Pharmacotherapy Update

COMMON MEDICAL CONDITIONS DURING PREGNANCY AND BREASTFEEDING

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Introduction

- Although the risk of drug-induced teratogenicity is of concern, the actual risk of birth defects is small.
- Although the risk of drug-induced teratogenicity is of concern, the actual risk of birth defects from most drug exposures is small.
- The baseline risk (also known as background risk) for congenital malformations is approximately 3% to 5%
- Medications are associated with less than 1% of all congenital anomalies
- There are approximately 30 medication or classes of medications that are considered teratogens
- A medication on this list is not necessarily contraindicated as severity and occurrence of malformations vary from one agent to another.
- Some can be used when benefits outweigh potential risks

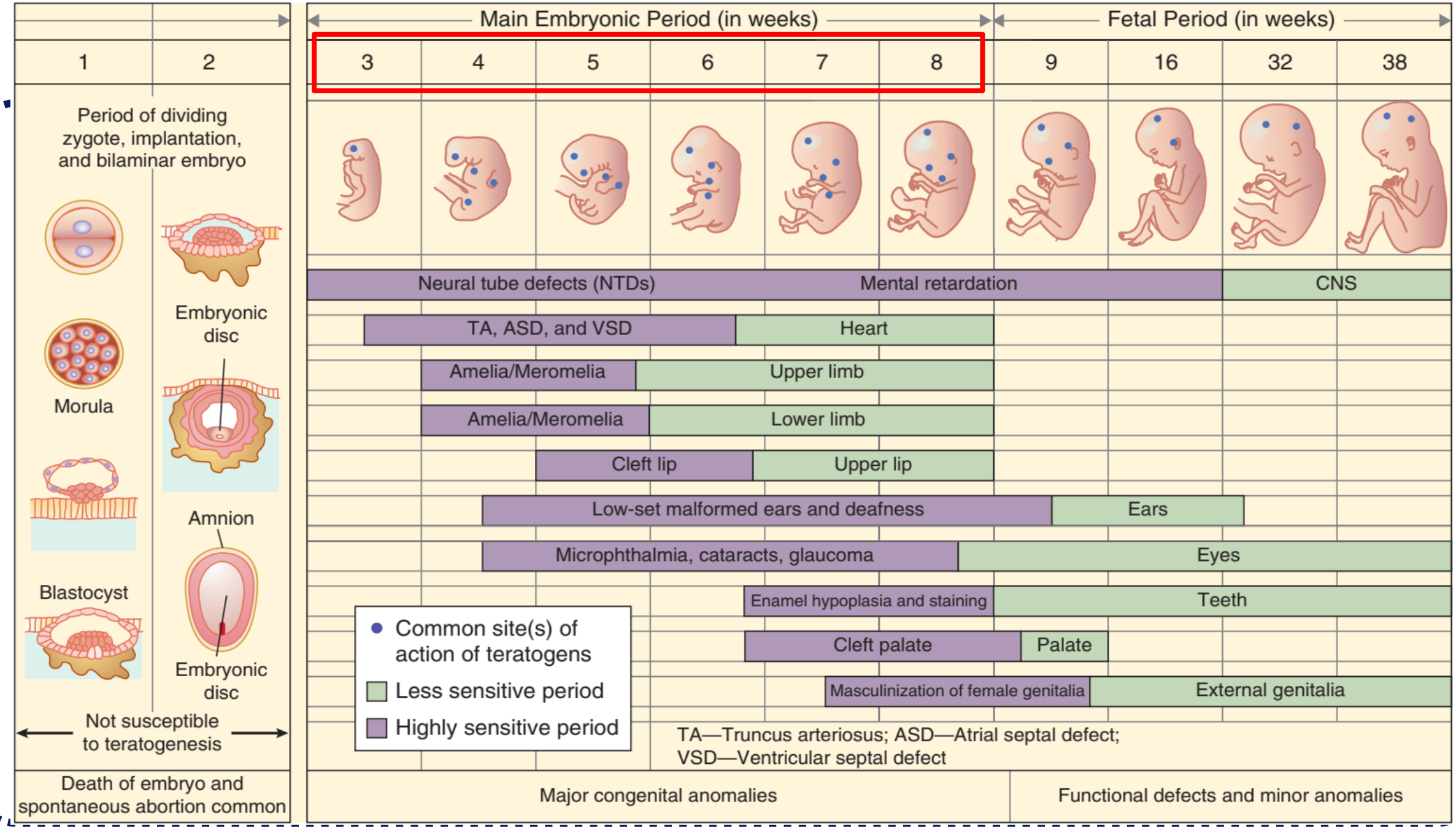
Introduction

- In the first 4 weeks of gestation (**Germinal** period), exposure to a teratogen may result in an "all-or-none" phenomenon which could either destroy the embryo or cause no problems
- **Organogenesis** occurs during the embryonic period (from weeks 3 through 8) when organ systems are developing; therefore, teratogenic exposures may result in structural anomalies.
- For the remainder of the pregnancy (**Fetal** period), exposure to teratogens may result in growth restriction, CNS abnormalities, impaired organ function (such as renal), and stillbirth (fetus loss after the 20th week).
- Factors such as the stage of pregnancy during exposure, medication route of administration, and dose can also affect outcomes

Phases of Embryonic and Fetal Development[3,4]

Phase of Development	Stage of Pregnancy[a]	Development Description	Potential Complications
Implantation and predifferentiation	0–14 days after conception (14–28 days after LMP)	Very little contact between the blastocyst and mother's blood Pluripotent cells, capacity to repair a damage Cells are fragile, miscarriage before pregnancy is detected if too many are destroyed	Spontaneous abortion; even if stopped during this period, long half-life drugs could affect organogenesis
Organogenesis (embryogenesis)	From day 14 until the 9th week after conception (From day 28 until the 11th week after LMP)	Organs are being formed; most critical period for structural anomalies Organs are being formed at different times; sensitivity for each organ differs Refer to Figure 47–1 for the time frame of organ formation	Major or minor structural anomalies; Spontaneous abortion; neurologic impairment
Fetogenesis	After the organogenesis and until birth	The fetus grows Organs begin to function (eg, glomerular filtration) Active cell growth, proliferation, and migration (eg, CNS)	Fetal growth retardation; functional deficit (eg, renal insufficiency), neurologic impairment; spontaneous abortion, stillbirth; neonatal complications

[a]Stage of pregnancy based on a menstrual cycle of 28 days.


Main Embryonic Period (in weeks)
Fetal Period (in weeks)
1
2
3
4
5
6
7
8
9
16
32
38
Period of dividing zygote, implantation, and bilaminar embryo
Morula
Blastocyst
Embryonic disc
Amnion
Embryonic disc
Not susceptible to teratogenesis
Death of embryo and spontaneous abortion common
Neural tube defects (NTDs)
Mental retardation
CNS
TA, ASD, and VSD
Heart
Amelia/Meromelia
Upper limb
Amelia/Meromelia
Lower limb
Cleft lip
Upper lip
Low-set malformed ears and deafness
Ears
Microphthalmia, cataracts, glaucoma
Eyes
Enamel hypoplasia and staining
Teeth
Cleft palate
Palate
Masculinization of female genitalia
External genitalia
Common site(s) of action of teratogens
Less sensitive period
Highly sensitive period
TA—Truncus arteriosus; ASD—Atrial septal defect;
VSD—Ventricular septal defect
Major congenital anomalies
Functional defects and minor anomalies

Preconception Risk Factors

Preconception Risk Factor	Potential Adverse Pregnancy Outcomes	Management or Prevention Options
Use of known teratogens		
• Antiseizure Medications	• Some are known teratogens; causes craniofacial, cardiac, and limb defects[a] • NTD • Fetal hydantoin syndrome	• Optimize to lower risk therapy while maintaining control prior to conception • Avoid valproic acid • use monotherapy if possible • Start folic acid at least 0.4 mg daily preferably at least 1 month prior to conception
• Retinoids	• Spontaneous abortion • Known teratogen; causes CNS, craniofacial, and cardiac defects[a]	• Discontinue at least 1 month (isotretinoin, bexarotene) or 3 years (acitretin) before attempting conception • Enrolled in iPLEDGE (isotretinoin), Education and Pregnancy Prevention for Acitretin (EPPA) or Do Your P.A.R.T. (acitretin). Follow manufacturer recommendations for contraception (isotretinoin, acitretin, bexarotene)
• Warfarin	• Fetal warfarin syndrome	• Switch to nonteratogenic anticoagulant (eg, LMWH) before becoming pregnant • Patients with mechanical valves may remain on warfarin for some or all of the pregnancy
Lifestyle factors		

Preconception Risk Factors

Lifestyle factors		
• Alcohol use	• Fetal alcohol syndrome	• Cease alcohol intake before conception
• Obesity	• Malformations (eg, NTD and orofacial) • Preterm delivery • Spontaneous abortion • Stillbirth • Macrosomia • Impaired growth • Cesarean section	• Weight loss with appropriate nutritional intake before pregnancy
• Tobacco use	• Preterm birth • Low birth weight • Spontaneous abortion • Increased perinatal mortality • Orofacial clefts • Intrauterine growth restriction • Sudden infant death syndrome	• Ideally, cease tobacco use before conception • Individualize approach with nonpharmacologic therapies (including psychosocial and behavioral interventions like CBT, motivational interviewing, and counseling) and can consider NRT products, bupropion, varenicline. Discuss risks and benefits with the patient
• Cannabis use	• Intrauterine fetal demise • Low birth rate[b] • Preterm delivery[b]	• Ask about medical and nonmedical use of marijuana in all patients • Educate about potential risks • Encourage to discontinue use ideally prior to conception

