesterone Thyroxine Bromocriptine
Immunological (AKA Acquired Thrombophilia)	Antiphospholipid antibodies (e.g. Lupus anticoagulant, anticardiolipin antibodies, beta-2-glycoprotein-1	Prednisone Heparin +/-ASA (? IV immunoglobulin)
Thrombophilia (AKA Hereditary Thrombophilia)	Factor V Leiden Prothrombin gene mutation Antithrombin III deficiency Protein C deficiency Protein S deficiency	Heparin
Microbiological	Cervical cultures	Antibodies
Psychological	Interview	Support group counselling
Environmental	Exposure to tobacco, ethanol, toxins	Eliminate exposure

Psychosocial Impact of Infertility and RPL (Government of Canada)

- Many people with fertility problems feel higher level of sadness and stress. The sadness they feel is akin to grieving the death of a loved one. Having to seek medical help to build family, they experience high levels of social, emotional, and relationship stress.
    - Sense of loss – loss of hopes and dreams, privacy, self-esteem, intimacy with partner
    - Social issues – family, friends, work colleagues not understanding or not involved
    - Treatment stress – Medical treatments have potential emotional side-effects. Disruptions to daily life because medications need to be taken on a regular basis and appointments can be frequent. Tough decisions are made.
    - Stress to relationship with partner – blaming of self and/or partner. Loss of intimacy due to fear of failure.
- Pregnancy loss is a significant negative life event and the repetitive nature of RPL may intensify the grieving.

Treatment

- Counselling with psychologist or social worker is recommended



Menstrual Abnormalities in Premenopausal Women - Part I

Menstrual Abnormalities in Premenopausal Women I Objectives:

At the end of the seminar, students should be able to:
Amenorrhea & Oligomenorrhea:

1. Define primary and secondary amenorrhea and oligomenorrhea
2. List the causes of amenorrhea/oligomenorrhea
3. Describe the evaluation of amenorrhea/oligomenorrhea with emphasis on:
    - Polycystic ovarian syndrome
    - Hyperprolactinemia
    - Premature gonadal failure
4. Describe the management of amenorrhea/oligomenorrhea according to the patient's desire for pregnancy and fertility control with particular emphasis on:
    - Polycystic ovarian syndrome
    - Hyperprolactinemia
    - Premature gonadal failure

Last revised: July 2019

OLIGOMENORRHEA & AMENORRHEA

Amenorrhea is the failure of menstrual function. The prevalence of amenorrhea not due to pregnancy, lactation or menopause is 3-4%.

Primary amenorrhea is defined as the absence of spontaneous vaginal bleeding by the age of 14 years in girls without other signs of secondary sexual development. In the presence of otherwise normal development of breasts and pubic hair, primary amenorrhea is diagnosed at the age of 16 years.

Secondary amenorrhea (most common) is defined clinically as the absence of menstruation for at least 6 months in a woman with previously normal and regular menses. For women with prior oligomenorrhea, the diagnosis necessitates up to12 months or 6 cycles without menstrual blood flow.

Oligomenorrhea is defined as light or infrequent menstruation (menstrual periods that occur at intervals greater than 35 days and only occur 4 – 9 times per year). Often included in the definition is the consideration that a woman with oligomenorrhea previously had normal menstrual cycles.

Anovulatory uterine bleeding is defined as noncyclic menstrual blood flow that may range from spotty to excessive, is derived from the uterine endometrium, is due to anovulatory sex steroid production and specifically excludes an anatomic lesion.

Amenorrhea is a symptom, not a diagnosis.

Common Causes of Primary Amenorrhea:

1. **With secondary sexual development:**
    - Mullerian agenesis
    - Androgen insensitivity
    - Vaginal septum
    - Imperforate hymen
    - Constitutional delay
    - Polycystic Ovarian Syndrome (PCOS)

2. **Normal breast development and normal pelvic examination:**
    - Hypothyroidism and Hyperprolactinemia: Both hypothyroidism and hyperprolactinemia can affect children and adolescents. These conditions suppress secretion of GnRH, FSH, and LH and thus inhibit the menstrual cycle. Unless pituitary destruction has reached an advanced stage, pubarche and thelarche are normal. Profound hypothyroidism is a rare cause of precocious puberty; it is usually caused by the FSH-like effect of high levels of thyroid-stimulating hormone (TSH).
    - Other Causes: Many of the causes of secondary amenorrhea-most notably, polycystic ovarian syndrome (PCOS) and hypothalamic dysfunction, can also cause primary amenorrhea in a patient with normal findings on physical examination.

3. **Normal breast development but absent uterus:**
    - *Complete Androgen Insensitivity Syndrome:* Profound androgen resistance caused by a mutation in the androgen receptor prevents the influence of testicular androgens on the development of a chromosomally male fetus (46 XY karyotype). As a consequence, the newborn is a phenotypically normal female. Internal genitalia, however, are affected by testicular secretion of anti-Mullerian hormone; thus, development of the upper part of the vagina and uterus is inhibited. Because the testicular tissue is ectopic (intra-abdominal or within the inguinal canal), later malignant transformation is a risk, and surgical removal of the testes is recommended. Hormone substitution therapy should follow surgical removal.
    - *Anatomic Abnormalities:* Failure of development of the uterus. Often associated with renal tract anomalies (Rokitansky-Kuster-Hauser syndrome). Failure of uterovaginal communication (uterovaginal septum), and imperforate hymen are rare but recognized causes of primary amenorrhea. In the two last-mentioned cases, cyclic pelvic pain is common because of normal hormonal influences on the intact uterine endometrium.

4. **Without secondary sexual development and high FSH (hypergonadotropic hypogonadism):**
    - *Gonadal dysgenesis:*
        - Abnormal sex chromosomes (e.g. Turner's syndrome – 45, X)
        - Normal sex chromosomes (46 XX or 46 XY)
    - *Gonadal Failure:* Gonadal dysgenesis is probably the most common cause of complete failure of pubertal development. The cause remains under investigation and current treatment is limited to hormone replacement therapy and fertility support.
    - *Turner's Syndrome:* The association of primary amenorrhea, delayed puberty, and short stature may suggest Turner's syndrome. Resulting from the inheritance of only one X chromosome, this syndrome is characterized by short stature, wide-spaced nipples, neck webbing, increased carrying angle of the elbows, and possible mild mental developmental delay. The ovaries are vestigial; thus, little or no estradiol is produced. The rest of the anatomy of the genitourinary tract is normal and hormone substitution results in onset of puberty and menstruation but not fertility. Some patients with Turner's syndrome exhibit a subtler phenotype, and rarely sexual maturation, menarche, and even fertility can occur spontaneously. These cases represent chromosomal mosaicism, in which a variable proportion of cells have a normal karyotype.

5. **Without secondary sexual development and low FSH (hypogonadotropic hypogonadism):**
    - Congenital abnormalities
        - Isolated GnRH deficiency
        - Forms of hypopituitarism
        - Congenital CNS defects
    - Constitutional delay

- Acquired abnormalities
    - Endocrine disorders
    - Pituitary tumours
    - Systemic disorders

Hypothalamic Failure: Constitutionally delayed puberty, a normal variant, is the most common cause of primary amenorrhea with delayed puberty. A thorough history often reveals that older siblings and the mother were also "late bloomers." Physical examination shows delayed but otherwise normal development of breasts and pubic hair and normal findings on a pelvic examination. Psychosocial deprivation may delay pubarche, and amenorrhea rarely may be the manifesting feature of child neglect or abuse. Delayed puberty and primary amenorrhea are also seen commonly in girls with anorexia nervosa, those who exercise excessively, or those who have low reserves of body fat. Investigators have postulated that leptin has a role in these phenomena. Similarly, type I diabetes, inflammatory bowel disease, juvenile rheumatoid arthritis, chronic infections, and malignant lesions all may result in delayed puberty and amenorrhea. The final common pathway through which these processes affect sexual maturation is suppression of pulsatile hypothalamic GnRH secretion by means of central mechanisms that remain poorly understood.

Pituitary Failure: Isolated GnRH deficiency and Kallmann's syndrome are both extremely rare. They cause pubertal failure because of reduced or absent pituitary FSH secretion. In Kallmann's syndrome, the deficiency of GnRH is associated with anosmia and other subtle neurologic features. It results from failure of migration of GnRH-secreting neurons into the hypothalamus. Gonadotropin (LH and FSH) deficiency may also result from trauma (especially head injury), pituitary adenoma, craniopharyngioma, or infiltrative and inflammatory diseases of the hypothalamus or pituitary (especially sarcoidosis and lymphocytic hypophysitis). Such deficiency is usually seen in association with hypopituitarism that affects several or all of the other pituitary hormones.

Common Causes of Secondary Amenorrhea:

1. Low or normal FSH levels:
    - Weight loss/anorexia
    - Non-specific hypothalamic
    - Chronic anovulation including PCOS
    - Hypothyroidism
    - Cushing's syndrome
    - Pituitary tumour, empty sella, Sheehan syndrome
2. Gonadal failure (high FSH):
    - 46 XX
    - Abnormal karyotype
    - Hyperprolactinemia
3. Anatomic:
    - Asherman syndrome

4. Hyperandrogenic states:
    - Ovarian tumour
    - Non-classic congenital adrenal hyperplasia (CAH)
    - Undiagnosed

Secondary amenorrhea can also result from structural causes, although by definition these must be acquired during postpuberty. Obliteration of the uterine cavity can occur during an intrauterine operation with subsequent fibrous adhesions (Asherman's syndrome). In addition, aggressive curettage or radiotherapy may almost completely destroy the endometrium. Infection, particularly tuberculous, is a rare cause of anatomic secondary amenorrhea. More commonly, however, secondary amenorrhea results from altered endocrine function that affects the hypothalamus, pituitary, or ovary. Broadly, the causes of secondary amenorrhea can be categorized into those with and those without evidence of hyperandrogenism.

Secondary Amenorrhea With Hyperandrogenism:

1. **Polycystic Ovarian Syndrome (PCOS)** - PCOS is by far the most common hyperandrogenic cause of amenorrhea. Although the term implies an ovarian cause and in the past this diagnosis was made on the basis of pelvic ultrasonography alone, polycystic ovaries merely signify chronic anovulation with continued production of FSH without ovarian failure. Patients with PCOS have an endocrine syndrome of mild to moderate androgen excess (of ovarian origin) in association with chronic anovulation. This results in irregular or absent menses, acne, greasy or oily skin, hirsutism, and, in severe cases, mild virilization. Although patients are anovulatory, estrogen levels remain normal and these women do not experience the consequences of hypoestrogenism. The chronic endometrial stimulation by estrogen, unopposed by progesterone, may result in abnormal uterine bleeding (often misinterpreted as menstrual bleeding) with chronic endometrial hyperplasia and an increased risk of endometrial carcinoma. FSH and LH levels are commonly normal, although the LH:FSH ratio may be increased because of higher than normal LH peaks. Such women are commonly (although not always) overweight and exhibit some degree of insulin resistance and hyperinsulinism, with features of the metabolic syndrome X (abdominal obesity, insulin resistance, predisposition to diabetes or impaired glucose homeostasis, hypertriglyceridemia, hypertension, and premature vascular disease).

2. **Autonomous Hyperandrogenism** - Adrenal or ovarian tumors and ovarian stromal hypertrophy (hyperthecosis) may secrete androgens autonomously beyond the normal feedback control mechanisms. Pronounced virilization may occur, commonly more severe than with PCOS. Amenorrhea in association with frontal balding, severe hirsutism, increased muscle bulk, deepened voice, or clitorimegaly, particularly when the findings are recent or progressive. This findings necessitate a search for ovarian or adrenal androgen-secreting tumors.

3. **Late-Onset or Mild Congenital Adrenal Hyperplasia** - Although late-onset or mild congenital adrenal hyperplasia is rare in most patient groups, it may also result in secondary amenorrhea and hyperandrogenism. Various partial deficiencies in enzymes in the cortisol biosynthetic pathway have been described, although their cause remains

obscure. The most common defect is 21-hydroxylase enzyme, which results in an increase of 17-hydroxyprogesterone, a useful diagnostic marker for congenital adrenal hyperplasia.

Secondary Amenorrhea Without Hyperandrogenism:

1. **Hypergonadotropic Hypogonadism:** Hypergonadotropic hypogonadism (premature ovarian failure) may be idiopathic, autoimmune, or due to radiotherapy or cytotoxic drugs (particularly cyclophosphamide) administered for malignant disease. Autoimmune ovarian failure may be seen in conjunction with other organ-specific autoimmune diseases, including Addison's disease, type I diabetes, and autoimmune thyroid disease. Autoantibodies against several antigens are also commonly detected in the serum. The diagnosis of ovarian failure is usually straightforward because FSH will be in the postmenopausal range (greater than 20 IU/L) and estradiol is low (less than 30 pg/mL).

2. **Hyperprolactinemia:** Hyperprolactinemia is most commonly the result of a small pituitary adenoma, which, in and of itself, does not affect pituitary function. It is a common cause of hypogonadotropic amenorrhea and is seen in up to 20% of women with secondary amenorrhea. Prolactin acts directly on the hypothalamus to reduce the amplitude and frequency of GnRH pulses. Other causes of hyperprolactinemia include drugs (especially dopamine receptor blocking agents), pituitary and hypothalamic masses (through their effect on the pituitary stalk), and hypothyroidism.

3. **Thyroid Disease and other Endocrinopathies:** Pronounced thyroid failure is associated with hyperprolactinemia. Hypothalamically released thyrotropin-releasing hormone also stimulates secretion of prolactin. There may also be a direct effect of both hypothyroidism and hyperthyroidism on the feedback control of LH, FSH, and estradiol on the hypothalamus and pituitary. Altered menstrual function is a common feature of many endocrine diseases, most likely through a mechanism affecting hypothalamic control of GnRH secretion.

4. **Hypogonadotropic Hypogonadism:** FSH secretion may be impaired directly by destructive processes affecting the pituitary, as well as indirectly through the hyperprolactinemia these processes induce. Pituitary compression or destruction may be caused by a tumor (most commonly an adenoma or craniopharyngioma), inflammation (for example, lymphocytic hypophysitis), infiltration (for example, by sarcoidosis), trauma (head injury or operation), or infarction (Sheehan's syndrome). These conditions rarely cause isolated gonadotropin deficiency, and evidence should be sought for failure of pituitary-adrenal and pituitary-thyroid axes.

5. **Functional Hypothalamic Amenorrhea:** Functional derangement is the most common cause of hypothalamic amenorrhea. Possibly mediated by endorphins, hypothalamic amenorrhea results in abnormal GnRH pulsatility, with consequent reductions in FSH secretion. It is commonly associated with stress, which may be emotional, physical, dietary, or social.

Evaluation of amenorrhea/oligomenorrhea

Although the list of causes of amenorrhea is long, the majority of cases are accounted for by four conditions: polycystic ovarian syndrome (PCOS), hypothalamic amenorrhea, hyperprolactinemia, and ovarian failure.

Evaluation of the Patient

History, physical examination, and estimation of follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and prolactin will identify the most common causes of amenorrhea. The presence of breast development means there has been previous estrogen action. Excessive testosterone secretion is suggested most often by hirsutism and rarely by increased muscle mass or other signs of virilization. The history and physical examination should include a thorough assessment of the external and internal genitalia. The genital examination is abnormal in approximately 15% of women with primary amenorrhea. A blind or absent vagina with breast development usually indicates Mullerian agenesis, transverse vaginal septum, or androgen insensitivity syndrome. If a genital examination is not feasible, an abdominal ultrasound may be useful to confirm the presence or absence of the uterus. When the physical examination is normal (the majority of cases), the initial investigations should exclude pregnancy and estimate FSH and prolactin concentrations. Estimation of TSH is useful to rule out subclinical hypothyroidism, even in the absence of thyroid-related symptoms.

If there is gonadal failure, a karyotype should be done if the woman is less than 30 years of age to identify chromosomal abnormalities, including the presence of a Y chromosome as may be seen in mosaic Turner syndrome or Swyer syndrome.

If the serum prolactin is persistently elevated, and there is no history of medication or drug use that may elevate prolactin, magnetic resonance imaging (MRI) is preferred to identify a pituitary tumor. When FSH values are normal or low, the problem is most often polycystic ovary syndrome or hypothalamic amenorrhea.

Polycystic Ovarian Syndrome

History:

- Focus on: onset and duration of the various signs of androgen excess, menstrual history, medication use, use of exogenous androgens.
- Family history: diabetes, cardiovascular disease
- Lifestyle factors: smoking, alcohol consumption, diet, exercise

Physical:

- Blood pressure
- Body mass index: 25-30 = overweight; >30 = obese
- Waist-hip ratio to determine body fat distribution: value >0.72 = abnormal
- Presence of stigmata of hyperandrogenism or insulin resistance
- Acne, hirsutism, androgenic alopecia, acanthosis nigricans, clitoromegaly
- Pelvic examination for ovarian enlargement

Laboratory:

- Documentation of biochemical hyperandrogenemia
    - Total testosterone and/or free testosterone
    - DHEAS if concerned about adrenal production (rapid virilization)
- Exclusion of other causes of hyperandrogenism
    - Thyroid-stimulating hormone levels (thyroid dysfunction)
    - Prolactin (hyperprolactinemia)
    - 17-hydroxyprogesterone (non-classical congenital adrenal hyperplasia)
- Consider screening for Cushing's syndrome and other rare disorders such as acromegaly
- Evaluation for metabolic abnormalities: 2 hour oral glucose tolerance test, Fasting lipid and lipoprotein levels

Optional tests to consider:

- Ultrasound examination of ovaries for baseline evaluation and morphology before ovulation induction or in cases of virilization or rapid conversion to an androgen excess state.
- Gonadotropin determinations to determine cause of amenorrhea
- Fasting insulin levels in younger women, those with features of insulin resistance and hyperandrogenism or those undergoing ovulation induction
- 24 h urine for urinary free cortisol with late onset of PCOS or stigmata of Cushing's syndrome

The Rotterdam PCOS diagnostic criteria in adults (two of clinical or biochemical hyperandrogenism, ovulatory dysfunction, or polycystic ovaries on ultrasound*) and where irregular menstrual cycles and hyperandrogenism are present can be helpful in reaching a diagnosis of PCOS. (*In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis; however, ultrasound will identify the complete PCOS phenotype.

Management of PCOS

'Multidisciplinary' approach depending on the results of evaluations performed as outlined above. Treatment is not simply directed at regulating menstruation/eliminating amenorrhea. For example, lifestyle interventions are very important – diet and exercise for patients with increased BMI. Metformin treatment in addition to lifestyle changes may be indicated for patients with impaired glucose tolerance. Diet and exercise for abnormal lipid profile, medication therapy for hypercholesterolemia if necessary.

Patient with PCOS who is NOT attempting to conceive:

- Oral contraceptives are the mainstay of long-term management of PCOS. They offer benefit through a variety of mechanisms: suppression of pituitary luteinizing hormone secretion, suppression of ovarian androgen secretion, and increased circulating SHBG. OCP's are also associated with a significant reduction in the risk for endometrial cancer.
- Progestins (both depot and oral) have been shown to suppress pituitary gonadotropins and circulating androgens in women with PCOS. Helps in the prevention of endometrial cancer.
- Insulin sensitizing agents have been used to treat PCOS. These agents decrease circulating androgen levels, improve ovulation rates and improve glucose tolerance.

Patient with PCOS who is attempting to conceive:

- Treatment should begin with a regiment of regular exercise and weight control and then proceed to other methods if necessary
- Letrozole should be considered first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates.
- Clomiphene citrate (CC) could be used alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and pregnancy rates.
- Gonadotrophins could be used as second line pharmacological agents in women with PCOS who have failed first line oral ovulation induction therapy and are anovulatory and infertile, with no other infertility factors (please note: increased risk of multiple pregnancies with these therapies).
- Metformin could be used alone in women with PCOS, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates, although women should be informed that there are more effective ovulation induction agents.
- Insulin-sensitizing agents: most randomized trials using metformin have shown that it improves ovulatory frequency in women with PCOS
- Dosage most frequently used is 1500 mg per day although some have used 2000 mg per day in divided doses
- Metformin has also been used as an adjunctive agent to both CC and gonadotropins
- Metformin has no known human teratogenic risk or embryonic lethality in humans and appears safe in pregnancy
- Laparoscopic ovarian surgery - ovarian drilling (surgical procedure whereby small incisions are made in the ovary): could be second line therapy for women with PCOS, who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors.
- Weight loss: can improve the fundamental aspects of the endocrine syndrome of PCOS by decreasing circulating androgen levels and causing spontaneous resumption of menses; even as little as 5% loss of the initial weight.

Hyperprolactinemia

Hyperprolactinemia is associated with decreased estradiol concentrations and amenorrhea or oligomenorrhea, with prolactin concentrations being higher in the former.

In the presence of both an intact uterus and normal breast development, measurement of serum prolactin and TSH will exclude pronounced hyperprolactinemia and hypothyroidism, respectively. Thereafter, investigation can proceed according to that of secondary amenorrhea. In the setting of persistent hyperprolactinemia, after ruling out primary hypothyroidism, MRI of the pituitary is indicated. Mildly elevated prolactin levels may be a sign of another organic CNS lesion. Prevalence of a pituitary tumor in women with hyperprolactinemia is 50% to 60%. There is a poor correlation between tumor presence and prolactin levels therefore MRI should be performed whenever prolactin levels are persistently elevated. NB patients with amenorrhea have larger tumors than patients with oligomenorrhea.

Hyperprolactinemia often responds well to dopamine agonists (e.g., bromocriptine, cabergoline). In most amenorrheic women with hyperprolactinemia, prolactin levels do not decline without treatment,

and the amenorrhea does not resolve as long as the prolactin levels remain high. In experienced neurosurgical hands, transsphenoidal excision of a pituitary microprolactinoma is associated with a low rate of complications and a high success rate. Late recurrence rates of up to 20% have been reported, however, even after apparent cure. In such cases further medical or surgical therapy may be necessary. Prolactinomas may shrink substantially with medical treatment. Surgical treatment is necessary for patients with large tumors affecting vision or creating a pronounced mass effect and for those in whom medical treatment fails. Assessment of the pituitary-adrenal and pituitary-thyroid axes is essential in patients with macroadenomas.

Premature Gonadal Failure

Lack of gonadal function is indicated by high FSH levels. This event can occur at any age, even during fetal development when it is typically the result of gonadal agenesis or gonadal dysgenesis. Gonadal failure in genetically XX patients is termed ovarian failure. When it occurs before the onset of puberty there will be primary amenorrhea and incomplete breast development. Genetically XY individuals with gonadal failure will have female genitalia because Mullerian inhibiting factor and testosterone will not be produced. Gonadal tumors occur in up to 25% of women with a Y chromosome and therefore should be removed ASAP (unlike complete androgen insensitivity where gonads secrete hormones important for development and removal is delayed).

Gonadal dysgenesis (streak gonads) occurs with normal XX and XY karyotypes as well as a variety of abnormal karyotypes, most commonly 45,X (Turner syndrome).

Premature Ovarian Failure (POF)

- Amenorrhea, persistent estrogen deficiency, and elevated FSH levels occur before age 40
- Affects 1% - 5% of women; iatrogenic causes (eg. chemo) may have the potential for recovery
- Ovarian function may fluctuate with increasing irregularity of cycles before the final depletion of oocytes
- If POF occurs at less than age 30, a karyotype should be obtained to rule out sex chromosome translocation, short arm deletions or the presence of an occult Y chromosome
- Obtain a thorough family history; several autosomal disorders have been associated with ovarian failure
- Up to 40% of women with POF have autoimmune abnormalities, most commonly autoimmune thyroiditis

Management Considerations for Premature Gonadal Failure

- Patients with ovarian failure should be offered estrogen and progestin treatment to promote and maintain secondary sexual characteristics and reduce the risk of developing osteoporosis
- In adolescents with gonadal failure, the aim is to mimic pubertal development with low-dose estrogens, increasing gradually to augment breast development, avoiding progestin until the breast mound and areola have developed
- Rarely, some ovarian follicles remain in women with ovarian failure so that spontaneous ovulation and conception are possible, even in women taking exogenous estrogen with or without a progestin

- Assessment of karyotype and possible removal of gonads if Y chromosome present
- Other genetic testing depending on age of POF and family history; autosomal traits could be cause and this information may be important in Counselling family members, etc.

Secondary amenorrhea:
A thorough history and physical examination are the cornerstones in making the diagnosis of secondary amenorrhea. In particular, previous menstrual and pregnancy history and symptoms of endocrine system disease should be sought. A history of weight changes and a drug, nutrition, and exercise history may also be useful. The physical examination should assess pubertal development and secondary sexual characteristics. Examination of the external genitalia and a pelvic examination are essential in the assessment of possible hyperandrogenism, in which clitoromegaly can be a useful sign.

The initial investigation should include a pregnancy test and determination of fasting glucose, TSH, and prolactin levels. Subsequently, estrogen status should be assessed. The most reliable assessment of estrogen status is the progestin challenge test. A more convenient alternative is measurement of plasma estradiol, FSH, and LH. Oral administration of medroxyprogesterone, 5 to 10 mg daily for 5 to 7 days, will induce withdrawal bleeding in most women with adequate circulating estrogen. In those who do not experience bleeding, some will respond to intramuscular administration of progesterone. In women who do not experience withdrawal bleeding within 2 weeks of these stimuli, the FSH level should be measured. High values indicate ovarian failure, whereas low or inappropriately "normal" values suggest either hypothalamic-pituitary failure (hypogonadotropic hypogonadism) or an acquired uterine abnormality. Confirmation, if necessary, can be obtained with use of a cyclic estrogen and progesterone challenge. No bleeding in response to this hormonal stimulation confirms a uterine abnormality, and gynecologic assessment is necessary. Further testing of pituitary function and possibly imaging of the pituitary and hypothalamus may be necessary in cases of hypogonadotropic hypogonadism.



