

Therapeutic Considerations in Pregnancy

Pharmacokinetic Changes During Pregnancy

- Normal physiologic changes of pregnancy may alter drug effects, **resulting in the need to monitor or adjust therapy.**
- Physiologic changes begin in the first and peak during the second trimester.
- Maternal plasma volume, cardiac output and GFR increase by 30-50%, **lowering the concentration of drugs** excreted by the kidney.

Pharmacokinetic Changes During Pregnancy

- Therefore, pregnant women may have different drug pharmacokinetics than non-pregnant women:
 1. As **fat increases during pregnancy**, the volume of distribution of fat-soluble drugs increases.
 2. **Plasma albumin concentration decreases**, leading to an increase in the volume of distribution of highly protein-bound drugs.

Pharmacokinetic Changes During Pregnancy

- **Unbound drug is also rapidly eliminated** by the liver or the kidney.
- 3. **Hepatic perfusion increases**, which may increase hepatic metabolism of certain drugs.
- 4. **Nausea and vomiting of pregnancy as well as delayed gastric emptying may alter drug absorption.**
- 5. **Pregnancy-induced increases in gastric pH may affect absorption of weak acids and basis.**
- 6. **High levels of estrogen and progesterone may affect hepatic enzyme activity.**

Pregnancy-Influenced Issues

Pregnant women may experience:

- Constipation, gastro-esophageal reflux disease, hemorrhoids, nausea and vomiting, gestational diabetes, gestational hypertension, and venous thromboembolism.
- These conditions **have the potential to cause adverse pregnancy consequences.**

Pregnancy-Influenced Issues

1. GIT:

- A. Constipation is prevalent during pregnancy, and can exacerbate hemorrhoids.
- Management of constipation starts first with moderate physical exercise and increased dietary intake of fibers and fluids.
 - If additional treatment is needed, supplemental fiber and/or stool softener is appropriate.

Pregnancy-Influenced Issues

- **Bulk-forming agents** (psyllium, methylcellulose, and polycarbophil) **are safe for long-term use because they are NOT absorbed.**
- **Osmotic laxative** (polyethylene glycol, lactulose, and sorbitol) and **stimulant laxatives** (senna and bisacodyl) **can be used with caution (they may cause abortion and electrolyte disturbances).**
- **Use of magnesium and sodium salts may cause electrolyte imbalance.**

Pregnancy-Influenced Issues

- **Castor oil and mineral oil should be avoided** because they **stimulate uterine contractions**, and **impair fat-soluble vitamin absorption**, respectively.
- Hemorrhoides should be treated conservatively.

Pregnancy-Influenced Issues

B. Management of gastro-esophageal reflux disease include:

- **Life-style and dietary modification** (small frequent meals, **alcohol and tobacco avoidance**, **food avoidance at bedtime**, elevation of the head of the bed).
- If symptoms are NOT relieved, **antacids** (aluminum, calcium or magnesium preparations) and **sucralfate** are acceptable.

Pregnancy-Influenced Issues

- **Sodium bicarbonate and magnesium trisilicate should be avoided.**
- **If the patient does NOT respond, histamine H₂-receptor blockers (ranitidine) can be used.**
- **Proton pump inhibitors (omeprazole) may NOT be associated with increased risk of major birth defects, but may be associated with other problems (?).**

Pregnancy-Influenced Issues

C. Nausea and vomiting of pregnancy:

- Affect ~90% of pregnant women.
- Begin within 4-6 weeks of gestation, peak between weeks 8-12 and resolve by 16-20 weeks.
- *Hyperemesis gravidarum* (severe vomiting causing weight loss, dehydration, electrolyte imbalance, and ketonuria) occurs in 0.5-2% of women.

Pregnancy-Influenced Issues

- **Dietary modifications** such as eating **frequent small bland meals (soft, low in fiber and cooked)**, and **avoiding fatty and spicy meals** may be helpful.
- Ginger (الزنجبيل) is effective and probably safe.
- (?)(?).
- **Pyridoxine (vitamin B₆)** and/or **antihistamines (doxylamine)** are effective and are first-line agents.

