OBSTETRIC MEDICINE HANDBOOK

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Clinical Pearls in OB Medicine

Managing a pregnant woman with medical disease can be simultaneously challenging and rewarding. Here are five basic principles to remember as you investigate and manage disease in the pregnant population.

1. Always ask yourself, "What would I do if this patient was not pregnant?"

Do not allow your unfamiliarity (and possible unease) with the pregnant patient to distract you from basic medical principles.

2. A healthy mother is a healthy baby.

Very often our perspective or outlook on management of common medical problems changes because of pregnancy. Remember, the key to a healthy pregnancy and baby is a healthy mother. Don't shy away from any interventions, even those with risk, if they will ultimately keep a mother healthy. In most cases, it's the disease and not the intervention that leads to poor outcomes.

3. Always remember that some medical problems in pregnancy are pregnancy unrelated.

As an example, a pregnant woman with abdominal pain and increased liver enzymes could have pre-eclampsia or cholangitis. One problem is specific and unique to pregnancy while the other is not. Keep your differential diagnosis broad and in two separate categories: pregnancy induced and medical disease occurring in pregnancy.

4. Know your basic pregnancy physiology.

Many vague, common concerns in pregnancy are normal and can be explained by understanding the physiology of a pregnant woman. Remember that different trimesters have different physiology. True pathology can often be difficult to distinguish from normal physiology in pregnancy. In addition, laboratory reference ranges are altered by pregnancy.

5. Drugs matter.

Always counsel women on the effects of drugs in pregnancy. These effects are often trimester specific. Don't forget about drugs in lactation. Women are more vigilant about possible drug effects on the fetus. Educate your patients to make an informed decision.

Abbreviations used throughout this handbook:

APLA	Antiphospholipid antibody syndrome
ATD	Antithyroid drugs
C/S	Cesarean section
dBP	Diastolic blood pressure
GA	Gestational Age
HTN	Hypertension
IUFD	Intrauterine fetal demise
IUGR	Intrauterine growth restriction
OCP	Oral contraceptive pill
OH	Overt hypothyroidism
PET	Preeclampsia/toxemia
SCH	Subclinical hypothyroidism
SGA	Small for gestational age
SLE	Systemic lupus erythematosus
SVR	Systemic vascular resistance
sBP	Systolic blood pressure
TBG	Thyroid binding globulin
TFT	Thyroid function test
TM	Trimester
TRAb	TSH receptor antibody
ULN	Upper limit normal

Normal Physiologic Changes in Pregnancy

Pregnancy is a unique state of increased physiologic stress. Maternal systems remodel to meet the demands for fetal homeostasis. When investigating a pregnant patient, it's important to be aware of the normal changes in pregnancy since in many cases pathology is difficult to distinguish from normal physiology.

Cardiovascular System

- Cardiac output and plasma volume increase by 40-50%, peaking in the 2nd trimester (around 26-28 weeks) and then remaining elevated.
    - Immediately postpartum there is a further 60-80% increase followed by a rapid decline. Hemodynamics generally return to normal by 2 weeks after delivery, but in some cases may not fully resolve until 6 months postpartum.
- Peripheral vascular resistance and blood pressure decrease in pregnancy and will recover postpartum.
- Enlarging uterus compresses IVC and pelvic veins
    - Decreased venous return (hypotension)
    - Increased venous pressure (varicose veins, hemorrhoids, leg edema)
- On physical examination
    - Prominent (but not elevated) JVP, hyperdynamic state
    - Apical impulse becomes displaced
    - Widely split S1/S2, S3 present, soft systolic flow murmur
- ECG: sinus tachycardia (upper limit normal ~ 110 bpm), PVCs, PACs, LAD, ST depression and T wave inversion in inferolateral leads

Respiratory System

- Major respiratory changes are secondary to mechanical factors, increased oxygen consumption and increased stimulation of respiratory centers
- Upper respiratory system
    - Increased blood flow to the nasopharynx leads to congestion, epistaxis, mucosal bleeding
- Lower respiratory system
    - Minute ventilation increases as a result of increased tidal volume. Respiratory rate unchanged.
    - Progesterone stimulates ventilation, leading to respiratory alkalosis and compensatory metabolic acidosis.
    - Dyspnea of pregnancy experienced in 60-70% of women
    - Total lung capacity, residual volume and functional residual capacity decrease
    - Oxygen consumption increases by 15-20%
    - Mechanical factors (elevation of diaphragm) alter respiratory volumes

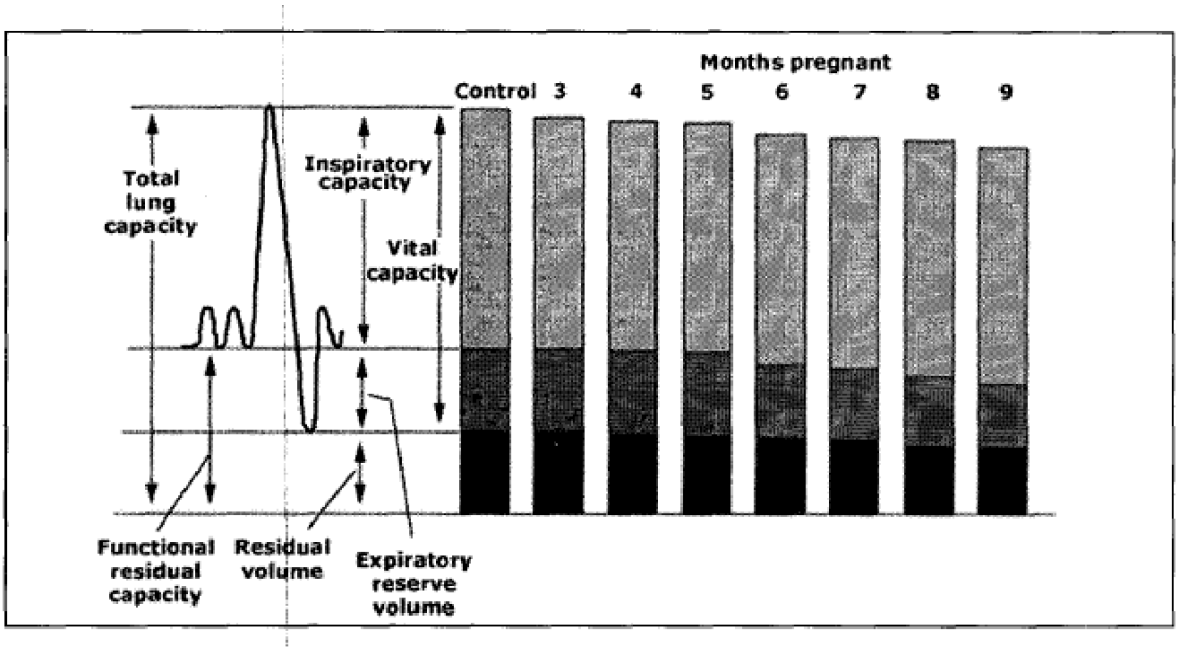

Figure 1. Serial measurements of lung function in pregnancy. (UpToDate June 2015)

Hematological System

- Pregnancy induces a relative hypercoagulable state
- Increased risk of thromboembolic disease secondary to increased clotting factors as well as venous stasis/pooling.
- White blood cell count increases slightly with neutrophilic predominance.
- Hemodilutional anemia (normal > 110 in 1st TM, > 105 in 2nd and 3rd TM)
- Thrombocytopenia can be seen with platelets as low as 115 considered “normal”.

Genitourinary System

- GFR rises dramatically by 40%, Cr and BUN decrease. Plasma volume rises secondary to increased renin and aldosterone.
- Renal calyces, pelvis and ureters dilate. Increased risk for pyelonephritis.

Gastrointestinal System

- Increased pressure from the gravid uterus, smooth muscle relaxation from progesterone, gastric stasis and relaxation of the lower esophageal sphincter lead to gastroesophageal reflux disease.
- Appendix displaced in superior and lateral directions.
- Constipation more common from decrease in GI transit time (progesterone) and pressure of gravid uterus.
- Hemorrhoids more common from increased venous pressure.

Hepatobiliary System

- Liver shifted in superior and posterior directions
    - Liver and spleen edges normally not palpable in pregnancy. Spleen can be mildly enlarged.
- Telangiectasia, spider angiomas and palmar erythema occur secondary to high estrogen state.
- Dilation of gallbladder and biliary tree from progesterone
    - Decreased gallbladder motility-> increased bile stasis and gallstones.
- Liver enzymes and bilirubin unchanged, with the exception of ALP (secreted from placenta)

Endocrine System

- Increased gland size (~10%) in iodine-replete countries
- Increased thyroid requirements by week 4-6 (30-35% increase).
- Increased TBG due to estrogen secretion from placenta. TBG binds T3 and T4, leading to higher levels of total thyroid hormone. However, free t4 levels do not change (increased placental breakdown with increased production by B-HCG leads to stable levels).
- TSH falls in 1st trimester secondary to 'B-HCG effect'
- Increased serum cortisol and androgen.
- Effects of aldosterone blunted.
- Peripheral insulin resistance secondary to placental hormones leading to risk of gestational diabetes around weeks 24-28 gestation.

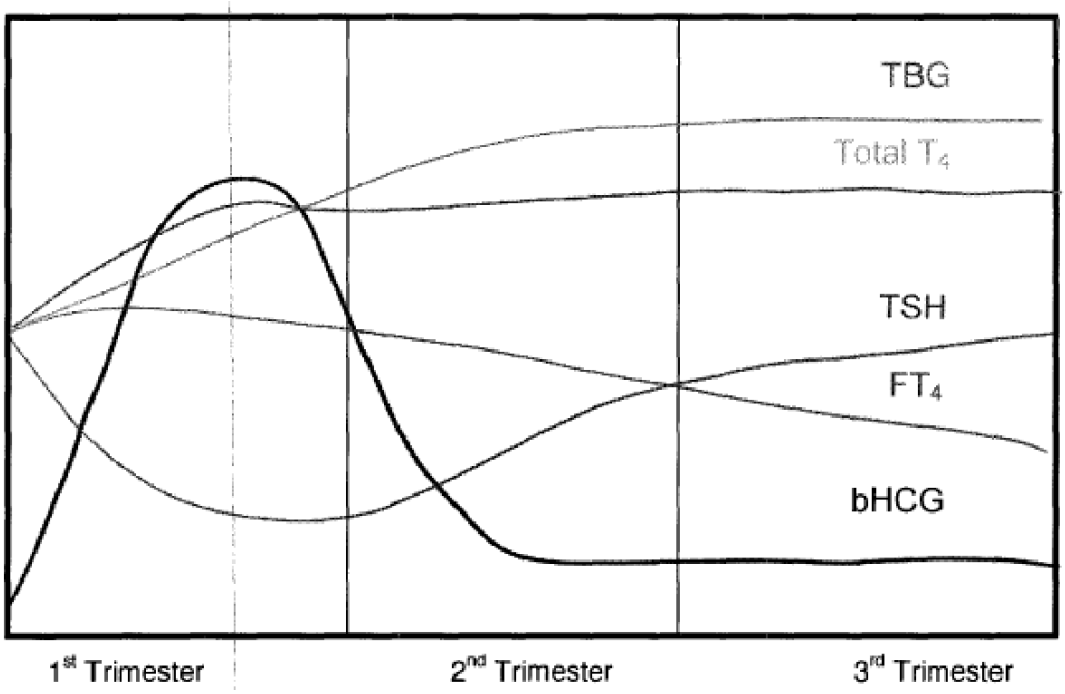

Figure 2. 'B-HCG effect' and natural changes in thyroid hormone in pregnancy.

Immune System

- Decreased cellular and humoral immunity
- Increased likelihood of flaring of TH2-mediated diseases, such as systemic lupus erythematosus.

Musculoskeletal system

- Ideal 25-35lbs weight gain in a patient with previously healthy body weight.
- Weight gain leads to increased load on joints.
- Recommendation for 150 mins/week of cardiovascular activity unless obstetric contra-indication
- Widened stance, lower back lordosis, forward neck flexion.
- Joint laxity.
- Fluid retention can cause nerve compression (carpal tunnel syndrome)
- A significant amount of calcium is required to build the fetal skeleton, making pregnancy a time of high bone turnover. Transfer of calcium continues during lactation and abates once breastfeeding is complete.

Integumentary System

- Hyperpigmentation secondary to estrogen, progesterone and melanocyte-stimulating hormone.
    - Linea nigra (darkened, vertical line in center of abdomen), melasma (hyperpigmented patches/macules usually found on face)
- Vascular changes
    - Gingival hypertrophy (good oral health is important), edema and hyperemia
    - Varicosities
    - Striae gravidarum (stretch marks)
- Changes in hair and nails
    - Hair goes into the anagen (growth) phase in pregnancy and then returns to the telogen (resting) phase postpartum, with shedding usually occurring 2-6 months after delivery (*telogen effluvium).*
    - Nails grow faster in pregnancy.

Psychological System

- Central themes emerge in pregnancy around changes in self-image, identity, marital structure, perceived societal or family expectations and anxiety
- Women with a personal history of psychiatric disease are at risk for deterioration, especially postpartum.
- Typical psychological stages associated with each trimester:
    - First trimester: reactions to being pregnant, dealing with associated adverse physical symptoms.
    - Second trimester: often physical and emotional quiescence.
    - Third trimester: heightened anxiety as delivery nears, “nesting”, anticipation of the next phase of life.

System	Lab Value	Change	Description and normal values in pregnancy
Hematologic	Hemoglobin	↓	Hemodilution >110 in T1, >105 in T2 and T3
	Platelets	↓	**Gestational thrombocytopenia** Generally >100
	WBC	↑	Stress leukocytosis response in pregnancy Neutrophilic predominance, WBC ≤13
	D-dimer	↑	Hyper-coagulable and hyper-fibrinolytic state Not validated to rule out VTE in pregnancy
	VWF	↑	Increase in coagulation factors due to hormones Repeat 6 weeks postpartum if suspecting VWD
Renal	Creatinine	↓	Typically ≈ 50, evaluate if > 70 Due to increase in GFR by 40%, urea also decreases
Hepatic	ALP	↑	Produced by the placenta, 2-4x increase in T2 and T3 AST/ALT/INR unchanged
	Albumin	↓	Increase plasma volume and alpha fetoprotein Generally albumin >30 Most other hepatic proteins unchanged
Endocrine	Cholesterol, Triglycerides	↑	Estrogen increases hepatic production of lipids Avoid measuring in pregnancy unless pancreatitis
	HbA1c	↓	Not diagnostic test or for monitoring glucose control in gestational diabetes Tends to fall early in pregnancy, if >5.2% then OGCT, aim for <6% during pregnancy
Biochemistry	Bicarbonate	↓	Metabolic compensation for respiratory alkalosis from hyperventilation due to progesterone
	ESR	↑	Increases with gestational age and concomitant anemia CRP not greatly altered

Table 1. Expected laboratory changes in pregnancy.

Hypertensive Disorders in Pregnancy

Physiologic blood pressure changes in normal pregnancy

- Blood pressure follows a gentle **U-shaped** curve with nadir around 20 weeks gestation as systemic vascular resistance decreases due to the vasodilatory effects of progesterone (Figure 1). BP then begins to steadily rise and will often increase at or around approximately 32 weeks GA as a result of the increase in plasma volume and cardiac output.
- This explains why ***20 weeks gestation*** divides pre-existing from gestational hypertension; if BP is elevated prior to 20 weeks, she likely has unrecognized pre-existing hypertension.

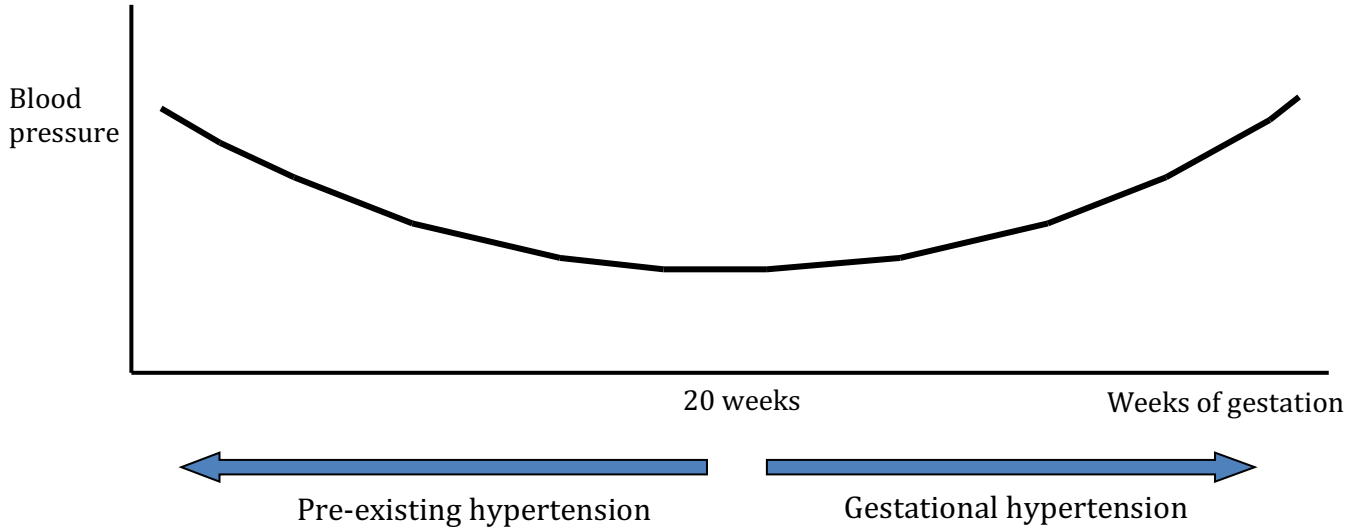

Figure 1. Expected blood pressure change over the course of pregnancy.

Epidemiology

- Hypertension complicates 7% of all pregnancies.
- Risk of pre-eclampsia is 3-5% at baseline, and increases to 15-20% for those with risk factors.
- Pre-existing hypertension has 20% risk of pre-eclampsia, gestational hypertension has 40% risk of pre-eclampsia

Diagnosis of Hypertension in Pregnancy (Canadian Hypertension Society 2018/SOGC2014)

- Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mm Hg, based on the average of at least 2 measurements, taken at least 15 minutes apart, using the same arm.

- Generally, hypertension that develops before 20 weeks gestation is pre-existing hypertension, and after 20 weeks is gestational hypertension.
- **Severe hypertension is BP ≥ 160/110 mmHg** that is pregnancy induced and it is a medical emergency in pregnancy.
- Resistant hypertension is the need for 3 antihypertensive medications for blood pressure control.
- Healthy women frequently have low pre-pregnancy blood pressure, so a significant change in blood pressure in pregnancy from baseline, >30mmHg systolic or >15mmHg diastolic, is concerning for an evolving hypertensive disorder even if the actual value does not meet diagnostic criteria.

Classification (Society of Obstetricians and Gynecologist of Canada (SOGC) 2014)

1. Pre-existing (chronic) (< 20 weeks)

2. Gestational (> 20 weeks)

3. Preeclampsia (see Preeclampsia section)

4. Other hypertensive effects
    a. Transient hypertensive effect
    b. White-coat hypertensive effect
    c. Masked hypertensive effect

The definition and classification of hypertensive disorders in pregnancy is evolving. SOGC 2014 guidelines sub-classifies pre-existing and gestational hypertension into those with co-morbid conditions (e.g. diabetes or kidney disease) or with evidence of pre-eclampsia. The Canadian Hypertension Society (CHS) 2018 guidelines make no reference to such subdivision. The concept of white-coat hypertension has been more recognized in recent years, making it imperative to distinguish from true hypertension. The definition of severe hypertension in pregnancy was reduced from 180/110 to 160/110 with association of stroke in pregnancy at a lower BP level. Hypertensive disorders in pregnancy represents a broad range of conditions with differing underlying pathophysiology. With ongoing research, the definition and classification is expected to be further revised in the near future.

Blood Pressure Target (Canadian Hypertension Society (CHS) 2018)

CHS 2018 guideline: **DBP < 85mmHg** (no recommendation on SBP)

Previous SOGC 2014 guideline:
- no comorbid conditions 130-155/80-105mmHg
- comorbid conditions 130-139/80-89mmHg

The target of diastolic blood pressure less than 85mmHg in pregnancy as recommended by the Canadian Hypertension Society (CHS) 2018 guideline is based primarily on the **CHIPS trial**. The **C**ontrol of **H**ypertension **I**n **P**regnancy **S**tudy (NEJM 2015) was designed to test the common belief that low pressure, particularly diastolic blood pressure, leads to reduced placental perfusion and potentially a small-for-gestational-age fetus; hence, target blood pressure previously was 130-155/80-105 mmHg. CHIPS was a multicenter randomized controlled trial of 987 women which showed diastolic blood pressure of 85 mmHg ("tight" control) had similar neonatal outcomes compared to 100 mmHg ("less tight" control). The neonatal outcomes included miscarriage, stillborn, neonatal death, small-for-gestational-age neonate, and need for NICU. However, women in the "less tight" group were more likely to develop severe hypertension but did not have an increase in serious maternal complications such as pre-eclampsia, placental abruption, renal failure, or stroke.

The CHIPS trial is a landmark trial which demonstrated tight control of diastolic blood pressure of 85mmHg has no adverse outcome on fetal outcomes. Therefore, it allows for greater comfort in treating hypertension to similar target ranges as non-pregnant individuals. However, the critical threshold of pressure, systolic or diastolic, to maintain adequate placental perfusion is still unknown. One must therefore remain vigilant if the blood pressure reduces significantly with the initiation or increase of antihypertensives, especially if associated with new onset maternal orthostatic symptoms or decline in fetal growth. We would recommend a target of 80-90 mm Hg (aiming for as close to 85 mm Hg), in keeping with the CHIPS trial.

The systolic blood pressure target is not part of the recommendation of the CHS 2018 guideline. One may consider using the non-pregnant target of SBP less than 140 or the systolic blood pressure recommendations of the SOGC guidelines in 2014. As a reminder, systolic blood pressure > 160 is a medical emergency and requires urgent attention for blood pressure reduction. Those with diabetes should have a target of <130/80 similar to non-pregnant individuals.

Antihypertensive Agents

The most common drugs used in pregnancy and their doses are listed below (Tables 1 and 2). Clonidine, Hydralazine and Nitroglycerin can be used if blood pressure is refractory to first-line medications. Thiazides aren't typically used because of the theoretical concern of reducing plasma volume and thus placental perfusion, but it is a second line antihypertensive in CHS 2018.

First line oral drugs	Second line oral drugs	Medications to avoid
Labetalol Methyldopa Long acting oral Nifedipine Other beta blockers (Acebutolol, Metoprolol, Pindolol, Propranolol)	Clonidine Hydralazine Thiazide diuretics	ACE/ARBs

Table 1. Antihypertensives used in treatment of non-severe hypertension. (CHS 2018)

Agent	Starting dose	Maximum dose	Side effects	Commentary
Labetalol	100mg po BID or TID	1200mg/day (300mg QID)	Bradycardia, hypotension, fatigue, headache (usually resolves after 48 hours)	Atenolol avoided because of fetal growth restriction, and during lactation due to neonatal bradycardia
Nifedipine XL (Adalat®)	30mg po daily. Can also start 20mg daily. Usually dosed twice daily in pregnancy	120mg/day (60mg BID)	Peripheral edema, headache, hypotension	Comes in 20, 30, 60 and 90 mg XL.
Methyldopa	250mg po BID	2g/day (500mg QID)	Fatigue, sedation	

Table 2. First line antihypertensives for non-severe hypertension. (CHS 2018)

ACE inhibitors/ARBs

ACE inhibitors and angiotensin receptor blockers are contraindicated during pregnancy. A large database study published in NEJM 2006 (Cooper et. al) showed an increased risk of cardiac and CNS malformations when exposed in the first trimester. This data is debated as the trial was not randomized and did not take into account confounders such as diet-controlled diabetes, which is known to be associated with congenital malformations. Second and third trimester use has been associated with oligohydramnios, fetal renal failure and hypocalvaria. Although there is less data on angiotensin receptor blockers (ARB), the existing data indicates that rates of the above are higher in fetuses exposed to ARB's than ACE's.

A small set of women may be counseled to continue ACE-I while attempting conception. For example, women with significant diabetic nephropathy clearly benefit from ACE-I long-term, and conception can easily take months to years to occur. In these patients, stopping ACE-I while planning pregnancy may worsen long-term maternal renal health. These patients could be counseled by obstetrics/obstetric internists/nephrologists/endocrinologists to continue ACE inhibition while trying to become pregnant, with clear instructions to discontinue the medication as soon as a positive pregnancy test is found.

ACE are generally safe in lactation although the evidence is limited to the use of Enalapril, Captopril and Quinapril. They are considered safe given the low levels found in breast milk which is not expected to cause adverse effects in the infant.

Mild to Moderate Hypertension

A Cochrane review in 2018 of 58 trials involving more than 5900 women studying the benefits of treating mild to moderate hypertension showed that it reduces the risk of severe hypertension (Abalos Cochrane 2018). Specifically, it halved the rate of severe hypertension in the moderate hypertension group. Beta blockers and calcium channel blockers were more effective than alternatives at preventing severe hypertension. No difference was found in maternal or fetal mortality, rates of pre-eclampsia, preterm delivery, or small for gestational age babies. Many studies were noted to be small and poorly designed, so more high quality RCTs are needed to provide outcome data in this group.

