OB Medications and Complications

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Lindsey Jackson Foster, PharmD, BCPS
OB Clinical Pharmacist
Northside Hospital
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Disclosures

I do not have any relevant financial relationships with any commercial interests to disclose

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Objectives

Pharmacists

1. Define commonly encountered pregnancy terminology
2. Describe physiological changes in pregnancy
3. Review references available for medication information during pregnancy and lactation
4. Define commonly encountered pregnancy complications and explain medications utilized for those complications

Technicians

1. Recognize commonly encountered pregnancy terminology
2. Identify references available for medication information during pregnancy and lactation
3. List medications available for commonly encountered pregnancy complications

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Northside Hospital

- Northside Hospital System
  - Northside Atlanta
  - Northside Cherokee
  - Northside Duluth (does not perform deliveries)
  - Northside Forsyth
  - Northside Gwinnett
- Northside Hospital Atlanta
  - ~ 16,000 annual deliveries
  - L&D: 42 labor beds, 19 high risk beds, 6 urgent care beds, 5 ORs
  - High Risk Perinatal: 34 beds
  - Center for Perinatal Medicine
  - Joint Commission Level IV Maternal Levels of Care Verification

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Pregnancy Definitions

- Gestational age (GA): time from start of last menstrual period (LMP);exceeds development by 2 weeks
- Estimated Date of Confinement (EDC): Due date
  - Naegele's Rule: add 7 days to the first day of the LMP, count back 3 months,and add 1 year
- Gravida (G): # of pregnancies regardless of outcome
- Parity (P): the # of deliveries after 20 weeks gestation
  - Independent of the # of fetuses
- Trimester: ~13 weeks duration
- Term infant: 37 weeks to 42 weeks
- Preterm infant: 20 weeks to <37 weeks

Ung KD and McNulty J. Obstetric Drug Therapy. Allredge BK, et al, eds. Applied Therapeutics: The Clinical Use of Drugs. Philadelphia: Lippincott Williams and Wilkins. 2013: 1107-48.

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Physiological Changes in Pregnancy

- Blood Volume ↑ - 40-45% at term
- Cardiovascular
  - Cardiac output ↑
  - Blood pressure ↓
- Renal
  - Renal blood flow ↑
  - Glomerular filtration rate ↑
- Hepatic
  - Serum albumin ↓
  - Enzymes ↑ or ↓
- GI
  - Gastric secretion ↓
  - Gastric emptying ↓
  - Nausea/vomiting ↑
- Coagulation ↑

Nageotte M. Physiologic Changes in Pregnancy. GG Briggs and M Nageotte, eds. *Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians*. Bethesda: American Society of Health-System Pharmacists. 2009: 3-14.

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Kinetics during Pregnancy

- Absorption
  - Gastric emptying and motility ↓ = ↑ or ↓ absorption
- Volume of distribution ↑
  - Aminoglycosides
- Metabolism
  - Dependent on enzyme
  - 1A2 ↓, 2A6 ↑, 2C9 ↑, 2C19 ↓, 2D6 ↑, 3A4 ↑?, UGT ↑
- Elimination ↑
- Medications to monitor:
  - Antiepileptics
  - Aminoglycosides
  - Vancomycin
  - Digoxin

Kildoo CW and Ambrose PJ. Clinical Pharmacokinetics in the Pregnant Patient. GG Briggs and M Nageotte, eds. *Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians*. Bethesda: American Society of Health-System Pharmacists. 2009: 55-78.

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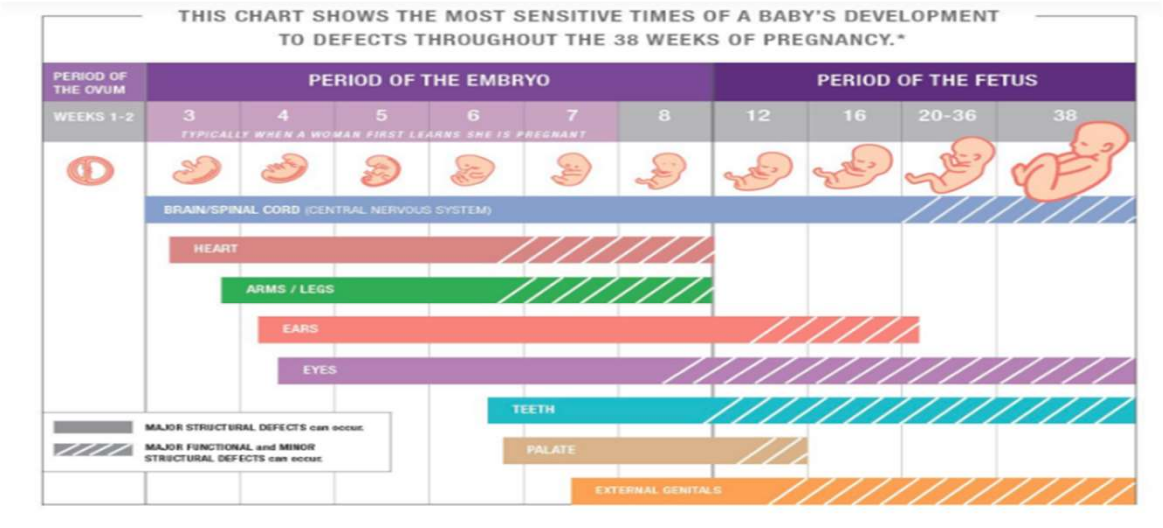
Teratogenicity



mothertobaby.org

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Pregnancy Categories

Effective 2015, the FDA phased out the use of Pregnancy Categories that had been in use since 1979

Category A	No risk in human studies (studies in pregnant women have not demonstrated a risk to the fetus during the first trimester)
Category B	No risk in animal studies (there are no adequate studies in humans, but animal studies did not demonstrate a risk to the fetus).
Category C	Risk cannot be ruled out. There are no satisfactory studies in pregnant women, but animal studies demonstrated a risk to the fetus; potential benefits of the drug may outweigh the risks.
Category D	Evidence of risk (studies in pregnant women have demonstrated a risk to the fetus; potential benefits of the drug may outweigh the risks)
Category X	Contraindicated (studies in pregnant women have demonstrated a risk to the fetus, and/or human or animal studies have shown fetal abnormalities; risks of the drug outweigh the potential benefits)

Leek JC and Arif H. Pregnancy Medications. Stat Pearls. 2022 July 25.

