TERATOLOGY AND SAFETY OF DRUGS IN PREGNANCY

Learning Objectives:

- Given the date of the last menstrual period, estimated date of ovulation, or estimated date of conception, calculate the estimated due date and the time periods of the trimesters of pregnancy for a given patient.
- Understand the critical periods in human development and be able to differentiate between major and minor anomalies and functional defects.
- List and describe the factors that influence the teratogenicity of a drug.
- Recognize the reference sources that are most likely to be useful in determining risk for a given drug exposure.
- Summarize the limitations of currently available references and outcomes data that are used to determine the risk of drug use during pregnancy.
- Discuss the strengths and weaknesses of the current FDA Pregnancy Labeling Categories and describe the labeling changes that are being recommended by the FDA Subcommittee that was convened to develop a more clinically useful label.
- Develop a care plan that incorporates the need for medication therapy with individual tolerances of the risks involved with the use of drugs during pregnancy.
- Develop a consultative approach for conveying information about drug use during pregnancy to other health care providers and patients.
- Explain the importance of incorporating information about baseline risk, estimated exposure, teratogenic timing and potential, and risk of untreated disease when consulting with a health care provider or patient about the potential harm from a drug used during pregnancy.

Required Reading:


Recommended Reading:


Introduction

Exposure Estimates

40-90% of all women receive prescription drugs during their pregnancy

FDA study of 2 years of data from HMO database to assess the numbers of prescriptions given during pregnancy

- Commonly prescribed prenatal vitamins, iron supplements, and tocolytic drugs were excluded
- Women <35 yo: average of 3 Rxs during course of pregnancy
- Women >35 yo: average of 5 Rx’s during course of pregnancy

Other studies have cited means of 5-9 medications/woman, the majority of which are being taken without medical supervision (old prescriptions, OTCs and natural products).

Some of the drugs used most extensively by pregnant women:

- Antibiotics, analgesics, narcotics, topical products, GI drugs, and autonomic drugs
- Antiepileptics, antihypertensives, psychotherapeutics, and respiratory/allergy therapies

Societal Factors
The Thalidomide Tragedy Raises Concerns about Drugs in Pregnancy and Results in Changes to the FDC Act
- Was widely prescribed for anxiety during the first trimester of pregnancy
- Animal studies did not reveal it to be teratogenic, 33% of women exposed during the 1st trimester gave birth to infants with severe limb defects and other organ defects
- Took several years before its harmful effect was recognized even though the rates of birth defects were high and the pattern of defects was characteristic
- Caused new rules to be promulgated requiring drugs to demonstrate an acceptable risk: benefit ratio for their intended uses

Over-reaction to Bendectin (doxylamine/pyridoxine)
- Was a very popular and effective treatment in the late 1950’s-1960’s for nausea and vomiting associated with pregnancy
- Lawsuits in the 1970’s caused this drug to be voluntarily withdrawn from the market despite good evidence that the rate of major malformations was no different from the background rate
- The rate of hospitalization for severe nausea/vomiting during pregnancy doubled after its removal

Women who contacted a Teratogen Information Service about an exposure to a non-teratogenic agent believed that there was a 1:4 chance that major malformations would develop before they received counseling. After counseling this estimate was reduced, indicating that numerous terminations of otherwise wanted pregnancies was probably avoided.

Role of the Pharmacist
- Pharmacists need to present a clear, unbiased understanding of the available literature to parents and other health care professionals
- Pharmacists can advise on DOC and drugs to avoid for conditions requiring drug therapy

Pregnancy “Cliff Notes”
Menstrual cycle length: LMP (last menstrual period) \(_{\text{day}1}\) – NMP (next menstrual period) \(_{\text{day}1}\) : ~28d (range 24 to 36d)
First half of menstrual cycle (follicular or proliferative phase):
- ~ 20 eggs (each in their own follicle) begin to ripen
- Estrogen predominates and causes the uterus lining to thicken, cervical mucus to thin, and follicles to ripen
- Ovulation: Lutenizing hormone surge causes the dominant follicle(s) to rupture → the egg(s) are expelled into the pelvic cavity where they are swept up by the fallopian tube
- Burst follicle begins secreting progesterone

Second half of menstrual cycle (luteal or secretory phase):
- Progesterone dominates and keeps uterus hospitable for implantation

Timing of ovulation: ~14d (range 12-16d) before onset of NMP. If cycle lengths are irregular from month to month it is harder to predict when ovulation will occur.
- OTC urine ovulation predictor kits detect the LH surge that happens 24-36h before follicle rupture. Kits ($20 to $50) usually provide five to nine days' worth of tests.
- Information for pharmacists on home ovulation tests (accessed 3/2008): \[ \text{www.uspharmacist.com, use search term = ovulation} \]

Conception: Small window of time each month (typically about four days) when conception can occur
- Egg only survives for 12-24h post ovulation if it is not fertilized, but sperm can survive 4-5d
- So period of highest fertility is from 4-5d prior to ovulation through NTE 24h post ovulation
- Without birth control, the odds of conceiving in any cycle are 25% and cumulative odds are 75-85% within one yr

Estimated date of confinement or estimated due date (EDC or EDD): calculated by wheels or charts or using Nagele’s rule. Most pregnancies are confirmed by ultrasound now for more accurate date prediction.
Nagele’s rule: date of first day of LMP, subtract 3 months, and add 7 days. Correct to within 2 weeks of delivery, works best in patients who have regular 28 day cycles.

Normal duration of human gestation is 267 days from conception or 280 days from first day of LMP, usually spanning 40 weeks.

Signs, Symptoms and Diagnosis of Pregnancy

Dx by S/S
- Amenorrhea (missed period)--although sometimes patient may experience implantation bleeding or cramping that can be confused with a spotty period
- Fatigue
- Frequent urination
- Tender, swollen breasts with increased pigmentation of nipple and areola
- “Morning” sickness (doesn’t usually start for a few weeks after conception and isn’t exclusive to the morning hours)

Dx by test: hCG is produced by placenta early in pregnancy and concentration doubles every 2-3 days and peaks between 8-12 weeks in a normal pregnancy
- OTC urine tests ($8 - $12): detect hCG 8-11d after implantation (a couple days before period is due). 97% accurate if used correctly. False negatives 25% of time (usually errors of performing test) vs. false positives less than 3% of time. More expensive tests generally have better sensitivity. Many doctor’s offices consider a positive home test indicative of pregnancy and would not repeat the test.
- Doctor’s office tests: hCG in urine and blood at similar concentrations. Blood assays are more sensitive and may detect pregnancy a few days earlier. However, many clinics use the same OTC urine tests sold for home use to verify pregnancies.

