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

2015 ACCP Global Conference on Clinical Pharmacy

Preconception Health
Erin Raney, Pharm.D., BCPS, BC-ADM
October 19, 2015

Conflict of Interest

- No conflicts of interest to disclose

Learning Objectives

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- Explain what supplements, immunizations, and other medications are needed for women preconception and during pregnancy
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- 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)

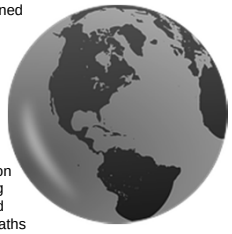
http://www.who.int/maternal_child_adolescent/documents/concensus_preconception_care/en/

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

http://www.who.int/maternal_child_adolescent/documents/preconception_care_policy_brief.pdf

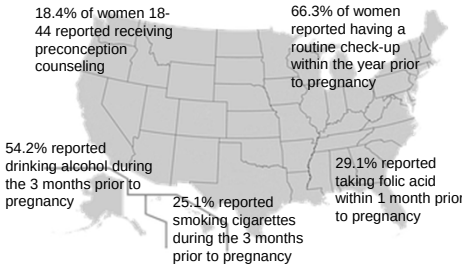
World Health Organization

Preconception Care Package

Nutrition	Tobacco Use	Genetic Conditions
Environmental Health	Infertility	Interpersonal Violence
Interpregnancy Interval	Sexually Transmitted Infections/HIV	Mental Health
Substance Abuse	Vaccine-Preventable Diseases	Female Genital Mutilation

http://www.who.int/maternal_child_adolescent/documents/preconception_care_policy_brief.pdf

U.S. Health Indicators



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

National Initiative on Preconception Health and Health Care (PCHHC)

http://www.cdc.gov/preconception/documents/ActionPlanNationalInitiativePCHHC2012-2014.pdf

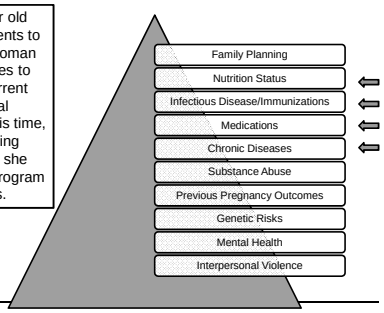
Clinical Toolkit

- 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

http://beforeandbeyond.org/toolkit/

Clinical Toolkit

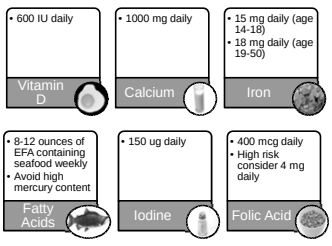
T.R. is a 30 year old woman who presents to clinic for a well-woman exam. She wishes to continue her current combined oral contraceptive at this time, but is considering pregnancy after she finishes an MBA program in 18 months.



http://beforeandbeyond.org/toolkit/

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.



http://beforeandbeyond.org/toolkit/

Weight Assessment

Underweight BMI	Normal BMI	Overweight BMI	Obese BMI
• Assess risks for eating disorders • Review impact on preterm birth, low birth weight	• Encourage weight maintenance and physical activity	• Counsel on long term health risks • Encourage weight loss • Consider pregnancy risk with medications for weight loss	• Same as overweight BMI • Consider lower efficacy of certain contraceptives

T.R.'s BMI is 26.4 kg/m^2 which has decreased from 28.2 kg/m^2 2 years prior.

http://beforeandbeyond.org/toolkit/

Immunizations

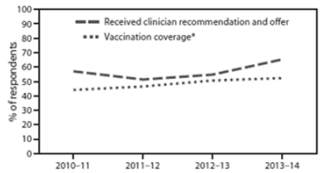
Avoid During Pregnancy	• MMR • Varicella/Zoster • Influenza LAIV • HPV
Give Only if Indicated	• Hepatitis A, B • Meningococcal conjugate/polysaccharide • Pneumococcal polysaccharide • Polio
Give During Pregnancy	• Influenza (IIV) • Tdap

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

FIGURE. Prevalence of clinician recommendation and offer of influenza vaccination and influenza vaccination coverage before and during pregnancy among women pregnant any time during October–January — Internet panel survey, United States, 2010–11 through 2013–14 influenza seasons



* Vaccination coverage estimates for the 2012–13 and 2013–14 influenza seasons were based on vaccinations given from July to mid-April. Coverage estimates for the 2010–11 and 2011–12 influenza seasons were based on vaccinations given from August to mid-April.