Severe Hypertension

Severe hypertension (**SBP≥160 or DBP≥110**) in pregnancy is a medical emergency due to the risk of maternal stroke, placental abruption, and potential multiorgan complications if the underlying cause is preeclampsia. Patients need to be transferred to an acute care setting for emergent treatment of their hypertension and assessment of maternal and fetal adverse sequelae. A list of antihypertensive treatments can be found in Table 3. Note that most obstetric labour and delivery units are unable to use continuous infusions of labetalol or hydralazine; treatment is with boluses of medications, in addition to starting oral anti-hypertensives concurrently to provide basal and ongoing control of blood pressure once the acute agents wear off.

Agent	Dosage	Commentary
Nifedipine IR	Start with a 5 mg rapid acting capsule. Onset 5-10 minutes, peak effect seen at 30 minutes, duration of 4-6 hours.	
Labetalol	Start with 20 mg IV, repeat 20-80 mg IV q30min, max 300 mg (then switch to oral). If pressure non-responsive, can run infusion at 1-2 mg/min.	Avoid in severe asthma and decompensated heart failure. Be aware of neonatal bradycardia.
Hydralazine	Start with 5 mg IV, repeat 5-10 mg IV q30 minutes. If unresponsive, can run infusion at 0.5-10 mg/hr IV.	Can cause reflex tachycardia without a beta-blocker.

Table 3. Antihypertensives for severe hypertension. (CHS 2018)

N.B. Nifedipine comes in two formulations **XL** (extended release) and **IR** (immediate release). Extended release comes in a slow release capsule and is used to treat non-severe hypertension. The pill cannot be “split in half” due to the capsule mechanism, therefore a separate prescription need to be given for dose reduction from 60mg to 30mg for instance. The immediate release is often used to treat *inpatient* severe hypertension. When given orally, time of onset is 30 to 45 minutes with duration of effect of 4-6 hours.

CHS 2018 Hypertension Algorithms

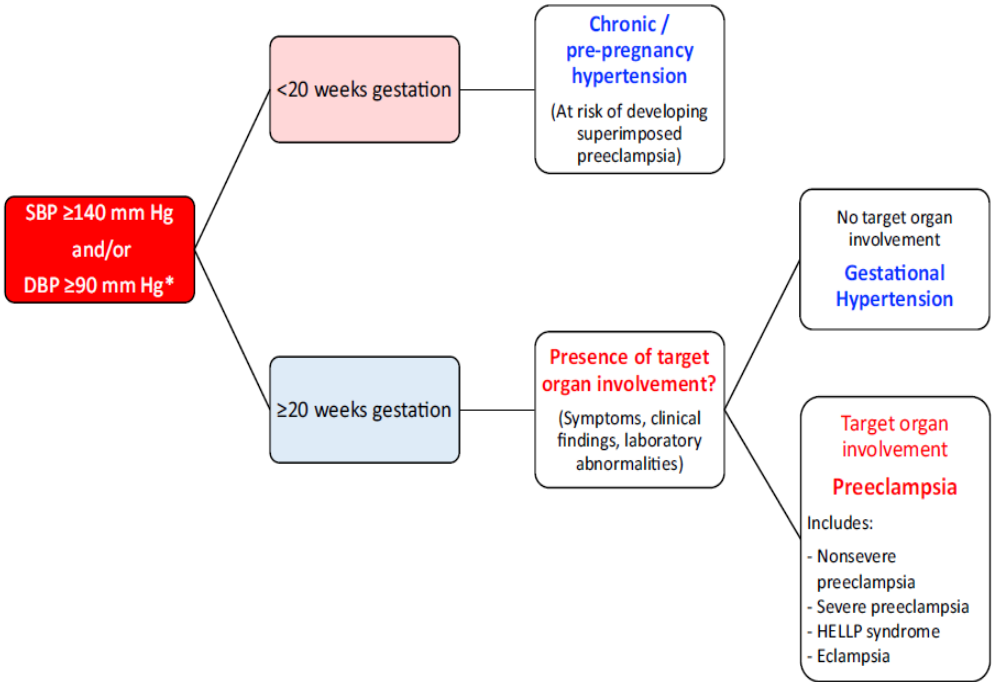

Figure 2. Diagnosis of hypertension in pregnancy.

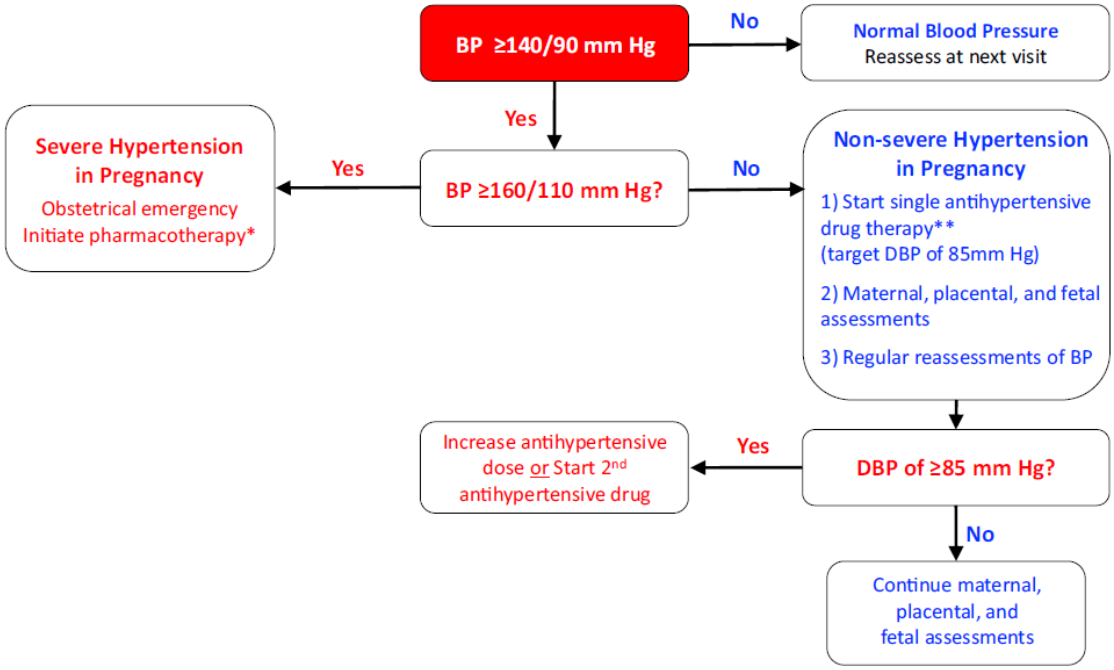

Figure 3. Treatment of severe and non-severe hypertension in pregnancy.

Pre-eclampsia

Definition

- Multisystem disorder usually occurring **after 20 weeks gestation**, related to underlying placental dysfunction. Characterized by hypertension plus new end-organ damage
- **Early onset pre-eclampsia** is onset before 34 weeks of gestation
- **Severe pre-eclampsia** is pre-eclampsia complicated by one or more severe complications (see diagnosis section)

Pathophysiology (currently accepted theory)

- Best understood using a 2-stage model.
- Stage 1 (first trimester): Placental Syndrome. Failure of maternal spiral arteries to remodel from high to low resistance and impaired depth of invasion of trophoblast leads to poor placentation and reduced placental perfusion.
- Stage 2 (after 20 weeks): Maternal/Fetal Syndrome. Clinical signs which occur as a result of endothelial activation/injury, characterized by hypertension with end-organ damage (described below) as well as fetal complications such as growth restriction and stillbirth.
- The link between Stages 1 and 2: remains unclear, but it appears that placental products act on a pre-disposed maternal constitution.
    - Theory 1: Angiogenic factors ("s-flt", soluble endoglin) circulate and antagonize VEGF, leading to endothelial dysfunction. This is the leading theory at present.
    - Theory 2: shedding of syncytiotrophoblast into maternal circulation causes vasoconstrictive process.

Risk Factors

Maternal Factors	Paternal Factors	Fetal Factors
Prior pre-eclampsia Age < 18 or > 35 First pregnancy Chronic hypertension Diabetes Chronic kidney disease Systemic lupus erythematosus Antiphospholipid syndrome Obesity Metabolic syndrome Family history of pre-eclampsia (mother or sister) African American/Hispanic	Previously fathered a preeclamptic child Primip paternity Family history of PET	Multiple gestation (twins) Molar pregnancy Genetically abnormal fetus

Table 4. Risk factors for pre-eclampsia.

History:

- headache/dizziness/altered LOC/vision changes (cerebral edema)
- dyspnea/chest pain (pulmonary edema)
- nausea/vomiting, RUQ pain (hepatic dysfunction/subcapsular hematoma/hepatic rupture or infarct)
- new edema/anasarca (interstitial edema/LV dysfunction/renal failure)
- seizure (eclampsia)

Physical exam:

- Vitals, complete exam, looking for signs of end organ dysfunction
- HEENT: papilledema, CNS exam if indicated (eg decreased LOC)
- CVS: heart sounds, JVP, peripheral edema
- Resp: pulmonary edema
- Abdo: RUQ pain, liver exam
- Neuro: hyperreflexia, clonus

Investigations:

- Hb, Plt, Cr, AST/ALT, Bilirubin, LDH, INR/PTT, fibrinogen, blood film, uric acid
- Evaluation for proteinuria:
    - Can screen with **urinary dipstick** testing when suspicion is low. Suspect significant proteinuria when urinary dipstick proteinuria is > 1+, however may be falsely elevated due to hemo-concentration so measure PCR for confirmation
    - Significant proteinuria is defined as ≥ 300m g/day in a complete 24-hour collection or **protein to creatinine ratio** (PCR) ≥ 30 mg/mmol in a random sample.

Diagnosis (SOGC 2014):

- Hypertension (two readings of >140/90 or one reading >160/110), *plus*
    - new or worsening proteinuria, *or*
        - ≥2+ on dipstick, PCR >30mg/mmol, or >300mg of protein on 24 urine collection
    - one or more adverse conditions, *or*
    - one or more severe complications (i.e. severe pre-eclampsia)

The definition of pre-eclampsia is evolving over time. Diagnosis of pre-eclampsia has progressed from a restrictive definition (hypertension plus proteinuria) to broader definition (hypertension plus one of proteinuria, adverse condition or severe complication). Currently, the presence of proteinuria is not needed to make a diagnosis of pre-eclampsia if you have evidence of end organ dysfunction. American guidelines have a more precise diagnostic criteria for pre-eclampsia, which includes specific symptoms (e.g. cerebral or visual symptoms), signs (e.g. pulmonary edema), and biochemical cutoffs (e.g. platelet <100, Cr >1.1mg/dL, liver enzymes >2x ULN). (ACOG 2013)

SOGC 2014 stratifies the severity of end organ damage into adverse conditions and severe complications (Table 5). It is important to realize that this classification is most used as outcome measures for research purposes and should be used with caution in guiding pre-eclampsia treatment. In other words, a patient with an adverse outcome is by no means "less sick" than a patient with a severe complication, as the maternal and fetal complications are not always congruent in pre-eclampsia. Therefore, the decision for delivery should be made taking into account the patient's clinical status as a whole, rather than assuming that those with severe complications should always be delivered more imminently than those with adverse conditions, as SOGC 2014 guideline suggests.

Organ system	Adverse Conditions	Severe Complications
CNS	Headache Visual symptoms	Eclampsia Stroke, TIA PRES Cortical blindness or retinal detachment GCS <13
Cardiorespiratory	Chest pain Dyspnea Oxygen saturation <97%	Uncontrolled severe hypertension (despite use of 3 antihypertensives) Oxygen saturation <90%, need for >50% oxygen, intubation, pulmonary edema Inotropic support MI
Hematologic	Elevated WBC Elevated INR or aPTT Low platelet count	Platelet < 50 HELLP Transfusion of any blood product
Renal	Elevated creatinine Elevated uric acid	Acute kidney injury (Cr <150) Dialysis
Hepatic	Nausea or vomiting RUQ or epigastric pain Elevated AST, ALT, LDH or bilirubin	Hepatic dysfunction Hepatic hematoma/rupture/infarct
Feto-placental	Abnormal fetal heart rate IUGR Oligohydramnios Absent or reversed end diastolic flow of umbilical artery	Placental abruption with maternal or fetal compromise Reverse ductus venosus A wave Stillborn

Table 5. Maternal and fetal adverse conditions and severe complications by body systems.

HELLP

HELLP is an acronym for Hemolysis, Elevated Liver enzymes, Low Platelets. It is a severe complication of pre-eclampsia, but about 10 to 20% of HELLP can occur without antecedent pre-eclampsia. Laboratory parameters include presence of microangiopathic hemolytic anemia, platelets <100, or AST more than twice above upper limit of normal; however, not all abnormalities are necessary to call it HELLP (somewhat like we don't require all the aspects of the pentad present in order to raise suspicion of TTP!) Liver enzymes are usually the first lab abnormality of HELLP and can be elevated into the thousands due to ischemic liver. It can lead to complications such as subcapsular hematoma, hepatic infarct, or hepatic rupture. It is therefore prudent to image those with severe right upper quadrant pain and consider general surgery or interventional radiology consultation as appropriate. Thrombocytopenia is the other leading presentation of HELLP and transfusion if recommended if bleeding, platelet count less than 20, or below the requirement for mode delivery or neuraxial anesthesia. By contrast, hemolytic anemia is frequently a late finding. Treatment of HELLP is the same as for pre-eclampsia (delivery, supportive care, eclampsia prophylaxis). After delivery, one should expect initial deterioration followed by rapid improvement of the laboratory abnormalities within days. If the biochemical derangements remain persistent or worsen, other differential diagnoses must be considered including ITP, TTP, or acute fatty liver of pregnancy.

Treatment

Treatment of pre-eclampsia consists of three aspects: hypertension treatment, monitoring and management of multiorgan involvement (including eclampsia prevention), and delivery of the fetus and placenta. Generally, intravenous fluids should be minimized in women with pre-eclampsia given the capillary leakage secondary to the systemic inflammatory state to prevent volume overload and in particular pulmonary edema.

1. Hypertension management

It is important to realize that treating the hypertension does not halt the progression of pre-eclampsia as it is a multisystem inflammatory disorder that stems from an abnormal placenta. Controlled blood pressure does provide maternal protection from the effects of severe hypertension, such as stroke and placental abruption. Blood pressure can usually be managed with mostly oral agents and in the setting of severe hypertension short acting IV agents alone (Table 2 and 3), without needing intravenous infusions of antihypertensives. If patients are started on Magnesium Sulfate infusion for eclampsia prevention or treatment, antihypertensives may need to be reduced or held during that period as magnesium is a potent vasodilator.

2. Eclampsia prevention

Magnesium Sulfate is used as prophylaxis against eclampsia in women with severe pre-eclampsia (Table 6). It is also the first line treatment of eclampsia. Often it is the obstetricians who make the decision to start Magnesium and varying clinical practices exist in terms of the indications for initiation. If started, Magnesium is given through an initial bolus (e.g. 4g IV) then 24-hour infusion (e.g. 1g/hr). The dose may be reduced if someone has renal dysfunction to prevent Magnesium toxicity. Its benefit of seizure prevention is only effective during the time the infusion is run, not thereafter. A recent RCT conducted in 1100 women with severe pre-eclampsia showed that there is no benefit to continuing Magnesium postpartum for seizure prevention if already exposed to it for a minimum of 8 hours before delivery (Vigil-DeGracia BJOG 2018). This is not to be confused with the Magnesium infusion given over 4 hours in preterm fetuses less than 34 weeks gestation to reduce the risk of cerebral palsy, which is a routine practice.

Indications for Magnesium Sulfate
Severe pre-eclampsia (see diagnosis section) (1-A) Non-severe pre-eclampsia with (1-C) - severe hypertension - headache/vision symptoms, RUQ pain - platelets <100 (i.e. HELLP), elevated liver enzymes, renal insufficiency Eclampsia

Table 6. Indications for Magnesium Sulfate use in pre-eclampsia (SOGC 2014).

The use of Magnesium Sulfate in eclampsia prevention comes from the landmark trial **MAGPIE** (Altman Lancet 2002). It is a multicenter trial of over 10,000 women diagnosed with pre-eclampsia, which was defined as BP > 140/90 mm Hg and proteinuria, clinical uncertainty regarding benefit, and were pregnant or within 24 hours of delivery, were randomized to receive Magnesium or placebo, with the primary outcome being the rates of eclampsia. Women receiving Magnesium had a 58% relative risk reduction in eclampsia compared to the placebo (0.8 vs 1.9%, AAR of 1.1%, NNT 91). There was a trend towards decreased maternal mortality that was non-significant. No difference was seen in fetal mortality, maternal or neonatal morbidity, except a lower rate of placental abruption. Increased rates of side effects from the Magnesium arm overall, with most common being injection site related problems, flushing, nausea and vomiting, and respiratory depression.

All patients are at risk of **magnesium toxicity**, especially those with concurrent renal dysfunction since magnesium is renally excreted. Therefore, all patients need increased monitoring and nursing care, usually in the labour and delivery unit. Symptoms of magnesium toxicity include altered level of consciousness, respiratory depression, hypotension and bradycardia. Signs include hyporeflexia (patient must all have a foley). Serum magnesium is not used to monitor levels or diagnose toxicity. In suspected toxicity, one should stop the Magnesium infusion and give the antidote Calcium Gluconate.

3. Delivery

The decision to deliver should always be made by the obstetrician. Obstetric internists can provide assistance particularly by identifying maternal complications of pre-eclampsia that warrant delivery. Below are the five common reasons why a patient with pre-eclampsia should be delivered, categorized into maternal and fetal indications (Table 7).

Maternal indications	Fetal indications (determined by OB)
• Resistant hypertension (exceeding max doses of 3 agents) • Refractory maternal symptoms • Severe end organ damage (ex. Pulmonary edema, Renal failure, DIC, HELLP)	• Fetal distress (ex. Abnormal fetal heart rate, severe IUGR) • Adequate gestational age achieved (ex >37 weeks)

Table 7. Indications for delivery in pre-eclampsia.

Ultimately, placental delivery is the only intervention that initiates the resolution of pre-eclampsia. It is important to remember that the disease does not resolve immediately upon delivery and often days to months is needed for all adverse conditions to normalize. Sometimes pre-eclampsia can persist or worsen postpartum and one must consider the possibility of retained products of conception and alert the obstetrician as appropriate. Of note, 10% of pre-eclampsia develops de novo postpartum despite an uneventful pregnancy. This could be because the inflammatory pre-eclamptic state had begun in the antepartum period but remained subclinical, becoming clinically evident shortly into the postpartum period.

In patients with pre-eclampsia, vaginal delivery can be considered unless C-section is indicated for obstetric reasons (e.g. breech fetus, extreme prematurity). Mode of delivery is determined by the obstetric team. Anesthesiologists should be informed when a woman with pre-eclampsia is admitted. In the absence of contraindications (i.e. severe thrombocytopenia), all forms of anesthesia are acceptable for women with pre-eclampsia: epidural, spinal, general anesthesia.

For gestational hypertension and mild pre-eclampsia, the 2009 HYPITAT study showed that after 36 weeks expedited delivery (with induction of labour) versus expectant management led to a lower risk of poor maternal outcomes and no difference in neonatal outcomes in delivered patients. The 2015 HYPITAT-II study showed that in a similar population of women between 34-37 weeks GA, immediate delivery significantly increased the risk of neonatal respiratory distress, with a non-significant reduction in the risk of maternal adverse outcomes. Therefore, the optimal timing for delivery is likely after 37 weeks gestation (term) for this cohort of women, whereas expectant management is recommended for preterm patients (<37 weeks) with gestational hypertension and pre-eclampsia without severe features or an indication for delivery (Table 7).

Pre-eclampsia prevention and prognosis

The risks of recurrent pre-eclampsia ranges from 10-40% depending on severity, gestational age at diagnosis, and outcomes in index pregnancy. Below are the investigations and treatments to consider in a patient with a history of pre-eclampsia in order to lower their risk for the same in a subsequent pregnancy.

1. Aspirin

- Indications (US task force)
    - Previous pre-eclampsia
    - Chronic hypertension
    - Type 1 or 2 diabetes
    - Chronic kidney disease
    - Systemic lupus erythematosus
    - Antiphospholipid syndrome
    - Multiple gestation
    - Two or more of the following: age >35, nulliparity, BMI>30, first degree family history of pre-eclampsia, personal history (low birthweight or small for gestational age baby, previous adverse pregnancy outcome, >10-year pregnancy interval), sociodemographic characteristics (African American, low socioeconomic status)

- Dose
    - 81-162mg daily
    - Aspirin 81mg at night shown to reduce recurrence by 10%, NNT of 114. ASPRE trial of 1770 women comparing Aspirin 150mg to placebo showed decreased risk of preterm pre-eclampsia, ie, delivery less than 34 weeks (Daniel NEJM 2017).
    - Generally, if at risk of pre-eclampsia and low risk of bleeding, suggest 162mg daily of Aspirin.

- Timing
    - Most effective if started before 16 weeks (typically 10-12 weeks). Stop at 36 weeks to minimize risk of bleeding at delivery.
    - Usually start between 8-12 weeks, but can start after 16 weeks if indicated and patient not already on it.
    - Can be continued to the time of delivery if high risk (ex. previous pre-eclampsia), since both delivery and neuraxial anesthesia can be done while on Aspirin. Aspirin should be continued peripartum if being used for other indications, such as antiphospholipid syndrome, coronary artery disease, cerebrovascular disease.

2. Calcium: 1000mg daily of calcium supplementation is recommended for women with low dietary intake of less than 600mg of calcium. Note that a serving of dairy has 200 mg of calcium.

3. Antiphospholipid testing

Should be done 3 months postpartum for patients with early pre-eclampsia (<34 weeks gestation). The clinical criteria for diagnosis of antiphospholipid syndrome include 1 preterm delivery < 34 weeks due to severe pre-eclampsia or other placental disease, 1 unexplained fetal loss after 10 weeks gestation, 3 or more spontaneous miscarriages before 10 weeks, or a venous or arterial thrombotic event (see APLA syndrome in Hematology section). If diagnosed with obstetric antiphospholipid syndrome, anticoagulation with prophylactic dose of LMWH may be used in prevention of pre-eclampsia in subsequent pregnancies in addition to Aspirin.

4. Biomarkers

Placental Growth Factor (PLGF) is a new and increasingly important marker in the management of pre-eclampsia. It is a member of the VEGF (Vascular Endothelial Growth Factor) family secreted by the placenta, thought to precede the manifestation of clinical disease in pre-eclamptic pregnancies. Low PLGF levels are associated with high likelihood of developing clinical pre-eclampsia (<12 pg/mL), high levels are thought to be protective (>100 pg/mL), and grey zone in between.

5. Placental ultrasound

Placental ultrasound is the anatomic assessment of the placenta as well as the Doppler measurements of the umbilical and uterine arteries. For patients with previous severe pre-eclampsia or catastrophic obstetric outcomes, having abnormalities on the placental scan can be the first sign of a recurrent abnormal pregnancy. Placental ultrasounds are usually performed around 22 weeks gestation but can be done as early as 16 weeks. Markers of placental vasculopathy that increases the risk of developing pre-eclampsia includes anatomic placental abnormalities (short and thick rather than the normal long and thin) and elevated resistance in umbilical or uterine arteries (increased Pulsatility Index).

Postpartum care

Due to the normalization of peripheral vascular resistance, shift of third space fluids intravascularly, and often excessive intravenous fluids administered peripartum, blood pressure tends to **rise 3 to 5 days** postpartum. Therefore, patients are encouraged to continue with antihypertensive therapy and to monitor blood pressure closely during the first week postpartum. The target blood pressure is < 140/90 mm Hg.

All agents safe in pregnancy can be used during lactation. Dihydropyridine calcium channel blockers and most beta blockers are safe in lactation, with the exception of Atenolol which should be avoided due to the risk of infant bradycardia. ACE inhibitors safe in lactation include Enalapril (twice daily), captopril (three times daily) and quinapril (once daily). ACE inhibitors should be resumed postpartum, provided if renal function is stable, in patients with pre-existing nephropathy. Thiazides are safe in lactation but should only be started once lactation and milk supply are well established.

Women with gestational hypertension or preeclampsia should be able to come off blood pressure medications in time. In general, the longer their disease was present before delivery, the longer it will take to titrate off medications. This could take weeks to months. Approximately 10% of patients will evolve into chronic hypertension and requires antihypertensives for life.

Future cardiovascular risk

One of the most critical roles of the obstetrical internist is to educate women with hypertensive diseases in pregnancy regarding their future cardiovascular risk. Women with preeclampsia have a nearly **4x increased risk** of developing hypertension later on in life and **2x risk** of heart disease, stroke or venous thromboembolism. The risk of developing diabetes and dyslipidemia are also increased by 1.8 and 1.3 times, respectively. (Stuart Annals Internal Medicine 2018).

Women need to be counseled after pregnancy on the importance of lifestyle modification, physical activity, healthy eating and smoking cessation. We would recommend an annual assessment of traditional cardiovascular risk factors and earlier screening by their primary care physician.