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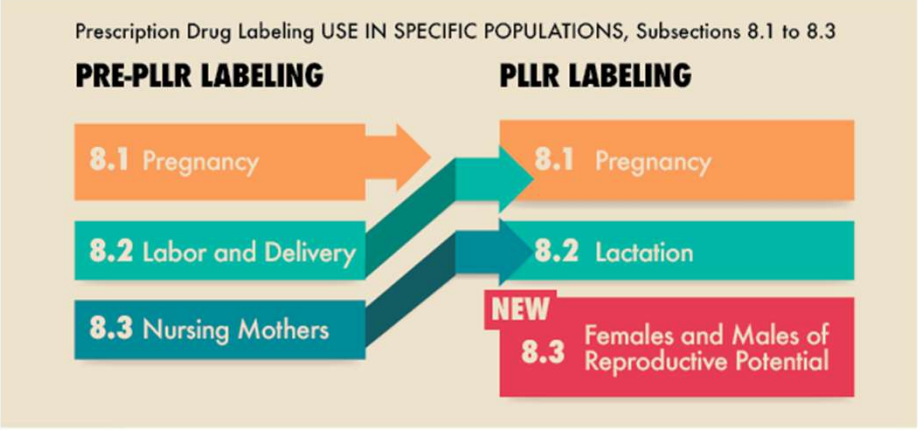
Pregnancy and Lactation Labeling Rule (PLLR)



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Pregnancy and Lactation Labeling (Drugs) Final Rule. US Food and Drug Administration. Accessed 1 Jan 2023. https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

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PLLR Content

8.1 Pregnancy	Pregnancy Exposure Registry Risk Summary Clinical Considerations Data
8.2 Lactation	Risk Summary Clinical Considerations Data
8.3 Females and Males of Reproductive Potential* *Included if information available	Pregnancy testing Contraception Infertility

Pernia S and DeMaagd G. The New Pregnancy and Lactation Labeling Rule. PT. 2016 Nov; 41(11): 713–715.

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PLLR Example

Emtricitabine/Tenofovir:

https://www.gilead.com/~/media/files/pdfs/medicines/hiv/descovy/descovy_pi.pdf?la=en

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to DESCOVY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Gilead Sciences 16

Risk Summary

Available data from the APR show no statistically significant difference in the overall risk of major birth defects for emtricitabine (FTC) or tenofovir alafenamide (TAF) compared with the background rate for major birth defects of 2.7% in a

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants, to avoid risking postnatal transmission of HIV-1.

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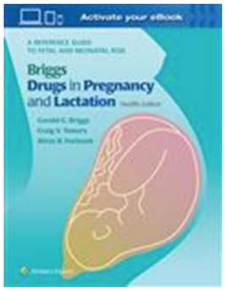
Pregnancy References

- Briggs Drugs in Pregnancy and Lactation
- Reprotox.org
  - Pregnancy, reproduction, development
- Shepard's
  - Focuses on teratology studies
- TERIS
  - Teratogen Information System
- Mothertobaby.org
  - Fact Sheets



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Pregnancy References: Briggs

Pharmacologic Category

Antiemetic

Pregnancy Recommendation

Human Data Suggest Risk in 1st Trimester

Breast-feeding Recommendation

No Human Data—Probably Compatible

Pregnancy Summary

Two large national studies, one from Denmark and the other from Sweden, have found significant increases of cardiac anomalies when ondansetron was used in the 1st trimester (Ref). Additionally, a large national study from the United States found an increased risk for oral clefts but not cardiac malformations (Ref). Although several smaller studies reported no association with structural defects, ondansetron was usually started after organogenesis, the critical period for causing cardiac anomalies. In contrast, the only Food and Drug Administration (FDA)-approved drug for nausea and vomiting in pregnancy is doxylamine-pyridoxine. This combination product does not cause birth defects and is not associated with harm in pregnancy (see Doxylamine). Consequently, ACOG recommends doxylamine-pyridoxine as the treatment of choice for nausea and vomiting in pregnancy (Ref). If ondansetron must be used, avoiding the 1st trimester is the safest course.

Fetal Risk Summary

Ondansetron is a selective 5-HT_3 receptor antagonist. It is an antiemetic that is indicated for the prevention and treatment of nausea and vomiting induced by chemotherapy, radiotherapy, and postoperative. The drug is extensively metabolized to metabolites that are unlikely to contribute to the parent drug's biological activity. The mean elimination half-life of a single 8-mg dose in women of reproductive age (18–40 years) is 3.5 hours (Ref).

Animal Data: No adverse effects on fertility or on the fetus were observed in reproduction studies in rats and rabbits with oral doses up to 6 and 24 times the maximum recommended human dose, respectively (Ref).

It was not carcinogenic nor mutagenic (Ref).

Placental Transfer: Consistent with its molecular weight (about 293), ondansetron crosses the human placenta to the fetus (Ref). In a prospective observational study of 41 women requesting pregnancy termination at a median gestational age of 10.6 weeks, ondansetron (8 mg) was given at 1400 and 22 hours, respectively, on the day before surgery, and a third dose was given 4 hours

Breast-feeding Summary

No reports describing the use of ondansetron during human lactation have been located. The molecular weight (about 293) and the moderate elimination half-life (3.5 hours) suggest that the drug will be excreted into breast milk, but the extensive metabolism may limit the amount in milk. The effect of this exposure on a nursing infant is unknown.

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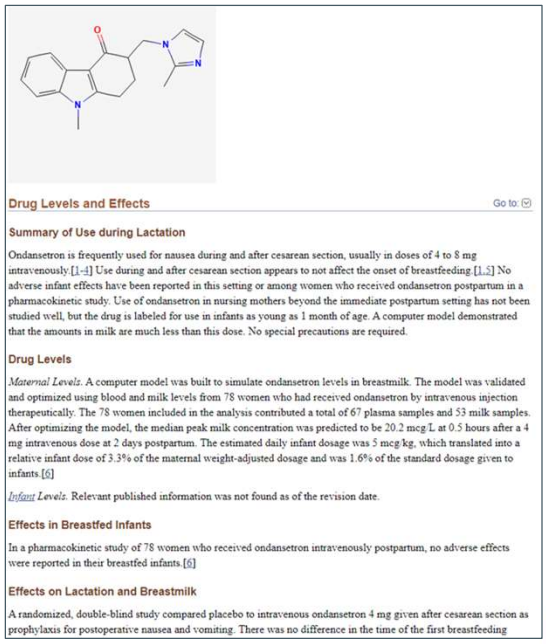
Lactation References

- Hale's Medications and Mothers' Milk
- LactMed
  - Free! Accessed through NIH
  - Drugs and Lactation Database
- Briggs



Drug Levels and Effects Go to:

Summary of Use during Lactation

Ondansetron is frequently used for nausea during and after cesarean section, usually in doses of 4 to 8 mg intravenously.[1-4] Use during and after cesarean section appears to not affect the onset of breastfeeding.[1,5] No adverse infant effects have been reported in this setting or among women who received ondansetron postpartum in a pharmacokinetic study. Use of ondansetron in nursing mothers beyond the immediate postpartum setting has not been studied well, but the drug is labeled for use in infants as young as 1 month of age. A computer model demonstrated that the amounts in milk are much less than this dose. No special precautions are required.