Influenza immunization trends

MMWR 2014;63(7):816-21

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 poor[1,2]
  - 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

Medication Safety

4.2	• Average number of medications used anytime in pregnancy in 2006-2008 in the Boston University Sloane Epidemiology Study, compared with 2.5 in 1976-1978[1]
93.9%	• Number of women reporting use of at least one medication during pregnancy in the 2006-2008 cohort of the Boston University Sloane Epidemiology Study[1]
9.4%	• Percentage of women reporting use of an herbal product during pregnancy[2] • 6.9% used an herbal product in the first trimester

[1]Am J Obstet Gynecol 2011;205(1):51.e1-51.e8
[2]Am J Obstet Gynecol 2010;202(5):443.e1-443.e6

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

http://federalregister.gov/a/2014-28241

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"

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

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.

Medication Safety

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 to inform any drug associated risks…Teratogenic effects were observed in animal reproduction studies following administration of rifaximin to pregnant rats and rabbits at approximately 0.9 to 5 times and 0.7 to 33 times, respectively of the recommended human doses…"

Xifaxan [package insert]. Raleigh, NC: Salix Pharmaceuticals; 5/2015.
Dicyclomine [package insert]. Eatontown, NJ: West-ward Pharmaceuticals; 9/2008.

Chronic Diseases

- General approaches to select conditions associated with maternal morbidity
  - Hypertension
  - Diabetes
  - Epilepsy
  - Asthma

Hypertension

- Uncontrolled chronic hypertension during pregnancy is associated with higher rates of cesarean delivery, gestational diabetes, postpartum hemorrhage, and preeclampsia
- Preconception care
  - Provide contraceptive counseling to women of childbearing age taking ACE inhibitors, angiotensin receptor blockers (ARBs), aliskiren, or spironolactone
  - Discontinue above agents and replace with safer alternative prior to pregnancy if possible
  - Antihypertensive medications with the most safety data during pregnancy: methyldopa, labetolol, nifedipine

Obstetrics and Gynecology 2013;122(5):1122-1131

Diabetes

- Poor glycemic control is associated with many adverse pregnancy outcomes, including macrosomia, premature birth, stillbirth, and preeclampsia
- Preconception care
  - Optimize weight and glycemic control
  - Consider teratogenicity of other diabetes-related medications (statins, ACE inhibitors/ARBs) and need for contraceptive planning
  - If planning pregnancy, consider proactive switch to insulin or antidiabetic medication with more data in pregnancy

Diabetes Care 2015;38(Suppl. 1):S77–S79

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 folic acid supplementation (e.g., 4-5 mg/day)

Epilepsia 2009;50:1237-1246

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

Obstet Gynecol 2008;111(2):457-464

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

- Centers for Disease Control and Prevention. Recommendations to improve preconception health and health care—United States. MMWR Recommendations and Reports. 2006;55(RR-06):1–23.
- Jack BW, Atrash HK, Coonrod DV, et al. The clinical content of preconception care: an overview and preparation of this supplement. Am J Obstet Gynecol 2008;199 (Suppl 2):S266-279.
- Moos M-K. From concept to practice: reflections on the preconception health agenda. J Womens Health 2010;19(3):561-7.
- Preconception interventions Reproductive Health 2014;11 (suppl 3). Available at http://www.reproductive-health-journal.com/supplements/11/S3?utm_source=PCHHC+Nov+2014+Newsletter&utm_campaign=PCHHC+Nov+2014&utm_medium=email
- Before, Between and Beyond Pregnancy (http://beforeandbeyond.org/)
- CDC (http://www.cdc.gov/preconception/index.html)
- CDC "Show Your Love" Campaign http://www.cdc.gov/preconception/showyourlove/index.html

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Self-Care for Common Concerns in Pregnancy

Kassandra Bartelme, Pharm.D., BCACP

October 19, 2015

Conflict of Interests

- I have no conflicts to disclose.

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.

SUBSTANCE USE

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)

CARE Study Group. BMJ 2008;337:a2332.
Committee Opinion No. 462. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2010;116:467-8.
Jarosz M, et. al. *Eur J Obstet Gyn R B.* 2012;160:156-160.
Li D-K, et. al. *Int J Obesity.* 2015;39:658-664.
MotherToBaby Fact Sheet. Organization of Teratology Information Specialists. http://www.mothertobaby.org/files/caffeine.pdf. Accessed July 15, 2015.

Caffeine

Average Amounts of Caffeine		
Coffee, 8 oz.		137 mg
Tea, 8 oz.	brewed: instant:	48 mg 26-36 mg
Caffeinated soft drinks, 12 oz.		37 mg
Red Bull energy drink, 8.4 oz.		80 mg
Excedrin, 2 tablets		130 mg
Coffee ice cream, 1 cup		58 mg

Committee Opinion No. 462. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2010;116:467-8.
MotherToBaby Fact Sheet. Organization of Teratology Information Specialists. http://www.mothertobaby.org/files/caffeine.pdf. Accessed July 15, 2015.

