Preconception through postpartum: Managing medications and diseases in pregnancy

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Disclosure/Conflict of Interest
Programming offered by Auburn University Harrison School of Pharmacy shall exhibit balance, providing the audience information of different perspectives from which to develop an informed professional opinion.

I, Lea S. Eiland, have no actual or potential conflict of interest in relation to this program.

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Objectives

- Participants will be able to explain pharmacokinetic differences in a pregnant patient compared to a non-pregnant patient.
- Participants will be able to devise a medication treatment plan for preconception in a female patient.
- Participants will be able to distinguish medications that should be avoided in pregnant patients.
- Participants will be able to develop a medication treatment plan for common disease states in a pregnant patient.
- Participants will be able to compare and contrast drug information resources for medication use in pregnancy.
- Participants will be able to compare and contrast drug information resources for medication use in breastfeeding.

LG is a 32 YOWF who presents to her Family Medicine physician for follow-up care.

PMH: HTN x 3 years
Dyslipidemia x 2 years
Depression x 1 year; Postpartum depression after 1st child

FH: Father—DM, died at 62 yo from massive stroke
Mother—HTN, otherwise healthy
Paternal grandfather—DM
Siblings (2)—younger—alive and well

SH: Married, 1 child (3yo female)
Works full time—teacher
Tobacco =  Alcohol =  Illicit Drugs = 
Rarely exercises
Tries fad diets for weight loss—has had little success
Administers meds herself

LG’s Medication History

<table>
<thead>
<tr>
<th>Date</th>
<th>Drug Name/Strength/Regimen</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/2014</td>
<td>One A Day® Women’s VitaCraves®</td>
<td>general health</td>
</tr>
<tr>
<td>2/2014</td>
<td>paroxetine 20 mg daily</td>
<td>depression</td>
</tr>
<tr>
<td>2/2013</td>
<td>atorvastatin 20 mg QHS</td>
<td>dyslipidemia</td>
</tr>
<tr>
<td>7/2012</td>
<td>Low-Dose Estradiol 0.03 mg and Norgestrel 0.3 mg</td>
<td>contraception</td>
</tr>
<tr>
<td>1/2012</td>
<td>bisoprolol 40 mg daily</td>
<td>HTN</td>
</tr>
</tbody>
</table>

Allergies: NKDA
Vaccinations: Up-to-date, Tdap during last pregnancy
LG’s Objective Info

PE:
Gen: The pt is an overweight white female who seems anxious. No other significant findings on exam.

Vitals:
- BP 122/82 without orthostasis
- P 70; RR 18
- Ht 5'4"; Wt 180 lbs; BMI = 30.9 kg/m²
- Waist circumference 38"
- Patient-rated Beck Depression Inventory [BDI] (today) - 7

LG’s Labs

Pertinent Laboratory Data (from today’s visit):

<table>
<thead>
<tr>
<th></th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>CO₂</th>
<th>BUN</th>
<th>Scr</th>
<th>Glucose</th>
<th>Hgb</th>
<th>Hct</th>
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<tbody>
<tr>
<td></td>
<td>143</td>
<td>3.8</td>
<td>100</td>
<td>30</td>
<td>14</td>
<td>1.0</td>
<td>102</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Total Chol</td>
<td>LDL</td>
<td>HDL</td>
<td>Triglycerides</td>
<td>AST</td>
<td>ALT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>190</td>
<td>120</td>
<td>38</td>
<td>160</td>
<td>24</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Question

Which of the following physiological parameters are affected by pregnancy?

A. Decrease in total body water  
B. Increase in renal blood flow  
C. Increase in gastric motility  
D. Decrease in CYP450 enzymes
### Physiological Changes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
<th>Pharmacokinetic/Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric emptying and small intestine motility</td>
<td>↓</td>
<td>Variable change in bioavailability, ( T_{\text{max}} ), ( C_{\text{max}} ) ↓</td>
</tr>
<tr>
<td>Increased total volume</td>
<td>↑</td>
<td>↑↑ Drugs that are inhaled</td>
</tr>
<tr>
<td>Tissue perfusion</td>
<td>↑</td>
<td>Increase in intramuscular delivery</td>
</tr>
<tr>
<td>Total body water</td>
<td>↑</td>
<td>Hydrophilic drugs distribute more, ↑ ( V_d )</td>
</tr>
<tr>
<td>CYP450 enzymes</td>
<td>↑↓</td>
<td>1A2, 2C19 ⇐, 2C9, 2D6, 3A4 ↑</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>↑</td>
<td>Enhanced elimination of drug, ⇐</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>↑</td>
<td>Cockcroft-Gault: may overestimate, MDRD: may underestimate</td>
</tr>
</tbody>
</table>

### Question

Which of the following is the best source to find the summary of a medication’s risk of use in pregnancy?