Drug Levels

Maternal Levels. A computer model was built to simulate ondansetron levels in breastmilk. The model was validated and optimized using blood and milk levels from 78 women who had received ondansetron by intravenous injection therapeutically. The 78 women included in the analysis contributed a total of 67 plasma samples and 53 milk samples. After optimizing the model, the median peak milk concentration was predicted to be 20.2 mcg/L at 0.5 hours after a 4 mg intravenous dose at 2 days postpartum. The estimated daily infant dosage was 5 mcg/kg, which translated into a relative infant dose of 3.3% of the maternal weight-adjusted dosage and was 1.6% of the standard dosage given to infants.[6]

Infant Levels. Relevant published information was not found as of the revision date.

Effects in Breastfed Infants

In a pharmacokinetic study of 78 women who received ondansetron intravenously postpartum, no adverse effects were reported in their breastfed infants.[6]

Effects on Lactation and Breastmilk

A randomized, double-blind study compared placebo to intravenous ondansetron 4 mg given after cesarean section as prophylaxis for postoperative nausea and vomiting. There was no difference in the time of the first breastfeeding

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Lactation References

- Hale's Medications and Mothers' Milk

L1	Compatible Drug which has been taken by a large number of breastfeeding mothers without any observed increase in adverse effects in the infant. Controlled studies in breastfeeding women fail to demonstrate a risk to the infant and the possibility of harm to the breastfeeding infant is remote; or the product is not orally bioavailable in an infant.
L2	Probably compatible Drug which has been studied in a limited number of breastfeeding women without an increase in adverse effects in the infant. And/or the evidence of a demonstrated risk which is likely to follow use of this medication in a breastfeeding woman is remote.
L3	Probably compatible There are no controlled studies in breastfeeding women; however, the risk of untoward effects to a breastfed infant is possible, or controlled studies show only minimal non-threatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant.
L4	Potentially Hazardous There is positive evidence of risk to a breastfed infant or to breastmilk production, but the benefits from use in breastfeeding mothers may be acceptable despite the risk to the infant
L5	Hazardous Studies in breastfeeding mothers have demonstrated that there is significant and documented risk to the infant based on human experience, or it is a medication that has a high risk of causing significant damage to an infant. The risk of using the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated in women who are breastfeeding an infant.

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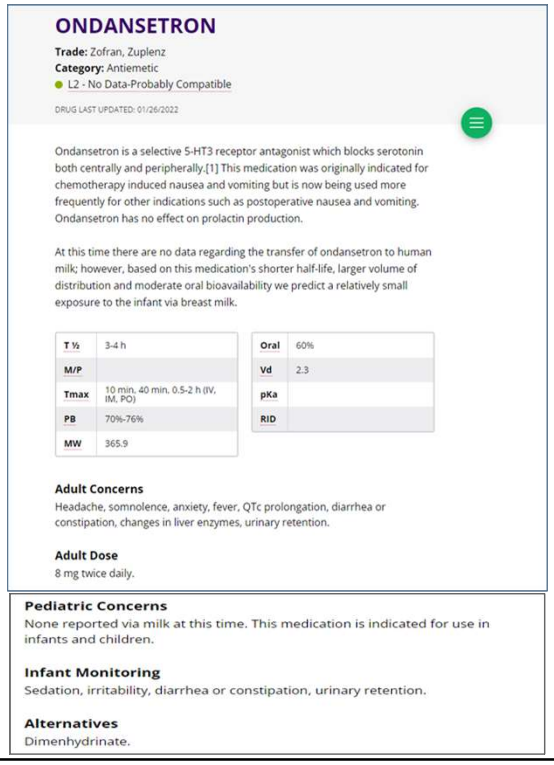
Lactation References

- Hale's Medications and Mothers' Milk



ONDANSETRON

Trade: Zofran, Zuplenz
Category: Antiemetic
L2 - No Data-Probably Compatible

DRUG LAST UPDATED: 01/26/2022

Ondansetron is a selective 5-HT3 receptor antagonist which blocks serotonin both centrally and peripherally.[1] This medication was originally indicated for chemotherapy induced nausea and vomiting but is now being used more frequently for other indications such as postoperative nausea and vomiting. Ondansetron has no effect on prolactin production.

At this time there are no data regarding the transfer of ondansetron to human milk; however, based on this medication's shorter half-life, larger volume of distribution and moderate oral bioavailability we predict a relatively small exposure to the infant via breast milk.

T ½	3-4 h	Oral	60%
M/P		Vd	2.3
Tmax	10 min, 40 min, 0.5-2 h (IV, IM, PO)	pKa	
PB	70%-76%	RID	
MW	365.9		

Adult Concerns
Headache, somnolence, anxiety, fever, QTc prolongation, diarrhea or constipation, changes in liver enzymes, urinary retention.

Adult Dose
8 mg twice daily.

Pediatric Concerns
None reported via milk at this time. This medication is indicated for use in infants and children.

Infant Monitoring
Sedation, irritability, diarrhea or constipation, urinary retention.

Alternatives
Dimenhydrinate.

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Patient Case

AB is a 34 year old female who is 20 weeks pregnant. She is allergic to ceftriaxone with difficulty breathing. She has a urine culture positive for E. Coli that is resistant to penicillin and nitrofurantoin. Her OB has prescribed Sulfamethoxazole/Trimethoprim. She asks you if this is compatible with pregnancy. How do you counsel AB?

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Patient Case Answer

Trimethoprim

Pregnancy Recommendation

Human and Animal Data Suggest Risk

Breast-feeding Recommendation

Compatible

Pregnancy Summary

Trimethoprim is a dihydrofolate reductase inhibitor that is teratogenic in animals and humans. Defects that have been associated with trimethoprim include cardiovascular defects and neural tube defects (NTDs) and possibly oral clefts. Folic acid supplementation, at least 0.4 mg/day, started before conception or concurrently with trimethoprim may reduce the risk of these congenital defects.

Fetal Risk Summary

Trimethoprim is available as a single agent and in combination with various sulfonamides (see Sulfonamides). Because trimethoprim is a folate antagonist, caution has been advocated for its use in pregnancy ([Ref]). Published case reports and placebo-controlled trials involving several hundred patients, during all phases of gestation, have failed to demonstrate an increase in fetal abnormalities ([Ref]). However, other reports ([Ref]) and the unpublished data cited below, are suggestive that trimethoprim use during the 1st trimester may result in structural defects. Maternal supplementation with multivitamins that contain folic acid may reduce this risk ([Ref]). It is about 44% bound to plasma proteins and has an elimination half-life of 8–10 hours ([Ref]).

