Use of Drugs During Pregnancy & Lactation

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Objectives
- Explain pharmacokinetic changes during pregnancy
- Explain the general principles of drug transfer across the placenta and into breast milk
- Discuss considerations of drug selection in pregnancy
- Review the most recent updates to the FDA categories for the use of medications during pregnancy
- Explain the need for folic acid supplementation in pregnancy
- Identify common acute and chronic conditions associated with pregnancy and the appropriate treatment options available
- Identify specified teratogens, drugs with nonteratogenic adverse effects, and safe drugs for use during pregnancy and breastfeeding
- Counsel pregnant and breastfeeding patients on appropriate medication use
- Aid patients and providers in selecting the appropriate pharmacotherapy for pregnant and breastfeeding patients while weighing risk versus benefit

Taking Medications while Pregnant

- Inadvertent exposure
- Treatment of a pre-existing condition
- Initiation of treatment for new condition
Practitioner Fears May Lead To...

- Omission of necessary treatment
  - By patient or clinician
  - Woman takes med intermittently

- Woman decides to have termination

- Unnecessary cessation of breastfeeding

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*RISK vs. BENEFIT*

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**True or False?**

- ACE inhibitors should be avoided during pregnancy.

- Paroxetine is the preferred SSRI for pregnant and breastfeeding women.

- NSAIDs are safe when breastfeeding but generally not in pregnancy.
Pharmacokinetic Changes

- Renal blood flow increases 30-50% → may lower conc. of renally cleared drugs
- Increased body fat → increased Vd of fat-soluble drugs
- Plasma albumin conc. decreases → increase Vd of highly protein bound drugs
- N/V → altered absorption
- Increase in gastric pH → affect absorption of weak acids and bases
- Higher estrogen/progesterone levels → alter liver enzyme activity → increase or decrease elimination of drugs

Congenital Malformations

- Incidence 3-5%
- Genetic 25%
- Unknown 72-73%
- Drugs 2-3%

Folic Acid Supplementation

- Folate is critical for cell division
  - Neural tube defects (NTDs)
    - Spina bifida
  - Cleft palate and lip
  - Cardiac anomalies

- 1-3 months prior and at least 3 months after conception
- Throughout reproductive years
Folic Acid Supplementation

- Low risk: 400mcg – 900mcg/day
- High risk: 4-5mg/day
  - Previous history of defects
  - Anticonvulsant therapy

Thalidomide

- Anxiolytic in 1950s-early 60s
- Tragedies led to U.S. laws that address medications during pregnancy

Drug Selection in Pregnancy

- **Embryonic stage**
- Route of administration
- Dose

<table>
<thead>
<tr>
<th>Gestational Period</th>
<th>Timeframe</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preimplantation</td>
<td>First 2 weeks</td>
<td>“All or nothing”</td>
</tr>
<tr>
<td>Embryonic</td>
<td>2 – 9 weeks</td>
<td>Malformations</td>
</tr>
<tr>
<td>Fetal</td>
<td>9 weeks – term</td>
<td>CNS, retardation, death</td>
</tr>
</tbody>
</table>
Transplacental Drug Transfer

- Cross placenta *more easily*
  - Low molecular weights (most drugs)
  - Lipophilic – opiates, antibiotics
  - Protein-bound drugs
    - Albumin increases in fetus

- Maternal blood flow ≈ fetal blood flow
  - Simple diffusion
  - Fetal drug conc. 50-100% of maternal

Placental and Fetal Protective Mechanisms

- Placental function
  - Semipermeable barrier
  - Limited drug metabolism

- Drugs enter fetus through umbilical vein
  - 40-60% of umbilical blood flow enters into fetal liver
**Determining Safety**

- Pregnancy exposure registries
  - www.fda.gov
- Case-control
- Animal studies
- Case reports/series
- Prospective cohorts
- Retrospective cohorts
- RCTs

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**FDA Pregnancy Risk Categories**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Controlled studies in women fail to demonstrate risk; fetal harm remote</td>
</tr>
<tr>
<td>B</td>
<td>Animal → no risk; human → no controlled studies</td>
</tr>
<tr>
<td></td>
<td>Animal → risk; human → controlled studies show no risk</td>
</tr>
<tr>
<td>C</td>
<td>Animal → risk; human → no controlled studies</td>
</tr>
<tr>
<td></td>
<td>No available studies in woman or animals (RISK vs. BENEFIT)</td>
</tr>
<tr>
<td>D</td>
<td>Positive evidence of fetal risk</td>
</tr>
<tr>
<td></td>
<td>(benefit may outweigh risk)</td>
</tr>
<tr>
<td>X</td>
<td>Definite fetal risk in animals or women (RISK outweighs BENEFIT): CONTRAINDICATED</td>
</tr>
</tbody>
</table>