Common Endocrine disorders in pregnancy

Pre-existing Diabetes

Diabetes and Pregnancy

Pregnancy is a time of insulin resistance. Placental secretion of growth hormone, corticotropin releasing hormone, placental lactogen and progesterone all increase maternal insulin resistance in order to meet the growing metabolic needs of the fetus. Gestational diabetes develops in those women whose pancreatic function is unable to meet these demands.

Hyperglycemia is a teratogen. Uncontrolled diabetes can lead to maternal, fetal and neonatal complications (Table 1).

Maternal	Fetal	Neonatal
Gestational hypertension Pre-eclampsia Worsening retinopathy, neuropathy, nephropathy Diabetic ketoacidosis Hypoglycemia Infection (e.g. UTI) Coronary artery disease Thromboembolism Cesarean and instrumental delivery Traumatic labour, including pelvic injuries Postpartum hemorrhage	Congenital malformations (e.g. cardiac defects, neural tube defects, cleft lip and palate) Miscarriage Macrosomia Preterm labour Stillbirth	Hypoglycemia Hypocalcemia Hyperbilirubinemia Respiratory distress syndrome Shoulder dystocia Erb's palsy

Table 1. Complications of diabetes in pregnancy.

Pre-conception Care (Diabetes Canada Guidelines 2018)

- Pregnancy should be planned for patients with type 1 or 2 diabetes.
- Aim for **A1c<7%**, ideally <6.5%. Need to counsel on contraception if diabetes is poorly controlled. HbA1c >10% is most closely associated with teratogenicity.
- Stop:
    - Non-insulin antihyperglycemic agents, except for Metformin and Glyburide.
    - Statins

- May continue:
    - ACE/ARB if overt nephropathy until pregnancy confirmed.

- Start:
    - Folic acid 1mg daily for 3 months preconception.
    - Insulin if target A1c if not achieved on Metformin and/or Glyburide.
    - Antihypertensive agents safe for pregnancy if hypertension not controlled.
- Screen for complications: eye exam, Cr, urine ACR, blood pressure, HbA1c, +/- ECG/ECHO.
- Ensure vaccinations are up to date.
- Aim for healthy BMI.

Antepartum management

- Patients should be managed in a diabetes clinic with multidisciplinary team including nurse educator and dietician.
- Insulin therapy with basal-bolus (T2DM) or continuous subcutaneous infusion (T1DM) is recommended to achieve glycemic targets during pregnancy.
- Women with type 1 diabetes should be offered a continuous glucose monitor (CGM) as it has been shown to achieve more time in target glucose, lower rates of neonatal hypoglycemia, large for gestational size, and NICU admissions (CONCEPTT Trial).
- Glucose monitoring and targets:
    - Glucose testing 4 times a day: fasting, 2 hours post breakfast, lunch and dinner.
    - Targets: fasting < 5.3 mmol/l, 2-hour post meals <6.7 mmol/l.
    - The target for 1-hour post meal is <7.8 mmol/l for patients that cannot measure the 2-hour post reading (e.g. due to time constraints).
- Insulin requirements may drop in first trimester followed by an increase seen in later trimesters due to the “anti-insulin” effects of placental hormones. Marked and **rapid decrease in insulin** need is thought to be **related to placental insufficiency** (ie. need to monitor for maternal pre-eclampsia and/or fetal compromise).
- Women with pre-existing diabetes should be monitored frequently by the obstetrician for fetal complications. Weekly monitoring starting at 34-36 weeks with induction planned between 38-39 weeks is aimed to reduce preventable stillbirths.
- Glycemic control during labour and delivery depends on the protocols established at each hospital. The goal is blood sugar of 4-7 to avoid maternal hypoglycemia while preventing significant hyperglycemia, which is associated with neonatal hypoglycemia. Options include watchful waiting until blood glucose rises above a certain level, presumptive initiation of intravenous insulin infusion, or continuing subcutaneous insulin bumps for type 1 diabetes.
- Beware of decreasing insulin requirements at the end of pregnancy as it indicates declining placental function, and may be the harbinger of preeclampsia or impending fetal compromise.
- Diabetic ketoacidosis during pregnancy can be a catastrophic event associated with severe fetal complications including fetal hypoxia and intrauterine fetal demise. A rare entity of euglycemic DKA, whereby ketosis and acidosis occur in the absence of overt hyperglycemia, is usually reported in type 1 diabetes and should be recognized early and treated promptly.

Postpartum management

- Insulin dose decrease immediately postpartum below pre-pregnancy dose in order to prevent hypoglycemia.
- Frequent blood glucose monitoring in the first day postpartum with titration of insulin as needed to achieve good glycemic control.
- Effective contraception should be discussed until preparation for a subsequent pregnancy is achieved.

Gestational Diabetes

Risk Factors

- Previous history of gestational diabetes, ethnicity (Aboriginal, Asian, African, Hispanic), age ≥ 35, obesity, previous macrosomic infant, previous stillborn or malformed infant, PCOS, family history, and metabolic syndrome.

Prevention

- Achieving a healthier body weight (i.e. BMI of 18.5-25) should be the goal for patient who are overweight or obese.
- Replacing high glycemic index carbohydrates with low glycemic index foods and consistency in spacing and intake of carbohydrates may help prevent diabetes and control weight.
- A minimum of 150 minutes per week of moderate to high level of aerobic exercise with at least two sessions of resistance exercise is recommended.

Screening (Diabetes Canada 2018)

- OGCT (oral glucose challenge test) at 24 to 28 weeks (Figure 1). 50g of glucose with 1-hour blood sugar measurement.
- If OGCT between 7.8-11.0, then go onto an OGTT (oral glucose tolerance test) of 75g of glucose with 1-hour and 2-hour measurements.
- For higher risk individuals (i.e. obesity, strong family history of diabetes, or those with a history of GDM), earlier screening with an HbA1c or glucose challenge test is recommended before 20 weeks gestation. This is to detect glucose intolerance in early pregnancy, perhaps unrecognized type 2 diabetes. Of note, pregnancy leads to a reduction in HbA1c. If HbA1c is >6.5%, patients should be considered to have diabetes in pregnancy and treated the same as patients with pre-existing diabetes.

Treatment

- Diet and exercise are prescribed initially. Nutritional counselling by a dietician should be provided to help achieve appropriate carbohydrate intake, weight and blood sugar goals.
- If blood sugar target is not achieved in 1-2 weeks with non-pharmacologic therapy, insulin should be initiated. Insulin in the form of basal-bolus regimen can be used as first line therapy.
- Glucose monitoring and targets:
    - Glucose testing 4 times a day: fasting, 2 hours post breakfast, lunch and dinner.

    - Targets: Fasting < 5.3 mmol/l, 1-hour post < 7.8 mmol/l, 2-hour post < 6.7 mmol/l. For patients on insulin maintain blood glucose >3.7.
- Women that decline insulin or do not tolerate it can be controlled on Metformin or Glyburide.
    - Glyburide is considered safe and effective in > 80% of women (Langer et al., NEJM 2000).
    - Metformin may be used as an alternative to insulin (MiG trial, NEJM 2008). Women need to be informed that Metformin crosses the placenta and longer-term studies of neonatal complications are not available. The MiTY trial is currently undergoing to determine the effect of adding Metformin to insulin in pregnancy in type 2 diabetes (expected publication summer 2020).
- Increased fetal surveillance in patients with GDM. Women are generally offered induction between 38-40 weeks to reduce the risk of stillbirth and cesarean section.
- Intrapartum the target of BS is between 4-7. The goals is to prevent severe hyperglycemia to prevent neonatal hypoglycemia. May require insulin infusion if elevated BS.

Postpartum

- Stop all insulin immediately postpartum as insulin requirements drop postpartum.
- Women should be encouraged to breastfeed immediately after delivery to prevent neonatal hypoglycemia.
- Screened with OGTT 6 weeks to 6 months postpartum to test for prediabetes or overt diabetes.
- Within 10 years, 20% of women with GDM will develop T2DM. Approximately 50% of women will have GDM again in subsequent pregnancies.

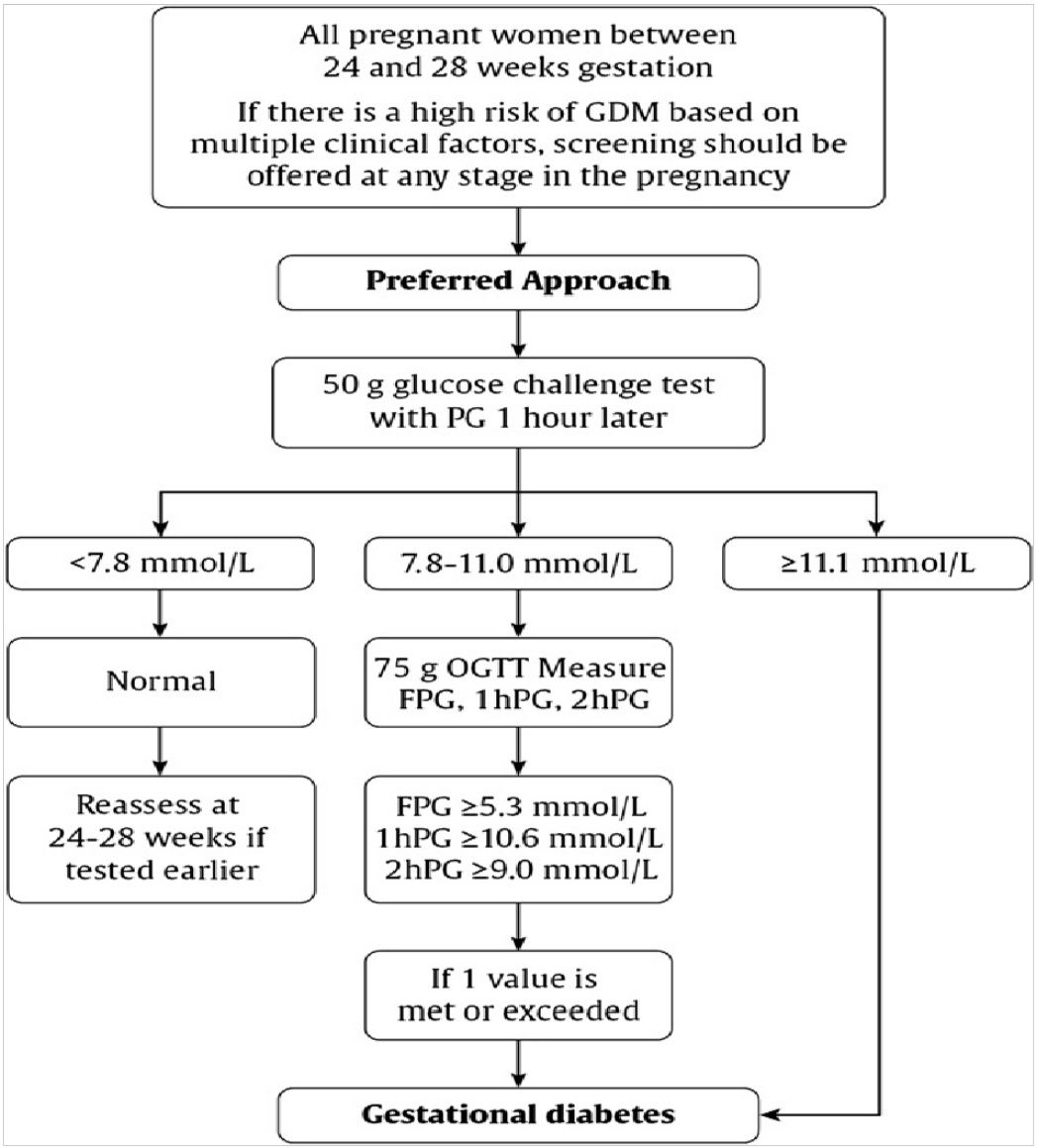

Figure 1. Screening for gestational diabetes in pregnancy (Diabetes Canada 2018).

Thyroid disease in pregnancy

Hypothyroidism in Pregnancy

Epidemiology

- Hypothyroidism affects approximately 1-5% of all pregnancies.
- The most common cause of hypothyroidism in pregnancy in iodine replete countries is autoimmune hypothyroidism (i.e. Hashimoto's). Other causes include post-ablation, post-thyroidectomy, central hypothyroidism, or medication induced.
- For those with Graves' disease who have undergone thyroidectomy or radioactive iodine and may be on thyroid replacement, it is important to still consider measuring thyroid receptor antibodies as it may be in the maternal circulation and can cross the placenta and cause fetal complications (see hyperthyroidism section).

Pathophysiology

- b-HCG has thyrotropic (TSH like) activity resulting in an increase of thyroid hormone production and a decrease in TSH concentrations. This results in a large decrease in TSH observed during the first trimester, and an overall lower TSH reference range in pregnancy (TSH 0.1-4).
- Thyroid binding globulin (TBG) increases due to placental secretion of estrogen, thereby increasing total T4 levels, while free T4 levels stays the same.
- Pregnancy is a state of increased maternal iodine requirements as a result of active transport to the feto-placental unit and increase renal clearance of iodine due to increase in glomerular filtration rate.
- Maternal T4 crosses the placenta and is detected in the fetal brain in the first half of pregnancy before the fetal thyroid maturation. T3 does not cross the placenta.

Definitions

The categorization of hypothyroidism is very important as the fetal outcomes are different for overt and subclinical hypothyroidism (see adverse outcomes section). Many may find this definition confusing as it continues to evolve.

Overt Hypothyroidism (OH)
- Elevated TSH (≥2.5) *and* decreased free T4 (fT4), *or*
- TSH >10.0

Subclinical Hypothyroidism (SCH)
- TSH 2.5 – 10.0 with normal fT4

Anti-thyroid peroxidase (anti-TPO)

- Associated with autoimmune hypothyroidism (Hashimoto's thyroiditis) and post-partum thyroiditis
- Positive antibody increases the risk of overt hypothyroidism in patients with subclinical hypothyroidism and autoimmune disease (e.g. Type 1 diabetes)

Adverse outcomes

Overt Hypothyroidism

- Strong association with adverse maternal-fetal outcomes if untreated. Adequately treated subclinical or overt hypothyroidism have no increased risk of any obstetrical complications.
- Maternal: gestational hypertension, preeclampsia
- Fetal: miscarriage, premature birth, low birth weight, fetal death, neurocognitive deficit (IQ, motor, language and attention) (Haddow NEJM 1999)

Subclinical Hypothyroidism: adverse fetal outcomes are early

- Increased rates of miscarriage, especially with anti-TPO positivity (Negro J Clin Endocrinol Metab 2010; Liu Thyroid 2014)
- No evidence of neurocognitive deficits at 3-5 years (Lazarus NEJM 2012; Casey NEJM 2017)

Thyroid screening

Despite the above complications, **routine thyroid screening is not recommended** in asymptomatic pregnant patients because universal screening has not been shown to decrease adverse events when compared with targeted screening. TSH testing is only recommended in women who are symptomatic or has one or more risk factors (Table 2). However, in clinical practice TSH is often measured as a part of the perinatal bloodwork, especially by family physicians and infertility specialists, with abnormal values often investigated and treated.

History of hypo/hyperthyroidism or current symptoms of thyroid dysfunction
Known thyroid Ab positivity or presence of goiter
History of head & neck radiation or prior thyroid surgery
Age >30 years
Type 1 diabetes or other autoimmune disorder
History of pregnancy loss, preterm delivery or infertility
Multiple prior pregnancies
Family history of autoimmune thyroid disease or thyroid dysfunction
Morbid obesity (BMI > 40)
Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
Residing in an area of iodine insufficiency

Table 2. Indications for TSH testing (American Thyroid Association 2017).
Approach to Thyroid Assessment (American Thyroid Association 2017)

Once thyroid function is tested, if initial TSH value is within normal limits (0.1-2.5), euthyroidism is diagnosed and further investigations and treatments are unnecessary unless there is a change in clinical condition (Figure 2). If overt hypothyroidism is found (TSH >2.5 and low fT4, or TSH > 10), then treatment with Levothyroxine is indicated. If TSH > 4 and normal fT4, then the diagnosis of subclinical hypothyroidism is made and thyroid replacement is indicated. If TSH is between 2.5 to 4, anti-TPO testing is suggested. If anti-TPO positive, Levothyroxine is indicated. If anti-TPO negative, thyroid replacement is generally not recommended unless patient has a history of recurrent miscarriages. Similarly, euthyroid patients (normal TSH and fT4) with positive anti-TPO may considered for thyroid therapy if has a history of miscarriages.

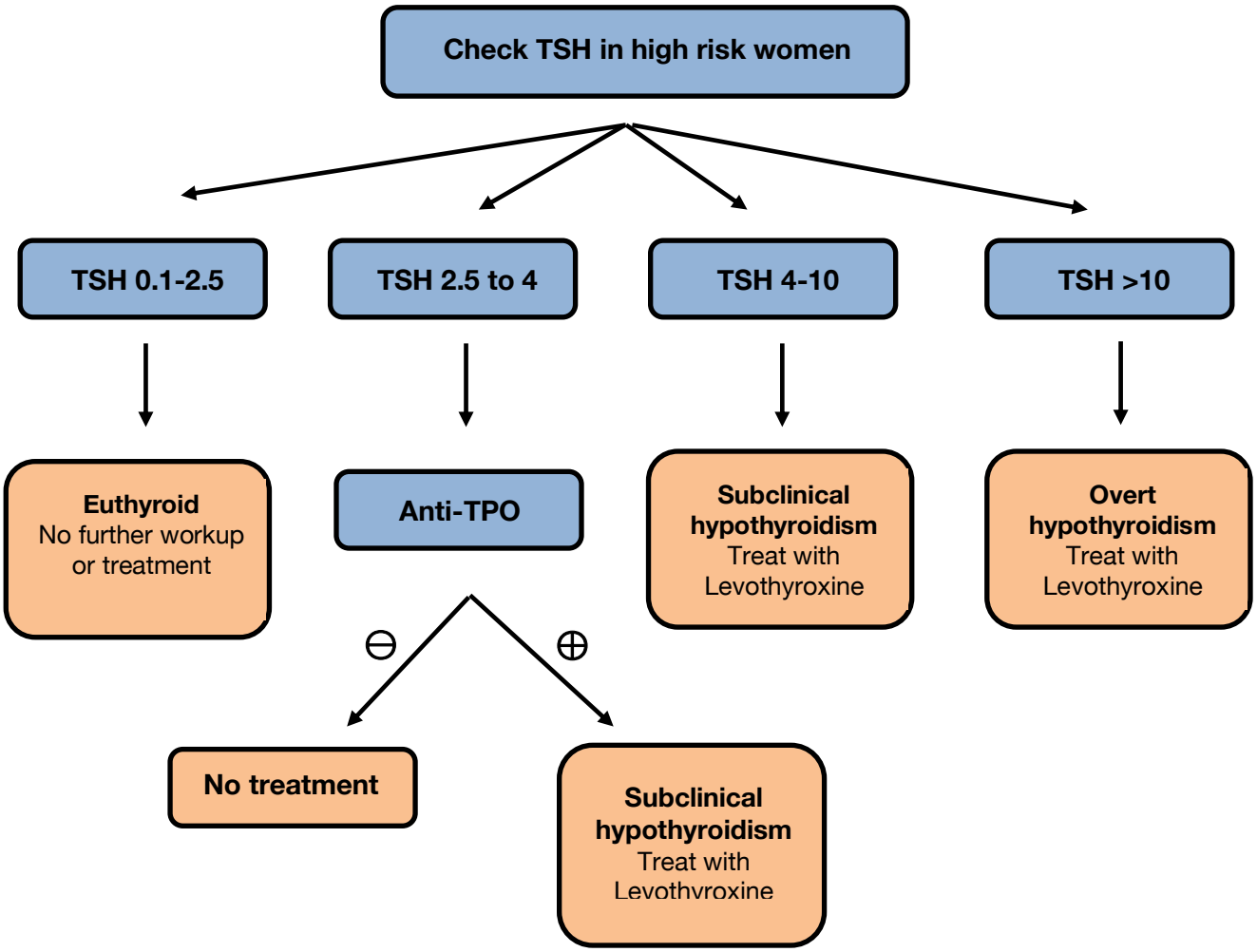

Figure 2. Algorithm of Hypothyroidism Investigation and Treatment Based on TSH Values. (ATA 2017)

Treatment

- Oral levothyroxine (LT4) is recommended for the treatment of maternal hypothyroidism. Oral T3 or desiccated thyroid should not be used in pregnancy.
- Starting dose
    - OH: start 50-100mcg daily (1.35 mcg/kg/day)
    - SCH: 25-50 mcg/day
- **Target TSH of 0.1 – 2.5** in all trimesters.
- Monitoring serial TSH and fT4 every 4 weeks until 20 weeks, then once between 26 – 32 weeks. TSH fluctuation and adjustment in thyroid dose is greatest in the first half of pregnancy and tend to stabilize for the remainder of pregnancy once optimal dose is achieved.
- Advise separating thyroxine from prenatal vitamins, milk, calcium or iron by at least 2 hours and meals by 1 hour due to interference with absorption.
- In adequately treated hypothyroidism, no additional obstetric testing or surveillance is indicated.

Pre-existing Hypothyroidism

- In hypothyroid women on treatment planning pregnancy, a serum TSH should be evaluated preconception and LT4 dose adjusted to achieve TSH value <2.5.
- **Empiric dose increase of 30%** should be done in patients with suspected or confirmed pregnancy. This can be done by doubling the weekend doses of thyroxine. For example, if chronically on Levothyroxine 50mcg daily, then take 50mcg Monday to Friday and increase to 100mcg Saturday and Sunday. Of note, in patients with prior thyroidectomy, thyroid ablation or history of thyroid cancer, larger additional dose increase of 40-45% may be required.
- Maintain TSH < 2.5 throughout pregnancy. Follow TSH every 4 weeks during the first 20 weeks and once between 26-32 weeks.
- Immediately postpartum LT4 should be **reduced to patient's preconception dose**. However, a study showed that women with Hashimoto's thyroiditis required an increase in pregestational thyroid hormone dose in the postpartum period (Galofre et al., Thyroid 2010).
- Repeat TSH testing should be performed at 6 weeks postpartum.

Postpartum care

- Levothyroxine is safe in breastfeeding.
- Overt hypothyroidism: patients newly started on LT4 in pregnancy should be continued on it postpartum.
- Subclinical hypothyroidism: LT4 is generally discontinued postpartum. Situations to continue thyroid replacement include those planning to conceive again, symptomatically improved, or anti-TPO positive (higher risk of postpartum thyroiditis and development of Hashimoto's).
- If antibody negative in pregnancy, recheck antibodies at least once postpartum as may convert after pregnancy.
- All women should have TSH checked 4-6 weeks postpartum or earlier if symptomatic.

- Patients who are anti-TPO positive have a high chance of developing postpartum thyroiditis and should be counselled on the symptoms of hypo and hyperthyroidism.
- Congenital hypothyroidism is universally screened by heel prick blood testing in all neonates in Ontario along with more than 25 other treatable conditions.

Hyperthyroidism in Pregnancy

Effects of Hyperthyroidism on Pregnancy

- Fetal complications include preterm birth, IUGR, fetal or neonatal hyperthyroidism.
- Maternal complications include gestational hypertension, pre-eclampsia, and thyroid storm.
- Anti-thyroid drugs (e.g. Methimazole) are associated with birth defects.
- Pregnancy should be postponed until a stable euthyroid state is reached.

Differential Diagnosis

- Pregnancy specific:
  - Gestational transient hyperthyroidism
  - Struma ovarii (teratoma with functional thyroid tissue)
  - Thyroiditis (e.g. postpartum)

- Non-pregnancy causes:
  - Graves' disease
  - Multi-nodular goiter
  - Toxic adenoma
  - Pituitary adenoma
  - Exogenous intake

The two most common causes of hyperthyroidism in pregnancy are gestational hyperthyroidism and Graves' disease. Less common causes include toxic multinodular goiter, toxic adenoma, and painful or painless thyroiditis.

Diagnostic approach to hyperthyroidism (American Thyroid Association 2017)

Any cause of hyperthyroidism can lead to symptoms such as palpitations, anxiety, tremor, and heat intolerance. If suspecting hyperthyroidism, begin by measuring the TSH (Figure 3). If TSH is low (<0.1) or undetectable, then measure free T4 and T3. If fT4 and fT3 are normal, then it is likely gestational hyperthyroidism (especially if between 12-16 weeks gestation) and no anti-thyroid treatment is indicated. If fT4 is elevated, thyrotoxicosis is diagnosed and it is important to differentiate between gestational hyperthyroidism and Graves' disease. Features consistent with gestational hyperthyroidism include lack of history of thyroid disease, self-limited mild disorder, and symptoms of hyperemesis. Presence of positive TSH receptor antibody (TRAb), ophthalmopathy, goiter, and dermatopathy can support a diagnosis of Graves' disease. Thyroid ultrasound can be ordered if evidence of a nodule on exam, however no studies have demonstrated the usefulness of ultrasound in differentiating gestational hyperthyroidism and Graves. **RAI uptake is contraindicated in pregnancy**.