Pregnancy-Influenced Issues

- Metoclopramide and phenothiazines may cause sedation and **extrapyramidal effects including dystonia** (but can be used in some refractory cases).
- Ondansetron (serotonin 5-HT₃ receptor antagonist) is controversial and may cause **oral clefts**.
- Corticosteroids may be effective. Reserved for use after the first trimester, because of risk of **oral clefts**.

Pregnancy-Influenced Issues

2. Gestational diabetes (GDM):

- GDM is diabetes diagnosed during the second and third trimesters.
- It develops in 3-5% of pregnant women.
- **Risks of GDM include: fetal loss, increased risk of congenital malformations, and macrosomia.**
- **Nutritional education** with dietary modifications, exercise and blood glucose monitoring are considered first-line for all women with GDM.

Pregnancy-Influenced Issues

- **85% of patients can achieve control with this first-line therapy.**
- **Human insulin is the drug of choice for GDM because it does NOT cross the placenta.**
- **Glyburide and metformin are alternatives but long-term safety data are limited.**

Pregnancy-Influenced Issues

3. Hypertensive disorders of pregnancy:

- **Complicate ~ 10% of pregnancies, and include:**
 - 1) Preeclampsia-eclampsia.**
 - 2) Chronic hypertension (preexisting hypertension or developing before 20 weeks of gestation).**
 - 3) Chronic hypertension with superimposed preeclampsia.**
 - 4) Gestational hypertension (without proteinuria developing after 20 weeks of gestation).**

Pregnancy-Influenced Issues

- Defined as hypertension $> 140/90$.
- Non-drug management: stress reduction and exercise.
- Use of supplemental calcium 1-2 g per day decreases the risk of hypertension and preeclampsia in patients with initial low calcium intake, **but NOT in those with adequate calcium intake.**

Pregnancy-Influenced Issues

- Initial choice include methyldopa, hydralazine, or labetalol.
- Slow release oral nifedipine may be used (but NOT the fast-acting).
- Magnesium sulfate when preeclampsia is present.

Pregnancy-Influenced Issues

Preeclampsia:

- **Develops after 20 weeks of gestation.**
- **Chronic and gestational hypertension may be complicated with preeclampsia.**
- **It is a multisystem syndrome: renal failure, maternal morbidity/mortality, preterm delivery, and intrauterine growth retardation.**

Pregnancy-Influenced Issues

- **Treatment: in addition to treatment of hypertension, low-dose aspirin 60-81 mg/day beginning late in the first trimester in women at risk of preeclampsia.**
- **The only cure is delivery of the placenta.**

Pregnancy-Influenced Issues

Eclampsia:

- Seizures on top of preeclampsia.
- It is a medical **emergency**.
- **May be prevented by low dose aspirin.**
- **Magnesium sulfate is effective in preventing eclampsia and treating its seizures.**
- **Usual dose 4-6 g IV over 15-20 min, followed by 2g/hr continuous IV infusion for 24 hours.**
- **Diazepam and phenytoin should be avoided.**

Pregnancy-Influenced Issues

4. Venous Thromboembolism (VTE):

- Risk of VTE in pregnant women is 5-10 fold higher than that in non-pregnant women.
- Low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin (UFH) for treatment of acute VTE in pregnancy.
- Treatment should be continued throughout pregnancy and for 6 weeks after delivery (minimum duration of therapy should NOT be less than 3 months).

Pregnancy-Influenced Issues

- **Fondaparinux** (synthetic pentasaccharide) **should be avoided.**
- The injectable direct thrombin inhibitors (**lepirudin, bivalirudin**) **should be avoided** unless the patient has heparin-induced thrombocytopenia.
- The oral agents **dabigatran** (direct thrombin inhibitor), **rivaroxaban** (direct factor Xa inhibitor), **apixapan** (direct factor Xa inhibitor) **are NOT recommended.**

Pregnancy-Influenced Issues

- **Warfarin** should NOT be used because it may produce:
 - Nasal hypoplasia.
 - Stippled epiphysis.
 - Limb hypoplasia.
 - Eye abnormalities.(risk period 6-12 weeks of gestation)
- CNS anomalies are associated with exposure during 2nd and 3rd trimesters.