Note: May vary depending upon trimester or duration of use

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**FDA Pregnancy Risk Categories: Shortcomings**

- Seen as grading system
- Incorrectly assume drugs in same category have same risk
- Do not distinguish between animal and human studies
- Rarely or too hastily revised
- Unable to address harm of NOT taking medication
Pregnancy and Lactation Labeling Rule (PLLR)

- Passed: December 2014
- Implementation: June 30, 2015
- Removal of pregnancy categories A, B, C, D, & X
- Drugs approved on or after June 30, 2001
  - Need to remove pregnancy category from labeling within 3-5 years

Labeling Changes

8.1 Pregnancy
Pregnancy Exposure Registry
Risk Summary
Clinical Considerations
- Disease-associated maternal and/or embryo/fetal risk
- Dose adjustments during pregnancy and postpartum period
- Maternal adverse reactions
- Fetal/neonatal adverse reactions
- Labor or delivery
Data
- Human Data
- Animal Data
Labeling Changes

8.2 Lactation
Risk Summary
Clinical Considerations
Data

8.3 Females and Males of Reproductive Potential
Pregnancy Testing
Contraception
Infertility

PLLRImpact: Safety Interpretations

- Use both systems during transition time
- Must rely heavily on clinical judgment
- Make patient-specific health care decisions

- Keep in mind → it’s not only about fetal risk
  - Severity of maternal disease
  - Disease impact on fetus
  - Co-existing conditions
  - Alternative therapies

Considerations for Drug Use in Pregnancy

- Is the drug necessary?
  - Especially avoid first trimester use (when possible)
- Most effective plus least risk
- Lowest effective dose
- Shortest possible duration

- Older drugs → more available evidence
Which of the following is the MOST important consideration for drug selection for a pregnant patient?
- a. Dose
- b. Embryonic stage
- c. Route of administration
- d. Therapy duration

Which gestational period has the highest risk of malformations from potentially teratogenic medications?
- a. Less than 2 weeks
- b. 2 – 9 weeks
- c. 9 weeks – term
- d. All gestational periods have similar risks for malformations
**Most Commonly Used C, D, & X Drugs in Pregnancy**

- Antiasthmatics
- Antibiotics
- NSAIDs
- Anxiolytics
- Antidepressants
- Oral contraceptives

**Teratogenic Drug Examples (D & X)**

- Excessive alcohol
- ACE Inhibitors
- Anticonvulsants
- Antineoplastics
- Cocaine
- Estrogens and progestogens
- Isotretinoin
- Lithium
- Statins
- Tetracyclines
- Warfarin

**Known Teratogenic Drugs**

- **ACE Inhibitors (1st- C; 2nd & 3rd D)**
  - CV and CNS malformations, renal failure
  - Still avoided in 1st trimester

- **Anticonvulsants (D, C)**
  - Maternal benefit >> fetal risk
  - Start folic acid (4mg/day) before conception
  - Valproate for migraine prevention (X)
**Known Teratogenic Drugs**

- Estrogens and progestogens (X)
  - Benefit *does not* outweigh potential risk
  - ↑ thromboembolism risk + pregnancy
  - Norethindrone → masculinization, CV defects?

- Isotretinoin (Accutane) (X)
  - 40% given to young women of childbearing age (13-19)
  - iPLEDGE

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**Known Teratogenic Drugs**

- Statins (X)
  - Benefit *does not* outweigh potential risk
  - Accidental use has no known consequences
  - Cholesterol important during fetal development

- Warfarin (X)
  - 6-12 week exposure → embryopathy → fetopathy
  - Microhemorrhages, fatal fetal hemorrhages

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**Drugs with Nonteratogenic Adverse Effects**

- Antithyroid drugs
- Aspirin
- Caffeine
- Diuretics
- Nicotine
- Oral hypoglycemics

- Aminoglycosides
- Barbiturates
- Benzodiazepines
- Beta blockers
- Narcotics (chronic)
- NSAIDs

**NSAIDs**: Constrict ductus arteriosus → persistent pulmonary hypertension
**NO Known Teratogenicity**

- Acetaminophen
- Erythromycin
- Narcotics
- Phenothiazines
- TCAs

**Narcotics:** B/C short-term; D long-term

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**EXAMPLE OB Clinic OTC List**