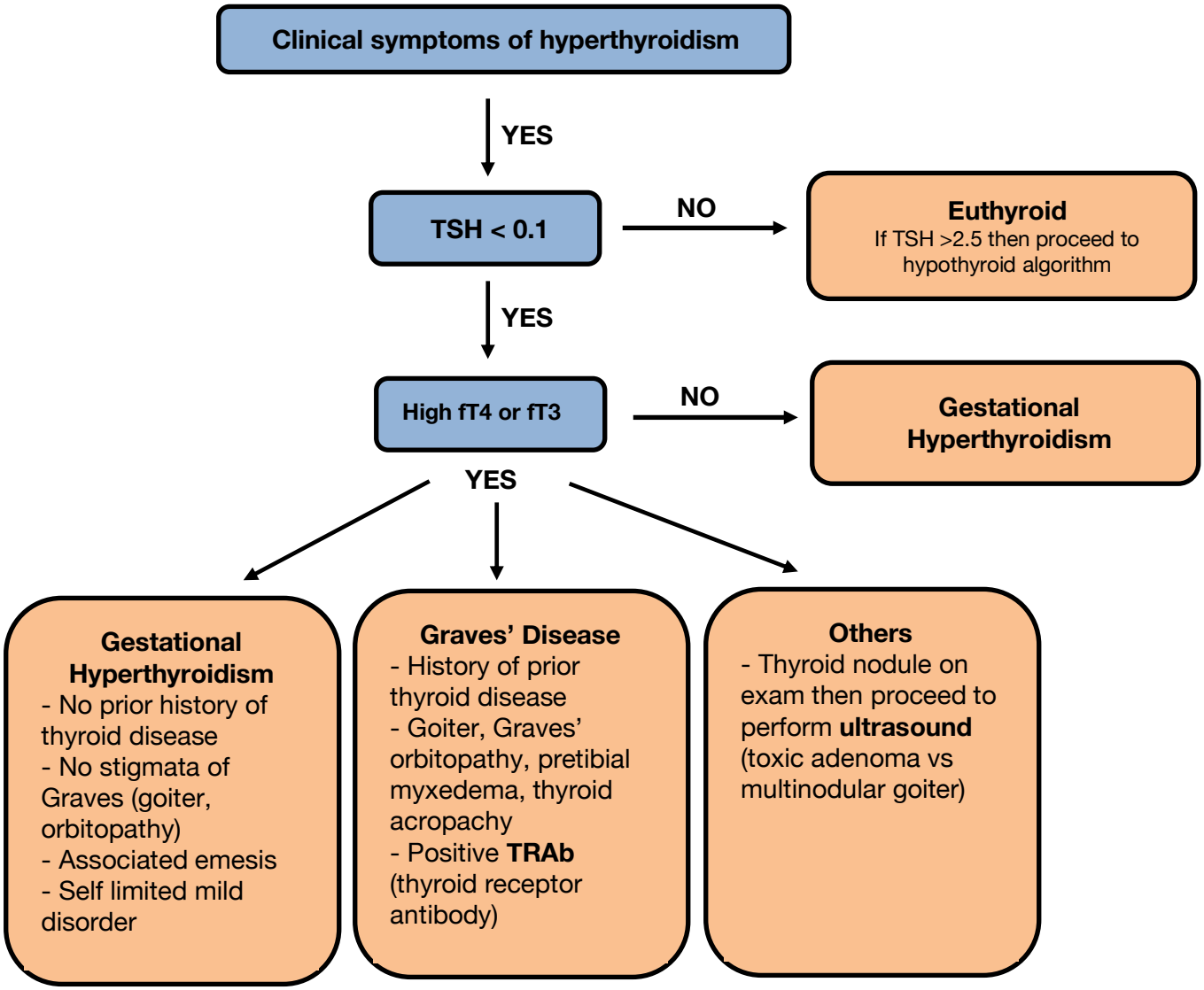

Figure 3. Algorithm of Hyperthyroidism Workup. (ATA 2017)

Indication for ordering a **TRAb** (thyroid receptor antibody) in pregnant women include those with established Graves related hyperthyroidism, a previous history of Graves post radioactive iodine ablation or thyroidectomy, and a previous history of delivering an infant with hyperthyroidism. If TRAb is undetectable or low, no further testing is required. Positive TRAb **>3x ULN** is associated with fetal and neonatal hyperthyroidism. If suspecting fetal hyperthyroidism, serial ultrasound is indicated to assess for fetal tachycardia, IUGR, presence of a fetal goiter, accelerated bone maturation, signs of congestive heart failure, and fetal hydrops.

Gestational Hyperthyroidism

Gestational hyperthyroidism is limited to the first half of pregnancy (peaks 10-12 weeks gestational) and is due to hCG-induced thyrotoxicosis, with elevated hCG levels activating TSH receptor and suppressing TSH production. It is most often associated with hyperemesis gravidarum. It can be also seen in multiple gestation, hydatidiform mole, and choriocarcinoma, which are all causes of elevated hCG.

Anti-thyroid drugs are not indicated as fT4 normalizes by 14 to18 weeks gestation. Beta-blockers can be used if symptomatic in small dosages and limited duration. Treat concurrent hyperemesis gravidarum if present with fluids, electrolyte replacement and anti-emetics. There are no impacts on obstetric outcomes.

Graves' Disease

Epidemiology

- Often goes into remission during pregnancy.
- 1/3 of women come off treatment by the 3rd trimester.
- Monitor for flare postpartum.

Medical treatment

- Propylthiouracil (PTU) recommended in the first trimester up to 16 weeks gestation. Need to monitor liver enzymes monthly due to risk of hepatotoxicity (1:10,000 risk).
- Methimazole causes aplasia cutis in first trimester. Can be used in second and third trimester.
- Beta-blocker for symptom control and peripheral conversion treatment.
- Monitor thyroid function every 2-6 weeks. Target fT4 at or moderately above upper limit of normal.

Thyroidectomy

- Rarely indicated but if needed, 2nd trimester is optimal.
- Indications include allergy to ATD, large doses of ATD, high TRAb titres.

Fetal effects

- Thyroid antibody (TRAb) can cross the placenta, and in rare cases, lead to fetal hyperthyroidism in utero.
- Must assess for TRAb in early pregnancy. If TRAb levels are normal, unlikely to develop fetal complications. If more than 3x upper limit of normal, can indicate risk of fetal/neonatal hyperthyroidism; repeat again 20-24 weeks, as it may go into remission. However, if remain elevated, increased fetal surveillance with fetal ultrasound is indicated (alert obstetrician to refer to a neonatologist).
- Clinical diagnosis of fetal hyperthyroidism includes fetal tachycardia, goiter, IUGR, advanced bone maturation, and fetal hydrops, in conjunction with TRAb titres.
- Cordocentesis can be used to assess fetal thyroid function in extremely rare cases.

Neonatal Graves

- Occurs in 1-3% of infants.
- Symptoms include tachycardia, poor weight gain and irritability.
- Symptoms usually resolve within 3-12 weeks postpartum as maternal antibodies pass.
- Baby requires observation for the first few days after birth as symptoms can be masked after delivery by the presence of maternal therapy in immediate postpartum period.

Postpartum

- Antithyroid drugs are safe. Take in divided doses after each feeding.
- Monitor baby for hypothyroidism.

Postpartum thyroiditis

Epidemiology

- Most common cause hyperthyroidism in postpartum period.
- 4x increase in risk of new Graves' disease due to thyroid autoimmunity.

Risk factors

- anti-TPO (30%), prior postpartum thyroiditis, Type I diabetes.

Symptoms

- Usually not present at 6 week postpartum visit, typically occurs in 1st year after delivery.
- 1/3 of women will only experience the hyperthyroid phase and 1/3 only the hypothyroid phase, 1/3 of women will remain hypothyroid permanently.
- Many cases are mild, short duration, spontaneously revert to euthyroidism.

Diagnosis

- If in question, RAI scan postpartum can distinguish between types of thyroiditis. **RAI is contraindicated during breastfeeding**. Can use shorter half-life ^{123}I vs ^{131}I, and women can continue to pump and discard breast milk around time of test.

Treatment

- Hyperthyroid phase use beta-blockers. Anti-thyroid drugs ineffective as this is a destructive thyroiditis.
- Hypothyroid phase treated with LT4 for 6-12 months, then wean to see if euthyroid state.
- Monitor TSH every 2 months until 1 year.

Gastrointestinal diseases in pregnancy

Nausea and Vomiting in Pregnancy (SOGC 2016 Guidelines)

Epidemiology

- Very common, affects 50-80% of pregnancies.
- Symptoms comparable to nausea experienced during chemotherapy.
- Hyperemesis Gravidarum is the extreme of nausea and vomiting spectrum.
- High morbidity physically and emotionally (e.g. absence from work, anxiety or depression, reduced quality of life).

Pathogenesis

- Not well understood but likely multifactorial (hormonal, autonomic, placental)
- Can be due to associated with hydatidiform mole and multiple gestation.
- Need to rule out other causes, including GI, urinary, central and metabolic causes.

Treatment

- Non-pharmacologic
    - Women should eat whatever pregnancy safe food that appeals to them.
    - Separate solids and liquids, small frequent meals, avoid full stomach, avoid fatty foods. Cold, clear, carbonated or sour fluids are helpful.
    - May stop iron containing prenatal vitamins and take folic acid only. Monitor for iron deficiency later in pregnancy
    - Ginger 250mg po QID, Acupuncture, Mindfulness.

- Pharmacologic
    - First line: Pyridoxine 200mg daily (Vitamin B6) or Pyridoxine-Doxylamine (Diclectin)
    - Second line: H1-blockers (e.g. Gravol)
    - Then: Metoclopramide, Chlorpromazine, or Prochlorperazine. Ondansetron is last line.
    - Consider treatment of reflux (H2 blocker or PPI)

Diclectin is the first line medication recommended for nausea and vomiting in pregnancy by SOGC. It is a preventative medication and should not be used for acute relief of vomiting. Usual starting dose is 4 times a day: one tablet at breakfast, one in the afternoon, and two tablets at night. Titrate up to 8 tablets daily as needed. Studies have shown safety up to 12 tablets daily. Diclectin can reduce the duration and severity of nausea and vomiting in women who take it at the onset of pregnancy. Recent re-analysis of original RCT which showed significant reduction in emesis scale by Diclectin compared to placebo (Koren et al., AJOG, 2010), revealed that statistical significance may have been achieved due to method of handling data, and more importantly the small absolute improvement in emesis scale (0.7 on a scale of 13 points) on Diclectin may not be clinically significant. (Persaud et al., PLOS ONE, 2018)

Dopaminergic antagonists are used after Diclectin and Gravol. Metoclopramide is widely considered the anti-dopaminergic of choice as it has not been shown to cause any increased risk of fetal anomalies, spontaneous abortion, or low birth weight. Ondansetron, while having a similar antiemetic effect as Metoclopramide, has been controversial in its safety in pregnancy. Some studies show it is not associated with major birth defects (Pasternak et al., NEJM 2013), where others have demonstrated an increased risk of cardiac anomalies when used in the first trimester (OR 1.62; Danielsson et al., Reproductive Toxicology 2014). Therefore, Ondansetron should be a later line antiemetic used only when other combinations have failed. Antacids, H2 blockers (ex. Ranitidine), and PPIs are safe in pregnancy. PPIs are an effective adjunct to anti-emetics for the treatment of nausea and vomiting or hyperemesis gravidarum.

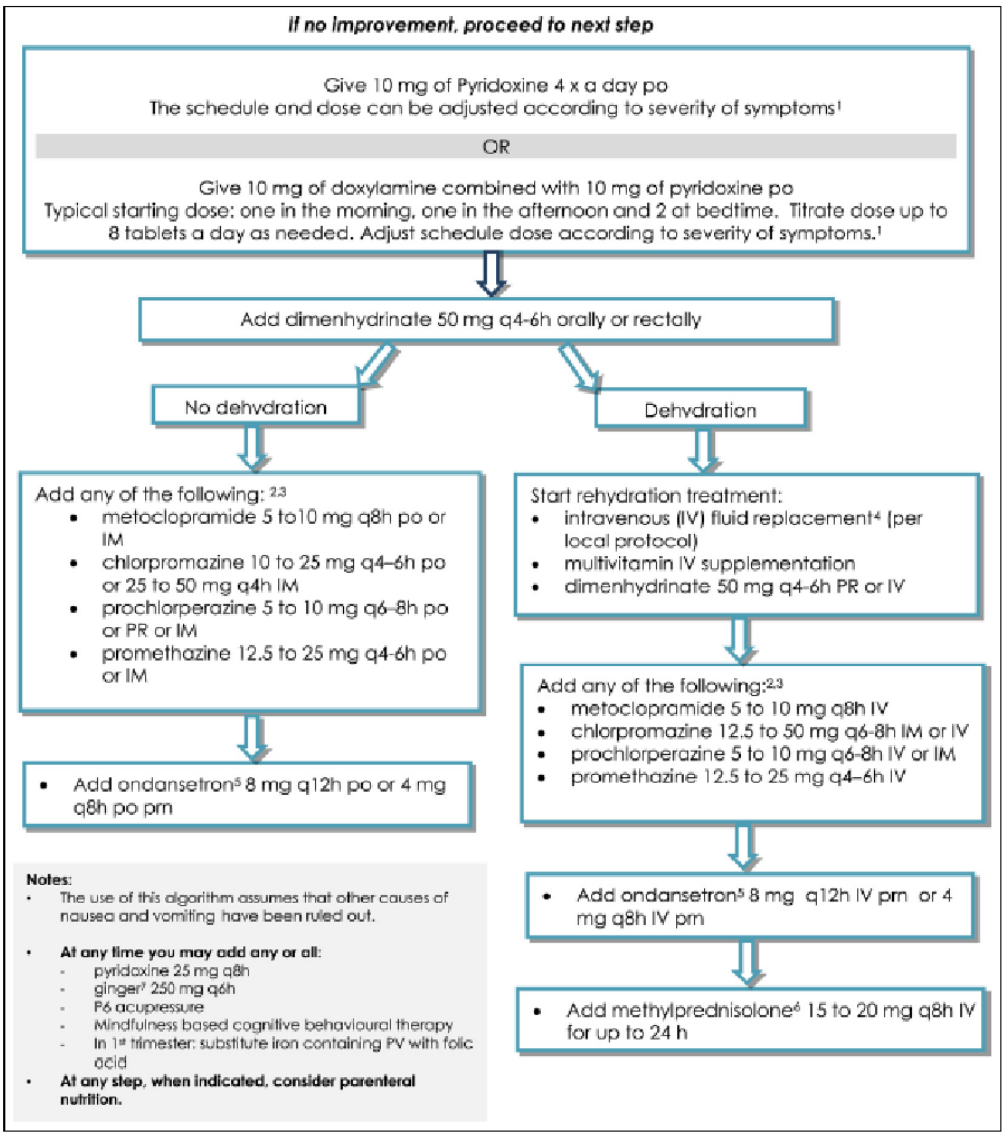

Figure 1. Treatment algorithm of nausea and vomiting in pregnancy. (SOGC 2016)

Pregnancy-related liver disease differential diagnosis

- Hyperemesis gravidarum
- Intrahepatic cholestasis
- HELLP syndrome
- Acute fatty liver of pregnancy
- Biliary disease (e.g. gallstones)
- Budd-Chiari Syndrome (most commonly occurs postpartum)

Don't forget other non-pregnancy causes of liver disease that can occur at any point in pregnancy! These include viral hepatitis, drug toxicities, and malignancy.

	Hyperemesis Gravidarum	**Intrahepatic Cholestasis**	**HELLP +/- pre-eclampsia**	**Acute fatty liver of pregnancy**
Gestation	T1	T2-3	>20 weeks	T3 (late)
Symptom	Vomiting	Pruritus, without rash, palms and soles, worse at night	RUQ pain (subcapsular hematoma, hepatic infarct or rupture), vomiting, pre-eclampsia	Vomiting, abdominal pain, encephalopathy, jaundice, ascites, polydipsia and polyuria
AST/ALT	100's	<1000's	Up to 1000's	< 500
Bilirubin	Normal	Normal or mildly elevated	↑, unconjugated bilirubin due to hemolysis	↑↑↑, conjugated bilirubin
Treatment	Anti-emetics Fluids and electrolyte replacement	Ursodiol Rifampin	Delivery BP control Eclampsia prevention	Delivery Liver transplant if hepatic failure

Table 1. Characteristics of the 4 common causes of elevated liver enzymes in pregnancy.

Hyperemesis Gravidarum

Epidemiology

- Affects 0.3-2% of pregnancies.
- Leading cause of hospitalization during the first half of pregnancy.

Pathogenesis

- Proposed mechanisms include abnormal gastric motility, hormonal factors, and autonomic nervous system changes.

Risks Factors

- Prior nausea and vomiting while on estrogen-based medications, motion sickness, migraines, multiple gestation, molar pregnancy (must rule out), GERD, family history (e.g. mother or sisters) of hyperemesis, and increased BMI.

Diagnosis

- Intractable vomiting resulting in dehydration, ketosis, electrolyte imbalance, and weight loss of >5% compared to pre-pregnancy weight.
- Can also have orthostatic hypotension, clinical and biochemical dehydration, hypersalivation (ptyalism).
- Motherisk-PUQE index can be used to score symptoms.
- Mean onset 8-12 weeks, and usually resolves by 20 weeks. Symptoms beyond 18 weeks may warrant additional investigations, such as gastroscopy.

Investigations

- Routine labs, liver enzymes, B-HCG, urinalysis for ketones, calcium, TSH
- Pelvic ultrasound to rule out molar pregnancy
- Liver enzymes frequently elevated, ALT > AST, mild (2-3x ULN), hyperbilirubinemia can occur as well (but should be mild). Jaundice is rare.
- Increased amylase and lipase can be seen
- Gestational thyrotoxicosis secondary to bHCG effect often seen as well. Important to distinguish it from true hyperthyroidism.

Treatment: Supportive

- Non-pharmacologic: similar to nausea and vomiting in pregnancy.
- Pharmacologic: anti-emetics, PPI, IV rehydration, electrolyte replacement, vitamin supplementation (thiamine).
- Recall that Diclectin is preventative not therapeutic in active vomiting!
- Recurrence is common in subsequent pregnancies.

Intrahepatic cholestasis of pregnancy (IHCP)

IHCP is diagnosed when there is unexplained pruritus in pregnancy with abnormal liver enzymes and/or raised bile acids. Pruritus is a common symptom in pregnancy so need to rule out other causes including dermatologic diseases, other liver disease (ex. primary biliary cirrhosis), and uremia. Contrary to the name, IHCP typically presents with transaminitis rather than cholestasis.

Pathogenesis

- incidence of 0.1-1.5% of pregnancies.
- Secondary to abnormal biliary transport across maternal canalicular membrane.
    - Hormonal effects induce cholestasis and inhibit bile salt export pump.
    - Mutations in bile salt export pump e.g. MDR3.

Risk factors

- History of OCP induced cholestasis, family history, prior IHCP, multiple gestation, certain ethnic groups (Scandinavian, Chilean), Hepatitis C, underlying genetic mutations (ABCB4).

Presentation

- Onset in the second and third trimesters.
- Intense pruritus, without rash (excoriation often present), beginning in palms and soles then generalized, worse at night. Pruritus can precede liver enzyme elevation for days to weeks.
- Jaundice extremely uncommon but if present is often 2-4 weeks after pruritus onset.
- May also have diarrhea or rarely steatorrhea.

Investigations

- Fasting bile acids >10 confirms diagnosis. Bile acids rise significantly after a meal so need to be obtained fasting. Normal bile acid levels does not exclude the diagnosis.
- AST and ALT can be elevated up to 20x ULN.
- ALP elevation is physiologic in pregnancy and is placental in origin so not reflective of liver disease.
- Bilirubin rise infrequent and usually mild if elevated.
- INR elevated as the absorption of Vitamin K, a fat soluble vitamin, may be impaired in cholestasis.
- Liver ultrasound – usually normal.
- Hepatitis C screen – as associated with IHCP.

Complications

- Fetal complications include stillbirth (1%), prematurity (up to 60%), and meconium aspiration. It is thought to be mediated through cardiotoxicity of bile acids
- Stillbirth is the major concern for those with IHCP. Fetal demise in utero is usually sudden, unexpected and can occur in the setting of previously normal ultrasound and other indices.
- Risk of complications if bile acid more than 40. Increasing fetal complications correlates with rising bile acid levels as highest risk of stillbirth if bile acid more than100.
- Maternal complications in those with IHCP include increasing rates of gestational diabetes, pre-eclampsia, C-section, and postpartum hemorrhage.

Treatment

- Ursodeoxycholic acid
    - First line treatment, safe in pregnancy, side effects include GI upset.
    - Max 10-15 mg/kg/day divided in BID-QID dosing, start at 250mg BID .
    - Relieves pruritus, improves liver enzymes and bile acid. Has not been shown to decrease stillborn rates, but does reduce iatrogenic preterm births.
    - Safe for mother and baby in 2nd and 3rd trimester as well as in breastfeeding.
- Second line treatment
    - Rifampin (EASL guideline 2009) – unclear mechanism for bile acid reduction. No RCT on treatment of IHCP or fetal effects. A retrospective trial of 27 patients showed reduced bile acids without adverse effects when used together with Ursodiol (Geenes et al., Eur J Obstet Gyne Reprod Biol, 2015).
    - Antihistamines (ex. Hydroxyzine) used concomitantly with Ursodiol for symptom control, but have no effect on improving bile acids.
    - Plasmapheresis last line if intractable symptoms or elevated bile acid levels
- Delivery is the definitive treatment and usually is recommended in the setting of persistently elevated bile acid levels (i.e. >40). Symptoms resolve hours to days after delivery and medical therapy is discontinued.

Prognosis

- Recurrence rate is 60-80% in subsequent pregnancies.
- Associated with future development of hepatobiliary disease and hepatitis C.
- Avoid contraceptives with estrogen as can have recurrence of symptoms on OCPs.

Acute Fatty Liver of Pregnancy

Epidemiology

- Rare but lethal condition seen late in pregnancy, often final weeks of third trimester.
- Complicates 1 in 7,000 to 1 in 20,000 pregnancies.

Pathophysiology

- Microvesicular fatty infiltration secondary to mitochondrial defect in fatty acid metabolism (LCHAD deficiency) in the fetus, leading to maternal liver failure.
- No correlation to NASH/fatty liver.

Diagnosis

- Swansea Criteria, need 6 of 14 for diagnosis of AFLP.
    - Vomiting
    - Abdominal Pain
    - Polyuria/polydipsia (secondary to placental secretion of vasopressinase causing diabetes insipidus)
    - Encephalopathy
    - Ascites
    - Leukocytosis
    - Coagulopathy
    - Hyperbilirubinemia – conjugated
    - Hypoglycemia
    - Transaminitis
    - Hyperammonemia
    - Renal impairment
    - Elevated urate
    - Pathologic evidence of microvesicular fat of liver
- Symptoms (e.g. jaundice, vomiting, encephalopathy, ascites) and signs (e.g. coagulopathy, hyperbilirubinemia, hypoglycemia) are reflective of liver failure.
- A normal ultrasound (i.e. without steatohepatitis) does not rule out AFLP as the fatty deposits are on a cellular level seen only on pathology.
- A liver biopsy is often needed to diagnose AFLP as the pathognomonic finding is microvesicular fat deposits.
- Unusual correlation with diabetes insipidus. Ask about change in thirst.
- Need to rule out other diseases that may cause elevated liver enzymes. The main differential diagnoses are pre-eclampsia with HELLP syndrome and sepsis.

Treatment

- Delivery and supportive management. With prompt diagnosis and management most patients liver function recovers by day 7-10 spontaneously.
- Significant morbidity can occur with liver failure warranting transplantation.
- Chronic liver disease does not develop from AFLP.
- Children born to mothers with AFLP should be investigated for LCHAD deficiency.

Inflammatory Bowel Disease

All women contemplating pregnancy or currently pregnant with Crohn's Disease or Ulcerative Colitis should be managed by a gastroenterologist and high risk obstetrician. The Toronto Consensus Statement on Inflammatory Bowel Disease in Pregnancy published in 2016 recommends all women of reproductive age with IBD should receive preconception counselling to improve pregnancy outcomes. This includes starting Folic acid, iron supplementation, updating immunization status, and discontinuing teratogenic medications. In women with IBD who are contemplating pregnancy, **disease remission of at least 3 months** should be attained preconception to decrease the rates of infertility, IUGR, preterm birth, congenital defects, and caesarean delivery. This recommendation is similar to that of other inflammatory conditions (e.g. rheumatoid arthritis) whereby optimal control of disease for 3 to 6 months preconception is advised to prevent relapse of disease in pregnancy and associated maternal and fetal complications.

Women contemplating pregnancy who are on 5-ASA (without DBP) or Azathioprine with optimal disease control can continue it through pregnancy and lactation. **Methotrexate is teratogenic** and associated with miscarriages, cardiovascular defects and cleft palate. It must be discontinued at least 3 months before attempting to conceive. If a woman becomes pregnant while taking methotrexate, immediate discontinuation of methotrexate, continuation of folic acid, and referral to obstetric counselling is recommended. The use of anti-tumour necrosis factor (anti-TNF) medications in pregnancy is controversial due to the paucity of evidence to guide practice. The Toronto Consensus Statement recommends continuation of anti-TNF in women with IBD during pregnancy given the low risk of adverse pregnancy outcomes and importance of maintaining disease remission. In select women with low risk of relapse or strong maternal desire to prevent fetal exposure, last dose can be given intrapartum with close follow up by gastroenterologist. Breastfeeding is likely safe given the large size of the molecule being unable to be absorbed by the neonatal gut. All newborns exposed to anti-TNF drugs in utero should avoid live attenuated vaccine for the first 6 months of life.

