Women’s Health PRN Focus Session—Healthy Mom, Healthy Baby: Best Practices in Optimizing Preconception Health and Pregnancy Outcomes

Activity Number: 0217-0000-15-124-L01-P, 1.50 hours of CPE credit; Activity Type: A Knowledge-Based Activity

Monday, October 19, 2015
1:30 PM to 3:00 p.m.
Continental Ballrooms 1-3

Moderator: Brooke L. Griffin, Pharm.D., BCACP
Professor, Midwestern University, Downers Grove, Illinois

Agenda

1:30 p.m. Preconception Health / Prenatal Health
Erin C. Raney, Pharm.D., BCPS
Professor, Department of Pharmacy Practice, Midwestern University
College of Pharmacy-Glendale, Arizona

1:50 p.m. Self-Care for Common Concerns in Pregnancy
Kassandra Bartelme, Pharm.D., BCACP
Assistant Professor of Pharmacy Practice, Concordia University Wisconsin
School of Pharmacy, Mequon, Wisconsin

2:10 p.m. Current Recommendations for Substance Abuse During Pregnancy
Alicia B. Forinash, Pharm.D., FCCP, BCPS, BCACP
Professor of Pharmacy Practice, St. Louis College of Pharmacy, St. Louis, Missouri

2:30 p.m. Recommendations for Emerging Drugs in Selected Cardiovascular Conditions in Pregnancy
Rebecca H. Stone, Pharm.D., BCPS, BCACP
Clinical Assistant Professor, University of Illinois Chicago, Chicago, Illinois

Conflict of Interest Disclosures

Kassandra Bartelme: no conflicts to disclose.
Alicia B. Forinash: Grants: (ASHP Resident Research Grant Co-Awardee).
Brooke L. Griffin: no conflicts to disclose.
Erin C. Raney: no conflicts to disclose.
Rebecca H. Stone: no conflicts to disclose.

Learning Objectives

1. Describe lifestyle, environmental, and medication factors that impact preconception health.
2. Explain what supplements, immunizations and other medications are needed for women preconception and during pregnancy.
3. Review how to use the new FDA medication labeling for use during pregnancy, lactation, and reproductive potential.
4. Discuss how to appropriately discontinue medications when risk outweighs benefit in pregnancy (e.g., statins, ACE-inhibitors).
5. Recommend appropriate use or avoidance of various substances including caffeine, alcohol, and tobacco.
6. Discuss self-care treatment options for common complaints during pregnancy, including nausea, vomiting, constipation, fatigue, reflux, and rhinitis.
7. Identify symptoms and complaints that warrant referral.
8. Discuss adverse pregnancy outcomes associated with substance abuse.
9. Describe appropriate treatment options for the management of substance abuse during pregnancy, including opioids and illicit drugs.
10. Describe treatment options for the management of thromboembolism during pregnancy.
11. Review cardiovascular medications to avoid in pregnancy.
12. Describe the current literature for emerging cardiovascular drug therapies in pregnancy.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Learning Objectives

- Describe lifestyle, environmental, and medication factors that impact preconception health
- Explain what supplements, immunizations, and other medications are needed for women preconception and during pregnancy
- Review how to use the new FDA medication labeling for use during pregnancy, lactation, and reproductive potential
- Discuss how to appropriately discontinue medications when risk outweighs benefit in pregnancy

Preconception Care

- “Preconception care is the provision of biomedical, behavioural and social health interventions to women and couples before conception occurs, aimed at improving their health status, and reducing behaviours and individual and environmental factors that could contribute to poor maternal and child health outcomes. Its ultimate aim is improved maternal and child health outcomes, in both the short and long term.” (World Health Organization)

Global Perspective

- 4 out of 10 pregnancies are unplanned
- Maternal malnutrition accounts for 20% of maternal mortality
- Smoking cessation prior to or during pregnancy could prevent 5-7% of deaths from preterm delivery
- Tetanus resulted in 58,000 neonatal deaths in 2010
- Preterm delivery occurs in 35% of pregnancies with untreated gonococcal infections

World Health Organization

- Preconception Care Package

Conflict of Interest

- No conflicts of interest to disclose
U.S. Health Indicators

18.4% of women 18-44 reported receiving preconception counseling
66.3% of women reported having a routine check-up within the year prior to pregnancy
54.2% reported drinking alcohol during the 3 months prior to pregnancy
25.1% reported smoking cigarettes during the 3 months prior to pregnancy
29.1% reported taking folic acid within 1 month prior to pregnancy

66.3% of women reported having a routine check-up within the year prior to pregnancy

CDC Core State Preconception Health Indicators 2009
MMWR 2014;63 (No.SS-3):1-62

Clinical Toolkit

- National Preconception/Interconception Clinical Toolkit
  - "One Key Question:" Would you like to become pregnant in the next year?
    - Women who desire pregnancy in the next year
    - Women who are ambivalent about pregnancy in the next year
    - Women who do not desire pregnancy in the next year

T.R. is a 30 year old woman who presents to clinic for a well-woman exam. She wishes to continue her current combined oral contraceptive at this time, but is considering pregnancy after she finishes an MBA program in 18 months.

Nutrition Status

T.R. states that she has modified her diet based on symptoms of irritable bowel syndrome and generally avoids dairy products. She does not use any vitamin supplements on a routine basis.