Sulfonamides

Pregnancy Recommendation

Human Data Suggest Risk in 3rd Trimester

Breast-feeding Recommendation

Limited Human Data—Potential Toxicity

Pregnancy Summary

Taken in sum, sulfonamides, as single agents, do not appear to pose a significant teratogenic risk. One study has found associations with birth defects, but a causative association cannot be determined with this type of study, and they may have been due to other factors, particularly if trimethoprim was combined with the sulfonamide. Confirmation is required. Because of the potential toxicity to the newborn, these agents should be avoided near term. ACOG states that sulfonamides are appropriate during the 1st trimester if no other suitable alternatives are available. Additionally, they remain as first-line agents for urinary tract infections during the 2nd and 3rd trimesters ([Ref]).

Sulfonamides. Briggs Drugs in Pregnancy and Lactation. Facts and Comparisons. Accessed 6 Jan 2023.
Trimethoprim. Briggs Drugs in Pregnancy and Lactation. Facts and Comparisons. Accessed 6 Jan 2023.

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Preterm Labor

- Definition
- Tocolytics
- Corticosteroids
- Neuroprotection
- Progesterone

womanlymag.com

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Preterm Labor

- Preterm labor
  - Regular uterine contractions PLUS cervical change
- Preterm birth
  - Birth between 20 0/7 and 36 6/7 weeks gestation
- Preterm birth is the leading cause of neonatal mortality
  - ~70% of neonatal deaths
  - ~36% of infant deaths
  - 25-50% of long-term neurologic impairment in children

The American College of Obstetricians and Gynecologists. Management of Preterm Labor. Practice Bulletin. Number 171.Oct 2016.

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Patient Case #2

CD is a G2P1 22 year old female at 24 weeks gestation. She presents with back pain and frequent contractions. She is found to have a short cervix on exam as well. What interventions should be performed during her stay?

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Preterm Labor Management

- GOAL: Inhibit labor in order to provide benefit to fetus
  - Corticosteroids
  - Neuroprotection

- Tocolytic agents = anti-contraction medications
  - Indomethacin
  - Nifedipine
  - Terbutaline
  - Magnesium

The American College of Obstetricians and Gynecologists. Management of Preterm Labor. Practice Bulletin. Number 171. Oct 2016.

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Tocolytic Agents: Indomethacin

webmd.com

Mechanism of Action	Block the conversion of arachidonic acid to prostaglandins, which are necessary for parturition
Dosing	50-100mg PO (PR) x 1; then 25-50mg PO Q 6 hours x 48-72 hours
Kinetics	Onset ~ 30 mins; Hepatic metabolism; duration 4-6 hours

1.Brombrys AE and Lewis DF. Preterm Labor and Delivery. GG Briggs and M Nageotte, eds. *Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians*. Bethesda: American Society of Health-System Pharmacists. 2009: 123-41.
2.Indomethacin. LexiComp. Accessed 1 Jan 2023.

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Tocolytic Agents: Indomethacin

Maternal Side Effects	• Nausea, esophageal reflux, gastritis, emesis • Platelet dysfunction
Fetal Side Effects	• Constriction of ductus arteriosus (use >48 hours) • Oligohydramnios (use > 48 hours)
Contraindications	• **Gestation age ≥ 32 weeks** • Platelet dysfunction or bleeding disorder • Hepatic dysfunction • Gastrointestinal ulcerative disease • Renal dysfunction • Asthma (aspirin hypersensitivity)

1. Brombrys AE and Lewis DF. Preterm Labor and Delivery. GG Briggs and M Nageotte, eds. *Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians*. Bethesda: American Society of Health-System Pharmacists. 2009: 123-41.
2. Indomethacin. LexiComp. Accessed 1 Jan 2023.
3. The American College of Obstetricians and Gynecologists. Management of Preterm Labor. Practice Bulletin. Number 171. Oct 2016.

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Tocolytic Agents: Nifedipine

drugs.com

Mechanism of Action	Block transmembrane flow of calcium
Dosing	10-20mg PO Q 4-6 hours
Kinetics	Onset ~ 20 mins; Hepatic metabolism; half life 2-5 hours

1. Brombrys AE and Lewis DF. Preterm Labor and Delivery. GG Briggs and M Nageotte, eds. *Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians*. Bethesda: American Society of Health-System Pharmacists. 2009: 123-41.
2. Nifedipine. LexiComp. Accessed 1 Jan 2023.

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Tocolytic Agents: Nifedipine

Maternal Side Effects	• Dizziness, flushing, hypotension, tachycardia, headache, peripheral edema • Could suppress heart rate, contractility, and left ventricular systolic pressure when used with magnesium sulfate
Fetal Side Effects	• None known
Contraindications	• Hypotension • Preload dependent cardiac lesions, such as aortic insufficiency • Caution with heart failure

1. Brombrys AE and Lewis DF. Preterm Labor and Delivery. GG Briggs and M Nageotte, eds. *Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians*. Bethesda: American Society of Health-System Pharmacists. 2009: 123-41.
2. Nifedipine. LexiComp. Accessed 1 Jan 2023.
3. The American College of Obstetricians and Gynecologists. Management of Preterm Labor. Practice Bulletin. Number 171. Oct 2016.

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Tocolytic Agents: Terbutaline

webmd.com

Mechanism of Action	β2-agonist
Dosing	0.25 mg SQ Q 20 mins for up to 3 doses; limited to 72 hours
Kinetics	Onset: 6-15 mins; Hepatic metabolism; Duration 1.5-4 hours

1. Brombrys AE and Lewis DF. Preterm Labor and Delivery. GG Briggs and M Nageotte, eds. *Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians*. Bethesda: American Society of Health-System Pharmacists. 2009: 123-41.
2. Terbutaline. Lexicomp. Accessed 1 Jan 2023.

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Tocolytic Agents: Terbutaline

Maternal Side Effects	• Tachycardia, hypotension, tremor, palpitations, shortness of breath, chest discomfort, pulmonary edema, hypokalemia, hyperglycemia, lipolysis, tachyphylaxis • Hold if HR >120 beats/min
Fetal Side Effects	• Fetal tachycardia • Hypoglycemia
Contraindications	• Tachycardia-sensitive maternal cardiac disease • Poorly controlled diabetes mellitus • Caution with massive hemorrhage risk

1. Brombrys AE and Lewis DF. Preterm Labor and Delivery. GG Briggs and M Nageotte, eds. *Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians*. Bethesda: American Society of Health-System Pharmacists. 2009: 123-41.
2. Terbutaline. LexiComp. Accessed 1 Jan 2023.
3. The American College of Obstetricians and Gynecologists. Management of Preterm Labor. Practice Bulletin. Number 171. Oct 2016.

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Tocolytic Agents: Terbutaline

- FDA WARNING
  - Feb 2011
  - Black Box Warning
  - Injectable terbutaline should not be used for prolonged treatment (>48-72 hours) of preterm labor due to serious maternal heart problems and death
  - Oral terbutaline is contraindicated for acute or chronic use for management of preterm labor

FDA. FDA Drug Safety Communication: New warnings against use of terbutaline to treat preterm labor. 17 Feb 2011. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-new-warnings-against-use-terbutaline-treat-preterm-labor Accessed 5 Jan 2023.

