Pregnancy-Induced Conditions and Pharmacologic Interventions in Primary Care

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Disclosures

LT Vaughn and LCDR Davis have no conflicts of interest to disclose
Learning Objectives

Upon conclusion of this presentation, participants should be able to:

• Explain pathophysiologic changes of pregnancy and how they affect drug pharmacokinetics

• Describe rationale behind removal of ‘pregnancy categories’ and understand the new FDA safety classification system for drugs during pregnancy

• Discuss appropriate outpatient pharmacologic interventions for commonly encountered primary care pregnancy-associated conditions, including: constipation, heartburn/reflux, nausea, rhinorrhea, pregnancy-induced hypertension (PIH) and Gestational Diabetes (GDM)
Physiologic Changes in Pregnancy

<table>
<thead>
<tr>
<th>INCREASED:</th>
<th>DECREASED:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output</td>
<td>Plasma protein (albumin)</td>
</tr>
<tr>
<td>Plasma volume</td>
<td>Gastric motility</td>
</tr>
<tr>
<td>Hepatic and renal blood flow</td>
<td>Activity of other hepatic enzymes</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>Lung capacity</td>
</tr>
<tr>
<td>Bowel transit time</td>
<td>Presence of a new organ – the placenta</td>
</tr>
<tr>
<td>Gastric pH</td>
<td>Increased/decreased renal tubule transport</td>
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<tr>
<td>Activity of some hepatic enzymes</td>
<td></td>
</tr>
<tr>
<td>Body volume</td>
<td></td>
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<tr>
<td>Presence of a new organ – the placenta</td>
<td></td>
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<tr>
<td>Vasodilation</td>
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<td>Edema in upper respiratory mucosa</td>
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<tr>
<td>Estrogen and progestin levels</td>
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<tr>
<td>Water retention</td>
<td></td>
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<tr>
<td>Coagulation</td>
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</tbody>
</table>
Pharmacokinetics in Pregnancy

**Absorption:** Bioavailability, or the fraction of the dose that enters the circulation

**Distribution:** Transfer of drug from circulation to the body ($V_d =$ volume of distribution)

**Metabolism:** Chemical modification of the drug by the body

**Elimination:** Removal of drug from the body

**Clearance:** Volume of plasma from which drug is removed per unit time, impacted by all parameters above

Feghali M, Venkataramanan R, Caritis S.
Mrs. K – Pregnancy Category Case

- Mrs K presents to the pharmacy to pick up a prescription for ondansetron for pregnancy-related nausea. You look up the drug and see that it is Pregnancy Category B.
- You dispense the drug to Mrs. K. She returns in 1 week with a new prescription for promethazine, which you look up and see is Category C. Mrs. K tells you that the ondansetron gave her a headache so she wanted to try something different and her doctor changed the prescription to promethazine.

- What does pregnancy category B mean? Is it safer than Category C? If so, to what degree?
# Old Pregnancy Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy</td>
</tr>
<tr>
<td>B</td>
<td>Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well controlled studies in pregnant women, or animal reproduction studies have shown adverse effects, but well controlled studies in pregnant women have shown no adverse effects to the fetus</td>
</tr>
<tr>
<td>C</td>
<td>Animal reproduction studies have shown an adverse effect on the fetus, or there are no animal reproduction studies and no well-controlled studies in humans</td>
</tr>
<tr>
<td>D</td>
<td>Positive evidence of fetal risk, but benefits may outweigh risks</td>
</tr>
<tr>
<td>X</td>
<td>Positive evidence of fetal risk, and risks clearly outweigh any possible benefit</td>
</tr>
</tbody>
</table>
Pregnancy and Lactation Labeling Rule (PLLR)

• Removes letter categories
• Includes narrative "risk summary" with data
• Added new section: contraception and fertility
• Pros: more relevant clinical information
• Cons: narrative summary format more complex, does not include OTC
8.1 Pregnancy Risk Summary

Based on its mechanism of action, trabectedin can cause fetal harm when administered during pregnancy [see Clinical Pharmacology (12.1)]. There are no available data with the use of YONDELIS during pregnancy. Animal reproductive and developmental studies at relevant doses have not been conducted with trabectedin; however, placental transfer of trabectedin was demonstrated in pregnant rats. Advise pregnant woman of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population are unknown; however, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.
8.3 Females and Males of Reproductive Potential

Contraception

Females
Advise female patients of reproductive potential to use effective contraception during and for 2 months after the last dose of YONDELIS [see Use in Specific Populations (8.1)].

