Teratology and Safety of Drugs in Pregnancy and Lactation

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Readings: Applied Therapeutics: The Clinical Use of Drugs, 8th Ed.
Required: Chapter 47, Recommended: Chapter 46
Learning objectives

• Drug use during pregnancy or lactation
  – How to respond to requests for drug information regarding an anticipated or actual exposure
  – How to minimize risk
    • During pregnancy: not as much can be done
    • During breast feeding: more can be done

• Lecture notes have supporting content and detailed learning objectives
What will I be able to do at the end of the lecture?

- **Expected**
  - Understand foundational concepts so you can accurately interpret the literature
  - Understand the limitations of the data we use to make decisions
  - Know the useful references for looking up information about risks of exposure
  - Suggest ways that risk can be minimized and monitored
  - Be able to communicate and consult on the perceived risks and benefits of drug use during pregnancy or lactation

- **Not Expected**
  - Recite DOC for pregnant or breastfeeding patients given any other concurrent medical condition
  - Won’t cover:
    - Female Reproductive Pathophysiology
    - Labor and Delivery Pathophysiology and Medications
    - Common Diseases of Pregnancy and Treatments
Pearls

- Watch for this symbol throughout the lecture
- Each pearl conveys an idea, concept, or fact that will be useful in everyday practice, but may not be widely known, published or taught.
Teratology and Safety of Drugs in Pregnancy

- Largely because of historical events like the thalidomide tragedy, there is societal concern about drug exposures during pregnancy.
- Exposures still occur commonly during pregnancy.
- “Use during pregnancy is not recommended” ≠ “use during pregnancy is unsafe”.
- Pharmacists often provide information on the risks and benefits of drug use during pregnancy.
Causes of malformations

- Genetic
- Multifactorial
- Envir-Drugs and Chemical
- Envir-Other
- Unknown
Foundational concepts

- Timing is (almost) everything
- Calculate the stage of pregnancy
- Not all birth defects can be seen
- The list of known teratogens is small
- You can’t predict who will have a negative outcome from exposure
Consider timing of exposure

(chart enlarged at end of handout)
Identifying conception date

Menstrual Cycle

- **LMP d1**
- **NMP d1**
- **7d**
- **14d**
- **21d**
- **28d**

**Conception Window** (4-5d prior to thru 24h post ovulation)

**Ovulation** (14d prior to NMP, range 12-16d)
Estimating gestational age

- Gestational age is the number of completed weeks of pregnancy since LMPd1
  - Wk 1-8: Conceptus is called an embryo
    - Time when major body organs developed
    - See Timetable of Human Prenatal Development Chart in reserve lecture notes for pictures of what happens wk 1-10
  - Wk 9-40+: Embryo becomes a fetus
    - Time when final differentiation, maturation occur
    - Time for major growth in height and weight
    - Major CNS development still occurring through first third of this period
    - 38wks gestation is considered full term
Estimating date of delivery (EDD)

- Estimation based on LMP and usual cycle length
  - With wheels and charts in OB’s office
  - Mathematical estimate (Nagele’s Rule)
- Agreement of fundal height to EDD also confirmatory
  - Measure from the pubic bone to the top of where the uterus can be felt
- Now most often confirmed or re-estimated by ultrasound findings
Mathematical estimate of EDD (Nagele’s Rule)

- \([\text{LMPd1} - 3 \text{ months}] + 7 \text{ days}\)
  - Correct to within 2 weeks of delivery. Best if patient has regular 28d cycles.
- Normal duration of gestation is 267 days from conception or 280 days from LMPd1
- 38 wks gestation is considered full term
Nagele’s Rule example:
(LMPd1 – 3 months) + 7 days = EDD +/- 2 weeks

• Pretty straight forward
  – LMPd1 = 1/10/06…Oct…Oct 17th…same yr

• Watch out for crossing a month and/or year
  – LMPd1 = 1/27/06…Oct → Nov 3rd…same yr
  – LMPd1 = 5/3/06…Feb…Feb 10th…next yr
  – LMPd1 = 5/31/06…Feb → March 7th…next yr
# Birth defect terminology