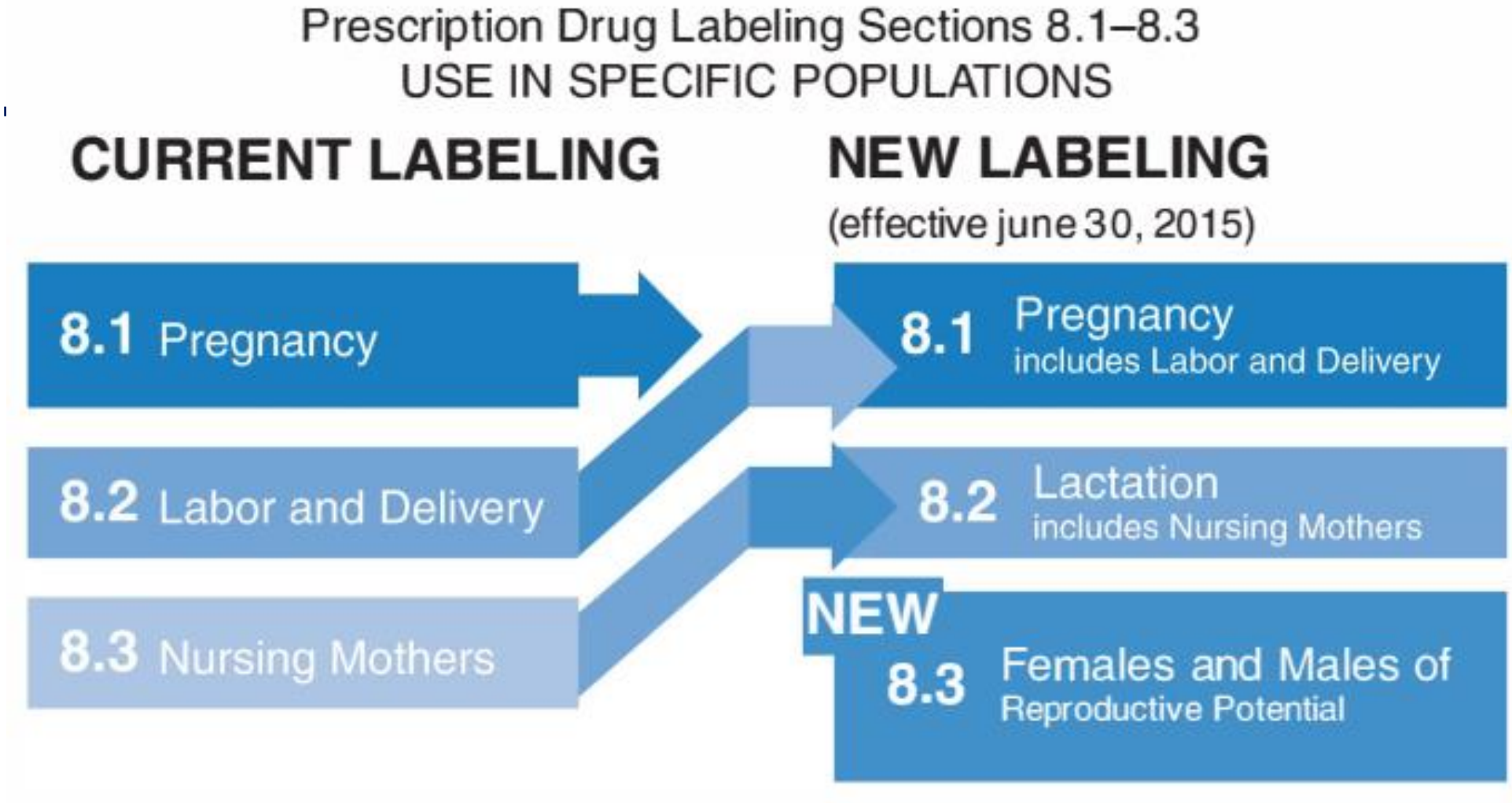


Figure 49-1 FDA Labeling. (Source: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm)

Table 9. Previous FDA Pregnancy Risk Categories

A: Controlled studies of women fail to show risk.
B: Animal studies indicate no risk, or animal studies show a risk that has not been shown in human studies.
C: No available studies of women or animals, or animal studies have shown a risk.
D: Positive evidence of fetal risk.
X: Definite fetal risk in animals or women.

3. The FDA decided current pregnancy risk categories were inadequate; therefore, in 2008 the FDA recommended a new labeling system that became effective June 30, 2015 that includes the following:
    a. Pregnancy (includes labor and delivery)
        i. Fetal risk summary
        ii. Clinical considerations
        iii. Data section
        iv. Information for exposure registries
    b. Lactation
    c. Females and males of reproductive potential
4. New labeling has taken place for new products approved after June 30, 2015; older products will be phased in over the next few years.

E. Factors to Consider When Initiating Medications in Pregnant Women (Tables 10, 11, 12, and 13)
    1. Risk-benefit ratio
    2. Is drug necessary?
    3. Most effective agent with least risk
    4. Lowest effective dosage for shortest possible duration
    5. Health of mother without drug

Factors Affecting the Fate of Drugs in Milk and the Nursing Infant

Maternal Parameters

- Drug dosage and duration of therapy
- Route and frequency of administration
- Metabolism
- Renal clearance
- Blood flow to the breasts
- Milk pH
- Milk composition

Drug Parameters

- Oral bioavailability (to patient and infant)
- Molecular weight
- pK_a
- Lipid solubility
- Protein binding

Infant Parameters

- Age of the infant
- Feeding pattern
- Amount of breast milk consumed
- Drug absorption, distribution, metabolism, elimination

Reducing Risk of infant Exposure during lactation

- Give the maternal dose immediately after the infant has been fed with aim of avoiding feeding at peak concentrations
  - This is often impractical, esp. where young infants are feeding frequently up to 2 hourly.
  - Accurate data on times of peak levels in milk are often unavailable, and it cannot be assumed that times of peak milk levels mirror those in plasma.
  - This technique should be used selectively, where the drug has a short half-life and where peak and trough levels are predictable (e.g. antibiotics, anaesthetics)
- Where the half-life is very long, the washout period necessary to avoid hazardous exposure to the infant may exceed the period of sustainable lactation (radiopharmaceutical)
- Avoid self-medication; If clearly indicated, the lowest effective dose for the shortest possible time.
- Use of topical therapy, such as eye/nasal drops for hay fever, would reduce drug exposure in comparison with oral antihistamines
- Pump and discard milk if the necessary medication is not considered compatible with breastfeeding

Reducing Risk of infant Exposure during lactation

- New drugs are best avoided if a therapeutic equivalent & Safe is available
- All infants exposed to drugs via breast milk should be monitored for any untoward effects
- Avoid herbal & drugs known to cause serious toxicity products because of lack of data to support safe use
- Recognize risk factors, e.g. prematurity, infant morbidity and multiple maternal medications
- If using a once daily medication, administration before the infant's longest sleep period
- Pediatric approved use of the medication
- Low or very low RID:< 10%, <5%, or<1%
- Shorter T1/2, high PB, and high MW, lower oral bioavailability and lower lipid solubility
- Previous experience with drug in lactation
- If the infant has a known or suspected G6PD deficiency?

Reducing Risk of Infant Exposure to Drugs in Breast Milk

A drug should be used only if medically necessary, and treatment cannot be delayed until the infant is ready to be weaned.
Drug Selection
Consider whether the drug can be safely given directly to the infant.
Select a drug that passes poorly into breast milk with the lowest predicted M/P ratio, and a RID <10%.
Avoid long-acting formulations (eg, sustained release).
Consider possible routes of administration that can reduce drug excretion into milk.
Determine length of therapy and if possible avoid long-term use.
Feeding Pattern
Avoid nursing during times of peak drug concentration.
If possible, plan breast-feeding before administration of the next dose.
Other Considerations
Always observe the infant for unusual signs (eg, sedation, irritability, rash, decreased appetite, failure to thrive).
Discontinue breast-feeding during the course of therapy if the risks to the fetus outweigh the benefits of nursing.
Provide adequate patient education to increase understanding of risk factors.

M/P, milk-to-plasma ratio; RID, relative infant dose.

References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Medications & Mothers' Milk™
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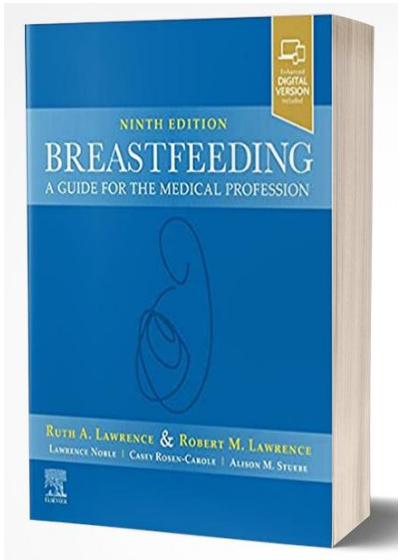
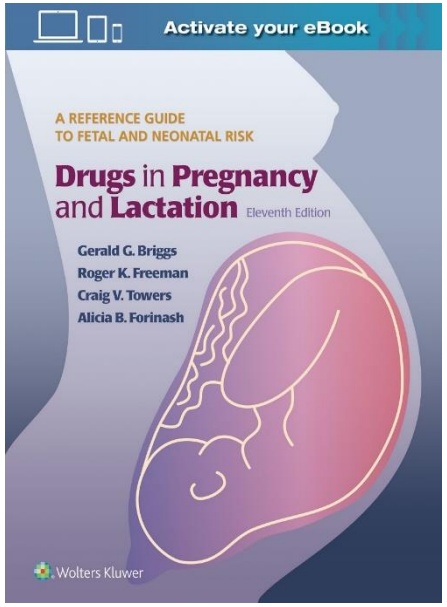
Thomas W. Hale, R.Ph., Ph.D.


NINTH EDITION
BREASTFEEDING
A GUIDE FOR THE MEDICAL PROFESSION
RUTH A. LAWRENCE & ROBERT M. LAWRENCE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A REFERENCE GUIDE
TO FETAL AND NEONATAL RISK
Drugs in Pregnancy and Lactation
Eleventh Edition
Gerald G. Briggs
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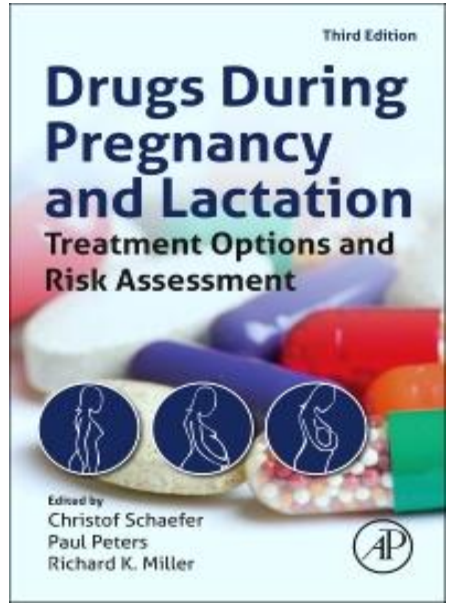
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Paul Peters
Richard K. Miller

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- Hale TW. Medications and Mother's Milk, 17th ed. New York: Springer Publishing Company, LLC, 2017.