A. Lexi-Comp Drug Information Handbook  
B. Micromedex  
C. Drugs in Pregnancy and Lactation: Briggs  
D. Package Insert

### Current FDA Drug Use in Pregnancy Classification System

A. Controlled studies show no risk. Adequate, well controlled studies in pregnant women have failed to demonstrate risk to the fetus.  
B. No evidence of risk in humans. Either animal findings show risk, but human findings do not, or if no adequate human studies have been done, animal findings are negative.  
C. Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify the potential risk.  
D. Positive evidence of risk. Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.  
X. Contraindicated in pregnancy. Studies in animals or humans, or investigational or postmarketing reports have shown fetal risk that clearly outweighs any possible benefit to the patient.
Percentage of Drugs in each Category

- Category A: 7%
- Category B: 7%
- Category C: 0.7%
- Category D: 46%
- Category X: 12%

Percentage of Drugs in each Category

FDA Categories/Labeling Changes

- Risk increases with level
  - Categories C, D, and X are based on risk alone, but risk weighed against benefit
  - Categories do not always distinguish between risks based on human versus animal data findings or between differences in frequency, severity, and type of fetal developmental toxicities

- Proposed Rule with FDA for Changes (May 2008)
  - Final rule approved in December 2014 by FDA
  - Pregnancy and Lactation Labeling Rule (PLLR)
    - Changes current format of labeling information
    - Remove A, B, C, D, and X from all drug product labeling
    - Requires labeling to be updated when outdated
    - labeling for over-the-counter (OTC) medicines will not change

- Goes into effect on June 30, 2015

Pregnancy and Lactation Labeling Rule

- Prescription drugs and biologic products submitted after June 30, 2015 will use the new format immediately
- Prescription drugs approved on or after June 30, 2001 will be phased in gradually

Pregnancy and Lactation Labeling Rule

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>Lactation</th>
<th>Sources and Modes of Reproductive Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Summary</td>
<td>Risk Summary</td>
<td>Pregnancy Testing</td>
</tr>
<tr>
<td>Risk and benefit statement</td>
<td>Presence of drug in human milk*</td>
<td>Contraception</td>
</tr>
<tr>
<td>Clinical considerations</td>
<td>Effects of drug on the breast-fed child*</td>
<td>Infertility</td>
</tr>
<tr>
<td>Disease-associated maternal and/or embryo/fetal risk</td>
<td>Effects of drug on milk production*</td>
<td></td>
</tr>
<tr>
<td>Dose adjustments during pregnancy and the postpartum period</td>
<td>Risk and benefit statement*</td>
<td></td>
</tr>
<tr>
<td>Maternal adverse reactions</td>
<td>Clinical considerations</td>
<td></td>
</tr>
<tr>
<td>Fetal/neonatal adverse reactions</td>
<td>Data</td>
<td></td>
</tr>
<tr>
<td>Labor or delivery</td>
<td>Data</td>
<td></td>
</tr>
<tr>
<td>Data</td>
<td>Data</td>
<td></td>
</tr>
<tr>
<td>Human Data</td>
<td>Data</td>
<td></td>
</tr>
<tr>
<td>Animal Data</td>
<td>Data</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Exposure Registry (if applicable)</td>
<td>Data</td>
<td></td>
</tr>
</tbody>
</table>

*If drug absorbed systemically

Sources of Teratogen Information

**Pregnancy and Lactation: Briggs**
- Monographs that provide FDA Pregnancy category, Fetal Risk Summary and Breastfeeding summary
- Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians: Briggs
- Written by pharmacists and physicians; Reviews basic pregnancy issues; Discusses complication with pregnancy and how to treat; Discusses disease states in pregnancy and how to treat
- Pregnancy Registries
  - [http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm)
- OTIS: Org of Teratology Information Specialists
  - [http://www.otispregnancy.org/](http://www.otispregnancy.org/)
- Fact Sheets on drugs, herbals, conditions, infections, vaccines, drugs of abuse, other exposure (mold, lead, tanning products, etc)
- Primary Literature

**Micromedex (Subscription needed)**
- REPRISE:
  - Paragraph description of information
  - Covers reproduction including fertility, male exposures, and lactation
- Discusses reproductive influences of industrial and environmental chemicals, prescription, over-the-counter, and recreational drugs, and nutritional agents
- THERIS (Teratogen Information System)
  - Provides magnitude of teratogenic risk and classifies the quality and quantity of data on which the risk estimate is based
  - Paragraph summaries of teratology studies
  - Includes Shepard's Catalog of Teratogenic Agents
  - Scientific reviews on the teratogenic effects of drugs, chemicals, and other physical and biological agents
LG – Preconception Care

<table>
<thead>
<tr>
<th>Start date</th>
<th>Drug name/strength/ regimen</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/2014</td>
<td>One A Day® Women’s VitaCraves® Gummies</td>
<td>General Health</td>
</tr>
<tr>
<td>2/2014</td>
<td>paroxetine 20 mg daily</td>
<td>depression</td>
</tr>
<tr>
<td>2/2013</td>
<td>atorvastatin 20 mg QHS</td>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>1/2012</td>
<td>buspirone 40 mg daily</td>
<td>MHTs</td>
</tr>
</tbody>
</table>

Are there medications that we would want to stop now that LG is planning to become pregnant?

Are there medications that we would feel comfortable continuing while LG is trying to conceive or even once she becomes pregnant?

How would you classify LG’s depression?