Pancreatitis

Acute pancreatitis in pregnancy is rare and most commonly occurs in the third trimester. The most common cause is gallstone pancreatitis. ERCP can be performed in pregnancy with cholecystectomy deferred postpartum. Where alcohol is the other leading cause of pancreatitis in non-pregnant patients, **hypertriglyceridemia** is often the culprit in pregnancy as all forms of cholesterol are markedly elevated. Treatment includes fibrates, insulin, or plasma exchange in the setting of refractory hypertriglyceridemia.

HELLP Syndrome

HELLP syndrome, which stands for Hemolysis, Elevated Liver enzymes, Low Platelets, is a severe complication of pre-eclampsia. The incidence is 6 in 1000 pregnancies overall and up to 10% of pre-eclamptic patients. As many as 10 to 20% of HELLP can occur without antecedent pre-eclampsia.

Diagnosis of HELLP syndrome includes the presence of microangiopathic hemolytic anemia, platelets <100, or AST >70 or more than twice above upper limit of normal. You do not need all three criteria for the diagnosis. Liver enzymes are usually the first lab abnormality and can be elevated into the thousands due to ischemic liver. It can lead to complications such as subcapsular hematoma, hepatic infarct, or hepatic rupture. It is therefore prudent to image those with severe right upper quadrant pain and consider general surgery or interventional radiology consultation as appropriate. Thrombocytopenia is the other leading presentation of HELLP and transfusion if recommended if bleeding, platelet count less than 20, or below the requirement for mode delivery or neuraxial anesthesia. By contrast, hemolytic anemia is frequently a late finding.

Treatment of HELLP is the same as for pre-eclampsia (delivery, supportive care, eclampsia prophylaxis). After delivery, one should expect initial deterioration followed by rapid improvement of the laboratory abnormalities within days. If the biochemical derangements remain persistent or worsen, other differential diagnoses must be considered including ITP, TTP, or acute fatty liver of pregnancy.

Hematological disease in pregnancy

Venous Thromboembolism

Epidemiology

- The absolute risk of venous thromboembolism (VTE) associated with pregnancy is approximately 0.1%.
- The risk of VTE is 5 to 10 times higher in pregnancy compared to age-matched women.
- The highest risk of VTE is in the first **6 weeks postpartum**, followed by the third trimester in pregnancy.
- 80% of DVTs occur in the left leg and 60% are in the ilio-femoral veins.

Pathophysiology

- Virchow's triad:
    - Venous stasis: secondary to hormonal influences on vascular tone, compression of pelvic vessels by gravid uterus, compression of the left iliac vein by iliac artery
    - Hypercoagulability: increased fibrinogen, increased factors V, VII, VIII, X and vWF, decreased protein S.
    - Vascular damage: intimal injury at the time of delivery.

Risk factors

Maternal Factors	Pregnancy Factors
Age > 35 Weight > 80kg Previous VTE (especially related to OCP or pregnancy) Thrombophilia (e.g. APLS, Protein C/S deficiency, antithrombin III def) Family history of VTE Sickle cell disease Inflammatory disease (e.g. SLE, IBD) Malignancy Nephrotic syndrome Varicose veins Smoking	Cesarean section Emergency delivery Pre-eclampsia Stillborn Postpartum hemorrhage Assisted reproduction techniques (OHSS) Hyperemesis gravidarum Multiple gestation (i.e. twins, triplets) Immobility

Table 1. Risk factors for venous thromboembolism in pregnancy.

Presentation

- Classic signs of DVT (leg swelling) and pulmonary embolism (tachycardia, tachypnea, dyspnea) may be a part of normal pregnancy.

- DVT presents differently in the pregnant population:
    - **80% occur in the left leg** as opposed to 55% in non-pregnant patients. This is secondary to compression of the left iliac vein by the artery and gravid uterus.
    - Thrombus tend to be proximal **(iliac or femoral vein)** as opposed to distal (popliteal), and progress distally rather than proximally in non-pregnant patients.
    - So more commonly present with **thigh/back/buttock pain** rather than calf pain.

Diagnosis (SOGC 2014 Guidelines)

The diagnostic algorithm for DVT and PE as per the SOGC 2014 guidelines are displayed below (Figure 1 & 2). It is prudent that if clinical suspicion for venous thromboembolism is high, **therapeutic anticoagulation should be given empirically** while awaiting results of diagnostic imaging. The majority of patients investigated for VTE (>90%) will not have VTE, but the index of suspicion and testing should be low as the consequences of failed diagnosis are significant (Thrombosis Canada 2018).

In suspected DVT (Figure 1), request for bilateral leg ultrasound. Ensure that the ultrasonographer has attempted to visualize the **proximal iliac vein** given the high prevalence of thrombosis in these vessels. If DVT is found, then anticoagulation should be continued. If ultrasound is negative, **repeat it at least once within 7 days** to confirm the absence of DVT, since there is currently insufficient evidence for ruling out DVT with a single negative ultrasound in pregnancy. As per the SOGC guidelines, MRI direct thrombosis imaging is an alternative modality to visualize the proximal veins but this is rarely done in practice.

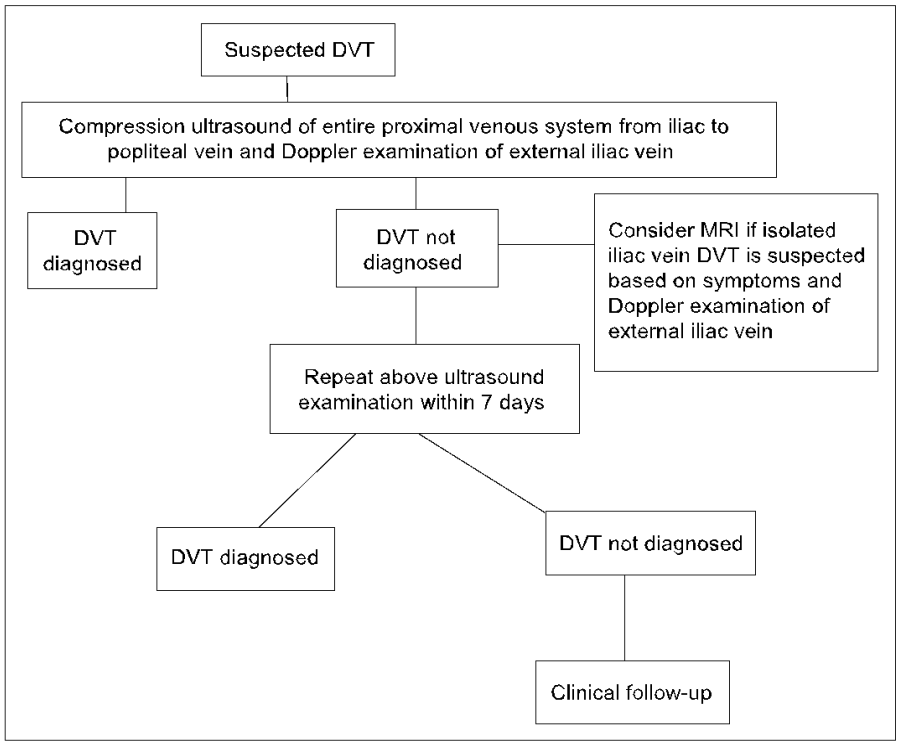

Figure 1. Diagnostic algorithm of DVT in pregnancy. (SOGC 2014)

If suspected PE (Figure 2), bilateral leg ultrasounds are recommended first given the lack of radiation and identical treatment for DVT and PE. If positive, anticoagulation should be started. If ultrasound negative, **CXR is generally performed** to rule out alternative diagnoses and to ensure absence of underlying lung disease, which if present would preclude the use of the V/Q scan. If CXR is normal, **V/Q scan is the modality of choice** to rule out PE given lower radiation risk to the maternal thorax as compared to CT pulmonary angiogram. The main concern is maternal breast uptake of radiation as it is in a proliferative phase in pregnancy. One could further reduce the radiation exposure by undergoing the perfusion (i.e. Q) portion of the V/Q scan only, given presumed normal ventilation with a normal CXR. If V/Q is non-diagnostic and clinical suspicion remains high, then serial leg ultrasounds or CTPA can be done.

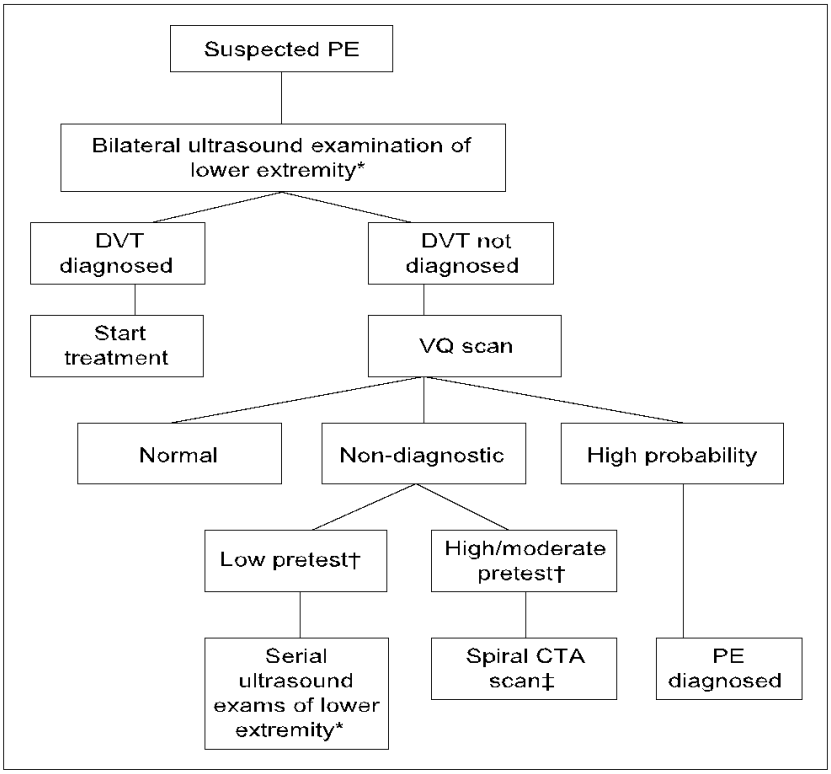

Figure 2. Diagnostic algorithm of pulmonary embolism in pregnancy. (SOGC 2014)

In non-pregnant patients, diagnostic approach for venous thromboembolism uses a combination of validated clinical prediction rules with or without d-dimer testing. In pregnancy, **neither clinical tools or D-dimer should be used** alone or in combination to diagnose or exclude VTE. In recent years, there have been several new studies aimed to validate clinical scores in combination with biochemical markers in pregnancy with the goal of minimizing unnecessary radiation. As per the most recent SOGC guidelines, first line investigation of VTE in pregnancy should still be imaging.

- D-dimer: typically elevated in normal pregnancy. Not part of the diagnostic algorithm for VTE in pregnancy. There have been case reports of normal d-dimer in pregnant women with thromboembolic events.
- Well's score: not validated in pregnancy.

The Pregnancy-Adapted YEARS algorithm for diagnosis of suspected PE was published in NEJM in March of 2018. 510 women presenting with symptoms of PE underwent the YEARS algorithm, with contains three clinical criteria (i.e. clinical signs of DVT, hemoptysis, PE as the most likely diagnosis) and measured d-dimer level. PE was ruled out if all three clinical criteria were negative with d-dimer <1000, or if one or more clinical criteria were met with d-dimer <500. If PE is not ruled out based on algorithm, leg ultrasounds were performed if symptoms of DVT, otherwise CT pulmonary angiogram was done. The primary outcome of the study showed that incidence of VTE at 3 months was diagnosed in 1 patient with a DVT (0.21%). No patients had PE at 3 months. CT pulmonary angiogram was avoided in 39% of patients with application of the algorithm. The algorithm was most efficient during the first trimester of pregnancy and least efficient in the third trimester, which is likely accounted by the rising d-dimer levels as pregnancy progresses.

Another prospective study aimed to validate an algorithm using the Geneva score and D-dimer for the diagnosis of PE in pregnancy (Righini et al., Annals of Internal Medicine 2018). Over 400 women presenting with a clinical suspicion of PE (i.e. chest pain or dyspnea without an identifiable cause) were stratified into low/intermediate versus high risk groups based on the Geneva clinical assessment score. In the low/intermediate risk group, a D-dimer was measured and if negative (<500 ug/L) PE was ruled out. Positive D-dimer patients were investigated the same as the high risk group, whereby bilateral leg ultrasound was performed first, and if negative then CTPA. If the CTPA was inconclusive then V/Q scan was done. The study found the rate of PE was 7%, mostly diagnosed with CTPA (67%) as opposed to ultrasound (25%). 11.6% of women avoided imaging by being in the low/moderate risk group with a negative d-dimer with a 3 month thromboembolic rate of 0%.

The LEFt score was studied in a cross section study of 194 women (Chan, Annals of Internal Medicine 2009). Three variables used to produce a score in predicting likelihood of DVT: symptoms in the left leg ("L"), calf circumference difference equal or greater than 2 centimeters ("E" for edema), and a first trimester presentation ("Ft"). Absence of all three variables had a 100% NPV. Presence of 2 or 3 variables had a PPV of 58%. This prediction score remains to be prospectively validated.

Imaging Modalities

Doppler ultrasound

- 91% sensitivity, 94% specificity.
- Direct visualization of the entire proximal venous system, iliac to popliteal with compression maneuvers.
- No radiation exposure.

- **Iliac vein thrombosis harder to detect**. Ensure ultrasonography has tried to visualize the iliac vein. If clinical suspicion is high, cannot rule out DVT with a single ultrasound.

V/Q scan (Ventilation Perfusion scan) vs CTPA (CT pulmonary angiogram)

- For mother: greater radiation to maternal breast tissue with CTPA than V/Q scan, with concerns for breast cancer since maternal breast tissue is in the proliferative phase in pregnancy.
- For fetus: greater radiation to fetus with V/Q scan compared to CTPA, resulting in higher risk of childhood cancer (1 in 280 000 with V/Q vs < 1 in a million with CTPA).

Radiation risk (see Radiation in Pregnancy section)

- 10 rads (100 mgray) is thought to be the threshold for teratogenicity or miscarriage.
- The cut-off for radiation exposure to the fetus in pregnancy is typically set at **<5 rads** (≤ 50 mgray).

Treatment

Once VTE is confirmed, therapeutic anticoagulation is indicated. Pregnant women with acute PE or large proximal DVT should be considered for hospitalization; if hemodynamically stable can be followed closely as outpatients. Heparins (both low molecular weight and unfractionated) are the anticoagulants of choice in pregnancy. They do not cross the placenta and therefore carry no teratogenic or fetal bleeding risks. **LMWH is the preferred treatment** given its better side-effect profile and ease of dosing, except in cases of renal dysfunction and history of Heparin Induced Thrombocytopenia (HIT). Women should be continued on anticoagulation for the duration of the pregnancy as well as 6 weeks postpartum, for a total minimum of 3 months.

The weight-based dosing for Heparin in pregnancy is the same as for non-pregnant patients. It is important to remember that appropriate adjustments need to be made based on weight changes over the course of the pregnancy (Table 2). Once or twice daily dosing are both acceptable. Twice daily dosing is preferred by some clinicians, especially in the first month of treatment, as LMWH is excreted by the kidneys and renal clearance increases in pregnancy. Monitoring of anti-Xa activity is controversial and varying practices exist. The American Hematology Association 2018 guidelines of VTE in pregnancy recommends against it. The risk of bleeding with LMWH is approximately 2% with highest risk postpartum. All patients are advised to seek medical attention immediately with any signs of bleeding. The risk of Heparin Induced HIT with LMWH is rare (<0.1%) and therefore regular monitoring of platelets is not recommended. Ensure adequate Calcium and Vitamin D intake as pregnant women have a physiologic relative osteopenia worsened by Heparins.

Agent	Prophylactic dose	Therapeutic dose
Unfractionated heparin	5000 U SC bid (7500 U SC bid)	150-200 U/kg twice daily. Consider a lower dose in women < 50 kg.
Dalteparin (Fragmin)	5000 U SC daily	200 U/kg daily or 100 U/kg SC twice daily
Enoxaparin (Lovenox)	40 mg SC daily (60 mg SC daily if weight >100 kg)	1 mg/kg SC bid or 1.5 mg/kg SC once daily
Tinzaparin (Innohep)	4500 U SC daily If obese, 75 U/kg daily	175 U/kg SC once daily

Table 2. Recommended dosing of anticoagulants. (SOGC 2014)

Vitamin K antagonists such as **Warfarin should not be used** for the treatment of VTE in pregnancy. Warfarin crosses the placenta and in the first trimester can cause miscarriage, warfarin embryopathy (mid-facial and limb hypoplasia) and stippled bone epiphyses. It also causes CNS malformations, microcephaly and optic atrophy in the third trimester.

There is currently no safety data with the use of Direct Oral Anticoagulants (DOACs), such as Rivaroxaban or Apixaban, as pregnant women were excluded from the trials. Ex vivo studies show that DOACs cross the placenta and maternal ingestion of these drugs result in detectable levels in human milk. The association between DOACs and congenital malformations are largely unknown. A study of 137 women inadvertently taking DOACs during pregnancy showed no clear association with embryopathy (Beyer-Westendorf et al., Thromb Haemost 2016). As per current guidelines, **DOACs are not recommended** for use in pregnancy or lactation.

Thrombolytic (e.g. tPA) has been used successfully for the treatment of VTE in pregnancy in case studies. However, the experience with this is limited. The use of thrombolytic therapy should be reserved for patients with massive life-threatening VTE with hemodynamic compromise or proximal DVT threatening leg viability. The indications for the use of IVC filters are the same as non-pregnant patients, such as those with contraindication for anticoagulation or recurrent VTE despite therapeutic anticoagulation.

There is limited research in the treatment of superficial venous thrombosis (SVT) and below knee DVTs in pregnancy. For SVTs, it is recommended to first undergo Doppler ultrasound to rule out associated deep vein thrombosis. Anticoagulation is recommended in those who are symptomatic and have SVTs of more than 5cm in length or less than 5cm away from a deep vein. Some clinicians start anticoagulation for all SVTs as it may progress to a DVT in the presence of the high estrogen milieu of pregnancy. This is the practice at Mount Sinai Hospital. Below knee DVTs are generally treated the same as above knee DVTs in pregnancy with therapeutic anticoagulation.

Post-thrombotic syndrome is a constellation of symptoms including chronic leg swelling, discoloration, and pain. It occurs in 20 to 40% of non-pregnant patients with proximal DVT. Compression stockings with 30-40mmHg of pressure can be helpful for symptom relief of post-thrombotic syndrome. A recent RCT indicates that it does not prevent post-thrombotic syndrome (Kahn, Lancet 2014).

Delivery

All patients on therapeutic anticoagulation need a **planned delivery** to minimize the risk of maternal hemorrhage and epidural hematoma. Patient on prophylactic anticoagulation can undergo a spontaneous delivery (ASH 2018). Management of anticoagulation around neuraxial analgesia and delivery largely comes from extrapolated data from non-obstetric patients and does not take into account the physiologic changes in pregnancy. There is great debate with regards to the management of anticoagulation peri-partum as guidelines and local anesthesia practices vary. As per SOGC 2014, women on **therapeutic** anticoagulation should have a planned date and mode of delivery (e.g. induction for vaginal delivery, or cesarean section) and without anticoagulation for 24 hours prior to neuraxial analgesia. Women on thromboprophylaxis must have a gap of 12 hours between last dose of LMWH and neuraxial blockade. All women should be instructed to withhold anticoagulation at the onset of contractions until further assessed by a physician. In special circumstances where the risk of thromboembolism is very high, such as new VTE less than 4 weeks from delivery or mechanical heart valves, bridging of LMWH to heparin infusion may be required to minimize time off anticoagulation (i.e. stop 4-6 hours prior to delivery or epidural).

Postpartum

Postpartum anticoagulation should be restarted as soon as it is safe to do so. If adequate hemostasis is achieved, anticoagulation can usually be resumed 4 hours after neuraxial removal, 6 hours after vaginal delivery, and 8 hours after C-section. If the patient breastfeeds, unfractionated Heparin, LMWH, or warfarin can be used. This is because minimal amounts of each are excreted in the breast milk. If the patient chooses not to breastfeed, then DOACs can also be used. Anticoagulation should be continued for at least **6 weeks postpartum,** and for a minimum of 3 months. For instance, a woman with VTE in the first trimester will be on anticoagulation for the entire duration of pregnancy *plus* 6 weeks postpartum. A woman with VTE at the end of pregnancy will require it for at least 6 weeks postpartum, ensuring that total duration is at least 3 months. Postpartum VTE is considered an estrogen provoked thrombotic event.

Should we screen for thrombophilia?

- Routine screening is not recommended.
- In most cases, screening for thrombophilia does not alter the treatment for VTE.
- Do not screen in acute VTE in pregnancy as coagulation factors are altered. Protein S is reduced in pregnancy and antiphospholipid antibodies can be increased or decreased.

Factor V Leiden and prothrombin are not affected as they are both genetic tests. If plan to screen, then test 8 to 12 weeks postpartum.

- Consider screening if thrombus occurs in an unusual place (i.e. sagittal vein, Budd Chiari) or if patient has a strong family history of VTE.

Thromboprophylaxis

Pregnancy confers a 5-10 times increased risk of VTE and the immediate postpartum period has increased risk of 15-25 fold. The highest risk of thrombosis is found in the first 3 weeks postpartum, with increased thrombosis risk lasting up to 12 weeks (Kamel NEJM 2014). Despite this, routine thromboprophylaxis is not recommended unless there are risk factors. Determining the absolute risk to warrant prophylaxis has been debated. Most experts agree that if the risk of VTE is above 10% prophylaxis should be instituted, while those with an estimated risk of less than 1% should not. Antepartum prophylaxis is given throughout pregnancy and 6 weeks postpartum, whereas postpartum prophylaxis is for 6 weeks after delivery. Table 3 lists the indications for antepartum and postpartum prophylaxis as recommended by the SOGC. There are notable differences in guidelines when it comes to thromboprophylaxis for genetic thrombophilias in pregnancy. The American Society of Hematology 2018 guideline places great emphasis on family history of VTE whereas SOGC does not. The variability in recommendations and clinical practice reflect the paucity of medical literature in this population.

Ante-partum Prophylaxis	Postpartum Prophylaxis
prior unprovoked VTE	prior VTE
prior VTE in pregnancy or while on OCP (i.e. estrogen related)	high risk thrombophilias (APLA, antithrombin deficiency, homozygous FVL, homozygous PGM, combined thrombophilias)
prior VTE and low risk thrombophilia (heterozygous Factor V Leiden (FVL), heterozygous Prothrombin gene mutation (PGM))	strict bed rest > 7 days before delivery
asymptomatic homozygous FVL, homozygous PGM, antithrombin deficiency or combined thrombophilias	postpartum hemorrhage > 1L or require blood product replacement, and concurrent surgery
non-obstetric surgery during pregnancy (duration procedure dependent)	peri-partum or postpartum infection
bedrest > 7 days and BMI > 25	≥ 2 of the following: BMI > 30, smoker, pre-eclampsia, IUGR, placenta previa, emergent C-section, PPH > 1L, maternal disease (SLE, cardiac, IBD, sickle cell), low risk thrombophilias, stillbirth, preterm delivery
	≥ 3 of the following: age > 35, parity > 2, assistive reproductive technology, multiple pregnancies, placental abruption, PROM, elective C-section, maternal cancer

Table 3. Indications for antepartum and postpartum thromboprophylaxis. (SOGC 2014)

Thrombocytopenia in pregnancy

Thrombocytopenia is common in pregnancy (~10%). Platelets are often between 115 to 150 x 10^9/L in pregnancy. In most cases it is an isolated finding with no clinical consequence. However, severe thrombocytopenia may impact delivery, neuraxial anesthesia, and the fetus.

Differential diagnosis (pregnancy related causes)

1) Gestational thrombocytopenia (75-80%)
2) Pre-eclampsia with HELLP (15-20%)
3) Idiopathic thrombocytopenic purpura (ITP) (5%)

Don't forget non-pregnancy related causes including viral (HIV, Hep B, Hep C), autoimmune (SLE), metabolic (B12 deficiency, thyroid), and drugs!

Investigation (ASH 2013)

- Recommended:
    - CBC, reticulocyte count, peripheral blood film, liver enzymes, HIV, HBV, HCV, ferritin
- Consider (only if indicated):
    - ANA, APLA antibodies, TSH, H. Pylori, DIC testing (INR, PTT), DAT, Vitamin B12
    - Abdominal ultrasound
- Tests not recommended:
    - Bone marrow biopsy, TPO levels, antiplatelet antibody testing

Platelet Targets for Delivery

Vaginal delivery >30
C-section > 50
Neuraxial anesthesia >80

Generally, platelet target in the third trimester should be at least 50 as one cannot predict whether emergency C-section may be needed. The target for neuraxial anesthesia (i.e. epidural) depends on the institution and experience of the anesthesiologist. In the hands of obstetric anesthesiologists a platelet level of 75 may be adequate, whereas others may require a platelet level above 100. Find out what the policy is at your local institution.