Menstrual Abnormalities in Premenopausal Women - Part II

Menstrual Abnormalities in Premenopausal Women II Objectives:

At the end of the seminar, students should be able to:
Abnormal Uterine Bleeding:

1. Describe the endocrinology and physiology of the normal menstrual cycle.
2. List causes of abnormal uterine bleeding.
3. Discuss the evaluation and diagnosis of abnormal uterine bleeding

Uterine Leiomyomata (Uterine Fibroids)

1. Describe the prevalence of uterine leiomyomas
2. Describe the symptoms and physical findings associated with uterine leiomyomata
3. Describe methods to confirm the diagnosis of uterine fibroids.
4. Discuss the indications for medical and surgical treatment of uterine fibroids.
5. Describe the complications that may arise during pregnancy or prior to conception.

Last revised: August 2019

ABNORMAL UTERINE BLEEDING

Bleeding is a common indication for gynaecologic referrals. It is estimated that 15% of women have abnormal uterine bleeding (AUB) and that the prevalence increases with age, peaking prior to menopause. Not only is AUB a cause of considerable morbidity (anemia), it also leads to embarrassment and the inconvenience of unexpected and unpredictable bleeding.

REGULATION OF THE MENSTRUAL CYCLE:

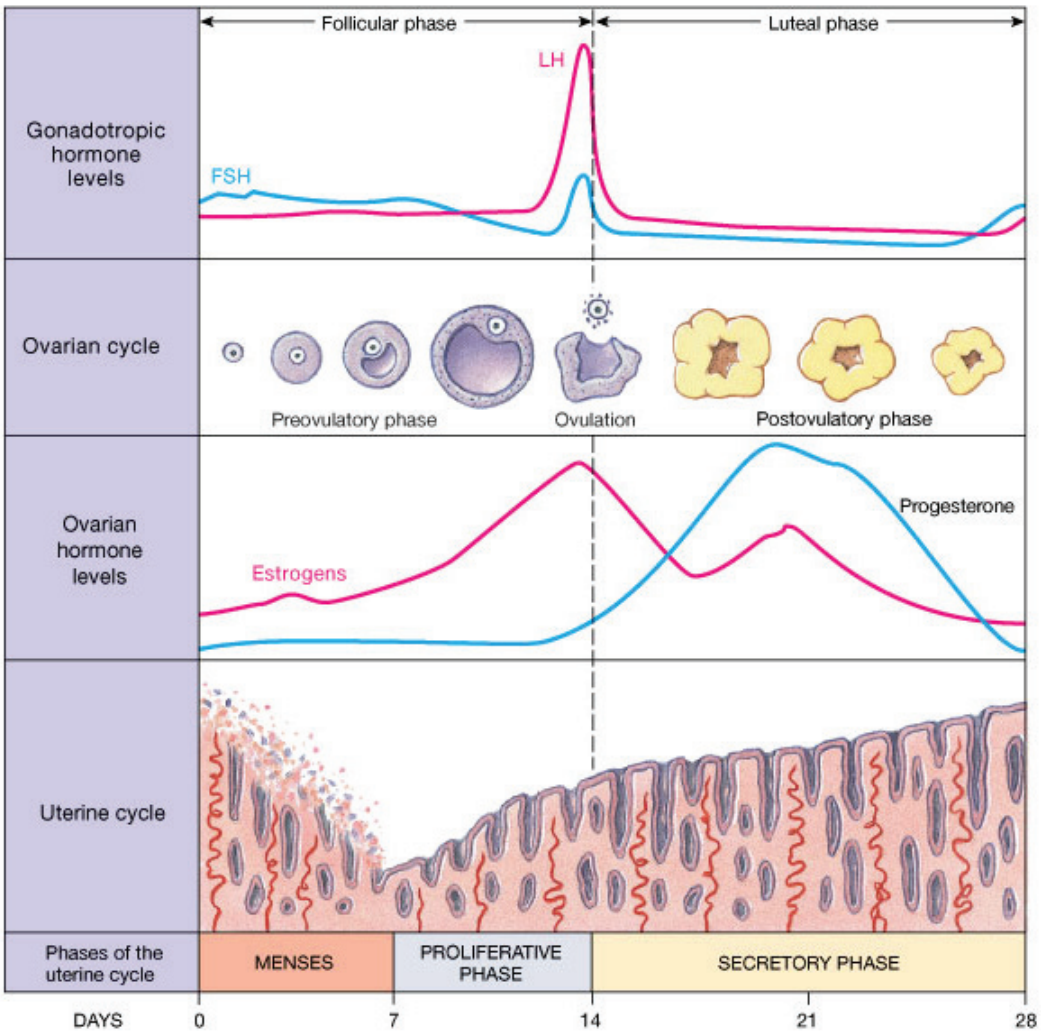
Brief Endocrinology and Physiology

The menstrual cycle is regulated by a dynamic, complex relationship between pituitary hormones (follicle stimulating hormone (FSH) and luteinizing hormone (LH)) and the primary ovarian hormones (estradiol (E2) and progesterone (P)).

One way to understand it is in terms of its three phases:

1. Follicular phase (proliferative)
2. Ovulation
3. Luteal phase (secretory)

Figure 1: Female Reproductive Cycle.



Follicular phase

- Orderly sequence of events resulting in release of one follicle per cycle (on average)
- Takes 10-14 days (7 to 21 days is within normal)
- FSH rises and follicles are recruited by Day 5
- Follicles start to secrete E2 that acts on granulosa cells (GC) to increase GC#
- Rising FSH and E2 inhibit further FSH secretion from the pituitary. This inhibits the development of all but the dominant follicle which secretes the greatest amount of E2 because it has the largest # of GC's and a high density of FSH receptors.
- FSH induces LH receptors on the GC.

The endometrium proliferates in this phase. E2 increases mitotic activity of endometrial cells and upregulates LH receptors.

Ovulation

- Midcycle, LH and FSH surge
- Ovulation occurs ~12 hours after the LH surge. P begins to be secreted which enhances production of proteolytic enzymes and prostaglandins in the follicle leading to rupture

Luteal Phase

- Granulosa cells become vacuolated and accumulate lutein, a yellow pigment—forming the corpus luteum. The primary hormone produced by the corpus luteum in progesterone. An increase in LH receptors occurs and progesterone secretion increases.
- FSH receptors are now suppressed and estrogen levels start to decline.
- This part of the cycle is FIXED at 14 days (the lifespan of the corpus luteum)
- The corpus luteum declines unless fertilization occurs—progesterone drops and the period occurs (signal is the decline of both E and P)

The endometrium stops dividing and secretes glycogen to feed a potential zygote. It reaches a maximal single thickness of 7-8 mm.

Practice Points:
These relationships are important to understand clinically:

1. *Delaying period:* With the OCP the signal for menstruation is E2 and P withdrawal, hence if you take pills continuously you will not menstruate. Issues with endometriosis, delaying onset of period on honeymoon/wedding and compliance.

2. *Reducing the amount of menstrual flow:* Progesterone dominates over estrogen in its effect on the endometrium—hence progesterone is used in many clinical situations to thin down the endometrium—e.g. heavy menstrual bleeding and perimenopause. Women on the OCP have very light flow as the endometrial thickness is halved—resulting is less anemia.

MENSES: Norms

The normal menstrual cycle frequency is 28 +/- 7 days (range 24-38 Days)
The average period lasts 4 +/- 2 days (range 4.5-8 days)
The average menstrual blood loss is 40 cc +/-20 cc (range 5-80)

Each woman has her own mean and variability, both of which may change with age. This is very subjective. When the norm is altered, it usually prompts a visit to the doctor's office.

Terms describing menstrual flow irregularities (FIGO 2011)*

The definitions currently advised are based on the patient's perception of the bleeding.

Heavy Menstrual Bleeding: excessive menstrual blood loss which interferes with the woman's physical, social, emotional, and/or material quality of life… (that) can occur alone or in combination with other symptoms. This term replaces the old term *menorrhagia*.

The following descriptors are then used:

- **Volume of flow:** defined by number and type of pads or tampons use and how often they need to be changed. A large menstrual pad soaked every hour or less over four or five days will result in iron deficiency anemia after three or four months. Normal flow is 5-80 cc/mo.
- **Frequency of flow:** frequent <24d, normal 24-38 and infrequent: >38d
- **Duration:** Normal is 4.5-8 days, prolonged >8 days
- **Other:** Intermenstrual, premenstrual or breakthrough
- The term *"dysfunctional uterine bleeding"* should no longer be used

*Menstrual Disorders Working Group – terminology has been accepted worldwide including ACOG and SOGC.

Table 1: Terminology for AUB.

Terminology for variations in menstrual bleeding				
Volume	Regularity	Frequency	Duration	Other
Heavy	Irregular	Frequent	Prolonged	Intermenstrual
Normal	Regular	Normal	Normal	Premenstrual
Light	Absent	Infrequent	Shortened	Breakthrough

SOGC Clinical Practice Guideline, No. 292, May 2013.

Table 2: Definitions of Terms for Uterine Bleeding.

Characteristic	Terminology	Description
Volume	Heavy menstrual bleeding	Excessive menstrual blood loss which interferes with the woman's physical, emotional, social, and material quality of life, and which can occur alone or in combination with other symptoms.
Regularity (Normal variation ± 2 to 20 days)	Irregular menstrual bleeding	A range of varying lengths of bleeding-free intervals exceeding 20 days within one 90-day reference period
	Absent menstrual bleeding (amenorrhea)	No bleeding in a 90-day period
Frequency (Normal every 24 to 38 days)	Infrequent menstrual bleeding	Bleeding at intervals > 38 days apart (1 or 2 episodes in a 90-day period)
	Frequent menstrual bleeding	Bleeding at intervals < 24 days apart. (More than 4 episodes in a 90-day period)
Duration (Normal 3 to 8 days)	Prolonged menstrual bleeding	Describes menstrual blood loss which exceeds 8 days in duration
	Shortened menstrual bleeding	Menstrual bleeding less than 3 days in duration.
Irregular, non-menstrual bleeding	Intermenstrual	Irregular episodes of bleeding, often light and short, occurring between otherwise fairly normal menstrual periods
	Post-coital	Bleeding post-intercourse.
	Premenstrual and post-menstrual spotting	Bleeding that may occur on a regular basis for one or more days before or after the recognized menstrual period.
Bleeding outside reproductive age	Post-menopausal bleeding	Bleeding occurring more than one year after the acknowledged menopause.
	Precocious menstruation	Bleeding occurring before the age of 9 years.
Acute or chronic AUB	Acute AUB	An episode of bleeding in a woman of reproductive age, who is not pregnant, that is of sufficient quantity to require immediate intervention to prevent further blood loss
	Chronic AUB	Bleeding that is abnormal in duration, volume, and/or frequency and has been present for most of the last 6 months

Adapted from SOGC Clinical Practice Guideline, No. 292, May 2013.

It is probably easiest to think of two sets of differential diagnoses of AUB at the extremes of the reproductive years: (1) **menarche** and at (2) **perimenopause** because the etiologies may differ.

Classification of uterine bleeding abnormalities is by etiology:
Divided into Structural (PALM) and Non-Structural causes (COEIN):

- **Structural:** polyps, adenomyosis, leiomyomas and malignancy
- **Non-structural:** coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not yet classified

AUB in Menarche

In the pubertal teen "O" or ovulatory dysfunction in the PALM-COIEN classification (anovulation secondary to an immature hypothalamic pituitary axis) is the primary cause of AUB, but this is a diagnosis of exclusion. The other causes of AUB must be excluded.

I. Coagulopathy

1. *Von Willebrand's Disease (VWD)* is present in up to 1% of the population. VWD is caused by abnormality of the VWB factor, which causes platelets to adhere to sites of injury. Absence of the VWB factor (Type I) or mutations in it (Type II) cause disease. The signs and symptoms can be quite subtle: bleeding, bruising, epistaxis, bleeding from the gums, bleeding after dental extraction and post-surgical hemorrhage.
   If persistent anemia sufficient to cause iron deficiency anemia occurs in a teen, in the absence of any structural uterine abnormality, she has a bleeding disorder until proven otherwise. Up to 50% of adolescents presenting with acute bleeding at menarche will have a coagulopathy. VWB is present in one third of those requiring transfusion.
2. *Platelet abnormalities:*
   - Thrombasthenia (Glanzman's Syndrome): platelets in excess of 400,000/cc that malfunction.
   - Immune thrombocytopenia (ITP)—platelets <150,000
3. *Leukemia*

II. Endocrine Causes

- *Polycystic Ovarian Syndrome (PCOS):* often presents in adolescence. Increasing since obesity is on the rise
- *Adrenal causes:* Congenital adrenal hyperplasia (CAH), Cushing's syndrome
- *Hypothalamic/pituitary dysfunction:* eating disorder, excessive exercise, stress, idiopathic
- *Thyroid disorders:* hypothyroidism
- *Prolactinomas*

III. Pregnancy

- Threatened, missed, or incomplete abortion
- Ectopic pregnancy
- Molar pregnancy

IV. Incorrect use of OCP

V. Sexual trauma

Work-up

A thorough history and physical will dictate the choice of appropriate laboratory tests. A pelvic exam will probably not be informative in a young girl. Ovarian masses can be felt abdominally.

Bloodwork

- CBC (cross and type if unstable)
- BhCG if applicable
- TSH, Prolactin
- Free testosterone, 17-hydroxy progesterone and DHEA (to r/o PCO, CAH)

Coagulation profile: A PTT and bleeding time can be prolonged in patients with VWB's disease but if the disease is mild and the concentration of factors is >30%, these tests will be normal.
Special testing for VWB: factor VIII level, VWF antigen, and VWF functional assay, which may need to be repeated several times to ascertain the diagnosis. Hematologic consultation is indicated

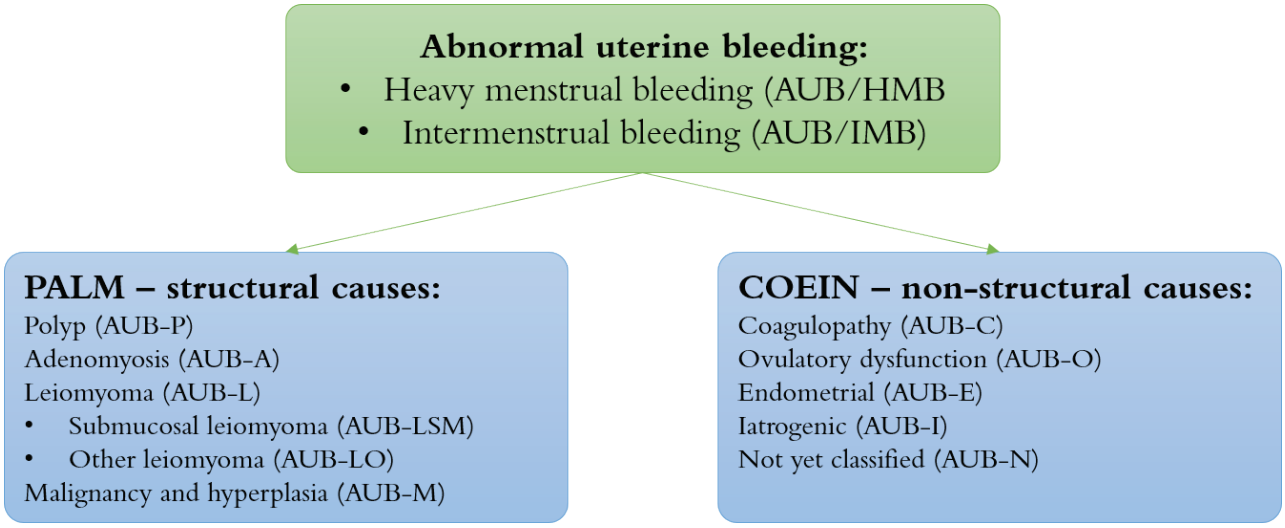
Management

Management of acute bleeding in the adolescent:

1. Stabilize the patient (ABC's)
2. Medical treatment is very successful in controlling the bleeding.
3. All therapies involve ESTROGEN, whose mechanism of action in stopping bleeding is not well understood
    - Premarin 25 mg. iv q6h x 24 hours (premarin in this dose causes +++nausea; add gravol)
      or
    - OCP 35ug (monophasic prep) one tablet po tid for 3 days, then bid for 3 days the once a day for 21 more days

Maintain the patient on a monophasic OCP for the next several months, thereby "regulating" the cycle until the HPO axis matures. The OCP will not close the epiphyses (likely already closed).

Figure 2: AUB in Perimenopausal Women: Palm-COEIN Classification System



In the mature woman, there are two major problems: i) anovulatory bleeding characterized by irregular menses and ii) ovulatory cycles characterized by a short luteal phase that also cause heavy menstrual bleeding. These are the commonest causes, but the causes listed above must be ruled out

Differential Diagnosis of AUB in Mature Women

PALM:

- Polyps, adenomyosis, leiomyomas and endometrial cancer and its precursors are common
- Coagulopathy—10% of VWB presents in the reproductive years, ITP, Leukemia

COEIN:

- *Coagulation disorders:*
  - VWB (10-15% of adult AUB is due to VWB that was not detected at adolescence or in the reproductive years)
  - Leukemia
- *Ovulatory dysfunction*
  - Hypothalamic causes—most commonly prolactinomas, stress, weight loss
  - Hypothyroidism
  - Adrenal causes—Cushing's disease and syndrome, congenital adrenal hyperplasia (adult onset)
  - Ovarian Causes—hormone secreting tumors e.g. granulosa cell tumors or Sertoli-Leydig cell tumors—rare
  - Polycystic Ovarian Syndrome—not picked up earlier or developing with metabolic syndrome

Endometrial Abnormalities: Hyperplasia and Cancer

Histology

Estrogen causes the endometrium to proliferate by increasing the mitotic activity in the basal cells. In the normal menstrual cycle, after ovulation, progesterone is secreted which inhibits mitosis of the endometrial cells and causes them to secrete glycogen.

If ovulation does not occur, the mitotic activity continues unopposed. After two or three months, the endometrium builds up to the point where the tissue becomes "unstable" and estrogen-dependent breakthrough bleeding occurs; this is *anovulatory bleeding or DUB.* A pipelle biopsy would show proliferative endometrium.

If the luteal phase is short the pipelle biopsy would show secretory endometrium.

Longstanding, untreated unopposed estrogen can also result in endometrial hyperplasia (EH), an alteration of the endometrial glands and stroma. EH can cause heavy menstrual bleeding, and precede or occur simultaneously with endometrial carcinoma. The risk of progression to carcinoma is related to the risk of cytologic atypia and chronicity of the anovulatory state. EH is premalignant only if cytologic atypia is present. 25% of women with atypical EH will progress to adenocarcinoma and 20 to 50% of women who undergo hysterectomy for atypical EH will have endometrial carcinoma

An endometrial biopsy must be obtained to exclude hyperplasia or malignancy in all women over 40 who present with AUB.

Iatrogenic

- IUD that is forgotten
- OCP/HRT incorrectly used or breakthrough bleeding
- Neuroleptics: interfere with dopamine and prolactin

N in COEIN: AUB not otherwise specified

Pregnancy: still a possibility; think ectopic because tubal ligation is common in this age group

Pre-malignant and malignant conditions

- Squamous cell carcinoma or adenocarcinoma of the cervix cause copious bleeding

Approach to AUB in mature women

History

In sorting out a patient with AUB pay special attention to the specific features of the menstrual flow and to what extent it restricts daily activities. Inquire about intermenstrual bleeding, contraceptive and medication use and systemic diseases. Follow leads, using the differential scheme listed above, match symptoms to the bleeding pattern to narrow things down and plan investigations.

Anovulation is fairly common, even in the reproductive years. If a woman skips just one cycle, often it is of enough concern to seek advice. If it occurs only once, reassurance and a menstrual diary are offered. If skipped cycles recur more than two or three times, then a work up is warranted.

Exam

- VSS, signs of anemia
- Pelvic and abdominal exam: **Pap smear**
- *Selective* endometrial biopsy. Every woman >40 with AUB has endometrial hyperplasia or endometrial cancer until proven otherwise.**
- You should also consider a **biopsy** if the patient has risk factors for endometrial cancer:
    - Nullip with history of infertility
    - New onset of heavy bleeding
    - Obesity, PCOS—give rise to unopposed estrogen
    - Family history of endometrial or colon cancer
- The accuracy of the pipelle in sampling the cavity is about 90% for endometrial cancer.
- **Labwork:**
    - CBC, ferritin, TSH, PRL, BhCG, coagulation profile if suspect VWB
- **Sonohysterogram:** also called saline infusion hysterography
    - 15 ml of saline is injected into the cavity using a transcervical catheter and then a TV-USS is done. It is very sensitive (>90%) for intrauterine pathology such as polyps and submucous fibroids which are outlined clearly in the cavity because of the fluid interface.

- **Ultrasound:** Prior to menstruation in the reproductive years the endometrial thickness (2 layer) can be up to 14 mm.
- **Hysteroscopy:** Generally done as an outpatient procedure under GA or neurolept anesthesia. This is the gold standard if workup is negative and HMB persists.

Treatment of Acute AUB

- The treatment goals are to control the episode of heavy bleeding and to reduce menstrual blood loss in subsequent cycles.
- Hormonal management is considered first line for patients without coagulopathy.

Medical Management of AUB (Table 3)

Drug	Mechanism	%decrease in flow	Other benefits
NSAID	inhibits COX	20-50	decreases dysmenorrhea
Cyclokapron	anti-fibrinolytic	40	"regulates" cycle
Progestin	decidualizes endometrium	~50	
OCP	inh Steroidogenesis	50	decreases dysmenorrhea
Mirena IUD	decidualizes endometrium	<80	treats endometrial hyperplasia

Don't forget to treat anemia and advise adequate dietary intake of iron

*Ferrous gluconate 300 mg po tid will raise Hb 10 points per week.

Surgical Management of AUB

- **Hysteroscopic resection:** removes submucous fibroids and polyps
- **Hysteroscopic endometrial ablation:** destroys the endometrium, leads to 80% improvement in menorrhagia over 5 years. However, the endometrium can grow back out of the tubal epithelium. Twenty percent of patients will need more treatment after 5 years.
- **Hysterectomy:** the last resort, definitive, with the highest morbidity, see next section for more details

UTERINE FIBROIDS (LEIOMYOMAS)

Fibroids are the most common gynecological tumors. They form in the reproductive years, by age 40, 40% of women develop fibroids and by menopause, 60-70% of women have them.
They are more common in black women in whom they tend to be larger and form at an earlier age. Frequently they regress after menopause.

In Canada, 75% of hysterectomies are performed for menorrhagia and fibroids.
Leiomyomas contain large amounts of extracellular matrix and are fibrous, which led to the descriptive term 'fibroids'.

- **Submucous fibroids** are those that grow into the endometrial cavity. A classification system has been developed based on the degree of myometrial involvement:
- **Submucous fibroids** grow into the uterine cavity.
- **Intramural fibroids** grow in the wall.
- **Subserosal fibroids** grow from the serosa.
- **Fibroids** can grow in the cervix and vagina.

The majority of fibroids grow slowly. There are no data to show that the rate of growth is related to the incidence of leiomyosarcoma.

Mechanism of growth:

Multifactorial:

1. Proliferation generally starts from a single cell i.e. fibroids are monoclonal.
2. 40% of fibroids have non-random chromosomal abnormalities.
3. Growth factors have been isolated from fibroids.
    - Angiogenesis growth factor—provides fibroids with a very rich blood supply
    - Basic fibroblast growth factor
    - Transforming growth factor-beta
    - Epidermal growth factor
    - Insulin-like growth factors etc. etc.—the list grows yearly.
4. Hormonal Stimulation
    - Estrogen and progesterone receptors have been identified in smooth muscle cells of fibroids. Progesterone is the gonadal hormone most responsible for fibroid growth, Estrogen causes little or no growth.
5. Apoptosis is inhibited in fibroids.

Clinical Features of Fibroids Depend on Size & Location

- **Asymptomatic:** The majority (60%) of fibroids are asymptomatic. These tend to be subserosal or intramural. They produce uterine enlargement or an abnormal uterine contour.
- **Bleeding (30% of women):** AUB can occur with all types of fibroids, however, submucosal fibroids cause the heaviest bleeding frequently resulting in secondary anemia.
    - The bleeding is copious, crampy, and with clots.
    - As a rule of thumb, if a woman soaks through more than one pad an hour for three or four consecutive days, after four to six months she will develop secondary anemia.
- **Pressure symptoms (Bulk symptoms):** Experienced by 20-50% of patients: Fibroids can grow to large sizes and fill the pelvis causing pressure on adjacent structures and giving rise to a sensation of fullness in the lower abdomen.
- **GI symptoms** such as constipation, bloating and abdominal distention are common.
- **Urinary symptoms** mimicking early pregnancy (frequency and urgency) are commonly present.
- Rarely, acute urinary retention can occur when a large (>6cm) fibroid incarcerates or falls into the true pelvis causing the cervix to compress the urethra. This is a surgical emergency.

Fibroids and Fertility

- There is controversy in the literature over the effect of fibroids on fertility.
- Very few RCTS are available to guide treatment.
- Most experts would agree that submucous fibroids cause failure of implantation and should be excised.
- Intramural fibroids larger than 5 cm have been shown to interfere with IVF-ET and increasingly reproductive endocrinologists are recommending removal.
- Myomectomy may be offered to a woman contemplating pregnancy if uterus >12 weeks size. If she conceives with large fibroids she is followed closely as there are many complications from fibroids in pregnancy. These complications include, bleeding, pregnancy loss and preterm labor.

Clinical note: Pain is not usually associated with fibroids. If a postmenopausal woman presents with a painful enlarging fibroid uterus, have a high index of suspicion for leiomyosarcoma.