LG’s BDI at today’s visit is 7 – what does this mean?

- **BDI** = Beck Depression Inventory
- Patient-rated, 21-item scale
- Interpretation of scores
  - 0–9 = normal mood
  - 10–15 = mild depression
  - 16–29 = mild to moderate depression
  - 20–29 = moderate to severe depression
  - 30–63 = severe depression
- BDI is considered the gold standard of self-rating scales

Example of Beck Depression Inventory available at: [link](http://www.med.navy.mil/sites/NMCP2/PatientServices/SleepClinicLab/Documents/Beck_Depression_Inventory.pdf)

Question

Based on the current assessment of LG’s depression is the benefit worth the risk to continue paroxetine?

A. Yes, no concerns – can continue throughout pregnancy
B. Yes, depression is severe, continue until pregnancy confirmed
C. No, would recommend stopping now (preconception)
D. No, would stop in 3rd trimester just before delivery
Approach to depression

**PRECONCEPTION**

- **Mild symptoms**
  - No prior history – lifestyle
  - Prior history – lifestyle OR pharmacotherapy OR combination

- **Moderate symptoms**
  - No prior history – pharmacotherapy + lifestyle OR psychotherapy
  - Prior history – pharmacotherapy + lifestyle

- **Severe symptoms**
  - No prior history – pharmacotherapy + lifestyle OR ECT

**PREGNANT**

- **Mild symptoms**
  - No prior history – lifestyle or psychotherapy
  - Prior history – continue pharmacotherapy OR lifestyle

- **Moderate symptoms**
  - No prior history – pharmacotherapy + lifestyle

- **Severe symptoms**
  - No prior history – pharmacotherapy + lifestyle OR ECT

Concerns with paroxetine

- FDA Category D
- Greatest risk appears to be in the first trimester.
- Recommended it be discontinued in most pregnant women, regardless of trimester unless the risk outweighs the benefits.
- Risk to fetus: cardiac teratogen (ventricular septal defects), persistent pulmonary hypertension of the newborn (PPHN)
- Risks to infants: poor neonatal adaptation syndrome

Antidepressants

- **Tricyclic antidepressants (TCAs)**
  - FDA Category
  - No association with major fetal malformations but may see neonatal withdrawal after birth

- **Selective serotonin reuptake inhibitors (SSRIs)**
  - FDA Category C except paroxetine
  - Serotonin-norepinephrine reuptake inhibitors (SNRIs)*
    - Desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine
    - FDA Category C

- **Dopamine-reuptake blocking**
  - Bupropion – FDA Category C
  - Noradrenergic antagonist*
    - Mirtazapine – FDA Category C

- **Serotonin reuptake inhibitor/antagonist**
  - Nefazodone, trazodone

- **Monoamine Oxidase Inhibitors (MAOIs)**
  - FDA Category C

Remember to consider the risk of antidepressants across the risk of not treating depression.
Question
Remember LG’s PMH includes dyslipidemia and her current medication is atorvastatin 20 mg QHS. Her last LDL was 120 mg/dL and TGs are 160 mg/dL.
What is the best recommendation for LG’s atorvastatin therapy now that she wants to become pregnant?
A. Continue atorvastatin 20 mg QHS
B. Continue atorvastatin 20 mg QHS and add colesevelam 625 mg 6 tablets daily
C. Discontinue atorvastatin and encourage a low fat diet
D. Increase atorvastatin to 40 mg QHS and reassess in 6 weeks

Dyslipidemia
Lipid changes during pregnancy
• Total cholesterol (TC) ↑ 25-50%
• Triglycerides (TG) ↑ 2-4X pre-pregnancy levels
• Low density lipoprotein (LDL) ↑ 50%
• High density lipoprotein (HDL) ↑ 30%

Weigh risk of elevated lipid panel in mom versus risk of lipid lowering therapies to fetus
• Patients with clinical atherosclerotic cardiovascular disease (ASCVD) or familial hypercholesterolemia (benefit of lipid lowering > risk)

Lipid lowering agents: Safe to use
Bile acid resin
• FDA Category B
• Do not pass into systemic circulation – Preferred
Fibrates
• FDA Category C
Ezetimibe
• FDA Category C
Nicotinic acid
• FDA Category C
*animal studies have shown teratogenic effects
Fish Oil
• FDA Category C
Plant sterols/stanols
• FDA Category unknown
Medium Chain Triglycerides (MCT)
• FDA Category unknown
Lipid lowering agents: Contraindicated

HMGI-CoA reductase inhibitors (statins)
- FDA Category X
- Structural birth defects in 1st trimester
- Debate whether it is with lipophilic statins (lovastatin, fluvastatin, simvastatin, atorvastatin)
  versus hydrophilic statins (pravastatin) versus statin exposure at all?
- 2nd – 3rd trimesters – concern of adverse effects on ongoing brain development

Hypertension

<table>
<thead>
<tr>
<th>General Population – JNC 8</th>
<th>In Pregnancy - ACOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why treat?</td>
<td>End organ damage; CV risk</td>
</tr>
<tr>
<td>Non-Pharm used?</td>
<td>Weight loss, exercise, DASH diet, limit alcohol and smoking</td>
</tr>
<tr>
<td>Concerning BP values/when to start treatment?</td>
<td>&gt;140/90</td>
</tr>
</tbody>
</table>