- 600 IU daily Vitamin D
- 1500 mg daily Calcium
- 15 mg daily (age 14-18) Iron
- 15 mg daily (age 19-50) Iron
- 8-12 ounces of EFA containing seafood weekly
- Avoid high mercury content
- 3-12 ounces of B12 containing seafood weekly
- Avoid high mercury content
- 400 mcg daily Folic Acid

Weight Assessment

T.R.’s BMI is 26.4 kg/m² which has decreased from 28.2 kg/m² 2 years prior.
Immunizations

Avoid During Pregnancy
- MMR
- Varicella/Zoster
- Influenza LAIV
- HPV

Give Only if Indicated
- Hepatitis A, B
- Meningococcal conjugate/polysaccharide
- Pneumococcal polysaccharide
- Polio

Give During Pregnancy
- Influenza (IIV)
- Tdap

T.R. is up-to-date on MMR, meningococcal, and polio vaccines. She has never received the Hepatitis A or B vaccines. Her last TD was 4 years ago. She doesn’t receive influenza vaccines, and has no history of varicella infection or vaccination.

http://www.cdc.gov/vaccines/pubs/preg-guide.htm

Immunizations

Influenza immunization trends

Medication Safety

- Interpretation of pregnancy risk is complicated by available information
  - Limited clinical trial data
  - Oversimplification of risk with letter categories
- Communication of risk prior to conception is also poor1,2
  - Studies indicate little attention given to contraception counseling for potentially teratogenic medications
  - ~50% of women receiving a prescription for a category D or X medication received contraceptive counseling

1 Ann Intern Med 2007;147:370-376
2 Med Care 2010;48:834-842

Product Labeling

- Final Rule: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling
  - Newly approved prescription drug products as of June 30, 2015 must comply with this rule
  - Previously approved products (since 2001) will be phased in over time
  - Letter categories will be removed from all products over time


Product Labeling

Use in Special Populations

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential

Subsections of 8.1 and 8.2 include “risk summary,” “data,” and “clinical considerations”


Medication Safety

- Average number of medications used anytime in pregnancy in 2006-2008 in the Boston University Sloane Epidemiology Study, compared with 2.5 in 1976-19781
  - 4.2
- Number of women reporting use of at least one medication during pregnancy in the 2006-2008 cohort of the Boston University Sloane Epidemiology Study1
  - 93.9%
- Percentage of women reporting use of an herbal product during pregnancy2
  - 6.9% used an herbal product in the first trimester

1 Am J Obstet Gynecol 2011;205(1):51.e1-51.e8
Preconception

- Poor
- Diabetes
- Chronic Diseases

Medication Safety

- General approach
  - Review medications for pregnancy risk
  - Identify potentially safer alternatives, if possible
  - Plan transition period for medications
  - Optimize other factors associated with disease control

In addition to her combined oral contraceptive, T.R. takes dicyclomine 10 mg approximately 3 times per week for abdominal cramping and ibuprofen 2-3 times per month for headaches. She has discussed completing a 2-week course of rifaximin with her gastroenterologist, but has not filled the prescription.

Dicyclomine

“Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 33 times the maximum recommended human dose... have revealed no evidence of impaired fertility or harm to the fetus... Epidemiologic studies in pregnant women... have not shown that dicyclomine increases the risk of fetal abnormalities if administered during the first trimester of pregnancy. There are, however, no adequate and well-controlled studies in pregnant women at the recommended doses (80-160 mg/day)...”

Rifaximin

8.1 "Risk summary: There are no available data on XIFAXAN use in pregnant women at the recommended doses (80-160 mg/day)..."

Epilepsy

- Poor seizure control is associated with negative pregnancy outcomes, including trauma, preterm birth, fetal growth restriction
- Preconception care
  - Provide counseling and contraceptive planning to women of childbearing age who require antiepileptics
  - Contraceptive choices are limited given the lower efficacy of hormonal options due to enzyme induction
  - Attempt withdrawal of antiepileptic medication if possible. If medication needed, monotherapy is preferred
  - All antiepileptics have associations with teratogenicity
  - Utilize higher doses of folate acid supplementation (e.g., 4-5 mg/day)

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Asthma

- Uncontrolled asthma during pregnancy is associated with poor maternal and fetal outcomes, including preterm birth, low birth weight, and preeclampsia
- Preconception care
  - Optimize asthma control according to stepwise approach in the National Asthma Education and Prevention Program
  - Emphasize continuation of individualized long-acting controllers and use of selective beta-2 agonists for exacerbations

Summary

- Preconception health should be addressed across a woman’s reproductive lifespan. Women and men who are planning pregnancy as well as those not planning pregnancy are appropriate candidates for interventions
- Preconception care addresses social and environmental factors as well as medical, and pharmacists can offer recommendations in areas beyond that of medication use
- Medication safety in pregnancy is an evolving focus, as improvements in data gathering and communication are investigated

Additional Resources

- Before, Between and Beyond Pregnancy (http://beforeandbeyond.org/)
Self-Care for Common Concerns in Pregnancy
Kassandra Bartelme, Pharm.D., BCACP
October 19, 2015

Learning Objectives

- Recommend appropriate use or avoidance of various substances, including caffeine, alcohol, and tobacco.
- Discuss self-care treatment options for common complaints during pregnancy, including nausea, vomiting, constipation, fatigue, reflux, and rhinitis.
- Identify symptoms and complaints that warrant referral.

Conflict of Interests

- I have no conflicts to disclose.

Caffeine

- Moderate intake of caffeine is safe
  - ACOG: 200 mg per day
  - OTIS: 200-300 mg per day
- Caffeine intake up to 300mg/day does not affect pregnancy duration, newborn weight or Apgar score
- Possible risks of consuming greater amounts
  - Increased risk of miscarriage
  - Increased risk of intrauterine growth restriction
  - Increased risk of obesity in child
- Compared caffeine intake of <150 mg (OR 1.77) vs ≥150 mg daily (OR 2.37)