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

Andersen AN, et. al. *Int J Epidemiol.* 2012;41:405-413.
Carter RC, et. al. *Alcohol Clin Exp Res.* 2012;36(11):1973-1982.
MotherToBaby Fact Sheet. Organization of Teratology Information Specialists. http://www.mothertobaby.org/files/Alcohol.pdf. Accessed July 15, 2015.
U.S. Surgeon General's Advisory on Alcohol Use in Pregnancy. 2005. http://come-over.to/FAS/SurGenAdvisory.htm. Accessed July 15, 2015.

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

Women who use tobacco	Babies exposed to tobacco
Have twice the risk for: -delay in contraception -ectopic pregnancy -premature rupture of membranes -placental abruption -placenta previa	Are more likely to be or to have: -premature -low birth weight* -small for gestational age -born with cleft palate or lip -higher risk for SIDS* -elevated levels of hyperactivity/inattention

*also applies to second-hand smoke exposure

American College of Obstetrics and Gynecology. http://www.acog.org/Patients/FAQs/Tobacco-Alcohol-Drugs-and-Pregnancy. Accessed July 1, 2015.
Centers for Disease Control and Prevention. http://www.cdc.gov/reproductivehealth/TobaccoUsePregnancy/Providers.html. Accessed July 13, 2015.
Melchior M, et. al. *Eur Psychiat.* 2015;30:562-568.

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

Committee Opinion No. 637. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2015;126:234-8.
MotherToBaby Fact Sheet. Organization of Teratology Information Specialists. http://www.mothertobaby.org/files/marijuana.pdf. Accessed Aug. 10, 2015.

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)

SELF-CARE TREATMENT OPTIONS FOR COMMON COMPLAINTS DURING PREGNANCY

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

Einarson TR, et. al. *J Popul Ther Clin Pharmacol.* 2013;20(2):e163-e170.
Herrell HE. *Am Fam Physician.* 2014;89(12):965-970.

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)
  - +/- Doxylamine
  - +/- other H_1 – receptor blockers
- Ginger
- Woman's perception of the severity of her symptoms plays a role in the decision of when and how to treat

Niebyl JR, Briggs GG. *J Fam Practice*. 2014;63(2):S31-S37.
Practice Bulletin Summary No. 153. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2015;3:687-8.

First Line of Therapy for NVP

Vitamin B6 (pyridoxine)	Doxylamine

▪ 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
	▪ 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

Badell ML, et. al. *Pharmacotherapy*. 2006;26(9):1273-1287.
Clarke SM, et. al. *Semin Perinatol*. 2014;38:496-502.
Herrell HE. *Am Fam Physician*. 2014;89(12):965-970.
Niebyl JR, Briggs GG. *J Fam Practice*. 2014;63(2):S31-S37.
Practice Bulletin Summary No. 153. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2015;3:687-8.

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

American College of Obstetrics and Gynecology. http://www.acog.org/Patients/FAQs/Morning-Sickness. Accessed July 1, 2015.
Badell ML, et. al. *Pharmacotherapy*. 2006;26(9):1273-1287.
Clarke SM, et. al. *Semin Perinatol*. 2014;38:496-502.
Herrell HE. *Am Fam Physician*. 2014;89(12):965-970.
Practice Bulletin Summary No. 153. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2015;3:687-8.
Tiran D. *Brit J Midwifery*. 2014;22(8):544-550.

Constipation

- 2nd to nausea 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 (eg. IBD)

American Gastroenterological Association. *Gastroenterology*. 2006;131:278-282.
Cullen G, O'Donoghue. *Best Pract Res Clin Ga*. 2007;21(5):807-818.
Trottier M, et. al. *Can Fam Physician*. 2012;58:836-838.
Verghese TS, et. al. *The Obstetrician & Gynaecologist*. 2015;17:111-5
Zielinski R, et. al. *J Perinat Neonat Nurs*. 2015;29(1):23-31.