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Tocolytic Agents: Magnesium

pfizer.com

Mechanism of Action	Exact is unknown; decreases levels of intracellular calcium
Dosing	4-6 gram bolus; 1-4 grams/hour infusion (generally infuse 2 grams/10 mins for loading dose)
Kinetics	IV: immediate onset Renally cleared ***Use with caution in renal failure*** Half life ~ 5 hours

1.Brombrys AE and Lewis DF. Preterm Labor and Delivery. GG Briggs and M Nageotte, eds. *Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians*. Bethesda: American Society of Health-System Pharmacists. 2009: 123-41.
2.Magnesium Sulfate. LexiComp. Accessed 1 Jan 2023.

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Tocolytic Agents: Magnesium

Maternal Side Effects	• Flushing, diaphoresis, nausea, loss of deep tendon reflexes (DTRs), respiratory depression, cardiac arrest, pulmonary edema, hypocalcemia • Could suppress heart rate, contractility and left ventricular systolic pressure when used with nifedipine
Fetal Side Effects	• Alterations in heart rate variability • Bone demineralization (prolonged use) • Hypotonia
Contraindications	• Myasthenia gravis • Avoid in known myocardial compromise or cardiac conduction defects • Caution with renal disease

1. Brombrys AE and Lewis DF. Preterm Labor and Delivery. GG Briggs and M Nageotte, eds. *Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians*. Bethesda: American Society of Health-System Pharmacists. 2009: 123-41.
2. Magnesium Sulfate. LexiComp. Accessed 1 Jan 2023.
3. The American College of Obstetricians and Gynecologists. Management of Preterm Labor. Practice Bulletin. Number 171. Oct 2016.

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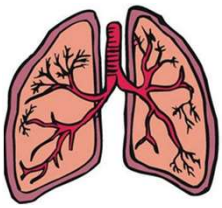
Antenatal Steroids



- Promotes fetal lung development
- Reduces
  - Neonatal mortality
  - Respiratory distress syndrome
  - Intracranial hemorrhage
  - Necrotizing enterocolitis

1. The American College of Obstetricians and Gynecologists. Management of Preterm Labor. Practice Bulletin. Number 171. Oct 2016.
2. The American College of Obstetricians and Gynecologists. Antenatal Corticosteroid Therapy for Fetal Maturation. Committee Opinion. Number 713. Aug 2017.

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Antenatal Steroids

- 24 0/7* and 33 6/7 weeks and at risk for delivery within 7 days
  - * Prior to 24 weeks, periviability period includes parents' desires for neonatal resuscitation
- 34 0/7 and 36 6/7 weeks and at risk for delivery within 7 days and who have NOT received a previous course (ALPS Trial)[1]
- Single repeat course -
  - Consider if < 34 0/7 weeks and imminent risk for delivery. Can give as early as 7 days from prior course.
  - Regular scheduled repeat courses or more than 2 courses are not currently recommended by ACOG

1. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, et al. Antenatal betamethasone for women at risk for late preterm delivery. NICHD Maternal-Fetal Medicine Units Network. N Engl J Med 2016;374:1311–20.
2. The American College of Obstetricians and Gynecologists. Management of Preterm Labor. Practice Bulletin. Number 171. Oct 2016.
3. The American College of Obstetricians and Gynecologists. Antenatal Corticosteroid Therapy for Fetal Maturation. Committee Opinion. Number 713. Aug 2017.

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Corticosteroids

- Betamethasone
  - 12mg IM Q 24 hours x 2 doses
  - 12mg betamethasone = 100mg prednisone = 400mg hydrocortisone

- Dexamethasone
  - 6mg IM Q 12 hours x 4 doses
  - 6mg dexamethasone = 40mg prednisone = 160 mg hydrocortisone

1. Berkowitz KM. Fetal Lung Maturity. GG Briggs and M Nageotte, eds. Diseases, Complications, and Drug Therapy in Obstetrics: A Guide for Clinicians. Bethesda: American Society of Health-System Pharmacists. 2009: 155-66.
2. The American College of Obstetricians and Gynecologists. Management of Preterm Labor. Practice Bulletin. Number 171. 2016 Oct.

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Magnesium for Neuroprotection

- Reduces severity and risk of cerebral palsy when birth is anticipated before 32 weeks

Table 1. Inclusion Criteria, Treatment Regimens, and Concurrent Tocolysis of Large Trials

Study	Total Number of Participants	Inclusions	Dose	Duration	Death and Cerebral Palsy	Death	Cerebral Palsy
Crowther	1,255	Less than 30 weeks of gestation; likely delivery within 24 hours	4 g load 1 g/hr	Up to 24 hours	RR, 0.83; 95% CI, 0.66–1.03	RR,0.83; 95 % CI, 0.64–1.09	RR, 0.83; 95% CI, 0.54–1.27
Marret	688	Less than 33 weeks of gestation	4 g load only	Loading dose only	OR, 0.80; 95% CI, 0.58–1.10	OR, 0.85; 95% CI, 0.55–1.32	OR, 0.70; 95% CI, 0.41–1.19
Rouse	2,241	24–31 weeks of gestation; at high risk of spontaneous birth	6 g load 2 g/hr	Up to 12 hours; treatment resumed when delivery imminent	RR, 0.97; 95% CI, 0.77–1.23	RR, 1.12; 95% CI, 0.85–1.47	RR, 0.55; 95% CI, 0.32–0.95

CI, confidence interval; RR, relative risk; OR, odds ratio.

Data from Crowther CA, Hiller JE, Doyle LW, Haslam RR. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. JAMA 2003;290:2669–76; Marret S, Marpeau L, Zupan-Simunek V, Eurin D, Leveque C, Hellot MF, et al. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial. PREMAG trial group. BJOG 2007;114:310–8; *and* Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, et al. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. N Engl J Med 2008;359:895–905.

The American College of Obstetricians and Gynecologists and The Society for Maternal Fetal Medicine. Magnesium Sulfate before Anticipated Preterm Birth for Neuroprotection. Committee Opinion. Number 455. March 2010. Reaffirmed 2020.