Information on sensitivity of pregnancy tests (accessed 3/2008):
Comparative chart - [http://www.craigmedical.com/pregnancy_chart.htm](http://www.craigmedical.com/pregnancy_chart.htm)
Overview – [www.uspharmacist.com](http://www.uspharmacist.com), use search term = pregnancy

Dx by exam: usually the first visit to an obstetrician or midwife takes place between eight and 12 weeks gestation
- Fetal heartbeat can be detected as early as 10 weeks using a handheld ultrasound device called a Doppler. Various factors can make it hard to hear the heartbeat this early.
- Some practitioners will perform full ultrasound at the 1st or 2nd visit to confirm pregnancy or if the heartbeat can’t be appreciated by Doppler

Human Development “Cliff Notes”
Refer to Timetable of Human Prenatal Development chart at end of handout

**Gestational age = number of completed weeks of pregnancy since LMP**
- Embryo = weeks 1-8 (conception to 56 days): major body organs are being developed
- Fetus = weeks 9-40plus (57 days to term): contains most of the stages of final differentiation, functional maturation, and growth in height and weight.

**Stages of Pregnancy**
1st trimester = gestational days 1 - 89 (embryo then fetus)
2nd trimester = gestational days 90 - 179 (fetus)
3rd trimester = gestational days 180 - 267 or term (fetus)

**How the obstetrician or midwife tracks development of the embryo/fetus:**
- Some practitioners routinely conduct an ultrasound at around 20 weeks as a mid-pregnancy diagnostic tool, to rule out anomalies or to verify the baby's due date
- If there is concern of anomalies or other problems, serial ultrasounds may be performed
- From week 20 to week 36, the practitioner will measure fundal height (in cm starting from the pubic bone to the top of the uterus) to check the baby's size, growth rate, and position. The measurement (in centimeters) will roughly correspond to the patient’s number of weeks of pregnancy
Birth Defects, Teratogens, and Critical Periods of Human Development

**Congenital Anomalies (Defects Existing at Birth)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overt</strong></td>
<td>Major anomalies (Significantly interfere with normal body functions. May be incompatible with life or will require major surgery for correction)</td>
<td>club foot, omphalocele, spina bifida, Tetralogy of Fallot (cardiac), Ebstein’s anomaly (cardiac)</td>
</tr>
<tr>
<td></td>
<td>Minor anomalies (“Of little medical significance” and so not included in frequency data even if the emotional impact is significant)</td>
<td>umbilical and inguinal hernias, slight hypospadias, cosmetic defects</td>
</tr>
<tr>
<td><strong>Covert</strong></td>
<td>Functional anomalies (abnormal physical or mental development)</td>
<td>behavioral problems, learning delays, physical growth retardation</td>
</tr>
</tbody>
</table>

**Reasons for Anomalies**

- 25%: congenital (pure genetic predisposition--Downs syndrome single most prevalent)
- 20%: heredity + environment (exact environmental factors unknown in most cases)
- 8-9%: solely environmental
  - 2-3% of which is drug induced--although small can do something about it
- for largest portion: cause is unknown

**US Population Background Rates of Adverse Pregnancy Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate</th>
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<tbody>
<tr>
<td>Spontaneous abortions (recognized pregnancies)</td>
<td>15%</td>
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<tr>
<td>Premature delivery</td>
<td>6-10%</td>
</tr>
<tr>
<td>Children with major malformations</td>
<td>4%</td>
</tr>
<tr>
<td>Additional births with minor malformations</td>
<td>5%</td>
</tr>
</tbody>
</table>


**Teratogen:** any agent, or type of exposure, that interferes with the normal differentiation and development of the embryo or fetus.
- Teratogens may be drugs, environmental exposures (e.g. chemicals, hot tubs), infectious agents, radiation, or certain disease states (e.g. folic acid deficiency, diabetes, PKU).

**Drugs Known or Highly Suspected to be Human Teratogens**

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Oral hypoglycemic drugs, C</td>
<td>Acetaminophen (2nd/3rd tri), D</td>
</tr>
<tr>
<td>Penicillamine, D</td>
<td>Acitretin**/ Etretinate, X</td>
</tr>
<tr>
<td>Phenytoin, D</td>
<td>Alcohol (high dose more risk, but no safe levels known), D/X</td>
</tr>
<tr>
<td>Ribavirin, X</td>
<td>Androgens, X</td>
</tr>
<tr>
<td>Rubella vaccine and other live vaccines, C/X</td>
<td>Antineoplastics (some but not all), D-X</td>
</tr>
<tr>
<td>Tetracycline, D</td>
<td>Carbamazepine, C</td>
</tr>
<tr>
<td>Thalidomide**, X</td>
<td>Cocaine (abuse), C/X</td>
</tr>
<tr>
<td>Trimethadione, D</td>
<td>Danazol, X</td>
</tr>
<tr>
<td>Valproic acid, D</td>
<td>Diethylstilbestrol, X</td>
</tr>
<tr>
<td>Vitamin A (both deficiency and excess), A/X</td>
<td>Iodides (including radioactive contrast media), X</td>
</tr>
<tr>
<td>Warfrin and coumarin derivatives, D/X</td>
<td>Isoxsalicylic acid, D</td>
</tr>
<tr>
<td><strong>Drugs with FDA special labeling or dispensing requirements due to teratogenic risk.</strong></td>
<td>Lithium, D</td>
</tr>
<tr>
<td>Bosentan, interferon alfa-2b/ribavirin, misoprostiol, mifepristone, topical tretinoin, also fit this definition but data is conflicting or limited re true teratogenic risk.</td>
<td>Methimazole, D</td>
</tr>
<tr>
<td>Methotrexate, D</td>
<td><strong>Drugs with FDA special labeling or dispensing requirements due to teratogenic risk.</strong></td>
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Critical Periods of Development
Refer to Critical Periods in Human Development chart at end of handout

Early Pregnancy
“All or none phenomena”: Exposure to a teratogenic drug at the time of conception/implantation (0-14 days) either
results in cell death if the dose is lethal or complete regeneration if the dose is sublethal

- If cell death occurs, the patient may never realize they were pregnant
- Embryo may not be damaged if the dose is sublethal since the embryonic cells are still totipotential (i.e. if one cell
  is damaged or killed, another can assume its function since they are capable of developing into any type of cell)
- Some scientists believe this is an evolutionary protection against toxins that are ingested before the mother
  realizes she is pregnant

The First Trimester
Debunking some misconceptions about the first trimester

- As noted above, if the embryo survives weeks 1-2 after an exposure confined to that time period, it is unlikely to
  have been adversely affected
- Organogenesis occurs 14-56 days post conception. Teratogen exposure during this time is likely to produce a
  type of birth defect that is recognizable (i.e. an obvious physical malformation) or that ultimately leads to an
  incompatibility with life. Unfortunately, since we are less good at recognizing minor abnormalities and functional
  abnormalities that are more likely to occur from later exposures, we have a higher apprehension of exposures that
  occur in the first trimester.
- Each organ develops on a timeline and a drug exposure must coincide with that specific timeline if it is to cause
  harm (e.g., if a single exposure to a drug that is known to affect upper limb development occurs before the “start
  date” of the major period of development for the upper limbs, then a structural defect in the upper limbs could not
  be due to that drug).
- Other factors also affect the embryo/fetus’ susceptibility to teratogens. Only a fraction of fetuses that are exposed
to a potential teratogen will be affected. See later section.