SUBSTANCE USE

Caffeine

<table>
<thead>
<tr>
<th>Average Amounts of Caffeine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee, 8 oz.</td>
</tr>
<tr>
<td>Tea, 8 oz.</td>
</tr>
<tr>
<td>Caffeinated soft drinks, 12 oz.</td>
</tr>
<tr>
<td>Red Bull energy drink, 8.4 oz.</td>
</tr>
<tr>
<td>Excedrin, 2 tablets</td>
</tr>
<tr>
<td>Coffee ice cream, 1 cup</td>
</tr>
<tr>
<td>137 mg</td>
</tr>
<tr>
<td>48 mg brewers:</td>
</tr>
<tr>
<td>26-36 mg instant:</td>
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<tr>
<td>37 mg</td>
</tr>
<tr>
<td>80 mg</td>
</tr>
<tr>
<td>130 mg</td>
</tr>
<tr>
<td>58 mg</td>
</tr>
</tbody>
</table>
Alcohol

- No amount of alcohol is known to be safe
- Risks of alcohol consumption
  - Leading cause of intellectual disability
    - Fetal Alcohol Spectrum Disorder or Fetal Alcohol Syndrome
  - Higher rates of miscarriage and stillbirth
  - Birth defects
  - Withdrawal if alcohol intake close to delivery
  - Lower birth weight, length/height, head circumference
- Risks are greatest in the first 16 weeks of gestation

Tobacco

- Tobacco use is not recommended in pregnancy
  - Nicotine causes vasoconstriction
  - Less oxygen and nutrients reach the fetus
  - Includes all tobacco products
  - Electronic cigarettes have not been studied

Marijuana

- Marijuana should not be used during pregnancy
- Risks include
  - Premature birth
  - Low birth weight
  - Stillbirth
  - Small length and head circumference
  - Problems with attention, impulsive behavior
  - Independent predictor of marijuana use by age 14
- Studies have not shown an increased risk for structural anatomic birth defects

Self-Assessment Question

CJ is a 28 year old female who is 16 weeks pregnant with her first child. She asks you about caffeine use because she’s seen conflicting information on the internet. She likes to drink Cherry Coke Zero throughout the day and one 12 oz can of has 34 mg of caffeine. How many cans of Cherry Coke Zero do you tell her is the most she should drink in one day?

- A. 2 cans (68 mg caffeine)
- B. 4 cans (136 mg caffeine)
- C. 6 cans (204 mg caffeine)
- D. 10 cans (340 mg caffeine)

Nausea and Vomiting of Pregnancy (NVP)

- Affects 44-89% of women during pregnancy
- Begins at 4-6 weeks’ gestation, peaks between 8-12 weeks, ends by 16-20 weeks
- Referral recommended if:
  - Onset of symptoms after 9 weeks’ gestation
  - Severe nausea and/or vomiting
  - Symptoms persist beyond the first trimester

SELF-CARE TREATMENT OPTIONS FOR COMMON COMPLAINTS DURING PREGNANCY
Self-care Treatment for NVP

- Non-pharmacologic treatments
  - Avoid triggers of NVP
  - Eat frequent, small meals
  - High protein snacks and meals
  - Adequate sleep
- Vitamin B6 (pyridoxine)
  - 1-2 mg/day, divided into 3-4 doses
  - ACOG recommends 250mg TID plus another dose before bed
- Ginger
  - Woman’s perception of the severity of her symptoms plays a role in the decision of when and how to treat

First Line of Therapy for NVP

Vitamin B6 (pyridoxine)
- First-line therapy
- Dose: 10-25 mg every 8 hours
  - Doses up to 100 mg or 500mg have been used
- Available as 25 mg, 50 mg, 100 mg, 250 mg
- Side effects: paresthesias, headache, fatigue

Doxylamine
- Add to pyridoxine if needed
- Dose: 12.5 mg with pyridoxine every 8 hours
- Available as a 25 mg tablet
  - Unisom
  - Generic options
- Side effects: drowsiness

Ginger (Zingiber officinale)

- ACOG states ginger can be considered a non-pharmacologic option for NVP
- Raw root ginger
  - Available as capsule, essential oil, tea
    - Most commonly available as 250 mg, 500 mg, or 550 mg capsules
- Dose: 1-2 g/day, divided into 3-4 doses
  - ACOG recommends 250mg TID plus another dose before bed
- Side effects: heartburn, drowsiness, belching, bloating, gas, possible exacerbation of n/v, may increase risk of bleeding
- Not regulated by the FDA

Constipation

- 2nd to nauseas as most common GI complaint
- Most common in 1st and 2nd trimesters
  - More common in subsequent pregnancies
- Risk factors
  - Low fiber diet, sedentary lifestyle, low fluid intake, bed rest and medications
- Referral recommended if:
  - Refractory to usual treatment or symptoms are severe
  - Rectal bleeding
  - Family history of colorectal cancer
  - Known history of GI disorders (e.g. IBD)

Fatigue

- Most common during 1st trimester, often returns in 3rd trimester
- Recommendations
  - Ask for support
  - Rest
  - Eat well
  - Avoid taking on extra responsibilities
- Exercise regularly
- Referral recommended if fatigue is accompanied by:
  - Signs of infection
  - Weakness, shortness of breath, heart palpitations, dizziness or lightheadedness
  - History of iron-deficiency anemia or suspicion of anemia
Self-Assessment Question

MK is a 32 year old female who is 7 weeks pregnant and she asks you what to take for the nausea and occasional vomiting she’s experiencing with her pregnancy. She has tried avoiding triggers and eating frequent protein-rich meals and snacks and while that has helped a little bit, she is still experience the nausea and vomiting. What of the following options is the best for MK?