Self-care Treatment for Constipation

- Non-pharmacologic treatments
  - Increase exercise, dietary fiber and fluid intake
- Pharmacologic treatments

Class	Examples	Side Effects	Notes
Bulk-forming agents	Psyllium (Metamucil®), wheat dextrin (Benefiber®)	Bloating, cramping, flatulence	Delay to benefit (few days), minimal benefit
Osmotic laxatives	**Polyethylene glycol (PEG),** lactulose, sorbitol	Flatulence, abdominal bloating	Prolonged use may lead to electrolyte imbalance
Stool softener	Docusate	Abdominal cramps, diarrhea	Short-term use only
Stimulant laxatives	Bisacodyl, senna	Abdominal cramps, diarrhea	Short-term use only

American Gastroenterological Association. *Gastroenterology*. 2006;131:278-282.
Cullen G, O'Donoghue. *Best Pract Res Clin Gastroenterol*. 2007;21(5):807-818.
Trottier M, et. al. *Can Fam Physician*. 2012;58:836-838.
Verghese TS, et. al. *The Obstetrician & Gynaecologist*. 2015;17:111-5
Zielinski R, et. al. *J Perinat Neonat Nurs*. 2015;29(1):23-31.

Fatigue

- Most common during 1st trimester, often returns in 3rd trimester
- Recommendations
  - Rest
  - Eat well
  - Exercise regularly
  - Ask for support
  - Avoid taking on extra responsibilities
- 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

Harms RW. *Mayo clinic: Guide to a healthy pregnancy*. New York, NY. Harper Collins Publishers, Inc. 2011.

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

Ali RAR, Egan LJ. *Best Pract Res Clin Gastroenterol.* 2007;21(5):793-806.
Gill SK, et. al. *Am J Gastroenterol.* 2009;104:1541-1545.
Law R, et. al. *Can Fam Physician.* 2010;56:143-144.

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
- H_2 receptor antagonists
  - Ranitidine, cimetidine, famotidine, nizatidine
- Proton-pump inhibitors (PPIs)
  - Omeprazole, lansoprazole

Ali RAR, Egan LJ. *Best Pract Res Clin Gastroenterol.* 2007;21(5):793-806.
Gill SK, et. al. *Am J Gastroenterol.* 2009;104:1541-1545.
Law R, et. al. *Can Fam Physician.* 2010;56:143-144.

Rhinitis

- "vasomotor rhinitis of pregnancy" or "pregnancy rhinitis"
- Up to 35% of women have significant rhinitis symptoms during pregnancy
  - May impact gestational nutrition, sleep, or stress
  - May cause snoring or an increased risk for sinusitis
- Definition: symptoms last 6 weeks or longer without other signs of respiratory tract infection, no known allergic cause and disappears completely within 2 weeks after delivery
- Referral recommended if:
  - Symptoms of sinusitis
  - Severe headaches

Namazy JA, Schatz M. *Mt Sinai J Med.* 2011;78:661-670.

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

Namazy JA, Schatz M. *Mt Sinai J Med.* 2011;78:661-670.

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

Hoyte FCL, Katial RK. *Immunol Allergy Clin N Am.* 2011;31:509-543.
Namazy JA, Schatz M. *Mt Sinai J Med.* 2011;78:661-670.
Wallace, et. al. *J Allergy Clin Immunol.* 2008;122:S1-84.

Self-Assessment Question

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

Complaint	First line therapy
Nausea/vomiting of pregnancy	Pyridoxine (vitamin B6) +/- doxylamine
Constipation	Polyethylene glycol (PEG)
Fatigue	Rest, exercise, eating healthy
Acid reflux	Antacids (calcium, aluminum, magnesium)
Pregnancy rhinitis	Oxymetazoline, pseudoephedrine
Allergic rhinitis	Chlorpheniramine, loratadine, cetirizine

2015 ACCP Global Conference on Clinical Pharmacy

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

Conflict of Interests

- No Conflicts of Interest to Disclose

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

Behnke M et al. Pediatrics 2013;131:e1009-24

Neonatal Abstinence Syndrome (NAS)

W	wakefulness
I	irritability
T	tremors, twitching, tachypnea
H	hyperventilation, hypertonia, hyperpyrexia, hyperacusis, hiccups
D	diarrhea, diaphoresis
R	rub marks
A	alkalosis
W	weight loss
A	apnea
L	lacrimation
S	seizures, sneezing, skin mottling

Rates are increasing!
-2004: 7 cases per 1000 admission (0.6%)
-2013: 27 cases per 1000 admissions (4%)
-Admission length mean 19 days

Tolia VN et al. N Engl J Med 2015;372:

Limitations to Studies

Pregnancy/Fetal Outcomes

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

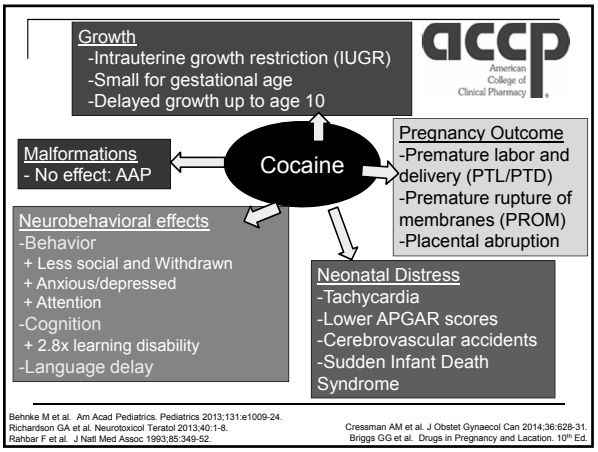
Child Neurobehavioral Factors

- 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)

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*

Cressman AM et al. J Obstet Gynaecol Can 2014;36:628-31
Briggs GG et al. Drugs in Pregnancy and Lacation. 10th Ed
Bingol N et al. J Pediatr 1987;110:93-6
Behnke M et al. Pediatrics 2013;131:e1009-24



Behnke M et al. Am Acad Pediatrics. Pediatrics 2013;131:e1009-24.
Richardson GA et al. Neurotoxicol Teratol 2013;40:1-8.
Rahbar F et al. J Natl Med Assoc 1993;85:349-52.
Cressman AM et al. J Obstet Gynaecol Can 2014;36:628-31.
Briggs GG et al. Drugs in Pregnancy and Lacation. 10th Ed.

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*

Golub M et al. Birth Def Res 2005;74:471-584.
Smith LM et al. Neurotoxicol Teratol 2008;30:20-8.
Chang L et al. Psychiatr Res 2004;132:95-106.
Briggs GG et al. Drugs in Pregnancy and Lacation. 10th Ed.
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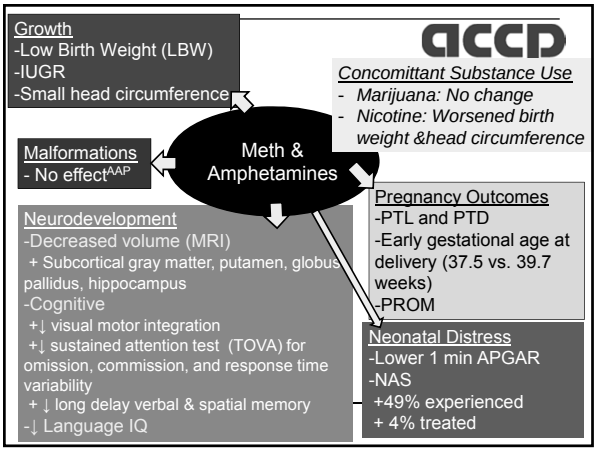


Bath Salts

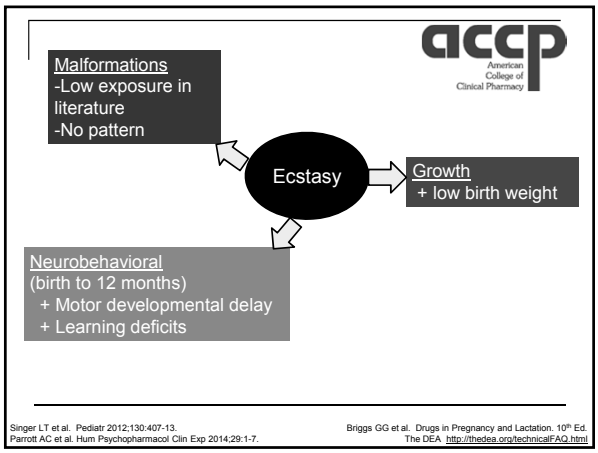
- Phenethylamine class
  - Khat plant--Cathinones and methcathinones
  - Synthetic versions
  - *Molecular weight: 275*
- No pregnancy data
- Khat data
  - Vasoconstriction -- ↓ uterine blood flow
    - IUGR, LBW, cardiovascular effects
  - Neonatal Withdrawal and ↓ APGAR scores
  - Case Report: hypertension, chest pain, tachycardia
  - Cohort: Maternal anemia and ↓ appetite

Kedir H et al. PLoS One 2013;8:e78601.
Gray BA et al. Nurs Women Health 2014;18:220-30.
DEA http://www.deadiversion.usdoj.gov/drug_chem_info/mdpv.pdf
Kuczkowski KM. Acta Anaesthesiol Belg 2005;56:19-21.