Later Trimesters
This is the period of histogenesis and functional maturation. Minor abnormalities, functional and behavioral defects have
been associated with later exposures. These are more difficult to recognize, diagnose, and associate with exposure.

At the time of Delivery/Postpartum
Some agents that are DOC or considered relatively safe during certain stages of pregnancy from a teratogenicity
standpoint are discontinued as term approaches to avoid complications in the perinatal period. Withdrawal
syndromes (benzodiazepines), increased risk of bleeding (heparin), and hyperbilirubinemia in the newborn
(TMP/SMX) have been attributed to late exposures to drugs.

Long Term
Long-term effects may not be recognized for years. The carcinogenic potential of diethylstilbestrol in the offspring of
users was not evident until after puberty.

Factors affecting teratogenicity
The Placenta

- At one time the placenta was thought to present a barrier to the passage of drugs and noxious chemicals to the
  fetus. However, it is now known that the fetus also consumes most drugs consumed by the mother.
- During gestation the surface area increases while the placental thickness decreases from 25 microns during the
  first trimester to 2-6 microns at term. Both favor increased transport to fetus.
- Placental transfer of nutrients, waste, and environmental exposures occurs starting at 5 weeks of life
- The mechanisms of transfer: Most cross by simple diffusion (dependent on concentration gradient); also
  facilitated diffusion (glucose); active transport (some vitamins and amino acids)
Although it acts as a biological membrane, the placenta is actually composed of 4 layers that separate two distinct individuals:

- Endothelial lining of fetal vessels
- Connective tissue in core of villus
- Cytotrophoblastic layer
- Covering syncytium

Teratogenic Potential of a Given Exposure is Influenced by:

- Genotypes of mother and fetus
- Developmental stage when exposure occurs
- Simultaneous exposure to other drugs or environmental agents that may increase or decrease risk
- MOA of drug
- Dose and duration of drug exposure
- Rate of chemical transfer across placenta
  - MW < 600 (most drugs) cross easily, >1000 (heparin) with difficulty or not at all
  - Degree of protein binding (only free drug passes)
  - Ionization (if ionized at physiologic pH, pass slowly); weak acids and bases with pKa 4.3-8.5 are transferred rapidly
  - Lipophilicity
  - Uterine and fetal blood flow (uterine blood flow increases throughout gestation, and is affected by maternal bp, cord compression, and drug tx)
  - Maternal disease (may increase or decrease transfer)

Pharmacokinetic changes in pregnancy

- Increased blood volume
  - Decreased peak serum concentration of many drugs (especially those with smaller Vd)
  - No net change on free drug concentration of highly protein bound drugs due to competing factors
- No change in hepatic blood flow
- Increased estrogen and progesterone can affect drug metabolism

Fetal factors

- Fetal drug clearance (fetal liver and placenta) - generally less than adults
- Total free drug often higher in fetus since fewer binding proteins
Determining Risk from Medical Information

Ethically studies to ascertain outcomes can’t be performed so we rely on animal data, case reports, case series, and observational studies (cohort or case-control epidemiological studies)

- Cohort studies look at whether mothers who took a specific drug during pregnancy have a larger number of malformed children than mothers who did not.
- Case-Control studies (aka trohoc studies, i.e. “cohort” backwards) look at whether mothers of children with a specific malformation took the drug more than mothers of children without the malformation.

Some limitations of available sources:
- Outcomes in animals don’t always correlate to human risk.
- Case reports are generally only useful if the drug in question is taken by relatively small numbers of women or it causes a rare malformation, because then a small number of cases can establish a strong association.
- Case reports aren’t useful for widely used drugs because they may actually be reflective of the normal “background rate” of malformations.
- Sample size: Large sample sizes are needed to detect small differences (very few drugs increase the total malformation rate by a factor of more than 2) or rare malformations.
- Effect of maternal disease: may contribute to overall risk and confound data trying to link teratogenicity to a particular drug
- Recall bias in retrospective studies
- Voluntary reporting bias
- Under-reporting of cases

Meta analysis of collective studies of similar design and prospective epidemiological data from teratology information services and pregnancy registries are beginning to fill some of the gaps in our ability to assign risk to a given exposure.

Drug Information References that Summarize Risk Data

Texts
Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. 7th ed. Philadelphia: Williams & Wilkins, 2005

Package Inserts or other texts that abstract information directly from package inserts (AHFS DI, Facts and Comparisons, Lexicomp Drug Information Handbook, PDR)

Electronic Media
Micromedex AltMedDex: herbs, supplements and natural medicines
Micromedex Drug Evaluation Monographs and Drug Consults: drug reviews
Micromedex Reprotox Databases (Reprotext, Reprotox, Shepherd’s, TERIS): drug reviews focused on fertility, pregnancy and lactation.
www.perinatology.com: mini-drug reviews with assigned risk levels, information on pregnancy registries (accessed 3/08)
www.otispregnancy.com: patient drug fact sheets, many available in Spanish and French (accessed 3/08)

Published Reviews/Guidelines
Many consensus and expert opinion documents are available on the web or in print

Expert Advice
Fee for service: CARE Northwest is one of 26 local organizations that operate in the United States under the umbrella of OTIS, the Organization of Teratology Information Services. Medical geneticists, nurses, and other health professionals staff it. Patients or health care professionals may call 1-900-225-2273 (WA) at eight dollars per call. Annual subscriptions are also available for pharmacies.
Prenatal Diagnosis Center or Drug Information Service via OHSU Consult Line: 503-494-4567 (OR)
FDA Pregnancy Risk Categories:
Current state of affairs:

- Since 1975, the FDA has required drug labeling to include a subsection on a drug's ability to cause birth defects and other effects on reproduction and pregnancy.
- Established in 1979, but only drugs after 1983 are required to have an assigned category (grandfathering of older drugs).
  - Briggs text provides risk assessments for earlier drugs too.
- Not all teratogens are category X.
- A public hearing in 1997 revealed that the current system is confusing and leads to oversimplification (“The letters imply a gradation of risk that doesn't necessarily exist”)

### Current FDA Pregnancy Labeling Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>Adequately controlled studies in pregnant women have not shown an increased risk of fetal abnormalities in the first trimester, and the possibility of fetal harm appears remote.</td>
</tr>
<tr>
<td><strong>B</strong> Animals no risk; human data reassuring</td>
<td>Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women.</td>
</tr>
<tr>
<td></td>
<td>or Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.</td>
</tr>
<tr>
<td><strong>C</strong> Human data lacking; animal data positive or not done (66% marketed drugs)</td>
<td>Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women.</td>
</tr>
<tr>
<td></td>
<td>or No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.</td>
</tr>
<tr>
<td><strong>D</strong> Human risk but benefit may outweigh</td>
<td>Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk (life threatening or serious diseases where other drugs are ineffective or carry a greater risk).</td>
</tr>
<tr>
<td><strong>X</strong> Human risk without benefit</td>
<td>Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.</td>
</tr>
</tbody>
</table>

Since 1997, the FDA has been developing a new regulation that will revamp the pregnancy labeling system. They convened a Pregnancy Labeling Taskforce in 1999 to complete this task. The proposed regulation would replace the letter categories with more detailed, narrative descriptions. Information on fertility, pregnancy, and breastfeeding would be included.
Sample Fertility, Pregnancy, and Lactation Subsection on Proposed New Label

| Fertility                  | Clinical management statement  |
|                          | Summary risk assessment       |
|                          | Discussion of data            |
| Pregnancy                | Clinical management statement  |
|                          | Summary risk assessment       |
|                          | Discussion of data            |
| Lactation                | Clinical management statement  |
|                          | Summary risk assessment       |
|                          | Discussion of data            |

Subsection of a Proposed Label for a Fictitious Product

Pregnancy

Clinical Management: Women who are taking Leural and become pregnant should be advised to consider discontinuing the drug and may warrant evaluation for potential effects on fetal growth and development. Women who are considering pregnancy should be advised to consider alternative treatments for asthma maintenance when feasible.

Summary Risk Assessment: Based on studies in animals, there is some concern for an increased risk of mortality and decreased growth in fetuses exposed to Leural. The time of gestation at which risk may be greatest is unknown. Also, based on animal studies, there is some concern for increased risk of fetal malformations.

Discussion of Data: There are no human data addressing the effects of Leural on pregnancy and its outcomes. In rats, the drug and its metabolites cross the placenta. Leural is also known to alter cellular signal transduction, a function important in embryogenesis (see Clinical Pharmacology).

Dysmorphogenesis. In studies in rats at 400 mg/kg (systemic exposure equivalent to 18 times that of humans at MRHD), there was an increased rate of skeletal variation. A greater than expected rate of cleft palate (3 of 118, or 2.5%) was observed in fetuses of rabbits treated with 100 mg/kg/day (systemic exposure equivalent to that of humans at MRHD).

Mortality and Growth. In a study in rats treated throughout gestation at doses of 70 mg/kg (systemic exposure equivalent to approximately 4 times the recommended dose) and higher, there was an increased rate of stillbirths and, at doses of 400 mg/kg, there were also reduced body weights of fetuses. In a study in rats treated in late gestation through lactation at 400 mg/kg (systemic exposure equivalent to approximately 18 times that of humans at MRHD), there was reduced pup survival and body weight.

Functional toxicities. There are no studies that assess infant neurobehavioral effects of Leural related to intrauterine exposure.
Tips for Consulting on Cases Involving Drug Exposures during Pregnancy

While the bulk of fetal exposures do not result in noticeable birth defects, our present state of knowledge does not allow us to predict, with any degree of certainty, when a particular drug will prove teratogenic to a particular fetus. We can describe only relative risks for a specific population, not specific risks for specific patients (Briggs)

Providing Consultation on Inadvertent Exposures (after the fact):
- Information to gather so that a useful response can be provided:
  - accurately determine drug, dose, route
  - exact gestational age at time of exposure
  - length of exposure
  - any other drugs taken concurrently
  - information on patient’s general health, previous obstetric history, and family history may be useful in assessing the possible risk
- Research and document information found. Look in multiple references if available.
- Be sure and discuss strengths and weaknesses of data when presenting findings.
- Discuss how data applies or doesn’t apply to their situation if you can.
- Include background rate in final response.
- All information given regarding a drug exposure in a pregnant patient should be carefully documented in the patient’s medical/prescription record
- Refer for further help/counseling if you are over your head or don’t feel you can be unbiased.

Providing Consultation on Intentional Exposures (before the fact):
“Although it would be ideal to avoid all drugs, the health and well being of the mother must also be considered” (Koren)
- Information to gather so that a useful response can be provided:
  - gestational age coinciding with anticipated exposure
  - anticipated therapy (drug, dose, frequency) and duration of therapy
  - any other drugs taken concurrently
  - information on patient’s general health, previous obstetric history, and family history may be useful in assessing the possible risk and tailoring drug therapy for a specific patient
- Insure that drug therapy is indicated
- Risk to benefit ratio assessment (consider risk of unchecked disease)
- Look for consensus or expert opinion documents on DOC for patient’s condition to guide therapy decision
- Research and document information found on treatment options. Look in multiple references if available
- Choose the most effective drug with the least risk of teratogenicity
- Recommend the lowest effective dose (or route with least exposure) for shortest duration possible
- All medications prescribed or recommended for a pregnant patient should be carefully documented in the patient’s medical/prescription record

General Advice on Consulting
Develop a standardized format for your responses to make sure you don’t miss covering relevant information.

Try to avoid using the term “safe”. Terms like low risk and minimal risk are probably more appropriate given our current knowledge of teratogenicity and the limitations of published data.
Also avoid conveying that a particular pregnancy is “doomed” based on your assessment of the exposure.

The decision to terminate or to continue the pregnancy should be made by the patient after they have had the information explained to them in language they can understand and have had the opportunity to ask questions.
- Women’s attitudes toward voluntary abortion differ
- The same information about the nature and magnitude of risk may prompt different decisions by different women according to the clinical situation and specific circumstances
Discuss pregnancy registries with patient and provide contact information if they are willing to participate:

- www.fda.gov/womens/registries contains lists of registries by drug or disease
- Others- contact the manufacturer and ask if they sponsor or are aware of a registry for patients with the disease being treated or visit www.perinatology.com for a good list of domestic and international registries.