Pregnancy-Influenced Issues

- In women with high risk of VTE, antipartum LMWH prophylaxis, with 6 weeks postpartum prophylaxis with LMWH or warfarin is recommended.
- **Women with prosthetic heart valves** should receive LMWH (or UFH) twice daily during pregnancy.
- **High risk women with prosthetic heart valves may also receive low-dose aspirin of 75-100 mg/day.**

Pregnancy-Influenced Issues

- LMWH should be adjusted to achieve a peak anti-Xa level (0.7 - 1.2 U/mL) at 4 hour post-subcutaneous dose.
- This value may be associated with subtherapeutic trough level.
- UFH treatment should target a mid-interval aPTT value at least twice the control value.

Acute Care Issues in Pregnancy

1. Urinary Tract Infections (UTIs):

- ***Escherichia coli*** is the primary cause of infection in 75-90 % of cases.
- Other gram-negative rods (***Proteus*** and ***Klebsiella***), as well as, group B ***Streptococcus*** (GBS) account for some infections.
- The presence of GBS in urine indicates heavy colonization of the genitourinary tract, increasing the risk for GBS infection in the newborn.

Acute Care Issues in Pregnancy

- UTIs are asymptomatic (asymptomatic bacteriuria) or symptomatic (cystitis and pyelonephritis).
- Treatment of asymptomatic bacteriuria and cystitis is necessary to prevent pyelonephritis. Duration of treatment 7-14 days.
- The most commonly used antibiotics to treat asymptomatic bacteriuria and cystitis are β -lactam antibiotics [penicillins (amoxicillin) and cephalosporins] and nitrofurantoin.

Acute Care Issues in Pregnancy

- β -lactam antibiotics are NOT teratogenic, but *E. coli* resistance to **ampicillin and amoxicillin** limits their use as single agents.
- **Nitrofurantoin** is not active against *Proteus* species and should not be used after week 37 in patients with G6PD deficiency because of the risk of hemolytic anemia in the newborn.
- **Sulfa-containing drugs (co-trimoxazole)** can contribute to the development of newborn kernicterus, and should be avoided during the last week of gestation.

Acute Care Issues in Pregnancy

- **Trimethoprim** is a folate antagonist that is **contraindicated** during the first trimester because of association with **cardiovascular malformations**.
- **Fluoroquinolones** are **contraindicated** because of association with **impaired cartilage development**.
- **Tetracyclines** are **contraindicated** because of association with **deciduous teeth discoloration**, if given after 5 months of gestation.

Acute Care Issues in Pregnancy

- **Pyelonephritis** is more severe and is associated with premature delivery, low infant birth weight, hypertension, anemia, bacteremia, and transient renal failure.
- **Hospitalization is the standard of care for pregnant women with pyelonephritis.**
- **Therapy include parenteral administration of 2nd and 3rd generation cephalosporins (cefuroxime and ceftriaxone), ampicillin + gentamicin, or ampicillin-sulbactam.**

Acute Care Issues in Pregnancy

- Switching to oral therapy is likely if the woman is afebrile for 48 hours.
- The total duration of therapy for acute pyelonephritis is 10-14 days.
- Nitrofurantoin should be avoided because it does not achieve therapeutic levels outside urine.

Acute Care Issues in Pregnancy

2. Sexually transmitted Infections (STIs):

Can be classified as:

- a. Infections that may be transmitted across the placenta and infect the infant prenatally (syphilis).
- b. Infections that can be transmitted during birth and cause neonatal infections (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or *Herpes simplex virus*).

Acute Care Issues in Pregnancy

- c. Infections that pose a threat for preterm labor (bacterial vaginosis, BV).

Treatment for some sexually transmitted diseases in pregnancy:

1. Bacterial vaginosis:

Recommended: Metronidazole.

Alternative: Clindamycin.

2. Chlamydia:

Recommended: Azithromycin.

Alternative: Erythromycin.