Antihypertensive Approach

**GENERAL POPULATION**

2nd line options
- Thiazide
- Angiotensin-converting enzyme inhibitor (ACEI)
- Angiotensin receptor blocker (ARB)
- Calcium channel blocker (CCB)

**CHRONIC HTN IN PREGNANCY**

Preferred
- Labetalol
- Nifedipine
- Methylasopa
ACEIs

- 1st line antihypertensive agent in general population (JNC 8)
- Black Box Warning: fetal toxicity when used in pregnancy
  - Developmental abnormalities
  - Large retrospective study (~30,000 women) – 209 infants exposed to ACEI in 1st trimester
    - Found an 2x increased risk of major congenital malformations (7.1% had major congenital malformations (CDC) compared to babies with no exposure to antihypertensive medications
    - CV and CNS malformations responsible for greatest increased risk
    - Increased risk of kidney malformations
  - FDA Categories: C (1st trimester), D (2nd and 3rd)
  - ACOG – “contraindicated in pregnancy and preconception period”

Thiazides

- 1st line antihypertensive agent in general population (JNC 8)
- 2nd line antihypertensive agent in pregnancy [ACOG]
- Safe in low doses if started prior to gestation
  - Concern – reduction of intravascular volume and electrolyte disturbances
  - May be useful in salt-sensitive HTN
  - FDA Category B

Question
Since LG is planning to become pregnant, how would you suggest managing her hypertension?

A. Continue lisinopril until LG conceives
B. Stop lisinopril and encourage lifestyle modifications
C. Stop lisinopril and start HCTZ 12.5 mg daily
D. Stop lisinopril and start labetalol 400 mg BID
**HTN - Nonpharmacologic**

**ACOG RECOMMENDS**
- Moderate physical activity
  - Continuation in those exercising prior to pregnancy
- If BP controlled during pregnancy

**ACOG DOES NOT RECOMMEND**
- Weight loss
- Extremely low-sodium diets (< 100mEq/day)

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**Recommendations from the American College of Obstetricians and Gynecologists**

**TABLE 7.3. Common Oral Antihypertensive Agents in Pregnancy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>200-400 mg orally in two to three divided doses</td>
<td>Well tolerated, potential bronchodilator effects, less prone to reflex tachycardia, antihypertensive effect</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>10-30 mg/day orally in a slow-release preparation</td>
<td>Caution with use in pregnancy, should be administered with caution due to potential adverse effects on fetal development</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>0.5-2.5 mg/kg/day in two or three divided doses</td>
<td>Careful use in pregnancy, should be administered with caution due to potential adverse effects on fetal development</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Diuretics vs. agent, thiazide agent</td>
<td>Caution with use in pregnancy, should be administered with caution due to potential adverse effects on fetal development</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Angiotensin receptor blockers</td>
<td>Associated with fetal anomalies, contraindicated in pregnancy and postpartum period</td>
</tr>
</tbody>
</table>

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LG

LG is now 10 weeks pregnant.

Her husband comes to the pharmacy and asks if there is anything he can give his wife for nausea and vomiting as she can't keep much down. He can call the OB and ask for a prescription if needed.
Question
Which of the following is the best recommendation to help LG with the nausea and vomiting of pregnancy?

A. Ondansetron
B. Pyridoxine
C. Droperidol
D. Metoclopramide

Nausea and Vomiting of Pregnancy (NVP)

- Common in 70-85% of all pregnant women
- 50% have both, 25% have nausea only, 25% are unaffected
- Various theories of etiology but none proven
- Risk Factors:
  - Multiple gestation (increase placental mass)
  - Family or personal history of hyperemesis gravidarum
  - History of motion sickness or migraines
- Several prevention and treatment options exists
  - Many patients go undertreated due to ineffective therapy or concerns of safety of medications

NVP-Prevention

- Patients taking a multivitamin daily at time of conception less likely need medical attention for vomiting
- Rest/Hydration
- Avoid sensory provoking stimuli
- Dietary changes: little evidence shows benefit of these interventions
  - Frequent, small meals
  - Avoid spicy foods
  - Watch iron intake
  - Eat bland or dry foods
  - Eat high protein meals
  - Eat crackers in the am

References:
NVP-Treatment

- Nonprescription
  - Vitamin B6 (pyridoxine)
  - Doxylamine
  - Ginger

- Prescription
  - Doxylamine and Pyridoxine (Diclegis®)
  - Ondansetron
  - Promethazine
  - Others

Vitamin B6 (pyridoxine)

- Two small studies
  - Pyridoxine, 25mg every 8 hours, reduced severe vomiting but not mild vomiting compared to placebo.
  - Pyridoxine, 10mg every 8 hours, reduced nausea and vomiting compared to placebo in larger study (n=342)

- FDA Category A
- Fewest adverse effects seen of all agents
- ACOG recommends use for first line agent
  - 10-25 mg PO 3 or 4 times daily