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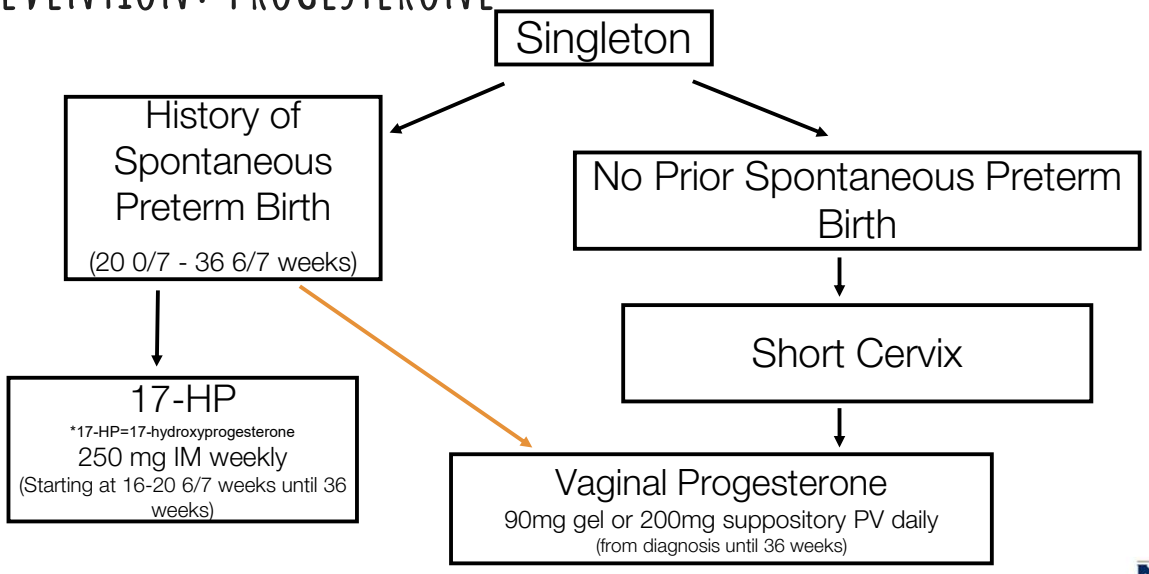
Prevention: Progesterone



1. Society of Maternal-Fetal Medicine Publications Committee with Berghella V. Progesterone and Preterm Birth Prevention: Translating Clinical Trials Data into Clinical Practice. AJOG. March 2012.
2. The American College of Obstetricians and Gynecologists. Prediction and Prevention of Preterm Birth. Practice Bulletin Number 234. Aug 2021.

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Prevention: Progesterone

Injectable	Vaginal
17- Hydroxyprogesterone caproate 250mg/mL Contains castor oil	Micronized progesterone 100mg, **200mg** Contains peanut oil
	Progesterone vaginal gel 4% (45mg), **8% (90mg)**
	Progesterone insert 100mg
	Progesterone suppository compounding kit 25mg, 50mg, 100mg, 200mg, 400mg

*Insufficient evidence that any of the vaginal preparations or doses are superior

1. Society of Maternal-Fetal Medicine Publications Committee with Berghella V. Progesterone and Preterm Birth Prevention: Translating Clinical Trials Data into Clinical Practice. AJOG. March 2012.
2. Progesterone. Lexicomp. Accessed 2 Oct 2016.
3. Hydroxyprogesterone caproate. Lexicomp. Accessed 2 Oct 2016.

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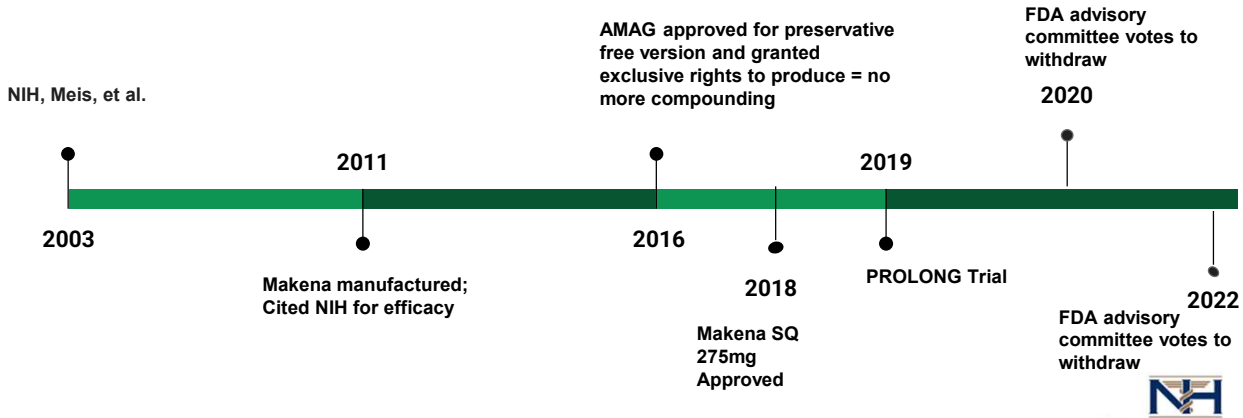
17-Hydroxyprogesterone Controversy



Society for Maternal Fetal Medicine Publications Committee. SMFM Statement: Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth. July 2020.

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Progestin Trial Comparison

NIH Meis, et al. 2003[1]	PROLONG 2019[2]
-N=463, US (1999-2002) -Multicenter, double-blind, randomized, controlled -59% black -51% married -23% tobacco use -**27.7%** had >1 prior Preterm Birth (PTB) -**91%** had additional risk factor for PTB -34% reduction at <37 weeks, 33% at <35 weeks, 42% at <32 weeks -PTB rate at <37 weeks was 36.3% vs **54.9%** (17-HP vs placebo) -Significant reductions in some neonatal complications	-N=1708, International (25% US) (2009-2018) -Multicenter, double-blind, randomized, controlled -87% white -89% married -8% tobacco use -**13%** had >1 prior PTB -**48%** had additional risk factor for PTB -Rate of PTB at <35 weeks of gestation did not differ -PTB rate at <37 weeks was 23.1% and **21.9%** (17-HP vs placebo) -Neonatal composite outcome also did not differ

1. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379–85.
2. Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG Study): a multicenter, international, randomized double-blind trial. Am J Perinatol 2020;37:127–36.
3. Society for Maternal Fetal Medicine Publications Committee. SMFM Statement: Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth. July 2020.

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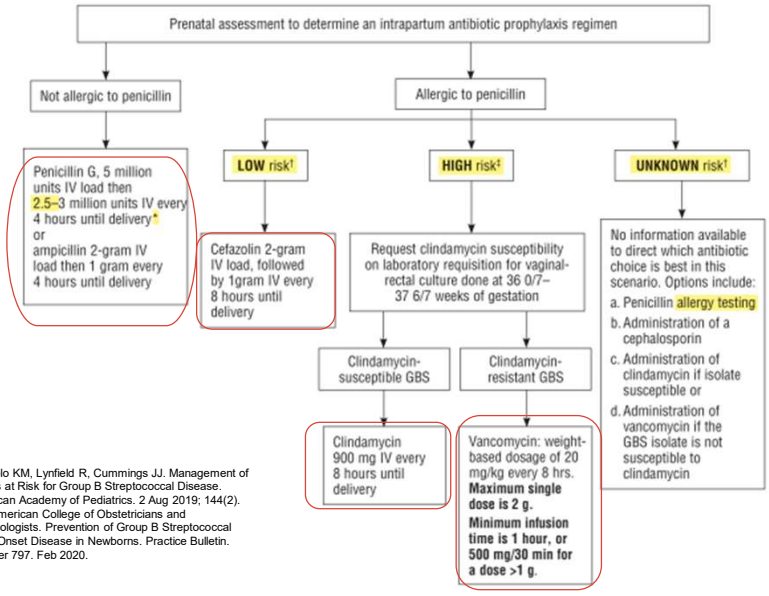
Group B Strep Prophylaxis



1. Puopolo KM, Lynfield R, Cummings JJ. Management of Infants at Risk for Group B Streptococcal Disease. American Academy of Pediatrics. 2 Aug 2019; 144(2).
2. The American College of Obstetricians and Gynecologists. Prevention of Group B Streptococcal Early-Onset Disease in Newborns. Practice Bulletin. Number 797. Feb 2020.