Acute Care Issues in Pregnancy

3. Genital herpes:

Recommended: Acyclovir or valacyclovir.

4. Gonorrhea:

Recommended: Ceftriaxone . Concurrent chlamydial infection should also be treated.

Alternative: Azithromycin.

5. Trichomoniasis:

Recommended: Metronidazole

Tinidazole should be avoided during pregnancy because of lack of information about safety.

Acute Care Issues in Pregnancy

3. Headache:

- a. **Primary headaches : tension and migraine headaches.**
 - b. **Secondary headaches: those caused by eclampsia, stroke, postdural puncture, cerebral angiopathy, and cerebral venous thrombosis.**
- **Migraine headaches are associated with estrogen fluctuations in women of child-bearing age.**

Acute Care Issues in Pregnancy

- 60-70% of pregnant women with a history of migraine headaches **experience improvement especially during second and third trimesters.**
- 20% experience complete cessation of attacks.
- **Improvement is more likely in**
 - a) women who have migraine without aura.
 - b) women who have a history of menstrual migraine.

Acute Care Issues in Pregnancy

- **However, some women experience migraine for the first time during pregnancy.**
- **Migraine developing during pregnancy may indicate an underlying structural or functional disorder:**
 - 1. Cerebral aneurysms**
 - 2. Cerebral arteriovenous malformations**
 - 3. Cerebral venous thrombosis**
 - 4. Idiopathic intracranial hypertension or intracranial hypertension secondary to cerebral venous thrombosis or coincidental brain mass.**

Acute Care Issues in Pregnancy

- Tension headaches are NOT well studied.
- Most women report NO change in frequency or intensity.
- Relaxation, stress management, and biofeedback are all effective non-pharmacological treatments, with minimal risk.
- For tension headaches acetaminophen or ibuprofen can be used.

Acute Care Issues in Pregnancy

- While ibuprofen is considered safe (?), **all NSAIDs are contraindicated** in the third trimester because of the **danger of premature closure of the ductus arteriosus**.
- **Aspirin** should also be **avoided in the third trimester** because in addition, it can cause **maternal and fetal bleeding** as well as **decreased uterine contractility** (prolonged labor).

Acute Care Issues in Pregnancy

- Pregnant women with migraine should NOT take drugs unless the frequency and severity of migraine is life threatening to the mother or fetus.
- For migraine headaches acetaminophen is indicated.
- Opioids may contribute to migraine-associated nausea, and long-term use near term can cause neonatal withdrawal.
- Meperidine suppositories can relieve severe pain.

Acute Care Issues in Pregnancy

- For non-responsive migraine, **sumatriptan can be used** (other triptans lack information about use in pregnancy).
- **Ergotamine is contraindicated** because of **effects on uterine tone**.
- Pregnant women should not use aspirin, nonsteroidal anti-inflammatory drugs, or vasoconstrictors.

Acute Care Issues in Pregnancy

- Promethazine, prochlorperazine, metoclopramide may be used for patients with migraine-associated nausea.
- Propranolol (given at the lowest effective dose) and amitriptyline (10-25mg PO daily) can be used for prophylaxis in patients who experience severe migraine.

Chronic Illnesses in Pregnancy

1. Allergic Rhinitis:

- Treatment strategies for allergic rhinitis in pregnancy are similar to non-pregnant women: avoidance of allergen, immunotherapy, and pharmacotherapy.
- Drugs that can be used: intranasal corticosteroids, intranasal cromolyn, and first-generation antihistamines (chlorpheniramine, diphenhydramine, and hydroxyzine).
- Topical oxymetazoline (nasal spray), α 1-agonist, may be preferable to oral decongestants.