Doxylamine

- H1 antihistamine receptor antagonists have demonstrated safety of use
  - Others: dimenhydrinate, hydroxyzine, meclizine with RCTs
  - Meta-Analysis of >24 controlled studies (~200,000 pregnant women) found no increase in teratogenicity during the first trimester

- Effective in decreasing nausea and vomiting of pregnancy
- FDA Category A, B, C
- ACOG recommend use as first line agent when added to pyridoxine
  - 12.5 mg PO 3 or 4 times daily
**Doxylamine and Pyridoxine**

- Combination product available in the US from 1938-1988 (Bendectin®)
- Doxylamine 10 mg and pyridoxine 30 mg
- Recommended that 2-3 doses of pyridoxine are needed to extend the combination
- Doxylamine was withdrawn due to possible teratogenicity
- Pyridoxine could be combined, but not effective as single agent
- Multiple reports of birth defects did not justify this combination
- Combination approved in the US
- Doxylamine 10 mg and pyridoxine 15 mg
- Improved nausea and vomiting of 113 patients
- No congenital malformations seen in studies
- Combination approved in 2013 in the US
- FDA Category B
- Doxylamine 10 mg and pyridoxine 10 mg ($6.36 per tablet)
- 261 pregnant women received 2 weeks of medication, improved nausea and vomiting compared to placebo
- Take 1 tablet at bedtime; take no more than 1 per day (one in the morning, one mid-afternoon and two at bedtime)
- Helped reduced tablet did not crush/chew, take as empty stomach
- ACR (Downgraded)

**Ginger**

- Thought to stimulate the gastrointestinal tract motility and flow of saliva, bile, and gastric secretions
- Ginger 250 mg QID for 4 days provided significant improvement of nausea and vomiting in 70 pregnant women with nausea and vomiting at 17 weeks gestation, p<0.001.
- Powder root ginger capsules (250 mg) decreased episodes of vomiting in 27 women with hyperemesis gravidarum
- Case control study of 187 pregnant women found not change in the rate of major malformations with ginger use in the first trimester
- ACOG states can be considered as nonpharmacologic option

**Selective Serotonin (5-HT₃) receptor agonists**

- Ondansetron 4-mg PO, IV three times daily
- Granisetron and dolasetron have not been studied in pregnancy
- FDA Category B
- Cohort of 608,385 pregnancies (exposed ranged from 1233-1915)
- Not associated with increased risk of spontaneous abortion, stillbirth, major birth defect, preterm delivery, delivery of a low birth weight infant, or small-for-gestational-age infant (no risk of adverse fetal outcomes)
- RCT of 36 women: 4 mg ondansetron patients reported less vomiting than 25 mg pyridoxine + 2.5 mg doxylamine patients over a 5-day period
- RCT of 30 women: No difference was found between IV ondansetron and IV promethazine in terms of:
  - Duration of hospitalization, nausea scores, numbers of doses received, treatment failures
- ACOG lists 5-HT₃ as option in patients who are dehydrated
- Clinically, this formulation used frequently
Phenothiazines

- Prochlorperazine 5–10 mg PO three times daily
- Promethazine 12.5–25.0 mg PO, PR, IV four times daily
- FDA Category C
- Safety not proven but widely used
  - Few small trials but confounder issues
  - Benefit of cost
- ACOG recommends promethazine as third line agent to add to pyridoxine and doxylamine

Others

- Metoclopramide
  - FDA category B; 10–20 mg QID, ADRs limit use (dystonia, restlessness, EPS)

  - Evaluation of 3,458 women exposed to metoclopramide in the first trimester did not show any adverse outcomes.
    - Major congenital malformations
    - Low birth weight
    - Preterm delivery
    - Perinatal death

- Acupuncture
  - Chinese acupuncture P6 (inside of wrist) - decrease nausea and vomiting

  - 593 women experienced less nausea and dry retching when treated weekly for 4 weeks versus controls

- Droperidol
  - Beneficial in nausea and vomiting but prolonged QT and torsades de pointes black box warning limits use


LG

LG is now 16 weeks and is presenting for her monthly check-up with her OB. She is complaining of burning when she urinates and pain over her bladder. She denies flank pain, CVA tenderness, and N/V.

Her vitals are: 132/80 mm Hg, HR 76 bpm, regular, Temp 98.6 F

The UA results are as follows: nitrite+, leukocyte esterase+, casts+, protein+, pH 6.0, specific gravity 1.01, blood-, ketones-, glucose-.
UTIs in pregnancy

**Acute cystitis** (involves lower urinary tract/bladder)
- Uncomplicated
- Complicated
- Symptoms: dysuria, frequency, urgency
- Denies: fever, hematuria, CVA tenderness, N/V, flank pain
- Typical findings on UA: + leukocyte esterase, + nitrites, +/- hematuria, - casts

**Pyelonephritis** (involves the upper urinary tract/kidneys)
- Uncomplicated
- Complicated (must be managed inpatient)
- Symptoms: fever, hematuria, CVA tenderness, N/V, flank pain
- Typical findings on UA: + leukocyte esterase, + nitrites, + hematuria, + casts

Complicated UTIs

**Complicated patient characteristics for cystitis:**
- recurrent UTIs
- institutionalization
- pregnant
- immune-compromised
- DM
- extremes in age
- abnormal urinary tract physiology

**Complicated patient characteristics for pyelonephritis:**
- pregnant
- fever
- men
- N/V
- dehydration
- s/sxs sepsis

Question

LG said she was successfully treated for a urinary tract infection a few months before she became pregnant. You notice in her pharmacy profile she was treated with nitrofurantoin 6 months ago. The resistance rate for trimethoprim (TMP)-sulfamethoxazole (SMX) is 22% in your area. Remember LG has NKDA. How should you manage LG’s urinary tract infection?