Males
YONDELIS may damage spermatozoa, resulting in possible genetic and fetal abnormalities. Advise males with a female sexual partner of reproductive potential to use effective contraception during and for 5 months after the last dose of YONDELIS [see Nonclinical Toxicology (13.1)].

Infertility
YONDELIS may result in decreased fertility in males and females [see Nonclinical Toxicology (13.1)].
Common Pregnancy Complaints

• Increased progesterone can cause nausea, vomiting, constipation

• Increased upper respiratory edema and reactivity can lead to rhinitis

• Stretching of the skin can lead to pruritus

• Frequent need to urinate and pressure on bladder and spine can lead to insomnia

• Increased vasodilation can lead to dizziness
"Sarah" is 16 weeks pregnant and is picking up her prenatal vitamins and iron in the pharmacy today. She has started to experience heartburn and asks what she can do to treat this. She also complains of nausea and constipation, though the nausea has been improving lately.

- **What can you recommend to treat her constipation? Reflux? Nausea?**
- **What may be contributing to her symptoms?**
- **What non-pharmacologic options are there?**
Gastrointestinal: **Constipation, Reflux, and Nausea, Oh My!**

- Up to 39% of pregnant women experience constipation

- Causes: increased progesterone--> reduced gastrointestinal motility; uterus places direct pressure on bowel

- Oral iron can exacerbate constipation

- Constipation contributes to hemorrhoids and reduce quality of life

- Non-pharmacologic: Increased water and dietary fiber intake (25g/day), don't hold stools, increase physical activity

- Preferred agents: bulk-forming laxatives, stool softeners
- Optional agents: stimulants (MgOH, bisacodyl, lactulose)
# Gastrointestinal: Constipation, Reflux, and Nausea, Oh My!

<table>
<thead>
<tr>
<th>Category</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk Forming Agents</td>
<td>Methylcellulose, Psyllium</td>
</tr>
<tr>
<td>Osmotic Agents</td>
<td>Lactulose, Polyethylene Glycol</td>
</tr>
<tr>
<td>Stimulating Agents</td>
<td>Sennosides, Bisacodyl</td>
</tr>
<tr>
<td>Prokinetic Agents</td>
<td>Lubiprostone – no human studies, increased fetal risk in animal studies</td>
</tr>
<tr>
<td></td>
<td>Linaclotide – Adverse events in animal studies</td>
</tr>
<tr>
<td></td>
<td>Avoid or use with caution!</td>
</tr>
<tr>
<td>AVOID</td>
<td>Emollients/lubricants: Mineral oil, castor oil, Saline hyperosmotic</td>
</tr>
</tbody>
</table>
Gastrointestinal: Constipation, Reflux, and Nausea, Oh My!

- 50-80% of pregnant women experience GERD
- Lower esophageal sphincter (LES) relaxation
- Nonpharmacologic: elevate head of bed, eat small more frequent meals, quit smoking, avoid spicy foods, avoid lying down immediately after eating, chew gum
- Options: Calcium Carbonate, ALOH, MgOH, Sucralfate, H2 receptor antagonists, Proton Pump Inhibitors
- Use acid-lowering agents with caution in those with existing iron deficiency
**Gastrointestinal: Constipation, Reflux, and Nausea, Oh My!**