Evaluation of Fibroids

- **Clinical examination** is accurate with a uterine size of 12 weeks or less. This correlates with a uterine weight of 300 g. Once out of the pelvis, the fibroid to symphysis height is recorded.
- **Ultrasound** is useful if the adnexae cannot be palpated.
- If the fibroids fill the pelvis and extend to the pelvic sidewall, occasionally hydronephrosis will be demonstrated in ultrasound of the kidney. Complete ureteric obstruction is extremely rare.
- **Sonohysterogram/saline infusion hysterography:** 30 cc of N/S are injected into the uterus via a transcervical catheter and a transvaginal USS done. Very useful for differentiating endometrial polyps from submucous fibroids.
- **Endometrial biopsy** is indicated in women over 40 to exclude underlying endometrial pathology.
- **Laboratory investigations:** CBC, TSH, LH/FSH, BHCG, coagulation profile if indicated

Treatment Options for Uterine Fibroids

- **Medical Management of Uterine Fibroids:**
  - Should be tailored to the needs of the woman and be geared to alleviating symptoms.
  - Goal of therapy: to decrease the size of the leiomyomas and/or to decrease the amount of bleeding
- **OCP** (will not make fibroids grow): may work; not if fibroids are large
- **Tranexamic acid** (antifibrinolytic agent)
- **GnRH agonist:** reduces fibroid volume 25%-50% within three months of therapy. This preparation cannot be used long term because it causes irreversible osteoporosis after 6 months of therapy. Once drug is withdrawn, fibroids regrow within three months.
- **SPERMs (Selective Progesterone Receptor Modulators):** Fibristal (Ulipristal Acetate 5mg po od) reduces fibroid volume by 25-50% after three months of therapy and stops fibroids related bleeding in most patients within three days of initiation of therapy. Used for shrinking fibroids preoperatively. SPERMs induce apoptosis, therefore fibroids do not regrow after therapy. Studies of longer term use are ongoing. Causes a unique effect at the level of the endometrium resembling hyperplasia histologically. Women on Fibristal need to have transaminases monitored as several cases of liver failure have been reported. This is a very rare and causality has not been proven.

- **Future therapies** may involve blocking the actions of growth factors.
- **Uterine Artery Embolization (UAE):** is performed by interventional radiologists. Both uterine arteries are occluded. Fibroids have a very rich blood supply and they are exquisitely sensitive to ischemia. Once the blood supply is blocked, they undergo necrosis and hyaline degeneration. The normal myometrium is spared.
- After UAE fibroids shrink by ~40% and menorrhagia improves within one or two months in 90% of patients.
- The durability of the procedure and need for further intervention are not known at present, along with effects of UAE on pregnancy.
- Approximately 10% of patients will require further interventions by three years as more fibroids develop.

Surgical Management of Uterine Fibroids

The surgical options are listed in order of invasiveness:

1. **Hysteroscopic Resection:** for submucous fibroids
    - Advantages:
    - Outpatient procedure
    - Quick recovery
    - Very effective
2. **Myomectomy:** for women wishing to preserve childbearing.
    - Approaches: Laparoscopy - an option if fibroids are <8cm. There is some concern that scar integrity may be weaker compared with myomectomy by laparotomy. Up to 30% of women who undergo myomectomy may require further intervention as fibroids regrow or new ones develop and become symptomatic.
    - *Advantage:* preserves the uterus
    - *Disadvantages:*
        - Significant blood loss
        - Adhesions may lead to infertility—esp. anterior location
        - Risk of new myoma formation—25 % if multiple
3. **Hysterectomy:** THE definitive treatment if childbearing complete. The most common major gynecological operation in the world.
    - *Advantages:* definitive, high patient satisfaction
    - *Disadvantage:* more complications (bleeding, injury to other pelvic organs: ureter, bladder, bowel)

FIBROIDS AND PREGNANCY

- Incidence of fibroids in pregnancy depends on ethnic/racial mix of the study population. It is approximately 5% in unselected populations.
- Most fibroids are symptomatic.
- Prospective ultrasound studies of women with fibroids show:
    - 60% of fibroids do not change size over pregnancy
    - 10% shrink
    - 30% grow

Complications before Labour

- **Pain** occurs in ~15% of patients with fibroids and is caused by red degeneration. When fibroids grow rapidly under the influence of E+P they outstrip their blood supply and become ischemic and necrotic.
- In about 50 percent of cases, the pain is of sufficient degree to require hospitalization for conservative treatment (bed rest and analgesics). Fortunately, in most cases, the acute symptoms settle and there is usually no deleterious effect on pregnancy

Complications in Labour

- Abnormal placentation
- Premature labor and premature rupture of membranes
- Dystocia secondary to low segment myoma
- Fetal malpresentation secondary to low segment myoma
- Increase in Caesarean deliveries (i.e. lower segment fibroids—50% rate if >10 cm)
- Increase in postpartum hemorrhage

These do not preclude pregnancy and require close follow-up with ultrasound especially in the third trimester. A trial of labor is often undertaken even when fibroids are in the lower segment.

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Contraception and Pregnancy Termination

Contraception and Pregnancy Termination Objectives:

At the end of the seminar, students should be able to:
Contraception:

1. List the available methods of female and male contraceptive methods:
    - Barrier
    - Intrauterine
    - Hormonal
    - Other
2. Counsel patients on these various methods of contraception with respect to:
    - Basis of action
    - Effectiveness
    - Advantages and disadvantages
    - Benefits and risks
3. Counsel patients on methods of female and male surgical sterilization:
    - Methods
    - Risks and benefits of procedures
    - Failure rates
    - Reversibility

Pregnancy Termination:

1. List the indications for pregnancy termination
2. List surgical and non-surgical pregnancy termination methods
3. List alternatives to pregnancy termination
4. List the potential complications
5. List the psychosocial considerations
6. Discuss the importance of Counselling and follow-up to discuss:
    - Prevention of STIs
    - Fertility control
    - Patient well-being

Special Legal Requirements Relating to Fertility Control:

1. Outline his/her responsibilities to provide confidential family planning when required by a minor
2. Outline the legal aspects of obtaining consent for sterilization
3. Outline the legal aspects of providing an abortion for a patient

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CONTRACEPTION

Contraceptive Options

Table 1: Contraceptive Options and Their Effectiveness in Preventing Pregnancy.

		Failures/100 women in 1st year of use:	
		Perfect use	**Typical use**
Hormonal			
	combined estrogen and progestin	0.1	3-8
	progestin only • injectable • oral • intrauterine • subdermal	 0.3 0.5 0.1-0.5 0.1	 0.3 5-10 0.1-0.5 0.1
Intrauterine			
	copper IUD	1-2	1-2
	progestin intrauterine system (Mirena, Kyleena)	0.1-0.5	0.1-0.5
Emergency	(reduced risk of pregnancy after unprotected intercourse)		
	• IUD • combined oral pill • progestin only pill		~100% 75-85% 75-95%
Barrier			
	• condoms • female condoms • cervical cap • diaphragm • sponge • Lea shield	3 5 9-26 6 10-20	14 21 20-40 20 18-36
Spermicides		6	26
	• foam • vaginal contraceptive film		
Natural family planning		1-9	20
Permanent			
	• tubal ligation • vasectomy	0.5 0.1	0.2-0.5 0.2
No method		85	85

Combined Hormonal Contraception

Progestin

- Thins endometrium - unfavourable for implantation
- Thickens cervical mucous slows/stops sperm
- Prevents LH surge - ovulation suppression
- Alters tubal transport

Progestin-related side effects/complications

- Breakthrough bleeding
- PMS - bloating, moods, water retention, breast tenderness
- Weight gain - increased appetite, dose dependent and typically only in very high doses seen with injectable only
- Acne

Estrogen

- FSH suppression - negative feedback loop, suppressing follicular development
- Endometrial proliferation

Estrogen-related side effects/complications

- Breakthrough bleeding
- Nausea
- Breast tenderness
- Thromboembolic disorders - stroke, venous thromboembolic disease (DVT/PE), CAD
- Headaches - Migraines
- Liver metabolism - active liver disease

Combination of progestin and estrogen allows for excellent efficacy with lowering of hormonal dosage to provide for fewer side effects, better cycle control and improved safety profile. All combined hormonal contraceptives in Canada contain Ethinyl estradiol (20-35 ug) and one of a variety of progestins. The dose of estrogen or progestin may vary, and the dosing schedule may vary (monophasic vs. triphasic). The delivery method may also vary (oral, transdermal or vaginal).

Non-contraceptive benefits of Combined Hormonal Contraception

- Menorrhagia, anemia
- Cycle regularity
- Dysmenorrhea and endometriosis - progestin
- Fibroids
- Ectopic risk
- Pelvic Inflammatory Disease (PID) – progestin effect on mucous
- Acne and hirsutism - ↑ SHBG due to estrogen
- Ovarian cancer - ↓ cell damage and turnover
- Endometrial cancer - progestin
- Benign ovarian cysts
- Benign breast disease

Contraindications to hormonal contraception:

Most contraindications to hormonal contraception are related to estrogen. Many women who may not take estrogen are still excellent candidates for progestin-only methods of contraception.

Absolute Contraindications

- active liver disease, liver malignancy
- uncontrolled hypertension
- migraines with neurologic symptoms, +/- aura
- diabetes with evidence of vascular damage
- suspected pregnancy
- undiagnosed vaginal bleeding
- personal history or strong family history ofVTE (thrombophilia workup may be indicated)
- estrogen-dependent malignancy
- smoker over the age of 35

Relative – must monitor effect

- controlled hypertension –blood pressure must be monitored and stay stable
- migraines without neurologic symptoms – if increase in frequency or new-onset of neurologic symptoms, must stop
- breastfeeding women – combined oral contraceptives are safe for lactation, but may decrease milk supply
- anti-epileptic medication – higher risk of failure and break through bleeding due to accelerated estrogen metabolism by liver. May help to control menstrual seizures.
- hyperlipidemia – may increase risk of pancreatitis
- gallbladder disease – small increase risk in symptomatic gallstones
- inflammatory bowel disease – slight risk of relapse; inadequate absorption
- SLE – may be considered if no evidence of nephritis or anti-phospholipid antibodies

Non-oral, non-daily – transdermal (weekly) and vaginal (monthly) administration aim to improve compliance by offering a less-intensive regimen of utilization

Extended-use – typical combined hormonal methods use 21 days of active pills, followed by 7 days of placebo. Extended-use cycles (greater than 21 days active pills followed by 7 day placebo) aim to decrease menstrual related symptoms and nuisance/cost of menses. May have long term health benefits (decreased anemia, dysmenorrhea, endometriosis, ovarian and endometrial cancer). 84 day regimen available in Canada; 84 and 365 days available in U.S., but can be achieved in any interval with any monophasic pill/patch/ring.

Shortened placebo interval - 4 or 5 day placebo interval appears to improve suppression of ovulation, and may have benefits with respect to efficacy. Ovulation is only suppressed in 70% of typical pill cycles (7 day placebo interval). Starting new pack on day 4 or 5 appears to improve ovulation suppression by preventing the early start of follicular development. Shortened placebo interval may also improve side effects related to estrogen withdrawal in pill-free week, i.e. headaches and hot flashes. Some formulations provide a low dose of estradiol during the 'pill-free week' instead of placebo, with the intent of further minimizing estrogen withdrawal symptoms

Progestin-Only Methods

- Excellent options for women who cannot take estrogen
- Safe for lactation, should not affect milk supply

Depo-Provera

- 150mg depo-medroxy progesterone acetate (DMPA) given IM q 12 weeks
- high rate of amenorrhea/oligomenorrhea – decreased anemia, dysmenorrhea, increased convenience
- highly efficacious
- high rates of side effects (break through bleeding, mood changes, weight gain, acne)
- up to 1 year delay in return to fertility
- questions with respect to effect on bone density
    - decrease in bone density seen after prolonged use, expected to return to baseline
    - data controversial
    - WHO recommends DMPA for appropriate candidates outside extremes of age where maximal bone laying/breakdown occurs (teens, peri-menopause)

Progestin-only Pill – Micronor, Mini-pill, POP

- progestin only daily pill
- must take every day (no placebo interval)
- may or may not have regular menses; high rates of break through bleeding
- high failure rates – must be taken consistently daily
- excellent option during breastfeeding and for women >35 that smoke

Norplant/Implanon

- implantable progestin rods, subdermal (not available in Canada)

Progestin Intrauterine System – Mirena, Kyleena LNG-IUS

- IUD effect, plus local progestin effect. See IUD's below.

Intrauterine Devices

Mechanisms of action

- Inflammatory response in uterus, hostile to egg implantation
- Pregnancy defined as implanted fertilized egg
- Copper is directly toxic to sperm
- Progestin IUS also has typical progestin effects
- Endometrial thinning, cervical mucous changes, tubal transport
- Minimal effect on ovulation
- Various Copper brands, effective for 30 months to 10 years; two Progestin IUS models, effective for 5 years
- Reliable, "forgettable", private contraceptive option

Copper IUD

- Increased menstrual flow, dysmenorrhea and length of menses
- Failure rates 1-2%
- Ectopic risk if pregnancy occurs, 15%

Progestin IUS (Morena/Kyleena)

- Decreases flow and dysmenorrhea
- Benefits for menorrhagia, menopause
- Failure rates 0.2 – 0.5%
- Ectopic risk if pregnancy occurs, 6%
- Cost

Mirena/Kyleena

Historically there have been concerns about using IUD's in nulliparous women, due to a perceived risk of PID and subsequent tubal damage, as well as concerns re: difficulty in insertion. PID risk with IUD insertion is about 1/1000, seen only in the first 20 days, and is related to insertion. Giving antibiotics prophylactically has not been proven to be risk-effective. STI's are caused by having sex with someone with an STI, not by an IUD. Evidence proves that PID rates and infertility rates are no higher in IUD users than non-IUD users. Pretreatment with misoprostol, paracervical blocks and pre-insertion pain medication have not been consistently shown to make insertion easier or less painful, but pre-treating with NSAID's has been shown to improve the post-insertion discomfort. Kyleena is smaller than Mirena, and is somewhat easier and less painful to insert.

Emergency Contraception (EC)

Intrauterine – insertion of Copper IUD up to 7 days after unprotected intercourse, to prevent implantation which typically occurs around day 7 post ovulation. Can be left in for ongoing contraception. Progestin IUS is not approved for this indication.

Hormonal – Progestin prevents LH surge thus prevents ovulation, and alters endometrial lining to prevent implantation. Original version of hormonal EC was the Yuzpe method – some combination of combined OC's with a high enough dose of progestin to achieve above effects. Actual dose for a variety of common OC's can be found in ePocrates. Nausea and vomiting, typically attributable to high estrogen dose, is a very common side effect and limits efficacy. Plan B, progestin-only EC, is available OTC. Packaged as 2 doses, 12 hours apart, to be taken within 72 hours of unprotected intercourse. Data now shows it can be effective up to 5 days after unprotected intercourse, and both doses can be taken together with equivalent efficacy. However, efficacy is improved the sooner it is taken.

Natural family planning

- Using knowledge of menstrual cycle and ovulation to have intercourse during "safe" period. Failure rates can be high, but can be used effectively by women with excellent cycle regularity, motivation and body-awareness. Pitfalls:
    - Sperm live 48-72 hrs
    - Egg lives 12-24 hrs
    - Cycles not always regular, particularly in "older women", i.e. early 40's

Withdrawal also has high failure rates due to failure for withdrawal to occur, and possibly due to sperm in pre-ejaculate fluid.

Permanent

Tubal ligation and **vasectomy** are both highly effective methods of contraception. While both can be reversed, reversal is costly, may have significant risks and is often unsuccessful. Permanent methods of contraception should truly be understood as permanent.

Tubal Ligation

- Requires General Anesthetic
- Failure rates 0.2-0.5%
- Higher failure rates in younger women
- Laparoscopic complications (bowel, bladder, ureteric and vascular injuries)
- Many providers now recommending complete salpingectomy for added benefit of ovarian cancer protection. Completely irreversible.

Vasectomy

- Can be done under local anesthetic
- Not intra-abdominal
- Failure rates 0.1-0.2%

PREGNANCY TERMINATION

In 2005, the abortion rate in Canada was recorded to be 28/100 live births. An estimated half of unintended pregnancies end in abortion. With the above statistics, all physicians and training physicians should be aware of the pregnancy termination options in Canada.

Termination of pregnancy (TOP) or therapeutic abortion (TA) is a safe and legal option for women in Canada who are experiencing an unplanned or unhealthy pregnancy. TA's can be performed medically or surgically in both the first and second trimester.

Most abortions in Canada are completed at gestational ages <9 weeks, less than 1% of pregnancy terminations are completed >20 weeks and no abortions are completed in Canada after 24 weeks. In extreme situations, OHIP will fund a woman to obtain an abortion after 24 weeks in the US.

From the limited reported data on abortion demographics, it appears that women in their 20's have the highest abortions rates. 33% of women are between ages 20-24; 19% are between 15-19 and 25% of women are greater than 30 years of age.

For women who are considering termination of pregnancy, whether medical or surgical, it is important that they be offered comprehensive, unbiased counselling. Options, including termination, continuation of the pregnancy or adoption should be considered. High risk patients (alcohol or drug abuse, domestic violence, mental health risk, etc.) need to be identified and supports provided. Contraceptive options post-procedure should be discussed.

Surgical Abortion

Surgical abortion can legally and safely be performed under local anesthesia, conscious sedation or general anesthesia. It can be performed in a hospital or clinic environment. *Dilatation and curettage (D&C)* is the technique used up to 14-16 weeks gestation. In larger gestations, D&C is combined with *dilatation and extraction/evacuation (D&E)*. Complications are rare, and include retained products of conception, bleeding, infection, uterine perforation, etc. Complication rates increase with advancing gestational age. Cervical preparation, using laminaria or misoprostol, can reduce the risk of cervical injuries and uterine perforation, particularly in more advanced gestations. Perioperative antibiotics will decrease the risk of post-operative endometritis.

In Toronto, surgical abortion procedures can be completed in a hospital, free standing clinic or the Bay Centre for Birth Control. Referral for hospital based procedures can be made through the Bay Centre for Birth Control, Mt Sinai's Women's Clinic or many private Gynaecologists office. Hospital procedures are completed under a general anesthetic. Free standing clinics use conscious sedation for procedures Some of these facilities are unlicensed institutions and therefore may charge a user fees for procedures. No escort is required for procedures completed at free standing clinics. The Bay Centre for Birth Control is able to complete early surgical abortions less than 8 weeks gestational age under local and oral analgesia.

Medical Abortion

Medical abortion in the first trimester can be highly effective. One advantage of medical abortion is that it affords women control and privacy. It also avoids surgical intervention and possible associated risks. Careful counselling, support and follow-up are required to ensure a complete abortion. The medications used could have teratogenic effects in the face of a failed abortion. In addition, medical abortion often results in significant bleeding and cramping. Women need to be properly educated as to what to expect and when to seek follow-up for bleeding and cramping beyond expectations.

Typically one medication is used to interrupt the pregnancy and a second medication is used to induce uterine contractions and passage of the products of conception. Options include: *methotrexate (MTX)*, followed by misoprostol given vaginally several days after MTX. *Mifepristone (RU-486)* may be used instead of MTX, with the same efficacy but faster time to completion. Misoprostol alone can be used, but it is not as effective as MTX or mifepristone in combination with misoprostol. Currently, 'Mifegymiso' is available which includes a package of Mifepristone (200mg oral as a single dose) and Misoprostol (800 mcg for buccal use, 24-48h after Mifepristone administration) tablets, with instructions for use. In general, the earlier the pregnancy, the higher the success rates of medical abortion (up to 95-98% if under 9 weeks GA). A D&C may be required in the case of a failed abortion, or incomplete medical abortion. In addition, ectopic pregnancy must be ruled out prior to commencing a medical abortion.

Medical abortion in the *second trimester* is often used in the case of genetic terminations of pregnancy. This approach can be especially useful if parents wish to see and/or hold their child or if pathologic examination may be required/requested to assist in making a diagnosis. Typically misoprostol is given vaginally and the process takes 8-24 hours on average. There is a higher risk of retained placenta in this approach, which is often easily managed with a D&C. A comprehensive support team involving genetics,

chaplaincy and/or social work, pain team, etc. is incredibly valuable to patients undergoing genetic termination of pregnancy.

Medical abortions can be accessed through various clinics in Toronto including; the Bay Centre for Birth Control, Mt. Sinai Women's Health Clinic, Free Standing Clinics and Private Providers.

If a woman is considering a late term abortion, options in Canada are limited. There are two clinics in Ontario, one in Toronto and the second in London, that are able to complete late term abortions at a gestational age greater than 20 weeks. Patients should be referred to clinics in the USA for gestational ages greater than 24 weeks that are interested in pregnancy termination.

For more information regarding the above pregnancy termination options please refer to the lecture: Walking Through the Abortion Process by Dr. Erika Feuerstein located on Elentra.

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Preinvasive and Invasive Diseases of the Lower Genital Tract

Preinvasive and Invasive Diseases of the Lower Genital Tract Objectives:

At the end of the seminar, students should be able to:

Cervical Neoplasia:

1. Describe the risk factors and pathogenesis of cervical neoplasia.
2. Describe the indications for screening and frequency of testing for the population.
3. Discuss the limitations of the Pap test as a screening procedure.
4. Describe the classification of the abnormal Pap test.
5. Describe the evaluation (including new technologies) and management of the patient with an abnormal Pap test.
6. Describe the prevention of cervical neoplasia, including the HPV vaccine.
7. Describe the impact of staging on the management and prognosis of cervical cancer.

Vulvar Neoplasia:

1. Describe the risk factors of vulvar neoplasia.
2. Describe methods of diagnosis (punch biopsy).
3. Describe the management of non-invasive and invasive vulvar neoplasia.
4. Describe impact of staging of invasive vulvar neoplasia on management and prognosis.

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CERVIX

Risk factors and pathogenesis of cervical neoplasia

HPV infection is the cause of cervical cancer.

- HPV is a double-stranded DNA virus
- Over 120 strains of HPV exist
- At least 40 types infect the anogenital tract
- At least 14 high-risk HPV types responsible for development of cancers of the cervix, vulva, vagina, anus, penis and oropharynx
- HPV is highly transmissible through sexual contact
- 80-90% of women exposed to HPV in lifetime
- Most women infected never develop neoplasia since latent viral infection is eventually cleared by their immune system
- Subtypes 16 & 18 responsible for ~70% of cases of invasive disease
- Subtype 18 related often to adenocarcinoma

The pathogenesis of cervical cancer involves integration of HPV DNA into the genome of susceptible epithelial cells of the cervix within the transformation zone after evasion of the host immune system. This integration leads to overexpression of genes within the HPV genome (E6 and E7) which produce proteins that overcome the function of tumour suppressor genes RB and p53. This leads to uncontrolled epithelial cell growth and eventually invasion of the cervical basement membrane (invasive disease).

Since most women who acquire HPV infection do not develop cervical cancer, it is clear that HPV infection alone is not sufficient to cause cervical cancer. Clearly there is a complex interplay between HPV and the host immune system. Co-factors are thought to facilitate the process of evading the host immune system, including smoking and immunodeficient states (HIV, immunosuppressive drugs/diseases), as well as the particular HPV strain.

Screening and frequency of testing for the general population

Screening for cervical cancer precursors using cervical cytology has successfully reduced the incidence of cervical cancer in Ontario. Cytologic methods, cytologic screening remains the main method for screening at this time, although other screening methods are currently being considered (including screening for HPV infection).

The current consensus recommendations in Ontario (Cancer Care Ontario Guidelines) suggest that screening should begin at age 21 for women who are or have ever been sexually active and be repeated every 3 years if cytology results are normal. Cervical screening may be discontinued for women above the age of 70 if they have had 3 adequate negative cervical cytologies over the past 10 years (3 negative cytology tests). Women who have had a hysterectomy which included removal of the cervix without a history of cervical neoplasia do not require ongoing cytologic screening.

Cervical cytology limitations

Cervical cytology is not a perfect screening test. False-positives are not unusual, especially when low-grade abnormalities (ASCUS, LSIL) are reported. Studies show the false negative rate of an individual screening test may be up to 50%, although this rate has improved with the introduction of liquid-based cytology. Such false negatives can be due to suboptimal collection and submission of the specimen or due to suboptimal detection of abnormalities during cytologic evaluation. However, the long period between HPV infection and development of cervical cancer (usually more than 10 years) permits regular serial cytologic screening to be sufficiently sensitive to detect most cases of cervical dysplasia prior to the development of cervical cancer. Given the high potential false negative rate of a single test, any woman with a visible cervical lesion should be referred for colposcopy in order to have a biopsy of the lesion for diagnostic testing (histology). Cytology alone is NOT adequate for diagnostic testing of women with a visible cervical lesion.

In Ontario, any woman between the ages of 21-70 who has not had a cervical screening test in the previous 3 years receives a mailed reminder that screening is due. Women who have been screened are informed if their results are normal or abnormal and if further testing is required. Lack of regular screening is now the number one risk factor for the development of cervical cancer in Ontario. A number of high-risk groups currently exist in Ontario, largely due to the fact that these groups are most likely not to be screened. These include Aboriginal women, women of low socio-economic status, sex-trade workers, women in Northern Ontario, and immigrant and refugee women. As a result, these groups of women are at greatest risk for developing cervical cancer in Ontario.

Bethesda classification of abnormal cervical cytology

Two important pieces of information should be contained within a cytology report.

1. **Satisfactory vs. unsatisfactory cytologic sample for evaluation**
    - Reasons for unsatisfactory cytology report include:
        - Low cellularity on specimen
2. **Epithelial cell abnormality detected vs. no epithelial cell abnormality detected**
    - Squamous cell abnormality detected
        - Atypical squamous cells of undetermined significance (ASC-US)
        - Atypical squamous cells – can't rule out high grade squamous intraepithelial lesion (ASC-H)
        - Low grade squamous intraepithelial lesion (LSIL)
        - High grade squamous intraepithelial lesion (HSIL)
        - Squamous cell carcinoma
    - Glandular cell abnormality detected (endocervical, endometrial, NOS - not otherwise specified)
        - Atypical glandular cells (AGC)
        - Atypical glandular cells – favour neoplastic
        - Adenocarcinoma in-situ (AIS)
        - Adenocarcinoma

Evaluation and management of abnormal cervical cytology report

The goal of cytologic screening is to identify women who are at risk for having cervical dysplasia that can be identified and treated prior to the development of cervical cancer. Women found to have an abnormal cervical cytology report should be referred for colposcopic evaluation as noted in the table below, although patients should be reassured that they are very unlikely to have cancer at the time of their abnormal cytology result (see Table 1).

Table 1: Cytology and Recommended Management.