A. Pyridoxine 25 mg every 8 hours
B. Doxylamine 12.5 mg every 8 hours
C. Ginger 250 mg three times daily
D. Refer her to her obstetrician

Acid Reflux/GERD

- Experienced by 40-80% of pregnant women
- Referral recommended if:
  - Severe symptoms and refractory to usual treatment
- Non-pharmacologic treatments
  - Avoid eating late at night or within 3 hours of going to bed
  - Elevate the head of the bed 4-6 inches (10-15 cm)
  - Lying on the left side of the body
  - Avoiding certain foods, alcohol and tobacco use

Self-care Treatment for Acid Reflux/GERD

- Antacids (first-line)
  - Aluminum, calcium, magnesium
  - Avoid high-dose and prolonged use of magnesium trisilicate (Gaviscon®)
  - Avoid bicarbonate-containing antacids
- H2 receptor antagonists
  - Ranitidine, cimetidine, famotidine, nizatidine
- Proton-pump inhibitors (PPIs)
  - Omeprazole, lansoprazole

Self-care Treatment of Rhinitis

- Non-pharmacologic treatments
  - Regular exercise, saline irrigation, raising the head of the bed, external nasal dilator
- Pharmacologic treatments
  - Topical intranasal decongestants
    - Oxymetazoline, used for ≤ 3 days
  - Intranasal corticosteroids-no benefit shown
  - Oral decongestants
    - Pseudoephedrine preferred in pregnancy
    - Reserved for severe rhinitis
    - Avoid in first trimester and in women with HTN

Allergic Rhinitis

- Likely already pre-existing pre-pregnancy
- Intranasal corticosteroids
  - More effective than antihistamines, especially for nasal congestion and post-nasal drip
  - No apparent difference in efficacy or safety between preparations
- Antihistamines
  - First-generation: chlorpheniramine is drug-of-choice
  - Second-generation: cetirizine, loratadine are drug-of-choice
TH is a 33 year old female who is 34 weeks pregnant. She states she has been experiencing heartburn symptoms about 4 nights per week that wake her up. She has not taken anything to help with the heartburn and has had an uneventful pregnancy thus far. Which of the following is the best option for her?

A. Calcium antacids 500mg PO 1-2 tablets as needed  
B. Ranitidine 150 mg PO once daily at bedtime  
C. Omeprazole 20 mg PO once daily 30 minutes before breakfast  
D. Refer her to her obstetrician

Summary Points

- Substance Use
  - Caffeine 200-300mg daily is safe  
  - Alcohol, tobacco and marijuana should be avoided

<table>
<thead>
<tr>
<th>Complaint</th>
<th>First line therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting of pregnancy</td>
<td>Pyridoxine (vitamin B6) +/- doxylamine</td>
</tr>
<tr>
<td>Constipation</td>
<td>Polyethylene glycol (PEG)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Rest, exercise, eating healthy</td>
</tr>
<tr>
<td>Acid reflux</td>
<td>Antacids (calcium, aluminum, magnesium)</td>
</tr>
<tr>
<td>Pregnancy rhinitis</td>
<td>Oxymetazoline, pseudoephedrine</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>Chlorpheniramine, loratadine, cetirizine</td>
</tr>
</tbody>
</table>
Current Recommendations for Substance Abuse During Pregnancy
Alicia B. Forinash, Pharm.D., FCCP, Pharm.D., BCPS, BCACP
St. Louis College of Pharmacy
Monday, October 19

Learning Objectives

- Discuss adverse pregnancy outcomes associated with substance abuse.
- Describe appropriate treatment options for the management of substance abuse during pregnancy, including opioids and illicit drugs.

Impact of Substance Abuse during Pregnancy

- 4.4% Obstetric patients use illegal drugs
- Increased risk for
  - Lack or Absent Prenatal Care
  - Poor nutrition
  - Concomitant drug, tobacco, and alcohol exposure
  - Poor environment
  - Mental illness
  - Maternal infection

Neonatal Abstinence Syndrome (NAS)

<table>
<thead>
<tr>
<th>W</th>
<th>Wakefulness</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Irritability</td>
</tr>
<tr>
<td>T</td>
<td>Tremors, twitching, tachypnea</td>
</tr>
<tr>
<td>H</td>
<td>Hyperventilation, hypertonia, hyperpyrexia, hyperacusis, hiccups</td>
</tr>
<tr>
<td>D</td>
<td>Diarrhea, diaphoresis</td>
</tr>
<tr>
<td>R</td>
<td>Rub marks</td>
</tr>
<tr>
<td>A</td>
<td>Alkalosis</td>
</tr>
<tr>
<td>W</td>
<td>Weight loss</td>
</tr>
<tr>
<td>A</td>
<td>Apnea</td>
</tr>
<tr>
<td>L</td>
<td>Lacrimation</td>
</tr>
<tr>
<td>S</td>
<td>Seizures, sneezing, skin mottling</td>
</tr>
</tbody>
</table>

Rates are increasing!
- 2004: 7 cases per 1000 admissions (0.6%)
- 2013: 27 cases per 1000 admissions (4%)

Admission length mean 19 days

Limitations to Studies

Pregnancy/Fetal Outcomes
- Amount used
- Trimester(s) used
- Concomitant exposure
  - Depression
  - Antidepressants
  - Alcohol, tobacco
  - Medications
- Past medical history
- Infections
- Genetic influence/Family history
- Other risky behavior

Child Neurobehavioral Factors
- Environment
  - Living situation
  - Caregiver stimulation
  - Community environment (violence)
- Ethnicity
  - Amount of prenatal care received
- Nutrition
- Abuse/Violence
- Maternal stress
- Maternal IQ, language IQ
- Pregnancy outcomes (gestational age, birth weight)

No Conflicts of Interest to Disclose
### Cocaine

**Changes During Pregnancy**
- Interferes with fetal neurotransmitters
- Vasoconstriction — ↓ uterine blood flow
- Cholinesterase metabolism
- Pregnancy: ↓ and Fetal: ↓

**Crosses Placental & Fetal Blood Brain Barrier**
- Hydro and Lipophilic properties
- Molecular Weight: ~340
- Low ionization

**Growth**
- Intrauterine growth restriction (IUGR)
- Small for gestational age
- Delayed growth up to age 10

**Malformations**
- No effect: AAP

**Neurobehavioral effects**
- Behavior:
  - Less social and Withdrawn
  - Anxious/depressed
  - Attention
  - Cognition
  - 2.8x learning disability
- Language delay