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- Reprotox: www.reprotox.org
- Teris (Teratogen Information System): http://depts.washington.edu/terisweb/teris/

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Websites/Applications

- www.mothertobaby.org
- www.motherisk.org
- www.marchofdimes.org
- www.cdc.gov
- www.fda.gov
- https://www.ncbi.nlm.nih.gov/pubmed/
- List of pregnancy registries: http://www.fda.gov/pregnancyregistries
- Lactmed: https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

Teratology Information Service

- MotherToBaby, a service of Organization of Teratology Information Specialists (OTIS): Go to *www.mothertobaby.org* to find your local Teratogen Information Service, or call National Toll-Free Number: (866) 626-6847

SELECTED COMMON PROBLEMS/MEDICATIONS IN PREGNANCY & LACTATION

Folic acid

- Folate is required to support the increase in red cell volume that occurs during pregnancy.
- Folate is absorbed better following ingestion of a supplement than when it is consumed in food sources.
- Low maternal folate levels are associated with an increased risk of neural tube defects in the fetus.
- **Society of Obstetricians and Gynaecologists of Canada**
- **Low risk:** 0.4 mg/day from 2-3 mo. before conception and continuing until 4–6 weeks postpartum or as long as breastfeeding continues.
- **Moderate risk**: 1 mg/day beginning at least 3 months before conception and continuing until 12 weeks' gestational age; then 0.4–1 mg/day until 4–6 weeks postpartum or as long as breastfeeding continues.
- **High risk:** 4-5 mg/day beginning at least 3 months before conception and continuing until 12 weeks' gestational age; then 0.4–1 mg/day until 4–6 weeks postpartum or as long as breastfeeding continues.

Other recommendations: UTD

- **All women without any specific RF**: 0.4 from 1 mo. before conception and continuing throughout pregnancy
- **Women with a previous pregnancy affected by an NTD or with an NTD in either parent:** 4 mg/day from 1 mo. before conception until first trimester then 0.4 mg/day
- **Family history of NTD in a first- or second-degree relative**: 1 mg/day
- **On VPA or CBZ:** 4 mg and other AED: 0.4 mg
- **On triamterene, sulfasalazine, TMP:** 1 mg
- **History of GDM or medical conditions associated folate deficiency:** 1 mg

Iron

Prevention of IDA in pregnancy

- Since 1998, the CDC has recommended that all women receive, as primary prevention, 30 mg per day (or 27 mg) of oral iron supplements starting at the first prenatal visit.
- **Intolerant to the iron in prenatal vitamins:** take prenatal vitamins without iron and to supplement with oral iron supplements on an every-other-day basis typical dose, 60 mg once every other day (improved absorption and reduced GI adverse effects)
- Routine iron supplementation during pregnancy in nonanemic women (hemoglobin >130 g/L) may not be without adverse effects and 16 mg/day total supplementation is proposed.

Iron

- Intermittent iron supplementation (± folic acid) may be an alternative for preventing gestational anemia in non-anemic women with adequate antenatal care.
- Additionally, the risk of high hemoglobin concentrations may be reduced.
- The most commonly used intermittent dosing schedule is 120 mg weekly elemental iron, given on 1 day of the week in 2 divided doses.
- This regimen is not recommended for women who are anemic at the start of their pregnancy
- Intermittent supplementation is less likely to result in adverse events such as nausea and GI disturbances compared with a daily regimen, and results in similar maternal and infant outcomes.

Iron

During breastfeeding

- The RDA is 9 mg daily for women 19 years
- This recommendation is less than the RDA for non-lactating women (18 mg daily) and adolescents (15 mg daily) due to lactation-induced amenorrhea, which reduces iron loss.
- Postpartum use of a prenatal multivitamin (which provides approximately 30 mg daily of iron) is not necessary for a lactating woman, unless she is known to be iron deficient
- A multivitamin that contains less than 30 mg of iron may have fewer gastrointestinal side effects and be better tolerated.

Treatment of IDA in pregnancy

- Defined as Hb < 11 g/dl or Hct<33% in first and Hb<10.5/Hct<32% in second trimester
  - The CDC recommends that pregnant women who are anemic take 60–120 mg of elemental iron orally each day;
  - Or 60-200 mg EOD
  - If the anemia does not respond after 4 weeks of such treatment, further evaluation is advised to assess iron stores and look for causes of anemia other than iron deficiency

	RDAs		ULs for pregnant and lactating women
	Pregnant women*	Lactating women*	
Fat-soluble vitamins			
Vitamin A	770 mcg	1300 mcg	3000 mcg
Vitamin D	600 international units (15 mcg)	600 international units (15 mcg)	4000 international units (100 mcg)
Vitamin E	15 mg	19 mg	1000 mg
Vitamin K¶	90 mcg	90 mcg	ND
Water-soluble vitamins			
Vitamin C	85 mg	120 mg	2000 mg
Thiamin	1.4 mg	1.4 mg	ND
Riboflavin	1.4 mg	1.6 mg	ND
Niacin	18 mg	17 mg	35 mg
Vitamin B6	1.9 mg	2 mg	100 mg
Folate	600 mcg	500 mcg	1000 mcg
Vitamin B12	2.6 mcg	2.8 mcg	ND
Minerals			
Calcium	1000 mg	1000 mg	2500 mg
Phosphorus	700 mg	700 mg	4000 mg
Iron	27 mg	9 mg	45 mg
Zinc	11 mg	12 mg	40 mg
Iodine	220 mcg	290 mcg	1100 mcg
Selenium	60 mcg	70 mcg	400 mcg

Constipation

- Because of hormonal (progesterone) and mechanical factors; affecting almost 40% of individuals
- Increasing dietary fiber and fluids or using bulk-forming laxatives (eg, psyllium) are safe for long-term use because they are not absorbed; can cause gas, bloating, and cramping and can aggravate NVP
- Osmotic laxatives (eg, **PEG**, Lactulose,, MOM, and sorbitol) can also be used. Polyethylene glycol is the preferred medication for patients with chronic constipation during pregnancy
- Use of magnesium and sodium salts may cause electrolyte imbalance.
- If those fail, a short-term application of bisacodyl (< 3 days per week) and rectal glycerol are acceptable
- Senna is probably safe in pregnancy in short term (< 10 days, some suggest to avoid due to possible uterine contraction and limited data)
- Castor oil and mineral oil should be avoided (stimulation of uterine contractions and impairment of maternal fat-soluble vitamin absorption, respectively).

Hemorrhoid

- Conservative treatment (i.e., high dietary fiber intake, adequate oral fluid intake, and use of sitz baths) should be tried first.
- Laxatives and stool softeners can be used if conservative management is inadequate for preventing or treating constipation.
- Topical anesthetics and skin protectants (Zinc) can be used for anal irritation and pain.
- Hydrocortisone may reduce inflammation and pruritus

GERD

- Up to 80% of individuals experience gastroesophageal reflux disease during pregnancy.
- Lifestyle and dietary modifications, such as eating smaller meals, avoiding late meals close to bedtime, and elevation of the head of the bed, should be tried first (first line).
- Antacids including AL-based (eg. Sucralfate), calcium, or magnesium hydroxides are considered safe during pregnancy and lactation (second line in intermittent episodes)
- Ca and Mg antacid reduce risk of hypertension, pre-eclampsia and eclampsia
- Famotidine, **omeprazole** and pantoprazole, if indicated in pregnancy and lactation; Twice daily dosing with
- H2RA therapy is commonly used in pregnancy
- Human pregnancy and lactation experience with other PPI is limited
  - Recent 2020 meta-analysis suggests an association between maternal PPI use and congenital malformation but, yet power was insufficient

Nausea and vomiting of pregnancy

- NVP usually begins between weeks 4 and 6 of gestation and usually resolves by weeks 16 to 20, peak symptoms occur between weeks 8 and 12; impacts 50% to 80% of pregnant individuals
- Hyperemesis gravidarum (HG; ie, unrelenting vomiting causing weight loss of more than 5 % prepregnancy weight, dehydration, electrolyte imbalance, and ketonuria) occurs in 0.3 % to 3 % of women.
- Nonpharmacologic measures, such as lifestyle (rest, avoidance of nausea triggers) and dietary changes (small/frequent meals q 1-2 hrs, fluid restriction during meals, avoiding spicy/fatty foods, consuming crackers upon rising, high protein snacks) should be used as first-line management
- ACOG recommends ginger 250 mg capsules four times daily if needed
- Treatment of NVP with vit-B6 alone or in combination plus doxylamine in combination is safe and effective and should be considered first-line pharmacotherapy (ACOG 2018)

Nausea and vomiting of pregnancy

- The standard recommendation to take prenatal vitamins for 1 month before fertilization may reduce the incidence and severity of nausea and vomiting of pregnancy (ACOG 2018)
- If symptoms persist, second line add-on therapies include dimenhydrinate, diphenhydramine, prochlorperazine, and promethazine.
- Phenothiazines or metoclopramide (<12 week duration) is usually prescribed if antihistamines fail.
- In next step, ondansetron can be used (controversies regarding anomalies in < 10 week)
  - Ondansetron use prior to 10 weeks gestation should be individualized by patient, after careful consideration of the associated risks and benefits
- Treatment of severe nausea and vomiting of pregnancy or hyperemesis gravidarum with IV fluied and other injectable agents (metoclopramide, ondansetron, or promethazine)
- Methylprednisolone may be efficacious in refractory cases; better to reserve until after 10 weeks gestation

First Line Therapy: Nonpharmacologic options

Convert prenatal vitamin to folic acid supplement only

Ginger capsules 250 mg four times daily

Consider P6 acupressure with wrist bands

↓ Persistent symptoms

Pharmacologic Options*

Vitamin B_6 (pyridoxine) 10–25 mg orally (either taken alone or in combination with Doxylamine† 12.5 mg orally), 3 or 4 times per day. Adjust schedule and dose according to severity of patient's symptoms.