(Chart enlarged at end of handout)

## Congenital Anomalies (Defects Existing at Birth)

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt</td>
<td><strong>Major anomalies</strong> (Significantly interfere with normal body functions. May be incompatible with life or will require major surgery for correction)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>club foot, omphalocele, spina bifida, Tetralogy of Fallot (cardiac), Ebstein’s anomaly (cardiac)</td>
<td>2-4% recognized at birth, similar rate also discovered in months or years following birth</td>
</tr>
<tr>
<td></td>
<td><strong>Minor anomalies</strong> (“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>Covert</td>
<td><strong>Functional anomalies</strong> (abnormal physical or mental development)</td>
<td>behavioral problems, learning delays, physical growth retardation</td>
</tr>
</tbody>
</table>
Drugs proven or highly suspected to be human teratogens

**Drugs with FDA special labeling or dispensing requirements due to teratogenic risk.**

| ACE-inhibitors (2\textsuperscript{nd}/3\textsuperscript{rd} tri), D | Oral hypoglycemic drugs, C |
| Alcohol (high dose more risk, but no safe levels known), D/X | Penicillamine, D |
| Androgens, X | Phenytoin, D |
| Antineoplastics (some but not all), D-X | Retinoids (Acitretin**, Etretinate, X) |
| Antithyroids (Methimazole and PTU, D) | ?Ribavirin, X |
| Barbiturates, D | ?Rubella vaccine, Inhaled Flu Vaccine, Small Pox Vaccine and other live vaccines, C/X |
| Carbamazepine, C | Tetracycline, D |
| Cocaine (abuse), C/X | Thalidomide**, X |
| Diethylstilbestrol, X | Trimethadione, D |
| Danazol, X | Valproic acid, D |
| Iodides (including radioactive contrast media), X | Vitamin A (both deficiency and excess >18,000 IU/d), A/X |
| Isotretinoin **, X | Warfarin and coumarin derivatives, D/X |
| Lithium, D | Misoprostol (oral), X |
Placenta: the thin red line

- It isn’t a barrier except to drugs with very large MW (i.e. a small minority)
- As pregnancy progresses, transport to fetus increases
Factors influencing teratogenicity

**Drug related**
- MOA
- Dose and duration of drug exposure (more is worse)
- MW< 600 (most drugs) cross easily, >1000 (heparin) with difficulty or not at all
- Degree of protein binding (only free drug passes)
- Ionization
- Lipophilicity
- Increased estrogen and progesterone of pregnancy can affect drug metabolism

**Mother related**
- Genetic makeup
- Concurrent exposures
- Uterine blood flow
- Maternal disease
- 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

**Baby related**
- Genetic makeup
- Developmental stage of exposure
- Fetal blood flow
- Fetal drug clearance
- Total free drug often higher in fetus since fewer binding proteins
Data used to make decisions

- The DBRPCT is not the gold standard
- The data we have available has limitations but is still useful
- The FDA pregnancy categories don’t do what we want
- Use specialized resources and references to get at helpful information
Levels of evidence are limited

Animal data
Case reports < Case series
Observational studies

Identify women who took drug

COHORT

Watch and learn, no intervention

?Did mothers take drug

Case-Control (aka TROHOC)

?Birth defects noted in offspring

Identify offspring with birth defects
Some limitations of available sources

The Bad News

- Outcomes in animals don’t always correlate to human risk
- Case reports
  - If rare malformation- useful
  - If drug used by few- useful
  - Otherwise, less helpful and may just be representative of “background rate”
- Sample size: Large sample sizes are needed to detect small differences 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
Some limitations of available sources

The Good News

• Meta analysis of collective studies of similar design

• Prospective epidemiological data from teratology information services and pregnancy registries
  – www.otispregnancy.org
  – www.motherisk.org

• FDA now has a great clearinghouse for registries and patient information
  – www.fda.gov/womens/registries
1979 FDA Pregnancy Risk Categories are outdated