**SOME HELPFUL SUGGESTIONS**

The following non-prescription medications may be safely used in a pregnant woman, following the package directions for adult dosages:

| Item | Acne | Common Ingredients | Self-label: Does Not Rx
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>Acne</td>
<td>Acneicin, Benzoyl Peroxide, Salicylic Acid</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Headache</td>
<td>Acetaminophen, NSAIDs, Ibuprofen</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Nausea</td>
<td>Acetaminophen, Ginger Oil</td>
<td></td>
</tr>
</tbody>
</table>
| UTI | UTI | Cephalosporins, Nitrofurantoin | Direct to pharmacist
| Constipation | Constipation | Docusate sodium, Laxatives | Direct to pharmacist
| Thyroid | Thyroid | Thyroid Hormones | Direct to pharmacist

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**Complications in Pregnancy**

- Nausea/Vomiting
- GERD
- Constipation
- UTI
- Headache
- Gestational Diabetes
- Hypertension
- Thromboembolism
Nausea and Vomiting of Pregnancy

- Up to 80%, mostly 1st Trimester
- Hyperemesis gravidarum – 1 to 3%
- Early treatment prevention

Nonpharmacologic
- Small, bland, frequent meals
- Cold, clear, and carbonated or sour fluids
- Frequent naps, shorter work days
- Avoid odors, heat, humidity, noise, flickering lights
- Acupressure (sea bands)

Nausea/Vomiting

- MVI
- B6 (A) +/- doxylamine (A)
- Diclegis
- Ginger (C)
- Ondansetron (B?)
- Metoclopramide (B)
- Promethazine or prochlorperazine (C)
- Corticosteroids (C)

Diet Lifestyle
Mild
Moderate - Severe
Complimentary and Herbal OTC and Rx
Ginger Acupressure B6 +/- doxylamine
Ondansetron Metoclopramide
Promethazine or prochlorperazine
Prednisone: Methylprednisolone
GERD
- Up to 80%
- Latter ½ of pregnancy
- Cause: enlarged uterus puts pressure on stomach → relaxes esophageal sphincter

1st – small, frequent meals; avoid alcohol, tobacco, food at bedtime; elevate head of bed
2nd - antacids (not Na bicarb), ranitidine (B)
3rd – metoclopramide (B), omeprazole (C), lansoprazole (B)

Constipation
- Cause: decreased peristalsis

1st – exercise, fiber, fluids
2nd - supplemental fiber (B)
Stool softener (docusate: C)
Occasional lactulose (B), bisacodyl (C)
Milk of magnesia (saline) → sodium retention
AVOID
  - Castor oil
  - Mineral oil
  - Hemorrhoids – Sitz bath, Witch hazel pads, Tucks

UTI
- Treat asymptomatic bacteriuria
- Cephalexin (B)
- Nitrofurantoin (B)
  - NOT > 37 wks: hemolytic anemia in newborns risk
  - 7 to 10 days
- Acute pyelonephritis
  - Hospitalization
  - Parenteral cephalosporin (i.e. cefazolin)
  - Recurrence: nightly nitrofurantoin 100mg
**Headache**
- Cause: Hormone fluctuations
- Migraine: 60-70% improve
  - Rest, ice packs
  - Tylenol (B) (w/ or w/out narcotics?)
  - NSAIDs? (C/D)
  - Sumatriptan (C) use controversial
  - Prophylaxis: propranolol (C), amitriptyline (C)
  - AVOID: valproate (X)
- Tension – nonpharmacologic measures
  - Acetaminophen (B), caffeine (B)

**Gestational Diabetes (GDM)**
- ~7% of all pregnancies
  - Pre-existing diabetes is not GDM
- ADA: prenatal screening if high risk
  - If normal screening, repeat at 24-28 wks
- Usually resolves after delivery
  - At higher risk for type 2 DM
  - Screen 6-12 weeks post-partum

**GDM Pregnancy Complications**

<table>
<thead>
<tr>
<th>1st Trimester</th>
<th>2nd Trimester</th>
<th>3rd Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malformations</td>
<td>Hypertrophic cardiomypathy (#1 issue with T1DM)</td>
<td>Macrosomia (#1 complication overall)</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>Polyhydramnios</td>
<td>Post-partum hypoglycemia</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>Low IQ</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>--</td>
<td>Placental insufficiency</td>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>--</td>
<td>Fetal loss</td>
<td>Intrauterine death</td>
</tr>
</tbody>
</table>
GDM Pregnancy Complications

Gestational Diabetes (GDM)
- A1C < 6%
- First line
  - Nutritional, caloric restriction (obese)
  - Daily SMBG
- Insulin (B)
- Glyburide? (B)
- Metformin? (B)