OR

Vitamin B_6 (pyridoxine) 10 mg/Doxylamine 10 mg combination product, two tablets orally at bedtime initially, up to four tablets per day (one tablet in the morning, one tablet in midafternoon, and two tablets at bedtime)

OR

Vitamin B_6 (pyridoxine) 20 mg/Doxylamine 20 mg combination product, one tablet orally at bedtime initially, up to two tablets per day (one tablet in the morning and one tablet at bedtime)

↓ Persistent symptoms

Add the following:

(presented here in alphabetical order)

Dimenhydrinate, 25–50 mg every 4–6 hours, orally as needed (not to exceed 200 mg per day if patient also is taking doxylamine)

OR

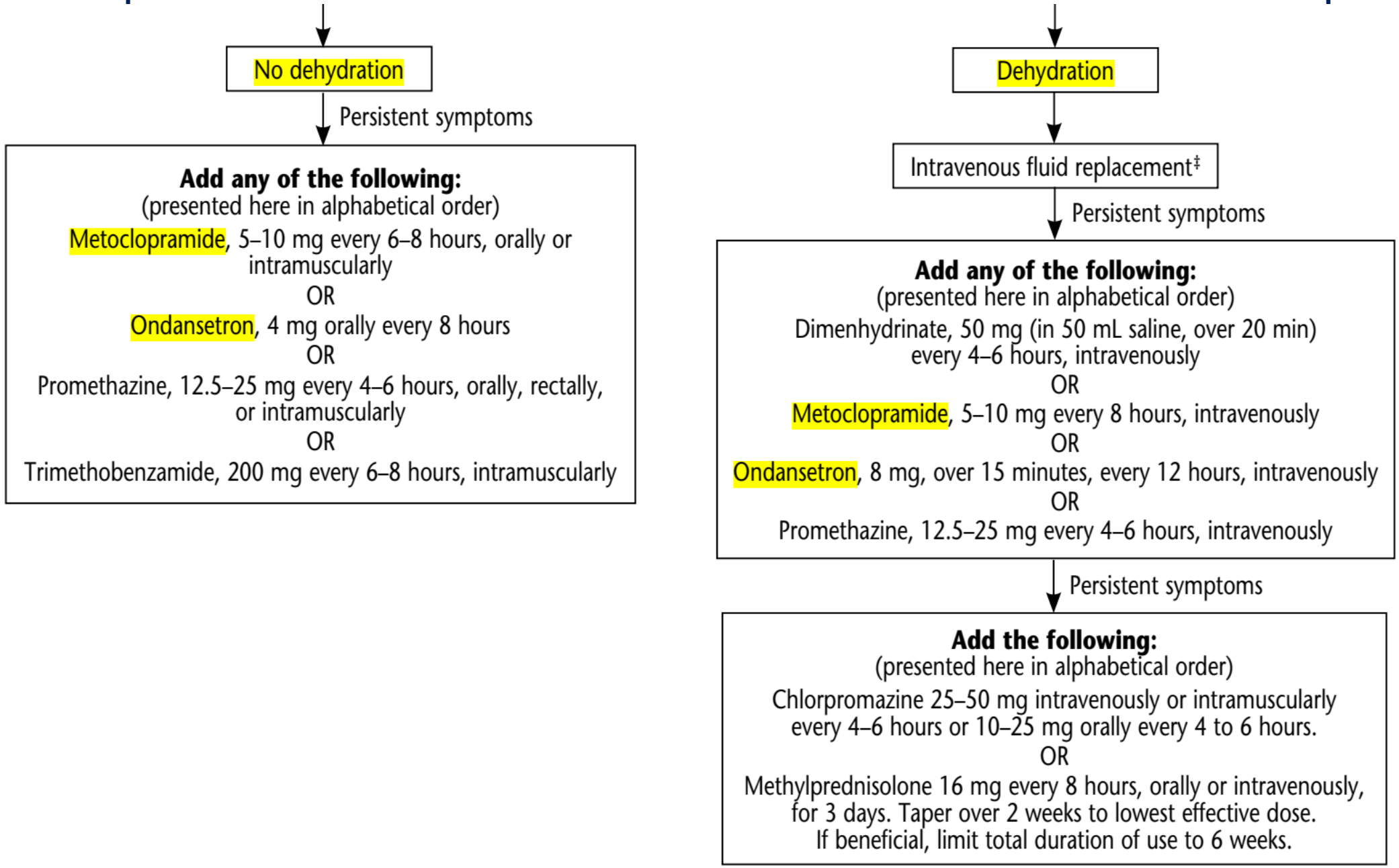
Diphenhydramine, 25–50 mg orally every 4–6 hours

OR

Prochlorperazine, 25 mg every 12 hours rectally

OR

Promethazine, 12.5–25 mg every 4–6 hours, orally or rectally


No dehydration
Persistent symptoms
Add any of the following:
(presented here in alphabetical order)
Metoclopramide, 5–10 mg every 6–8 hours, orally or intramuscularly
OR
Ondansetron, 4 mg orally every 8 hours
OR
Promethazine, 12.5–25 mg every 4–6 hours, orally, rectally, or intramuscularly
OR
Trimethobenzamide, 200 mg every 6–8 hours, intramuscularly
Dehydration
Intravenous fluid replacement‡
Persistent symptoms
Add any of the following:
(presented here in alphabetical order)
Dimenhydrinate, 50 mg (in 50 mL saline, over 20 min) every 4–6 hours, intravenously
OR
Metoclopramide, 5–10 mg every 8 hours, intravenously
OR
Ondansetron, 8 mg, over 15 minutes, every 12 hours, intravenously
OR
Promethazine, 12.5–25 mg every 4–6 hours, intravenously
Persistent symptoms
Add the following:
(presented here in alphabetical order)
Chlorpromazine 25–50 mg intravenously or intramuscularly every 4–6 hours or 10–25 mg orally every 4 to 6 hours.
OR
Methylprednisolone 16 mg every 8 hours, orally or intravenously, for 3 days. Taper over 2 weeks to lowest effective dose.
If beneficial, limit total duration of use to 6 weeks.

Cold/Allergy

- Rest, fluids, humidified air, nasal saline, and acetaminophen for the common cold symptoms.
- Avoiding irritants and known allergens
- Avoid NSAID for more than 48 hours in 20-28 weeks of GA (kidney dysfunction , oligohydramnios). If used, F/U with ultrasonography; Avoid NSAID after 28 week with any duration
- Treat cough with occasional oral dextromethorphan in pregnancy and lactation
- (a) Avoid oral decongestants during the first trimester owing to the risk of fetal gastroschisis (incidence 4–6 per 10,000 treated women vs 1/10,000) (F/U US if used)
- Pseudoephedrine can be used in the second and third trimesters in women without HTN.

Cold/Allergy

- Phenylephrine best to avoided (malformations, lower efficacy, strong α2-agonist in uterine)
- (b) Short-term topical oxymetazoline, or INCs may be preferable to use of oral decongestants, especially during early pregnancy
- (c) Most first- and second-generation antihistamines are safe (cetirizine, loratadine, diphenhydramine in pregnancy and cetirizine and loratadine in lactation)
- (d) Intranasal cromolyn and INCs (budesonide/beclomethasone/fluticasone/ mometasone) are choice for chronic rhinitis in pregnancy/lactation
- ACC & Bromhexine safe in pregnancy and lactation.
- Use of Pseudoephedrine in lactation is not recommended (it may cause irritability occasionally and decrease milk supply)

Asthma

- The general principles are similar to non-pregnant patients and involve a step-wise approach, as recommended by national and international guidelines
- Use Salbutamol for quick relief of symptoms or alternatively, formetrol/low dose ICS
- Budesonide is preferred during pregnancy and lactation, although other ICS corticosteroids that were effective before pregnancy can be continued
- LABA is safe in pregnancy and lactation
- Montelukast could be considered as alternative but NOT preferred with extra-caution in first trimester (F/U sono due to possible malformation in some report)
- Treat attack in similar manner with non-pregnant (SABA, CSs, SAMA, Mg)
- 2000-4000 IU/day VIT.D reduce the risk of early life asthma/wheeze in the offspring

Urinary Tract Infection

- Bacteriuria occurs commonly in pregnancy, typically during early pregnancy.
- Common causes: Escherichia coli (75% to 90%), Proteus, Klebsiella
- Screen all women at 12-16 week of GA with U/C
- Treat ASB and simple cystitis with potential options for 3-7 days.
- Beta-lactams (usually ampicillin, amoxicillin or cephalexin), nitrofurantoin (avoid near term after week 37 and caution in first trimester), and fosfomycin (3 gram single dose) & F/U culture
- TMP-SMX should be avoided during organogenesis (congenital malformations; TMP) and near term or 3rd trimester in some guidelines (theoretical risk of kernicterus; SMX)
- Quinolones are reserved for resistant infections due to theoretical concerns of arthropathy

FQs during lactation

- Fluoroquinolones have traditionally not been used in infants because of concerns regarding adverse effects on joint development. Studies indicate little risk.
- Short-term use of ciprofloxacin, levofloxacin, norfloxacin or ofloxacin is acceptable in nursing mothers. These quinolones are transferred into breast milk in small amounts and do not result in significant serum concentrations in breastfed infants.
- Avoiding breastfeeding for 4–6 h after a dose should decrease infant exposure to the drug.
- The calcium in breast milk may also decrease quinolone absorption in the infant.
- There are no data available for moxifloxacin.

Bacterial Vaginosis

- Associated with spontaneous abortion, premature rupture of the membranes, chorioamnionitis, preterm birth, post-cesarean wound infection, postpartum endometritis, and pelvic inflammatory disease
- Treatment is recommended in symptomatic women or in asymptomatic women at high risk for preterm delivery.
- Pregnant women with symptomatic disease should be treated with one of the following recommended regimens (CDC):
  - Metronidazole 500 mg twice a day for 7 days, or
  - Metronidazole 250 mg orally 3 times a day for 7 days, or
  - Clindamycin 300 mg orally twice a day for 7 days

Bacterial Vaginosis

- Meta-analysis has not found any relationship between metronidazole exposure during the first trimester of pregnancy and birth defects
- Metronidazole is deemed safe for use by the CDC during all stages of pregnancy despite package labeling listing a contraindication in the first trimester.
- Concern regarding mutagenic in bacteria and carcinogenic in mice but there is no evidence of harm in humans.
- Tinidazole is not recommended in pregnancy.
- Oral clindamycin is an option for women who do not tolerate metronidazole, but its efficacy is lower than that of metronidazole in non-pregnant populations.
- Avoid clindamycin vaginal cream in pregnancy due to association with low birth weight and neonatal infection.