Chronic Illnesses in Pregnancy

2. Bronchial Asthma:

- Health consequences of untreated or poorly treated asthma include: preterm labor, preeclampsia, intrauterine growth retardation, premature birth, low birth weight, and stillbirth.
- Risks of medications use to the fetus are less than risks of untreated asthma.
- Drugs:

Chronic Illnesses in Pregnancy

**Step 1: short-acting β_2 -agonists (SABA),
albuterol + inhalational corticosteroids,
budesonide.**

**Step 2: long-acting β_2 -agonists (LABA),
salmeterol.**

Chronic Illnesses in Pregnancy

3. Diabetes Mellitus:

- Poorly controlled diabetes can cause fetal malformations, fetal loss, and maternal morbidity.
- Women with diabetes should use effective contraception until optimal glycemic control is achieved before attempting pregnancy.
- Human insulin is safe during pregnancy.
- Alternative for type 2 DM include glyburide and metformin.

Chronic Illnesses in Pregnancy

3. Epilepsy:

- Seizure frequency does not change for most pregnant women with epilepsy.
- Seizures may become more frequent because of changes in:
 - a) maternal hormones.
 - b) sleep deprivation.
 - c) medication adherence problems because of fear of teratogenic risk.

Chronic Illnesses in Pregnancy

- d) changes of free serum concentration of antiseizure drugs resulting from:**
 - i. increased maternal volume of distribution.**
 - ii. decreased protein binding from hypoalbuminemia.**
 - iii. increased hepatic drug metabolism.**
 - iv. increased renal drug clearance.**

Chronic Illnesses in Pregnancy

- **The risks of uncontrolled seizures to the infant are greater than those associated with antiepileptic drugs. (especially for tonic-clonic seizures).**
- **Major malformations are 2-3 times more likely to occur in children born to women taking antiseizure drugs than to those who do not.**

Risk of Antiseizure Drugs During Pregnancy

<https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1111/tog.12413>

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4784252/pdf/10.1177_1756285615623934.pdf

When to avoid or postpone pregnancy?

- 1. Uncontrolled epilepsy**
- 2. Drug-resistant epilepsy**
- 3. Polytherapy**
- 4. High dose antiseizure drugs**
- 5. Non-compliance with medication**
- 6. Poor general health**

Antiseizure Drug (ASD)	Risk of Congenital Malformation
No ASD	2-%
Carbamazepine	2-5%
Lamotrigine	2-5%
Levetiracetam	1-2%
Oxcarbazepine	1-3%
Phenobarbital	2%, 5.5%
Phenytoin	1-2% , 2.9-3.7%
Sodium valproate	6-10%
Topiramate	4-7%
Gabapentin	0.7-3%
Clonazepam	3.1%
Monotherapy	3-5%
Polytherapy	6-8%
Polytherapy with valproate	Up to 10%

Chronic Illnesses in Pregnancy

ASDs status:

- a. **Probably safest ASDs:** Carbamazepine, lamotrigine, levetiracetam, phenytoin.
- b. **Lower risk (than VPA):** Gabapentin, oxcarbazepine, zonisamide.
- c. **Significant risk:** VPA, topiramate, phenobarbital.

Chronic Illnesses in Pregnancy

- Use of valproic acids should be avoided during pregnancy.
- Major malformations with valproic acid are **dose-related** and range from 6-8%.
- Include neural tube defects (**spina bifida**), **facial clefts** and **cognitive teratogenicity**.
- **ASD monotherapy is recommended with dose optimized before conception**.

Chronic Illnesses in Pregnancy

- All women taking antiseizure drugs should receive folic acid supplementation (4-5 mg daily) starting before pregnancy and continuing at least through the first trimester, and preferably throughout pregnancy.
- Important !!

Chronic Illnesses in Pregnancy

4. Hypertension:

- **A physiologic decrease in blood pressure occurs during the first part of pregnancy reaching lowest point between 16-18 weeks of gestation.**
- **By the third trimester, blood pressure returns to pre-pregnancy levels.**

Chronic Illnesses in Pregnancy

Chronic hypertension of pregnancy:

Defined as :

- 1) hypertension occurring before 20 weeks of gestation
- 2) the use of antihypertensive medications before pregnancy
- 3) or the persistence of hypertension beyond 12 weeks postpartum.