Bibliography

### Critical Periods in Human Development

<table>
<thead>
<tr>
<th>Period</th>
<th>Age of Embryo (in weeks)</th>
<th>Fetal Period (in weeks)</th>
<th>Full Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>period of dividing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>zygote, implantation</td>
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<td>3</td>
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<td>4</td>
<td>bilaminar embryo</td>
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<td>5</td>
<td>CNS</td>
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<td>6</td>
<td>heart</td>
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<tr>
<td>11</td>
<td>external genitalia</td>
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<tr>
<td>12</td>
<td>brain</td>
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*Red indicates highly sensitive periods when teratogens may induce major anomalies.*

LACTATION AND RISK OF DRUG USE DURING BREASTFEEDING

Learning Objectives:
- List the benefits of breastfeeding to the infant and the mother.
- Identify factors that predict a drug’s concentration in breast milk.
- Describe actions that can be taken to minimize drug exposure to the breastfed infant.
- Recognize the reference sources that are most likely to be useful in determining risk for a given drug exposure.
- Summarize the limitations of currently available references and outcomes data that are used to determine the risk of drug use during breastfeeding.
- Develop a care plan that incorporates the need for medication therapy with individual tolerances of the risks involved with the use of drugs during breastfeeding.
- Develop a consultative approach for conveying information about drug use during breastfeeding to other health care providers and patients.

Required Reading:

Recommended Reading:

Introduction
Exposure Estimates
Not really known since there is no data on how frequently women are advised by health professionals to discontinue breastfeeding when they are required to take a medication.

It is likely that women’s concern about safety issues translates into a drug compliance issue:
- Prospective study of Teratogen Information Service advice on safety of antibiotics during breastfeeding
  - Despite reassuring advice, 15% of women didn’t start therapy and 7% stopped breastfeeding during therapy
  - Non-compliance presumably higher in patients not receiving counseling or who receive misinformation

Societal Factors
64% of women in US breast-fed their infants while in the hospital postpartum (newer figures indicate it may now be as high as 80%)
- 6 months later 42% of these women were still breastfeeding (29% of all women breastfeed for at least 6 months)

Healthy People 2010 Goals include the objectives for 75% of women initially breastfeeding and at least 50% still breastfeeding at 6 months and 25% still breastfeeding at 1 year

Cultural messages that undermine parents’ confidence in breastfeeding include: viewing breasts as sexual organs and not as mammary glands, belief that babies need supplemental food in early months because mother’s milk isn’t enough, belief that breast feeding should end once baby starts solid foods, view that breastfeeding is not a natural event but is instead something that has to be learned and clinically managed
Role of the Pharmacist

- Pharmacists need to present a clear, unbiased understanding of the available literature to parents and other health care professionals
- Pharmacists can advise on DOC and drugs to avoid for conditions requiring drug therapy
- Pharmacists can suggest ways to minimize drug exposure to the breastfed infant when drug therapy is indicated for the mother

Breastfeeding Benefits

AAP, ACOG, WHO and UNICEF all recommend and endorse breastfeeding as the optimal way to feed newborns and infants.

Sufficient nutrition can be provided exclusively via breastfeeding through at least the 6th month after birth

AAP current recommendation is for at least 1 year of breastfeeding based on proven medical benefits

Most mothers should be strongly encouraged to breastfeed. The situations in which it is contraindicated or should be cautiously advised are few (e.g. contraindicated = HIV+ mother, human T-cell Leukemia viruses, infant with galactosemia, active herpes on breast/nipple, very few drugs; caution: PKU, s/p breast reduction surgery)

Some of the Benefits to Baby*

- Perfect food for human infants (contains everything needed to grow well and stay healthy)
- Enhances proper development of baby’s oral muscles and facial bones and promotes dental health
- Emotional as well as nutritional advantages (bond with mother, have needs met, feel safe)
- Reduced incidence of constipation, diarrhea, and vomiting
- Reduced incidence of SIDS
- Reduced incidence of obesity, IDDM, Crohn’s disease/ulcerative colitis, allergic diseases/asthma, juvenile RA, MS, and all childhood cancers
- Protects against most infections (well documented for reduced incidence and severity of respiratory, ear, intestinal and urinary tract infections) and enhances response to vaccines
- Enhances GI, immune system, and hormonal/endocrine development
- Enhances psychomotor, social, and cognitive development (including IQ)

Some of the Benefits to Mother*

- Develop a close bond with baby
- Important to mother’s psychological/emotional well-being
- Reduced risk of postpartum bleeding and helps uterus return to pre-pregnant size
- Help regain figure and ideal weight earlier since metabolizing more calories
- Induces lactational amenorrhea in first 6 months that can be 98% effective for birth control. Promotes more desirable inter-pregnancy intervals (sufficient birth spacing so mother’s system is not overtaxed).
- Reduced incidence of premenopausal breast cancer and endometrial, uterine and ovarian cancers
- Possible protection against adult onset obesity, menopausal sx, osteoporosis, and SLE
- Reduced incidence of UTI while breastfeeding
- Save over $100-200/month by avoiding cost of formula and equipment


Breastfeeding “Cliff Notes”

Breast Milk Composition

- Major macronutrients are sugar (lactose), milk fat (triglyceride mainly), proteins and minerals
  - Contains 100’s of nutrients, growth factors, hormones and antibodies
  - Many components of breast milk cannot be artificially manufactured. The infant formula act of 1980 specifies that just over 40 of the components found in breast milk must be in infant formula. Prior to 1980 there were no standards for infant formula.
  - The different kinds of breast milk
Colostrum: 30ml/24hr (FIRST 24HR, first milk, present immediately after birth): high protein, low volume, lots of vitamins, minerals, and electrolytes, clear amber fluid. Ideal first food for baby since higher protein helps stabilize infant’s blood sugar, easy on baby’s gut, serves as a laxative to help baby pass meconium stools, and helps baby coordinate sucking, swallowing and breathing patterns.

Transition milk: 500ml/24hr (DAY 2 through 2 WEEKS, mother should experience “engorgement” by day 3): baby is born with extra stored calories in the form of fat to weather this transition to mature milk production. This is why it is common for babies to weigh less at their first check up than they did on their delivery date. Up to a 10% loss is considered normal. Breastfed babies’ weights should be on an upward track by day 4-5.