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)*

Singer LT et al. Pediatr 2012;130:407-13.
Parrott AC et al. Hum Psychopharmacol Clin Exp 2014;29:1-7.
Briggs GG et al. Drugs in Pregnancy and Lactation. 10th Ed.
The DEA http://thedea.org/technicalFAQ.html



Singer LT et al. Pediatr 2012;130:407-13.
Parrott AC et al. Hum Psychopharmacol Clin Exp 2014;29:1-7.
Briggs GG et al. Drugs in Pregnancy and Lactation. 10th Ed.
The DEA http://thedea.org/technicalFAQ.html

Treatment for Non-Opioid Use

Cochrane Review

- Psychosocial intervention (n=14)
- Contingency management interventions (n=9)
- Motivational interviewing based interventions (n=5)

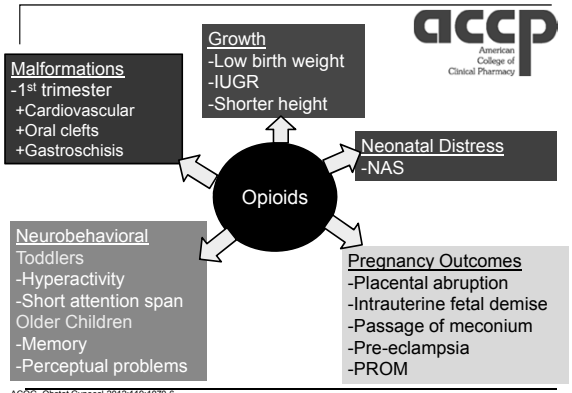
No Difference
- Pre-term delivery
- Maternal toxicity at delivery
- Low birth weight
- End of study retention or maternal abstinence

Contingency management
- Shorter infant hospital stay

Terplan M et al. Cochrane Database Syst Rev. 2015 Apr 2:4:CD006037

Opioids

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



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Broussard et al. Am J Obstet Gynecol 2011;204:314.e1-11.
SAHMSA/CSAT treatment improvement protocols. 2008.
Hudak et al. Pediatrics 2012;129:e540.

Opioid Treatment Options

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

3rd Option: Naltrexone once monthly
Not recommended in PG

Methadone vs. Buprenorphine

PROMISE
Opioid addicted patients 16-30 weeks
(Stabilized on morphine)

Buprenorphine	Methadone
(n=15, 9 completed)	(n=15, 11 completed)
Target dose 12 mg/d	Target dose 60 mg/d

NAS EVALUATION/TREATMENT
Hospital: 6-8 times per day
Research center: 2 times per day
-At least 10 days after birth

Jones HE et al. Drugs Alcohol Depend 2005:79;1-10.

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

Jones HE et al. N Engl J Med 2010;363:2320-31.

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

Wiegand SL et al. Obstet Gynecol 2015;125:363-8.

Methadone vs. Buprenorphine

	Promise (n=30)			Mother (n=175)			Bup/Nal vs. Meth (n=62)		
	Meth	Bup	p-value	Meth	Bup	p-value	Meth	Bup/ Nal	p-value
NAS treated	45.5%	20%	NS	57%	47%	NS	**51.6%**	**25.1%**	**0.01**
Total Morphine	1.9mg	0.4mg	NS	**10.4 mg**	**1.1 mg**	**0.0091**	5	3.4	NS
Hospital stay	**8.1d**	**6.8d**	**0.021**	**17.5 d**	**10d**	**0.0091**	11.4d	10.6d	NS
GA at delivery	38.8	38.8	NS	**37.9**	**39.1**	**0.007**	**38.1**	**39.7**	**0.01**
NAS duration	**8.1d**	**6.8d**	**0.021**	**9.9d**	**4.1d**	**0.0091**	**9.8d**	**5.6d**	**0.02**

Meth = methadone
Bup = Buprenorphine
Nal = Naloxone
GA = gestational age

Jones HE et al. Drugs Alcohol Depend 2005:79;1-10.
Jones HE et al. N Engl J Med 2010;363:2320-31.
Wiegand SL et al. Obstet Gynecol 2015;125:363-8.

WISH Clinic

Specialty High Risk Interdisciplinary Clinic

- Maternal Fetal Medicine Specialist
- Pharmacist
- Nurse Practitioners
- Social Worker
- RN (Lactation, Coordinating)
- Neonatologist
- Sonographers

Pharmacist Role

- 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 (≥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

2015 ACCP Global Conference on Clinical Pharmacy

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

Chang et al. *Morb Mortal Wkly Rep* 2003
ACOG *Practice Bulletin #138.* 2013
Wik et al. *J Thomb Haemost* 2012

Etiology

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

ACOG *Practice Bulletin #138.* 2013

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)
  - Practice Bulletin #138. Inherited thrombophilias in pregnancy. September 2013.
- American College of Chest Physicians (ACCP)
  - Bates et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. Chest. 2012.