Classified as:

- a. Mild/non-severe: 140-159/90-109 mmHg
- b. Severe: $\geq 160/\geq 110$ mmHg

Chronic Illnesses in Pregnancy

- Chronic hypertension can cause fetal growth restriction, maternal complications and hospital admissions.
- When treating chronic hypertension in pregnant women **we should be careful NOT to compromise utero-placental blood flow. (BP should be Lowered over a period of hours).**
- If there is NO end organ damage, we may NOT use antihypertensive drugs to treat non-severe hypertension. (<160/<105 mmHg).

Chronic Illnesses in Pregnancy

- When using antihypertensive medication sustain blood pressure at 120-160 / 80-105 mmHg.

Drugs:

- Initial choice include methyldopa, hydralazine, or labetalol.
- Oral slow-release nifedipine may be used, but not fast-acting nifedipine.
- Magnesium sulfate when preeclampsia is present.

Chronic Illnesses in Pregnancy

- ACEis, ARBs, renin inhibitors, and mineralocorticoid receptor antagonists **should be avoided, because of teratogenicity and toxicity to fetus.**
- Atenolol may be associated with **fetal growth restrictions.**
- Thiazides are second line, but they may reduce plasma volume.

Treatment of Chronic Hypertension in Pregnancy

Drug/Class	Comments
Methyldopa	Long-term follow-up data supports safety; considered a preferred agent
Labetalol	Increasingly used over methyldopa because of fewer side effects; considered a first-line agent
ACEi, ARB, direct renin inhibitor	Contraindicated; major teratogenicity reported with exposure (fetal toxicity and death)
β -Blockers	Intrauterine growth retardation reported (mostly with atenolol)
Clonidine, thiazides, CCBs	Limited data

Chronic Illnesses in Pregnancy

5. Mental health conditions:

- Most women with mental health conditions discontinue or refuse treatment because of concern about teratogenicity, or because of paranoid or delusional thinking.
- In general, **monotherapy is preferred over polytherapy, even if higher doses are required.**

Chronic Illnesses in Pregnancy

A. Depression:

- Maternal depression is associated with greater risk for premature birth, low birth weight, miscarriage, and fetal growth restriction, and long-term implications for normal infant development.
- SSRIs (paroxetine) are NOT considered major teratogens, and are relatively safe.
- Risks with SNRIs are less defined.

Chronic Illnesses in Pregnancy

- Use of SSRIs, SNRIs, and TCAs in the later part of pregnancy is associated with:
 - a) Persistent pulmonary hypertension of the newborn.
 - b) “Prenatal Antidepressant Exposure Syndrome” (cardiac, respiratory, neurological, GI, and metabolic complications from drug toxicity or withdrawal of drug therapy).
- Women who stop taking antidepressants are more likely to relapse, which have negative implications on the well being of the fetus.

Chronic Illnesses in Pregnancy

Benzodiazepines:

- The use of **diazepam** during pregnancy is associated with **increased risk of oral clefts**.
- **Benzodiazepines used in the third trimester can cause infant sedation and withdrawal symptoms** (restlessness, hypertonia, hyperreflexia, tremulousness, apnea, diarrhea and vomiting).
- “Floppy-Baby Syndrome” has also been described (low-Apgar scores, hypothermia, poor muscle tone, feeding difficulties, and poor temperature adaptation).

Chronic Illnesses in Pregnancy

Mood Stabilizers:

- Commonly used drugs in non-pregnant patients are **lithium**, **lamotrigine**, **carbamazepine**, and **valproic acid**.
- **Lithium** use for bipolar disorders during pregnancy was associated with **increased risk of cardiac malformations** (especially Ebstein's anomaly, which involves the tricuspid valve).