- A system that needs fixing
  - Older drugs (pre 1983) were exempted from being categorized
  - Not all teratogens are category X
  - Although implied, the categories DO NOT provide a gradation of risk
    - Particularly in the murky area of “B” and “C”
  - Provides no help on how to assess risk or manage patient
  - Manufacturers are allowed to assign categories and are influenced by risk management issues
  - Categories not updated when new data available
## Current FDA Categories

(Chart enlarged at end of handout)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>Apparently safe (&lt;1% marketed drugs)</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Animals no risk; human data reassuring</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>Human data lacking; animal data positive or not done (66% marketed drugs)</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>Human risk but benefit may outweigh</td>
</tr>
<tr>
<td><strong>X</strong></td>
<td>Human risk without benefit</td>
</tr>
</tbody>
</table>

### A
Adequate, well-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.

### B
Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women.  
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.

### C
Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women.  
Or  
No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.

### D
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).

### X
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.
A better way?

- FDA Categories do not always agree:
  - with other countries risk rating systems
  - with teratologist consensus
- FDAs Pregnancy Labeling Task Force is working to revise the labeling system to be more clinically useful.
  - With so much controversy, a date for implementation has not been set
FDA 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
Useful print references

- Briggs’ Drugs in Pregnancy and Lactation
  - 7th ed, 2005
  - $100
  - Now available for PDA, $60

Bottom Line: Gold standard text + improvements. You get both pregnancy and lactation data in one reference.
Useful electronic references: Micromedex **Drug Evaluations**

**Bottom Line:** Think of it as the PDR+. Incorporates manufacturers info with published literature. If you have access to it, use it!
Useful electronic references:

Micromedex RepROTOX

Bottom Line: Reproductive risk section is like four texts in one. Covers fertility, pregnancy, and lactation. If you have access to it, use it!
Useful print references

- Facts and Comparisons ImmunoFacts
- 2006 Softback
- $75
- Full pocket version available for $40
- Product tables RX-FACTS for $5

Bottom Line: Every clinic that administers immunizations should have this incredibly useful book. Also, helpful for pregnancy and breastfeeding questions.
Useful combo print/electronic reference

• Pharmacist’s Letter/Prescriber’s Letter Natural Medicines Comprehensive Database (web based version also available)
• $90 book or web (+ $40 book)
• Now available for PDA, $92 (solo purchase)

Bottom Line: In my opinion the best on the market right now for natural products questions of any kind. Includes sections for pregnancy and breastfeeding.
Less useful references

• Many drug references that are generally very useful are not extremely helpful for pregnancy and lactation questions
  – They usually just repeat the manufacturer’s labeling category warning without sharing other info
Take home points

• Percentage of defects due to drugs is small BUT can often be modified
• Most studies focus on the overt anomalies because we can see them
• A 3-6% “background” rate of birth defects is quoted
  – All types of malformations total is probably around 12%
Take home points

• The first trimester isn’t the only time of risk but it is the most studied
• Timing is paramount when linking a defect with an exposure
• The first 2 wks of gestation may be a “no effect” period
• The drug, the mom and the baby all influence the risk
• Just like with drug interactions, there is substantial interpatient variability
Take home points

• Levels of evidence are different for interpreting pregnancy risk
• The FDA Categories should not be the only thing you consider when judging risk
• Know and use specialized references; your general references aren’t that helpful
Tips for consulting on cases

• There are basically two situations you will encounter:
  – Providing information after the fact
  – Providing information before the fact / Preconception planning
    • Try to avoid using the term “safe”
    • Terms like low risk and minimal risk are probably more appropriate.

• Respect the patient’s autonomy. DO NOT assume a paternal or authoritarian role and suggest what should be done about the pregnancy
  – Your role is to provide unbiased information so that they can make an informed decision
  – Avoid conveying a sense that the pregnancy “is doomed”

• See e-reserve lecture notes for guidelines
Case 1-Drugs in Pregnancy (before the fact)

- 30 yo female, G₁P₀ (0-0-1-0)
- Hx of DVT five weeks ago
  - Presents for annual gyn exam
  - Wants to become pregnant sometime over next three months
  - Has been on warfarin since hospitalization for DVT
- Ob/Gyn resident consults you about best therapy for her
Guidelines: Providing consultation on intentional exposures