**Neonatal Distress**
- Tachycardia
- Lower APGAR scores
- Cerebrovascular accidents
- Sudden Infant Death Syndrome

**Pregnancy Outcome**
- Premature labor and delivery (PTL/PTD)
- Premature rupture of membranes (PROM)
- Placental abruption

**Growth**
- Low Birth Weight (LBW)
- Small head circumference

**Concomitant Substance Use**
- Marijuana: No change
- Nicotine: Worsened birth weight & head circumference

**Pregnancy Outcomes**
- PTL and PTD
- Early gestational age at delivery (37.5 vs. 39.7 weeks)
- PROM

### Meth and Amphetamines

**Changes During Pregnancy**
- Vasoconstriction
- Crosses Placental & Fetal Blood Brain Barrier
- Molecular weight: Amphetamine 135.20 and Meth 149.24
- Variable half-life depending on agent and route used
  - Meth > Amphetamine

**Growth**
- IUGR
- Small head circumference

**Concomitant Substance Use**
- Marijuana: No change
- Nicotine: Worsened birth weight & head circumference

**Neonatal Distress**
- Lower 1 min APGAR
- NAS +49% experienced + 4% treated

**Pregnancy Outcomes**
- PTL and PTD
- Early gestational age at delivery (37.5 vs. 39.7 weeks)
- PROM

### Bath Salts

**Phenethylamine class**
- Khat plant — Cathinones and methcathinones
- Synthetic versions
- Molecular weight: 275

**Growth**
- Intrauterine growth restriction (IUGR)
- Small for gestational age
- Delayed growth up to age 10

**Malformations**
- No effect: AAP

**Neurobehavioral effects**
- Behavior:
  - Less social and Withdrawn
  - Anxious/depressed
  - Attention
  - Cognition
  - 2.8x learning disability
- Language delay

**Neonatal Distress**
- Tachycardia
- Lower APGAR scores
- Cerebrovascular accidents
- Sudden Infant Death Syndrome

**Pregnancy Outcome**
- Premature labor and delivery (PTL/PTD)
- Premature rupture of membranes (PROM)
- Placental abruption

### Ecstasy (MDMA)

**Changes in Pregnancy**
- Up to 66% renally eliminated unchanged
- Metabolism: 2D6 (↑ PG), 1A2 (minor, ↓ PG), 2B6 (metabolite)

**Placental Transfer**
- Molecular weight 179
- Long-half life (8-9 hours)
Opioids

- Changes in Pregnancy
  - Increased metabolism
  - Increased elimination
  - Crosses the placenta
    - Rapidly reaches fetal system (1h)

Opioid Treatment Options

<table>
<thead>
<tr>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Full mu agonist</td>
<td>- Partial mu agonist, κ antagonist, and δ agonist</td>
</tr>
<tr>
<td>Dosing</td>
<td>Dosing</td>
</tr>
<tr>
<td>- Only at a methadone clinic</td>
<td>- Take in the pharmacy (home storage)</td>
</tr>
<tr>
<td>- Liquid given daily</td>
<td>- Sublingual tab 1-3 x/d</td>
</tr>
<tr>
<td>- No max dose</td>
<td>- Call dose: 30 mg/d</td>
</tr>
<tr>
<td>- Many need dose increased during PG</td>
<td>- May need dose increases during PG</td>
</tr>
<tr>
<td>Induction</td>
<td>Induction</td>
</tr>
<tr>
<td>- Simple dosing for induction</td>
<td>- Longer induction period</td>
</tr>
<tr>
<td>- Can start with presentation</td>
<td>- Need to be in mild-moderate withdrawal</td>
</tr>
<tr>
<td>Other</td>
<td>Other</td>
</tr>
<tr>
<td>- Many drug interactions</td>
<td>- Less drug interactions</td>
</tr>
<tr>
<td>- CYP 2B6, 3A4, 2C19, 2D6, 2C8</td>
<td>+ CYP 3A4, 2C8, UGT</td>
</tr>
<tr>
<td>- No food interactions</td>
<td>- Food interaction with grapefruit</td>
</tr>
</tbody>
</table>

Methadone vs. Buprenorphine

<table>
<thead>
<tr>
<th>PROMISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid addicted patients 16-30 weeks (Stabilized on morphine)</td>
</tr>
<tr>
<td>Buprenorphine (n=15, 9 completed)</td>
</tr>
<tr>
<td>Target dose 12 mg/d</td>
</tr>
</tbody>
</table>

NAS EVALUATION/TREATMENT

Hospital: 6-8 times per day
Research center: 2 times per day
- At least 10 days after birth
Methadone vs. Buprenorphine

MOTHER
Opioid addicted patients 6-30 weeks (Stabilized on morphine)

Buprenorphine (n=86, 58 completed)
Methadone (n=89, 73 completed)

NAS EVALUATION/TREATMENT
Hospital: Q4 hours
-At least 10 days after birth


Methadone vs. Buprenorphine + Naloxone

SUBUTEX
-Opioid addicted patients
-Retrospective
Therapy for at least 30 days before delivery

Buprenorphine + Naloxone (n=31)
Methadone (n=31)

NAS EVALUATION/TREATMENT
Hospital: Q2-4 hours


Methadone vs. Buprenorphine

Promise (n=30)
Mother (n=175)
Bup/Nal vs. Meth (n=62)