"Adequate GBS intrapartum antibiotic prophylaxis is defined as the administration of penicillin G, ampicillin, or cefazolin for at least 4 hours before delivery." – AAP[1]

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Patient Case #2

CD is a G2P1 22 year old female at 24 weeks gestation. She presents with back pain and frequent contractions. She is found to have a short cervix on exam as well. What interventions should be performed during her stay?

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Patient Case #2 Answers

- Terbutaline 0.25mg SQ x 1
- Penicillin 5 million units IV x 1, then 3 million units IV Q 4 hours until end of labor/delivery or GBS results as negative
- Magnesium sulfate 4 grams IVPB x 1, 1 gram/hour IV x 12 hours or until delivery
- Indomethacin 50 mg po x 1, 25 mg po Q 6 hours x 48 hours
- Betamethasone 12 mg IM Q 24 hours x 2 doses
- Begin progesterone 200 mg vaginally HS

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OB Hemorrhage

- ACOG: Cumulative blood loss of greater than or equal to 1000mL or blood loss associated with sign/symptoms of hypovolemia within 24 hours after birth process
  - Primary - first 24 hours
  - Secondary - after 24 hours up to 12 weeks postpartum
- Treatment is based on etiology
  - Abnormal tone (uterine atony) accounts for 70-80%
  - Uterotonics!
- Prophylactic oxytocin

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OB Hemorrhage

Table 3. Acute Medical Management of Postpartum Hemorrhage

Drug*	Dose and Route	Frequency	Contraindications	Adverse Effects
Oxytocin	IV: 10–40 units per 500–1,000 mL as continuous infusion or IM: 10 units	Continuous	Rare, hypersensitivity to medication	Usually none. Nausea, vomiting, hyponatremia with prolonged dosing. Hypotension can result from IV push, which is not recommended.
Methylergonovine	IM: 0.2 mg	Every 2–4 h	Hypertension, preeclampsia, cardiovascular disease, hypersensitivity to drug	Nausea, vomiting, severe hypertension particularly when given IV, which is not recommended
15-methyl $PGF_{2\alpha}$	IM: 0.25 mg Intramyometrial: 0.25 mg	Every 15–90 min, eight doses maximum	Asthma. Relative contraindication for hypertension, active hepatic, pulmonary, or cardiac disease	Nausea, vomiting, diarrhea, fever (transient), headache, chills, shivering hypertension, bronchospasm
Misoprostol	600–1,000 micrograms oral, sublingual, or rectal	One time	Rare, hypersensitivity to medication or to prostaglandins	Nausea, vomiting, diarrhea shivering, fever (transient), headache

Abbreviations: IV, intravenously; IM, intramuscularly; PG, prostaglandin.

*All agents can cause nausea and vomiting.

Modified from Lyndon A, Lagrew D, Shields L, Main E, Cape V, editors. Improving health care response to obstetric hemorrhage version 2.0. A California quality improvement toolkit. Stamford (CA): California Maternal Quality Care Collaborative; Sacramento (CA): California Department of Public Health; 2015.

The American College of Obstetricians and Gynecologists. Postpartum Hemorrhage. Practice Bulletin. Number 183. Oct 2017.

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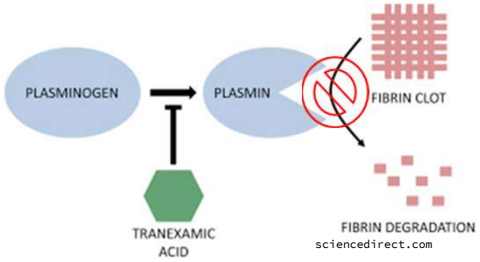
OB Hemorrhage: TXA



- Tranexamic Acid (TXA)
  - Anti-fibrinolytic
- WOMAN Trial
  - The Lancet; April 26, 2017
  - N = 20,060
  - Postpartum hemorrhage following vaginal or cesarean birth
  - Death due to bleeding was significantly reduced by 19%
  - When treatment given with 3 hours of birth, by 31%
  - Adverse events (including thromboembolic events) did not differ significantly
- Postpartum Hemorrhage
  - Consider when initial medical therapy fails, favoring earlier treatment
  - TXA 1 gram IV x 1
  - If after 30 mins bleeding continues or if it stops and restarts within 24 hours after the 1st dose, may repeat dose as above

Shakur H, et al. Effect of Early Tranexamic Acid Administration on Mortality, Hysterectomy, and Other Morbidities in Women with Post-Partum Haemorrhage (WOMAN): An International, Randomised, Double-Blind, Placebo-Controlled Trial. The Lancet. 26 April 2017.

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Pregnancy Induced Hypertension

Chronic Hypertension (CHTN): Diagnosed or present before pregnancy or before 20 weeks of gestation. Also includes HTN that is diagnosed for the first time during pregnancy and that does not resolve in the typical postpartum period.

Gestational Hypertension (GHTN): A systolic blood pressure 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation, in a woman with a previously normal blood pressure

1. The American College of Obstetricians and Gynecologists. Chronic Hypertension in Pregnancy. Practice Bulletin. Number 203. Jan 2019.
2. The American College of Obstetricians and Gynecologists. Gestational Hypertension and Preeclampsia. Practice Bulletin. Number 222. June 2020.

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Pregnancy Induced Hypertension

Pre-Eclampsia: New-onset HTN, which occurs most often after 20 weeks of gestation. Often accompanied by new-onset proteinuria but other markers include: thrombocytopenia (platelet count less than 100,000), impaired liver function (LFTs 2x ULN), severe persistent right upper quadrant or epigastric pain, renal insufficiency (SCr greater than 1.1 or a doubling of the SCr in absence of renal disease), pulmonary edema, new-onset headache unresponsive to acetaminophen, visual disturbances

Eclampsia: New-onset tonic-clonic, focal, or multifocal seizures in a pregnant or post-partum patient with pre-eclampsia

HELLP Syndrome: a form of pre-eclampsia characterized by hemolysis, elevated liver enzymes, and low platelet count

1. The American College of Obstetricians and Gynecologists. Chronic Hypertension in Pregnancy. Practice Bulletin. Number 203. Jan 2019.
2. The American College of Obstetricians and Gynecologists. Gestational Hypertension and Preeclampsia. Practice Bulletin. Number 222. June 2020.