“Although it would be ideal to avoid all drugs, the health and well being of the mother must also be considered” - Briggs

• Guidelines and explanations detailed in lecture notes
• What information do we need?
• What should we consider?
• What resources should we consult?
Case 1 – Response “Talking Points”

All medications prescribed or recommended for a pregnant patient should be carefully documented in the patient’s medical/prescription record

- Warfarin is avoided during pregnancy due to fetal warfarin syndrome (6-12 wks gestation).
- Some CNS anomalies have been associated with 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester exposure to warfarin.
- CHEST guidelines recommend use of heparin or LMWH.
- Patient does not have prosthetic heart valve.
- Duration of therapy for DVT is likely to overlap with pregnancy if gets pregnant soon.
All medications prescribed or recommended for a pregnant patient should be carefully documented in the patient’s medical/prescription record

- Recommend LMWH based on actual body weight. Dose round or exact dose as per protocol.
- Differing opinions on whether to give as split doses or single daily dose. OHSU recommends split doses.
- Monitoring indicated. Titrate to 1.0 U/mL Anti-Xa level drawn at 4 hr post dose
Case 1 – **Take home points**

- Consider usual factors when selecting an anticoagulant for the mother
- Familiarize yourself with weight of teratogenic evidence for each therapeutic option
- Look for guidance from experts/landmark publications like CHEST
- Risk: benefit assessment should consider both mother and embryo/fetus
- Minimize exposure, when possible
All medications prescribed or recommended for a pregnant patient should be carefully documented in the patient’s medical/prescription record.

...would your response change if she was 10 weeks pregnant, in her second trimester, or nearing the time of delivery?

...would your response change if she had a mechanical heart valve in place?

...would your response change if she had a prior hx of DVT/PE or a hx of hypercoagulability?

...would your response change if she had ongoing sx of DVT/PE?
Questions

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• 503-494-0475
• E-mail for questions
Break
Safety of Drug Use During Breastfeeding

- The numbers of women breastfeeding is on the rise
- Many people interpret that “use during lactation is not recommended” = “use during lactation is unsafe” OR “breastfeeding needs to be discontinued”
- Clinicians are often contacted to provide information on drug use during lactation
Breastfeeding benefits

• AAP current recommendation is for at least 1 yr of breastfeeding
• “Breast is best”: detailed list of benefits in lecture notes
  – Nutritionally
  – Passage of antibodies from mother helps protect against infectious diseases
  – Linked with prevention of other diseases (mom and baby)
  – Part of natural process of mother’s body returning to pre-pregnancy state
  – Mother: baby bond
  – Cost savings
Breastfeeding physiology

• Milk production is a supply and demand process
  – Milk production is relatively constant
    • In the end, the larger and smaller breast produce the same amount of milk
  – The rate that milk is made is related to the emptiness or fullness of the breast
    • Empty = faster
  – Estimate of 150 ml/kg infant weight/day is useful for gauging infant’s nutritional needs
    • Most women can make twice as much milk as needed
    • Most babies feed 8-12x/24hr by day 5
Breast milk composition

- Major macronutrients are sugar (lactose), milk fat (triglyceride mainly), proteins and minerals
  - Many components can’t be artificially manufactured
  - Prior to 1980 no standards for infant formula
- The different kinds of breast milk

<table>
<thead>
<tr>
<th>Type</th>
<th>Duration</th>
<th>Volume 1/24hr</th>
<th>Volume 2/24hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colostrum</td>
<td>24 hrs</td>
<td>30ml</td>
<td>500ml</td>
</tr>
<tr>
<td>Transition Milk</td>
<td>d2-2 wks</td>
<td>500ml</td>
<td>800ml</td>
</tr>
<tr>
<td>Mature Milk</td>
<td>2wks-indefinite</td>
<td>800ml</td>
<td></td>
</tr>
</tbody>
</table>

by d3: engorgement = “drama”
Key Questions:
Drug Use During Breastfeeding

• Is the drug contraindicated?
• How much gets through?
• What do we know about its safety?
Drugs contraindicated in breastfeeding