Bacterial Vaginosis

- In **breastfeeding**: Metronidazole 500 mg BD or 250 mg TDS for 7-10 days (FSRH, NHS, UTD) with the lowest breastfeeding in peak of drug
- In other indications, metronidaozle single dose 2 gram and 2 gram daily up to 3 days are considered to be compatible with breastfeeding (NHS); monitor infant for loose stools, candidiasis, rash, lactose intolerance and metallic/bitter taste
- Pumping and expelling breast milk for 12 hours after metronidazole SD or for 72 hours after tinidaozle is an option.
- Clindamycin is an option in breastfeeding with special attention for side effects in infant gastrointestinal flora (diarrhea, candidiasis (thrush, diaper rash) or, rarely, blood in the stool indicating possible antibiotic-associated colitis)

Vulvovaginal candidiasis

- For pregnant and lactation women with symptomatic VVC, application of a vaginally imidazole (clotrimazole or miconazole) for 7 days is preferred
- Fluconazole, used in high doses (>400 mg daily) for a prolonged period of time during the 1st trimester of pregnancy, may be associated with fetal malformations (craniofacial, skeletal and cardiac malformations)
- Nystatin 100,000-200,000 nightly for 14 days is an option
- Use of boric acid in pregnant women is not recommended
- Oral single dose of fluconazole is safe in lactation, widely distributed in tissues, and the highest concentrations in breast milk are less than neonatal dosage

Trichomoniasis

- T. vaginalis infection in pregnant women is associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and delivery of a low birth weight infant
- All symptomatic pregnant women should be treated, regardless of pregnancy stage.
- CDC-recommended regimen metronidazole **500 mg BD for 7 days** (preferred by some clinicians to lessen N/V) or 2 g orally in a single dose in pregnancy and lactation
- Pumping and expelling breast milk for 12 hours after metronidaozle SD or for 72 hours after tinidaozle is an option.

TABLE 99-5 Management of Sexually Transmitted Infections in Pregnancy

STI	Recommended Therapy	Alternative Therapy
Bacterial vaginosis	Metronidazole 500 mg by mouth twice daily for 7 days Metronidazole 0.75% gel 5 g intravaginally once daily for 5 days Clindamycin 2% cream 5 g intravaginally at bedtime for 7 days	Clindamycin 300 mg by mouth twice daily for 7 days Clindamycin ovules 100 mg intravaginally at bedtime for 3 days
Chlamydia	Azithromycin 1 g by mouth for 1 dose	Amoxicillin 500 mg by mouth three times a day for 7 days
Genital herpes	Suppression (starting at 36 weeks) Acyclovir 400 mg by mouth three times a day Valacyclovir 500 mg by mouth twice daily	
Gonorrhea	Ceftriaxone 500 mg IM for 1 dose. If chlamydia has not been excluded, treat for chlamydia as well.	Consult with infectious disease specialists or STI clinical expert if patient has a cephalosporin allergy or other reasons to not use the preferred treatment.
Syphilis[a]		
Primary, secondary, early latent	Benzathine penicillin G 2.4 million units IM for 1 dose; a second dose can be given 1 week after initial dose to help reduce the risk for congenital syphilis	
Tertiary[b], late latent[c]	Benzathine penicillin G 2.4 million units IM for 3 doses at 1-week intervals	
Neurosyphilis, ocular syphilis, otosyphilis	Aqueous crystalline penicillin G 3-4 million units IV every 4 hours or 18-24 million units IV continuously for 10-14 days	Procaine penicillin 2.4 million units IM daily for 10-14 days PLUS Probenecid 500 mg by mouth four times daily for 10-14 days
Trichomoniasis	Metronidazole 500 mg by mouth twice daily for 7 days	

Management of Pruritus during Pregnancy

- Calamine lotion are generally considered safe during pregnancy.
- There are no reports of teratogenicity with topical use of menthol or camphor.
- The local **anesthetics** lidocaine and prilocaine are generally considered safe for use on small areas for short periods of time (e.g., to facilitate skin biopsy or dental procedures) since their absorption is low
- There have been no reports of teratogenicity topical use of crotamiton during pregnancy
- Topical corticosteroids are useful if pruritus is caused by an inflammatory skin condition.

Management of Pruritus during Pregnancy

- Oral antihistamines are helpful in the specific case of urticaria.
  - Cetirizine and loratadine are the antihistamines of choice during pregnancy in lactation
  - Fexofenadine and desloratadine are safe alternatives
  - If the sedative side effect of a first-generation antihistamine is desired to improve sleep in patients with pruritus of any etiology, chlorpheniramine, diphenhydramine have the most evidence of safety in pregnancy (**caution in lactation**)
- Cromolyn sodium is considered compatible as it is poorly absorbed into the systemic circulation, and human data have not shown any risk of congenital malformations

Table 35-10 Drugs Used to Treat Intrahepatic Cholestasis of Pregnancy

Drug: Generic (Brand)	Dose	Formulation	Mechanism of Action
Cholestyramine (Questran)[a]	8–16 g/day in divided doses	4 g cholestyramine contained in 9-g powder packet	Bile acid sequestrant that binds bile acids in the gut to facilitate excretion
Diphenhydramine (Benadryl)	25–50 mg PO every 6–8 hours Maximum dose: 300 mg/day	25- or 50-mg tablets	Antihistamine treats itching but does not treat disorder
Hydroxyzine (Vistaril)	25–50 mg PO/day	25- or 50-mg tablets	Antihistamine treats itching but does not treat disorder
Ursodeoxycholic acid (ursodiol; Urso, Actigall)	15 mg/kg/day PO in divided doses Usual dose: 900 mg per day in divided doses	300-mg capsules 250- or 500-mg tablets	Natural water-soluble bile acid interferes with the nonsoluble bile acids that injure cell membranes, thereby decreasing release of pruritic agents
Vitamin K	10 mg PO/day	5-mg tablet	Fat-soluble vitamin that plays a role in the clotting cascade used to replace vitamin K as cholesteramine interferes with absorption of fat-soluble vitamins

[a] Cholestyramine is not as effective as ursodeoxycholic acid in reducing pruritus. Women treated with cholestyramine should be given supplemental fat-soluble vitamins and vitamin K 10 mg/day.

Pain medications

- Acetaminophen 650-1000 mg qid is first line in pregnancy and lactation
- Codeine for <9 days/month in pregnancy is next option (best to avoid in lactation)
- Ibuprofen, diclofenac and naproxen in pregnancy (<20 weeks GA) and lactation in next
- Avoid NSAIDs in third trimester and for more than 48 hours in >20 weeks GA (kidney dysfunction , oligohydramnios). If used, follow with ultrasonography
- Caffeine containing drugs (30-50 mg in drugs to total < 200 mg/day) is safe
- Occasional use of sumatriptan or rizatriptan (pregnancy) and eletriptan (lactation) for moderate to severe migraine
- Avoid ergotamine in pregnancy and lactation

Antidepressants during Pregnancy and lactation

- Sertraline, citalopram, escitalopram, fuxoetine are acceptable in pregnancy
- Sertraline, citalopram, paroxetine, nortriptyline and amitriptyline in lactation (not change medications for the purpose of breastfeeding if stable)
- Fluxetine and doxepine better to avoid in lactation
- SSRI peak between 4-8 hours after intake (minimize breastfeeding in this period time)
- Some data suggest that SSRIs (particularly paroxetine) may be associated with a small absolute increase in congenital heart defects, several studies have found no such association
- SSRIs are associated with postpartum hemorrhage.

Insomnia

- Orofacial malformations were the most feared consequence of benzodiazepine exposure but the risk appears small (0.1% vs. 0.06%) and, in some studies, nonexistent
- Benzodiazepines are associated with more prenatal and perinatal risks than zopiclone
- If needed, short term use of oxazepam and lorazepam
- Zolpidem has been associated with a higher risk of preterm deliveries
- There are no published data addressing the effectiveness and safety of L-tryptophan or low-dose doxepin in insomnia during pregnancy and their use should thus be avoided.
- Diphenhydramine, an antihistamine commonly used as a nonprescription hypnotic in pregnancy

Antidepressants during Pregnancy and lactation

- Tricyclics are reasonable to use during pregnancy (with the exception of clomipramine)
- Venlafaxine: is associated with more birth defects than any other antidepressant taken in the first months of pregnancy (JAMA 2020)
- Caution when use venlafaxine in lactation because infant exposure is relatively high, compared with some other antidepressants
- Minimize non-selective NSAID with serotonergic antidepressants

Depression	Citalopram, fluoxetine, sertraline,[88][90][91][100][101] tricyclic antidepressants	Other selective serotonin reuptake inhibitors, bupropion, venlafaxine	Neonatal withdrawal may occur when used in 3rd trimester. A questionable increase in the risk of cardiac malformations observed in some studies, mainly with paroxetine.[100][102][103][104] A small (<0.6%) absolute risk of persistent pulmonary hypertension of the newborn when SSRIs taken in the 2nd half of pregnancy suggested by some studies.[105][106][107] These are possibly associated with the underlying psychiatric disorder and confounding variables.

Hypertension

- Management of hypertension in pregnancy depends on the BP, gestational age, and the presence of associated maternal and fetal risk factors.
- Methyldopa, beta-blockers (most data available for labetalol), and CCB (most data available for nifedipine) are the drugs of Choice
- Beta-blockers appear to be less effective than calcium antagonists and may induce fetal bradycardia, growth retardation, and hypoglycaemia; consequently, their type and dose should be carefully selected, with atenolol best avoided
- Women with pre-existing hypertension may continue their current antihypertensive medication unless on ACEi, ARBs, and direct renin inhibitors, which are contraindicated due to adverse foetal and neonatal outcomes esp. in second and third trimester

Hypertension

- The use of diuretics during pregnancy carries a potential risk of oligohydramnios. Unless there is a compelling indication for the use of diuretics (e.g., heart failure), their use is not recommended.
- Atenolol is associated with fetal growth restriction and generally not utilized during pregnancy.
- For acute and Severe hypertension(≥ 160/110 mmHg): IV labetalol, hydralazine
- When HTN persists after delivery, antihypertensive drugs should be continued.
- In breastfeeding: Captopril, enalapril, CCBs (including amlodipine) and optional use of BBs (labetalol, metoprolol and propranolol)
- The ACOG suggests avoid methyldopa in postpartum women (postpartum depression risk)
- in breastfeeding women, furosemide is avoided unless prompt maternal diuresis is essential.