<table>
<thead>
<tr>
<th></th>
<th>Promise (n=30)</th>
<th>Mother (n=175)</th>
<th>Bup/Nal vs. Meth (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meth</td>
<td>Bup</td>
<td>p-value</td>
<td>Meth</td>
</tr>
<tr>
<td>NAS treated</td>
<td>45.5%</td>
<td>20%</td>
<td>NS</td>
</tr>
<tr>
<td>Total Morphine</td>
<td>1.9mg</td>
<td>0.4mg</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>8.1d</td>
<td>6.8d</td>
<td>0.021</td>
</tr>
<tr>
<td>GA at delivery</td>
<td>38.8</td>
<td>38.8</td>
<td>NS</td>
</tr>
<tr>
<td>NAS duration</td>
<td>8.1d</td>
<td>6.8d</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Meth = methadone
Bup = Buprenorphine
Nal = Naloxone

WISH Clinic

Specialty High Risk Interdisciplinary Clinic
Pharmacist Role
- Maternal Fetal Medicine Specialist
- Pharmacist
- Nurse Practitioners
- Social Worker
- RN (Lactation, Coordinating)
- Neonatologist
- Sonographers

Created agreements and patient education materials
New Patients
- History, Med Rec, ROS (addiction, medical, & acute PG)
- Assessments, Drug Interactions, Recommendations
- Medication options, education, agreements
Existing Patients (2/monthly)
- Vaccines at visits

Evaluating impact currently

2015 ACCP Global Conference on Clinical Pharmacy

Current Recommendations for Substance Abuse During Pregnancy
Alicia B. Forinash, Pharm.D., FCCP, Pharm.D., BCPS, BCACP
Monday, October 19
Recommendations for Emerging Drugs in Selected Cardiovascular Conditions in Pregnancy
Rebecca Stone, PharmD, BCPS, BCACP
October 19, 2015

Conflict of Interests
- No conflict of interest to declare

Learning Objectives
1. Describe treatment options for the management of thromboembolism during pregnancy.
2. Review cardiovascular medications to avoid in pregnancy.
3. Describe the current literature for emerging cardiovascular drug therapies in pregnancy.

TREATMENT OF THROMBOEMBOLISM DURING PREGNANCY

VTE incidence during pregnancy
- VTE complicates 1 in ~1000 births
- One of the leading causes of maternal morbidity in the United States
- Greater risk of embolic complication and post-thrombotic syndrome than non-pregnant patients

Etiology
- Pregnancy
  - Increased clotting potential
  - Decreased anticoagulant activity
  - Decreased fibrinolysis
  - Increased venous stasis in lower extremities
  - Hormone-mediated increase in venous capacitance

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Anticoagulation indications

- Prevention of thrombosis during pregnancy
  - Prophylaxis against VTE
  - Prophylaxis against arterial thrombosis
- Treatment of thrombosis during pregnancy
  - Treatment of VTE during pregnancy
  - Treatment of arterial events during pregnancy
- Prevention of pregnancy loss

Pregnancy specific anticoagulation guidelines

- American Congress of Obstetricians and Gynecologists (ACOG)
- American College of Chest Physicians (ACCP)

Defined regimens

<table>
<thead>
<tr>
<th>ACOG</th>
<th>ACCP</th>
<th>Agent</th>
<th>Dose (SC administration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic LMWH</td>
<td>Prophylactic LMWH</td>
<td>Enoxaparin</td>
<td>40 mg q 24 hrs</td>
</tr>
<tr>
<td>Prophylactic LMWH</td>
<td>Enoxaparin</td>
<td>Dalteparin</td>
<td>5,000 units q 24 hrs</td>
</tr>
<tr>
<td>Prophylactic UFH</td>
<td>---</td>
<td>Preservative free UFH</td>
<td>5,000-7,500 units q 12 hrs, 1st trimester</td>
</tr>
<tr>
<td>Prophylactic UFH</td>
<td>---</td>
<td>Preservative free UFH</td>
<td>7,500-10,000 units q 12 hrs, 2nd trimester</td>
</tr>
<tr>
<td>Prophylactic UFH</td>
<td>---</td>
<td>Preservative free UFH</td>
<td>10,000 units q 12 hrs, 3rd trimester, unless aPTT elevated</td>
</tr>
<tr>
<td>Minidose prophylactic UFH</td>
<td>---</td>
<td>Preservative free UFH</td>
<td>5,000 units q 12 hrs</td>
</tr>
<tr>
<td>Minidose prophylactic UFH</td>
<td>Intermediate dose LMWH</td>
<td>Enoxaparin</td>
<td>40 mg SC q 12 hrs</td>
</tr>
<tr>
<td>Minidose prophylactic UFH</td>
<td>Intermediate dose LMWH</td>
<td>Dalteparin</td>
<td>5,000 units q 12 hrs</td>
</tr>
</tbody>
</table>

Therapeutic LMWH

<table>
<thead>
<tr>
<th>ACOG</th>
<th>ACCP</th>
<th>Agent</th>
<th>Dose (SC administration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic LMWH</td>
<td>Enoxaparin</td>
<td>1 mg/kg q 12 hrs</td>
<td></td>
</tr>
<tr>
<td>Therapeutic LMWH</td>
<td>Dalteparin</td>
<td>200 units/kg daily OR 100 units/kg q 12 hrs</td>
<td></td>
</tr>
<tr>
<td>Therapeutic LMWH</td>
<td>Tinzaparin</td>
<td>175 units daily</td>
<td></td>
</tr>
</tbody>
</table>

Therapeutic UFH

<table>
<thead>
<tr>
<th>ACOG</th>
<th>ACCP</th>
<th>Agent</th>
<th>Dose (SC administration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic UFH</td>
<td>Preservative free UFH</td>
<td>≥10,000 units q 12 hrs</td>
<td></td>
</tr>
<tr>
<td>Therapeutic UFH</td>
<td>Preservative free UFH</td>
<td>≥10,000 units q 12 hrs, aPTT target range 6 hrs after injection</td>
<td></td>
</tr>
<tr>
<td>Therapeutic UFH</td>
<td>Preservative free UFH</td>
<td>1.5-2.5</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted-dose UFH