| First Line: Antacids       | • Calcium Carbonate, MgOH, and AlOH are considered safe  
|                           | • AVOID – Magnesium trisilicate (Gaviscon)  
|                           | • AVOID – Sodium bicarbonate |
| Second Line: Non-absorbable drugs and H2-blockers | • Sucralfate, 1 gram PO TID  
|                                                        | • H2-receptor antagonists  
|                                                        |   • Cimetidine  
|                                                        |   • Famotidine  
|                                                        |   • Ranitidine |
| Third Line: PPIs and Dopamine antagonists | • Proton pump inhibitors  
|                                                        |   • Lansoprazole  
|                                                        |   • Omeprazole |
Gastrointestinal: Constipation, Reflux, and Nausea, Oh My!

• Nausea is the most reported discomfort in pregnancy, with incidence up to 85%
  – Severe form: hyperemesis gravidum, rare (< 3%)
• Most common in early pregnancy
• First intervention: dietary changes
  – Smaller more frequent meals
  – Increase protein
  – Drink fluids before and after meals
  – Avoid nausea triggers
  – Switch PNV to folic acid supplement only, discontinue oral iron
**Gastrointestinal: Constipation, Reflux, and **Nausea**, Oh My!**

| First Line                  | Convert PNV to folic acid only supplement  
|                            | Ginger: 250 mg QID  
|                            | Accupressure or "SeaBand"  
|                            | **aromatherapy, psychotherapy, acupuncture**  
| Second Line                | Pyridoxine 10-25 mg PO TID-QID  
|                            | Pyridoxine as above, plus Doxylamine 10-12.5 mg  
|                            | Can titrate both Pyridoxine and Doxylamine up to 20 mg BID  
| Third Line                 | Dimenhydrinate 25-50 mg PO Q4-6 hours  
|                            | Diphenhydramine 25-50 mg PO Q4-6 hours  
|                            | Prochlorperazine 25mg RECTAL Q12 hours  
|                            | Promethazine 12.5-50 mg Q4-6 hours, PO or RECTAL  
| Fourth Line                | Metoclopramide 5-10 mg q6-8 hours PO, IM, or IV  
|                            | Ondansetron 4mg PO Q8 hours, or 8mg IV Q12 hours  
|                            | Promethazine 12.5-25 mg Q4-6 hours, PO, RECTAL, or IM  
|                            | Trimethobenzamide 200 mg IM Q6-8 hours  
|                            | Chlorpromazine 25-50 mg IM or IV, or 10-25 mg PO, Q 4-6 hours  
|                            | Methylprednisolone 16mg Q8 hours, PO or IV x 3 days, taper over 3 weeks  
|                            | IV fluid replacement (NS or dextrose saline)  
|                            | **Gabapentin, transdermal clonidine, diazepam**  

**IV fluid replacement (NS or dextrose saline)**

**Second Line**

**aromatherapy, psychotherapy, acupuncture**

**Fourth Line**

**Gabapentin, transdermal clonidine, diazepam**
Rhinitis, Dyspnea, and Pruritus Case

Sarah returns to your pharmacy at 32 weeks pregnant. Her nausea has resolved, constipation is controlled with increased physical activity and water intake, and she is no longer taking medication other than her PNV and occasional Miralax. Today she complains of persistent stuffy nose, slight difficulty breathing, and itchy skin that is "driving me crazy!"

- **What OTC agents are appropriate for rhinitis?**
- **What can she do for pruritus?**
- **When would this require immediate referral?**
Rhinitis and Dyspnea

- Rhinitis and nasal congestion are reported by up to 30% of pregnant women
  - Increased vascular blood flow, increased estrogen and progesterone
  - Sinusitis: 6 times more common in pregnancy
  - Saline rinse is first-line
  - If allergic rhinitis, can use intranasal cromolyn, oral antihistamines
  - Can consider intranasal steroids
  - Use oral decongestants with caution