Cytology result	**Recommended Management**
ASCUS (atypical squamous cells of undetermined significance)	Repeat at 6 and 12 months; if Normal x2 can resume N screening; if either abnormal refer to colposcopy If over age 30, offer reflex HPV testing* vs. repeat cytology
ASC-H (atypical squamous cells, cannot rule out HSIL)	Colposcopy
LSIL (low grade squamous intraepithelial lesion)	Repeat at 6 and 12 months; if Normal x2 can resume N screening; if either abnormal refer to colposcopy
HSIL (high grade squamous intraepithelial lesion)	Colposcopy
AGC (atypical glandular cells)	Colposcopy
AGC – favour neoplasia	Colposcopy
AIS (Adenocarcinoma-in-situ)	Colposcopy,
Squamous cell carcinoma or Adenocarcinoma	**Urgent** colposcopy

*This is currently the main role for HPV testing in clinical practice, and is the most cost-effective method for triaging those patients with ASC-US to colposcopic evaluation (based on a positive test for one or more of the 14 high-risk HPV subtypes included in the test). Any woman with an abnormal appearing cervix or symptoms suggestive of cervical cancer and an abnormal cytologic report should be referred for **urgent** colposcopic evaluation, as they may already have cervical cancer.

Colposcopy is the clinical tool used to investigate women with an abnormal cervical cytologic report. This involves examination of the cervix under magnification using a colposcope. Acetic acid is used to highlight dysplastic cells which turn acetowhite in response to its application. This technique facilitates identification and colposcopic-directed biopsy of cells suspicious for dysplasia (which are presumed to be the cause of the abnormal cytology result). After histologic confirmation of the diagnosis of cervical dysplasia has been confirmed, treatment may be carried out.

Treatment modalities for cervical dysplasia are broadly classified as ablative vs. excisional. Ablative techniques include laser ablation, cryotherapy, and electrocoagulation, all of which destroy the tissue containing the presumed dysplastic cells (see table below for details of each modality), but do not provide a specimen for analysis at the time of treatment. They are all equally effective, approximately 90% of patients will require one treatment only, and the choice of modality will depend on patient factors, operator's preference, and availability. It is essential to rule out cervical cancer before proceeding with ablative therapy or simple hysterectomy, as both of these may seriously undertreat a patient with

undetected cervical cancer. Consequently, ablative techniques can only be used when cervical cancer has been ruled out by a satisfactory colposcopic evaluation (by definition this means that the entire dysplastic lesion is seen and does not extend into the endocervical canal and does not appear invasive to the colposcopist). Otherwise, an excisional method should be used. Similarly, an excisional technique should be used in cases with a positive endocervical curettage, suspected glandular abnormality, histologically confirmed microinvasive cervical cancer, or in cases with significant discrepancy between cytology, colposcopy, and histologic findings.

The benefit of all excisional techniques (LEEP, cone biopsy) is that a definitive pathology specimen is obtained, which permits confirmation of the absence of cancer in the area removed. LEEP (loop electrosurgical excision procedure) is an easy, office-based excisional technique that has almost replaced cone biopsy as both the diagnostic and therapeutic method of choice for cervical neoplasia.

Notes on treatment modalities for cervical dysplasia

1. **Electrocoagulation:** obtained by passing high voltage electricity to tissue, causing destruction of tissue via fulguration and electrocoagulation
2. **Laser ablation:** Use of CO2 laser to ablate abnormal tissues
3. **Cold knife cone:** requires general anaesthetic, scalpel excision of transformation zone and endocervical canal; clean margins obtained
4. **Laser cone:** using CO2 laser as the cutting tool, using a focused beam on superpulse mode
5. **Loop electrosurgical excision procedure or LEEP:** requires local anaesthetic; different shape of semi-circular loop electrodes to conform to area of excision; use of ball electrode for hemostasis
6. **Hysterectomy:** A last resort for Rx. Appropriate if patient has other pathology i.e. adnexal mass, has minimal cervical length and therefore local excisional treatment may not be technically feasible

Prevention of cervical neoplasia and cancer

Primary prevention refers to preventing the development of cervical dysplasia.

- Reduction of primary HPV infection
    - Abstinence (avoid HPV exposure)
    - Condom use (reduce HPV exposure by 70%)
    - HPV immunization (avoid HPV infection when exposed)
- Reduction of development of dysplasia in HPV infected women
    - Avoidance of co-factors (smoking, HIV, others?)
    - Improvement of immune clearance? (yet unknown)

Secondary prevention refers to detecting and treatment of cervical dysplasia prior to the development of invasive cervical cancer.

- Cytology screening
- HPV screening over age 30

Tertiary prevention refers to detecting and treating women with cervical cancer to avoid morbidity and mortality from cervical cancer.

Traditionally, secondary and tertiary prevention have been the successful tools used to reduce the mortality rate from cervical cancer in Canada.

Primary prevention in the past has relied on trying to reduce exposure to HPV through encouraging safer sex practices. Not surprisingly, this has not been largely successful in preventing cervical cancer. More recently primary prevention has been addressed through the development and availability of HPV immunization, and is already a significant contributor to reducing the population burden of disease.

In Canada, there are 2 currently available HPV vaccines. The bivalent HPV vaccine (Cervarix) protects against types 16 and 18 which are responsible for 70% of HPV-related cancers. The nine-valent vaccine (Gardasil 9) protects against type 6 and 11 (the two most common low-risk strains, responsible for 90% of external genital warts) and the 7 most common high-risk oncogenic strains (types 16, 18, 31, 33, 45, 52, 58). If under age 15, two doses are used at 0 and 6 months. If 15 or older, three doses are used at 0 months, 2 months and 6 months.

HPV vaccination is recommended for all males and females over age 9 whether or not they have a history of HPV or HPV-related disease currently or in the past. In Ontario, HPV vaccination is funded in a school-based program using nine-valent nonavalent vaccine for males and females in grade 7

Vaccination does not prevent all cervical dysplasia therefore all women must be counselled on the importance of continuing cytologic screening and avoidance of co-factors despite vaccination.

Management and prognosis of cervical cancer

An estimated 1,550 new cervical cancer cases were diagnosed in Canada in 2017, with 400 women dying of this cancer in 2017 despite being a completely preventable disease.

The most common histologic subtype of cervical cancer is squamous cell cancer. Other subtypes include adenocarcinoma (affects younger women and is increasing in frequency), adenosqaumous, clear cell, small cell, sarcoma, melanoma. Remember that cervical malignancy may also be secondary spread from a primary uterine cancer.

Patients may be asymptomatic (detected on abnormal pap smear as noted above), but most commonly present with abnormal vaginal bleeding, especially post-coital bleeding. With advanced stage disease may have malodorous vaginal discharge, weight loss, pelvic pain, sciatica, obstructive uropathy, or GI symptoms.

The four major routes of spread of cervical cancer (in decreasing frequency) are:

1. Directly into cervix, uterine corpus, vagina and parametrium
2. Lymphatic metastasis (to pelvic then para-aortic lymph nodes)
3. Blood-borne metastasis (liver, lung)
4. Intraperitoneal implantation

Cervical cancer is the only gynaecologic malignancy that is clinically staged as determined by FIGO staging system (International Federation of Gynaecology and Obstetrics). This means that the extent of disease is primarily determined by clinical examination including vaginal speculum, bimanual, and pelvirectal examinations. CXR, cystoscopy, proctoscopy, and IVP are allowed to influence the patient's stage, as these tests are largely available in those countries where cervical cancer is common (which is the point of clinical staging – to facilitate standard communication regarding the patient's prognosis around the world). Therefore, the results of CT scans and MRIs are not considered when determining the stage of the patient's cancer, though the information they provide may influence the ultimate treatment recommendation.

Treatment and prognosis of cervical cancer

Patients with early stage invasive disease (confined to cervix) may be treated with either radical surgery or primary chemoradiation therapy. The cure rate for either modality with stage I disease is equal (about 85-90%), so the choice of modality is tailored to the individual needs of the patient. The use of radical surgery allows preservation of ovarian function and improved future sexual function compared to the use of chemoradiation therapy, so is often preferred in younger women. Patients at higher risk for relapse post-surgery may be treated with chemoradiation instead of surgery to avoid the possible need for post-operative chemoradiation based on the final surgical pathology report.

Patients with large early-stage cancers (≥4 cm) or advanced-stage invasive disease (not confined to cervix) are treated with chemoradiation therapy, as they have a better prognosis with this form of therapy due to the high risk of having disease outside the surgical field. The survival of such patients is highly dependent on the extent of their disease, but is clearly lower than those patients whose disease is confined to the cervix at the time of presentation.

I. Surgery for cervical cancer

The traditional surgical treatment for early stage cervical cancer is a radical hysterectomy, which is different from the "usual" hysterectomy as more tissue around the cervix is removed. This includes removing a cuff of the vagina 1-2 cm, and the parametria to obtain a good surgical margin. At the same time, a pelvic (+/- para-aortic) lymphadenectomy is carried out which includes removing the lymph nodes along the common iliac, external and internal iliac vessels and those in the obturator fossa. As noted above, depending on the patient's age and tumor type, the ovaries may be left in-situ.

In those women with small invasive cancers requiring radical treatment who desire fertility preservation, radical trachelectomy has become an accepted alternative to radical hysterectomy. This surgical procedure removes the cervix with surrounding parametrium and vaginal cuff, but leaves the uterine fundus in place, along with the adnexa, to facilitate future pregnancy. The uterine fundus, usually surrounded by a cervical cerclage (suture) to prevent cervical incompetence during pregnancy, is re-connected to the vagina. The resulting pregnancy rate in patients who later attempt to become pregnant is about 60%, and the oncologic outcome is identical.

In those patients with very early cervical cancer (**microinvasive disease** is squamous cell carcinoma with less than 3 mm invasion and no lymphatic involvement), a simple hysterectomy (or cone biopsy if they desire fertility preservation) may be carried out.

Surgery can also be used in patients who experience disease recurrence within the central pelvis after chemoradiation therapy (**pelvic exenteration**). This form of ultraradical surgery may include removal of the bladder, rectum, and/or entire female reproductive tract, depending on the location of the pelvic recurrence. It is important to rule out metastatic disease before considering pelvic exenteration, as this potentially morbid procedure is only considered in patients who might be cured of their disease as a result.

II. Radiation Therapy

Radiation therapy as the primary treatment is reserved for women with early cervical cancers who are not surgical candidates (ie. medically unfit, wish to avoid surgery). It is the mainstay of treatment for women with more advanced disease (stages IIb-IV). The intent of RT may be curative or palliative. In curative RT, the patient will receive external beam RT (usually delivered daily over 5 weeks) followed by brachytherapy (radiation delivered directly into the cervix continuously over a few days). Some surgical patients will receive adjuvant postoperative RT based on the interpretation of the surgical specimen (i.e. positive microscopic margin, positive lymph node…)

III. Chemotherapy

Cisplatin chemotherapy is typically used as a radiosensitizer and given concomitantly with external beam radiation on a weekly basis during primary treatment for cervical cancer. It is also used in the palliative setting as treatment for women with metastatic disease who are incurable. Other drugs are also used in clinical trials for recurrent cancers.

VULVA

Vulvar intraepithelial neoplasia (VIN):

- Lesions are graded as VIN I-III
- May be associated with cervical dysplasia or vaginal dysplasia (VAIN)
- Commonly multifocal lesions
- Hairless skin of interlabial groove, posterior fourchette and perineum frequently affected
- More extensive disease is often confluent, involving the labia majora and minor and perianal skin
- Lesions may be macular or papular, often with a keratotic and roughened surface.
- Discoloration is usual with white lesions reflecting epithelial thickening and hyperkeratosis, red reflecting hypervascularity and parakeratosis, and gray or brown reflecting melanocytic overactivity and pigment incontinence
- Invasive vulvar carcinoma is often associated with preinvasive disease
- Progression of VIN to invasive ca most frequently in immunosuppressed and elderly women
- May be associated with HPV infections, but is not always

Role of punch biopsy in vulvar lesions

BIOPSY, BIOPSY, BIOPSY (any suspicious vulvar lesion)!!!

Punch biopsies are easy to carry out and should be used liberally in the management of vulvar lesions. The abnormal area is identified and infiltrated with local anaesthetic (ie. Xylocaine 1%) using a 25 gauge needle. Using a 2 or 4 mm punch, depending on the size of the lesion and location, the punch is placed

over the area to biopsy and by applying some pressure is circumferentially rotated (to cut through skin). Using a fine pick-up forceps, the edges of the specimen are raised and the base is excised with fine scissors. The specimen is sent for pathological analysis. Pressure and occasionally Monsel's solution (ferric subsulphate) are used for hemostasis; suturing is rarely needed.

Management of VIN

Options:

- Wide local excision
- Superficial skinning vulvectomy
- CO_2 laser vaporization (preferred option in most cases)

*Only the excisional Rx options will provide further material for pathological analysis. About 8% of VIN will have an associated invasive cancer, which is often superficial (<1 mm). If suspicious of invasive disease, excision should be carried out.

Vulvar Dystrophies:

- Confusing classification, more recently simplified
- **Lichen sclerosus:**
  - Pruritus, burning, dyspareunia, dysuria
  - On exam: loss of anatomy, thinned out skin, patchy white/red papules, diffuse erythema, purpuric spots, hemorrhage, figure of 8 distribution
  - Secondary changes: lichenification, purpura and excoriation; no other mucous membranes involved; 1-3% develop ca
  - **RX:** After diagnosis is proven, consider combination of hygiene, cold packs and STEROIDS (Clobetasol 0.05% twice a day for the acute period, then reduce potency and frequency of steroid i.e. 1% corticosteroid 1-2/week
- **Squamous hyperplasia:**
  - Relentless pruritus, marked lichenification, excoriation, crusting and loss of pigment
  - Rule out: candida, tinea, contact dermatitis, diabetes, atopic dermatitis
  - RX: After diagnosis proven: stop irritants, cold packs prn, STEROIDS (as above), Rx candida if present
  - Risk of cancer 1-3%
- Vulvar lesion may reflect a systemic problem. Think of lichen planus, psoriasis, Behcet's, Crohn's, aphthous ulcers, diabetes, HIV.

Vulvar pain syndromes

- **Vulvar Vestibulitis Syndrome:**
  - Painful red vestibular lesions
  - Often history of infection (yeast?)
  - Fair skin, usually young women
  - Oral contraceptive use
  - Introital dyspareunia

    - RX: Remove obvious contributing factors (ie. yeast, BCP), moisturize with bland emollients, dietary changes (inc. citrate, decr. Oxalate), tannic acid may be effective, biofeedback techniques to resolve secondary vaginismus, cognitive therapy, local resection for persistent reproducible disease (may worsen problem re: scar formation)

- **Vulvodynia:**
    - Persistent pain with no visible lesions
    - Usually 45-50 yrs
    - Occasional triggering infection, relationship change, trauma
    - Entire vulva involved
    - **RX:** Legitimize the complaint, moisture, cold compress, neuronal block systemic therapy (i.e. amitriptyline, neurontin, desipramine), local xylocaine ointment, biofeedback

Paget's Disease:

- Extramammary Paget's is associated with an underlying adenocarcinoma in 20% of patients (unlike in the breast is invariably associated with underlying ductal ca)
- In postmenopausal women, usually white lesion on vulva
- Pruritus and vulvar soreness are usual
- Lesions has eczematoid appearance macroscopically and usually begins on hair-bearing portion of vulva; may extend to mons, thighs and buttocks, rectum, vagina
- Persistent weeping in extensive disease (raised and velvety appearance)
- A second synchronous or metachronous primary neoplasm is associated with Paget's in 30%; common sites include cervix, colon, bladder, gallbladder and breast
- **RX:** Disease usually extends beyond the gross lesion, therefore positive surgical margins are not uncommon, and requires repeat resections

Vulvar Cancer

- Mean age at diagnosis about 65 years
- Most patients have a mass, often with a history of pruritus; may present with groin mass
- Lesion is often raised, fleshy, ulcerated, leukoplakic or warty in appearance
- Most lesions are squamous in type; others: melanoma, bartholin's gland, basal cell, sarcoma, verrucous, lymphoma, metastatic
- Most squamous ca occur on the labia majora, but can also be seen on labia minora, clitoris and perineum
- Clinical assessment should include all of lower genital tract and groin lymph nodes
- Biopsy required for diagnosis
- Route of spread:
    - Direct to vagina, urethra and anus
    - Lymphatic embolisation to regional lymph nodes
    - Hematogenous spread to distant sites (lung, liver and bone)

Staging of vulvar cancer

- Surgically staged according to FIGO system

Management of vulvar cancer

- In most patients, surgical excision is the treatment of choice
- Extent of surgical excision will depend on the size and location of the tumor to ensure negative margins
- Extensive lesions may require skin grafts for closure, or may be treated with preoperative chemoradiation therapy (to reduce the size of the tumor) followed by resection
- Primary chemoradiation is reserved for patients with advanced unresectable cancers
- Inguinal-femoral lymphadenectomy has traditionally been required for all patients with tumors with >1mm of invasion; if the lesion is midline, both groins need to be dissected; if the lesion is 1 cm beyond the midline, then ipsilateral groin dissection only is appropriate
- Sentinel node procedures are recently being accepted as alternative to morbid lymphadenectomy in patients with vulvar cancer
- Post-operative (adjuvant) chemoradiation therapy will be individually determined based on the pathology report (close margins, positive lymph nodes)

VAGINA

Just a few points to keep in mind. Patients with a visible vaginal lesion should have a biopsy performed.

Vaginal intraepithelial neoplasia is analogous to cervical dysplasia.

- May be asymptomatic or present with vaginal bleeding/discharge.
- May be detected by cytologic screening of cervix or vagina.
- Caused by HPV.
- Can progress to invasive disease, slower rate of progression.
- Usually treated with destructive means vs. excision after ruling out invasive disease with colposcopic-directed biopsy.

Primary vaginal cancers are rare (squamous cell carcinoma more common than melanoma).

Secondary involvement from cancer of cervix, endometrium, vulva, and anus are much more common (so don't forget to look at all of these sites on physical examination too!).

Exception: Women exposed to DES (diethylstilbestrol) as fetuses develop clear cell adenocarcinoma of the vagina.

Patients with primary squamous cell carcinoma of vagina are usually treated with combined chemoradiation similar to cervical cancer above. Alternatively, radical hysterectomy with upper vaginectomy can be used in selected cases.



Pelvic Masses: Benign and Malignant Ovarian Neoplasms

Pelvic Masses: Benign and Malignant Ovarian Neoplasms Objectives:

At the end of the seminar, students should be able to:
Functional ovarian cysts:

1. Explain the physiologic basis for the development of functional ovarian cysts
2. Describe the clinical presentation of these cysts
3. Describe the investigations used to differentiate these cysts from complications of pregnancy and other ovarian neoplasms
4. Outline the expectant management of the functional ovarian cyst and indicate when they should be managed surgically

Benign and Malignant Ovarian Neoplasms:

1. Describe the evaluation of the patient with an adnexal mass
2. Describe the characteristics:
    - Functional cysts
    - Benign ovarian neoplasms
    - Ovarian malignancies
3. List the risk factors for ovarian cancer
4. List the symptoms and physical findings of a patient with ovarian malignancy
5. Describe the histological classification of carcinomas of the ovary
6. Describe the impact of staging on management and prognosis of ovarian cancer
7. Describe how the investigation and surgical management would differ in these two women and explain why
8. Describe the management of carcinoma of the ovary

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FUNCTIONAL OVARIAN CYSTS

Functional ovarian cysts are benign ovarian cysts, which occur as a result of a normal physiologic process.

1. **Follicular Cysts** arise from either nonrupture of a mature follicle or failure of an immature follicle to undergo atresia. These may arise as a result of abnormal release of anterior pituitary gonadotropins. These cysts are thin walled, unilocular and range in size from 1-2cm. to 8-10cm. They are lined by an inner layer of granular cells.
2. **Corpus Luteum Cysts** occur as a result of intracystic hemorrhage as a normal part of the stage of vascularization, 2-4 days after ovulation. With time the blood is replaced by clear fluid. Cysts are usually hormonally inactive.

Clinical presentation of functional ovarian cysts

Functional ovarian cysts are usually asymptomatic and are most often discovered incidentally (on physical exam or ultrasound). Occasionally they may present with acute onset pelvic pain due to one of three classic "adnexal accidents": rupture, hemorrhage, or torsion (in decreasing frequency). Rupture may result in intraabdominal bleeding and peritonitis. Torsion usually presents with a relatively sudden onset of pain which is initially unilateral and may later be accompanied by peritonitis.

Patients undergoing fertility treatment may develop multiple functional type ovarian cysts as the result of therapy. Ovarian hyperstimulation syndrome (OHSS) is a clinical syndrome related to excessive ovarian response to fertility drugs that can be accompanied by excessive edema and ascites. OHSS can produce severe abdominal pain and/or respiratory symptoms and these patients may need to be admitted to hospital and treated with supportive care. They are rarely treated surgically.

Differential Diagnosis

A combination of clinical evaluation (history and physical examination), lab tests (beta hCG) and diagnostic imaging (pelvic ultrasound) are useful in distinguishing functional ovarian cysts from complications of pregnancy and ovarian neoplasms. Other than surgical removal (see objective #4), diagnostic laparoscopy is the most definitive investigation to rule out the presence of an ovarian neoplasm.

Clinical information (date of last normal menstrual cycle, symptoms, previous history, family history, history of fertility therapy, findings suggestive of an ovarian neoplasm on physical examination) need to "fit" with the findings on lab tests and diagnostic imaging to be confident labeling an adnexal mass as functional. One point to remember is that as pregnancy advances the ovaries move higher in the abdomen which means that symptoms related to an ovarian mass may be mid abdominal rather than in the pelvis as they would be in the non-pregnant state.

A positive qualitative and/or quantitative β-hCG must prompt consideration of the diagnosis of ectopic pregnancy.

Pelvic ultrasound is the best imaging tool to evaluate these cysts. Remember that transvaginal ultrasound is the preferred route, since one obtains the best information regarding the gynecologic organs with transvaginal scanning (higher resolution than transabdominal ultrasound, better than pelvic CT).

Follicular cysts are usually unilocular cysts without septations or solid components and range in size from 2-10 cm. If associated with significant pain or peritonitis a diagnostic laparoscopy can be used to confirm the diagnosis. Corpus luteum cysts are usually at least 3 cm in size, and are yellow in colour if seen at laparoscopy. Ultrasound may suggest the diagnosis of ectopic pregnancy (no intrauterine pregnancy and positive beta hCG) or an adnexal accident (rupture and/or hemorrhage with free fluid in pelvis, torsion with lack of blood flow to adnexa).

Expectant management of functional ovarian cysts

In general, functional ovarian cysts should be managed conservatively depending on the individual's symptoms. These cysts typically regress over a 4-6 week period of time on serial ultrasound. While ultrasound identifies a cyst that is consistent with being a functional one, it is only when the cyst regresses spontaneously that you are certain of the diagnosis. Cysts that persist are likely not functional and further investigation with diagnostic laparoscopy may be appropriate for such patients.

Surgery may be necessary when the patient is symptomatic, since symptoms may be related to intraabdominal bleeding and/or torsion, which can usually be controlled through laparoscopic surgical techniques. Surgery should also be considered in cases of a persistent cyst to rule out an ovarian neoplasm.

OVARIAN NEOPLASMS

Ovarian neoplasms are growths of ovarian tissue, which do not occur as a result of a normal physiologic process. They may be either benign or malignant (or borderline malignant for the epithelial tumours), and may be broadly classified according to the type of cell from which they originate as follows:

Classification of Ovarian Neoplasms

Germ cell

- The most common benign germ cell tumour is a mature teratoma (dermoid). It has a 15% chance of being bilateral.
- Germ cell malignancies account for 3% of malignant ovarian tumours but comprise two thirds of all ovarian tumours in children and adolescents. They are very uncommon in adult women.
- Several subtypes of malignant germ cell tumours exist (see tumour markers section below)
- Malignant tumours are usually unilateral and treatment includes surgery +/- chemotherapy.
- One of the most remarkable features of these tumours is that 25 years ago mortality was very high. Due to effective chemotherapy mortality today is very low, even with advanced stage disease.

Stromal cell

- The most common benign stromal cell tumours are fibromas and thecomas. They are usually unilateral, although they may be associated with ascites and/or a pleural effusion (Meig's syndrome).
- Rare, comprising 2-3% of all ovarian cancers. May occur in any age group.
- Several subtypes of malignant stromal cell tumours exist (see tumour markers section below).
- These tumours may be suspected clinically based upon clinical manifestations related to hormone secretion.

Epithelial cell

- The most common benign epithelial tumours are serous or mucinous cystadenomas.
- Epithelial ovarian cancers are the most common type of ovarian cancer and makes up 90% of all malignant ovarian tumours. Subtypes include:
    - Serous 65%
    - Mucinous 10%
    - Endometrioid 15%
    - Clear Cell 5%
    - Undifferentiated 5%
- Epithelial ovarian cancers (EOC) tend to present in more advanced stages as they tend not to produce recognized symptoms in the early stage.
    - 70% present as stage 3 or 4, only 30% as stage 1 or 2.
- Over 60% of women with EOC will die from it.
    - Cure rates (5-yr survival) highly dependent on stage:
        - Stage 1 - 90%
        - Stage 2 - 70%
        - Stage 3 - 20%
        - Stage 4 - <5%
- There is another subcategory of EOC, called tumours of low malignant potential or borderline tumours. These refer to a group of tumours where malignant cells arise from the ovarian surface but do not invade the ovarian stroma. They can be bilateral and they can metastasize. Yet in general they are treated primarily with surgery and have a very high cure rate.

Other cell

- For example, small cell neuroendocrine tumours

Extraovarian

- For example, endometriosis or metastatic malignancy (commonly from the GI tract, breast, lymphoma)

Completing a pelvic examination including palpation of the adnexae

The best way to palpate the adnexae is through a combined bimanual (abdominal-vaginal) plus rectovaginal examination. Students should gain experience with performing such examinations during their clinical rotation.

Risk factors for ovarian cancer

The pathogenesis of germ cell, stromal cell, and other nonepithelial ovarian malignancies remains unclear, and no significant risk factors have been elucidated.