<table>
<thead>
<tr>
<th>ACOG</th>
<th>ACCP</th>
<th>Agent</th>
<th>Dose (SC administration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted-dose UFH</td>
<td>Preservative free UFH</td>
<td>q 12 hrs</td>
<td></td>
</tr>
<tr>
<td>Adjusted-dose UFH</td>
<td>Preservative free UFH</td>
<td>q 12 hrs, mid-interval aPTT adjusted to target therapeutic range ≥2x the control</td>
<td></td>
</tr>
</tbody>
</table>

Postpartum anticoagulation

<table>
<thead>
<tr>
<th>ACOG</th>
<th>ACCP</th>
<th>Agent</th>
<th>Dose (SC administration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postpartum anticoagulation</td>
<td>LMWH, UFH, or VKA as appropriate</td>
<td>ACOP 4-6 weeks</td>
<td></td>
</tr>
<tr>
<td>Postpartum anticoagulation</td>
<td>LMWH, UFH, or VKA as appropriate</td>
<td>ACCP 6 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Acute VTE during pregnancy: ACCP 2012

- Recommend adjusted-dose SC LMWH over adjusted-dose UFH (1B)
- Anticoagulation should be continued ≥6 weeks postpartum, for minimum total duration of 3 months (2C)

Alternatives for patients experiencing HIT

- Limited data: reserve use for pregnant women with HIT or history of HIT (ACCP 2C)
  - Fondaparinux
    - Case reports or case series, did not demonstrate fetal harm
    - May cross the placenta
  - Direct thrombin inhibitors
    - Argatroban, bivalirudin, lepirudin
    - Insufficient data to evaluate safety
## ACOG recommended thromboprophylaxis

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Antepartum management</th>
<th>Postpartum management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous single VTE associated with transient risk factor that is no longer present - excludes pregnancy or estrogen-related</td>
<td>Surveillance without anticoagulation therapy</td>
<td>Postpartum anticoagulation therapy</td>
</tr>
<tr>
<td>Previous single episode of VTE associated with transient risk factor that was pregnancy- or estrogen-related</td>
<td>Prophylactic-dose LMWH or UFH</td>
<td>Postpartum anticoagulation therapy</td>
</tr>
<tr>
<td>Previous single episode of VTE without an associated risk factor (dipathic) - not on long-term anticoagulation</td>
<td>Prophylactic-dose LMWH or UFH</td>
<td>Postpartum anticoagulation therapy</td>
</tr>
<tr>
<td>Thrombophilia or no thrombophilia with ≥ 2 episodes of VTE - not receiving long-term anticoagulation</td>
<td>Therapeutic-dose LMWH or UFH</td>
<td>Resumption of long-term anticoagulation therapy</td>
</tr>
</tbody>
</table>

ACOG Practice Bulletin #138. 2013

## Anticoagulation during labor and delivery

- **Neuraxial anesthesia**
  - Used in 95% of cesarean deliveries; >60% of vaginal deliveries

- **Epidural catheter should not be inserted or removed if a patient is anticoagulated**
  - Increases risk of spinal epidural hematoma
  - May result neurological deficit or paralysis, even when surgically decompressed emergently

## Epidural catheter insertion

- **Time delay to insert catheter**
  - LMWH
    - Prophylactic: ≥12 hours since the last dose
    - Intermediate & therapeutic: ≥ 24 hours since the last dose
  - UFH
    - Once aPTT has normalized
    - Prophylactic: ~6 hours since the last dose
    - Therapeutic: ~12 hours since the last dose
    - Prophylactic UFH 5,000 units SC q 12 hours have no contraindications to neuraxial anesthesia

## Resuming anticoagulation after delivery

- **No neuraxial anesthesia**
  - Restart anticoagulation 12-24 hours following delivery if no bleeding concerns
  - Consider IV UFH if high bleed risk
  - Restart warfarin once stable, bridge with LMWH or UFH as appropriate

## Resuming anticoagulation after delivery

- **Following neuraxial anesthesia**
  - Twice daily LMWH
    - Remove catheter; 1st dose ≥ 24 hours post op
  - Once daily LMWH
    - Catheter may be maintained; 1st dose 6-8 hours post op
    - Remove catheter no sooner than 10-12 hours after LMWH dose
  - After removing catheter wait ≥ 2 hrs before giving the next dose

---

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CARDIOVASCULAR MEDICATIONS TO AVOID IN PREGNANCY

### Anticoagulants

<table>
<thead>
<tr>
<th>Use</th>
<th>Class</th>
<th>Agent</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid</td>
<td>Warfarin</td>
<td></td>
<td>1st trimester: ↑ risk of malformation 2nd &amp; 3rd trimester: ↑ risk of CNS abnormalities</td>
</tr>
<tr>
<td></td>
<td>Direct thrombin inhibitors</td>
<td>Apixaban</td>
<td>Limited data to evaluate safety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rivaroxaban</td>
<td>Cross or likely to cross the placenta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dabigatran</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Edoxaban</td>
<td></td>
</tr>
<tr>
<td>Caution</td>
<td>Indirect Xa inhibitor</td>
<td>Fondaparinux</td>
<td>Limited data to evaluate safety</td>
</tr>
<tr>
<td></td>
<td>Direct thrombin inhibitors</td>
<td>Argatobran</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bivalirudin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lepirudin</td>
<td></td>
</tr>
<tr>
<td>Preferred</td>
<td>LMWH</td>
<td></td>
<td>Does not cross placenta</td>
</tr>
<tr>
<td></td>
<td>U4H</td>
<td></td>
<td>No demonstrated fetal harm</td>
</tr>
</tbody>
</table>