A. cephalexin 500 mg orally BID x 7 days
B. ciprofloxacin 250 mg orally BID x 3 days
C. nitrofurantoin 100 mg orally BID x 14 days
D. TMP-SMX DS 1 tablet orally BID x 3 days
Treatment of cystitis (in the general population)

Areas with < 20% TMP-SMX resistance:
- TMP-SMX DS 1 tablet BID x 3 days OR
- Nitrofurantoin 100 mg BID x 5 to 7 days OR
- Fosfomycin 3 g once

Areas with > 20% TMP-SMX resistance:
- FQ
- Ciprofloxacin 250 mg BID x 3 days OR
- Ciprofloxacin ER 500 mg daily x 3 days OR
- Levofloxacin 250 mg daily x 3 days

AVOID moxifloxacin for tx due to poor urine concentrations
- Nitrofurantoin 100 mg BID x 5 to 7 days OR
- Fosfomycin 3 g once

All Antibiotics PLUS pyridium 200 mg TID x2 days


Treatment of cystitis in pregnancy

Avoid TMP-SMX in 1st trimester due to folate antagonism and birth defects associated with low folate levels.
Avoid TMP-SMX in 3rd trimester close to anticipated delivery due to increased incidence of kernicterus/bilirubin displacement.
Avoid nitrofurantoin in the 3rd trimester due to association with hemolytic anemia.
LG is in her 2nd trimester, so nitrofurantoin could be safely used.
She was treated with it 6 months prior, but resistance rates are low and develop infrequently to nitrofurantoin.
The duration of treatment with nitrofurantoin is the same in pregnancy as with a non-pregnant patient: 5 to 7 days

Preferred antibiotics for cystitis in pregnancy:
- beta-lactams (e.g., amoxicillin, amoxicillin–clavulanate, cephalaxin, cefpodoxime)
- Pyridium is pregnancy category B, crosses the placenta. No adverseevents in animals have been reported.

Avoid FQs unless the benefit outweighs the risk (all trimesters).

Question
LG is now 20 weeks pregnant. LG’s BP has been averaging 150 – 164/90-102 at home for the last few weeks. The average of her 2 BP readings today in clinic is 162/94. She denies headaches and right upper quadrant pain. Her UA protein (-) and her SCr, platelets, and LFTs are within normal limits.
LG’s lisinopril was stopped at her preconception visit. Now the OB feels LG’s blood pressure warrants treatment. Which of the following agents would be preferred based on evidence?
A. nifedipine
B. atenolol
C. clonidine
D. furosemide
Chronic HTN: Diagnostic Criteria

- Diagnosis is made if women are hypertensive before pregnancy or if they become hypertensive before 20 weeks of gestation.
- Only diagnosed after 20 weeks gestation if hypertension lasts longer than the postpartum period of 12 weeks after delivery.
- Severe chronic HTN when BP is ≤160/105 mmHg

Symptoms:
- Chronic – typically asymptomatic
- Severe – visual disturbances, headaches, dizziness, malaise


Chronic HTN in Pregnancy

<table>
<thead>
<tr>
<th>Mild (&lt;140/100)</th>
<th>Severe (≥160/100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Pharmacologic treatment</td>
<td>Pharmacologic treatment initiated</td>
</tr>
<tr>
<td>Delay pharmacologic treatment until HTN becomes severe</td>
<td>No end-organ damage: treat to 140-159/90-100</td>
</tr>
<tr>
<td>Monitor BP at each visit</td>
<td>End-organ damage: treat to &lt;140/90</td>
</tr>
<tr>
<td></td>
<td>Monitor BP at each visit</td>
</tr>
</tbody>
</table>

Once patients are on antihypertensive therapy, BP targets 120-160/80-100.