- Alcohol (probably low risk if used in moderation)
- Amiodarone
- Antineoplastic agents (esp. cyclophosphamide, doxorubicin, methotrexate)
- Bromocriptine*
- Chloramphenicol
- Cyclosporine
- Drugs of abuse (amphetamines, cocaine, hallucinogens, heroin, marijuana, PCP)
- Ergotamine*
- Gold salts
- Iodine containing compounds
- Lithium
- Nicotine (smoking)- lower risk from patches, variable risk with gum
- Pseudoephedrine*
- Radiopharmaceuticals- temporary cessation of BF
- Retinoids
- Tetracyclines (chronic)

*Decrease the production of breastmilk
Factors influencing dose consumed by nursling

- 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*
Factors influencing dose consumed by nursling

- 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 (vancomycin)
    - Some drugs are largely removed by hepatic first pass effect and so not much of a dose is left to reach the infant
Yikes!! That’s more complex than in pregnancy

• “Compartments in compartments”…it’s hard to sort out
• From a practical standpoint we know that nearly all drugs pass into human milk, but that they appear in very small amounts (<1% total maternal dose)
  – This process is a more effective barrier than the placenta is in pregnancy
  – By end of first post-partum week the barrier is more like BBB (i.e. tight epithelial junctions)
  – During the neonatal period more gets through
• Bottom line: Very few drugs are contraindicated in breastfeeding
Maternal Capillary

Drugs

Maternal Capillary

Alveolar cells

14-days Post-partum

Adapted from Hale TJ (2002)
A word (or two) about the M:P Ratio

M:P = Concentration of drug in milk/Concentration of drug in mother's plasma

- <1 low, >1-5 high (drug sequestered in milk)

- Not a qualitative measure
- Can be helpful but can be misleading
- Remember that mother’s actual plasma level is still the key determinant
  - High M:P drug but low actual plasma level in mom = low drug received by infant
Better: Theoretic or Relative Infant Dose

- Some references publish the actual amount of drug in the milk
- Hale’s text has converted this to a theoretic infant dose
- Use the published amount to calculate the relative infant dose (RID)

\[ \text{RID}^* = \frac{\text{Milk Infant dose (mg/kg/day)}}{\text{Maternal dose (mg/kg/day)}} \]

*For many drugs RID <10% is considered safe
And we thought the data was bad for drug use in pregnancy!

- 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:
  - 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.
Useful print references

- Hale’s Medications & Mothers' Milk: A Manual of Lactational Pharmacology
- 12th edition, 2006, $33
- Available for PDA, $27 on sale (Medilact 2006)

Bottom Line: A bargain for what you get. A standard text for lactation consultants. Has hard to find info like drug pKa’s, estimated infant doses, and lactation safety ratings. Author is active researcher in this area.
Hale’s Breastfeeding and Medication Forums

http://neonatal.ttuhsc.edu/lact/medicationforums/epage.html

Free resource for drugs not in current edition answered by the expert
Useful Internet references: AAP Policy Statement

Bottom Line: Price = free. Need I say more? Actually, this is the authoritative reference that many texts abstract from. Because they are so conservative, I feel fine saying “no problem” if the AAP says it is compatible with breastfeeding.
Useful print references

- Lexicomp Pediatric Dosage Handbook
  - 13th edition, 2006
  - $50
  - Available for PDA, $75
  - http://www.lexi.com

Bottom Line: Worth having this or Harriet Lane for general practice anyway. Many pediatric pharmacists that used to use Harriet Lane now use this. Lists infant doses.
Useful print references

- The John’s Hopkins Hospital: Harriet Lane Handbook
  - 17th edition, 2005
  - $50
  - Comes with downloadable PDA software

Bottom Line: Worth having this or the Lexicomp pediatrics book for general practice anyway. Has schematic that rates pregnancy risk and breastfeeding risk for each drug. Lists infant doses.
Stepwise approach to minimizing drug exposure during breastfeeding*

