Therapy of Certain Disorders During Pregnancy

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. ↑ blood volume → dilutional hypoalbuminemia, high cardiac output & high GFR ↑ body fat
- 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. → volume distribution of water soluble drugs
- 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. → volume distribution of fat soluble drugs
- Plasma albumin concentration decreases due to dilution, which increases the volume of distribution of highly protein-bound drugs. → more in the free fraction
- Unbound drug is also rapidly eliminated by the liver or the kidney.
- 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 basis.
- High levels of estrogen and progesterone may affect hepatic enzyme activity.

Pregnancy-Influenced Issues: Issues/Diseases modified by pregnancy

- 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.

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. vegetables, certain fruits, خلوية البرتقال مثلا + fluid intake
- If additional treatment is needed, supplemental fiber and/or stool softener is appropriate.
- 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. إذا اضطرينا
- Use of magnesium and sodium salts may cause electrolyte imbalance.
- Castor oil ~~should be avoided~~ contraindicated because it stimulates uterine contractions, causes diarrhea, dehydration, and GIT adverse effects (abdominal pain, nausea & vomiting). → may cause abortion
- Mineral oil impairs fat-soluble vitamin (ADEK) absorption, and may cause severe bleeding in the newborn if used for long time. vitamin K def.
- Hemorrhoides should be treated conservatively.

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.

→ source of calcium that is needed during pregnancy, but when you stop it there will be rebound acid secretion (excess over baseline)

→ Antacids properities ألمنيوم

→ surface active agent, forms a layer on the mucosa to protect from acids

Antacids
- Sodium bicarbonate (sodium overload) and magnesium trisilicate (no data available on safety) 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.

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.
- 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 B6) and/or antihistamines (doxylamine) are effective and are first-line agents (Pyridoxine – doxylamine).

should not be used during pregnancy
- Metoclopramide and phenothiazines may cause sedation and extrapyramidal adverse effects including dystonia.
- 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.

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.
- 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.

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.

- 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.
- 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.

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.
- 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.

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.

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.
  but with anti-Xa level ← Not with aPTT ← we monitor in 3 cases, one of them is pregnancy. also, children & obesity; monitored by aPTT; from the diagnosis
- Treatment should be continued throughout pregnancy and for 6 weeks after delivery (minimum duration of therapy should not be < 3 months).
- Fondaparinux (synthetic pentasaccharide) should be avoided. *the active sequence of heparin & LMWH; لأنه الأخ heparin*
- 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. *New drugs, we don't know about their safety during pregnancy*
- Warfarin should not be used because it may produce:
  Teratogenic
  - 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.

  low albumin in the mother circulation & high free fraction of Warfarin → cross placenta to the fetus with increasing albumin in fetal circulation Warfarin bound to it → تتجمع عند الجنين

- In women with high risk for VTE, antipartum LMWH prophylaxis, with 6 weeks postpartum prophylaxis with LMWH or warfarin is recommended. *injection; oral → non contraindicated بعد الولادة, لأنه البروتين بالحليب قليل*
- Women with prosthetic heart valves should receive LMWH twice daily (or UFH every 12 hours) during pregnancy. *or unfractionated heparin*
- High risk women with prosthetic heart valves may also receive low-dose aspirin of 75-100 mg/day.
- LMWH should be adjusted to achieve a peak anti-Xa level (0.7 - 1.2 U/mL) at 4 hour postsubcutaneous 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. *but this is more expensive*

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.
- 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. *2nd & 3rd generation*
- β-lactam antibiotics are not teratogenic, but E. coli resistance to ampicillin and amoxicillin limits their use as single agents. *مشاكلهم*
- 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. *Also may cause hemolytic anemia in the newborn; highly protein bound, can displace bilirubin from albumin → unbound bilirubin can cross blood-brain barrier & get precipitated in the brain.*
- Trimethoprim is a folate antagonist that is contraindicated during the first trimester because of association with cardiovascular malformations. *موجود بال co-trimoxazole*
- 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.

- 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 or 3rd generation cephalosporins (cefuroxime and ceftriaxone), ampicillin + gentamicin, or ampicillin-sulbactam.
- 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.

Treatment for some sexually transmitted diseases in pregnancy:

1. Bacterial vaginosis:
Recommended: Metronidazole.
Alternative: Clindamycin.

2. Chlamydia:
Recommended: Azithromycin.
Alternative: Erythromycin.

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.
→ we don't know about its safety

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.

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.

Treatment: like non-pregnant lady
1. Step 1: short-acting β2-agonists (SABA), albuterol + inhalational corticosteroids, budesonide.
2. Step 2: long-acting β2-agonists (LABA), Salmetrol + inhalational corticosteroids, budesonide.

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.

4. 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.
    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.

- The risks of uncontrolled seizures to the infant 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. → Most antiseizure drugs are teratogens, which one to use?

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.