Chronic HTN in Pregnancy

Treatment: Non-Pharmacologic

For mild and severe HTN:
- Bed rest to prevent pre-eclampsia
- Scarce evidence
- Limit activity
- Unless pt is accustomed to exercising and BP is well controlled
- Diet: extremely low Na diet (<100 mEq/day) is not used for managing chronic HTN in pregnancy
- Strength of recommendation: low
- Stress reduction
- Cessation of smoking and alcohol use

Chronic HTN in Pregnancy
Treatment: Pharmacologic

<table>
<thead>
<tr>
<th>Preferred oral agents:</th>
<th>Second-line agents:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol</td>
<td>Thiazides</td>
</tr>
<tr>
<td>Nifedipine</td>
<td></td>
</tr>
<tr>
<td>Methyldopa</td>
<td></td>
</tr>
</tbody>
</table>

Preferred for urgent control:
- Labetalol – 1st line
- Hydralazine
- Nifedipine
- administer IV

Calcium Channel Blockers

- FDA Category C
- Not extensively studied but most evidence with nifedipine
  - No increased adverse fetal outcomes
  - Not thought to affect blood flow to uterus or umbilical cord
- ACOG recommends nifedipine
  - Avoid sublingual form
- Other CCBs?
- May be safe
- Remember ADRs, especially constipation and HA

Methyldopa

- FDA Category B
- History of safety – pregnancy/fetus
  - Not thought to cause ADRs on hemodynamics of fetus or uteroplacenta
  - No adverse effects on fetus
- History of safety – infants/children
  - Eosinophilia seen in infants; no difference in intelligence or neurocognitive development
- ACOG recommends
  - Monitor LFTs and CBC – serious ADRs
  - Hepatic dysfunction and necrosis
  - Hemolytic anemia
- May be less effective in preventing severe HTN
Labetalol

- FDA Category C
  - No increased in perinatal outcomes versus placebo or atenolol
  - Metoprolol: normal flow seen, uncomplicated
  - In 2nd and 3rd trimester, caution with decreased placental weight and intrauterine growth restriction (IUGR)

- ACOG recommends, especially mild – moderate HTN
  - Remember MOA: α/β-blocker

- Use close to term/delivery
  - Monitor newborns 24-48 hours for bradycardia and hypotension

Other β-Blockers

- Propranolol, metoprolol, carvedilol
- FDA Category C
- Pindolol, acebutolol
- FDA Category B

β-blockers to avoid?
- Atenolol
  - FDA Category D
  - Can cause intrauterine growth restriction (IUGR) and reduced placental weight
  - The risk of IUGR is increased by 2-3 times.
  - β-blocker increases iugr and placental weight
  - In trimester – decrease in weight (fetus and placenta)

LG

LG is now 7 months pregnant and returns to the pharmacy with complaints of constipation. Her MD told her to just ‘grab something over the counter to help, if it occurred.’ She asks you what would be best to take. What is the best recommendation for LG?

A. Mineral Oil
B. Senna
C. Bisacodyl
D. Magnesium citrate
Constipation

• Up to 40% of women can experience constipation at some stage throughout pregnancy
  • Most common in the 1st and 2nd trimester
• Patients with existing constipation can experience an increase in severity during pregnancy
• Hormonal and mechanical changes impact constipation in pregnancy
• More common in the multiparous woman
• Nonpharmacologic treatment recommended for everyone
  • Try to continue with prenatal vitamins with iron
• Pharmacologic treatment recommended for patients with intractable symptoms

Nonpharmacologic Treatment

• Adequate water intake
• High fiber foods
• Light physical exercise

**Most constipation can be resolved with nonpharmacologic therapies

Bulk-forming Laxatives

• Bran, agar, psyllium, methylcellulose, calcium polycarbophil, pectin, flax seed
• Likely the safest for constipations since they are not systemically absorbed
• Cochrane Review found bulk forming laxatives to be helpful in pregnant women
• Onset is 1-3 days
• Recommend 25-40 grams/day
• ADRs: gas, cramps, abdominal bloating
• Contraindicated for impaction
Stool Softeners

- Docusate sodium appropriate for use
- Efficacy is questioned more than safety
- It has not been associated with congenital abnormalities

Osmotic Laxatives

- Polyethylene glycol
  - No electrolytes
  - Minute absorption from the GI tract
  - Commonly used
- Lactulose, glycerine, and sorbitol are generally considered safe
  - Animal studies have shown no evidence of teratogenicity
  - ADRs of bloating and cramping may limit use
- Magnesium hydroxide, sulfate, and citrate
  - May cause sodium retention
- Saline Osmotic Laxatives
  - Magnesium citrate and sodium phosphate should be avoided for long-term use
  - May cause sodium retention

Stimulant Laxatives

- Senna and bisacodyl may be used for short-term relief
  - Cochrane Review: Stimulants likely to be more effective than bulk-forming laxatives (few studies, very old)
  - Long term use is not recommended
  - Studies not shown to be teratogenic
  - Bisacodyl- only 5% is absorbed but cramping may limit its use
- Avoid castor oil
  - May stimulate premature uterine contractions
Lubricant Laxative

• Avoid mineral oil
• Interfere with fat-soluble vitamin absorption (Vit K concerns in infants)
• Concerns with aspiration

LG – Postpartum Visit #1
LG delivered her baby at 39 weeks. When she comes back for her 1 month postpartum visit with her OB, she reports feeling overwhelmed trying to care for her infant daughter and her husband.

LG’s Edinburgh postnatal depression scale (EPDS) is 15.
LG’s OB wants to prescribe her an antidepressant but LG is nervous about taking an antidepressant. LG wants your opinion about the risk to her infant since she is breastfeeding.

What are the considerations for postpartum antidepressant use while breastfeeding?