Chronic Illnesses in Pregnancy

- **Other neonatal adverse effects include floppy baby syndrome, nephrogenic diabetes insipidus, hypoglycemia, cardiac arrhythmias, thyroid dysfunction, polyhydramnios, and premature delivery.**
- **Lithium level, thyroid and renal functions should be monitored during pregnancy.**

Chronic Illnesses in Pregnancy

During lactation:

- **Lithium may cause lethargy, hypotonia, hypothermia, cyanosis, and changes in ECG in breastfed infants.**
- **In breastfeeding, lithium level, thyroid functions and CBC should be monitored.**

Chronic Illnesses in Pregnancy

B. Schizophrenia:

- Maternal schizophrenia is associated with increased risk of perinatal death, low birth weight, small-for-gestational-age infants, cardiovascular malformation, pre-term delivery, stillbirth, and infant death.
- **Both the typical and the atypical antipsychotics were NOT adequately evaluated for use during pregnancy.**

Chronic Illnesses in Pregnancy

- The typical antipsychotics (**chlorpromazine, haloperidol, and perphenazine**) were used during pregnancy with NO reported congenital malformations.
- Atypical antipsychotics (**olanzapine, clozapine, quetiapine, and risperidone**) use during pregnancy **showed a higher rate of low-birth-weight, and cardiovascular defects.**
- **Atypical antipsychotics can cause weight gain, gestational diabetes, and metabolic syndrome with poor obstetric outcomes.**

Chronic Illnesses in Pregnancy

6. Thyroid disorders:

- Untreated **hypothyroidism** increases the risk of preeclampsia, premature birth, miscarriage, growth restriction, and impaired neurological development in the fetus.
- Thyroid **replacement** should be instituted with 0.1 mg/day **levothyroxine**.
- Women taking thyroid replacement before pregnancy **usually have increased requirement** during pregnancy.
- Follow TSH level during pregnancy every 4-6 weeks for dose titration.

Chronic Illnesses in Pregnancy

- **Hyperthyroidism** during pregnancy is associated with fetal death, low birth weight, intrauterine growth restriction, and preeclampsia.
- Therapy include thionamides (**methimazole and propulthiouracil [PTU]**).
- Use PTU in first trimester, followed by switch to methimazole in second & third trimesters to balance the risk of PTU-induced hepatotoxicity, and methimazole embryopathy.

Chronic Illnesses in Pregnancy

- The risks of uncontrolled hyperthyroidism outweigh the risks of thionamides.
- Iodine 131 (I^{131}) is **contraindicated** because of the **risk of damage of fetal thyroid**.

Labor and Delivery

1. Preterm labor:

- Preterm labor occurs between 20-37 weeks of gestation.
- It is a leading cause of infant morbidity and mortality.

Tocolytic (relaxation of uterus) therapy:

- The purposes of tocolytic therapy:
 1. Postpone delivery to allow for maximal effect of antenatal corticosteroid therapy.

Labor and Delivery

2. Allow for transportation of the mother to a facility equipped to deal with high-risk deliveries.
 3. Prolongation of pregnancy when there are underlying, self-limiting conditions that can cause labor (pyelonephritis, abdominal surgery).
- Tocolytics are NOT used beyond 34 weeks of gestation.

Labor and Delivery

- **Tocolytic therapy should NOT be used in cases of** previability, intrauterine fetal demise, a lethal fetal anomaly, intrauterine infection, fetal distress, severe preeclampsia, vaginal bleeding, or maternal hemodynamic instability.
- **Tocolytic agents: β -agonists, magnesium, calcium channel blockers, and prostaglandin inhibitors (NSAIDs).**
- **All prolong pregnancy 2-7 days, but do NOT reduce overall rates of respiratory distress syndrome, neonatal death or preterm delivery.**

Labor and Delivery

β -agonists (terbutaline, ritodrine):

- **Have higher incidence of maternal adverse effects:** hypokalemia, arrhythmias, hyperglycemia, hypotension, and pulmonary edema.
- **Oral dosing or prolonged parenteral (sc) use may be associated with maternal cardiotoxicity and death.**

Labor and Delivery

Intravenous magnesium sulfate:

- Its use is **NOT supported by evidence of effectiveness as tocolytic agent.**
- However, **it has a neuroprotective role** – it decreases the occurrence of cerebral palsy.
- Maternal adverse effects: pulmonary edema.
- Toxic effects: hypotension, muscle paralysis, tetany, cardiac arrest, and respiratory depression.
- Dose adjustment is needed in renal dysfunction.