Gestational thrombocytopenia

- Presentation
    - Women without history of thrombocytopenia pre-pregnancy and with normal antenatal platelet count.
    - Usually mild and insidious onset of thrombocytopenia.
    - Identified in late second trimester or third trimester as a result of hemodilution and increased clearance.

    - > 90% of women will have platelet counts > 100, rarely causes platelets below 70 (would need investigation for alternative etiology).
- Treatment
    - No treatment required.
    - Mothers are asymptomatic; no effect on baby.
    - Platelets will return to normal after pregnancy.

ITP (Immune Thrombocytopenic Purpura)

- Presentation
    - Can present at any trimester in pregnancy, often in patients with pre-existing ITP.
    - Can differentiate from gestational thrombocytopenia as likely to have abnormal pre-pregnancy platelet count, which can worsen throughout pregnancy due to concurrent gestational thrombocytopenia.
    - Platelets are young, large and have excellent hemostatic properties.

- When to treat
    - T1/T2: if platelets <30 or clinical bleeding. If platelets 30-150 and no bleeding, can monitor monthly until 34-36 weeks.
    - T3 (34-36 weeks): if platelets are below target for expected mode of delivery and 30% of women will require treatment for ITP in pregnancy
    - Monitor with CBCs in 1st and 2nd trimester, every other week in 3rd trimester, weekly after 36 weeks and then the day of delivery.
    - Neuraxial anesthesia (ie below 80 if considering epidural).

- Treatment:
    - Steroids
        - Prednisone 0.5-1mg/kg/day, 2-4 weeks for response, start at week 34-36 in anticipation for labour
    - IVIG: 1 g/kg/day x 2 days, 24-48 hours for response, effect lasts 2-4 weeks
        - Only 60% of people respond to the 1st dose of IVIG, another 4-5% respond to the 2nd dose.
    - Platelet transfusion: can be given during delivery if below target

- Fetal outcomes
    - antiplatelet antibodies can cross the placenta and cause transient fetal/neonatal thrombocytopenia.
    - Infant nadir occurs in day 2-5 after delivery, with spontaneous rise by day 7 as maternal antibodies are cleared.
    - 10% of neonates will have severe thrombocytopenia with platelets < 50.
    - Overall, risk of mortality is <1% and intracranial hemorrhage is <1.5%.
    - It is difficult to predict neonatal thrombocytopenia as the maternal platelet count doesn't correlate with neonatal platelet count. Treating maternal ITP does not prevent fetal ITP. Previous history of neonatal thrombocytopenia and maternal splenectomy are risk factors for recurrent neonatal ITP.

- Delivery considerations
    - Consult anesthesia and neonatology.

- C-section only for obstetric indications (i.e. no evidence that operative delivery will prevent fetal hemorrhage). If require a C-section but platelets too low for epidural, then will need general anesthesia.
- Avoid fetal scalp monitoring in the event there is fetal thrombocytopenia.
- Cord blood sampling for platelet count and CBC at birth. If platelets in baby suppressed, baby needs frequent CBCs +/- treatment (IVIG) - at the discretion of neonatology.

Iron deficiency anemia

Physiology

- Iron requirements increase in pregnancy. A total of 1000mg of iron is required during pregnancy, from 1-2mg daily in early trimesters to 6mg daily in third trimester. This is in comparison to 1mg daily in non-pregnant patients.

- An increase in iron consumption by approximately 15-30 mg of elemental iron per day is recommended (to achieve the daily absorbed iron needs). This amount is readily met by most prenatal vitamin supplements (e.g. Pregvit contains 35mg of elemental iron).

- Common sources of iron include heme sources (fish, red meat, poultry) and non-heme sources (dried beans, legumes).

- Traditional teaching is that iron replete women were less likely to have babies of low birth weight, hence the indication for treatment. A systematic review in the Annals of Internal Medicine demonstrated no difference in fetal weights, C-section, or maternal quality of life with iron supplementation in iron deficient women (Cantor et al.,, 2015).

Stages of Iron Depletion

- Stage 1: iron depletion without anemia, ferritin < 30 (ferritin increases in pregnancy)
- Stage 2: iron depletion with mild anemia (normocytic, ferritin < 30, increased TIBC)
- Stage 3: iron deficiency with severe anemia (microcytic, “classic” anemia)

Definition of anemia in pregnancy

- 1st trimester: Hb < 110
- 2nd and 3rd trimester: Hb < 105
- Postpartum: Hb < 100

Diagnosis (similar to a non-pregnant patient)

- Causes of iron deficiency:
    - Decreased intake: dietary review including compliance with prenatal vitamin
    - Malabsorption: Celiac disease, IBD, gastrectomy
    - Bleeding history: easy bruising, bleeding with prior dental extractions, prior menstrual history, familial bleeding disorders

- Symptoms of anemia
    - Weakness, fatigue, poor exercise tolerance, shortness of breath
    - Pica - cravings for clay, dirt, paper products
    - Pagophagia – cravings for ice, quite specific
    - Restless legs syndrome

- Laboratory tests

- CBC (part of routine antenatal blood work), MCV, blood film, reticulocytes, and red cell indices
- Iron profile
    - Ferritin <30. Ferritin typically rise early in pregnancy and falls by 32 weeks to 50% pre-pregnancy levels in iron-replete women. First marker to become abnormal.
    - Transferrin saturation <20%.
    - Iron level and TIBC are unreliable indicators as they fluctuate due to recent iron ingestion, diurnal rhythm and inflammation.

Goals of management

- Start with counselling on iron rich foods. Ensure taking prenatal vitamins with iron. If already on prenatal vitamin containing iron, then need to start iron replacement if anemic with low ferritin (<30).
- Start with 300mg daily of iron (Table 4). Iron is best absorbed when taken on an empty stomach with juice or Vitamin C, approximately 1 hour before or 2 hours after eating. Avoid taking with calcium, fiber, or tea as can decrease absorption.
- Majority of patients will experience side effects (nausea, constipation, diarrhea, abdominal pain). This tends to have a dose dependent effect. One can try alternate day dosing, administration with meals (recognize this will lower absorption), iron that is better tolerated with lower elemental iron content (ex. Ferrous Gluconate) or parenteral iron replacement.
- Check CBC 2 weeks after starting treatment. A rise in hemoglobin confirms the diagnosis. Hemoglobin should rise by 20 points over 3-4 weeks.

Preparation	Dose / tablet	Elemental iron
Ferrous fumarate	300 mg	~ 90 mg
Ferrous sulfate	300 mg	~ 60 mg
Ferrous gluconate	300 mg	~ 30 mg

Table 4. Available iron preparations.

Parental iron

- Consider if iron deficiency beyond 34 weeks gestation on oral iron replacement in anticipation of blood loss during delivery.
- Venofer (Iron Sucrose) used most commonly in pregnancy. Good safety profile. Can give 300 mg at a time, maximum 2 infusions / week. Generally avoid in first trimester.
- Venofer dose can be determined using the following formula:

    Total dose = [110 g/l – actual hemoglobin] x weight (kg) x 0.22 + 500 mg
- Monitor patients during infusion for hypersensitivity reactions and hypotension.

Lactation

- Iron requirements still remain elevated during lactation so women need to be monitored and replaced as indicated.

Antiphospholipid antibody syndrome (APLAS)

Antiphospholipid syndrome occurs either as a primary condition or in the setting of systemic diseases, such as systemic lupus erythematosus. Diagnosis of Antiphospholipid syndrome requires at least one clinical and one laboratory criteria. In the absence of any clinical criteria, the patient is said to have positive antiphospholipid antibodies rather than the syndrome.

Clinical Criteria

- Any thrombosis (venous or arterial)
- Pregnancy complications
    - > 3 unexplained, consecutive, spontaneous miscarriages before 10 weeks
    - > 1 fetal loss after 10 weeks in a genetically sound fetus
    - > 1 preterm delivery < 34 weeks due to severe preeclampsia or other placental disease

Laboratory Criteria

- Lupus anticoagulant (strongest association with thrombosis)
- IgG anti-cardiolipin antibody
- B2-glycoprotein

Diagnosis

- Need to fulfil one clinical criteria and one laboratory criteria.
- The positive antibody need to be demonstrated on at least **2 occasions at least 12 weeks apart**, within the preceding 5 years.
- Obstetric APLA syndrome is where the clinical criteria is one of the three pregnancy complications together with the laboratory criteria.
- Secondary causes of APLA includes autoimmune disease (i.e. SLE), malignancy, drug reactions or infections.
- Do not test for antiphospholipid antibodies during pregnancy as the values are altered. **Check 8-12 weeks postpartum**.

Management

- Thrombotic APLAS
    - Patients typically on lifelong Warfarin pre-pregnancy. Switch to therapeutic LMWH at the time of conception to be continued throughout pregnancy, in addition to Aspirin for pre-eclampsia prevention. Postpartum switch back to Warfarin to be continued indefinitely.

- Obstetric APLAS
    - Prophylactic LMWH for prevention of previous obstetric outcome (i.e. three early miscarriages or fetal loss) and Aspirin for pre-eclampsia prevention. Continue prophylactic LMWH for 6 weeks postpartum.

- Test **anti-Ro and anti-La antibodies** to determine the risk of fetal congenital heart block and neonatal lupus, given the frequent association of APLA with lupus. If positive, notify obstetrician for fetal cardiac monitoring (e.g. fetal ECHOs).
- For patients who only meet laboratory criteria but not clinical criteria, Aspirin may be used during pregnancy as per expert opinion as there is a paucity of data in this population. If there is concurrent lupus then Aspirin is strongly recommended for pre-eclampsia prevention.

Sickle Cell Disease

Impact on Pregnancy

- Maternal risk: increased maternal mortality, gestational hypertension, pre-eclampsia, urinary tract infections, and chorioamnionitis.
- Fetal risk: increased IUGR, preterm delivery, stillborn, and fetal mortality.

Impact of Pregnancy on Sickle Cell Disease

- Increased risk of vaso-occlusive crises, mostly in the third trimester and postpartum.
- Increased risk of acute chest crises and infections (ex. Urinary tract infections).
- Difficult to predict which patients will have increased risk of complications, as little correlation with disease control pre-pregnancy.

Investigations

- RBC genotyping and phenotyping
    - In case of needing transfusions to avoid acquisition of allo-antibodies.

- Assessment of end organ damage
    - Renal and hepatic function
    - ECHO for pulmonary hypertension
    - PFTs if previous acute chest syndrome
    - Ophthalmology referral for sickle cell related retinopathy
    - Iron profile for iron overload from transfusions, avoid iron containing prenatal vitamins if elevated ferritin

Treatment (RCOG Guidelines 2011)

- Vaso-occlusive crisis
    - Similar treatment as non-pregnancy patients including oxygen, opioids, fluids, and exchange transfusion if acute chest syndrome.
    - Tylenol, Morphine, Hydromorphone are safe in pregnancy. If mother on chronic opioids, consult pediatrician to monitor for neonatal abstinence syndrome.
    - NSAIDs only in second trimester up until 32 weeks. Avoid in first trimester due to interference with implantation causing miscarriage. Avoid after 32 weeks due to premature closure of PDA. Can cause oligohydramnios in any trimester.

- Other considerations
    - Stop Hydroxyurea 3 months pre-pregnancy. Evidence of teratogenicity in animal models but retrospective observational data suggest no adverse outcome in fetus and childhood. Stop iron chelators.
    - Folate 5 mg: prevent neural tube defects, and because of high red cell turnover
    - Aspirin 81mg daily: prevent pre-eclampsia.
    - Thromboprophylaxis 6 weeks postpartum: prevent VTE.
    - Calcium and vitamin D supplementation: reduce osteopenia.
    - Vaccinations: hyposplenia (Streptococcus pneumonia, Haemophilus influenza, Neisseria meningitidis).

- Screen partner for hemoglobinopathies: offer genetic counselling regarding fetal risk of sickle cell disease.
- Will require very close monitoring of fetal growth with obstetrics. Also placental scans as can have placental insufficiency due to sickling in the placental circulation

Cardiac Diseases in Pregnancy

Peripartum Cardiomyopathy

Epidemiology

- Risk factors: African race, older age, multiple previous pregnancies, pre-eclampsia, and prior history of peripartum cardiomyopathy.

Diagnosis

- Classically occurs in the last 4 weeks of pregnancy up to 5 months postpartum. Variations can occur outside of this range.
- EF <40% without other cause identified (e.g. acute coronary syndrome, toxins). A diagnosis of exclusion.

Treatment

- Prompt delivery should be considered in patients with advanced heart failure, once stabilized. Unknown whether urgent delivery will improve cardiac recovery. Decision for delivery should be made by obstetrician in conjunction with cardiology.
- Treatment similar to other causes of heart failure:
    - Lasix for pulmonary edema
    - Afterload reduction (e.g. Hydralazine)
    - Beta blocker (not atenolol) once out of acute heart failure
    - Nitrates and Digoxin are also safe
- Avoid ACE-I, ARB and Spironolactone in pregnancy. Postpartum can use selective ACE-I including enalapril, captopril or quinapril (safe in lactation)
- Up to one third of patients will recover spontaneously. High mortality, especially in women of African origin.
- New data suggesting that high prolactin may be playing a role. Consider cessation of lactation, and bromocriptine under investigation as potential therapy
- Repeat ECHO postpartum.

Counselling for subsequent pregnancy

- Preconception planning after an episode of peripartum cardiomyopathy is critical.
- If ejection fraction recovers to > 40%
    - 20% recurrence rate in subsequent pregnancy with no associated mortality
- However, if the ejection fraction remains < 40%

- 50% recurrence rate and 20% associated mortality in subsequent pregnancy
- Should be heavily counselled to ensure adequate contraception; if unplanned pregnancy occurs, should discuss termination for maternal safety (multi-disciplinary discussion with cardiology and obstetrics)

Arrhythmias

Cardiac arrhythmias are among the most common cardiac complications in pregnancy. The cardiovascular system in pregnancy undergoes a steep increase in plasma volume and cardiac output beginning in late first trimester and persists until delivery. Increase in heart rate, particularly in the third trimester, and biatrial stretch can further promote arrhythmogenicity. As a result, pregnancy can bring on first time arrhythmias or exacerbate those with pre-existing arrhythmias.

Palpitation is a frequent symptom of pregnant women. Fortunately, they are often not caused by a malignant arrhythmia. Sinus tachycardia, premature atrial contractions, premature ventricular contractions, and SVT are common in pregnancy. All women with frequent palpitations especially when associated with other cardiac symptoms should undergo further investigations. This includes a 12 lead ECG, Holter and ECHO. Contributing metabolic disorders including hyperthyroidism should be excluded. Those with frequent or sustained arrhythmia or associated red flag symptoms like syncope should be referred to a cardiologist.

The approach to managing arrhythmia is similar to that in a non-pregnant patient. The majority of antiarrhythmic drugs are not well studied in pregnancy and as a result the fetal risk is largely unknown. The concern is disrupted fetal organogenesis in first trimester and reduced growth in later trimesters. Generally, adenosine, beta blockers (e.g. Metoprolol, Bisoprolol) and calcium channel blockers (e.g. Verapamil and Diltiazem) are used for arrhythmias in pregnancy. Digoxin is also safe and effective. In terms of antiarrhythmic, Flecainide is safe whereas Amiodarone should be avoided due to risks of IUGR and preterm delivery. Electric cardioversion can be performed in all stages of pregnancy if indicated and does not compromise blood flow to the fetus.

The question of how to prevent arrhythmias during delivery often arises in the clinical setting. This is because the cardiovascular changes in pregnancy are augmented by the sympathetic drive related to pain and anxiety during labour. Adequate pain control and selective use of telemetry in malignant arrhythmias (e.g. VT) are recommended. Vaginal delivery is not contraindicated. Epidurals should theoretically reduce arrhythmias given its effects in decreasing sympathetic drive, however studies have failed to show an association. The only intervention to demonstrate a decrease in arrhythmia rates is cesarean delivery, but this should be performed for obstetric indications (e.g. breech fetus) rather than on the basis of arrhythmias alone. Immediately postpartum, there is a rapid decline in cardiac output and plasma volume followed by normalization of pregnancy related changes in most by two weeks.

Syncope

Syncope can affect up to 5% of pregnancies and is most likely to occur in the second trimester. The most common mechanisms are orthostatic syncope or neurogenic syncope. Other causes include pulmonary embolism, amniotic fluid embolism, arrhythmias, hemorrhage, or exacerbation of a pre-existing cardiac condition. Approach to investigating syncope should be similar to that of a non-pregnant patient.

Mechanical Valves

Anticoagulation of mechanical heart valves is tricky in pregnancy. While vitamin K antagonists such as Warfarin is superior in preventing valve thrombosis compared to LMWH, Warfarin use in first and third trimester can be associated with Warfarin embryopathy and fetal neurologic sequelae, respectively. LMWH does not cross the placenta and hence is without risk of teratogenicity or fetal hemorrhage. There may be a dose response relationship with Warfarin and fetal complications occurring at doses more than 5mg.

Current American Heart Association guideline suggests continuation of Warfarin throughout pregnancy if the dose to maintain therapeutic anticoagulation is less than 5mg. In reality, due to patient preference, women generally are maintained on LMWH throughout pregnancy in order to avoid any concerns about teratogenicity. If more than 5mg, then Warfarin should only be used in the second trimester and replaced with LMWH in first and third trimester. All Warfarin should be switched to LMWH at 36 weeks. Every woman with a mechanical heart valve must undergo a planned delivery (e.g. induction of vaginal delivery or C-section). This comprises of admission to hospital the day prior to delivery and bridged onto unfractionated Heparin infusion, in order to minimize time off anticoagulation during labour. Postpartum, Warfarin should be resumed given its safety in breastfeeding and superior anticoagulation properties.

Cardiac Conditions that Contraindicate Pregnancy

Congenital heart disease is the most common heart condition seen in pregnancy. Pregnant women with underlying heart disease are at risk of complications due to the cardiovascular changes in pregnancy, including arrhythmias, heart failure and stroke. Pulmonary hypertension can worsen and lead to combined fetal and maternal mortality of almost 50%. Women with underlying aortopathy, such as Marfan syndrome and coarctation, are at risk of aortic dilatation, dissection and rupture. As a result, women with structural heart disease are followed closely by in pregnancy by a cardiologist. Very few women are counselled to avoid pregnancy but rather informed of the risks of being pregnant. The exception is very high risk conditions such as pulmonary hypertension whereby one would advise against pregnancy and counsel on termination if pregnant. Below are the cardiac conditions that have relative contraindications to pregnancy (JACC, High Risk Cardiac Disease in Pregnancy, July 2016)

1. Pulmonary hypertension, of any etiology*
2. EF <30%
3. Outflow obstruction: HOCM, severe AS, severe MS
4. Marfan syndrome with aortic root dilatation of 4cm
5. Peripartum cardiomyopathy with persistent EF <50%
6. Aortic coarctation

*Women with pulmonary artery hypertension should be followed by a pulmonary hypertension clinic during pregnancy. Newer data suggest that women with controlled or mild pulmonary hypertension can plan and undergo pregnancy with close monitoring.

An excellent resource for information on a comprehensive list of cardiac diseases in pregnancy is provided through the University of Toronto: http://www.heartdiseaseandpregnancy.com.

Respiratory disease in pregnancy

Asthma

Epidemiology

- Asthma complicates 4-8% of pregnancies and is a common consultation request.
- Asthma typically follows the rule of 1/3^{rds} in pregnancy: 1/3 of patients experience no change in their disease, 1/3 worsen and 1/3 improve.
- Increased rates of prematurity, IUGR and preeclampsia with poorly controlled disease.

Management

- Assess control at each visit by inquiring about frequency of symptoms, presence of nocturnal symptoms and use of reliever medications (SABA).
- Review smoking cessation, proper inhaler technique, use of aerochamber, avoidance of triggers.
- Beware of other conditions that can worsen asthma, such as GERD, postnasal drip, pneumonia, or PE.
- Encourage monitoring of FEV1/peak flows as outpatient.
    - < 60%, 60-80% vs. > 80% indicates severity / control of disease.
- The management of asthma in pregnancy is essentially unchanged from management in the non-pregnant state.
    - Short acting beta-agonists are safe.
    - Inhaled corticosteroids - budesonide (Pulmicort) is the most studied and safe.
    - Long-acting beta agonists- not as well studied but thought to be safe. Symbicort commonly used.
    - Oral steroids - small risk of oral cleft palate (OR 2-3) if given < 13 weeks gestation when palate is forming. However, the benefit of treating severe asthma with oral steroids usually outweighs this risk, therefore always **treat asthma exacerbation with Prednisone**.
    - Leukotriene antagonists - not first line. No evidence of harm, and would be safe to continue in a patient that is benefiting.

Renal disease in pregnancy

Physiologic Change in Pregnancy

- GFR increases by 50% in pregnancy and returns to baseline by one week postpartum.
- This results in reduction of Cr in pregnancy compared to pre-pregnancy values and worsening of pre-existing proteinuria.
- MDRD is not reliable for calculating GFR in pregnant patients as it significantly underestimates it. 24 hour Cr is the gold standard for calculating GFR.
- Right hydronephrosis or hydroureter is a normal physiologic phenomenon seen in up to 80% of pregnant women. It is caused by compression of the ureter by the gravid uterus and is most common in the second and third trimester. It is often incidentally discovered on abdominal ultrasound for another indication or routine fetal ultrasounds. If not associated with flank pain, UTI or acute kidney injury, further investigation and treatment is not required. It typically resolves within days of delivery. Left sided or bilateral hydronephrosis would be atypical and usually require further investigations.

Chronic Kidney Disease

Complications in pregnancy

- Maternal complications: progression of kidney disease (see section below), flare of underlying disease (e.g. lupus nephritis), gestational hypertension, pre-eclampsia, and C-sections.
- Fetal complications: drug related risks (e.g. immunosuppressive drugs), miscarriage, preterm birth, IUGA, stillborn, and NICU admissions.

Preconception counselling

- Contraception until pregnancy is desired. Start Folic acid if planning pregnancy.
- Baseline Cr, Urine protein/creatinine ratio (PCR), 24 hour urine to determine baseline severity of CKD.
- Systemic renal diseases (e.g. lupus nephritis) need to be in remission for 6 months prior to conception.
- Control of blood pressure to <140/90. Switch ACE/ARB to pregnancy safe antihypertensives in preconception period, unless has nephrotic range proteinuria then switch at onset of pregnancy.
- Patients on immunosuppressants need to be switched to medications safe in pregnancy. Discontinue MMF, Cyclophosphamide and Sirolimus 3 months pre-pregnancy. Switch to Plaquenil, Azathioprine, Cyclosporin, and Tacrolimus.

Intrapartum management

- Start Aspirin 162mg daily before 16 weeks until 36 weeks for pre-eclampsia prevention.
- Ultrasound to confirm pregnancy rather than b-HCG since its renally cleared and can be falsely elevated.
- If renal function or proteinuria worsens, may be due to relapse of underlying renal disease (e.g. lupus nephritis), but need to **rule out pre-eclampsia**.
- Renal biopsy can be performed in pregnancy in early trimesters, but preferred before or after pregnancy.
- Nephrotic syndrome patients with peripheral edema can be managed with compression stockings and judicious use of loop diuretics. Prophylactic anticoagulation may be considered due to increased risk of thromboembolism and should be guided by a nephrologist.

Progression of CKD in pregnancy

- Highest risk in advanced stages of CKD (stage 4 or 5 CKD), with associated proteinuria (>1g), presence of hypertension, or systemic disease.
- Patients in the high risk category need to be counselled on the risk of renal failure and potential need of dialysis in pregnancy.
- Stage 1-2 CKD without proteinuria or hypertension are most likely to preserve renal function throughout pregnancy.

Other Kidney Diseases

Asymptomatic bacteriuria should be treated in pregnancy to reduce the risk of pyelonephritis and preterm labour. The 2018 Canadian Task Force recommends one-time screening with urine culture in first trimester. More frequent screening is warranted in those with higher risk of asymptomatic bacteriuria, including women with diabetes, recurrent UTIs, PCKD, or sickle cell disease. Those with symptoms of a urinary tract infection should be tested and treated.

Kidney stones are more common in pregnancy, particularly in the second or third trimester. Abdominal ultrasound is the diagnostic test of choice in order to avoid radiation exposure. Distal stones can be missed by trans-abdominal ultrasound and only picked up by transvaginal ultrasound. Most stones pass spontaneously due to dilated urinary tract in women. Ureteric stents or nephrostomy tubes can be used in pregnancy in the setting of obstructive uropathy.

Rheumatologic disease in pregnancy

Physiologic Changes in Pregnancy

Pregnancy is a state of decreased cellular and humoral immunity. **CRP is the maker of choice** for assessing inflammation in pregnancy. ESR increases with gestational age so is falsely elevated in pregnancy.

Effect of Disease on Pregnancy

All systemic inflammatory diseases affect the pituitary ovarian axis contributing to hypogonadism and infertility. Women trying for pregnancy and unsuccessful for more than a year with good disease control are encouraged to get reproductive potential testing.