- Dyspnea -- "shortness of breath" is reported by up to 79% of pregnant women, and is more common during later stages
  - Progesterone-induce hyperventilation?
  - Positioning changes can be helpful
  - Refer for worsening symptoms if patient has asthma
  - Usual asthma medications should be continued in pregnancy
  - Oral steroids should ONLY be used in serious cases (e.g. severe asthma)
Dyspnea in Pregnancy

Immediate Referral:

• Sudden onset of shortness of breath, with or without pain
• Diagnosis of asthma, acute worsening control
• Mental status changes, syncope
Pruritus and Rash in Pregnancy

- Pruritus is reported by up to 46% of pregnant women and is more common as pregnancy progresses
- Caused by hormonal and physical changes
- Non-pharmacologic: avoid over-drying the skin with hot showers or baths, use moisturizer and soaps without perfumes, avoid itchy or tight clothing
- Antihistamines or H2 antagonists may help
- Topical and oral corticosteroids
- Refer for more serious symptoms dermatoses in pregnancy:
  - **Pruritic urticarial papules and plaques of pregnancy (PUPPPs)**
    - MOST COMMON
    - No identified risk to fetus
    - Papules and plaques often starts in striae, occurs in third trimester
    - Face is usually not affected
  - **Intrahepatic Cholestasis of pregnancy**
    - Risk of premature delivery, meconium stained amniotic fluid, intrauterine fetal demise
    - Distribution nonspecific, no primary rash but tears in skin from scratching, affects soles of feet and hands, laboratory markers
# Pruritus in Pregnancy

| First Line | • Non-pharmacologic: Limit/change topical soaps, take cooler baths or showers, avoid irritating or tight clothing  
|           | • Oatmeal baths, hydrophilic topicals (e.g. Eucerin) |
| Second Line | **Oral Antihistamines:**  
|             | • Chlorpheniramine 4 mg PO Q4-6h (First generation)  
|             | • Cetirizine 5-10 mg PO once daily  
|             | • Loratadine 10 mg PO once daily  
|             | **Topical corticosteroids (Med to High potency):** Apply topically 1-2X daily until improvement  
|             | **Medium potency:**  
|             | • Fluocinolone acetonide ointment 0.025%  
|             | • Hydrocortisone valerate ointment 0.2 %  
|             | • Triamcinolone acetonide cream or ointment 0.1%, spray 0.2 mg/2 sec spray  
|             | **High potency:**  
|             | • Triamcinolone acetonide ointment or cream 0.5%  
|             | • Fluocinonide cream, ointment or gel 0.05%  
|             | • Betamethasone valerate ointment 0.1% |
| Third Line | **Systemic corticosteroids** – for severe cases  
|           | • Prednisone or prednisolone 0.5 mg/kg PO daily x 1 week, taper over 1-2 weeks |
| Disease-specific | • Ursodiol (Ursodeoxycholic acid) 300 mg PO 2-3 times/day – for more severe cases of intrahepatic cholestasis of pregnancy  
|           | • Systemic corticosteroids – for pemphigoid gestationis, impetigo herpetiformis, extreme PUPPPs  
|           | • Topical benzoyl peroxide, UV light therapy – for pruritic folliculitis of pregnancy |
• **Striae gravidarum (Stretch marks)**
  – Can be pruritic as well
  – Cause: physical and hormonal factors
  – Usually occur in:
    • The second and third trimester and have a familial and racial predisposition
    • Occur in up to 90% of women (severe in 10% of cases)
    • Younger women, women with larger babies, and higher BMI
  – Treatment is nonspecific with limited evidence
    • Creams and emollients
    • Tretinoin and laser treatments (post pregnancy)
"Megan" is seen in the primary care clinic for routine prenatal visit at 16 weeks gestation. Her urine culture shows E. coli, \( \geq 10^5 \) cfu/mL. She has no pain with urination, and no abdominal, flank or back pain.

She does complain of itching in the vulvovaginal area and recent white discharge which she believes to be a yeast infection. Exam revealed erythematous and edematous vulva. Vaginal pH is normal, and candida is present on wet mount with KOH test.