Defined regimens

ACOG	ACCP	Agent	Dose (SC administration)
Prophylactic LMWH	Prophylactic LMWH	Enoxaparin	40 mg q 24 hrs
		Dalteparin	5,000 units q 24 hrs
		Tinzaparin	4,500 units q 24 hrs
Prophylactic UFH	----	Preservative free UFH	5,000-7,500 units q 12 hrs, 1st trimester
			7,500-1,0000 units q 12 hrs, 2nd trimester
			10,000 units q 12 hrs, 3rd trimester, unless aPTT elevated
Minidose prophylactic UFH	----	Preservative free UFH	5,000 units q 12 hrs
----	Intermediate -dose LMWH	Enoxaparin	40 mg SC q 12 hrs
		Dalteparin	5,000 units q 12 hrs

Defined regimens

ACOG	ACCP	Agent	Dose (SC administration)
Therapeutic LMWH	Adjusted-dose LMWH	Enoxaparin	1 mg/kg q 12 hrs
		Dalteparin	200 units/kg daily OR 100 untis/kg q 12 hrs
		Tinzaparin	175 units/kg daily
Therapeutic UFH	----	Preservative free UFH	≥10,000 units q 12 hrs • aPTT target range 6 hrs after injection • 1.5-2.5
----	Adjusted-dose UFH	Preservative free UFH	q 12 hrs • mid-interval aPTT adjusted to target therapeutic range ≥ 2x the control
Postpartum anticoagulation		LMWH, UFH, or VKA as appropriate	• ACOG 4-6 weeks • ACCP 6 weeks

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)

Bates et al. *Chest Guidelines*, 9th ed. 2012

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

Bates et al. *Chest Guidelines*, 9th ed. 2012

ACOG recommended thromboprophylaxis

Clinical Scenario	Antepartum management	Postpartum management
Previous single VTE associated with transient risk factor that is no longer present - excludes pregnancy or estrogen-related factor	Surveillance without anticoagulation therapy	Postpartum anticoagulation therapy
Previous single episode of VTE associated with transient risk factor that was pregnancy- or estrogen-related	Prophylactic-dose LMWH or UFH	Postpartum anticoagulation therapy
Previous single episode of VTE without an associated risk factor (idiopathic) - not on long-term anticoagulation	Prophylactic-dose LMWH or UFH	Postpartum anticoagulation therapy
Thrombophilia or no thrombophilia with ≥ 2 episodes of VTE - not receiving long-term anticoagulation	Prophylactic or therapeutic-dose LMWH or UFH	Postpartum anticoagulation therapy, OR therapeutic LMWH/UFH for six weeks
Thrombophilia or no thrombophilia with ≥ 2 episodes of VTE - Receiving long-term anticoagulation	Therapeutic-dose LMWH or UFH	Resumption of long-term anticoagulation therapy

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

Anticoagulation during labor and delivery

Delivery	Approach	Anticoagulation plan

Spontaneous labor	Unscheduled discontinuation	• Instruct pt to stop anticoagulation at onset of labor
		  • Change LMWH to UFH at 36 wga
		  • OR, continue LMWH
		• Assess heparin levels during labor and delivery if needed

Induction of labor or Caesarean	Scheduled discontinuation	• Discontinue prophylactic LMWH doses 12-24 hours prior • Discontinue treatment LMWH doses 24-36 hours prior
	Conversion due to VTE in past 4 weeks	• Wait 10 hrs after last LMWH dose to initiate IV UFH

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

Bates et al. *Chest Guidelines*, 9th ed. 2012

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

Horlocker TT et al. *Reg Anesth Pain Med* 2010

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

Horlocker TT et al. *Reg Anesth Pain Med* 2010

CARDIOVASCULAR MEDICATIONS TO AVOID IN PREGNANCY

Anticoagulants

Use	Class	Agent	Details
Avoid	Vitamin K antagonist	Warfarin	• 1st trimester: ↑ risk of malformation • 2nd & 3rd trimester: ↑ risk of CNS abnormalities • ↑ risk of miscarriage, fetal anticoagulation
	Direct oral anti-coagulants	Apixaban Rivaroxaban Dabigatran Edoxaban	• Limited data to evaluate safety • Cross or likely to cross the placenta
Caution	Indirect Xa inhibitor	Fondaparinux	• Limited data to evaluate safety
	Direct thrombin inhibitors	Argatroban Bivalirudin Lepirudin	
Preferred	LMWH	See previous slides	• Does not cross placenta • No demonstrated fetal harm
	UFH		