Hypertension & Preeclampsia
- 1/10 of pregnancies
- Gestational HTN = pregnancy-induced
- Preeclampsia = HTN + proteinuria
  - 2-8% of pregnancies
  - Occurs > 20th week
- Eclampsia = preeclampsia + seizures
  - Renal failure
  - Coagulation complications
  - Preterm delivery
  - Limits intrauterine growth
Hypertension & Preeclampsia

**Prevention**
- Low dose Aspirin (C)
  - 81mg to begin week 24-28
  - For high risk: previous severe preeclampsia, renal disease, diabetes, chronic HTN
- Calcium 1g/day
  - Abnormality in fetal calcium regulation?
  - Recommended for all pregnant women
  - Decrease relative risk of pre-eclampsia ~ 50%

Hypertension & Preeclampsia

- Mild to moderate HTN: drug therapy?
  - 140-159 / 90-109mmHg
- Severe HTN
  - 160+mmHg / 110+mmHg

- Nondrug treatment
  - Activity restriction
  - Psychosocial therapy
  - Delivery

Hypertension & Preeclampsia

**Outpatient Drug Treatment**

- **First Line**
  - Labetalol (C)
  - Nifedipine ER (C)
  - Metyldopa (B)
- **Second Line**
  - Thiazide diuretics (B/C)
- **AVOID**
  - ACE I & ARBs (C then D)
Thromboembolism

- Preferred
  - Low Molecular Weight Heparin (LMWH) (B)
- AVOID warfarin (X)

A 33 YOF is 8 weeks gestation. She has been experiencing mild nausea and vomiting from pregnancy for a couple of weeks. She is currently taking a prenatal vitamin once daily, vitamin B6 100mg po BID and is chewing ginger gum. She has tried lifestyle recommendations to help her symptoms but has had little relief. What is the next MOST appropriate recommendation for the patient at this time?
  a. Add doxylamine
  b. Add ondansetron
  c. Add methylprednisolone
  d. Increase the dose of vitamin B6

Other Problems Encountered During Pregnancy

- Allergic rhinitis
- Asthma
- Mental Health
- Epilepsy
**Allergic Rhinitis**
- Avoid allergens, saline nasal spray
- Intranasal corticosteroids (C)
- 1st gen. antihistamines (B)
  - Probably 2nd generations
  - Loratadine (B), cetirizine (B), fexofenadine (C)
- Decongestants
  - Oxymetazoline nasal spray (C)
  - Pseudoephedrine, phenylephrine (C)
  - Possible gastrochisis & ↓ blood supply to fetus
- Breathe Right nasal strips

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**Asthma**
- Improves, worsens, or remains unchanged
- Control decreases risks to fetus (& mother)
- Conventional treatment is used (benefits > risks)
  - Inhaled corticosteroids (B/C)
    - Budesonide (B)
    - Albuterol (B/C)
    - Montelukast (B)
    - Prednisone (C)

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**Mental Health**
- Antidepressants
  - SSRIs OK – pulmonary hypertension risk?
    - Fluoxetine (C)
    - Sertraline (C)
    - Citalopram (C)
    - Paroxetine (D)
  - TCAs OK
    - Amitriptyline (C)
    - Doxepin (C)
    - Bupropion (C)
Mental Health

- Benzodiazepines (D)
  - Oral cleft risk?
  - Infant withdrawal
  - “Floppy baby syndrome”
- Mood stabilizers
  - Lithium (D)
  - Fetal and neonatal cardiac arrhythmias
- Antipsychotics
  - Typical > atypicals

Epilepsy

- All antiepileptics ↑ risk of malformations
  - Craniofacial, cardiac, limb, neural tube defects
  - 4-5mg folic acid before conception
  - Continue at least through first trimester
- Monotherapy is ideal
  - Lamotrigine (C) levels fall 50% in 1st trimester
  - Valproate (D) → developmental delays

Uncontrolled epilepsy is dangerous

EXAMPLE OB Clinic OTC List

**SOME HELPFUL SUGGESTIONS**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommended Medications</th>
<th>Full Dose When Repeatedly Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Ibuprofen, Acetaminophen</td>
<td>Full dose once every 6-8 hours</td>
</tr>
<tr>
<td>Heartburn</td>
<td>Sodium Bicarbonate, Famotidine</td>
<td>Full dose once daily</td>
</tr>
<tr>
<td>Constipation</td>
<td>Laxatives, Fiber Supplements</td>
<td>Full dose once daily</td>
</tr>
<tr>
<td>Migraines</td>
<td>sumatriptan (Imitrex)</td>
<td>Full dose once daily</td>
</tr>
<tr>
<td>Morning Sickness</td>
<td>Dopamine, Vitamin B6</td>
<td>Full dose once daily</td>
</tr>
</tbody>
</table>

The following along with current medications may be taken during pregnancy. Always consult a pharmacist for adult dosages/uses.
Patient Case
MT is a 26 y/o female who presents to your pharmacy to ask for an OTC recommendation because she has a ‘cold’; congestion, HA, and runny nose x 2 days.
She is pregnant in her 2nd trimester.