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Magnesium: Eclampsia and Pre-Eclampsia

Medication	Dosing	Comments
Magnesium Sulfate Loading Dose	4 grams-6 grams	-Infuse over 20 -30 mins (each 2 grams over 10 mins) -Can give additional 2 grams IVPB if recurrent seizure on maintenance infusion
Magnesium Sulfate Maintenance Infusion	1 to 2 grams/hours	-Magnesium 20grams/500mL -Continue for 24 hours -Dose adjustment for renal dysfunction
Monitoring		Urine output, respirations, deep tendon reflexes (DTRs), magnesium levels (?)
Caution/Contraindications		Pulmonary edema, renal failure, myasthenia gravis

The American College of Obstetricians and Gynecologists. Gestational Hypertension and Preeclampsia. Practice Bulletin. Number 222. June 2020.

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Magnesium Monitoring

Check Magnesium level if –

- Altered consciousness, absence of DTRs, decreased respirations, muscle weakness
- Calcium gluconate 1g IV push over 3 mins for life-threatening magnesium toxicity

Table 2. Serum Magnesium Concentration and Toxicities

Serum Magnesium Concentration			
mmol/L	mEq/L	mg/dL	Effect
2–3.5	4–7	5–9	Therapeutic range
>3.5	>7	>9	Loss of patellar reflexes
>5	>10	>12	Respiratory paralysis
>12.5	>25	>30	Cardiac arrest

Data from Duley L. Magnesium sulphate regimens for women with eclampsia: messages from the Collaborative Eclampsia Trial. Br J Obstet Gynaecol 1996;103:103–5 *and* Lu JF, Nightingale CH. Magnesium sulfate in eclampsia and pre-eclampsia: pharmacokinetic principles. Clin Pharmacokinet 2000;38:305–14.

The American College of Obstetricians and Gynecologists. Gestational Hypertension and Preeclampsia. Practice Bulletin. Number 222. June 2020.

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Pregnancy Induced Hypertension

Table 3. Antihypertensive Agents Used for Urgent Blood Pressure Control in Pregnancy

Drug	Dose	Comments	Onset of Action
Labetalol	10–20 mg IV, then 20–80 mg every 10–30 minutes to a maximum cumulative dosage of 300 mg; or constant infusion 1–2 mg/min IV	Tachycardia is less common with fewer adverse effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.	1–2 minutes
Hydralazine	5 mg IV or IM, then 5–10 mg IV every 20–40 minutes to a maximum cumulative dosage of 20 mg; or constant infusion of 0.5–10 mg/hr	Higher or frequent dosage associated with maternal hypotension, headaches, and abnormal fetal heart rate tracings; may be more common than other agents.	10–20 minutes
Nifedipine (immediate release)	10–20 mg orally, repeat in 20 minutes if needed; then 10–20 mg every 2–6 hours; maximum daily dose is 180 mg	May observe reflex tachycardia and headaches	5–10 minutes

Abbreviations: IM, intramuscularly; IV, intravenously.

The American College of Obstetricians and Gynecologists. Gestational Hypertension and Preeclampsia. Practice Bulletin. Number 222. June 2020.

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Pregnancy Induced Hypertension

Table 2. Common Oral Antihypertensive Agents in Pregnancy

Drug	Dosage	Comments
Labetalol	200–2,400 mg/d orally in two to three divided doses. Commonly initiated at 100–200 mg twice daily	Potential bronchoconstrictive effects. Avoid in women with asthma, preexisting myocardial disease, decompensated cardiac function, and heart block and bradycardia.
Nifedipine	30–120 mg/d orally of an extended-release preparation. Commonly initiated at 30–60 mg once daily (extended-release)	Do not use sublingual form. Immediate-release formulation should generally be reserved for control of severe, acutely elevated blood pressures in hospitalized patients. Should be avoided in tachycardia.
Methyldopa	500–3,000 mg/d orally in two to four divided doses. Commonly initiated at 250 mg twice or three times daily	Safety data up to 7 years of age in offspring. May not be as effective as other medications, especially in control of severe hypertension. Use limited by side effect profile (sedation, depression, dizziness).
Hydrochlorothiazide	12.5–50 mg daily	Second-line or third-line agent

The American College of Obstetricians and Gynecologists. Chronic Hypertension in Pregnancy. Practice Bulletin. Number 203. Jan 2019.

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Chronic Hypertension and Pregnancy (CHAP) Trial

NEJM, May 2022

- N=2408
- Open-label, multicenter, randomized
- Pregnant women with mild CHTN
- Target blood pressure <140/90 was associated with better pregnancy outcomes with no increase in risk of small for gestational age birth weight

★ **ACOG recommends utilizing 140/90 as the threshold for initiation or titration of medical therapy for CHTN in pregnancy, rather than the previously recommended threshold of 160/110**

Tita AT, et al. Treatment for Mild Chronic Hypertension during Pregnancy. NEJM. 12 May 2022. 386(19): 1781-92.

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Aspirin for Preeclampsia Prevention

Table 1. Clinical Risk Factors and Aspirin Use*

Level of Risk	Risk Factors	Recommendation
High†	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Type 1 or 2 diabetes • Renal disease • Autoimmune disease (ie, systemic lupus erythematosus, the antiphospholipid syndrome)	Recommend low-dose aspirin if the patient has one or more of these high-risk factors
Moderate‡	• Nulliparity • Obesity (body mass index greater than 30) • Family history of preeclampsia (mother or sister) • Sociodemographic characteristics (African American race, low socioeconomic status) • Age 35 years or older • Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, more than 10-year pregnancy interval)	Consider low-dose aspirin if the patient has more than one of these moderate-risk factors§
Low	• Previous uncomplicated full-term delivery	Do not recommend low-dose aspirin

Aspirin 81mg for pre-eclampsia prophylaxis initiated between 12 - 28 weeks (optimally before 16 weeks of gestation) and continuing until delivery

The American College of Obstetricians and Gynecologists. Gestational Hypertension and Preeclampsia. Practice Bulletin. Number 222. June 2020.

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Conclusions

- Physiological changes occur during pregnancy and should be accounted for when dosing medications.
- Pregnancy and lactation references should be consulted in order to provide risk vs benefit information to providers and patients.
- Tocolytics are utilized to perform interventions that may have neonatal benefits (steroids and/or magnesium).
- Progesterone may be considered for prevention of preterm birth.
- Hospitals should be equipped to handle postpartum hemorrhage.
- Hypertensive disorders of pregnancy are one of the leading causes of maternal and perinatal mortality worldwide.
- Aspirin may be recommended, depending on patient risk factors, for pre-eclampsia prevention.

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Questions?

Lindsey.Foster@northside.com

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