There are two currently accepted theories regarding the pathogenesis of epithelial ovarian cancer: one focuses on the role of ovulation (incessant ovulation) and the second on ovarian cancer originating in the fallopian tube. Incessant ovulation: ovulation results in a break in the surface epithelium lining the ovary. As the epithelium undergoes repair, inclusion cysts can develop which sit in the ovarian stroma just under the epithelium. It is hypothesized that the epithelium in the inclusion cysts may undergo changes

influenced by its environment and develops into ovarian cancer. Support for this theory comes from epidemiologic studies which link the degree of risk of developing epithelial ovarian cancer to factors which alter the number of ovulations a woman experiences during her reproductive life (ie. pregnancy and OCP use appear to be protective by reducing ovulation – see list below). Fertility drugs increase ovulation and while there are some studies linking ovarian stimulation to an increase risk of cancer there is considerable controversy regarding this correlation. Fallopian tube origin: Since the identification of genetic mutations that cause an increased risk of ovarian and breast cancer (BRCA) prophylactic surgery has been recommended. Prophylactic surgery includes the removal of the ovaries and fallopian tubes after the age of 35, once family planning is complete. While examining these specimens pathologists identified a preinvasive lesion in the tubes of these women with a high chance of developing ovarian cancer (a preinvasive lesion in the ovary has never been identified).

Genetic predisposition to epithelial ovarian cancer is related to several clinical familial syndromes which are linked to defined genetic loci including BRCA1 & 2 as well as other defined DNA mismatch repair genes (HNPCC - Lynch syndrome). Germ line mutations in these loci appear to predispose affected women to the development of epithelial ovarian cancer and account for the familial risk factors noted in clinical studies.

Protective factors

- Pregnancy
- Use of Birth Control Pill
- Tubal Ligation

Risk factors

- Personal history of malignancy (breast, endometrium, colon)
- Family history of malignancy (breast, ovarian, endometrium, colon)
- Use of fertility drugs (controversial)

Characteristics of benign ovarian neoplasms and ovarian malignancies

Although it can be difficult to differentiate benign from malignant ovarian neoplasms based on their clinical characteristics, medical history and physical examination can provide useful information in this regard. In general, clinical features that suggest an adnexal mass may be malignant include: rapid growth, weight loss or other constitutional symptoms, a personal history or family history of cancer, the presence of bilateral adnexal masses, solid adnexal mass, mass fixed within the pelvis, presence of ascites, other masses palpable (e.g. omental cake, disease in cul-de-sac).

In general, pelvic *ultrasound* is a very effective radiologic examination that will provide you with additional helpful information to characterize ovarian neoplasms to facilitate identification of those neoplasms which are likely to be malignant including:

- Size of mass
- Location of mass
- Presence/absence of bilateral masses
- Presence/absence of solid components
- Presence/absence of septations (especially if thick or have vascularity within them)
- Presence/absence of ascites
- Presence/absence of other masses (suggesting metastases)

Symptoms and physical findings of a patient with ovarian malignancy

Symptoms for ovarian cancer are often non-specific, and may include abdominal discomfort, abdominal distention, nausea, urinary symptoms, or abnormal vaginal bleeding. Symptoms of bowel obstruction may occur and occasionally patients may present with severe pain. Often, in retrospect, patients report vague symptoms often related to the bowel function which preceded the diagnosis of ovarian cancer by as much as 6-8 months.

The *physical examination* findings are largely dependent on the stage of the disease. Apart from the presence of a pelvic mass, woman with early stage disease may have no significant abnormalities detected. However, as noted in #3 above, women with advanced stage ovarian malignancies are often found to have bilateral adnexal masses, ascites, an upper abdominal mass (omental cake), cachexia, and disease palpable in the cul-de-sac on pelvirectal examination.

Table 1: Tumour markers associated with various ovarian malignancies

	Blood Test
Germ cell	
Dysgerminoma	LDH
Endodermal sinus tumour/yolk sac tumour	AFP
Choriocarcinoma	β-hCG
Immature Teratoma	None
Embryonal cell	AFP + β-hCG
Stromal cell	
Granulosa cell tumour	Inhibin
Sertoli-Leydig tumour	Androgens
Epithelial cell	CA-125
Other	
Small cell of hypercalcemic type	Calcium
Metastatic	

CA125 has a sensitivity of only 25-50% in early stage ovarian cancer, which means that by itself it is not a reliable marker for ovarian cancer. CA125 can be elevated in many benign or non-gynaecologic conditions including endometriosis, fibroids, pregnancy, menstruation, PID, etc. Age influences the reliability of CA-125 as a tumour marker, where its specificity for ovarian cancer is especially low in pre-menopausal women. The main use of CA-125 at time of diagnosis is in combination with u/s and menopausal status and it's main use in patients diagnosed with epithelial ovarian cancer is to monitor response to treatment in those women with an elevated CA-125 at diagnosis.

All of these tumour markers are used only in women with pelvic masses to help determine the pre-operative risk of malignancy or to follow the response to therapy in women with histologically proven ovarian malignancy. **None** of these should be used as screening tests for ovarian cancer in the general population, as they do not reduce the mortality from ovarian cancer yet can lead to unnecessary anxiety, further investigation, and/or surgery for women (with their possible complications).

Management of a patient with an adnexal mass

All adnexal masses require evaluation and consideration of the possibility that they are malignant. Women with unilateral unilocular ovarian cysts <5 cm in size are usually observed unless they are symptomatic. Women with other ovarian neoplasms are typically managed with surgery to rule out malignancy and/or manage symptoms.

When deciding the management of a woman with an ovarian mass age is an essential factor that must be considered. In young women germ cell tumours must be considered and serum tumour markers may be helpful during assessment before surgery. In general, germ cell tumours are unilateral and therefore lend themselves to more conservative treatment (conservation of contralateral ovary and uterus, and therefore fertility-sparing). As a result, many of those who develop germ cell tumours as young women go on to have children after the completion of curative therapy. In women over 35, and in particular over 40 years of age, the most likely diagnosis for an adnexal mass is an epithelial neoplasm. The main differential diagnosis will be between benign and malignant. Ultrasound and CA125 can be helpful, but the diagnosis can ultimately only be made through pathology.

Clinical evaluation, ultrasound characteristics, and tumour marker testing (see #3&4 above) are typically used to determine a pre-operative index of suspicion that an ovarian neoplasm is malignant. In fact, simple formal scoring systems have been developed to provide clinicians with a systematic approach to determine the pre-operative risk of malignancy, and the routine use of such a scoring system has been demonstrated to improve the pre-operative recognition of ovarian malignancies and thereby facilitate appropriate pre-operative referral of women with suspicious masses to gynaecologic oncologists for optimal surgery (which has been demonstrated to improve outcome in women with ovarian cancer).

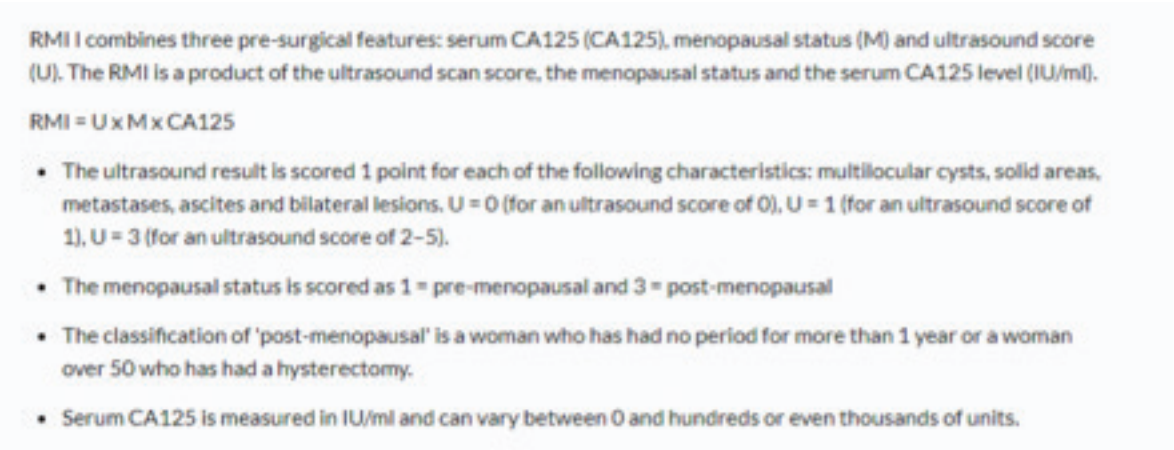
Characterizing pre-operative likelihood of malignancy for a woman with an adnexal mass

There are a number of versions of a **Risk of Malignancy Index (RMI)** published in the literature, and there is not good evidence that any one is superior to all others. One such example has been included in this handout. However, it has been demonstrated in a number of studies from many different populations and jurisdictions that use of a standardized tool such as the RMI improves the pre-operative identification of ovarian cancers compared to use of individual factors alone such as CA-125 or ultrasound diagnosis. Ultimately, use of this strategy helps ensure optimal surgery is carried out during the initial surgical procedure by promoting pre-operative referral to a gynaecologic oncology surgeon. Remember, this helps improve the outcome of the patient!

The RMI given performs reasonably well in predicting which adnexal masses are likely to represent cancers. The positive predictive value of an RMI score >200 is around 80% (if score is high, high chance it is a cancer), the negative predictive value of a score <200 is around 90% (if score is low, high chance it is NOT a cancer). It is important to emphasize that the RMI has been found to be much more reliable in post-menopausal women and in cases suspicious of serous ovarian cancer (serous ovarian cancer commonly causes an elevated CA125). In cases of premenopausal women or when a nonserous ovarian cancer is suspected then clinical impression together with expert u/s should guide management.

The use of the RMI should be demonstrated and practiced during your seminar and during your clinical rotation using a number of case examples, and it is recommended that you use this in your future clinical practice by clinical practice guidelines in a number of countries (including Canada).

Figure 1: Calculating the RMI for Adrenal Masses.
RMI > 200 = Pre-Op Gynecologic Oncology Referral



RMI I combines three pre-surgical features: serum CA125 (CA125), menopausal status (M) and ultrasound score (U). The RMI is a product of the ultrasound scan score, the menopausal status and the serum CA125 level (IU/ml).

RMI = U x M x CA125

- The ultrasound result is scored 1 point for each of the following characteristics: multilocular cysts, solid areas, metastases, ascites and bilateral lesions. U = 0 (for an ultrasound score of 0), U = 1 (for an ultrasound score of 1), U = 3 (for an ultrasound score of 2–5).
- The menopausal status is scored as 1 = pre-menopausal and 3 = post-menopausal
- The classification of 'post-menopausal' is a woman who has had no period for more than 1 year or a woman over 50 who has had a hysterectomy.
- Serum CA125 is measured in IU/ml and can vary between 0 and hundreds or even thousands of units.

Note: A 2011 study, Comparison of three malignancy risk indices and CA-125 in the preoperative evaluation of patients with pelvic masses, BMC Research Notes, 2011, 4:206, showed no statistically significant difference between the RMI 1, RMI 2 and RMI 3 in differentiating between benign and malignant pelvic masses.

CASE EXAMPLES:

A 45-year old pre-menopausal woman having acute pelvic pain is found to have a 5 cm mobile firm right adnexal mass on pelvic examination and undergoes a transvaginal ultrasound and CA-125. Her CA-125 is 50. The ultrasound reports the presence of a cystic right adnexal mass with no internal septations. There is a small degree of free fluid noted in the cul-de-sac. The left adnexa is reported as normal, and no other masses are seen.

Q. What is the likelihood that she has ovarian cancer?
Her RMI score is 50 (1 x 50 x 1) – and given the NPV of ~90%, it is unlikely this woman has ovarian cancer.

A 60 year old asymptomatic post-menopausal woman with an 8 cm mobile cystic right adnexal mass detected on pelvic examination and undergoes a transvaginal ultrasound and CA-125. Her CA-125 is 60. The ultrasound reports the presence of a mixed solid/cystic right adnexal mass with multiple internal septations. There is no ascites. The left adnexa is reported as normal, and no other masses are seen.

Q. What is the likelihood that she has ovarian cancer?
Her RMI score is 450 (3 x 50 x 3) – and given the PPV of ~80%, it is quite likely this woman has ovarian cancer and a referral to a gynecologic oncologist should be made.

Optimal surgery for adnexal mass

Women with an adnexal mass generally undergo surgery to treat symptoms and/or to rule out ovarian malignancy.

Surgery for ovarian cancer has 4 purposes, which ideally should be achieved at any surgery for an adnexal mass:

1. Confirm the diagnosis of ovarian cancer.
2. Determine the stage of disease (surgical staging using FIGO system).
3. Treat the patient.
    - Relieve symptoms
    - Act as therapy for the cancer
4. Define the optimal post-operative treatment.

Optimal surgery involves:

- Inspection and palpation of all structures and peritoneal surfaces in pelvis and abdomen.
- Biopsy of any lesions suspicious for metastatic lesions.
- Collection of peritoneal washings/fluid for cytologic examination.
- Removal of the affected adnexa.
- Frozen section (intraoperative pathologic consultation) if useful to determine surgical procedure necessary.
- *For women with a non-suspicious mass:*
    - Removal of the contralateral adnexa and uterus is often performed simultaneously in women who have completed childbearing and do not wish to preserve endocrine ovarian function.
- *For women with a suspicious mass (or confirmed malignancy on frozen section):*
    - Removal of the contralateral adnexa and uterus is often performed simultaneously in women who have completed childbearing.
    - Surgical staging biopsies including omentum, diaphragm, multiple sites of peritoneum, and pelvic and para-aortic lymphadenectomy.
    - Debulking of gross metastatic disease (if present).
    - Insertion of an intraperitoneal chemotherapy catheter (if optimally debulked of metastatic disease).

The cornerstone of optimal management of patients with EOC is optimal surgery. Women who have not had an ideal surgical procedure at diagnosis that completes optimal staging (in cases with apparent early stage disease) and/or debulking of cancer (in cases with known advanced stage disease) might be subjected to a second operative procedure to complete these critical tasks, since both have been directly related to survival in patients with EOC. Staging is an essential part of the surgical procedure with ovarian cancer. It is particularly important to meticulously stage cancers that have no obvious spread and may be stage 1, as these patients may not benefit from adjuvant chemotherapy. Staging is simply defining the histologic extent of the cancer. Is it involving the upper abdominal cavity, the diaphragms, the bowel, and/or the para-aortic lymph nodes?

Debulking refers to the removal of as much metastatic tumour as possible at the time of surgery. The less cancer volume present after completion of the surgery, the better the survival for the patient. It is felt that chemotherapy works better on smaller tumour volumes. The reason for this is postulated to be related to greater access of chemotherapy to the tumour. Larger tumour masses have less vasculature, less

blood supply and are more likely to have necrotic areas which would likely be resistant to chemotherapy. Optimal debulking also facilitates the use of intraperitoneal chemotherapy (see section on management below).

Surgery for an adnexal mass is often performed laparoscopically, in order to minimize the morbidity of the procedure. Use of laparoscopy is reasonable even in cases of ovarian cancer, so long as the principles of oncologic surgery are followed and optimal surgery is carried out in a similar manner to laparotomy.

Management of carcinoma of the ovary

As suggested above, the management of patients with ovarian cancer is highly dependent on the type of ovarian cancer, as well as the stage of the disease. Ovarian cancer is the second most common gynecologic malignancy but accounts for more deaths than all other gynaecologic malignancies combined.

Women with germ cell and stromal cell cancers are often young and desire fertility preservation. Conservative surgery +/- adjuvant chemotherapy (for patients with advanced stage disease or high-risk histology) is the typical management strategy for patients with these types of ovarian cancer. Similarly, young women with borderline epithelial cancers typically undergo curative conservative surgery resulting in fertility preservation.

As noted above, epithelial ovarian cancer (EOC) is associated with a worse prognosis, which is highly dependent on the stage of disease at presentation. Women with stage 1 EOC may receive post-operative (adjuvant) intravenous chemotherapy in cases where they have not been optimally staged (in case they have undetected metastatic disease) or in cases where significant risk factors exist that predict a high likelihood of recurrence.

Women with advanced stage EOC typically receive adjuvant chemotherapy. This chemotherapy is traditionally delivered via the intravenous route. However, recently it has been accepted that those patients who have optimal debulking of their cancer (<1 cm largest residual tumour) at their initial operation live longer if they receive their chemotherapy intraperitoneally. Again, this highlights the importance of optimal primary surgery for women with EOC.

Those women who are judged not medically fit for a major surgical procedure or are judged not likely to be optimally debulked may be treated initially with so-called "neoadjuvant" chemotherapy rather than undergoing upfront surgical debulking, although these patients seem to have a poorer prognosis as a result. In these situations, may be a survival benefit to proceeding with surgical debulking followed by completion of adjuvant chemotherapy after such a debulking operation, similar to that noted in patients who undergo a second attempt at debulking surgery after being non-optimally debulked at their initial operation.

Though women with early-stage EOC can be cured, most women are diagnosed at an advanced stage and experience recurrence of their disease despite surgery and chemotherapy as noted above. Patients with recurrent EOC are not curable. They typically die from sequelae of bowel obstruction after their disease becomes resistant to chemotherapy, on average 2-4 years after diagnosis.



Postmenopausal Bleeding and Endometrial Carcinoma

Postmenopausal Bleeding & Endometrial Carcinoma Objectives:

At the end of the seminar, students should be able to:

1. Define postmenopausal bleeding
2. List the causes of postmenopausal bleeding
3. Describe the management of the patient with postmenopausal bleeding
4. List the risk factors for endometrial carcinoma
5. Describe the symptoms and physical findings of a patient with endometrial cancer
6. Describe methods to diagnose endometrial carcinoma
7. Describe the impact of staging on the management and prognosis of endometrial carcinoma
8. Describe the management of the patient with endometrial carcinoma

Last revised: July 2019

POSTMENOPAUSAL BLEEDING (PMB)

Postmenopausal bleeding is any vaginal bleeding that occurs at least one year following the cessation of spontaneous menstruation. Withdrawal bleeding lasting 3-4 days commonly occurs in patients treated with cyclic hormone replacement therapy (mimics premenopausal menstrual cycles), but is less common with continuous combined hormone replacement therapy. Other causes of irregular bleeding are listed below:

Etiology of Postmenopausal Bleeding

- Endometrial and/or vulvovaginal atrophy (most common causes)
- Exogenous estrogen
- Endometrial cancer (10-15%)
- Endometrial hyperplasia
- Endometrial or cervical polyps
- Cervical ectropion
- Other gynecologic malignancies
    - Carcinoma of cervix
    - Carcinoma of vagina
    - Uterine sarcoma
    - Fallopian tube/ovarian cancer
- Coagulation disorder

Diagnostic Evaluation

Though most women with PMB will have endometrial and/or vulvovaginal atrophy or some other benign underlying cause, all women with PMB should be evaluated to rule out endometrial cancer, since 10-15% of women with this symptom will have the disease. The risk of harbouring endometrial cancer increases with age from a low of 10% in the immediately postmenopausal cohort to 50% in patients 80 years or older.

Initial evaluation should include a relevant history and physical examination, which must include a pelvic examination. An endometrial biopsy should be performed and any obvious lesion of the cervix or vagina should be biopsied directly. **Endocervical curettage (ECC)** should be considered if there is clinical concern regarding the possibility of cancer within the endocervical canal.

Endometrial sampling should be routinely considered for patients with PMB to rule out endometrial cancer. Contemporary endometrial biopsy is preferentially carried out in the office; a variety of sampling devices are available and the technique can be facilitated by the use of local anaesthesia and anti-inflammatories (to minimize discomfort) and/or misoprostol (to minimize cervical stenosis). Endometrial biopsies can also be obtained using hysteroscopy and the traditional dilatation and curettage (D+C) under general anesthesia, if necessary due to cervical stenosis or patient discomfort. If the office endometrial biopsy is negative (or if the specimen is inadequate) and the patient continues to have vaginal bleeding, a formal D+C (+/- hysteroscopy) is indicated.

Pelvic ultrasound can occasionally be useful as an adjunct to pelvic examination and endometrial sampling in the evaluation of women with PMB. This test is most useful in women where adequate endometrial sampling is not feasible without invasive methods (ie D+C +/- hysteroscopy). Ultrasound performed using an endovaginal probe can serve two purposes: to rule out the presence of other pelvic pathology not detected on pelvic examination (e.g. ovarian neoplasms) and to directly measure the endometrial thickness as a surrogate for the likelihood of an underlying endometrial carcinoma. An endometrial thickness of 5mm or more is considered abnormal. Although women with a thin endometrium rarely have an underlying type I endometrial cancer, women with type II endometrial cancer may have an endometrial thickness less than 5mm. A thickened endometrium is not always indicative of an underlying endometrial cancer, as large endometrial polyps, submucous fibroids, characteristic tamoxifen effects (subendothelial cystic hyperplasia), or adenomyosis may result in an apparent thickened endometrium on ultrasound. As a result of this lack of diagnostic sensitivity and specificity, ultrasound is not acceptable as an alternative to pelvic examination or endometrial sampling for ruling out endometrial cancer in patients with PMB.

ENDOMETRIAL CANCER

Epidemiology

Endometrial cancer is the most frequent gynecologic malignancy in North America and the fourth most common cancer in women. The median age at diagnosis is 61 years. 90% of cases occur in women older than 50 years; less than 5% of women are younger than 40 years. The incidence is dependent on age with 12 cases per 100,000 women at 40 years of age and 84 cases per 100,000 at 60 years.

Risk Factors

As suggested above, excessive estrogen unopposed by progesterone is associated with most of the clinical risk factors linked to endometrial carcinoma (obesity, nulliparity, early onset menarche, late onset menopause, unopposed estrogen replacement therapy – see table below for degree of risk associated with each). Obesity facilitates the development of endometrial carcinoma as the result of increased endogenous estrogen levels due to conversion of androstenedione to estrone by the enzyme aromatase in adipose tissue.

Tamoxifen, a synthetic antiestrogen commonly used in the treatment of breast cancer patients has been shown to have estrogenic effects on the endometrium; however the risk of endometrial cancer is minimal and routine screening is not warranted in these women. Women taking tamoxifen who develop abnormal vaginal bleeding should undergo appropriate evaluation to rule out endometrial cancer (see above).

Rare risk factors are ovarian estrogen-secreting neoplasms (granulosa – theca cell ovarian tumors), other ovarian neoplasms (endometrioid epithelial ovarian cancer) and inherited genetic predisposition such as hereditary non-polyposis colorectal cancer syndrome (HNPCC, also known as Lynch Syndrome). Women who have had at least one full-term pregnancy and those who have taken oral contraceptives have a lower risk of developing endometrial cancer, presumably through reduction of exposure to unopposed estrogen levels.

Table 1: Estimated Risk Ratios for Endometrial Cancer

Risk Factor	Risk Ratio
Overweight†	
9-23 kg (20-50 lb)	3.0
>23 kg (50 lb)	10.0
No children (vs 1 child)	2.0
No children (vs 5 children)	5.0
Late menopause (age, 52 yr or later vs <49 yr)	2.4
Diabetes mellitus	2.7
Unopposed estrogen therapy	6.0
Tamoxifen therapy	2.2
Use of combination oral contraceptives	0.5

Source: Rose et al., NEJM, 1996.

Prototypical Clinical Features

There are two distinct clinical phenotypes of endometrial carcinoma.

- **Type I** is typically related to unopposed estrogen, either endogenous (obesity or ovarian pathology) or exogenous (unbalanced estrogen supplementation). Women with type I endometrial cancers typically have clinical risk factors including obesity, nulliparity, and late onset menopause. These tumours are commonly diagnosed at an early stage because most women experience abnormal vaginal bleeding that is amenable to definitive investigation early during the course of the disease (office endometrial biopsy). Type I endometrial cancers are usually characterized by histology consistent with endometrioid adenocarcinoma that are often well-differentiated and only superficially invasive tumours at diagnosis. The prognosis for women with these tumours is usually excellent since they are often cured with definitive surgery alone.
- **Type II** is characterized as non-estrogen related, and seem to have a different pathogenesis according to mutation analyses (p53 mutations common). Women with type II cancer are typically normal weight, multiparous and may be African American. Women with these tumours often present with advanced stage disease or more aggressive underlying histologic subtypes (papillary serous or clear cell carcinoma, deeply invasive and poorly differentiated endometrioid adenocarcinoma), which may not have abnormal vaginal bleeding early in their course. The prognosis for type II endometrial carcinoma is typically worse than type I with a poor five-year survival.

Some women with endometrial cancer present with a watery vaginal discharge but this is uncommon. Pelvic examination usually shows a normal sized uterus unless there are associated fibroids, pyometra, or an underlying uterine sarcoma (see pathology below).

Pathology

Preinvasive Lesions

There are two preinvasive lesions that can precede the diagnosis of Type I endometrial cancer: *Endometrial hyperplasia without atypia* and *EIN (Endometrioid Intraepithelial Neoplasia)*, the latter can also be referred

to as Atypical Endometrial Hyperplasia. These precancerous lesions develop due to exposure of the endometrium to unopposed estrogen. Approximately 30% of patients diagnosed with EIN will have an endometrial cancer on the hysterectomy specimen and the remainder have a 45 fold elevated cancer risk. A component in the pathway to malignancy of the high-grade histologic subtype serous endometrial cancer is *EIC (endometrial intraepithelial carcinoma)*. This lesion is treated similar to invasive serous endometrial cancer due to its malignant potential.

Adenocarcinoma

Endometrial cancers are malignancies of the glandular epithelium of the inner lining of the uterus. The most common type of endometrial cancer is endometrioid adenocarcinoma. Other histologic types such as (papillary) serous, clear cell carcinomas and carcinosarcomas, which have more aggressive behavior, account for 10-15% of endometrial cancers. Endometrioid adenocarcinomas may have areas of squamous metaplasia (adenoacanthoma) or areas of squamous carcinoma (adenosquamous carcinoma). A less common type is mucinous adenocarcinoma.

Uterine Sarcomas

Uterine sarcomas are rare and account for less than 4% of cases of uterine malignancies. They arise from stromal components of the uterus, either the endometrial stroma or the mesenchymal or myometrial tissue. Sarcomas tend to be more advanced at the time of diagnosis and are more likely than endometrial cancers to disseminate hematogenously (e.g. lungs). As a result, they have a lower five-year survival than endometrial cancers (approximately 35%).