Labor and Delivery

Nifedipine:

- It is associated with fewer adverse effects than β -agonists and magnesium sulfate.
- One significant adverse reaction is **hypotension with consequent effect on uteroplacental blood flow.**
- Associated with reduced neonatal morbidity.

Labor and Delivery

NSAIDs (Indomethacin):

- Associated with increased rate **of closure of the ductus arteriosus** when used after 32 weeks of gestation, for more than 48 hours.

Progesterone:

- Reduce cervical ripening, reduce uterine wall contractility, and modulate inflammation.
- It prevents spontaneous preterm birth

Labor and Delivery

Antenatal Corticosteroids:

- Used for fetal lung maturation to prevent respiratory distress syndrome, intraventricular hemorrhage and death of infants in premature delivery.
- **Betamethasone** 12 mg/day IM for 2 doses.
- **Dexamethasone** 6 mg IM every 12 hours for 4 doses.

(between 24-34 weeks of gestation)

Labor and Delivery

Group B *Streptococcus* (GBS) infection (*S. agalactiae*):

- **Maternal infection with GBS is associated with invasive disease of the newborn.**
- **Associated with increased risk of pregnancy loss, premature delivery, and transmission of the bacteria to the infant during delivery.**
- **Neonatal infections include bacteremia, pneumonia, meningitis leading to fatality.**
- **Penicillin G 5 million units given IV, followed by 2.5 million units every 4 hours until delivery is the recommended treatment.**

Labor and Delivery

- **Ampicillin** is an alternative at 2g IV followed by 1g every 4 hours until delivery.
- In women with penicillin allergy but NOT at risk of anaphylaxis, **cefazolin** 2g IV, followed by 1g every 8 hours.
- In women with high risk of anaphylaxis, **clindamycin** 900 mg IV every 8 hours, or **erythromycin** 500 mg IV every 6 hours.
- If resistant to clindamycin and erythromycin, **vancomycin** 1g IV every 12 hours until delivery.

Labor and Delivery

Cervical Ripening and Labor Induction:

- Cervical ripening is mediated by hormonal changes, including final mediation by prostaglandin E_2 and $F_{2\alpha}$ which increase collagenase activity in the cervix leading to thinning and dilation.
- **Concerns with induction of labor** are: ineffective labor and hyperstimulation that may adversely affect the fetus.

Labor and Delivery

- **Prostaglandin E₂ analogs (dinoprostone)** are commonly used for cervical ripening **administered intracervically**. The patient should remain supine for 30 min.
- **The insert is removed when labor begins or after 12 hours.**
- The patient should be attached to the **fetal heart monitor for the entire period of insertion and 15 min after its removal.**

Labor and Delivery

- **Prostaglandin E₁ analogs (Misoprostol) can be used and is effective.**
- **More effective when inserted intravaginally.**
- **Adverse effects: hyperstimulation, and meconium-stained amniotic fluid.**
- **Misoprostol is contraindicated in women with previous uterine scar because of its association with uterine rupture.**

Labor and Delivery

- **Oxytocin** is most commonly used for labor induction after cervical ripening.

Labor Analgesia:

1. The first phase of labor starts from onset of labor to complete cervical dilation. **Women perceive visceral pain because of uterine contractions.**
2. The second phase of labor is the period between complete cervical dilation and delivery. **Women perceive visceral pain because of perineal stretching.**

Labor and Delivery

Pharmacologic approach to labor pain management:

1. Parenteral opioids:

- Commonly used to alleviate labor pain.
- In comparison with epidural analgesia, they have lower rates of oxytocin augmentation, result in shorter stages of labor, and require fewer instrumental deliveries and cesarean section for fetal distress.

Labor and Delivery

2. Epidural analgesia:

- **Better pain relief than other analgesic modalities.**
- **Constitutes administration of an opioid or an anesthetic (fentanyl and/or bupivacaine) into the epidural space.**

Labor and Delivery

- **Adverse effects:** hypotension, pruritus, inability to void, prolongation of the first and second stages of labor, higher numbers of instrumental deliveries and cesarean section for fetal distress, nausea and vomiting, and maternal fever.
- Rarely, **puncture of subarachnoid space leading to sever headache.**