### Antiplatelet agents

<table>
<thead>
<tr>
<th>Use</th>
<th>Class</th>
<th>Agent</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid or Caution</td>
<td>Salicylate</td>
<td>Aspirin</td>
<td>Crosses placenta • Dose dependent increased risk of: premature ductus arteriosus closure near delivery • fetal mortality, intrauterine growth retardation, pulmonary hypertension</td>
</tr>
<tr>
<td>Caution</td>
<td>P2Y12 receptor blockers</td>
<td>Clopidogrel Prasugrel Ticagrelor Ticlopidine</td>
<td>No evidence of fetal toxicity in animal studies • Limited human studies</td>
</tr>
</tbody>
</table>

### Chronic antihypertensives

<table>
<thead>
<tr>
<th>Use</th>
<th>Class</th>
<th>Agent</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>Beta-blocker</td>
<td>Labetalol</td>
<td>Possible preservation of uteroplacental blood flow, both alpha and beta adrenergic blocking activity • Demonstrated long-term safety for fetus</td>
</tr>
<tr>
<td></td>
<td>Calcium Channel Blocker</td>
<td>Nifedipine</td>
<td>Demonstrated long-term safety for fetus</td>
</tr>
<tr>
<td></td>
<td>Alpha, adrenergic agonist</td>
<td>Methyldopa</td>
<td>Demonstrated long-term safety for fetus</td>
</tr>
</tbody>
</table>

### Chronic antihypertensives

<table>
<thead>
<tr>
<th>Use</th>
<th>Class</th>
<th>Agent</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid</td>
<td>ACEI/ARB All agents in this class</td>
<td></td>
<td>↑ risk of fetal morbidity and mortality • Documented risk in all trimesters, especially 2nd &amp; 3rd trimester</td>
</tr>
<tr>
<td>Caution</td>
<td>Calcium Channel Blockers All agents excluding nifedipine</td>
<td></td>
<td>Limited data to evaluate safety</td>
</tr>
<tr>
<td></td>
<td>Diuretics: Thiazide, Loop, &amp; Potassium-sparing All agents in this class</td>
<td></td>
<td>Limited data to evaluate safety • Possible volume depletion • Thiazide potassium-sparing cross placenta</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers All agents excluding labetalol</td>
<td></td>
<td>Reports of fetal growth restriction (especially atenolol), bradycardia, hypoglycemia, neonatal apnea</td>
</tr>
<tr>
<td></td>
<td>Alpha, adrenergic agonist</td>
<td>Clonidine</td>
<td>Rebound hypertension if stopped abruptly • Less data available than methyldopa</td>
</tr>
<tr>
<td></td>
<td>Vasodilator</td>
<td>Hydralazine</td>
<td>Reflex tachycardia, fluid retention • No demonstrated fetal adverse effects</td>
</tr>
</tbody>
</table>

### Anti-hyperlipidemia agents

<table>
<thead>
<tr>
<th>Use</th>
<th>Class</th>
<th>Agent</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid</td>
<td>HMG CoA reductase inhibitors All agents in this class</td>
<td></td>
<td>Maternally toxic doses associated with adverse fetal outcomes • Inadvertent exposure unlikely to increase adverse outcomes • Lack of treatment benefit during gestation</td>
</tr>
<tr>
<td>Caution</td>
<td>Fibrates All agents in this class</td>
<td></td>
<td>Animal studies demonstrate adverse fetal effects • Limited human data</td>
</tr>
<tr>
<td></td>
<td>Nicotinic acid All agents in this class</td>
<td></td>
<td>Limited data to evaluate safety • No adverse effects reported with normal daily recommended dose</td>
</tr>
<tr>
<td>Preferred</td>
<td>Bile acid sequesterant All agents in this class</td>
<td></td>
<td>Limited data to evaluate safety • No documented fetal harm</td>
</tr>
</tbody>
</table>
CURRENT LITERATURE FOR EMERGING CARDIOVASCULAR DRUG THERAPIES IN PREGNANCY

Emerging Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct oral anticoagulants</td>
<td>Pradaxa®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Xarelto®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eliquis®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Savaysa®</td>
<td></td>
</tr>
<tr>
<td>PCSK9 inhibitors</td>
<td>Praluent®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Repatha®</td>
<td></td>
</tr>
<tr>
<td>Heart failure agents</td>
<td>Corlanor®</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Entresto®</td>
<td></td>
</tr>
</tbody>
</table>

Pregnancy data for emerging cardiovascular agents

- Animal reproduction studies required for FDA approval
  - Typically compared to maximum recommended human dose (MRHD)
  - Available in agent package insert
  - Section 8
- No human controlled trials
  - Limited case reports, case series

Summary of potential adverse effects in pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Animal Data</th>
<th>Human Data</th>
<th>Preg Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crosses placenta</td>
<td>Embryo or fetal demise</td>
<td>Malformation</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Y</td>
<td>None at ≤ 8x MRHD</td>
<td>None at ≤ 8x MRHD</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Y</td>
<td>≥ 2.6x MRHD</td>
<td>≥ 2.6x MRHD</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>?</td>
<td>≥ 20x MRHD</td>
<td>≥ 49x MRHD</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Y</td>
<td>≥ 4x MRHD</td>
<td>N</td>
</tr>
</tbody>
</table>

Summary of potential adverse effects in pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Animal Data</th>
<th>Human Data</th>
<th>Preg Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crosses placenta</td>
<td>Embryo or fetal demise</td>
<td>Malformation</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>Y</td>
<td>None at ≤ 81x MRHD</td>
<td></td>
</tr>
<tr>
<td>Evolocumab</td>
<td>Y</td>
<td>None at ≤ 30x MRHD</td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Y</td>
<td>≥ 1-5x MRHD</td>
<td>1-3x MRHD</td>
</tr>
<tr>
<td>Sacubitril/Valsartan</td>
<td>ACEI/ARBs in 2nd &amp; 3rd trimester of human pregnancy are associated w/fetal renal damage, skull defects, oligohydramnios, &amp; fetal death.</td>
<td>No Sacubitril data available</td>
<td>ARBs</td>
</tr>
</tbody>
</table>

References

References