The three major types of uterine sarcoma are:

1. *Leiomyosarcoma*
2. *Endometrial stromal sarcoma*
3. *Undifferentiated sarcoma*

Screening

To date, there is no documented benefit associated with any screening modality for endometrial cancer in any patient population. Specifically, pelvic ultrasound should NOT be used as a screening test for endometrial cancer (unacceptably high level of false positive scans resulting in patient morbidity from resulting further investigation/surgery without evidence of survival benefit).

Staging (determining extent of disease spread) & Prognostic Factors

Determining the extent of cancer spread allows the clinician to predict the likely prognosis of an individual patient relative to others with the disease, since surgical stage is the most important predictor of survival for patients with endometrial cancer. Only after appropriate staging may optimal recommendations be made regarding the role, if any, for post-operative (adjuvant) radiation and/or chemotherapy.

Like all gynaecologic malignancies except cervical cancer, endometrial cancer is surgically staged at the time of definitive surgery (see treatment below) according to the FIGO staging system (see below for the current uterine cancer staging classification and associated survival rates and relative incidences).

Staging for Carcinoma of the Corpus Uteri

Table 2: Carcinoma of the corpus uteri.

Stage		5-year survival	Proportional incidence
Stage I	Tumor confined to the corpus uteri	91%	81%
Stage IA	No or less than half myometrial invasion	88%	
Stage IB	Invasion equal to or more than half of the myometrium	81%	
Stage II	Tumor invades cervical stroma, but does not extend beyond the uterus	67%	11%
Stage III	Local and/or regional spread of the tumor		6%
Stage IIIA	Tumor invades the serosa of the corpus uteri and/or adnexae	60%	
Stage IIIB	Vaginal and/or parametrial involvement	41%	
Stage IIIC **IIIC1** **IIIC2**	Metastases to pelvic and/or para-aortic lymph nodes Positive pelvic lymph nodes Positive para-aortic lymph nodes w/ wo positive pelvic lymph nodes	37%	
Stage IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases		2%
Stage IVA	Tumor invasion of bladder and/or bowel mucosa	20%	
Stage IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes	5%	

Source: International Journal of Gynaecology and Obstetrics 105 (2009) 103–104.

Note: Positive cytology has to be reported separately and does not change the stage.

Besides stage, multiple other prognostic factors have been identified as independent predictors of patient prognosis including histologic subtype (endometrioid better than papillary serous or clear cell carcinoma, tumour grade (well-differentiated [=grade 1] better than moderately differentiated [=grade 2] better than poorly differentiated [=grade 3]), and patient age. The presence of malignant cells in peritoneal cytology or the presence of tumour within capillary-like spaces (CLS - also known as lymph vascular space involvement or LVSI) within the myometrium are not independent prognostic factors, however when

combined with other negative prognostic factors such as deep myometrial invasion and/or high grade often predict a poorer prognosis that merits consideration of adjuvant therapy.

Treatment

Patients with endometrial cancer typically undergo (simple) total hysterectomy, bilateral salpingo-oophorectomy, and surgical staging at the time of definitive primary surgery. Surgical staging (see above) includes thorough inspection and palpation of all the peritoneal surfaces of the abdomen and pelvis with biopsy of any suspicious lesions identified, peritoneal cytology collection, and sampling of pelvic and para-aortic lymph nodes. The incorporation of sentinel lymph node biopsies to assess spread of disease to the lymph nodes is being incorporated into the paradigm of treatment. There is controversy regarding the role of omentectomy and complete pelvic and para-aortic lymphadenectomy as part of surgical staging for endometrial cancer, although this is routinely performed in many centres across North America, especially for women with high-risk histologic subtypes (see pathology above). Increasingly, a laparoscopic approach is being utilized to perform definitive surgery for endometrial cancer, as this has recently been associated with an improvement in patient quality of life.

After completion of definitive surgery, the relevant prognostic factors according to the final pathology report are reviewed to determine the role, if any, for post-operative (adjuvant) therapy.

- **Most patients with stage I disease** require no further therapy, as they have few negative prognostic factors and an excellent prognosis is expected. However, some subgroups of stage I patients may benefit from adjuvant radiation therapy and/or chemotherapy as they have a high risk of disease relapse after surgery alone including those with high-risk histology (papillary serous or clear cell carcinoma) or those with multiple poor prognostic factors such as deep myometrial invasion, high grade endometrioid adenocarcinoma, LVSI (lymph vascular space involvement) and older patient age, especially if they have not undergone complete lymphadenectomy as part of their definitive surgical procedure (since these categories of patients have a high risk of harbouring microscopic metastatic disease in pelvic and/or para-aortic lymph nodes).
- **Patients with stage II disease** typically receive adjuvant radiation therapy that often includes external pelvic radiation and vaginal brachytherapy to reduce the likelihood of disease recurrence within the pelvis (due to undetected microscopic lymphatic metastases) and the vaginal vault.
- **In patients with stage III disease,** treatment is highly individualized based on the particular poor prognostic factors present and typically consists of a combination of radiation therapy (pelvic +/- vaginal brachytherapy) with either systemic chemotherapy.

For women with disseminated disease at presentation (stage IVB) or recurrent disease treatment is individualized with the intent to provide optimal palliation of symptoms rather than cure. Definitive surgery may not be undertaken in this patient population, to avoid its inherent morbidities. Radiation therapy is often used for palliation of vaginal bleeding with excellent results. Systemic therapy with progestational hormones (Provera, Megace), or combination chemotherapy (Carboplatinum/Taxol or Adriamycin) can be considered, and has recently been associated with improvements in length of survival. Well-differentiated tumors positive for estrogen and progesterone receptors are most likely to respond to hormonal therapy.



Menopause and Urogenital Aging

Menopause and Urogenital Aging Objectives:

At the end of the seminar, students should be able to:
Menopause:

1. Describe the stages and physiologic changes in menopause.
2. Describe the health issues associated with the perimenopause including abnormal uterine bleeding.
3. List the validated symptoms of menopause. and their treatments.
4. Describe the long-term health changes associated with postmenopause.
5. Describe the management of peri- or postmenopausal women including:
    - Lifestyle changes
    - CAM alternatives
    - Non-hormonal medications
    - Bone health
    - Sexuality
    - Psychosocial health
    - Options for hormone replacement therapy
6. Counsel a patient regarding the risks and benefits of hormone replacement therapy.

Urogenital Aging:

1. Know the predisposing risk factors for pelvic organ prolapse and urinary incontinence.
2. Describe the signs and symptoms of pelvic organ prolapse.
3. Describe the physical findings related to:
    - Cystocele
    - Rectocele
    - Enterocele
    - Vaginal vault or uterine prolapse
4. Describe nonsurgical and surgical treatments for pelvic organ prolapse.
    - Pessary
    - Surgery
5. Know the 4 basic types of urinary incontinence
    - Stress incontinence
    - Urge incontinence
    - Overflow incontinence
    - Functional incontinence

Continued on next page…

6. Describe the signs and symptoms associated with the different types of incontinence.
7. Describe the evaluation of urinary incontinence:
    - Urine testing: culture and cytology
    - Post-void residual
    - Cystoscopy
    - Urodynamic testing
8. Describe the treatments (nonsurgical +/- surgical) for the different types of urinary incontinence

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MENOPAUSE

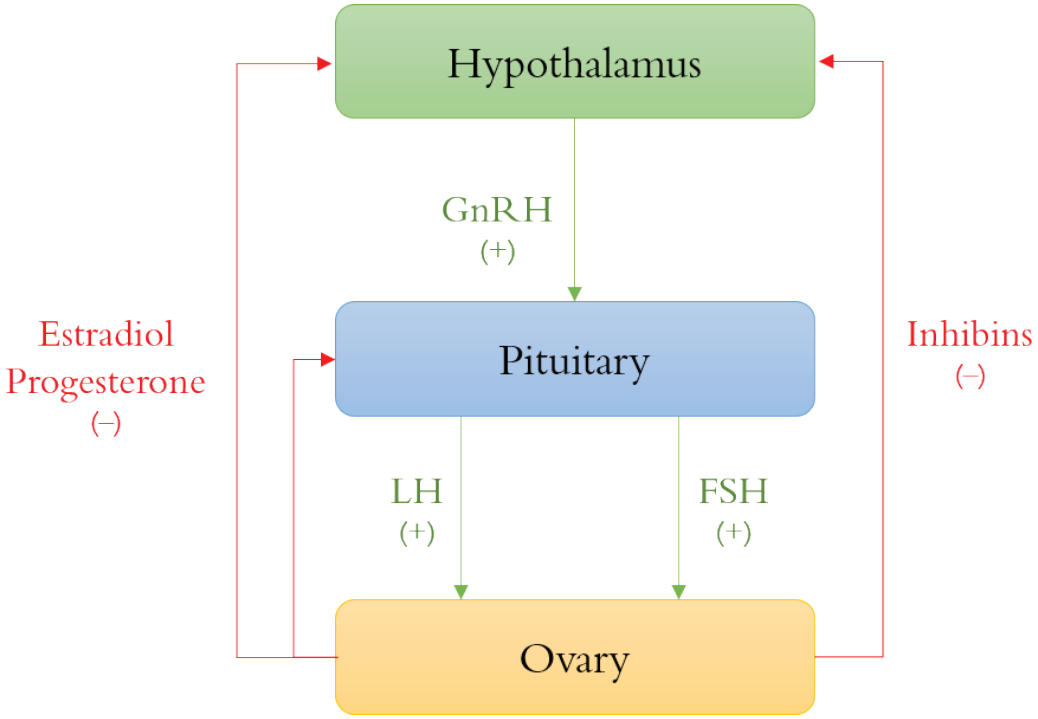
- "The last menstrual period"
- Made retrospectively after 12 months of amenorrhoea
- Average age 51.5 (range 42-58) years
- Occurs because of depletion of oocytes in the ovaries and CNS aging
- Reflects reproductive aging not equal to chronologic age
- Women born with 700,000 follicles.
- By menopause few follicles remain
- <400-500 ovulations over lifetime
- Most lost to atresia-quality declines with age
- Smokers' menopause is 2 years earlier

Premature ovarian failure or Premature ovarian insufficiency

- In 1% of the population <age 40
- Etiology
    - Genetic e.g. (XO) or Turner's syndrome, mosaicism XO/XX etc. fragile X
    - Latrogenic- chemotherapy, radiation and surgery (most common cause)
    - Autoimmune
    - Infectious
    - Metabolic-galactossemia
    - Environmental toxins
    - Most common spontaneous reason idiopathic or 90% unknown

Perimenopause or menopausal transition refers to 4-5 years when hormones wax and wane prior to menopause and ends 12 months after FMP (final menstrual period).

Figure 1. Hypothalamic-pituitary-ovarian axis.



Reproductive Phase Physiology

- Normal menses follow follicular (proliferative), ovulatory and luteal or secretory phases
- Resting primordial follicles develop from arrested state of prophase of meiosis 1 become either a dominant follicle or atretic via increasing FSH
- Hallmark is regular, predictable cycles = ovulatory cycles
- Cells around the egg (granulosa cells) produce estrogen after stimulation of FSH. Increasing estrogen causes LH surge
- LH surge triggers ovulation from dominant follicle
- Location of dominant follicle in ovary becomes corpus luteum after ovulation
- Corpus luteum produces progesterone
- Inhibin B secreted from granulosa cells
- Inhibin B and FSH have a closed-loop feedback system during the first half of the cycle with inhibin B providing fine-tuning regulation of FSH levels
- Estradiol provides the other negative feedback signal for pituitary hormones.
- 95% of estradiol (E2) comes from dominant follicle
- Estrone (E1) is derived from metabolism of estradiol and peripheral conversion of androstenedione in adipose tissue and muscle
- Other major estrogen is estriol (E3) - breakdown product of E1 and E2
- Newly discovered estrogen E4-estretol in fetus
- Levels of E2 fluctuate between 37-370 pmol/l in follicular phase to 730-2,930 pmol/l at mid-cycle and 730-1250 pmol/L during luteal phase
- AMH (Antimullerian hormone) produced by granolosa cells of ovarian follicles is marker of ovarian reserve. Can be measured at any time during the cycle or while on oral contraceptive
- Estrogen affects target tissues via the specific alpha or beta receptors for estrogen and ultimately gene stimulation or suppression and via co-factors
- Estrogen receptors-α are primarily expressed in organs of the reproductive system (eg, uterus, ovary, and breast) but also found in liver, bone, adipose tissue, and brain. Estrogen receptors-β more prevalent in other tissues (eg, colon, vascular endothelium, lung, bladder, and brain). Both ER-α and ER-β present in the ovary, the central nervous system, and cardiovascular tissues. Estradiol binds to both
- SERMS are selective estrogen receptor molecules that bind selectively to alpha or beta receptors and have various effects based on the individual tissue stimulated or suppressed examples are tamoxifen, raloxifene, basodoxifene, ospemifene, clomiphene

Late Reproductive Phase

- Hallmark is changes in menstrual cycle flow and length
- FSH and E2 variable
- AMH and inhibin B low
    - Acceleration of follicular atresia occurs at age 37-38
- FSH > 10m IU/ml on day 3
    - Indicates decreased follicular cohort, CNS aging and waning fertility.
- Increased FSH sustains follicle development and ovulation initially.
- Recruitment of follicles occurs earlier (actually in luteal phase of previous cycle) as FSH levels rise and cycles shorten.

- Increased stimulation of follicles and temporary higher levels of estrogen cause symptoms of hyperestrogenism:
    - Sore breasts
    - Anovulation
    - Bloating
    - Irritability
    - Menorrhagia
    - Growth of fibroids
    - Nausea
    - Increase in mirgraines

Menopausal Transition: (Perimenopause)

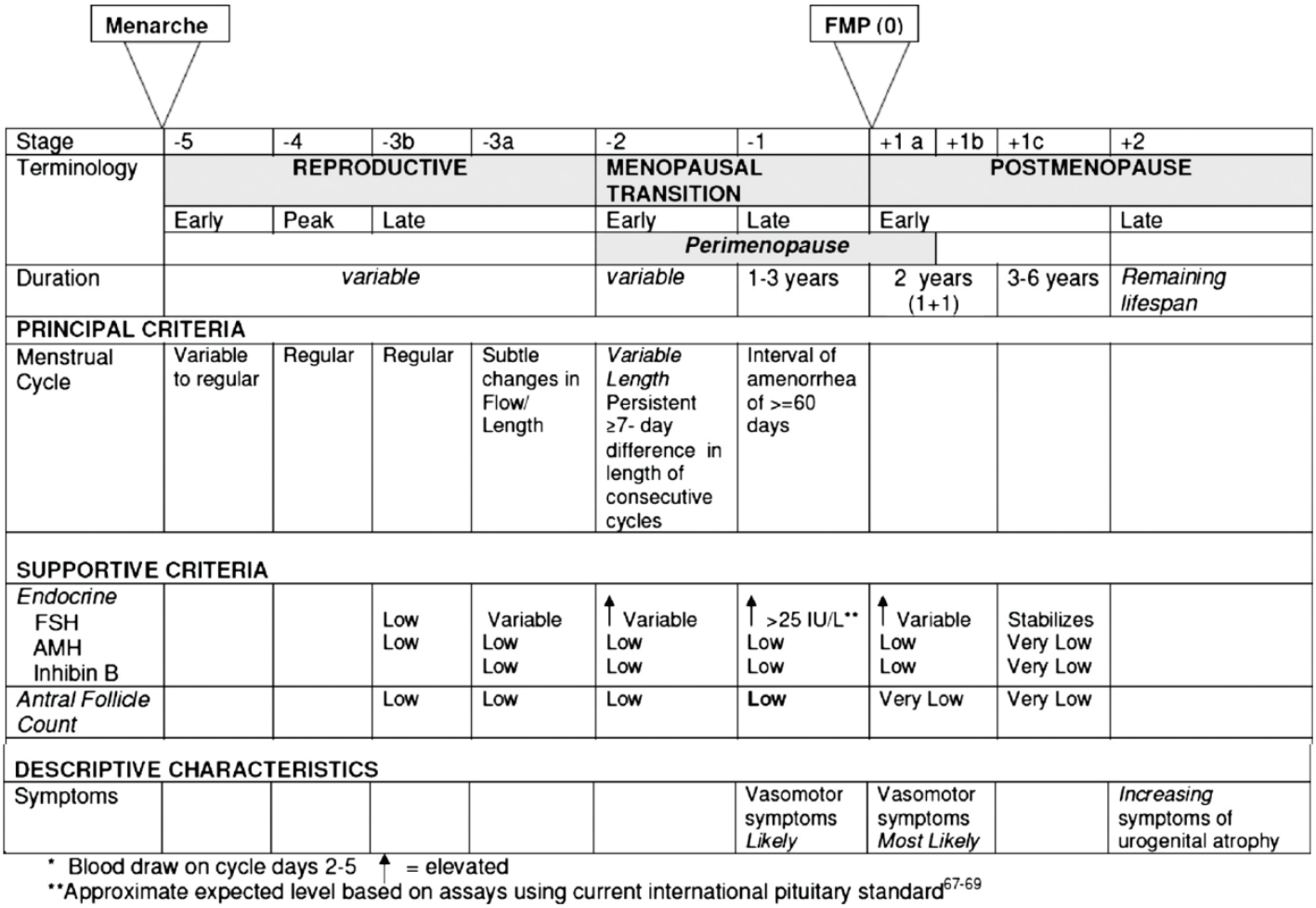
- Characterized by erratic hormonal secretion, cycle irregularity and finally cessation of menses.
- Menses may be heavier, closer together, further apart, lighter or cease suddenly.
- Heavier and erratic bleeding needs to be further investigated to rule out significant pathology.
- Any bleeding one year after the last menses needs to be investigated.
- Change in menstrual cycle length of at least 7 days reflects formal onset of transition
- Late in transition ovulation more irregular
- More anovulatory cycles occur
- Estrogen and progesterone production disrupted
- Women have irregular bleeding and oligomenorrhea
- **Contraception still advised**
- Major source of estrogen declines 6 months before LMP
- Progesterone production is low during anovulatory cycles
- Testosterone is unchanged or slightly decreased
- Steroid Hormone Binding Globulin (SHBG) decreases by 40% before menopause
- Adrenal hormonal contribution declines significantly with age

Postmenopausal Stage

- Can only diagnose last menstrual period in retrospect.
- Endocrine findings are:
  ↑ FSH, ↑ LH (10-15X)
- Loss of negative feedback
  ↓ estradiol (37-135 pmol/L) - 10% level of reproductive women
- Estrone becomes dominant estrogen
- Estrone produced by metabolism of adrenal precursor steroids in peripheral fat (higher in obese)
- No ovulation, no progesterone

Straw Stages of Menopause: Stages of Reproductive Aging Workshop +10 convened in 2010 to standardize and update nomenclature. FMP refers to Final Menstrual Period-time 0

Figure 2: The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women.



Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine										
FSH			Low	Variable	↑ Variable	↑ >25 IU/L**	↑ Variable		Stabilizes	
AMH			Low	Low	Low	Low	Low		Very Low	
Inhibin B			Low	Low	Low	Low	Low		Very Low	
Antral Follicle Count			Low	Low	Low	**Low**	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

* Blood draw on cycle days 2-5 ↑ = elevated
**Approximate expected level based on assays using current international pituitary standard[67-69]

Adapted from Harlow et al, Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging, Menopause, Vol. 19, No. 4, 2012.

Validated Symptoms and Signs and Health Risks of Hypoestrogenism

Hot flushes and night sweats (Vasomotor symptoms)	Depression, Anxiety and Irritability
Vaginal symptoms (vaginal dryness, dyspareunia, itching)	Memory loss
Trouble sleeping	Joint pains
Urinary frequency incontinence and urgency (stress peaks in 40's)	Weight gain
Sexual dysfunction	Fatigue
	Decreased sense of well-being

Hot Flashes

- Physiologic event
- Vasomotor symptoms and hot flushes and night sweats
- Sudden feeling of warmth or burning arising in the face, neck or chest - may be associated with anxiety, panic, palpitations, crawling of skin
- Duration averages 1-5 minutes, may occur multiple times a day and night
- Affects quality of life
- Maximal in late menopausal transition and early menopause
- Up to 75% of women - 25% severe
- Current research - average duration over 7-11 years, 10-15% into 70s
- More common in African-Americans and Hispanic, then Caucasian, fewest in Asian
- Increased by smoking, obesity, alcohol lack of physical activity and lower socioeconomic status
- Severity may be genetically determined
- Core temperature rises before flash
- Objectively measured by peripheral rise in skin temperature and increase in heart rate
- Body attempts to cool itself by peripheral vasodilatation
- Shivering can occur afterwards and core temperature decreases
- Represents a narrowing of thermoregulatory centre in anterior hypothalamus that responds to temperature changes
- Hypothalamic temperature also impacted by alpha adrenergic neurons
- New research postulates a model of (GnRH) (LH pulse generator consisting of KNDy neurons -kisspeptin, neurokinin B, and dynorphin) found in arcuate nucleus that connect to warm-sensing neurons in median preoptic nucleus to drive hot flashes.
- Classical symptoms in late 40's-50's – no need to investigate
- Differential diagnosis:
    - Hyperthyroidism
    - Infections
    - Malignancy: carcinoid, leukemia, insulinoma, lymphoma, pheochromocytoma
    - Medications such as nitrates, tamoxifen, aromatase inhibitors
- Women with flashes have less work productivity, lower levels of health, quality of life
- Vasomotor symptoms associated with memory changes, depression and sleep problems (increased white matter hyperintensities)
- Flashes that have early onset with persistent high frequency are associated with increased endothelial reactivity and increased cardiovascular health risk
- Hormone therapy most effective treatment, other treatments-SSRI's, clonidine, gabapentine, CBT and yoga have some efficacy

Decline in Fertility

- Occurs around age 35; more rapid after 37,
- Increased incidence of:
    - Spontaneous abortion (50% by age 45)
    - Chromosomal abnormalities in the fetus
- Decreased antral follicle count, decreased AMH and increased day 3 FSH

Vaginal Symptoms (Genitourinary Syndrome of Menopause-GSM)

- Changes to vagina, vulva, urinary tract and pelvic floor muscles as a result of decline in estrogen
- Symptoms - Dryness, discomfort, itching, odour, dyspareunia, urgency, recurrent UTIs
- Reported by 50% within 2 years of menopause, 70% by age 70
- Persists or worsens with age, may occur before LMP
- Decreased thickness of stratified squamous epithelial layer of vagina from multiple cells to one or two cell layers
- Tissues more vulnerable to infection from normal mixed organisms of vagina and rectum as lactobacilli decline and flora more diverse
- PH rises
- Vaginal lubrication affected by decreased transudation across vaginal wall and decreased secretions from endocervical, and Bartholin's glands
- Decreased vaginal blood flow and hyalinization of collagen, fragmentation of elastin and proliferation of vaginal connective tissue changes vagina to elastic organ to more rigid structure
- Introitus narrows, vagina shortens and cervix becomes flush with vaginal wall
- On examination
    - Pallor, dryness and decreased rugosity of the vaginal mucosa
    - Vaginal tissues become fragile and may easily bleed with touch
- Most common cause of postmenopausal bleeding
- A treatable cause of sexual pain; impacts sexual function and quality of life
- Lubricants, moisturizers, local estrogens best treatments-systemic HT also benefits

Urinary Incontinence

- Stress, urgency, frequency, dysuria, nocturia and incontinence
- Not clearly correlated with menopause
- Stress and urge increase ages 45-55
- Prevalence 5% severe and 60% mild
- Bladder and urethra have estrogen receptors and tissues thin after menopause
- Greater problem in obese, diabetics, parous, depressed, weight gain, hysterectomy and family history
- Recurrent urinary tract infections may be related to decreased levels of estrogen and anatomic and microbial causes
- See syllabus section on Urogenital Aging below

Sleep Problems

- 46% aged 40-54 and 48% ages 55-64 report sleep problems
- Perimenopausal women and postmenopausal women sleep less and more frequent insomnia
- May be age-related or due to sleep disorders
- Sleep disorders include:
    - Sleep apnea - increased around menopause and with obesity
    - Restless leg syndrome
- Most women require 6-9 hrs
- May be related to hot flashes
- During first half of night sleep disruption occurs following a hot flash

- During the second half with REM sleep, thermogenesis is suppressed
- Sleep problems are associated with:
    - Somatic and mood/cognition symptoms
    - Muscle aches
    - Dysphoria
    - Irritability
    - Fatigue
    - Inability to concentrate
- Linked to:
    - Chronic illness
    - Fibromyalgia
    - Cardiac problems
    - Mood disorders
    - Work-related injuries
- Therapies include:
    - Regular schedule for bed
    - Avoiding screens prior to bed
    - Cool dark environment
    - Relaxation techniques, sleep app's
    - Cognitive therapy
    - Avoidance of caffeine, alcohol, and exercise, heavy meals, nicotine close to bed
    - Yoga, acupuncture, cognitive behavioural therapy
    - Estrogen not primary therapy but may help
    - Prescription therapies-sedatives and hypnotics

Mood Changes

- Depressive symptoms occurs in up to 45-65% of peri- and postmenopausal women.
- Common symptoms include:

Irritability	Fatigue
Mood swings	Decreased memory and concentration
Sadness	Depression, anxiety, stress
Tearfulness	Decreased sense of well-being
Insomnia	

- First episode of depression may occur and is more common during perimenopause
- Mood more stable post-menopausally
- Women with history of depression during times of hormonal variability such as premenstrual or postpartum may be more vulnerable to major depression around menopause
- Patients with more vasomotor symptoms have an increase in new mood disturbance
- Estrogen has effects on serotonergic and catecholaminergic systems
- May require evaluation by psychiatrist if symptoms persist
- Estrogen not recommended for primary treatment of depression but may help during perimenopause and as a co prescrtiption with SSRI's and SNRI's

Weight Gain

- Metabolism slows at menopause
- Weight redistributes onto abdomen, increased insulin resistance
- Average weight gain 2-4 kg
- Lean body mass decreases with age
- >40% of Canadian women overweight, prevalence of obesity peaks ages 55-59
- Also associated with sleep deprivation
- More health consequences-CVD, DM, high BP, osteoarthritis breast CA, premature mortality
- Have to exercise 300 minutes/week to maintain weight