Preconception counseling is essential to ensure women enter pregnancy is well informed of the inherent risks related to their disease. Women with quiescent disease for **at least 3 to 6 months** prior to pregnancy fare the best, although the disease can flare at any point during pregnancy or postpartum. Both uncontrolled inflammatory diseases and its disease modifying drugs can have detrimental effects on pregnancy. In particular, systemic diseases with renal complications (e.g. lupus nephritis) and antiphospholipid syndrome have the greatest impact on pregnancy. Common complications among all inflammatory conditions include gestational hypertension, pre-eclampsia, thromboembolism, miscarriage, preterm labour and IUGR.

Effect of Pregnancy on Disease

A successful pregnancy depends on the dampening of the maternal immune system in order to support the growth of a genetically different fetoplacental unit. Where pregnancy is an overall immunosuppressed state, not all inflammatory conditions are in remission. This is because pregnancy is a time of transition from helper T-cell 1 (T_H1) dominance to T_H2. As a result, T_H1-dominant diseases such as multiple sclerosis, rheumatoid arthritis and thyroiditis tend to improve during pregnancy (and flare postpartum), while T_H2-dominant diseases such as SLE often worsen.

Rheumatoid Arthritis

Majority of rheumatoid arthritis go into remission in pregnancy. However, up to 90% of patients flare in the first 3 months postpartum. Hydroxychloroquine, Azathioprine, steroids, and biologics can be continued in pregnancy. Methotrexate and Leflunomide need to be discontinued before conception (see Medication Safety section).

SLE

The relationship between lupus activity and pregnancy is not predictable. Some patients remain in remission while others have mild to moderate flares, most commonly in the second half of pregnancy or postpartum. Pregnancy in the setting of SLE is associated with poor fetal and maternal outcomes. Women with SLE are at risk of pregnancy loss, pre-eclampsia, worsening disease activity, preterm labour, morbidity and mortality. Patients with co-existing Antiphospholipid syndrome are at even higher risk. Pre-eclampsia prophylaxis with **Aspirin** should be prescribed for all patients with SLE or antiphospholipid syndrome. **Anti-Ro and anti-La** antibody testing must be done in all women with SLE or APLA syndrome. If positive, there is a small risk (5%) of fetal congenital heart block and neonatal lupus. The patient should be followed by a pediatric cardiologist and monitored with fetal ECHO in utero. If impending heart block is identified, steroids +/- IVIG may be considered, and potentially a pacemaker postnatally indicated for the neonate.

Obstetric internists may be asked to differentiate between lupus nephritis and pre-eclampsia. Table 1 lists the key differences.

	Lupus nephritis	**Pre-eclampsia**
Hypertension	Onset anytime in pregnancy, including before 20 weeks	Onset after 20 weeks
Proteinuria	> 3 g/day	Protein/creatinine ≥ 30 mg/mmol
Urinary sediment	Active	Inactive
Anti-dsDNA	Present, rising	Absent
Complement levels	Reduced	Normal
CRP	Elevated	Normal
Microangiopathic hemolytic anemia	Absent	Present in HELLP

Table 1. Differentiation of pre-eclampsia from active lupus nephritis. Adapted from the paper by Baer et al., Obs Gyne Surv, 2011.

Other rheumatologic diseases such as vasculitis, dermatomyositis, and scleroderma in the absence of renal impairment or pulmonary hypertension are generally not affected by pregnancy. All patients with rheumatologic diseases should be assessed by a rheumatologist in the preconception period and during pregnancy. Anti-rheumatic drugs and their safety in pregnancy are discussed separately in the Medication Safety section.

Infectious Disease in Pregnancy

Antimicrobials

- Most antimicrobials are safe in pregnancy. This includes Penicillins, Cephalosporins, Macrolides (Azithromycin preferred, possible hypospadias with Clarithromycin), Vancomycin, Metronidazole and Acyclovir.
- Avoid Tetracyclines (teeth staining) and Quinolones (cartilage deformities in animal studies). Caution with Sulfa (avoid in T1, but use with folate if no other options). Nitrofurantoin in the third trimester may also increase the risk of neonatal jaundice.

Common infections

- Treatment considerations for majority of infectious diseases are similar to outside of pregnancy. Major consideration is antibiotic safety.
- Pneumonia and URTI are treated similarly in pregnant patients.
- Remember to cover for Listeria in CNS infections with Ampicillin.
- Asymptomatic bacteriuria: pregnancy is one of the few indications to treat this condition because of the increased risk of pyelonephritis and preterm labour.

Influenza

- Increased risk of hospitalization and death in pregnant women with influenza.
- Increased risk of preterm birth or low birth weight.
- Vaccine should be offered to <u>all</u> pregnant women, <u>regardless of gestation.</u> Vaccination decreases the risk of influenza not only in mothers but also for infants during the first 6 months of life. In addition, one study indicated a decreased risk of malformations with the vaccine.
- All pregnant women with suspected influenza should be treated with antivirals, regardless of severity, history, risks, or results of diagnostic tests.
    - Rapid influenza antigen tests are often falsely negative.
- Clinical benefit still present when treatment is begun after 48 hours.

Viral hepatitis

- Hepatitis A: similar to nonpregnant patient.
- Hepatitis B: See below.
- Hepatitis C: usually uneventful with vertical transmission ~ 5-10%. Peg-Interferon and Ribavirin are contraindicated in pregnancy, but not during breastfeeding. Breastfeeding in hepatitis C is considered safe.
- Hepatitis E: Pregnant population more vulnerable to Hepatitis E (and fulminant liver failure from this virus) than any other viral hepatitis (endemic in southeast asia; consider in the returning traveler).

Hepatitis B in pregnancy (2012 Canadian Association for the Study of Liver Disease Guidelines)

- Current standard of care is baby should receive Hepatitis B vaccine immediately upon birth (in delivery suite), 2 months and 6 months. Babies should also receive Hepatitis B immunoglobulin at birth.
    - Without treatment, 90% risk of vertical transmission during birth in HbeAg + cases.
    - With treatment, risk reduced to < 10%.
- Decision to treat mother with antivirals (e.g. Tenofovir) is controversial but usually done if there is an indication for treatment irrespective of pregnancy, or with HBV DNA > 2 x 10^6 IU/ml in an e-antigen positive pregnant patient.
    - Treatment usually started at 28 weeks gestation to allow time for suppression of virus before delivery.
- Remind all women of the importance of "liver protection"- alcohol cessation, avoidance of obesity.
- Fetal scalp sampling and other invasive measures should be avoided at birth.
- Breastfeeding is safe as virus is transmitted primarily through blood.
- Don't forget about screening mothers for hepatoma, as in the context of Hepatitis B one would screen even without the presence of cirrhosis.

HIV (SOGC 2014 guidelines)

- Preconception planning should address folic acid supplementation, achieving pregnancy in a discordant couple, need for treatment or discontinuation of teratogenic medications.
- Vertical transmission of HIV from an untreated mother to fetus is about 25%. There is a 14% rate of HIV transmission when mothers with HIV breastfeed their infants. The risk of transmission can be reduced to less than 1% with effective treatment of mother, C-section, AZT administration in the neonate (see below), and abstinence from breastfeeding.
- The current standard of care is to offer all women HAART treatment in first trimester to aim for an undetectable viral load. PJP can be treated with Septra, ensure high dose Folate.
- ACTG-076 trial demonstrated a major role for Zidovudine in decreasing perinatal transmission risk by 67% when given antepartum, intrapartum, as well as to the newborn for six weeks.
- C-section indicated if high viral load (>1000/ml) as it significantly reduces transmission to baby, otherwise vaginal delivery is preferred. Avoid invasive monitoring, instrumentation, prolonged rupture of membranes to reduce transmission.

- All newborns of mothers with HIV should get post-exposure prophylaxis regardless of viral load. All women are instructed to avoid breastfeeding to further reduce transmission.

Zika (CDC 2019)

- Zika is a virus spread by mosquitos or sexual contacts that can pass from a pregnant woman to her fetus and lead to serious birth defects.
- Infection during pregnancy can lead to fetal microcephaly and other severe brain defects.
- Majority of those infected with Zika are asymptomatic. Symptoms include acute onset of fever, maculopapular rash, arthralgia, conjunctivitis, myalgia and headache. Symptoms usually mild and lasting for days to a week. Cases of Guillain-Barre Syndrome have been reported.
- Testing can be done using PCR and serology. Women with symptoms of Zika or abnormal fetal ultrasounds should be tested. Routine testing for pregnant women exposed to these areas who do not have symptoms is not recommended. Patients with suspected Zika virus infection should also be evaluated for Dengue and Chikungunya.
- Pregnant women should not travel to areas with Zika outbreak. If a pregnant woman must travel to a Zika endemic area, measures should be taken to lessen the risk of mosquito bites, including long-sleeved clothing, bug repellents, staying indoors, and removing standing water. Male partners who have travelled to Zika endemic areas can still transmit the virus for 3 months via intercourse to their pregnant partners; abstinence or the use of condoms are recommended.
- If couples are planning to conceive and have travelled to an area with Zika outbreak, they should avoid sex or use condoms for 3 months if male partner is at risk of exposure and 2 months for females, even if they are asymptomatic. This is because Zika has been genetically identified in semen months after an infection.
- There is currently no vaccines or targeted treatment for Zika. Treatment is supportive.
- Pregnant women with confirmed Zika infection should be evaluated for fetal neurologic abnormalities and counselled by an obstetrician.

Neurologic Diseases in Pregnancy

Headache

Primary headache syndromes are common in pregnancy and postpartum. A good history is critical in determining the diagnosis and identifying red-flag symptoms. Differential diagnosis of headache in pregnancy includes:

- Primary headache syndrome: tension, migraine, cluster headache.
- Vascular causes: cerebral venous sinus thrombosis, intracranial hemorrhage from AV malformation, pre-eclampsia/severe hypertension, stroke, cerebral or cervical dissection, reversible cerebral vasoconstriction syndrome (RCVS).
- Infectious causes: meningitis, encephalitis, abscess.
- Increased ICP: tumour, pseudotumour cerebri.
- Others: PRES, medication rebound headache, withdrawal headache (e.g. caffeine).

A woman with a history of tension, migraine or cluster headache may continue to experience this in pregnancy. The frequency of tension and cluster headaches generally remain stable in pregnancy as they are not hormonally mediated. Further diagnostic testing may not be necessary if the characteristic of the headache has not changed from pre-pregnancy. Pre-eclampsia should be ruled out in every pregnant woman over 20 weeks of gestation with new or worsening headache. Neurovascular causes should be ruled out if the headache is sudden onset and of thunderclap quality, such as intracranial hemorrhage, dissection or RCVS. Indications for neuroimaging and lumbar puncture are similar to nonpregnant patients. MRI is safe in pregnancy but the use of Gadolinium has been associated with increased nephrogenic systemic fibrosis like disease and non-specific rheumatologic or skin conditions in the newborn.

Migraine

Treatment of migraines is indicated for maternal wellbeing. Migraines do not have any impact on the health of the fetus or maintenance of pregnancy. Approximately 2/3rd of women have stability or improvement of migraine in pregnancy and 1/3rd experience worsening of headache. A high percentage of women with migraine provoked by menstruation will remit in pregnancy. Generally, migraines tend to improve after 20 weeks gestation.

Prevention:

- Patients should keep headache diaries so they can begin to identify and avoid common triggers for their headaches.
- 'Migraine hygiene' is critical, including adequate rest, hydration and oral intake.
- Magnesium and Riboflavin (Vitamin B2) supplementation have been shown to be safe and effective in migraine prevention. Approximately 400mg of Vitamin B2 can be taken daily throughout pregnancy.
- Amitriptyline can be given before bed (side effect is sedation). Caffeine (in moderation) can also be helpful in prevention.
- Beta-blockers (Metoprolol, Propranolol) and calcium channel blockers (Verapamil) can also be used for headache prevention. Beta-blockers are associated with IUGR and neonatal bradycardia. Atenolol should be avoided intrapartum and during breast feeding for this reason.

Acute treatment:

- For severe migraines, options include anti-emetics, opioids, and intravenous fluids. Metoclopramide is effective in treating acute migraine and vomiting. Hydromorphone and Morphine are safe in pregnancy when used in the short-term.
- Tylenol can be taken on an as-needed basis. NSAIDS can be used in the second trimester up to 32 weeks. After that, NSAIDs are associated with premature closure of the ductus arteriosus. NSAIDs are also associated with oligohydramnios, so clarify with OB that it can be used safely.
    - Tylenol taken for more than 15 days/month can be associated with overuse syndromes, leading to rebound headaches on the days Tylenol is not consumed. If this is the case, Tylenol needs be stopped abruptly and then slowly reintroduced. Patients should expect worsening of their headaches when Tylenol is abruptly stopped, but gradual improvement thereafter.
- Other medications can be used cautiously include triptans (Sumatriptan preferred).
- Ergotamine is absolutely contraindicated in pregnancy.
- Dexamethasone can be used in status migrainosus.
- In most cases, migraines get better on their own as women progress through pregnancy. Reassurance is just as important as medication.

RCVS (Reversible Cerebral Vasoconstriction Syndrome)

RCVS is a rare condition caused by multifocal narrowing of intracerebral vessels typically affecting females age 20-50. It most commonly presents postpartum in the context of pregnancy. The presentation is sudden, severe, **thunderclap** headache, that occurs days to weeks postpartum. It can be associated with focal neurologic deficits due to non-aneurysmal subarachnoid hemorrhage. Diagnosis requires vascular imaging with CTA or MRA, demonstrating angiographic abnormalities with "sausage on a string" appearance. Symptoms generally self-resolve over days to weeks. Calcium channel blockers (e.g. Nimodipine) can be used in addition to supportive treatment of the headache, hypertension, and seizures.

Stroke

The Canadian Stroke Best Practice released guidelines in 2018 on the prevention and acute management of stroke in pregnancy. The risk of stroke is increased by three fold in pregnancy and most commonly occurs at the time of delivery and postpartum. High risk women should be maintained on Aspirin throughout pregnancy and during breastfeeding for stroke prevention. Stroke as a result of pre-eclampsia should undergo aggressive blood pressure control and treated with Magnesium Sulfate for eclampsia prevention. EVT (endovascular thrombectomy) is not contraindicated in pregnancy and those eligible should be treated as per existing guidelines. tPA does not cross the placenta therefore has no impact on fetal bleeding, but the main concern is possible association with placental abruption. tPA can be considered for a pregnant patient with disabling stroke but the risk-benefit considerations are complex and should be undertaken by a physician with experience in stroke treatment. Stroke is not a contraindication for vaginal delivery unless associated with increased intracranial pressure.

Epilepsy

Over 90% of women with epilepsy have good outcomes in pregnancy. The frequency of seizures does not change for most women in pregnancy provided adequate seizure control was achieved pre-pregnancy. There are however potential maternal and fetal complications of epilepsy in pregnancy that patients need to be made aware of.

Preconception counseling

- Antiepileptic drugs (AEDs) are associated with contraceptive failure because they are inducers of the cytochrome P450 enzymes, which metabolize OCPs.
- Certain AEDs inhibit folate production, therefore, women should be on 4mg of Folic Acid for 1-3 months pre-conception and throughout pregnancy.
- Seizure control, choice of medication (i.e. teratogenic potential), and dose of AEDs should be ideally determined pre-conception.

Antenatal care

- Generally, the AED that controls the seizures is the one that should be used in pregnancy, except for Valproate due to its high risk of teratogenicity.
- In the general population, there is a 2-3% risk of major congenital malformations. This risk rises to 4-6% in women exposed to AEDs. Factors which increase the likelihood of teratogenicity include choice of drug, polytherapy, family history of birth defects, gestational timing of exposure, prior AED-exposed child with congenital abnormalities.
    - Note, women were considered “exposed” to AEDs if the drugs were taken in the first four months of pregnancy.
- Teratogenicity is medication specific and dose dependent (Table 1).
- Most commonly, congenital malformations follow a similar pattern to that seen in the general population. Cardiac defects are usually the most frequent (with the exception of Valproate where neural tube defects are the most common), followed by facial clefts, hypospadias and neural tube defects.
- Medication (Levetiracetam, Topiramate, Oxcarbazepine, Lamotrigine, Phenytoin) levels must be monitored because of the increased metabolism which occurs in pregnancy. It is very common to need to increase drug dosing in pregnancy, particularly lamotrigine. However, these drugs will need to be titrated down postpartum to avoid maternal toxicity.
- Risk of medications versus risk of seizure is an important discussion to have with patients. Generalized seizures are of greatest concern because of the possibility of trauma, placental abruption, preterm labour, hypoxia, electrolyte changes and hypotension, all of which can seriously impact the fetal central nervous system and immature brain.

- The AEDs with the most effective seizure control tend to be associated with the highest risk of malformations (Figure 1).

Anti-epileptic drug	Risk (%) of major congenital malformations (based on multiple international registries)	Risk (%) of major congenital malformations (based on North American AED registry)	Primary teratogenic effect (based on North American AED registry)
Untreated epilepsy	1.1 – 3.3 (baseline risk in general population)	1.1	
Valproate	4.7- 13.8	9.3	Neural tube defects Cardiovascular Hypospadias
Carbamazepine	2.6- 5.6	3.0	Oral clefts
Lamotrigine	1.9 – 4.6	2.0	Oral clefts
Phenobarbital	5.5 – 7.4	5.5	Cardiovascular
Phenytoin	2.4 – 6.7	2.9	Cardiovascular
Levetiracetam	0.7 – 2.4	2.4	Neural tube defects Cardiovascular
Oxcarbazepine	1.8 – 5.9	2.2	Not quoted
Topiramate	2.4 – 7.7	4.2	Oral clefts

Table 1. Rates of major congenital malformations in fetuses. Data taken from multiple international birth registries. Note that more data exists for exposures to older AEDs (Valproate, Phenytoin) versus newer AEDs (Topiramate, Oxcarbazepine, Levetiracetam), making the precision of estimates of these newer drugs suboptimal. Tomson et al., Seizure, 2015. Hernandez-Diaz et al., Neurology 2012.

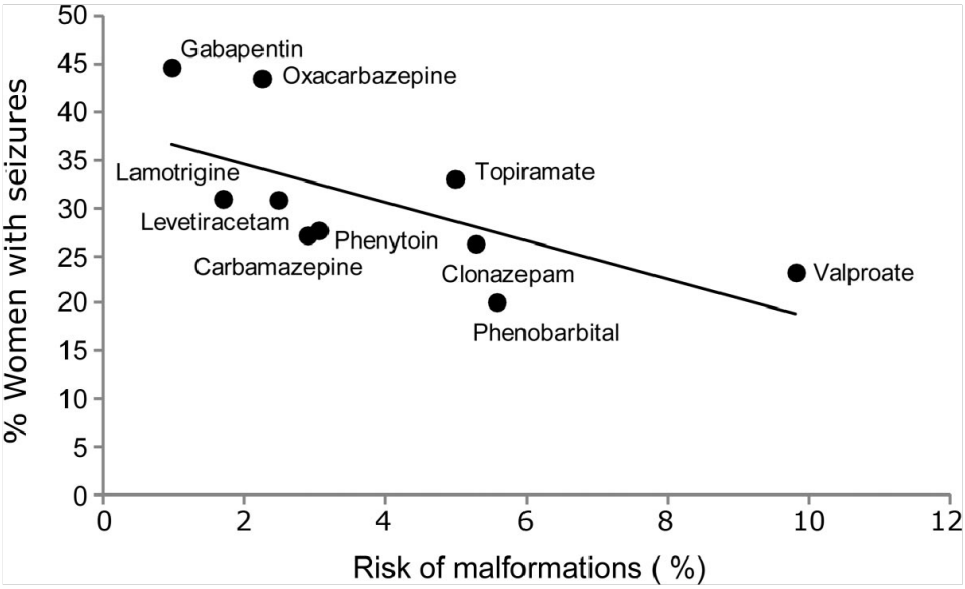

Figure 1. Risk of major malformations by proportion of women having at least one seizure during their pregnancy within each antiepileptic drug group among women with epilepsy. Data taken from the North American AED Pregnancy Registry 1997-2011. Hernandez-Diaz, Neurology 2012.

Postpartum care

- The early postpartum period is a time of high risk for seizure recurrence.
    - Mothers may need help to ensure adequate sleep, medication compliance, and supervision for the first 4-6 weeks (no unsupervised baths, diaper changing on the floor (not change table), no stairs with baby).
    - All AEDs are measured in breast milk, but the general consensus is that the benefits of breastfeeding outweigh potential risks.

Dermatologic Diseases

Women will experience skin, nails and hair changes in pregnancy. Increase in pregnancy hormones, such as estrogen, progesterone, and melanocyte-stimulating hormone, can cause melasma (hyperpigmented macules and patches on face) and linea nigra (dark vertical line in the center of abdomen). Women are more likely to get acne, spider or varicose veins, and striae in pregnancy. Nails grow faster in pregnancy. Postpartum alopecia is common within 6 months of delivery. Dermatologic conditions can be pre-existing or pregnancy specific, with common examples discussed below (AAFP 2007).

Polymorphic Eruptions of Pregnancy (PEP)

Previously known as PUPPP (pruritic urticarial papules and plaques of pregnancy). It presents as intensely pruritic erythematous papules or plaques that first appears in abdomen, often along the striae, and occasionally extends into the extremities. The spared umbilicus is a distinguishing feature to pemphigoid gestationis. Figure 1 displays two varying presentations of PEP. The diagnosis is clinical and it is not associated with any fetal complications. Treatment includes supportive therapies, topical steroids, and oral antihistamines. Oral steroids can be used for extreme symptoms. It is self-limiting postpartum.

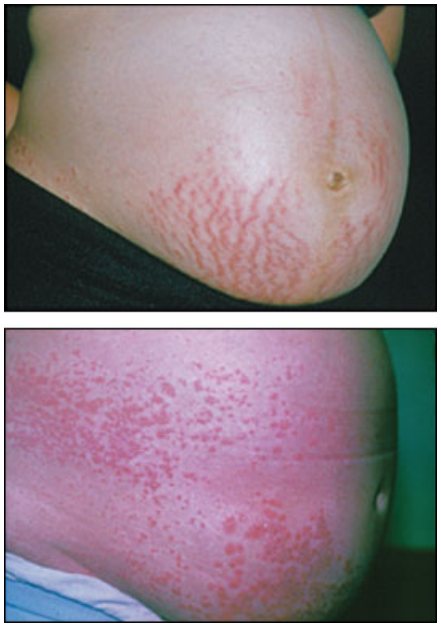

Figure 1. Two patients with PEP (AAFP 2007).

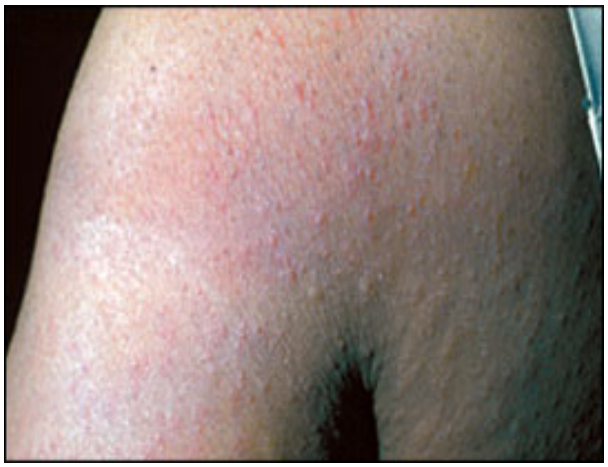

Figure 2. Prurigo of Pregnancy (AAFP 2007).

Prurigo of Pregnancy

Erythematous papules and nodules on the extensor surfaces of extremities. Etiology is unclear and there are no recognized adverse effects for mother or fetus. Association with intrahepatic cholestasis and atopy has been suggested. Topical steroids and oral antihistamines are used for symptom relief.

Pemphigoid Gestationis

A rare autoimmune condition seen in the second and third trimesters or postpartum, presenting with pruritic papules, vesicles, and bullae. The lesions are initially periumbilical that can generalize. The face and mucous membranes are usually not affected. Strong association with auto-immune conditions, particularly Graves' disease. Skin biopsy often required for diagnosis. Treatment includes antihistamines, topical steroids for mild cases, and oral steroids for severe cases. Due to transplacental transfer of auto-antibodies, newborns can have urticarial, vesicular or bullous lesions, and are at risk of premature delivery and small for gestational age.

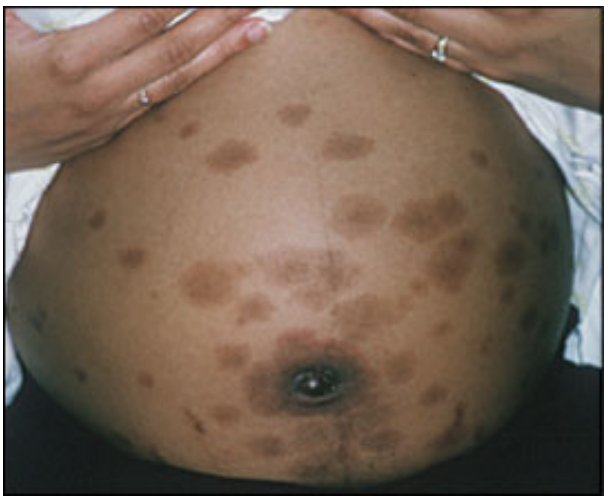

Figure 3. Pemphigoid gestationis (AAFP 2007).