Antiplatelet agents

Use	Class	Agent	Details

Avoid or Caution	Salicylate	Aspirin	• Crosses placenta
			• Dose dependent increased risk of:
			  • premature ductus arteriosus closure near delivery
			  • fetal mortality, intrauterine growth retardation, pulmonary hypertension

Caution	P2Y12 receptor blockers	Cangrelor Clopidogrel Prasugrel Ticagrelor Ticlopidine	• No evidence of fetal toxicity in animal studies • Limited human studies

Chronic antihypertensive agents

Use	Class	Agent	Details
Preferred	Beta-blocker	Labetalol	• Possible preservation of uteroplacental blood flow, both alpha and beta adrenergic blocking activity. • Demonstrated long-term safety for fetus
	Calcium Channel Blocker	Nifedipine	• Demonstrated long-term safety for fetus
	$Alpha_2$ adrenergic agonist	Methyldopa	

Chronic antihypertensives

Use	Class	Agent	Details
Avoid	ACEI/ARB	All agents in this class	• ↑ risk of fetal morbidity and mortality • Documented risk in all trimesters, especially 2nd & 3rd trimester
Caution	Calcium Channel Blockers	All agents excluding nifedipine	• Limited data to evaluate safety
	Diuretics: Thiazide, Loop, & Potassium-sparing	All agents in this class	• Limited data to evaluate safety • Possible volume depletion • Thiazide, potassium-sparing cross placenta
	Beta-blockers	All agents excluding labetalol	• Reports of fetal growth restriction (especially atenolol), bradycardia, hypoglycemia, neonatal apnea
	$Alpha_2$ adrenergic agonist	Clonidine	• Rebound hypertension if stopped abruptly • Less data available than methyldopa
	Vasodilator	Hydralazine	• Reflex tachycardia, fluid retention • No demonstrated fetal adverse effects

Anti-hyperlipidemia agents

Use	Class	Agent	Details
Avoid	HMG Co-A reductase inhibitors	All agents in this class	• Maternally toxic doses associated with adverse fetal outcomes • Inadvertent exposure unlikely to increase adverse outcome • Lack of treatment benefit during gestation
Caution	Fibrates	All agents in this class	• Animal studies demonstrate adverse fetal effects • Limited human data
	Nicotinic acid	All agents in this class	• Limited data to evaluate safety • No adverse effects reported with normal daily recommended dose
Preferred	Bile acid sequesterant	All agents in this class	• Limited data to evaluate safety • No documented fetal harm

CURRENT LITERATURE FOR EMERGING CARDIOVASCULAR DRUG THERAPIES IN PREGNANCY

Emerging Agents

Class	Medication	Brand name
Direct oral anticoagulants	Dabigatran Rivaroxaban Apixaban Edoxaban	Pradaxa® Xarelto® Eliquis® Savaysa®
PCSK9 inhibitors	Alirocumab Evolocumab	Praluent® Repatha®
Heart failure agents	Ivabradine Sacubitril/Valsartan	Corlanor® Entresto®

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

Drug	Animal Data				Human Data	Preg Cat.
	Crosses placenta	Embryo or fetal demise	Malformation	Bleeding w/fetal death at delivery		
Apixaban	Y	?	N	**None** at ≤ 5x MRHD	None	B
Dabiga-tran	Y	≥ 2.6x MRHD	≥ 2.6x MRHD	≥ 2.6x MRHD	None	C
Edoxaban	?	≥ 20x MRHD	≥ 49x MRHD	?	Case reports n=10	C
Rivaroxa-ban	Y	≥ 4x MRHD	N	≥ 6x MRHD	Case series n=64	C

Information obtained from Package Insert(s); Hoeltzenbein et al. *Clin Res Cardiol*. 2015

Summary of potential adverse effects in pregnancy

Drug	Animal Data				Human Data	Preg Cat.
	Crosses placenta	Embryo or fetal demise	Malformation	Other		
Alirocu-mab	Y	**None** at ≤ 81x MRHD	**None** at ≤ 81x MRHD	Fetal immune suppression ≥13x MRHD	None	--
Evolocu-mab	Y	**None** at ≤ 30x MRHD	**None** at ≤ 12x MRHD	Fetal immune suppression?	None	--
Ivabra-dine	Y	≥ 1-5x MRHD	1-3x MRHD	Destabalizati on of CHF	None	--
Sacubitril-Valsartan	ACEI/ARBs in 2nd & 3rd trimester of human pregnancy are associated w/fetal renal damage, skull defects, oligohydramnios, & fetal death.			No Sacubitril data available	ARBs	D

Information obtained from Package Insert(s)

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