Mature milk: 800ml/24hr or 1 oz/hr (2 WEEKS – INDEFINATE as long as milk is removed on a regular basis): complete nutrition for baby (88% water, 5-7% carbohydrate, 3-4% lipid and 1-2% protein)

- Foremilk (first 1/3 of expressed milk)
- Hindmilk (last 2/3 of expressed milk): 2-3x higher in fat and higher pH than foremilk
- Fat content of milk expressed by pump vs. suckling is higher
- Fat content is highest in evening (helps baby to sleep)
- When the breast is emptied, the difference between foremilk vs. hindmilk with regard to delivering nutrition and drugs becomes moot because the infant gets all of both kinds of milk.

Lactation Physiology

- During pregnancy estrogen and progesterone stimulate mammary tissue maturation but inhibit breast milk production
- Both hormones decrease just prior to birth and thus the effect of their inhibition on lactation is removed
- When the infant suckles, increased levels of prolactin and oxytocin are triggered. Prolactin is necessary for milk production. Oxytocin is involved in the milk ejection or letdown reflex.
- Milk is produced and stored in alveolar units
- Contraction of the surrounding myoepithelial cells forces milk from the alveoli into the milk ducts
- The ducts coalesce into 15-25 main ducts that empty into small sinuses which open on the nipple
- Milk synthesis is remarkably constant at around 800 mL/day.
- The actual volume of milk secreted, however, may be adjusted to the requirement of the infant; the rate of synthesis of milk is related to the degree of emptiness or fullness of the breast. An emptier breast makes milk faster than a fuller one.
- An average value of 150mL/kg/day is often used to estimate an infant’s daily milk ingestion

MILK PRODUCTION IS A SUPPLY AND DEMAND PROCESS

- Most women can make twice as much milk as the baby needs
- Even women with smaller storage or production capacity can produce the same total amount of milk as those with larger capacities (they just have to breastfeed more often)
- Most babies feed 8-12x/24hr and produce 6-8 wet dilute urine diapers/24hr by day 5 after birth
Factors Affecting Excretion of Drug into Milk and Resulting Dose Consumed by Infant

Maternal factors
- Drug, dose, frequency, route
- Clearance rate
- Plasma protein binding
- Metabolite profile

Breast
- Blood flow and pH
- Yield capacity
- Ion and other transport mechanisms
- Drug metabolism (?resorption)
- During neonatal period larger intracellular gaps let more things through, once mature milk has come in these gaps are much smaller and the system is more similar to the blood-brain-barrier

Milk
- Composition (fat, protein, water)
- pH

Infant
- Suckling behavior, including equal time on each breast
- Amount consumed per feeding
- Feeding intervals
- Time of feeding in relation to maternal dosing
- ADME parameters- route is always po
  - Premature infants have immature kidney and liver function
  - Even a full term infant’s metabolic system is not fully developed at 1 week of life

Drug
- pKa (ionization at plasma and milk pH)—only non-ionized drug can cross biological membranes
  - plasma is slightly basic (pH 7.4) vs. breast milk is relatively acidic (pH 6.4-7.6, average pH 7.1)
  - basic drugs (pKa >7.2) will have a greater proportion in the ionized state and are more likely to be “trapped” in the breast milk
- Solubility characteristics in fat and water
- Protein binding characteristics (highly bound drugs are less likely to pass)
- MW < 200 easily pass through mammary epithelium via small pores
- MW >200 must pass through capillary and alveolar membranes which act as semipermeable lipid barriers (lipid soluble will pass easier)

A comment about the Milk: Plasma ratio:  M: P Ratio = [drug] mother’s milk/[drug] mother’s plasma. If high (>1-5) it is useful as an indicator of drugs that may sequester in milk at high levels. If low (<1) it is a good indicator that only minimal levels of the drug are transferred to milk. While it is best to choose drugs with low M: P, the amount of drug which transfers is largely determined by the level of drug present in the mother’s plasma compartment at the time of breastfeeding. It should not be construed that a high M: P ratio means large amounts of drugs are going to transfer. Since it is a ratio, it does not provide the user with information as to the absolute amount of drug transferred to the infant via milk. Even if the M: P is high, if the mother has a low plasma concentration; the amount of drug that transfers is still low. It also isn’t a precise measurement since the reported M: P ratio is based on a fixed point in time when the milk was collected and is thus influenced by factors like timing of collection of milk relative to dose and what type of milk was collected (i.e. colostrum vs. foremilk vs. hindmilk).

Bottom line = this is a very complex process involving many factors. However, from a practical standpoint based on the literature available, we know that nearly all drugs pass into human milk but that almost all medications appear in very small amounts (Rule of thumb: usually less than 1% of maternal dose). For many drugs, a relative infant dose <10% of the maternal dose is considered safe.
The relative infant dose = \[
\frac{\text{infant dose (mg/kg/day)}}{\text{maternal dose (mg/kg/day)}}
\]

**Key Determinants of Drug Transfer to Milk**
- Plasma level in mother
- Lipid solubility of drug and fat content of milk
- Milk pH
- MW/size of drug
- Degree of protein binding of drug in mother’s plasma
- Half-life of drug in mother

*single most important factor, determines drug entry and exit from milk*

**Key Determinant of Amount of Drug Infant is Exposed to When Consuming Mother’s Milk**
- Oral bioavailability
  - Some drugs destroyed/denatured in infants GI system (heparin, insulin, aminoglycosides, many iv cephalosporins)
  - Some drugs are poorly absorbed orally
  - Some drugs are largely removed by hepatic first pass effect and so not much of a dose is left

### Drugs Contraindicated in Breastfeeding

<table>
<thead>
<tr>
<th>Contraindicated Drugs</th>
<th>Contraindicated Drugs</th>
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<tbody>
<tr>
<td>Alcohol (possibly low risk if used in moderation)</td>
<td>Gold salts</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Iodine containing compounds</td>
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<tr>
<td>Antineoplastic agents (esp. cyclophosphamide, doxorubicin, methotrexate)</td>
<td>?Lithium</td>
</tr>
<tr>
<td>Bromocriptine (decrease milk production)</td>
<td>Nicotine (smoking, lower risk from patches, variable with gum)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>?Pseudoephedrine (decrease milk production)</td>
</tr>
<tr>
<td>?Cyclosporine</td>
<td>Radiopharmaceuticals-temporary cessation of BF</td>
</tr>
<tr>
<td>Drugs of abuse (Amphetamines, Cocaine, Hallucinogens, Heroin, Marijuana, PCP)</td>
<td>Retinoids</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>Tetracyclines (chronic)</td>
</tr>
</tbody>
</table>

### Determining Risk from Medical Information

Many of the same limitations of the current literature previously discussed in the pregnancy section also apply to data on risk in breastfeeding. In fact the situation is worse since there is less published literature in general on breastfeeding than on teratogenic risk. A large number of drugs have never been studied during lactation and manufacturers are under no obligation to investigate this issue. The reason many manufacturers recommend avoiding use of their product during breastfeeding is because of this lack of data and not because of definitive evidence that harm is likely.