Atypical Eruptions of Pregnancy

This is a category of pre-existing skin conditions that may flare in pregnancy. It includes atopic dermatitis, psoriasis, candida and other fungal infections. Atopic dermatitis can worsen or improve in pregnancy and is associated with prurigo of pregnancy. Psoriasis is likely to improve with pregnancy. Treatment for these conditions are similar to the non-pregnant patient with special attention paid to medication safety.

Obstetric Emergencies

Cardiac Arrest

Cardiac arrest most commonly occurs in hospital around the time of delivery at an incidence of 1 per 12,000 admissions. Mortality rate differs depending on the etiology of arrest. Common causes of cardiac arrest in pregnancy include cardiac disease, peripartum hemorrhage, amniotic fluid embolism, sepsis, hypertensive disorders, and thromboembolism. Causes specific to pregnancy should also be considered, including magnesium toxicity (ie stop magnesium infusion and give Calcium Gluconate) and amniotic fluid embolism. The resuscitation team of an arrested pregnant patient should be multidisciplinary, including internist, intensivist, obstetrician, anesthesiologist, and neonatologist.

The physiologic changes in pregnancy impacts every phase of the resuscitation process. There is significant aortocaval compression and pooling of up to 30% of maternal circulation in the uteroplacental unit. As a result, lateral uterine displacement and IV access above the diaphragm are recommended (Table 1). Lateral uterine displacement is the two-handed manual technique performed by a dedicated person standing to the left of the patient and pulling the abdomen to the left but not off the bed. This is suggested if the patient is more than 20 weeks gestation, which can be estimated by the uterus being at or above the level of the umbilicus. Tilt or wedge placement over the right flank is no longer recommended as it caused inadequate chest compressions. The respiratory changes in pregnancy include pharyngeal edema, decreased chest wall compliance, and less oxygen reserve. Therefore, pregnant women will need early airway attention by the most experienced intubator. Chest compressions, resuscitative drugs, and defibrillator settings are identical to a non-pregnant patient.

Identical to ACLS guidelines	**Relevant differences**
Rate, rhythm, and depth of compressions	Airway difficulties Shorter apnea to desaturation time
Drugs types and doses	Aortocaval compression – Lateral uterine displacement – IV access above the diaphragm
Energy for defibrillation	Remove fetal scalp monitoring – shouldn't delay defibrillation
Cycles of compression to ventilation (30:2)	Precipitating causes to consider: • Mg toxicity • Anesthetic toxicity/allergy • Embolic
	Perimortem C-section

Table 1. Similarities and differences of resuscitation of a pregnant patient compared to traditional ACLS protocol (Ash et al., Anaesthesia & Intensive Care Medicine 2016).

Perimortem c-section should ideally be done **within 4 minutes** of an arrest if return of spontaneous circulation is not achieved. This is done at the site of an arrest since transfer to an OR is associated with poorer outcomes due to delay of delivery. A size 10 scalpel and antiseptic solution are the only two equipment required by the obstetrician. Often there is a sudden and dramatic improvement of the mother, including return of spontaneous circulation, once the fetus is delivered. After successful resuscitation, patients should be transferred immediately to an intensive care unit. Left lateral decubitus position should be maintained if the fetus is not delivered. Therapeutic hypothermia is no longer an absolute contraindication but requires continuous fetal monitoring.

Amniotic Fluid Embolism

Epidemiology

- 1-12 cases per 100,000 deliveries.
- Maternal mortality of 20-30%. Risk of cardiac arrest 50-60%.

Pathophysiology

- Amniotic fluid entering maternal circulation, leading to acute pulmonary hypertension, cardiovascular collapse, systemic inflammation, and hypoxemic respiratory failure.
- Risk factors are C-section, instrumental vaginal delivery, placental previa/abruption/accrete, amniocentesis, abortion, miscarriage, etc..

Presentation

- >90% occur during labour or immediately after delivery.
- Most present with abrupt, catastrophic, rapidly progressive instability in hemodynamics and oxygenation, many leading to cardiac arrest.
- Symptoms include dyspnea, cyanosis, hemorrhage (DIC), cardiac arrest, seizure or stroke.
- Two most common signs including hypoxia (ARDS) and hypotension (cardiogenic shock).

Diagnosis

- Clinical diagnosis and diagnosis of exclusion.
- Need to rule out other causes, such as PE and cardiomyopathy.

Treatment

- Supportive treatments with early resuscitation (intubation, vasopressors, ACLS).
- Prompt delivery of fetus if viable.
- Avoid aggressive fluid resuscitation given ARDS. Transfuse blood products if in DIC.
- Prognosis is poor with 95% suffering from anoxic brain injury and neonatal mortality rate of 20-60%.

Radiation Risk

Diagnostic imaging in pregnancy causes a great amount of concern for patients and the medical provider due to fear of fetal teratogenicity and long-term sequelae. Apprehension regarding fetal risk should be weighed with the medical indication for the test in a given clinical scenario. The choice of imaging study should be made jointly by the provider and patient after an informed and in-depth discussion. An imaging modality can often be substituted (e.g. ultrasound for CT for appendicitis) or modified (e.g. Q scan only of V/Q study) for the goal of minimizing radiation. Ionizing radiation has been associated with fetal congenital anomalies, miscarriage, genetic diseases, growth retardation and developmental disorders. The background rate of congenital defects is 3 to 4% in the general population.

The radiation threshold associated with teratogenicity or miscarriage is 10 rads. Empirically, it was decided that half that dose should be considered the upper limit of acceptable accumulated radiation dose in pregnancy ie, **less than 5 rads**, or equivalent to 50 mgray (Toppenberg et al., AAFP 1999). The risk to a fetus from radiation is dependent on the gestational age at the time of exposure and dose of ionizing radiation. The radiation dose of common diagnostic imaging tests as per the American College of Obstetricians and Gynecologists (ACOG) guidelines are listed in Table 1. Single X-ray or CT is generally at a much lower dose than the exposure associated with fetal harm, and should not be withheld if medically necessary from a pregnant patient. CT abdomen and pelvis confers the highest radiation due to the fetus being directly exposed to the radiation field.

Ultrasound and MRIs are not associated with fetal risk and are the imaging modalities of choice in pregnancy. Gadolinium should be avoided due to increased risk of nephrogenic systemic fibrosis like disease and non-specific rheumatological, inflammatory, or infiltrative skin conditions in the newborn (Ray et al., JAMA 2016; 316(9):952-61). Breastfeeding should not be interrupted after gadolinium administration.

Radioactive iodine is contraindicated in pregnancy and breastfeeding due to the active absorption of radioiodine isotopes by the fetal thyroid and risk of future thyroid cancer.

Type of Examination	Fetal Dose (Rads)
Chest x-ray	0.00005-0.001
Abdominal x-ray	0.01-0.3
Extremity x-ray	<0.0001
Lumbar spine x-ray	0.1-1
Head or neck CT	0.0001-0.001
Chest CT or CT pulmonary angiogram	0.001-0.066
Abdominal CT	0.13-3.5
Pelvic CT	1-5
V/Q scan	0.03-0.07
Mammogram	0.0001-0.001

Table 1. Fetal radiation dose associated with common radiologic examinations (ACOG 2017)

Non-obstetric Surgery

Residents are traditionally taught if surgeries must be done in pregnancy it is safest to do in the second trimester. This is based on the associated risk of miscarriage in the first trimester and preterm labour in third trimester. However, when considering whether to undergo a surgical procedure in pregnancy, one must weigh the benefit and risk of the surgery with that of the untreated underlying condition. Take for instance a patient with appendicitis who is in her third trimester: the systemic inflammatory and infectious state of untreated appendicitis will likely inflict more harm to the mother and fetus than the laparoscopic surgery itself. Studies have supported this line of reasoning and found that surgery delay is associated with worse outcomes particularly for infectious surgical indications. Remember, a healthy mother is a healthy baby. It is important to note that not all surgeries impose the same risk of miscarriage and preterm labour. Surgeries with greater hemodynamic shifts confer highest risk, such as cardiac surgery, whereas spine and orthopedic surgeries have lower risk.

The American College of Obstetrician and Gynecologists (ACOG) released 2019 guidelines on non-obstetric surgery in pregnancy. It recommends that a pregnant woman should never be denied medically necessary surgery regardless of trimester because this can adversely affect the pregnant woman and her fetus. Elective surgeries on the other hand should be deferred to postpartum if possible. Woman should be monitored for signs of preterm labour in the perioperative period and surgery be done at a center with neonatal and pediatric services in case of preterm delivery. Anesthetic agents have not been shown to be associated with teratogenicity at any gestational age. Routine perioperative thromboprophylaxis should be administered.

Immunization

Vaccination in Pregnancy (SOGC 2018 Guidelines)

Indicated in pregnancy

- Inactivated influenza vaccine. Universally recommended. Given in all trimesters. Decreases risk of influenza in neonates in first six months of life if administered to mother. Egg allergy is not a contraindication to the flu vaccine.
- Tdap (Tetanus, Diphtheria, acellular Pertussis) – given between 21-32 weeks.
- Select women can be vaccinated for Hepatitis A, Hepatitis B, Pneumococcus, and Meningococcus, if have risk factors.

Contraindicated in pregnancy

- **All live or live-attenuated vaccines**.
- Including measles, mumps, rubella, varicella, yellow fever, and live influenza vaccine.
- Nonpregnant patients receiving a live or live-attenuated vaccine should be counselled to delay pregnancy for at least 4 weeks.
- All pregnant women inadvertently received vaccination with live or live-attenuated vaccine should not be counselled to terminate pregnancy for reasons of teratogenic risk.
- If required, these vaccines should be given postpartum.

Postpartum or breastfeeding

- All vaccinations can be administered.
- With the except for yellow fever due to cases of infant meningoencephalitis associated with breastfeeding mothers.

Medication safety

The decision to start a medication should always be based on maternal as well as fetal risk. Many women understandably shy away from using medication in pregnancy. However, a medication that keeps a mother healthy and her disease at bay will lead to a healthier pregnancy overall. When prescribing medications in pregnancy and lactation, always consult the latest evidence to determine medication safety, if unsure. Reprotox and LactMed are useful resources for this purpose. Below are 5 categories of medications frequently encountered by internists and their safety profile in pregnancy and lactation. Safety of antibiotics in pregnancy is discussed separately in the Infectious Disease section of this handbook.

1. **Pain medications (Tylenol, NSAIDS, narcotics).**
    - Tylenol is safe throughout pregnancy and lactation.
    - NSAIDs are generally only used in the second trimester due to risk of miscarriage in first trimester and premature closure of ductus arteriosus after 32 weeks gestation. It can also cause oligohydramnios in any trimester.
    - Opioid analgesics can be used if indicated, but should be done with caution and at the lowest possible dose. If chronic opioid exposure occurs during pregnancy, newborns must be monitored for opioid withdrawal. Concern also exists in lactation if a mother is an "ultrarapid metabolizer", as higher levels of morphine can then be found in breastmilk. There have been cases of fetal death due to opioid overdose through this mechanism. Therefore, mothers taking opioids need to monitor babies for increased sedation, respiratory depression or difficulty feeding.

2. **Antiemetics, H2-blockers, proton pump inhibitors**
    - Diclectin, Dimenhydrinate (Gravol), Metoclopramide (Maxeran), and Prochlorperazine are safe in pregnancy. In women on multiple antiemetics, need to assess for QT prolongation.
    - Gravol is safe in lactation. Metoclopramide is also safe in lactation and can act as a galactagogue. However, Metoclopramide can cause depression so avoid use in women at risk of postpartum depression.
    - Ondansetron has been associated with an increased risk of cleft palate in some studies but not in others. It is generally only used when other antiemetic agents have failed.
    - H2-blockers are safe in pregnancy and lactation. Ranitidine and Cimetidine have the most safety data.
    - Experience with proton pump inhibitors is less extensive but are considered safe in pregnancy. Pantoprazole, Lansoprazole and Omeprazole have the most safety data. Pantoprazole is present in low levels in breastmilk and is not expected to cause adverse effects in breastfed infants.

3. **Disease-modifying agents / medications for auto-immune disease**
    - Hydroxychloroquine (Plaquenil), Sulfasalazine, 5-ASA, and Azathioprine (Imuran) are safe in pregnancy and lactation.

- Methotrexate is contraindicated in pregnancy as it is associated with skeletal anomalies. Also contraindicated in lactation.
- Biologics are generally continued in pregnancy with the advice of a specialist. They can be stopped in the 3rd trimester to avoid infant immunosuppression at birth. They are also considered safe in lactation although data is limited.

4. **Psychiatric medications**
   - Lorazepam and Clonazepam are preferred over long-acting benzodiazepines like Diazepam as they are more likely to accumulate in the fetus.
   - Lorazepam is safe in lactation. Diazepam is excreted in breast milk and because of its long half-life can lead to infant sedation, therefore other agents are preferred.
   - Selective serotonin receptor antagonists (SSRI) are associated with little to no risk of teratogenicity. However, paroxetine may be associated with a small increase in congenital heart defects.
   - Tricyclic antidepressants (TCAs) have a low risk of teratogenicity.

5. **Steroids**
   - Steroids are safe in pregnancy and lactation. Approximately 10% of the total amount of Prednisone will enter fetal circulation, as compared to 30% of Betamethasone (Celestone) and 50% of Dexamethasone. Absolute risk of cleft palate exists in first trimester but overall risk is low (0.2-0.4%) in an old study, but more recent studies have not reproduced these results. Steroids are also associated with gestational hypertension, gestational diabetes, premature ROM, and fetal adrenal suppression.

Landmark trials

1. **CHIPS.** (Control of Hypertension in Pregnancy Study). *NEJM, 2015*
   - International multicenter, large (n~1000) randomized study which showed that hypertensive women with diastolic blood pressure of 85 mm Hg (vs. 100 mm Hg) had similar fetal outcomes (ie, previous hypothesis that lower blood pressure leads to fetal growth restriction was disproved); mothers were protected from severe hypertension if BP was in the "tighter" controlled group.
   - Changed current practice in Canada about treatment targets for hypertension in pregnancy and reflected in the Canadian Hypertension Society 2018 guidelines.

2. **MAGPI.E.** (Magnesium Sulphate for the Prevention of Eclampsia). *Lancet, 2002*
   - International, multicenter, large (n=10,000) randomized study that demonstrated a 58% reduced risk of eclampsia in pre-eclamptic women given magnesium.
   - Established magnesium as the standard of care for eclampsia ***prevention.***

3. **ASPRE.** *NEJM, 2017*
   - Multicenter, large (n=1776), double blinded randomized control trial, comparing Aspirin 150mg to placebo in high risk women for preterm pre-eclampsia prevention. Showed preterm pre-eclampsia rates significantly reduced with Aspirin group, with highest benefit in pre-eclampsia onset before 34 weeks followed by 37 weeks. No difference in pre-eclampsia after 37 weeks.
   - This is a practice changing trial demonstrating the importance of intermediate dose Aspirin as a cornerstone for preterm pre-eclampsia prevention.

4. **YEARS Algorithm**. *NEJM, 2019*
   - Multicenter, large (n=510), prospective study with pregnant women with symptoms of pulmonary embolism assessed by the YEARS algorithm for prediction of PE in pregnancy. Three clinical criteria (clinical signs of DVT, hemoptysis, and PE being the most likely diagnosis) and D-dimer were used. Patients with three negative clinical criteria and D-dimer <1000, or one or more positive clinical criteria with D-dimer <500, had PE ruled out and did not require further investigations. The remaining patients underwent leg ultrasound if having symptoms of DVT or CT pulmonary angiogram. Results showed that at three months follow up, there were no PEs and one patient had a DVT. CT pulmonary angiogram was avoided in 39% of patients. Efficiency of algorithm was highest in the first trimester and lowest in third trimester.
   - This trial is among several recent trials designed to validate clinical algorithms for predicting venous thromboembolism in pregnancy. It has not been reflected in guidelines at this time.

5. **Diagnosis of PE.** *Ann Intern Med, 2018*

- Multicenter prospective trial of 395 pregnant women presenting with clinically suspicious PE using the Geneva score and D-dimer for risk stratification. Results showed no thromboembolism diagnosed at three months follow-up after PE was excluded with the low/intermediate risk Geneva score and D-dimer <500. 11% of women avoid diagnostic imaging using the algorithm. When imaging studies were indicated, venous thromboembolism were mostly diagnosed with CT pulmonary angiogram rather than leg ultrasound.
- This trial is among several recent trials designed to validate clinical algorithms for predicting venous thromboembolism in pregnancy.

6. **ARRIVE.** *NEJM, 2018*
   - Multicenter, large (n=6106), randomized controlled trial, comparing induction of labour at 39 weeks compared to expectant delivery, with primary outcome of composite perinatal death or severe neonatal complications. Results showed no improvement of adverse perinatal outcomes in the induction group compared to expectant management. There was reduced rates of C-section in the induced group.
   - The American College of Obstetricians and Gynecologists (ACOG) released new practice guidelines incorporating the Arrive trial findings. They recommend that it is reasonable to offer elective induction to low risk first time mothers at 39 weeks gestation, but collaborative discussion with shared-decision making should take place with the pregnant woman.

7. **Vitamin D**. *NEJM, 2018*
   - Randomized, double blinded, placebo controlled trial of 1164 pregnancies, studying the effect of Vitamin D supplementation on affecting fetal and infant growth. High dose Vitamin D given in pregnancy and lactation was not associated with improved fetal or infant growth compared to placebo. Secondary outcomes including gestational hypertension, preterm birth, stillbirth, mortality, and congenital anomalies were also similar among both groups.
   - In the era of Vitamin D administration, high dose supplementation does not appear to have any pregnancy related benefits. Standard Vitamin D replacement is recommended in pregnancy.

8. **Duration of MgSO4**. *BJOG, 2018*
   - Multicentered, randomized controlled trial of 1113 women, showed women with severe pre-eclampsia who had received a loading dose of Magnesium Sulfate followed by 8 hours pre-delivery, did not benefit from continuing Magnesium for 24 hours postpartum for eclampsia prevention compared to stopping Magnesium.
   - This trial provides important insight into guiding prescription of Magnesium Sulfate for eclampsia prevention, which currently vastly differs among prescribers in indication and duration.

9. **WOMAN**. *Lancet, 2017*
   - Randomized, double blinded, placebo controlled trial of 20,060 women demonstrating tranexamic acid reduced death due to bleeding in women with postpartum hemorrhage

as compared to placebo. Hysterectomy rates were not different in the two groups. Adverse events including thromboembolic events did not differ significantly in the two groups.
- This trial solidified the importance of tranexamic acid in the treatment of postpartum hemorrhage without increased risk of thrombosis.

10. **CONCEPTT**. *Lancet*, 2017.
    - Randomized controlled trial of 325 women with type 1 diabetes planning pregnancy or less than 14 weeks to capillary glucose monitoring with continuous glucose monitor (CGM) versus without. A small difference in lowering HbA1c was seen with CGM group as well as more time spent in target and less time hyperglycemic. There were no differences in rates of hypoglycemia. There was a significant reduction in fetal hypoglycemia, large for gestational age, and NICU admissions seen in the CGM group. The study also found no apparent benefit of CGM in women planning pregnancy.
    - This trial showed the benefit of CGM in type 1 diabetes use intrapartum to lower neonatal complications, and therefore should be offered to all pregnant women with type 1 diabetes using intensive insulin therapy.

11. **Hypertension in Pregnancy.** *Cochrane Database Syst Rev, 2018*
    - Meta-analysis of 63 RCTs evaluating the effects of blood pressure control in pregnant women with mild to moderate hypertension. Use of antihypertensive drugs halved the risk of developing severe hypertension. No effects were seen in pre-eclampsia, preterm births, small for gestational age baby, or fetal death. Beta-blockers and calcium channel blockers together are more effective than Methyldopa in avoiding severe hypertension.
    - This trial reinforces the idea that treating hypertension in pregnancy prevents severe hypertension but doesn't alter the course of pre-eclampsia. Beta-blockers and calcium channel blockers appear to be more effective than alternatives for preventing severe hypertension.

12. **HYPITAT**. *Lancet, 2009*
    - Multicenter, large (n=800) study of women in the Netherlands, near term, with mild pre-eclampsia or hypertension that showed improved maternal outcomes for women induced as compared to those managed expectantly.
    - Reinforced the indication for delivery at 37 weeks in this specific population.

13. **ECLAMPSIA TRIAL**. *Lancet, 1995*
    - International, multicenter, large (n=1687) randomized study that compared standard anticonvulsant regimens (magnesium vs. Dilantin or magnesium vs. diazepam) in eclampsia. Overwhelmingly in support of magnesium in both groups.
    - First large-scale randomized study to demonstrate strong evidence for routine use of magnesium over other medications for the treatment of eclampsia, changing the course of how we manage this disease.

14. **CHAMPS.** *Lancet, 2005*

- Retrospective database study of over 1 million women that found a two-fold increase in risk of future cardiovascular disease in women with placental syndromes in pregnancy.
- Raised awareness of the importance of long-term lifestyle modification and risk factor reduction in these women after pregnancy is complete.

15. **Pediatric AIDS Clinical Trials Group 076.** *NEJM, 1994*
    - Randomized controlled trials of approximately 500 HIV positive (CD4 count > 200 cells/mm^3) women showing that antepartum, intrapartum and infant zidovudine (for the 1^{st} 6 weeks) led to a 2/3 reduction in transmission.
    - Study was stopped prematurely because data was so compelling, ultimately changing the course of how we treat HIV + women in pregnancy (and reduce transmission).

16. **A retrospective 11-year analysis of obstetric patients with ITP.** *Blood, 2003*
    - Retrospective study of 119 pregnancies that furthered our understanding of ITP in pregnancy at a time when little work had been done to explore outcomes in this population. Identified the magnitude of fetal risk of mortality of 1.5% (from antibodies crossing the placenta, leading to fetal/neonatal thrombocytopenia)
    - Emphasized that for most women, pregnancy with ITP is uncomplicated, and even those with severe thrombocytopenia have good outcomes

17. **TIPPS**. *Lancet, 2014*
    - Multicenter, randomized controlled trial of 300 women with thrombophilia or at risk of placental insufficiency that found no difference in rates of venous thromboembolism, pregnancy loss or placental disease in when randomized to receive prophylactic anticoagulation compared to placebo.
    - Heparin had been used off-label since the 1990's for these indications, thus TIPPS laid to rest a key therapeutic question of whether or not antepartum heparin leads to improved outcomes in this specific population. More research is needed in determining its effect in women with severe recurrent PET, severe SGA infants or abruption.

18. **MATERNAL AND FETAL OUTCOMES OF SUBSEQUENT PREGNANCIES IN WOMEN WITH PERIPARTUM CARDIOMYOPATHY**. *NEJM, 2001*
    - Through a national survey of cardiologists, 44 women were identified who had peripartum cardiomyopathy in a previous pregnancy (PPCM) and conceived again. Little was known at the time about outcomes in the population of women with PPCM in subsequent pregnancies.
    - If women did not completely recover their ejection fraction (≤eject after the index pregnancy, in the next pregnancy there was a ~50% recurrence rate and 20% mortality rate.
    - If their ejection fraction had recovered, there was a 20% recurrence rate and no excess mortality.

19. **A COMPARISON OF GLYBURIDE AND INSULIN IN WOMEN WITH GESTATIONAL DIABETES MELLITUS.** *NEJM, 2000*

- Randomized study of 400 women with GDM which showed equivalent perinatal outcomes for women receiving glyburide or insulin alone in pregnancy.
- Added to the literature on safety of oral agents for gestational diabetes.

20. **MiG**. *NEJM, 2008*
    - Randomized 750 women with GDM to either metformin or insulin and showed there was no significant difference in composite fetal outcome.
    - Reinforced the safety of metformin use in pregnancy in the GDM population. Note that this study did not address the safety of metformin from the start of pregnancy, ie, in Type 2 DM (stayed tuned for the results of MiTY, summer 2020)

21. **MATERNAL THYROID DEFICIENCY DURING PREGNANCY AND SUBSEQUENT NEUROPSYCHOLOGICAL DEVELOPMENT OF THE CHILD**. *NEJM, 1999*
    - Tested serum from ~ 25,000 women for TSH values, then analyzed outcomes in children of 62 women with TSH values above the 98th percentile, compared to controls, 7-9 years after delivery.
    - Showed that maternal untreated hypothyroidism can adversely affect neuropsychological performance in children.

Useful resources

- Clinical practice guidelines
    - SOGC (Society of Obstetricians and Gynecologists of Canada)
    - Canadian Hypertension Society
    - Thrombosis Canada
    - Diabetes Canada
    - Canadian Stroke Best Practices
    - AGOC (American College of Obstetricians and Gynecologists)
    - RCOG (Royal College of Obstetricians and Gynaecologists) – European guidelines
    - American Thyroid Association
    - AAFP (American Academy of Family Physicians)
    - ASH (American Society of Hematology)
    - AHA (American Heart Association)
    - CDC (Center for Disease Control and Prevention)

- Reprotox- review of all medications in pregnancy and lactation. Requires a subscription

- Lactmed (under ToxNet) – free resource on medication use during lactation

- OTIS – Organization of Teratology Information Specialists

- Heart Disease and Pregnancy- provided by the University of Toronto

  (www.heartdiseaseandpregnancy.com)

- UK NICE guidelines on the management of iron deficiency anemia in pregnancy

- ACP Medical Care of the Pregnant Patient. Second edition.

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