Lactation

Benefits of Breastfeeding

Baby
- Enhances GI maturity
- ↓ risk of acute infections
- ↓ risk of obesity
- ↓ risk of childhood cancers
- ↓ risk of type 2 diabetes
- ↓ risk of adult CV disorders
- ↓ risk of allergic disorders
- ↓ risk of SIDS
- ↑ neurodevelopment (↑ IQ)
- ↑ bonding and security

Mother
- ↓ risk of breast cancer
- ↓ risk of ovarian cancer
- ↓ risk of type 2 diabetes
- ↓ economic burden
- ↑ bonding
**Breastfeeding Recommendations**

- Per CDC, in 2011:
  - 79% started to breastfeeding
  - 49% at 6 months, 27% at 12 months

- American Academy of Pediatrics (AAP)
  - Exclusively for first 6 months
  - Continue for first year +

- World Health Organization (WHO)
  - Up to 2 years or beyond

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**Lactation**

**Drug Transfer to Breast Milk**

- **First 3-4 days**
  - Produce little milk → colostrum production

- **Early milk production** (First 4-10 days)
  - More space between alveolar cells for large molecules

- **>10 days**
  - Less space between cells → high molecular weights cannot pass easily

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**Lactation**

**Drug Transfer to Breast Milk**

- **High** amount of transfer
  - Little protein binding
  - Low molecular weights
  - Higher lipid solubility
  - Highly concentrated in maternal serum
  - Longer half-lives

- Generally, < 10% of maternal dose → infant
Minimizing Effects of Drugs During Breastfeeding

- Short half-life
- Administer drug shortly after feeding or before long sleep period
- Low bioavailability
- Is drug given to neonates?
- Acceptable during pregnancy?
  - Many exceptions

Minimizing Effects of Drugs During Breastfeeding

- Short-term drug
  - May need to pump and discard milk while on risky drug(s)
  - Discourage use of meds to treat self-limited mild conditions
  - May need to obtain drug levels in infant
  - Risk of AEs highest in infants < 2-3 months
Relatively Safe in Breastfeeding
- Acetaminophen
- NSAIDs
- Antacids
- Antihistamines
- Laxatives
- Antiasthmatics
- SSRIs
  - Sertraline, paroxetine
- Most antibiotics
  - Penicillins, cephalosporins, erythromycins
- Insulin
- Moderate alcohol consumption
- Moderate caffeine consumption

Use with Caution in Breastfeeding
- Benzodiazepines
- Beta blockers
- Opiates
- Antipsychotics
- Lithium
- Pseudoephedrine \(\rightarrow\) milk production

Contraindicated in Breastfeeding
- Antineoplastics
- Radiopharmaceuticals
- Iodine-based
- X-ray contrast fluids
- Nicotine
- Drugs of abuse

Which of the following antidepressants is preferred to use in a breastfeeding patient?
- a. Fluoxetine
- b. Paroxetine
- c. Sertraline
- d. Either b or c

Which of the following may help to minimize the effects of drugs to the child during breastfeeding?
- a. Administer drug before a feeding or after a long sleep period
- b. Choose a drug that is safe to use when pregnant because that means it is safe to use when breastfeeding
- c. Choose a drug with a long half-life
- d. Discourage use of medications to treat self-limited mild conditions

Helpful Resources
- Current primary literature
- LactMed (app)
- Thomas Hale: Medications and Mother’s Milk
  - [www.infantrisk.com](http://www.infantrisk.com)
  - [www.fda.gov](http://www.fda.gov)
  - [www.mothertobaby.org](http://www.mothertobaby.org)
  - [www.reprotox.org](http://www.reprotox.org)
- Briggs: Drugs in Pregnancy & Lactation
- Drug Package Insert – labeling changes!
Pregnancy & Lactation
Clinical Pearls

- Avoid use of medications unless absolutely necessary
- Manage minor complaints with non-drug therapy if possible (but DO NOT overlook patient welfare)
- Chronic medical conditions must be treated
- When medication is necessary
  - Check most up-to-date information/trials
  - Use therapeutic doses
  - Use shortest duration of therapy possible
  - Monitor closely

RISK
VS.
BENEFIT

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