Therapy of Certain Disorders During Pregnancy

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Pharmacokinetic Changes During Pregnancy

- Normal physiologic changes that occur during pregnancy may alter medication effects, resulting in the need to monitor or adjust dose or type of therapy.
- Physiologic changes begin in the first trimester and peak during the second.
- 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.**
- **As fat increases during pregnancy, the volume of distribution of fat-soluble drugs increases.**
- **Plasma albumin concentration decreases due to dilution, which increases the volume of distribution of highly protein-bound drugs.**
- **Unbound drug is also rapidly eliminated by the liver or the kidney.**

Pharmacokinetic Changes During Pregnancy

- **Hepatic perfusion increases, which may increase hepatic extraction of drugs.**
- **Nausea and vomiting as well as delayed gastric emptying may alter drug absorption.**
- **Pregnancy-induced increases in gastric acid may affect absorption of weak acids and bases drugs.**
- **High levels of estrogen and progesterone may affect hepatic enzyme activity.**

Pregnancy-Influenced Issues

- **Pregnancy causes or exacerbates conditions that pregnant women experience: constipation, gastro-esophageal reflux, hemorrhoids, nausea and vomiting.**
- **Gestational diabetes, gestational hypertension, and venous thrombo-embolism 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 laxatives (polyethylene glycol, lactulose, and sorbitol) and stimulant laxatives (Senna and bisacodyl) can be used.**
- **Use of magnesium and sodium salts may cause electrolyte imbalance.**

Pregnancy-Influenced Issues

- **Castor oil should be avoided because it stimulates uterine contractions, causes diarrhea, dehydration, and GIT adverse effects (abdominal pain, nausea & vomiting).**
- **Mineral oil impairs fat-soluble vitamin (ADEK) absorption, and may cause severe bleeding in the newborn if used for long time.**
- **Hemorrhoides should be treated conservatively.**

Pregnancy-Influenced Issues

B. **Management of gastro-esophageal reflux disease includes:**

- **Life-style and dietary modification (small frequent meals, avoiding spicy and fatty 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 (sodium overload) and magnesium trisilicate (no data available on safety) should be avoided.**
- **If the patient does not respond, histamine H_2-receptor blockers (ranitidine) can be used.**
- **Proton pump inhibitors (omeprazole) may not be associated with increased risk of major birth defects.**

Pregnancy-Influenced Issues

C. **Nausea and vomiting of pregnancy affect ~90% of pregnant women.**

- **It begins within 4-6 weeks of gestation, peeks between weeks 8-12 and resolves 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 soft meals, and avoiding fatty and spicy meals may be helpful.**
- **Ginger (الزنجبيل) is effective and *probably* safe.**
- **Pyridoxine (vitamin B_6) and/or antihistamines (doxylamine) are effective and are first-line agents (Pyridoxine - doxylamine).**

Pregnancy-Influenced Issues

- **Metoclopramide and phenothiazines may cause sedation and extrapyramidal adverse effects including dystonia.**
- **Ondansetron (serotonin 5-HT_3 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 trimester.**
- **It develops in 3-5% of pregnant women.**
- **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.**
- **Risks of GDM include: fetal loss, increased risk of congenital malformations, and macrosomia.**

Pregnancy-Influenced Issues

3. Hypertensive disorders of pregnancy:

- **Complicate ~ 10% of pregnancies, and Include:**

1) **Gestational hypertension (without proteinuria developing after 20 weeks of gestation).**
2) **Preeclampsia/eclampsia.**
3) **Chronic hypertension (preexisting hypertension or developing before 20 weeks of gestation).**
4) **Chronic hypertension with superimposed preeclampsia.**

Pregnancy-Influenced Issues

- **Defined as blood pressure > 140/90.**
- **Non-drug management: stress reduction, and exercise.**
- **Activity restriction (?): prolonged bed rest may increase the risk of venous thrombo-embolism.**
- **Use of supplemental calcium 1-2 g per day decreases the risk of hypertension and preeclampsia in patients with initial low calcium intake.**

Pregnancy-Influenced Issues

- **Calcium supplements are not effective in patients with adequate calcium intake.**
- **Initial drug choices include methyldopa, hydralazine, or labetelol.**
- **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 Thrombo-embolism (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 < 3 months).**

Pregnancy-Influenced Issues

- **Fondaparinux (synthetic pentasaccharide) could be third line.**
- **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 (chondodysplasia punctata).**
- **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 for VTE, antipartum LMWH prophylaxis, with 6 weeks postpartum prophylaxis with LMWH or warfarin is recommended.
- Women with prosthetic heart valves should receive LMWH twice daily (or UFH every 12 hours) 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 recommendation may be associated with subtherapeutic trough level.
- UFH treatment should target a mid-interval aPTT value at least twice the control value or an anti-Xa level of 0.35-0.7 U/mL.