Diagnosis is asymptomatic bacteriuria and vaginal candidiasis

• Should the bacteriuria be treated with antibiotics or not?
• How should the yeast infection be treated?
Bacteriuria, UTI, and Vaginitis in Pregnancy

- UTI and bacteriuria in pregnancy are common, and are more likely to progress to pyelonephritis than in non-pregnant patients
  - Without treatment, 30%-40% of asymptomatic bacteriuria in pregnancy will develop into UTI
  - Treatment of asymptomatic bacteriuria lowers risk of pyelonephritis by 25%-30%
  - Untreated bacteriuria has been associated with preterm birth and perinatal mortality

- Screen asymptomatic women for bacteriuria early in pregnancy, treat if positive
### Recommended Antibiotic Therapy for Bacteriuria in Pregnancy

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Amoxicillin (500 mg PO Q12 hours for 7 days)</th>
<th>Amoxicillin-clavulanate (500 mg PO Q12 hours for 7 days)</th>
<th>Cephalexin (500 mg PO Q12 hours for 7 days)</th>
<th>Fosfomycin (3 g PO as a single dose)</th>
<th>Nitrofurantoin** (100 mg PO Q12 hours for 7 days)</th>
<th>Sulfamethoxazole-TMP** (1 DS tablet PO Q12 hours for 7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Trimester</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second Trimester</strong></td>
<td>Nitrofurantoin (100 mg PO Q12 hours for 5 days)</td>
<td>Amoxicillin (500 mg PO Q12 hours for 7 days)</td>
<td>Amoxicillin-clavulanate (500 mg PO Q12 hours for 7 days)</td>
<td>Cephalexin (500 mg PO Q12 hours for 7 days)</td>
<td>Fosfomycin (3 g PO as a single dose)</td>
<td>Sulfamethoxazole-TMP (1 DS tablet PO Q12 hours for 7 days)</td>
</tr>
<tr>
<td><strong>Third Trimester</strong></td>
<td>Amoxicillin (500 mg PO Q12 hours for 7 days)</td>
<td>Amoxicillin-clavulanate (500 mg PO Q12 hours for 7 days)</td>
<td>Cephalexin (500 mg PO Q12 hours for 7 days)</td>
<td>Fosfomycin (3 g PO as a single dose)</td>
<td>Nitrofurantoin (100 mg PO Q12 hours for 7 days) –may use early in third trimester, but CONTRAINDICATED AT TERM</td>
<td>Avoid SMX/TMP close to term, CONTRAINDICATED at ≥32weeks</td>
</tr>
</tbody>
</table>

**Note:**
- **$:** Indicates a more effective option.
- **TERM:** Indicates a treatment that is generally avoided closer to term, specifically at ≥32 weeks.
Bacteriuria, UTI, and Vaginitis in Pregnancy

- **Candida Vulvovaginitis**
  - More common in pregnancy, up to 50% of pregnancies affected by vaginal candidiasis
  - Topical agents first (clotrimazole, miconazole daily for 7-14 days)
  - If topical agents fail, oral fluconazole 150mg daily 7-14 days

- **Bacterial Vaginosis**
  - Up to 30% of pregnancies affected
  - ACOG and CDC do not recommend routine screening
  - If symptomatic, or incidentally found, must treat
  - Metronidazole, Clindamycin (oral vs. Topical?)

- **STDs should all be treated**
  - Chlamydia (Azithromycin, Amoxicillin, Erythromycin)
  - Gonorrhea
  - Syphilis
  - Hepatitis B
  - HIV
  - *Trichomonas*, HSV-2
Gestational Hypertension and Preeclampsia

"Amy" is a 38 year old seen in the primary care clinic today for routine prenatal visit at 28 weeks pregnant with her first baby. She has no complaints today. Her blood pressure is elevated today at 160/90. Value is repeated and confirmed on other arm, 4 hours later after resting. She denies headaches, vision changes, shortness of breath, or upper abdominal pain. Her urinalysis, CBC, and CMP are all within normal limits. Her past medical history has no chronic conditions and she is otherwise healthy. She has no previous history of elevated blood pressure.