Cognitive Changes

- Difficulty concentrating and remembering common, especially name finding
- More evidence recently of specific not global declines at menopause
- Estrogen has effects on neurotransmitter systems and blood flow to the brain which could influence mental processes

Joint Pains and Stiffness

- Common symptoms
- If severe or associated with swelling and erythema - rule out other causes

Other symptoms associated with hypoestrogenism and aging

Skin changes	Headaches
Palpitations	Changes in hair, nails, teeth and gums
Formication (itching) - crawling skin	Dry eyes, burning mouth syndrome

Perimenopausal Symptoms - Abnormal Uterine Bleeding

- 90% of women have 4-8 years of cycle change ending in amenorrhoea
- Includes:
    - Change in amount of flow both lighter (70%) and
    - Heavier (18%)
    - Shorter or longer cycle length
    - Skipped periods
    - Sudden stoppage (12%)
- Rule out organic pathology if heavy and continual or if bleeding occurs more than one year after LMP: (PALM-COIEN) - (**P**olyp, **A**denomyosis, **L**eiomyoma, **M**alignancy and hyperplasia) - structural causes and other - (**C**oaguation, **O**vulatory, **E**ndometrial Iatrogenic, **N**ot yet diagnosed)
    - Examine patient and rule out other organ systems (bladder and rectum)
    - Rule out pregnancy first for amenorrhoea
    - CBC, TSH
    - Pap
    - Cultures if new sexual partner
    - Endometrial biopsy

    - Ultrasound
    - Hysterosonogram or hysterocopy
- Eventually periods stop as a reflection of low estrogen levels

LONG-TERM HEALTH CHANGES ASSOCIATED WITH HYPOESTROGENISM

Sometimes difficult to differentiate effects of aging from effects of decreased estrogen

Bone

- Osteoporosis defined as bone mineral density (BMD) greater than 2.5 standard deviations below the mean of young, healthy adult women or clinical fragility fracture
- Quality (microarchitecture) and quantity of bone are affected
- Menopause associated with rapid bone loss due to loss of estrogen-mediated inhibition of bone resorption without compensatory increase in bone formation
- Advancing age also increases the prevalence of osteoporosis
- Other significant risk factors include:
    - Age
    - History of previous fractures
    - Family history
    - X-ray changes of osteopenia
    - Smoking
    - Low BMI
    - Use of medications:
        - Anti-epileptics
        - Long term glucocorticoids
        - Aromatase inhibitors
        - GNRH agonists
        - Heparin
        - Immunosuppressives
        - Cytotoxic agents
    - Hyperthyroidism
    - Alcoholism
    - Malabsorption
- In US white women >age 50 have a 40% risk for osteoporotic fracture in their lifetime
- 2/3 of fractures occur after age 75
- 90% of hip and spine fractures in elderly white women are due to osteoporosis
- Bone loss accelerates at menopause up to 3-5% loss per year then but slow loss may continue yearly
- 1000 IU Vitamin D recommended for all menopausal women
- Calcium 1250 mg/day preferably via diet (300 mg in each dairy serving-milk, cheese, yogurt)
- On line Risk calculators for fracture include FRAX and CAROCv

Cardiovascular Disease (CVD)

Number 1 cause of mortality in both men and women

- Rare for a woman to have a heart attack before menopause
- By age 65 incidence of heart disease in women is the same as men
- Heart disease accounts for 31% of all deaths in women
- Higher incidence and death from heart failure
- Risk associated with:
    - Family history
    - Smoking
    - Hyperlipidemia
    - Hypertension
    - Diabetes
    - Sedentary lifestyle
    - Metabolic syndrome [central obesity, elevated TG (>1.7 mmol/L), low HDL (<1.3 mmol/L) and elevated BP (>130/85)]
    - Poor exercise capacity
    - Subclinical atherosclerosis
    - Obstetrical history-IUGR, pre-eclampsia
    - Early and persistent vasomotor symptoms
- **Premature menopause and early menopause** associated with 2-3X increased MI and increased CHF if not replaced up to at least age 51
- Menopause can be used as marker to optimize healthy living
- Weight control, regular exercise, stopping smoking can reduce death from CVD
- Menopause results in lipid changes:
    - LDL-C and very low LDL-C increase
- Changes in LDL-C and apolipoprotein B occur independently during menopause transition
- These can be reversed by lifestyle changes
- Also direct vascular effects of **hormone change**:
- Estrogen and Progesterone receptors found in vascular tissues including coronary arteries.
- **Coagulation balance** may also be involved:
    - Fibrinolytic factor (antithrombin 3 and plasminogen) increase as well as procoaguation-factor 7 and fibrinogen
    - Nitric oxide increases and ACE decrease
- Even non-obese have decrease in CHO tolerance as insulin resistance increases
- **Hypothesis - that benefits of estrogen may be confined to a "window of opportunity" while the vessels are healthy**
- Higher incidences of both stroke and thrombotic events with age
- Higher doses of estrogen and oral route also increase risk of thrombosis and strokes

Source: NAMS Guideline July 2017 Menopause

Sexual Dysfunction

- Increases with age
- Validated menopausal symptoms
- Distressing sexual problems peak ages 45-64
- Sexual function is multi-factorial
- Major categories of sexual dysfunction:
    - Decreased desire, and or arousal
    - Increased pain
    - Inability to have orgasm
- Multifactorial Include psychological, sociocultural, interpersonal and biologic factors
- These include lack of partner, illness or impotence of partner, lack of good health, changes in body image, weight gain, incontinence, sleep disturbances stressors and medications
- At menopause, decreased vascularity, lubrication and vaginal atrophy may cause pain, decreased arousal, impaired touch and vibration impairing orgasm and decreased satisfaction
- Bilateral oophorectomy (surgical removal of ovaries decreases circulating testosterone levels by 50%) and abrupt menopause by chemotherapy cause more severe symptoms
- Testosterone contributes to sexual drive in women. Levels decline slowly with age
- Currently no approved treatment for decreased desire in postmenopausal women in Canada
- Flibanserin approved in Canada and US to improve sexual desire in premenopausal women – daily dosage 200mg qhs increases desire in about 30%
- Low dose transdermal testosterone increases number of satisfying sexual events per month by 1-2 at 300 microgram level – not approved by Health Canada
- Off label testosterone use available if troubling sexual decline only related to menopause
- Levels have to be monitored-works in 30%-no regulated products for women

Dementia

- Higher incidence in women
- Not one disease (Alzheimer's, vascular etc.)
- Change in memory common complaint not verified objectively
- Relates to stressors, lack of sleep, multi-tasking and hot flashes
- Exact causal relationship to estrogen lack is controversial
- Estrogen improves blood flow to brain and increases branching of neurons
- WHIMS study suggested women ages 65-69 given HRT had worsening of cognitive decline
- Previous observational studies suggested estrogen administered from the time of menopause had a protective effect
- KEEPS –MRI of brains in women on transdermal hormones maintained dorsofrontal anatomy
- Controversy not yet resolved
- Estrogen currently not approved for treatment of dementia

MANAGEMENT OF SYMPTOMATIC PERI-OR POSTMENOPAUSAL WOMEN

Treatment is determined by the woman's personal preference, symptom severity, personal history of risks, benefits and family history.

Lifestyle Changes: Nutrition & Exercise

- Optimal diet and exercise – recommended for any peri- and postmenopausal woman
- Since metabolism slows may need to eat fewer calories and exercise more
- No single diet effective-need changes in eating habits which will persist for life
- Eat at regular intervals
- Recommended exercise:
    - 300 minutes of exercise per week or
    - 30 minutes of moderate exercise most days
- Three types of exercise
    - **Strength training and resistance**
        - Provides muscle resistance
        - Increases bone density
        - Lean muscle mass
        - Improves caloric metabolism
    - **Aerobic exercise:**
        - Improves cardiovascular and respiratory capacity
        - Low impact aerobics easier on joints
    - **Flexibility and stretching:**
        - Reduces stiffness with aging and protects against falls
    - **Balance exercises**

Exercise may improve symptoms and reduce risks:

Promotes restorative sleep	Improves balance
Increases endorphins that improve mood and analgesia	Reduces risk of breast cancer
Reduces osteoporosis	Reduces cardiovascular disease
Reduces risk of falls	Reduces diabetes

Lifestyle Changes: Diet

- High in grains and high fiber foods and rich in vegetables and fruits (plant based foods)
- Consume fish, especially oily fish at least twice weekly
- Reduce total calories as metabolism slows and eat smaller portions
- Exact makeup of optimal diet is controversial
- Reduce sugar, salt and consume alcohol in moderation
- Adequate fluid intake-water preferred
- Minimize intake of caffeine and alcohol (can be a flash trigger)
- Reduce fried foods and baked goods
- Maintain a healthy body weight
- Instead of diet, change eating habits for rest of life-tips like dividing plate into quarters with ¼ protein, ¼ CHO, ½ vegetables are useful
- Organizations such as Weight Watchers are helpful

Complementary and Alternative Medicine (CAM) alternatives

- 70% of Canadian women report use of Natural Health Products including herbal, vitamins, and homeopathic remedies
- Many of the Complementary and Alternative Medicine (CAM) herbal products are viewed as safe by public but may have drug interactions and side effects
- All therapies should be compared to placebo –which has 30% efficacy for vasomotor symptoms
- Black cohosh,Vitamin E -minimal benefit compared to placebo
- Other CAM therapies NOT shown to be beneficial in prospective randomized controlled trials. Includes ginseng, red clover, oil of primrose, dong quai, chasteberry
- Soy studies inconclusive.
- Phytoestrogens found in soy act as weak estrogens.
- Hypnosis-5 sessions a week shown to be effective in one trial
- Cognitive behavioural therapy proven to be helpful
- Dressing in layers, cold showers, fans, lowering thermostat, avoiding alcohol and smoking – suggestions for patients only with mild vasomotor symptoms

Non-hormonal medications for treatments of hot flashes - take symptom seriously

- SSRI's and SNRI's variable results for treatment of hot flashes:
    - Venlafaxine 37.5-75 mg
    - Paroxetine 12.5 mg approved in US for treatment of hot flashes (Not recommended for women on tamoxifen- interactions with CYP 450 enzyme)
    - Fluoxetine 20 mg
    - Escitalopram
- Found to be 37-62% effective especially in breast cancer patients
- Side effects nausea, headaches, sexual dysfunction
- Particularly useful in patients with mood changes
- Eszopiclone effective in treatment of nighttime flashes
- Clonidine:
    - 0.025mg 2 tabs bid 45% effective.
    - (Works centrally)
    - Side effects dry mouth, drowsiness, may lower BP
- Gabapentin:
    - Divided doses (up to 2400 mg/ day) effective
    - May be used in smaller dose at bedtime
    - Side effects may limit usage (drowsiness)
    - Start at bedtime with low dose (eg. 200mg)
    - Work up to 700 mg by increasing dose by 100 mg every 3-4 days stop at effective dose
    - Especially good for night sweats

Treatments for vaginal dryness:

- Lubricants at the time of intercourse
- Vaginal Moisturizers-products to coat vagina (Maintenance)
- Polycarbophil –based (Replens)
- Hyaluronic acid products

- Local estrogen products-do not have any long term detrimental effects in long-term follow-up study from WHI on any health outcome
- Available as intravaginal creams, tablets or ring

Bone Health

- Regular weight bearing exercise, fall prevention
- Adequate calcium 1250 mg/day and vitamin D 1000 IU/day
- Routine BMD not recommended until age 65 unless there are risk factors or fractures

Medications for osteoporosis (see bone unit)

- Usage determined by:
    - Assessment of risk
    - Age
    - BMD measurement
    - History of fragility fracture
    - Fracture Risk Assessment Tool (FRAX) calculations or VAROC (Canadian)
- HRT may be considered for prevention in symptomatic women and younger women
- Primary Treatments:
    - Bisphosphonates-(alendronate and risedronate)-daily or q weekly
    - May affect quality of bone
    - Major problem esophageal reflux
    - Risedronate also q monthly
    - IV Zoledronic acid q yearly
        - For both prevention and treatment
- Etidronate - older bisphosphonate less GI irritation and less efficacy
- SERMs- raloxifene:
    - Prevents spinal fractures
    - Increases risk of DVT
    - Does not improve hot flashes
    - Reduces the risk of breast cancer up to 70% (STAR trial)
- Parathyroid hormone:
    - Reserved for patients with severe osteoporosis
    - Daily injections
    - First agent to increase osteoblastic activity
- Denosumab
    - Subcutaneous injection twice yearly
    - RANK ligand inhibitor

Sexuality

- Sexual problems affect 20-50% of women
- Distressing problems peak at midlife and are lowest after age 65
- Multifactorial: biological, psychological and interpersonal
- Need history of previous sexual function and other health and relationship history
- Dysfunction increases with age

- Perimenopause associated with:
    - Decreased libido
    - Decreased sexual frequency
    - Decreased responsiveness
    - Increased vaginal discomfort
    - Increased problems with partner's response and erectile dysfunction
- Lower estrogen levels are associated with vaginal discomfort
    - One of first factors to address
- Other factors include:
    - Previous attitudes towards sex
    - Lack of partner
    - Partner's loss of interest, inability to achieve erection with age or renewed interest with erectile meds
    - Age-related changes
    - Body image
    - Poor health
    - Weight gain
    - Incontinence
    - Sleep disturbances
    - Stressors
    - Medications - especially SSRI's
    - Hormonal decrease of estrogens and androgens

Options for management

1. Improve vaginal discomfort
    - With local lubricants or estrogen
    - Frequent intercourse improves blood flow to vagina
    - May need vaginal dilator use
    - New modalities may include laser treatments
    - Pelvic physiotherapy
2. Identify partner issues and treat
3. Education regarding normal age-related sexual response changes
4. Identify arousal triggers:
    - Sensate focusing
    - rotic literature
    - Videos
    - Sex aids
    - Change routine
    - Explore non-coital sexual activities
    - Warm baths
    - May require sexual counselor
5. Testosterone therapy
    - Used for low libido especially in patients with previous bilateral salpingo-oophorectomy (BSO)
    - Also systemic estrogen can be tried

- No approved androgen therapies for menopausal women
- All off label use

Psychosocial Health

- 1/3 of women's life is postmenopausal
- Menopause:
  - Reflects aging
  - Loss of fertility
  - Increased risk of serious illnesses
  - Loss of youth
  - Changing emotions and body image
  - "Empty nest"
- Aging in youth oriented society
- Sandwich generation (responsibilities for older aging parents and dependent older children)
- Positive aspects: May be used as marker to improve general health, accomplish unrealized ambitions
- Some women report sense of equanimity after reproductive phase and perimenopausal highs and lows
- Increasing proportion of population as "Boomers" age

Hormone Therapy

- Refers to replacing estrogen and progestin to treat symptoms – blood levels of administered hormones do not exceed estrogen levels in the follicular stage of a menstruating woman
- Preferable term is HT- "hormone therapy"
- Estrogen is the primary symptom reliever
- Estrogen is given alone for women without a uterus
- **Systemic HT: most effective agent for treatment of vasomotor symptoms. Effective in up to 90% of women**
- Progestins are added if the woman has a uterus for protection against uterine cancer
- Estrogen alone increases risk of uterine cancer
- Oral Estrogens are usually given daily
- Options for Progestin component:
  - Daily (continuous combined therapy)-produces amenorrhoea
  - Sequentially from 10-14 days a month or every other month to minimize the progestin dosage
  - If given sequentially patients may menstruate
  - Lower doses produce fewer side effects and less bleeding
- **PRIMARY Usage of systemic estrogen is currently for symptomatic relief including treatment of hot flashes, and vaginal atrophy** (although local vaginal products should be considered first for vaginal symptoms)
- Currently HRT is not recommended for primary or secondary protection against heart disease
- Recommended also for prevention of osteoporosis in symptomatic women or when alternative products are causing side effects

- Available E&P products
    - **Estrogens:**
        - **Conjugated equine estrogen (Premarin)**
            - Derived from pregnant horse urine
            - Contains many different estrogens- estrone sulphate largest human estrogen in mixture - also equilin estrogens
            - Oldest commercial product >70 years of use
        - **Oral estradiol 17β**
        - **Estradiol transdermal - gels and patches**
    - **Use Local estrogens for vaginal symptoms:**
        - Ring, vaginal tablets or cream
        - Systemic estrogen levels remain in the menopausal range
        - Little systemic absorption
    - **Progestins:**
        - Progesterone oral
        - Medroxyprogesterone acetate oral
        - Norethindrone acetate oral
        - Progestin IUD
        - **TSEC** - tissue selective estrogen complex-combines conjugated equine estrogen with a SERM basodoxifene,no progestin required due to anti estrogen effects on uterus
    - **Combination E+P therapies:**
        - Patches
        - Pills
    - **Absolute contraindications for HRT:**
        - Pregnancy
        - Undiagnosed vaginal bleeding
        - Estrogen dependent neoplasm (breast or uterine cancer)
        - History of DVT or Pulmonary Embolus
        - Recent MI or stroke
        - Severe liver dysfunction
        - Hypersensitivity to HRT
- Non-smoking women in perimenopause who are still menstruating with symptoms can use oral contraceptives. (OCP's) up to age 54
- Advantage: providing contraception, superior cycle control, and relief of flashes
- Disadvantage: higher amount of estrogen (4-5X amount of estrogen to HRT). Increased thrombotic risk
- Progestins alone are also efficacious for hot flashes (but inferior to estrogen)

RISKS AND BENEFITS OF HORMONE THERAPY

Hormone replacement therapy was initially prescribed to improve sense of well-being and sexuality since 1960s, then fell out of favour in 70's when increased incidence of uterine cancer was discovered in unopposed estrogen users.

In the 1980's, very popular when Nurse's Health Study and other observational studies suggested usage decreased the incidence of cardiovascular disease by 30%. Risk of uterine cancer was decreased by giving progestins to women with a uterus.

NIH initiated large prospective randomized controlled trial called Women's Health Initiative (WHI) to investigate whether HT had effects on the diseases of aging. 3 arms included continuous combined (E+P) HT (CCHT) for women with a uterus and ET alone after hysterectomy as well as large observational trials in aging women.

Usage of HT fell out of favour after 2002, when results of 16,608 women (Women's Health Initiative) CCHT showed increased risks of:

- Cardiovascular disease, stroke, DVT and breast cancer
- For women who had used Premarin .625 mg. (conjugated equine estrogen and medroxyprogesterone acetate 2.5 mg.) for 5.2 years
- Average age 63. (Range 50-79).
- Women with previous hysterectomy-unopposed estrogen arm (premarin 0.625 mg vs. placebo showed an minimal increased risk of stroke alone after 6.8 years (10 739 women)
- See addendum for results
- Re-evaluation of the trial for women ages 50-59 on unopposed estrogen show no significant risk

Other findings in combination hormone therapy arm per 10,000 women (ages 50-79):

- 8 more cases of breast cancer
- 8 more cases of stroke
- 7 more cases of heart attack
- 6 fewer cases of colon cancer
- 5 fewer hip fractures
- **No difference in death between placebo and medication arms – see chart in addendum for most recent figures**

Recent re-evaluation of estrogen alone arm patients 10 years after of >5yrs of usage showed reduction in breast cancer risk:

- Usage is now selective and for symptom relief not prevention
- Re-analysis suggests no increase of cardiovascular disease for women 50-59 with a trend towards reduction of cardiovascular disease
- Recently less coronary calcification found in estrogen users aged 50-59 than nonusers. Less progression of intimal medial thickness of common carotid artery in users from menopause compared to women initiating therapy 10 years after menopause (Elite trial)
- Supports **"window of opportunity"** hypothesis in surgically menopausal monkeys fed atherogenic diets at menopause
- Estrogen significantly prevented plaque development compared to placebo
- If started too many years after menopause plaque was minimally prevented
- Currently major reason to prescribe is treatment of symptoms
- Philosophy - to treat as long as necessary if benefits outweigh risks and patient continues to have symptoms Re-evaluate periodically (NAMS Guidelines 2017)

- However, long-term usage may be considered if woman is aware of risks and quality of life is poor without therapy
- **Very little risk for usage for short time for symptomatic women at menopause**
- **Local estrogens are recommended for vaginal symptoms**

Current benefits of systemic therapy

- Hot flash relief
- Improvement of mood and depression
- Improvement of vaginal dryness
- Prevents osteoporosis
- Possible improvement in sleep
- **Currently not recommended for primary or secondary treatment of cardiovascular disease**
- **Decision to treat should be based on individual risks and benefits and patient wishes**
- Try and discontinue or taper HRT periodically
- **Risks of medications may not apply to all HRT preparations or lower doses**
- **"Benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause."** (Global Consensus Statement of Menopausal Hormone Therapy 2013)

Risks of systemic therapy

- Increased risk of stroke-rare risk and higher for older women and oral therapies
- Increased risk of breast cancer in some combination formulations after 5 years
- Breast Safety for 7 years demonstrated for unopposed estrogen
- Increased risk of gall bladder disease > for oral therapies
- Increased incidence of medical interventions related to unexpected bleeding
- Increased risk of endometrial cancer on sequential therapies
- Possibly small increased risk of ovarian cancer (not shown in all studies)
- Major deterrent to using HRT is increased risk of breast cancer:
    - Risk higher longer HRT is used
    - Probably related to type of progestin used (progesterone less risky)
    - Risks for breast cancer comparable to:
        - Being 20% overweight
        - Delaying childbirth until > age 30

Table 1: Summary Table of Hormone Therapy Options

Preparation	Generic Name	Common Name	Dose
Oral	Conjugated estrogens	Premarin	0.3, 0.625, 0.9, 1.25mg
	17-β-estradiol	Estrace	0.5, 1mg
Transdermal	17-β-estradiol	Estradot Oesclim	25, 37.5, 50, 75, 100 mcg 2X wk
	17-β-estradiol	Climera	25, 50, 100 mcg q wkly
	17-β-estradiol	Estrogel	1-2 metered pumps 0.06% delivers 1.25 mg of gel with 0.75 mg E
Intravenous	Conjugated estrogens for acute bleeding	Premarin	25 mg IV
Vaginal	Conjugated estrogens	Premarin cream	0.625 mg/gm cream 1-2g 2-3X wk
	17-β-estradiol	Estring	2mg releases 7.5 μg/day inserted q 3 monthly
	Estradiol hemihydrates	Vagifem	10 μg or 25μg E2 tablet inserted daily X 2wks; then 1 twice per week
	Estrone	Estragyn	0.1% 0.5g daily as loading dose then twice weekly
Progestogen			
	Micronized progesterone	Prometrium	100 mg
	MPA	Provera	2.5, 5, 10 mg
	Norethindrone Norethindrone acetate	Micronor Norlutate	0.35 mg 5 mg
IUD	Levonorgestrel	Mirena 20 μg/d-q5 yearly	
Oral combinations (new category)	Conjugated estrogens and MPA	Premplus	0.625 conjugated equine estrogen mg + 2.5 mg medroxyprogesterone acetate
	17-β-E + NETA	Activelle	5 mg E + 0.1 mg NETA 1 mg E + 0.5 mg NETA
	17-β-E + drospirenone	Angelique	1 mg E + 1mg Drospirenone
TSEC	CEE+ basodoxifene (SERM)	Duavive	.45 mg CEE + 20 mg basodoxifene
Transdermal Combination	17-β-estradiol – norethindrone acetate	Estalis	50 μgm 17-β-estradiol + 140-250 NETA twice weekly

Table 2: Results of WHI: women ages 50-59, difference in number of events per 1000 women over 5 years

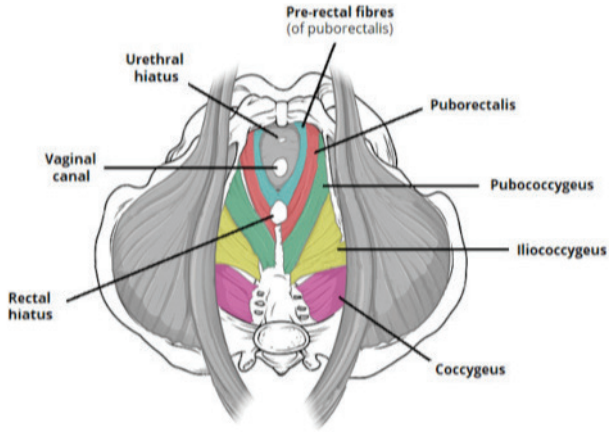
Relative Risks of Disease Outcomes from the WHI	**Intergroup difference in No. events per 1000 women over 5 yrs**	**Intergroup difference in # events per 1000 women over 5 yrs**
Outcome	**E+P**	**E alone**
Coronary heart disease	2.5	-5.5
Stroke	2.5	-0.5
DVT	5.0	2.5
Invasive breast cancer	3.0	-2.5
Colon cancer	-0.5	-1.5
All fractures	-12.0	-8.0
Diabetes	-5.5	-13.0
Death from any cause	-0.5	-5.5

[1]Manson JE Menopause Management- Getting Clinical Care Back on Track NEJM 2016; 374: 803-806.