### Drug Information References that Summarize Risk Data

**Texts**
- Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. 7th ed. Philadelphia: Williams & Wilkins, 2005
- Comprehensive Database. Stockton: Therapeutic Research Faculty, 2007 (see web-based reference below)

Package Inserts or other texts that abstract information directly from package inserts (AHFS DI, Facts and Comparisons, Lexicomp Drug Information Handbook, PDR)--Note current FDA risk categories provide no guidance on risk in breastfeeding.
Electronic Media
Micromedex AltMedDex: herbals, supplements and natural medicines
Micromedex Drug Evaluation Monographs and Drug Consults: drug reviews
Micromedex Reprotox Databases (Reprotext, Reprotox, Shepherd’s, TERIS): drug reviews focused on fertility, pregnancy and lactation.

Published Reviews/Guidelines
Consensus and expert opinion documents are available on the web or in print
The most widely referenced is: AAP, Committee on Drugs. The transfer of drugs and other chemicals into human milk. Pediatrics 2001; 108:776-89. http://aappolicy.aappublications.org/, then search by title of article (accessed 3/08). It contains 6 tables on drugs in breastfeeding (3 on contraindicated drugs, 1 on “unknown effects but of concern”, 1 on “drugs that should be given with caution”, and 1 on “drugs compatible with breastfeeding”)
Nice F, Coghlan RJ, and Birmingham BT. Herbals and breastfeeding. www.uspharmacist.com, use search term = lactation herbal (accessed 3/08)

Expert Advice
Fee for service: 24 hour Lactation Fax Hotline. It is staffed by lactation researchers. Health care professionals may call 1-806-358-8138 (TX). A password is required which is available for a small fee. There is also a charge for each document sent.
Fee for service: Lactation Study Center. It is staffed by lactation specialists and pharmacists. Health care professionals may call 1-716-275-0088 (NY).
Nursing Mothers Counsel, www.nursingmotherscounsel.org, 503-293-0661 (Portland), 360-750-0656 (Vancouver): rents, leases and sells pumps. If outside of the Portland metro area, check with a local hospital for a similar program.
OHSU/Doernbecher Lactation Services via OHSU Consult Line: 503-494-4567 (OR)

- Withhold drug and try non-drug therapy
- Delay therapy
- Choose drugs that pass poorly into breast milk
- Choose an alternative route of administration
- Avoid drugs with long half-lives, sustained release forms, active metabolites, low protein binding, or M:P >1
- Avoid nursing when it may coincide with the peak drug concentration in milk, feed towards end of dosing interval
  - Peak: 1-3 hrs post oral immediate release dose (or if taken 30-60 minutes prior to feeding)
  - Take medication just after nursing
  - If the peak time cannot be avoided (e.g. multiple daily doses of drug or frequent feeding), pump and discard milk that coincides with peak time feeding and substitute previously collected breast milk or formula
- Take advantage of the infant’s longest sleep period (if predictable) and dose after last feeding of the evening
- Temporarily withhold breastfeeding
- Substitute an alternate feeding source (pre-collected milk or formula) during the period of abstinence
- Pay attention to maintaining milk supply during this time
- Pumping will not necessarily remove the drug from the mother’s circulation faster
- Length of time to withhold depends on the drug and the threat of toxicity
  - Waiting 1-2 maternal t½ may be sufficient for some drugs since 50-75% of the drug will have been eliminated
  - The ultraconservative would advise waiting 4-5 maternal half-lives to insure 94-97% elimination
  - Don’t forget to consider the half-lives of active metabolites and redistribution of “fat seeking” drugs back into plasma
- Discontinue nursing
Tips for Managing Drug Exposures during Breastfeeding

*With a fair degree of accuracy we can predict if a drug will be excreted into human milk in measurable quantities. The problem is in predicting the effects in the infant from consuming the drug.* (Briggs)

**General Factors to Consider when Providing Consultation for Inadvertent or Intended Exposures**

- To what extent is a drug excreted into breast milk (i.e. what is the milk to plasma ratio, M: P or % excreted or % of maternal dose)?
- In general, avoid drugs with long half lives (>12 hrs), sustained release dosage forms, active metabolites, low protein binding (<90%), and M:P 1 or greater
- Determine the time to peak interval and see if it is practical to feed “around” the peak time. This is often difficult to do in the early postpartum period when feeding is frequent.
- If excreted, what is the predicted dose that would be received by the infant based on the amount of excretion and the volume of milk consumed?
- If the drug is commonly prescribed for infants, it is likely that a nursing infant would get a much lower dose from milk than from taking it directly
- Even if the infant is unlikely to receive a pharmacologically important dose of the drug, don’t forget the potential for non-dose related toxicities such as allergic sensitization and antimicrobials effects on infant’s GI flora
- Be more cautious with preterm, low birth weight, or ill infants
- Drugs that alter milk production may be more risky during the neonatal period than later when the milk supply is well established
- In general, drugs considered safe during pregnancy are usually, but with few exceptions, safe to take while nursing
- Waiting 4-5 half lives after the last dose of a drug before resuming breastfeeding should result in there being <5% of the drug remaining in the mother’s body (and thus even less in mother’s milk). Waiting 1-2 half lives may be sufficient for some drugs. Note: Consult a nuclear medicine or radiopharmaceutical expert or Hale’s Medications and Mothers’ Milk text for radioactive drug half life predictions.

**Providing Consultation on Inadvertent Exposures (after the fact):**

- Information to gather so that a useful response can be provided:
  - accurately determine drug, dose, route
  - accurately determine timing of exposure (especially related to frequency of nursing) and length of exposure
  - gestational age and clinical status of infant coinciding with exposure
  - any other drugs taken concurrently
  - information on mother’s general health, previous obstetric history, and family history may be useful
  - assess if any symptoms, reactions or behavioral changes in the infant have been noticed
- Research and document information found. Look in multiple references if available.
- Be sure and discuss strengths and weaknesses of data when presenting findings
- Discuss how data applies or doesn’t apply to their situation if you can
- All information given regarding a drug exposure in a lactating patient should be carefully documented in the patient’s medical/prescription record
- Consider referral to a lactation specialist for further help/counseling if you are over your head or don’t feel you can be unbiased
Providing Consultation on Intentional Exposures (before the fact):

For patients with chronic conditions, plans for nursing and concomitant medication should ideally be discussed before delivery.