Question - depression
It is determined LG needs treatment for postpartum depression and intends to continue breastfeeding. Which of the following would be the best to recommend?

A. fluoxetine
B. mirtazapine
C. paroxetine
D. venlafaxine
Postpartum Depression

• One in 7 women treated for depression in year before pregnancy – year after pregnancy
• Depression leading cause of disability in women
• Screening and treatment benefits patient and family
• Important to watch women with history of depression
• Incidence of postpartum depression 10 – 15%

Postpartum depression - Considerations

• Risks if depression is not adequately treated
• Mother’s desire to breastfeed her infant vs. disadvantages to the infants of not receiving their mother’s milk
• Risks of infant exposure to an antidepressant
• Are there ways to reduce the drug exposure to the infant?
• Even if the risk of adverse effects in the infant due to antidepressant, should the infant be monitored in any way?
• Could monitor – little evidence for causality and ADRs
• Infant symptoms – non-specific

Question

Which of the following is the best source to find information regarding a medication’s risk of use in lactation?

A. LactMed
B. Micromedex
C. American Academy of Pediatrics Breastfeeding Recommendations
D. Package Insert
Lactation Resources

• American Academy of Pediatric (AAP) Recommendations (2001)
  • Update on select topics (2013)
    - Psychotropic medications
    - Substance use treatments
    - Narcotics
    - Galactagogues
    - Herbal products
    - Immunizations
  • Free Access Online to PDF article

Lactation Resources

• Medication and Mother’s Milk, 16th Edition, 2014
  • Book updated every 2 years, annual online subscription available
  • Thomas Hale, RPh, Ph.D, Hillary E. Rowe, Pharm.D.
  • Prescription, OTC, Radiologic
  • Details of studies and below info provided
    - Uses
    - AAP Recommendations
    - Summary of Use During Lactation
    - Pregnancy Risk Category (FDA)
    - Lactation Risk Category (His Own)
    - Adult and Pediatric Concerns
    - Drug Interactions
    - Relative Infant Dose
    - Adult Dose Pharmacokinetics
    - Alternative Drugs to Consider

Lactation Resources

• LactMed
  • Free database through National Library of Medicine
    (http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm)
  • Free app available (Apple/Android)
  • Updated monthly
  • Provides
    - Summary of Use During Lactation
    - Drug Levels
    - Effects in Breastfeeding Infants
    - Possible Effects on Lactation
    - Alternative Drugs to Consider
LG – Postpartum Visit #2

LG comes back in 6 weeks (she is now 2 ½ months post-delivery). She reports she has not had any problems with her antidepressant therapy and feels like she is coping with her infant and family much better. LG says breastfeeding is going well. She says she has been successful in eating healthy and walks 2 miles 4 days a week.

In clinic:
- EPDS – 7
- BP - 148/154/86-92 (over the last 2 visits)
LG reports her BP at home consistently averages 146 - 152/82-90.

What are the considerations for postpartum management of hypertension while breastfeeding?

Question

What would be the best recommendation for management of LG’s hypertension, postpartum while she is breastfeeding?
A. methyldopa
B. clonidine
C. atenolol
D. lisinopril

Hypertension and Lactation

ACOG encourages all women to breastfeed their infants, including women with chronic hypertension

Most antihypertensive medications considered safe
- Most tend not to be secreted into breast milk
Antihypertensives in Lactation

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Hydrochlorothiazide (HCT)</td>
</tr>
<tr>
<td>ACEIs</td>
<td>Enalapril, Captopril</td>
</tr>
<tr>
<td>ARBs</td>
<td>Losartan, valsartan</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Atenolol, metoprolol</td>
</tr>
<tr>
<td>Nonsteroidal calcium</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Magnesium sulfate</td>
</tr>
</tbody>
</table>

Question

LG’s lipid panel at her visit today is LDL 140, HDL 48, TG 155, TC 219. LG’s other lab work, including SCr and LFTs, is within normal limits. LG does not have a history of clinical ASCVD and her FH is non-contributory.

What is the best recommendation for management of LG’s lipids at this time?

A. Counseling to reinforce healthy eating and exercise
B. Start pravastatin 20 mg po QHS
C. Start colesevelam 625 mg 6 tablets PO daily
D. Start fish oil 1 g 2 tablets po BID

When would LG need follow-up for her lipids?

Dyslipidemia and Lactation

- No contraindications just because dyslipidemia
- In general, lactation + TG and ? HDL

Normalization of lipid panel:
- TG returns to baseline by 6 weeks postpartum
- LDL does not reach baseline until ~9 months postpartum

NOT recommended – lack of human data/contraindicated by manufacturers:
- HMG Co-A reductase inhibitors (statins)
- Niacin
- Bile acid resins

NOT recommended – lack of human data:
- Ezetimibe
- Fibrate acids - fenofibrate, gemfibrozil
- Fish oils
- Medium-chain triglycerides (MCTs)
- Plant sterols/sterols

Weigh the risk to the infant versus the benefit to mother

Questions?
*Thank you!

References


References


ACOG. Screening for depression during and after pregnancy. Committee Opinion 85. 3029. PDF 2010.