• What pregnancy-induced condition may she have? How should it be treated?
Gestational Hypertension and Preeclampsia

• Preeclampsia
  – *New onset* HTN with proteinuria OR end organ dysfunction
  – After 20 weeks gestation
  – May progress to eclampsia or HELLP syndrome

• Gestational hypertension
  – Same as preeclampsia above, but without proteinuria or end organ dysfunction
  – "pre-pre-eclampsia, "watch closely for progression to preeclampsia

• Only cure is delivery, supportive treatment until then
  – Expectant management for mild symptoms
  – Induction or cesarean delivery for severe symptoms
# Gestational Hypertension and Preeclampsia

**First Line**
- Labetalol 200-2400mg daily PO divided BID or TID
- Nifedipine ER 30-120mg daily PO
- Methyldopa 0.5-3g daily PO divided BID or TID

**Second Line**
- Hydralazine – typically only used IV under observation
- Thiazide diuretics – typically not for new-starts

**Specific patients**
- Systemic corticosteroids 48 hours before delivery for viable fetus
- Magnesium Sulfate IV, 2g/hour infusion
  - During and after labor

**No evidence to support, do not recommend**
- Salt restriction
- Bed rest
- Antioxidants: Vitamin E or Vitamin C

**AVOID**
- ACE inhibitors
- ARBs
- Spironolactone, Eplerenone
"Diane" is referred to you for assistance with GDM management. She is 28 weeks pregnant and has new onset GDM diagnosed today with the 75-OGTT. The provider has asked you to instruct on use of the glucose meter, and review blood sugar monitoring and goals with the patient. She is also starting Diane on two new medications today: metformin ER 1000 mg BID, and aspirin 81 mg daily.

1. **How often do you instruct Diane to check her blood sugar and what are her goals?**

2. **How would you counsel Diane on her new medications today? Do you need to intervene with the prescriber?**

3. **What agents would you recommend in future if further pharmacologic management of blood sugar is needed?**
Gestational Diabetes Mellitus (GDM)

• First diagnosis of DM in 2nd or 3rd trimester that is not clearly pre-existing Type 1 or 2

• 75g-Oral Glucose Tolerance Test (OGTT)
  – Fasting ≥ 92 mg/dL
  – 1 hour ≥ 180 mg/dL
  – 2 hour ≥ 153 mg/dL

• Goals:
  – A1c < 6.5%
  – Fasting BG < 95 mg/dL
  – 1 hour post-prandial BG < 140 mg/dL
  – 2 hour post prandial BG < 120 mg/dL
Gestational Diabetes Mellitus (GDM)

- Self monitoring of blood glucose (SMBG)
  - At least QID to start
  - Fasting, post prandial
- Teach patients good technique
- May reduce frequency if BG is controlled
- May increase frequency with initiation of sulfonylurea or insulin therapy
- Education on treatment of hypoglycemia if utilizing glucose-lowering agents
### Gestational Diabetes Mellitus (GDM)

| First Line | • Nutritional counseling by dietician  
|           | • Insulin: Regular, Apart, Lispro, NPH, glargine, detemir  
|           | Elevated Fasting values only? Consider bedtime NPH  
|           | Elevated post-prandial only? Consider post-prandial rapid acting or regular  
| Second Line | • Metformin  
|           | • Glyburide  
| AVOID | • Bedtime sulfonylurea dosing  
|       | • ASA for prevention of preeclampsia unless patient has PREEXISTING DM 1 or 2  
|       | • Any other antihyperglycemic agent other than those listed above  

Summary

• Pregnancy causes a variety of physiologic changes
• These changes can contribute to pathological conditions of pregnancy
• Most conditions resolve post-partum
• Most conditions can be treated safely with drugs if treatment is needed
• New FDA labeling provides better clinical guidance
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