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 t1/2, SR forms, active metabolites, low protein binding, and M:P>1
Avoid nursing when it may coincide with the peak drug concentration in milk. Feed toward the end of the dosing interval.
Take advantage of the infant’s longest sleep period (if predictable) and dose after last feeding of the evening

Stepwise approach to minimizing drug exposure during breastfeeding*

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

Discontinue nursing
Tips for consulting on cases

• There are basically two situations you will encounter:
  – Providing information after the fact
  – Providing information before the fact
• Try to avoid using the term “safe”
  – Terms like low risk and minimal risk are probably more appropriate.
• AVOID the knee jerk reaction that the woman should temporarily or permanently discontinue breastfeeding without looking into it further
• See lecture notes for guidelines
Case 2- Drugs in Lactation (after the fact)

- Mother of 1 month old infant has been diagnosed with mastitis
- Mother has been breastfeeding since infant’s birth
- Doctor in urgent care clinic gave her 3d clarithromycin samples last evening and a Rx for dicloxacillin x10d
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)

- Guidelines and explanations detailed in lecture notes
- What information do we need?
- What should we consider?
All information given regarding a drug exposure in a lactating patient should be carefully documented in the patient’s medical/prescription record:

- **Was infant full-term vs. premature at birth?**
  - Full-term

- **What has mother taken thus far?**
  - Taken 3d of Biaxin (clarithromycin)
  - Ready to start taking dicloxacillin

- **What is DOC for mastitis? Patient Allergies?**

- **To what extent is a drug excreted into breast milk?**
  - Theoretically Clarithromycin M/P > 1
  - Dicloxacillin ➔ PB > 90%, zero detected in milk 6-hrs after dose, M/P = ?
Case 2- Response
“Talking Points”

• 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?
  – Assume mom has received Clarithro 500 mg po BID and she is 60 kg ➔ Daily Dose for Mom = 1000 mg/60 kg = 17 mg/kg/day

• 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?
  – Clarithro bioavailability ~50%
    ➔ Max infant could receive = 8.5 mg/kg/day
  – This is much less than actual dose infant would receive for URI
    (Usual peds dose (> 6 months) = 15 mg/kg/day)
Bottom Line:

• Most antibiotics are minimal risk in nursing infants

• Consider usual factors when selecting an antibiotic for the mother and infant

• Pain relief will probably be necessary and should be recommended in anticipation of need

• Interruption of breast feeding should be avoided (especially since it is beneficial in mastitis)
Helping to *Go with the Flow*

- Copious milk production occurs 30 – 40 hours postpartum
  - Lactogenesis II = milk “coming in”
- Once lactation starts, infant feeding drives the continued process
  - No suckling = Lactation ceases in 2 to 3 weeks
- Inability to produce sufficient milk supply can be due to many factors
Simple Lactation process

Pain, Stress, Insecurity
   ↓
   Negative
   Oxytocin

Hypothalamus
   ↓
   +
   -
   +
   -

Post. Pituitary
Spinal cord
Nursing Frequency
GI activation
Uterine contractions

Ant. Pituitary

Myoepithelial cells
Alveolar cells

Nipple/Areola

Milk

Maternal Cerebrum

Prolactin Inhibitory Factor

Maternal Infant Bonding

Baby’s Cerebrum

Baby

GI activation

Nursing
Oral Stimulation

Oxytocin

Gabbe. Obstetrics - Normal and Problem Pregnancies, 4th ed (via MD Consult; 10/04)
Galactagogues

• Dopamine Antagonists
  – Blocks dopamine receptors \(\rightarrow\) increased prolactin release
  – Agents most clinically useful include:
    • Metoclopramide
    • Domperidone (not FDA approved) – need to get from compounding pharmacy
  – Traditional use of natural products: fenugreek


Academy of Breastfeeding Medicine. ABM Protocol #9: Use of galactagogues in initiating or augmenting maternal milk supply.
Bottom Line: Galactagogues

- Endocrine control starts milk production, but autocrine control maintains the process
- Patient/infant modifiable factors should be addressed prior to use of any galactogogue
- If galactogogue benefit outweighs risk, consider Rx:
  - Safety and efficacy data
  - Ease of product procurement
  - Cost

Questions

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