- Use of valproic acids should be avoided during pregnancy.
- Major malformations with valproic acid are dose-related and range from 6-9%. ≈ 3-4 x the baseline
- Include neural tube defects (spina bifida), facial clefts and cognitive teratogenicity.
- Antiseizure drug monotherapy is recommended with dose optimized before conception.
- 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, may be due to lack of adherance, inadequate dose, inadequate drug ...
2. Drug-resistant epilepsy control جربنا عدة أدوية وما في نسبة عالية من الحوامل ≈ ٢٥٪
3. Polytherapy
4. High dose ASDs Dose Dependent ← congenital malformation لازم نقلل
5. Non-adherance
6. Poor general health

5. 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 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).
- When using antihypertensive medication sustain blood pressure at 120-160 / 80-105 mmHg.

→ Drugs:

- Initial choice include methyldopa, hydralazine, or labetelol. (Mixed β & α blocker)
- Magnesium sulfate when preeclampsia is present.
- ACEis, ARBs, renin inhibitors (aliskiren), and mineralocorticoid receptor antagonists should be avoided, because of teratogenicity and toxicity to fetus.
- Atenolol (β_1- blocker) may be associated with fetal growth restrictions.
- Thiazides are second line. They reduce plasma volume.

وهذا الجدول ← 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

6. Thyroid disorders:

Untreated thyroid diseases (hypo or hyper) are detrimental to the fetus

- 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. (→ larger than the dose given to non-pregnant ladies or male patients; because of increased requirement during pregnancy)
- Women taking thyroid replacement before pregnancy usually have increased requirement during pregnancy.
- Follow TSH level (for monitoring:) 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.
- Therapy include thionamides (methimazole and propylthiouracil (PTU).
- Use PTU in first trimester (it is significantly ionized at physiologic pH, does not cross the placenta significantly), and switch to methimazole in second & third trimesters to balance the risk of PTU-induced hepatotoxicity, and methimazole embryopathy (Choanal and esophageal atresia). (↳ if given in the first trimester)
- The risks of uncontrolled hyperthyroidism outweigh the risks of thionamides.
- Iodine 131 (I131) 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.

and associated with Respiratory Distress Syndrome, due to impaired maturation of the surfactant in the lung

→ So, we need to pevent preterm labor, and that is done by drugs that relaxes the uterus = Tocolytic drugs

Tocolytic therapy:

- The purposes of tocolytic therapy:

1. Postpone delivery to allow for maximal effect of antenatal corticosteroid therapy.
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).

Contra-indications
- Tocolytics are not used beyond 34 weeks of gestation.
- 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_2-agonists, magnesium, calcium channel blockers, and prostaglandin inhibitors (NSAIDs).
- All prolong pregnancy 2-7 days (only), but do not reduce overall rates of respiratory distress syndrome, neonatal death or preterm delivery.

β2-agonists (terbutaline, ritodrine):

- Have higher incidence of maternal adverse effects: hypokalemia (ناتج عن دخوله للخلايا), arrhythmias, hyperglycemia (stimulate gluconeogenesis & glycogenolysis), hypotension (vasodilation), and pulmonary edema.
  - ✓ vasodilation : بسبب...
  - ✓ may be stimulation of β_1-receptors
- May be associated with maternal cardiotoxicity and death.

Remember:
Selectivety is relative & not absolute
→ certainly at high doses it is not selective any more

Intravenous magnesium sulfate:

- Its use is not supported by evidence of effectiveness as tocolytic agent.
- However, it has a neuroprotective role & it is beneficial in preeclampsia – it decreases the occurrence of cerebral palsy.
- The most common adverse effects include flushing (vasodilation), nausea, headache, generalized muscle weakness (antagonist for calcium), and diplopia.
- The patient must be monitored (due to large dose (in grams) & IV) for signs of magnesium toxicity: absent deep tendon reflexes, respiratory depression, pulmonary edema, cardiac arrhythmias, and cardiopulmonary arrest.
- Dose adjustment is needed in renal dysfunction. → because magnisium is eliminated by the kidney

Also, Tetany may result as a consequence of hypocalcemia

Nifedipine (slow release): → Calcium Channel Blocker

↳ Immediate release should not be used for hypertension or relaxation of the uterus → extensive vasodilation / hypotension / Steal Syndrome

- 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.

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: → can be used to dely labor

- Reduces cervical ripening, reduces uterine wall contractility, and modulates inflammation.
- It prevents spontaneous preterm birth

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. 2 days

(between 24-34 weeks of gestation)

Group B Streptococcus (GBS) infection: (if it happened close to labor & delivery)

- 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.
- **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 of clindamycin and erythromycin, **vancomycin** 1g IV every 12 hours until delivery.

Cervical Ripening and Labor Induction:

- Cervical ripening is mediated by hormonal changes, including final mediation by prostaglandin E2 and F2α 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.
- **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.
- **Prostaglandin E1 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 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.

→ Pharmacologic approach to labor pain management:

1. Parenteral opioids:

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

2. Epidural analgesia: (local يعتبر)

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

- 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.

3. Nitrous oxide (laughing gas):

→ affect the awareness of pain, rather than reducing the pain.

- 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. → Not very effective
- Nitrous oxide was found to be safe for the newborns.