Anticoagulants

- Heprarin and LMWH (+ anti Xa monitoring) is safe in pregnancy and lactation
- Fondaparinux and injectable direct thrombin inhibitors (e.g., lepirudin, bivalirudin) should be avoided unless severe allergy to heparin (e.g., heparin-induced thrombocytopenia)
- DOACs is not recommended
- Warfarin should be avoided in pregnancy (except in women with mechanical heart valves), particularly in the first trimester (6-12 weks GA), because it may be teratogenic (Di Sala syndrome) can result in embryopathy (limb defects and nasal hypoplasia, CNS abnormalities, skeletal abnormalities) in 0.6–10% of cases
- Breastfeeding women may be treated with warfarin.

Anticoagulants

- The rates of embryopathy, miscarriage, and stillbirth occur with increased frequency with daily doses >5 mg
- Women with mechanical heart valves:
  - Guidelines recommend that women taking >5 mg of VKA during the first trimester should be switched to LMWH UFH by the end of the sixth week of gestation to decrease the risk of embryopathy.
  - Substitution of a VKA with UFH or LMWH in weeks 6–12 almost eliminates the risk of embryopathy
  - Continuation of warfarin during the first trimester is reasonable for pregnant women with a mechanical valve if the dose of warfarin ≤5 mg (AHA/ACC IIA)
  - Switch to LMWH/Heprarin at 36 weeks of GA

Anticoagulant

Table 6 – Anticoagulants Considered Safe in the Context of Breastfeeding

Drugs to use	Drug Levels in Breast Milk
UFH[1]	Undetectable
LMWH[1]	Detectable (low) but not orally absorbed
Warfarin[1]	Undetectable
Acenocoumarol[1]	Undetectable
Danaparoid	Undetectable
Fondaparinux	Data Unavailable; unlikely to be orally absorbed

[1] The agents with greatest experience in this patient population and the best evidence for safety were warfarin, acenocoumarol, LMWH, and UFH.

Table 7 – Anticoagulants Considered Unsafe in the Context of Breastfeeding

Drugs not to use	Drug Levels in Breast Milk
Rivaroxaban	Detectable (low)
Other DOACs[2]	Data Unavailable

[2] It is possible that DOACs are safe, but until further evidence and experience are available, clinicians should avoid prescribing these agents to women who are breastfeeding.

ANTENATAL CORTICOSTEROIDS

- Administration of ante-partum CSs to the mother to accelerate the maturation of the fetal lungs, decreases **incidence** and **severity** of neonatal RDS, IVH, NEC, and Death
- A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation who are at risk of preterm delivery within 7 days, including for those with ruptured membranes and multiple gestations.
- It may also be considered starting at 23 0/7 weeks or between 34 0/7 weeks and 36 6/7 weeks if they did not receive a previous course.
- Betamethasone 12 mg IM every 24 hours for two doses (preferred in some references) or Dexamethasone 6 mg IM every 12 hours for four doses

Diabetes

- Insulin is the preferred medication for treating hyperglycemia in pregnancy, if indicated
- Using of metformin as an adjunct or alternative to insulin in some guidelines (NICE), but **ADA 2024** recommended metformin and glyburide should not be used as first-line agents,
- Women with pre-existing type 2 diabetes who are breastfeeding can resume or continue metformin (NICE guideline)
- Glibenclamide may also be taken in lactation (Monitor infants for sign of hypoglycemia)
- Women with type 1 or 2 diabetes or HTN should be prescribed low-dose aspirin 100–150 mg/day (>100 mg) starting at 12 to 16 weeks of gestation to lower the risk of preeclampsia.
- A dosage of 162 mg/day may be acceptable

Thyroid medications

- LT4 is safe. Increase dose by 30-45% to maintain TSH in lower half of the trimester-specific reference range
- Short term use of BB (<2-6 week) (propranolol and metoprolol)
- PTU in first trimester
- Switch to MMI at 16 weeks of GA
- Given the concerns about potential PTU-associated hepatotoxicity, MMI is preferred over PTU for nursing mothers (esp. if <20-30 mg/day needed), although PTU has more PB
- If MMI>20 mg is used in lactation, TFT of infant after 1-3 month of initiation

Lactational Mastitis

- Rest and drink plenty of fluids.
- Avoid deep massage (light sweeping of the skin similar to that for manual lymphatic drainage may be helpful
- Wear an appropriately fitting supportive bra (ie, not too tight).
- Keep patients and infants together if feasible.
- Data on the use of probiotic use to treat or prevent mastitis are inconsistent
- If symptoms persist beyond 24 to 48 hours or are accompanied by fever or systemic symptoms, treatment additionally includes antibiotic therapy with activity against S. aureus
  - Antibiotic may be initiated at the first along with other interventions for patients with evidence of bacterial infection.
  - Infection can progress to local abscess formation if not treated promptly.

Lactational Mastitis

- The risk of developing lactational mastitis can be reduced by frequent on-demand feeding (or milk expression) and by optimizing breastfeeding technique.
- Aim to relieving pain and maintaining milk flow through the milk ducts of the breast
- Continue breastfeeding from both breasts throughout treatment and to pump if breasts are not emptied completely with feedings; Feedings should start on the affected breast and occur more frequently
- For pain relief:
  - Topical – Warm or cold compresses (ie, soak a cloth in warm or cold water and place it on the breast). While use of either heat or cold may reduce pain, applying cold may decrease associated tissue edema and inflammation.
  - Application of heat just prior to feeding may also be helpful along with direct slight massage of the affected area toward the nipple during feeding as tolerated. Cold compresses after feedings can be utilized to help decrease pain and edema.
  - Systemic – Acetaminophen or ibuprofen can be used to relieve pain and reduce inflammation and fever

Lactational Mastitis

- Empiric therapy should include activity against S. aureus
- Treatment regimen selected based on severity and resistance risk factors
- *Nonsevere* without MRSA risk factors:
  - (Di)-cloxacillin 500 mg orally four times daily.
  - Flucloxacillin 500 mg orally four times daily.
  - Cephalexin 500 mg orally four times daily.
  - For patients with beta-lactam hypersensitivity; trimethoprim-sulfamethoxazole (TMP-SMX), clindamycin.
- *Nonsevere* with MRSA risk factors:
  - TMP-SMX; 1 double-strength tablet orally twice daily.
    - TMP-SMX may be used in patients who are breastfeeding healthy, full-term infants who are at least one month old
    - Should be avoided in patients who are breastfeeding newborn infants (<1 month old) or infants with G6PD deficiency, and should be used cautiously in patients who are breastfeeding infants who are jaundiced, premature, or ill .
  - Clindamycin 300-450 mg orally three times daily; monitor infant for diarrhea

Lactational Mastitis

- *Severe* infection:
  - Patients with severe infection (eg, fever, hypotension, tachycardia), rapid expansion of infection, or infection that progresses despite appropriate oral antibiotics warrant intravenous treatment that provides coverage of both Gram-positive and Gram-negative organisms.
  - Initial empiric inpatient therapy with intravenous vancomycin + Either ceftriaxone (2 g intravenously once daily) or piperacillin-tazobactam (3.375 g intravenously every six hours).
  - If beta-lactam agents are not an option, vancomycin can be combined with an aminoglycoside (eg, gentamicin). Aminoglycosides are used in this setting because of their safety in breastfeeding
  - Subsequent drug selection should be tailored to culture and sensitivity results from breast milk and/or blood cultures.
- Duration of therapy: Symptomatic improvement is typically seen within 24 to 48 hours
  - in general, five to six days of therapy is appropriate for patients whose condition has improved. Extension of antibiotic therapy (10-14 days) may be warranted in the setting of severe infection, slow response to therapy, or immunosuppression.

Antibiotic Selection for Bacterial Mastitis

TABLE 11.4 Antibiotic Selection for Bacterial Mastitis

Antibiotic	Spectrum	Dose	Safety	Comment
Dicloxacillin	Nonmethicillin-resistant *Staphylococci*	500 mg PO qid	Yes	Highest activity against MSSA
Clindamycin	Penicillin allergic Many CA-MRSA Test susceptibilities	300 mg PO qid	Probably safe	Excreted in milk; active against many strains of CA-MRSA
Erythromycin	Penicillin allergic	500 mg PO qid	Yes	GI intolerance
Azithromycin	Penicillin allergic	500-mg load, then 250 mg/day × 4 days	Probably safe	Limited *Staphylococcus aureus* activity; less GI upset than erythromycin
Trimethoprim Sulfamethoxazole	Some CA-MRSA	One DS tab (160mg/800mg) PO bid	Yes	Less effective when abscess present
Cephalexin	MSSA	500 mg PO qid	Yes	Relatively poor levels in breast tissue

Stimulation of Lactation

- Using a galactagogue to augment milk production can help women continue breastfeeding in the setting of lower milk production.
- The most effective stimulus for lactation is suckling; more of an effect on increasing prolactin
- Many patients nurse in the delivery room after uncomplicated vaginal deliveries because nursing increases maternal–infant bonding and helps establish good milk production.
- If a patient does not nurse immediately after delivery, she should be encouraged to do so as soon as she is physically able
- Should emphasize appropriate feeding techniques and proper positioning for breast-feeding.
- Most new patients who have difficulty breast-feeding initially respond to the emotional and educational support of a good obstetric nursing staff.
    - Few require pharmaceutical intervention
    - Maternal caloric and fluid intake is also essential to maintain milk supply. Applying warm compresses or taking a warm shower may help