UROGENITAL AGING: GENITAL PROLAPSE

Active Support Structures (Figure 3)

- *Muscles*
  - Levator ani
    - Puborectalis muscle
    - Pubococcygeus muscle (includes pubovaginalis)
    - Iliococcygeus muscle
  - Coccygeus
- *Nerves*
  - Pudendal nerve (S2,3,4)
  - Sacral plexus (S2,3)



http://teachmeanatomy.info/pelvis/muscles/pelvic-floor/

Risk Factors for Pelvic Floor Prolapse and Urinary Incontinence (Figure 4)

- Pelvic floor relaxation
  - Age
  - Menopause
  - Parity
  - Vaginal deliveries (strongest risk factor)
- Chronic repetitive increases in intra-abdominal pressure
  - Obesity
  - Chronic coughing
  - Constipation
  - Occupations/hobbies requiring heavy work/lifting



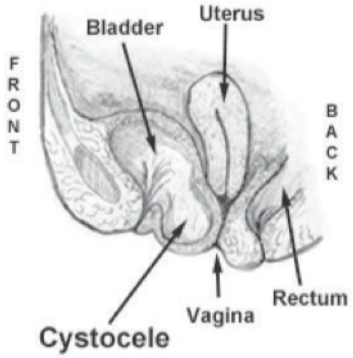
- Connective tissue (genetics)
    - e.g. Ehlers-Danlos
- Pelvic neuropathies
    - S1-4
    - Diabetes
    - Congenital Factors

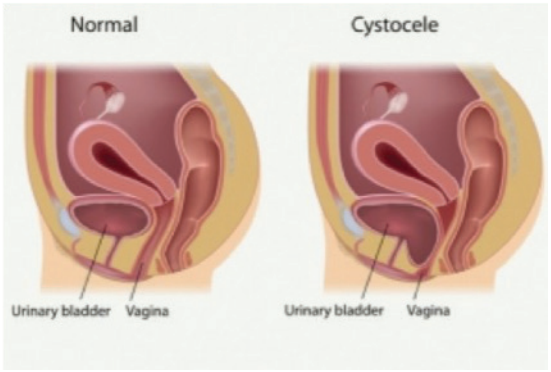
Symptoms of Prolapse

- Mass or bulge at introitus
- Feeling of heaviness
    - Worse with lifting, prolonged standing
    - Worse at the end of the day
- Bladder or bowel symptoms (see below e.g. with cystocele and/or rectocele)

Cystocele (Anterior compartment prolapse) (Figure 5 and 6)

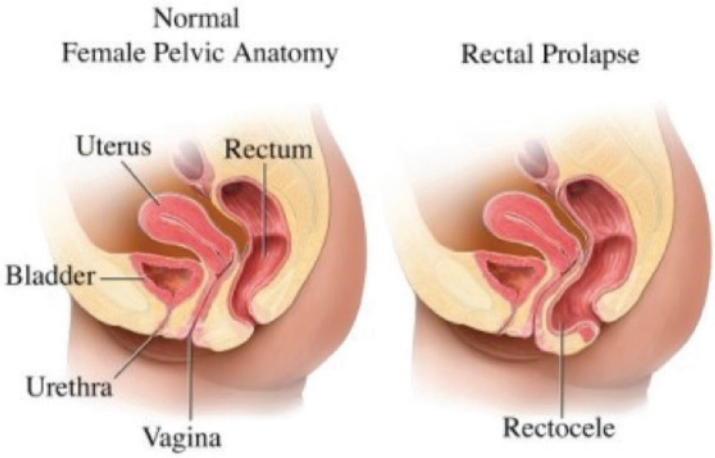
- Protrusion of bladder into the vagina
- Sensation
    - Of fullness or pressure
    - Occasional urgency
    - Incomplete emptying
- Associated with urinary incontinence
- Splinting/digitation for complete emptying
- Recurrent urinary tract infections
- Ureteric obstruction only when severe





Rectocele (posterior compartment prolapse) (Figure 7)

- Protrusion of rectum into the vagina
- Pressure in vagina
- Constipation
- Splinting/digitation for defecation
- Incomplete rectal emptying



Uterine Prolapse (apical prolapse)

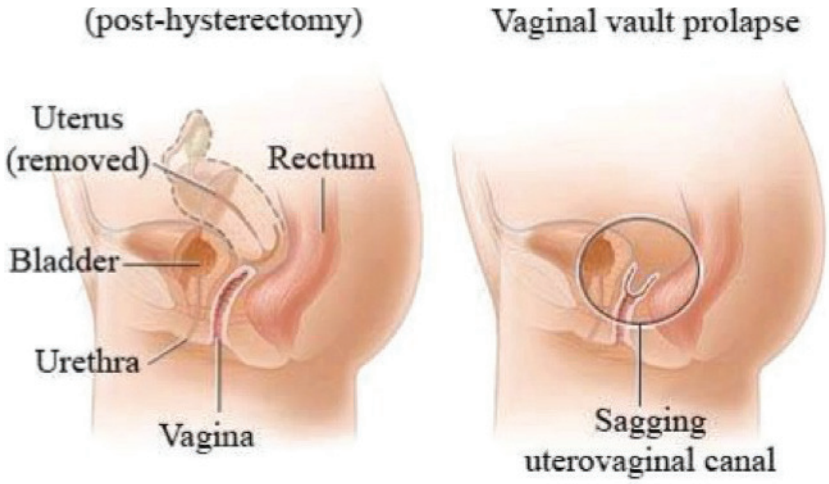
- Protrusion of cervix and uterus into the vagina
- Procidentia
    - Complete protrusion from vagina

Enterocele

- *The only true hernia of the pelvic floor*
- Often seen with procidentia or post hysterectomy
- Can occur with anterior compartment, posterior compartment or apical prolapse
- Contents: small bowel +/- omentum

Vault Prolapse (post-hysterectomy) (apical prolapse) (Figure 8)

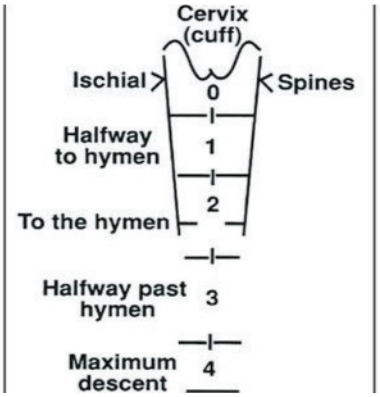
- Protrusion of the apex of the vault into the vagina



Physical Exam

- Inspect for genitourinary atrophy
- Patient should strain (valsalva) or cough
- Use half a speculum to isolate each compartment
- Grade each compartment for prolapse: anterior, posterior, apical
- Reduce the prolapse and then have the patient cough to unmask occult stress urinary incontinence
- Check for levator ani strength (voluntary Kegel contraction)

Grading of Prolapse (Figure 9)



Two commonly used systems: Baden Walker or POP-Q

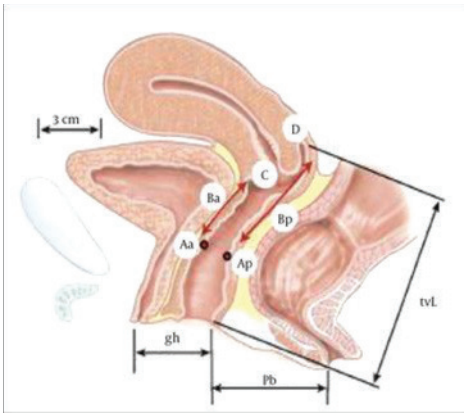
- *Baden-Walker:* Consider the most dependent portion of the prolapse
  - Grade 0: Normal position, no prolapse
  - Grade 1: Halfway to hymen
  - Grade 2: To hymen
  - Grade 3: Halfway beyond hymen
  - Grade 4: More than halfway beyond hymen

POP-Q: Nine measurements (6 points and 3 lengths) (Figure 10 and 11)

⋆ post graduate level of knowledge, included in this syllabus chapter for completeness

- Stage 0: Normal position, no prolapse
- Stage 1: Most dependent portion is less than 1 cm above hymen
- Stage 2: Within 1 cm of hymen
- Stage 3: More than 1 cm beyond hymen, but less than total vaginal length – 2 cm

Anterior Wall **Aa**	Anterior Wall **Ba**	Cervix or cuff **C**
Genital Hiatus **gh**	Perineal Body **pb**	Total Vaginal Length **tvl**
Posterior Wall **Ap**	Posterior Wall **Bp**	Posterior Fornix **D**



- Stage 4: Complete procidentia/eversion

- Point A is fixed at 3 cm from the urethral meatus along the midline of the anterior (Aa) vaginal wall and 3 cm from the posterior forchette along the midline of the posterior (Ap) vaginal wall
- Point B is the most dependent point of the vaginal wall in the midline anteriorly (Ba) and posteriorly (Bp)
- Point C is the cervix
- Point D is the posterior fornix (absent post-hysteroctomy)

Management of Prolapse

- Expectant
  - Suitable for those with minimal symptoms
  - Education, reassurance

- Pelvic floor muscle training
    - Kegels
    - Pelvic floor physiotherapy
- Pessaries
    - Medical grade silicone devices
    - Many different types and sizes depending on patient's anatomy and lifestyle (including whether they are sexually active)
    - Option for patients who decline surgery, those awaiting surgery, or those who are not fit for surgery
    - Patients may choose to take care of it themselves or may attend a pessary clinic at regular intervals (every 3 months)
    - Risks of pessaries: vaginal bleeding, infection, worsening urinary or bowel symptoms, rare fistulas
- Surgery

All of the above options may be combined with vaginal estrogen or non-hormonal lubricants.

Available pessaries (Figure 12):



Surgical Management of Prolapse

- *Cystocele*: anterior repair
- *Rectocele*: posterior repair
- *Uterine prolapse*: vaginal hysterectomy + vault suspension
- *Enterocele*: pursestring closure of sac +/- McCall's culdoplasty
- *Vault prolapse*: vaginal vault suspension or laparoscopic sacrocolpopexy (with mesh)

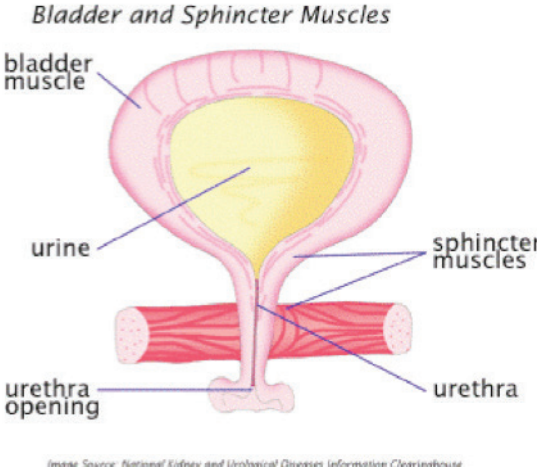
For those who are not sexually active and not planning to be, and/or those who have multiple medical comorbidities and have greater peri-operative risks, an obliterative procedure such as colpocleisis or vaginectomy carries less morbidity and is another option for complete procidentia or complete vault prolapse.

A concurrent incontinence procedure may be considered if occult stress urinary incontinence is found during the physical exam.

UROGENITAL AGING: URINARY INCONTINENCE

Anatomy of Continence (Figure 13)

- Bladder: 3 continence mechanisms
  - Involuntary internal sphincter
  - External sphincter
  - Mucosal coaptation



Urinary Symptoms:

- *Frequency:* increased daytime frequency (>8 times/day), complaint by the patient who considers that she voids too often by day
- *Nocturia:* complaint that the individual has to wake at night >2 times to void
- *Urgency:* complaint of sudden compelling desire to pass urine, which is difficult to defer
  - Urgency as a symptom of strong desire to void may be associated with two possible dysfunctions
    - Related to bladder overactivity (motor urgency)
    - Hypersensitivity (sensory urge)
- *Urge Urinary Incontinence (UUI):* complaint of involuntary leakage of urine associated with urge to void
- *Enuresis:* involuntary loss of urine
- *Nocturnal enuresis:* loss of urine occurring during sleep.
- *Continuous urinary incontinence:* complaint of continuous leakage.

Types of Urinary Incontinence (UI)

Urinary Incontinence is the involuntary loss of urine, which is objectively demonstrable, with such a degree of severity that it is a social or hygienic problem. It can be classified as stress, urge, mixed (both stress and urge), overflow or functional.

Stress Urinary Incontinence (SUI) is the involuntary urethral loss of urine with coughing, laughing, sneezing, or any effort or exertion. It occurs when the intravesical pressure exceeds the maximum urethral pressure but in the absence of detrusor activity. It is most commonly caused by urethral hypermobility.

Urgency Incontinence (UUI) is the involuntary loss of urine associated with urinary urgency

Overactive bladder (OAB)

- Definition on symptoms alone
- Triad of symptoms: urgency, frequency, nocturia with or without urge incontinence
- Rule out other causes (e.g. UTI, genitourinary syndrome of menopause (GSM) etc)
- Can have a significant impact on patients' quality of life, including special precautions with clothing (daily pads), physical (cessation of physical activities), occupational, reduction in social interactions
  (planning travel around toilet accessibility), sexual, and psychological (fear of urine odor).

Mixed Urinary Incontinence (MUI): complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing. This is essentially a combination of SUI and UUI (OAB).

Overflow Incontinence is the involuntary release of urine from an overfull urinary bladder, often in the absence of any urge to urinate. This condition occurs in people who have a blockage of the bladder outlet, or when the muscle that expels urine from the bladder is too weak to empty the bladder normally.

Functional Incontinence is the involuntary loss of urine that results from an inability to reach the toilet due to cognitive, functional or mobility impairments in the presence of an intact lower urinary tract system.

Other Causes of Incontinence

Infection	Suburethral diverticulum
Bladder tumors	Fistulae
Bladder stones	Interstitial cystitis/ Painful bladder syndrome
Foreign body	

Evaluation of Urinary Incontinence

Urinary History

Frequency	Voiding symptoms: • Slow stream • Splitting or spraying • Intermittency • Hesitancy • Straining • Terminal dribbling • Bladder Sensation • Post-micturition symptoms • Feeling of incomplete emptying • Post-micturition dribbling
Urgency	UTI • Dysuria • Hematuria
Incontinence • With activity (i.e. SUI) • With urge • With running water (UUI) • Continuous loss of urine • Overflow • Fistula	
Nocturia	
Impact on quality of life	

Contributing Factors:

Caffeine History	MS, Strokes, Alzheimer's, Parkinson's
Medical History	Disc disease
DM	Drugs
Thyroid disease	Psych (depression, anxiety)
Central nervous system diseases	

Physical Exam

- Inspect for urogenital atrophy
- Patient should cough/ strain – examine for bladder neck hypermobility
- Reduce any concurrent prolapse and have the patient cough to check for SUI (occult stress incontinence)
- Can palpate bladder neck + urethra to check for diverticulum

Evaluation

- Post-void residual urine (either by bladder scan, or, in-and-out catheter)
- Urinalysis and urine culture and sensitivity
- Consider cystoscopy to assess for stones, tumors
- Consider urodynamics

Urodynamics

- Objective assessment of how the bladder fills and empties
- Not all patients require this testing
    - Consider if the history/physical are unclear, if history and physical are inconsistent, if the patient has previously had an incontinence procedure, or if the patient is not responding to treatment
- Can help distinguish between SUI and OAB
    - Filling cystometrogram
    - There may be involuntary detrusor contractions as the bladder fills in patients with OAB
- For SUI, can help distinguish between hypermobility & intrinsic sphincter deficiency
    - Maximum urethral closure pressure (MUCP)
    - Or valsalva leak point pressure (VLPP)

Filling Cystometry

- Measures the pressure-volume relationship in the bladder
- One catheter is inserted into the bladder and another catheter in the vagina or rectum
- Patients are then assessed as the bladder is filled with fluid through the catheter
- Normal capacity 350 – 600 cc
- Sensation (ref Int Urogynecol J (2012) 23:269–277DOI 10.1007/s00192-011-1585-y)
    - First sensation 100 -- 250 cc
    - First desire to void 200 – 330 cc
    - Strong desire to void 350 – 560 cc
- Compliance
    - Δ in volume / Δ in detrusor pressure
- Detrusor stability / overactivity

Treatment of Overactive Bladder

- R/o other causes
- Behavior modification
    - Eliminate irritants (e.g. caffeine, alcohol)
    - Total Fluid Intake 1.5 to 2 L/day
- Bladder Retraining
    - Timed voiding every 2-3 hours
    - Double voiding to ensure complete emptying
- Pelvic floor muscle training / Pelvic floor physiotherapy

- Medications (anticholinergics, mirabegron)
- Botox injections
- Sacral neuromodulation

Anticholinergics have traditionally been used to treat OAB. However, there are significant side effects including dry mouth, constipation, and dry eyes, which can affect compliance and long-term adherence to medication.

The choice of anticholinergics depends on the patient's comorbidities, considering cardiac concerns, pre-existing cognitive dysfunction, and other medications (drug interactions with CYP 450 inhibitors).

Examples of anticholinergics include Oxybutynin, Tolterodine, Trospium, Solifenacin, Darifenacin, and Fesoterodine.

Contraindications to anticholinergies include urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and known hypersensitivy to the medications/ingredients.

In recent years, mirabegron (Myrbetriq), which is a beta-3 adrenergic agonist, has become a popular alternative as it does not carry the same side effects as anticholinergics. The most common side effect is hypertension (10%). Contraindications to mirabegron include a known hypersensitivity to the medication/ingredients.

Treatment of Stress Urinary Incontinence

Expectant	Continence Pessaries

Bladder drills	Surgery
	• Retropubic Urethropexy (Burch)
	• Laparoscopic sling (with mesh)
	• Autologous fascial sling
	• Midurethral slings
	  • Retropubic (Tension free Vaginal Tape)
	  • Transobturator Tape (TOT/TVT-O)

Pelvic floor muscle exercises	
Pelvic floor physiotherapy	

Figure 14

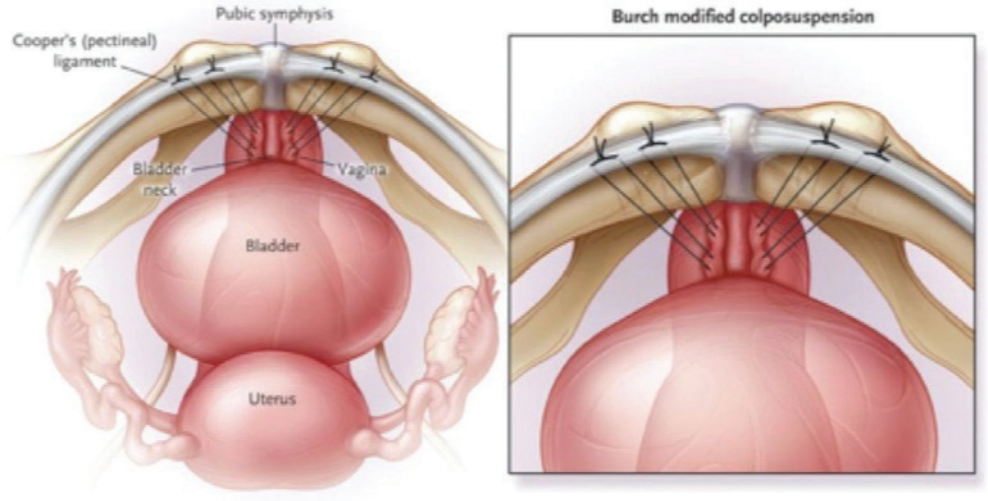


Figure 15

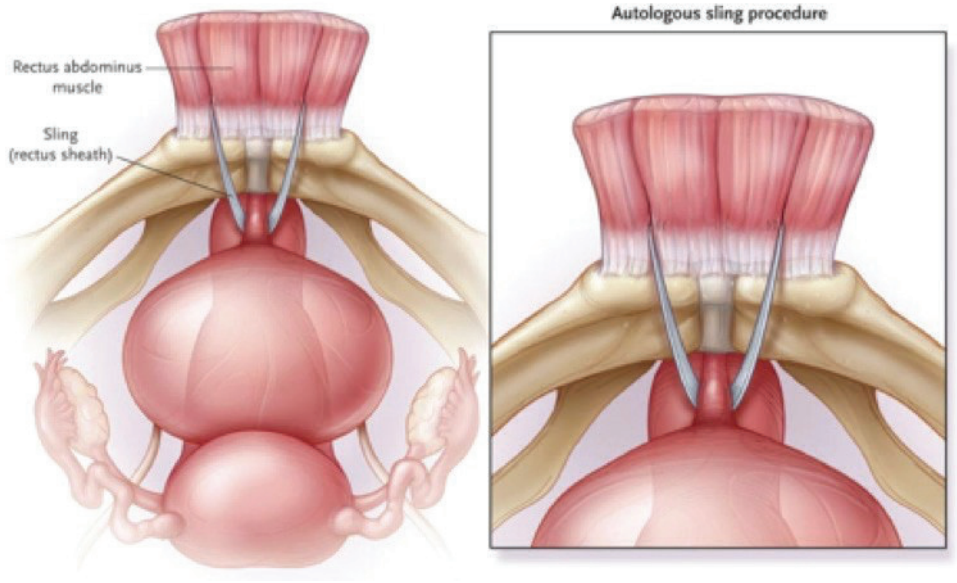
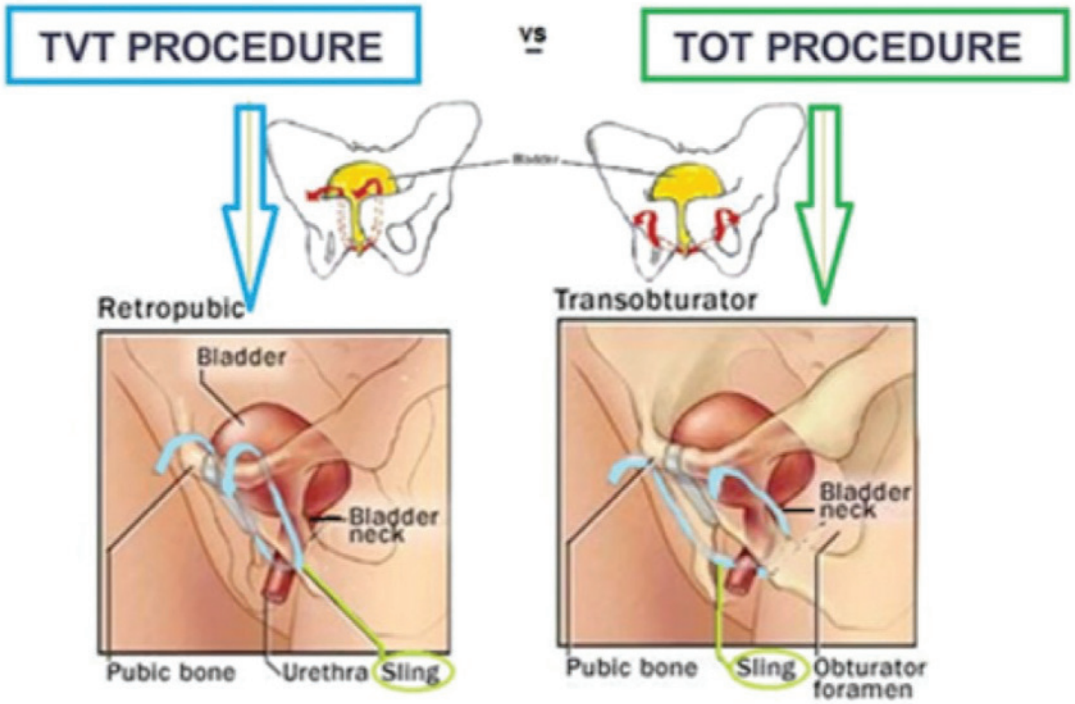


Figure 16



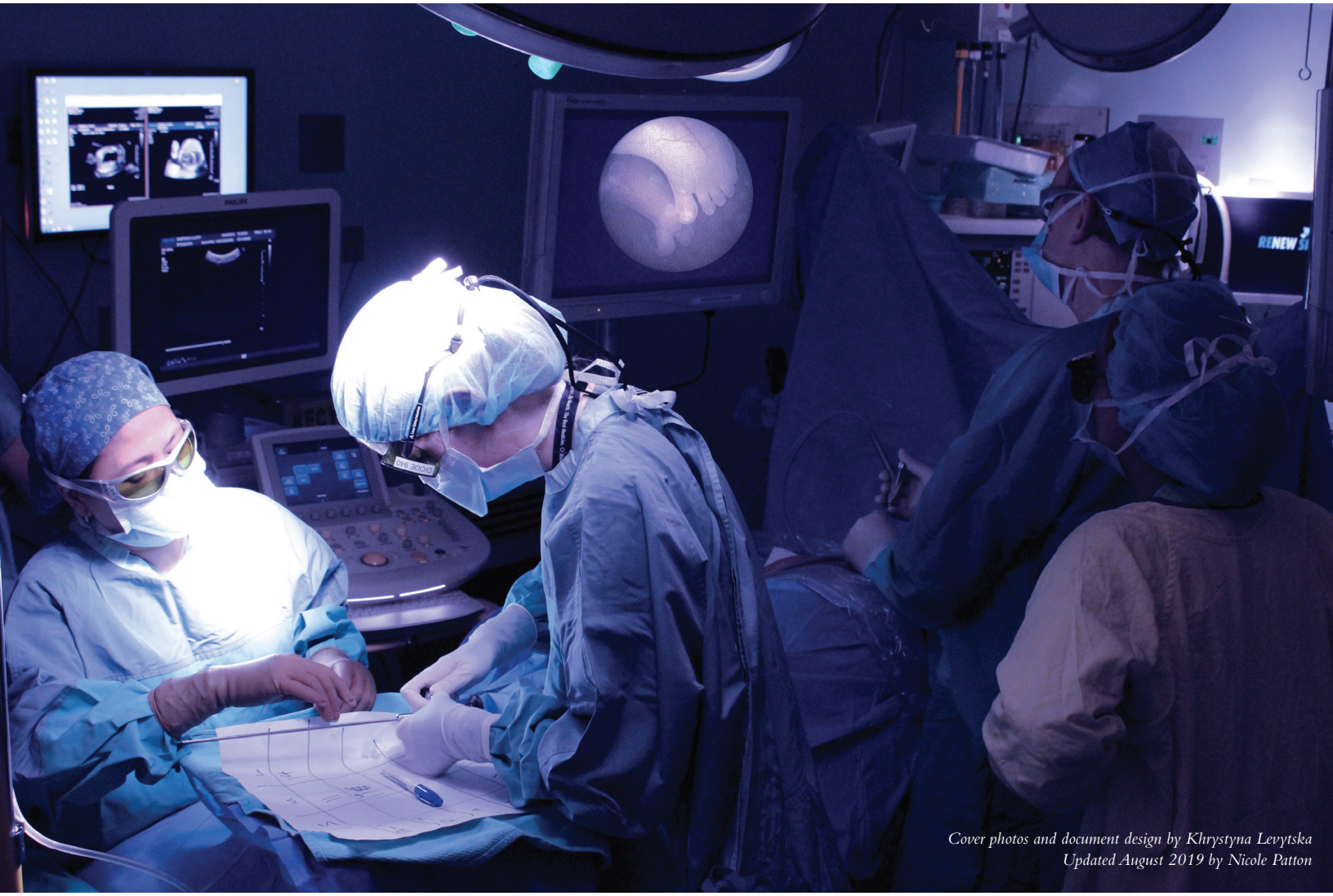
Retopubic Approach **Transobturator Approach**

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