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) may cause UTI.**
- **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 [amoxacillin 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 containdicated because of association with impaired cartilage development.**
- **Tetracyclines are containdicated 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

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 , treat chlamydial infection concurrently.

   Alternative: Azithromycin.

5. **Trichomoniasis:**

   Recommended: Metronidazole

   Tinidazole should be avoided during pregnancy.

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 (α-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.**

Chronic Illnesses in Pregnancy

Treatment:

1. **Step 1: short-acting β_2-agonists (SABA), albuterol + inhalational corticosteroids, budesonide.**
2. **Step 2: long-acting β_2-agonists (LABA), Salmetrol + inhalational corticosteroids, budesonide.**

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.**

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 antiepileptic 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 embryo are greater than those associated with antiseizure 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.**

Chronic Illnesses in Pregnancy

ASDs status:

a. **Probably safest ASDs: Carbamazepine, lamotrigine, levetiracetam, ~~phenytoin~~ (??).**
b. **Lower risk than valproic acid (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 6-9%.**
- **Include neural tube defects (spina bifida), facial clefts and cognitive teratogenicity.**
- **Antiseizure drug monotherapy is recommended with dose optimized before conception.**

Chronic Illnesses in Pregnancy

- **All women taking antiepileptic 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 !!**

When to avoid or postpone pregnancy?

1. Uncontrolled epilepsy
2. Drug-resistant epilepsy
3. Polytherapy
4. High dose ASDs
5. Non-adherance
6. Poor general health

Chronic Illnesses in Pregnancy

4. 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: ≥160/≥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 you should be careful NOT to compromise utero-placental blood flow. (Lower BP over a period of hours).**
- **If there is no end organ damage, antihypertensive drugs may not be used 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 labetelol.**
- **Magnesium sulfate when preeclampsia is present.**

Chronic Illnesses in Pregnancy

- **ACEis, ARBs, renin inhibitors (aliskiren), 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. They reduce plasma volume.**

Therapy of Hypertension

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

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.**

Chronic Illnesses in Pregnancy

- **Women taking thyroid replacement before pregnancy usually have increased requirement during pregnancy.**
- **Follow TSH level during pregnancy every 4-6 weeks for dose titration.**
- **Hyperthyroidism during pregnancy is associated with fetal death, low birth weight, intrauterine growth restriction, and preeclampsia.**

Chronic Illnesses in Pregnancy

- **Therapy include thionamides (methimazole and propylthiouracil (PTU).**
- **Use PTU in first trimester (it is significantly ionized at physiologic pH), and switch to methimazole in second & third trimesters to balance the risk of PTU-induced hepatotoxicity, and methimazole embryopathy (Choanal and esophageal atresia).**

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 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 <u>not</u> 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_2-agonists (terbutaline, ritodrine):

- **Have higher incidence of maternal adverse effects: hypokalemia, arrhythmias, hyperglycemia, hypotension, and pulmonary edema.**
- **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.**
- **The most common adverse effects include flushing, nausea, headache, generalized muscle weakness, and diplopia.**
- **The patient must be monitored for signs of magnesium toxicity: absent deep tendon reflexes, respiratory depression, pulmonary edema, cardiac arrythmias, and cardiopulmonary arrest.**
- **Dose adjustment is needed in renal dysfunction.**

Labor and Delivery

Nifedipine (slow release):

- **It is associated with fewer adverse effects than β-agonists and magnesium sulfate.**
- **One significant adverse reaction is hypotension with consequent effect on utero-placental 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:

- **Reduces cervical ripening, reduces uterine wall contractility, and modulates 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. (given to the mother)**
- **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:

- **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 E_2 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 E_1 analog, Misoprostol, can be used and is effective.
- More effective when inserted intravaginally.
- Adverse effects: hyperstimulation, and meconium-stained amniotic fluid.
- It is containdicated in women with previous uterine scar because of its association with uterine rupture.
- Oxytocin is most commonly used for labor induction after cervical ripening.

Labor and Delivery

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:**

- **May be used to alleviate labor pain.**
- **Maternal adverse reactions: drowsiness, nausea, vomiting.**

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 than opioid analgesia, nausea and vomiting, and maternal fever.**
- **Rarely, puncture of subarachnoid space leading to sever headache.**

Labor and Delivery

3. **Nitrous oxide (laughing gas):**

- **It is an inhaled anesthetic gas that may help reduce anxiety and make patients less aware of pain, but does not eliminate it.**
- **Many patients ask for another method of analgesia, epidural analgesia.**
- **Nitrous oxide was found to be safe for the newborns.**