Stimulation of Lactation

- Medical reasons for decreased milk supply should be eliminated such as maternal stress (illness, emotional), pregnancy, primary or secondary breast tissue insufficiency, Sheehan syndrome, retained placenta, heavy alcohol or cigarette use, and use of certain drugs
- If natural or pharmacologic therapies are warranted, they should be effective within days. If they provide no benefit to milk volume, cessation of the therapy is recommended
- Consider galactagogues with caution, noting drug and herb interactions, an individualized risk-benefit assessment, and informed consent with the mother
- A partial list of herbs considered to have galactagogue properties includes **fenugreek** seed (Trigonella foenum-graecum), fennel seed (Foeniculum vulgare), anise seed (Pimpinella anisum), goat's rue herb (Galega officinalis), nettle leaf (Urtica dioica), alfalfa herb (Medicago sativa), marshmallow root (Althaea offficinalis), caraway seed (Carum carvi), blessed thistle seed (Cnicus benedictus), torbangun herb (Coleus amboinicus), shatavari (Asparagus racemosus), milk thistle (Silybum marianum), and chasteberry (Vitex agnuscastus)

Stimulation of Lactation

- Although not an FDA-approved indication, metoclopramide can be used to stimulate lactation in patients with decreased or inadequate milk production.
  - Dopamine antagonist, increases PRL secretion.
  - Metoclopramide 10 mg PO three times daily for 1 to 2 weeks has been shown to help restore milk production.
  - Improvement in lactation occurs within 2 to 5 days of starting therapy and persists after discontinuing metoclopramide
  - Maternal doses of 30 mg/day do not alter PRL, TSH, or fT4 serum concentrations in breast-fed infants.
  - The only adverse effect reported in nursing infants has been intestinal gas. The short-term use of metoclopramide for reestablishing lactation appears to be safe, even in preterm infants; Poor efficacy in patients with recent preterm deliveries.
- Domperidone also increases prolactin as a dopamine receptor blocker
  - Dosage is 10 to 20 mg three to four times per day for 3 to 8 weeks. Some women respond within 24 hours, some take 2 weeks, and some never respond.
  - The mean RID was 0.012% at 30 mg and 0.009% at 60 mg maternal dose per day.
  - The AAP rates domperidone a category compatible with lactation.10 Hale rates it L3, probably compatible, and Schaefer considers it safer than metoclopramide and more effective. The FDA has explicitly recommended against the use of Domperidone to increase milk production
  - Screen mothers for a history of cardiac arrhythmias and the use of other medications associated with prolonged QTc interval

ABM protocol

ABM Clinical Protocol #9
*Use of Galactagogues in Initiating or Augmenting Maternal Milk Production, Second Revision 2018**

- Unknown if all women with low milk supply have low levels of prolactin and whether increasing prolactin increases milk supply in women with both low and normal prolactin levels
- Potential side effects (minor and significant) should be weighed carefully against any potential benefit
- There is little or no scientific evidence for herbs effectiveness or safety.
- The placebo effect when taking herbal preparations may be the reason for widespread anecdotal experience of their effectiveness
  - Lack of standardized dosing preparations (other than in research settings), possible contaminants, allergic potential, and drug interactions
- ABM cannot recommend any specific galactogogue at this time.
- Healthcare provider chooses to prescribe a galactogogue after weighing potential risks versus potential benefits of these agents
- Better to taper; If milk production wanes after stopping the drug and improves again with resumption of medication, gradually decrease the drug to the lowest effective dose and then discontinue

Lactation Suppression

ABM Clinical Protocol #32
*Management of Hyperlactation**

- Suppression of lactation is indicated for patients who do not want to breast-feed, patients who have delivered a stillborn infant, and those who have had an abortion.
- Both drugs and nonpharmacologic methods have been used
- In 1988, the FDA, however, recommended against drug-induced suppression of lactation
  - The only drug therapy that the FDA recommends in patients who are not breast-feeding is analgesic for the relief of breast pain
- Bromocriptine was approved for the postpartum suppression of lactation; however, the FDA rescinded its approval for that indication because of cardiovascular complications (eg, stroke, myocardial infarction)
- One technique to help reduce milk supply is to breastfeed only on one side or the other for blocks of time throughout the day, allowing no stimulation of one breast for several hours.
- Ice packs may be applied to the breasts for comfort, and a mild analgesic may be used if necessary
- Single dose Cabergoline 1 mg within 24-48 hours of delivery or 0.25 mg q12hrs for 4 dose in established lactation or 0.25 mg every 3-5 days in Hyperlactation syndrome

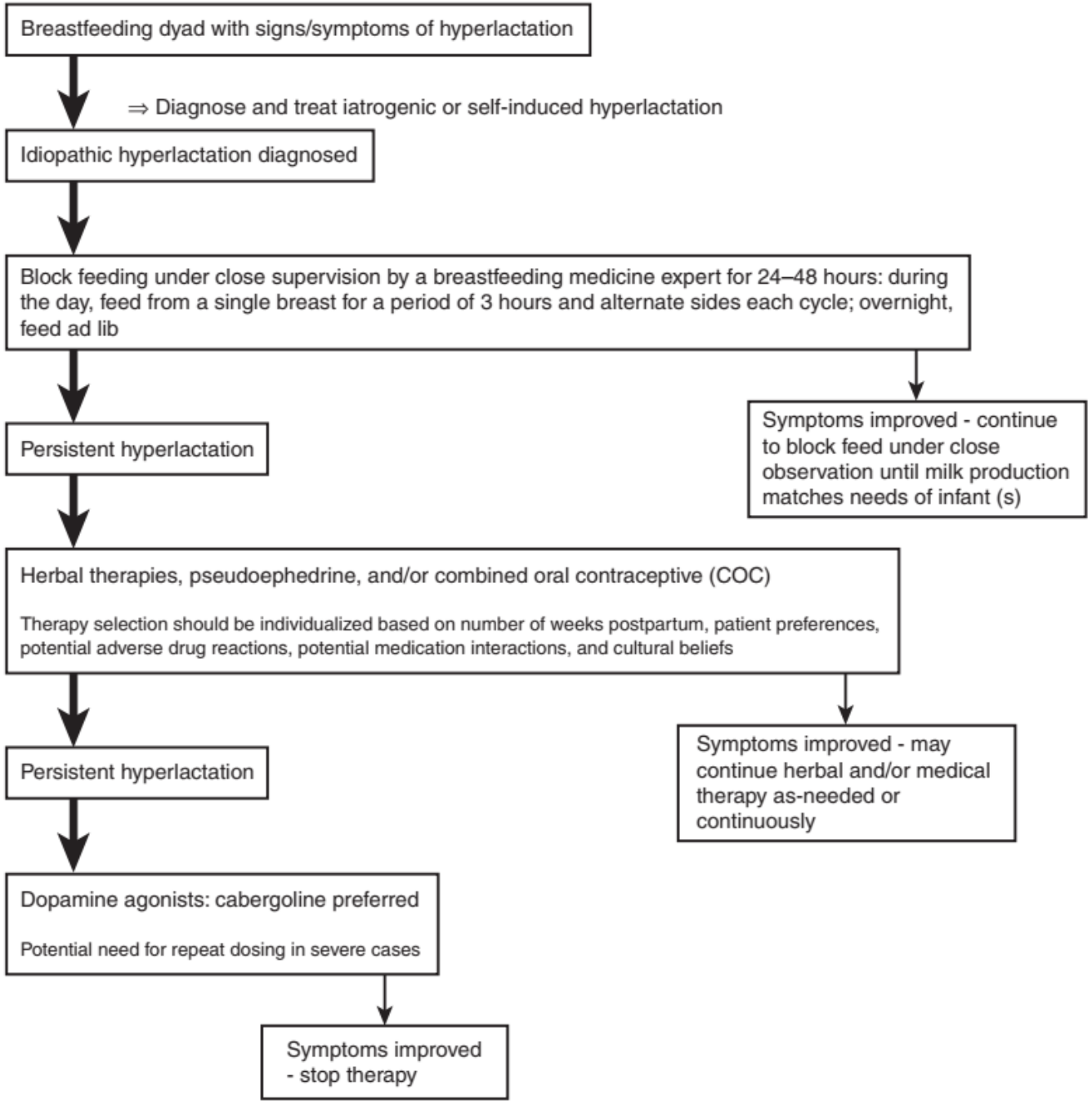


Fig. 1 Algorithm for the diagnosis and management of idiopathic hyperlactation.

Suppression of milk production

- Suppression of lactation is indicated for women who do not want to breast-feed, women who have delivered a stillborn infant, and those who have had an abortion.
- In 1988, the FDA, recommended against drug-induced suppression of lactation
- The only drug therapy that the FDA recommends in women who are not breast-feeding is analgesic for the relief of breast pain.
- FDA rescinded Bromocriptine approval for this indication because of cardiovascular complications (e.g., stroke, myocardial infarction) associated with its use
- Cabergoline 1 mg, single dose in first 24 hours of delivery in some cases
- 0.25 mg q 12 hours for 4 doses (total 1 mg) in established lactation in some cases

Suppression of milk production

TABLE 3 Common Prescription Medications Used for Hyperlactation Management

Medication	Dosing/ administration	Potential adverse drug reactions
Pseudoephedrine	30–60 mg once to twice daily	Jitteriness, insomnia, irritability, hypertension, tachycardia, arrhythmia
Estrogen	Combined oral contraceptive with 20–35 μg estradiol	Venous thromboembolism, pulmonary embolism
Cabergoline	0.25–0.5 mg every 3–5 days as needed	Headache, nausea, depressed mood, dizziness, drowsiness or nervousness
Bromocriptine	2.5 mg daily for 3 days	Stroke, seizure, severe hypertension, myocardial infarction, psychosis

Medications with Proven Teratogenic Effects in Humans[4-7]