- Information to gather so that a useful response can be provided:
  - gestational age and clinical status of infant coinciding with anticipated exposure
  - current frequency of breastfeeding and volume of milk consumed by infant
  - anticipated therapy (drug, dose, frequency, route) and anticipated duration of therapy
  - clinical indication for therapy
  - any other drugs taken concurrently
  - information on mother’s general health, previous obstetric history, and family history may be useful
- Insure that drug therapy is indicated. Avoid marginally effective treatments (i.e. anti-influenza, unsubstantiated herbal treatments)
- Choose a drug for which we have more accumulated knowledge about its effects in breastfeeding
- Can risk be decreased or avoided by minimizing exposure via the methods previously discussed?
- Look for consensus or expert opinion documents on DOC for patient’s condition to guide therapy decision
- Research and document information found on treatment options. Look in multiple references if available
- Assess whether drug under consideration is likely to interfere with lactation
- Risk to benefit ratio assessment (advantages of breastfeeding vs. safety concerns for infant vs. mother’s need for medication vs. adverse effect on lactation)
- Choose the most effective drug with the least risk of harm to the infant
- Recommend the lowest effective dose (or route with least exposure) for shortest duration possible
- If breastfeeding must be interrupted >2d and can be anticipated in advance, the mother should be encouraged to pump milk ahead of time and store it for later use
- If breastfeeding must be interrupted >2d, the mother should continue pumping (but discard milk) during the period of exposure to keep her milk supply sufficient for when she can return to breastfeeding her infant. Pumping about as often as her baby was nursing should minimize her discomfort and insure adequate milk for later.
- All medications prescribed or recommended for a lactating patient should be carefully documented in the patient’s medical/prescription record
- Consider referral to a lactation specialist for further help/counseling if you are over your head or don’t feel you can be unbiased.

General Advice on Consulting

Try to avoid using the term “safe”. Terms like low risk and minimal risk are probably more appropriate given our current knowledge and the limitations of published data.

Avoid the knee jerk reaction that the woman should temporarily or permanently discontinue breastfeeding. Be sure and perform a risk: benefit analysis and give fair balance to the benefits of breastfeeding, the risks of formula feeding, and the risk of the mother losing her milk supply.

Discuss lactation registries with patient/health care provider and provide contact information if they are willing to participate:
- International Registry for Lactation Research: Maintains a list of conditions and medications for which research is needed. Mothers may register online by drug and disease to be listed in a registry as available for contact for recruitment into research studies on drugs and breastmilk.

Enhancing Lactation (Galactogogues)

Lactogenesis (revisited)
Lactogenesis I (One): Milk synthesis begins 15 – 20 weeks into pregnancy
  - High levels of estrogen and progesterone inhibit prolactin effects on milk production
Lactogenesis II (Two): Copious milk production 30 – 40 hours postpartum
  - Dramatic reduction in progesterone levels following delivery ➔ lactation
Key Players
Oxytocin ➔ Contraction of myoepithelial cells of the breast ➔ milk letdown
Prolactin ➔ Regulates volume of milk produced
Infant ➔ Once lactation is established, infant feeding continues to drive the process. Once suckling stops, lactation will also completely stop in 2 to 3 weeks.

Reasons for insufficient milk supply
- Endocrine related disorders/issues: hypothyroidism, ovarian cysts, PCOS
- Infant-related: latching and sucking not optimal, prematurity
- Others: breast-pump quality (eg. double kit for simultaneous bilateral expression vs. single kit), complete drainage

Figure 22-4 Oxytocin and the let-down reflex. The major reflex includes feedback stimulation from the nipple/areola to the hypothalamus to increase/decrease the release of oxytocin from the posterior pituitary and prolactin inhibitor factor (PIF-dopamine). The PIF affects the release of prolactin. Prolactin increases milk production. Oxytocin causes milk ejection. The release of both hormones is affected by positive or negative influences from the upper central nervous system. Oxytocin has three different target sites, the gastrointestinal tract (GI), uterus (contractions), and the upper central nervous system (mother-infant bonding). Oral stimulation in the infant initiates oxytocin release to improve GI activities and maternal-infant bonding. (From Rolland R, DeJong FH, Schellekens LA, et al: The role of prolactin in the restoration of ovarian function during the early postpartum period in the human: a study during inhibition of lactation by bromergocryptine. Clin Endocrinol 4:23, 1975, with permission.)

From Gabbe: Obstetrics: Normal and Problem Pregnancies, 5th ed. (via MD Consult; 03/31/08)
Galactogogues

**Dopamine Antagonists**

- Block endogenous dopamine receptors \(\rightarrow\) increased production of prolactin
- Agents reported in the literature include:
  - Metoclopramide (Reglan)
    - Most extensively studied
    - Usual dose as galactogogue: 10 mg po TID x 7-14 days (10 days)
    - Onset: usually 3 to 5 days
    - Adverse effects: diarrhea, CNS effects (drowsiness, fatigue, anxiety, depression), extrapyramidal effects including dystonic reactions
  - Domperidone (Motilin)
    - Only available through compounding pharmacies in the US
    - Thought to have a lower incidence of adverse events compared to metoclopramide as less drug crosses blood-brain-barrier
    - May be cost prohibitive since needs to be compounded
  - Chlorpromazine and Sulpiride (not available in US)
    - Typical/Classic Antipsychotics
    - Literature for chlorpromazine is limited to case reports
    - Adverse effects similar to metoclopramide, though possibly higher likelihood of occurrence

**Fenugreek**

- Hypothesized to increase sweat production (breast is modified sweat gland)
- Anecdotal reports published, but clinical trial data are not available
- Issues of standardization of dietary supplements in US
- Dose: 2 to 3 capsules TID \(\Rightarrow\) unclear what amounts this will provide
- Reported adverse events: maple-like odor of body fluids, diarrhea, exacerbation of asthma, GI bleeding

**Oxytocin**

- Nasal preparation no longer available on the market: need to have compounded
  - 40 unit/mL \(\Rightarrow\) 3 units/spray in each nostril just prior to feeding/pumping
- Buccal/sublingual preparations also reported in the literature
- Adverse effects: blood pressure changes, uterine contractions, arrhythmias

**Bottom Line on galactogogues**

- Non-pharmacologic intervention should be attempted to optimize milk production
  - complete emptying of breasts during feeding
  - rule-out other causes of insufficient milk supply (medications, underlying dx, etc.)
  - adequate stimulation and frequency of feeding/pumping
- Weight risk to mother and infant against benefit of breastfeeding
- Base decision on current safety and efficacy literature, product availability, and cost
  - Metoclopramide and domperidone are agents currently deemed as most useful
Bibliography