Drug or Drug Class	Teratogenic Effects	Critical Period[a]
Alkylating agents	Malformations of many different organs	Organogenesis
Amiodarone	Transitory hypothyroidism (risk of 17%, goiter in some cases) or transitory hyperthyroidism	From 12th week after LMP
Androgens (danazol, testosterone)	Masculinization of genital organs in female fetus	From 9th week after LMP
Angiotensin converting enzyme inhibitors; angiotensin II receptor antagonists	Renal failure, anuria, oligohydramnios, pulmonary hypoplasia, intrauterine growth restriction, limbs contracture, skull hypoplasia	After the first trimester
Anticonvulsants (first generation) • Carbamazepine • Phenytoin • Phenobarbital • Valproic acid, divalproex	NTD (carbamazepine and valproic acid); oral cleft, skeletal, urogenital, craniofacial, digital, and cardiac malformations Major malformations: up to 5%–10% depending on the agent used, with variation with dosage used (10%–15% or more for valproic acid). Valproic acid: abnormal neurologic development	Organogenesis for structural anomalies Valproic acid: whole pregnancy for neurologic impairment
Corticosteroids (systemic)	Oral cleft (risk of 3–4/1000 vs 1/1000 in general population)	Organogenesis (most critical period for palate formation: 8 and 11 weeks after LMP)
Diethylstilbestrol	Girls: cervical or vaginal adenocarcinoma, incidence: 1/1000. Structural genital anomalies (eg, of cervix, vagina) Boys: genital anomalies, spermatogenesis anomalies	First and second trimesters
Fluconazole high doses	Skeletal and craniofacial malformations, cleft palate, cardiac anomaly (with chronic dose ≥ 400 mg/day; not reported with 150 mg single dose)	Not defined, but cases are reported where exposure was throughout pregnancy

Iodine (supraphysiologic dosage)	Hypothyroidism, goiter	From 12th week after LMP
Isotretinoin, other systemic retinoids (acitretin, bexarotene, etretinate), and high dose of vitamin A (vitamin A > 10,000 IU/day not recommended)	Spontaneous abortion, CNS, skull, eyes and ears malformations, micrognathia, oral cleft, cardiac malformations, thymus anomalies, mental retardation: estimated risk at 25%–30% (may be higher for neurologic development impairment) Isotretinoin and bexarotene: discontinue 1 month before pregnancy, isotretinoin prescribed under a special program called iPLEDGE Acitretin: discontinue 3 years before pregnancy	Organogenesis (risk of teratogenic effect after organogenesis not excluded)
Lithium	Cardiac malformations: risk of 0.9%–6.8% (higher risks in small studies) (baseline risk ~1%) Includes Ebstein anomaly: risk estimated at 0.05%–0.1%	Cardiac organogenesis (5–10 weeks after LMP)
Methimazole/propylthiouracil	Methimazole: aplasia cutis, choanal atresia, esophageal atresia, omphalocele, minor facial anomalies, growth delay; risk of 2%–4% Methimazole/propylthiouracil: fetal hypothyroidism in 1%–5% of newborns, goiter	Organogenesis Second and third trimesters
Methotrexate	Spontaneous abortion, CNS, and cranial malformations (large fontanelles, hydrocephalia, incomplete cranial ossification, craniosynostosis), oral cleft, ear, skeletal and limb malformations, mental retardation; discontinue at least one ovulatory cycle before pregnancy	Organogenesis (8–10 weeks after LMP for structural anomalies but some exceptions reported)
Misoprostol	Moebius syndrome ± limb anomalies ± CNS anomalies Abortion, preterm birth	Organogenesis Throughout pregnancy for abortion/preterm birth
Mycophenolate mofetil, mycophenolic acid	Anomalies including ear anomalies, oral cleft, micrognathia, ophthalmic, cardiac, and digital anomalies (risk of structural anomalies estimated from 20%–25%); spontaneous abortion (30%–50%)	Organogenesis (risk unknown after)
Nonsteroidal anti-inflammatory drugs	In utero closure of ductus arteriosus (constriction is rare before 27 weeks, 50%–70% at 32 weeks [GA]) and neonatal pulmonary hypertension Renal toxicity and oligohydramnios possible after prolonged use from second half of second trimester from 20 weeks of gestational age	Third trimester
Penicillamine	Cutis laxa Joints and CNS anomalies Risk probably low	Not defined
Tetracyclines	Teeth discoloration	From 16 weeks after LMP

Thalidomide	Limb anomalies (amelia, phocomelia) Cardiac, urogenital, gastrointestinal, and ear malformations Risk of 20%–50% Prescribed under a special program called STEPS (System for Thalidomide Education and Prescribing Safety)	34–50 days after LMP
Trimethoprim	Cardiac and urogenital malformations, NTD, oral cleft; overall risk probably < 6%	Organogenesis
Warfarin/acenocoumarol	Before 6 weeks: baseline risk of anomalies Taken between 6 and 12 weeks: nasal hypoplasia, epiphysis dysplasia, vertebral malformations, rarely ophthalmic anomalies, scoliosis, hearing loss; risk estimated of 6%–10% and possibly dose-dependent 12 weeks after LMP: rarely, heterogeneous CNS anomalies	Between weeks 6 and 12 after LMP; some risks persist after

[a]Stages of pregnancy in this table are calculated after last menstrual period (gestational age) and not after conception to be more clinically useful.

Drugs of Concern During Breast-Feeding[4,5,16]

Drug or Class	Comments
Drugs that can decrease the breast milk production	
Clomiphene	Has been used to suppress lactation
Ergot derivatives (bromocriptine, cabergoline, ergotamine)	Have been used to suppress lactation
Estrogens	Contraceptives with ethinylestradiol should be delayed for 3–6 weeks postpartum to decrease effect on lactation and to prevent thrombosis
Pseudoephedrine	Do not use in women with low milk production; a few doses will probably not have effect

Drugs for which use during breast-feeding may expose the neonate to a significant quantity and may necessitate a strict follow-up

β-Blocking agents (acebutolol, atenolol, sotalol)	Neonatal β-blockade reported Concern for acebutolol, atenolol, and sotalol, but other β-blocking agents such as metoprolol, propranolol, and labetalol are safe
Amiodarone	May accumulate (long half-life); possible neonatal thyroid and cardiovascular toxicity
Antineoplastics	Neonatal myelosuppression possible
Chloramphenicol	Severe adverse effects reported when used to treat babies (blood dyscrasia, grey baby syndrome)
Ergotamine	Symptoms of ergotism (vomiting and diarrhea) reported
Illicit drugs	Unknown contents and effects
Lamotrigine	A breast-fed infant could have blood concentrations between 10% and 50% of maternal blood concentrations (variable but can be in therapeutic range); monitor for CNS side effects (sedation, hypotonia, weight gain, and poor sucking) and rash
Lithium	Up to 50% of maternal serum levels have been measured in infants; cases of infant toxicity (lethargy, cyanosis, electrocardiogram anomalies, dysthyroidism, tremors) reported; if breast-feeding, monitor infant serum lithium, creatinine, urea, and TSH levels every 4–12 weeks and other side effects (jitteriness, feeding problems, signs of dehydration)
Phenobarbital/ primidone	Drowsiness and reduced weight gain reported; up to 25% of a pediatric dose can be ingested via breast milk; monitor for CNS adverse effects (sedation, hypotonia, weight gain, and poor sucking)
Radioactive iodine-131	No breast-feeding for days to weeks to achieve nonsignificant radiation levels (long radioactive half-life); monitor radioactive levels in milk before allowing breast-feeding; for diagnostic purposes, prefer Tc99m or iodine-123
Tetracyclines	Chronic use may lead to dental staining or decreased epiphyseal bone growth (theoretical)

Table 1-5. Agents Contraindicated During Lactation, Hazardous to Milk Production

Drug Class	Agents	Comments
Antiestrogens	Danazol GNRH agonists (e.g., leuprolide)	Ovarian suppression through pituitary-ovarian axis, inhibiting hormone production
	Anastrazole	Estrogen suppression through aromatase inhibition
Antiviral	Amantadine	Can suppress lactation by increasing dopamine
Dopamine agonists	Ropinirole Selegiline Rotigotine Dopamine	Lower serum prolactin concentrations, preventing lactation
Decongestants	Pseudoephedrine Propylhexedrine Phenylephrine	Oral intake can suppress milk production with single doses; topical application has a significantly lower risk unless overused
Ergots	Ergotamine Dihydroergotamine	Inhibit prolactin, preventing lactation
Ergot derivatives	Bromocriptine Cabergoline	Likely safe if treating hyperprolactinemia; otherwise contraindicated
Ethanol	Alcohol	Chronic ingestion will suppress milk production
Nicotine	Cigarettes	Decreased prolactin concentrations, reduced antioxidant properties of breast milk
Selective estrogen receptor antagonists	Tamoxifen Raloxifene	Inhibit estrogen effects in breast tissue

Table 1-6. Agents Contraindicated During Lactation, Hazardous to the Infant

Drug Class	Agents	Comments
Antiarrhythmic	Amiodarone	Several potential toxicities (e.g., pulmonary)
Anticholinergic	Dicyclomine	Contraindicated in infants < 6 months, apnea
Anti-infectives	Dapsone	Hemolytic anemia
	Rifabutin	Rash, suppression of white blood cells
	Flucytosine	Bone marrow suppression
	Foscarnet	Renal toxicity, seizures
CNS stimulants	Dextroamphetamine Amphetamines Methylphenidate	Not recommended; monitor infant for adverse events and appropriate weight gain
Cytotoxic agents	Antimetabolites, alkylating agents, etc Hydroxyurea	High potential of toxicity for the infant, including immunosuppression
Illicit substances	Cocaine, heroin, marijuana, etc.	High potential for significant toxicities in the infant
Immunosuppressants	Cyclosporine Tacrolimus	Not recommended; if used, monitor infant (for serum concentrations and adverse events)
	Everolimus Sirolimus	Not recommended until more information is available on these agents
	Mycophenolate	Not recommended, increase in infection rate

Table 1-6. Agents Contraindicated During Lactation, Hazardous to the Infant

Drug Class	Agents	Comments
Leprostatic	Thalidomide	Several potential toxicities
Mood stabilizer	Lithium	High potential of toxicity in the infant, near therapeutic serum levels
Monoamine oxidase inhibitors	Isocarboxazid Phenelzine Selegiline Tranylcypromine	No information is available regarding these agents in breastfeeding. Other antidepressants are better options
Radioactive substances	I^{131}, etc.	Transfer of radioactive agents to the infant, destruction of thyroid tissue
Skeletal muscle relaxant	Tizanidine	Sedation, hypotension
Tetracyclines	Tetracycline Doxycycline Minocycline	Low penetration into milk, but therapy > 3 wk is not recommended due to potential of staining of teeth or changes in bone growth
Tricyclic agent	Doxepin	Significant sedation, respiratory depression
Vitamin A derivatives	Etretinate Isotretinoin	Excessive vitamin A intake and related toxicities, including liver damage and death


با تشکر از توجه شما