Principles in Counseling Women with Drug Exposure During Lactation

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Determined of Drug Bioavailability and Efficacy

- Dose and route of delivery
  i. Circulating level achieved
  ii. Distribution
- Availability and coupling to its effector mechanism
- Clearance
- Physiologic adaptations

Prescription Medication Use

Although many medications do pass into breast milk, most have little or no effect on milk supply or on infant well-being. Few medications are contraindicated while breastfeeding.

Is it safe for mothers to use prescription medications while breastfeeding?

According to the American Academy of Pediatrics, "The Transfer of Drugs and Therapeutics into Human Breast Milk. An update on Selected Topics." indicates that most medications and supplements are safe to use during lactation.

Review <a href="https://www.aap.org/en-us/policy-resources/downloads/Pediatric-Drugs-in-Milk.pdf" target="_blank">for the most up-to-date information available</a> when advising breastfeeding mothers on medication safety.

Note to Breastfeeding Mothers:
Tell your health care provider and your baby’s provider about any medications or supplements you are taking, including vitamins, herbs, and over-the-counter products.

- Need for the drug to the mother.
- Potential effects of the drug on milk production.
- Amounts of the drug transferred into human milk.
- Extent of oral absorption by the breastfeeding infant.
- Potential adverse effects on the breastfeeding infants.
- Age of the infant.
- Proportion of feedings that are breast milk.
Pharmacogenetics

- The pharmacogenetics of mother determines the effectiveness of metabolism and thus the potential amount of drug available
- Drug metabolites reflect specific pharmacokinetic pathways that may be altered by sex hormones
- The pharmacogenetics of the second hand user - the child- determines the oral bioavailability

Anything that alters breast development can alter drug transfer

- Normal breast consists of ducts and lobules; 6-10 major ducts open onto the surface of the nipple
- Large ducts travel to the terminal duct lobular unit where it branches into grape-like clusters of small acini to form a lobule
- 3 types of lobules that reflect the stage of development; they increase progressively in number and size, and by term delivery, the breast is almost entirely composed of lobules separated by small amounts of the stroma
- Only with the onset of pregnancy does the breast become completely mature and functional
- Prior surgery can disrupt ‘smile’ vs. armpit or navel

Anything that alters breast development can alter drug transfer

Exclusion of Women from Clinical Trials

<table>
<thead>
<tr>
<th>Obstacles to Studies in Women</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential effect on fertility</td>
<td>Little safety information</td>
</tr>
<tr>
<td>Potential effect on fetal development</td>
<td>Little knowledge of fetal risks</td>
</tr>
<tr>
<td>Potential effect on cognitive development</td>
<td>Little opportunity for risk reduction</td>
</tr>
</tbody>
</table>

By-products of Exclusion

- A lack of information on the pregnancy effect on drug PK and similarly, the effect of the drug on pregnancy
- FDA reviewed 575 Rx drugs and biologics approved 2015-17; only 15% of labels included human data on lactation. Pregnancy was studied in 11 drugs post marketing but only 27 women enrolled
- Pregnant and lactating women are often inappropriately denied medical therapy they need
- Pregnant and lactating women are often inappropriately treated with drugs they should not be receiving at that stage of reproduction
Prescription Drug Use is Common During Pregnancy

- 4 - 7% use at least one Category D or X drug
- Other common classes include
  - Antibiotics (62%)
  - Analgesics (18%)
  - Asthma medications (18%)
  - Antiemetics (17%)
- Women with infertility or chronic illnesses were most likely to be exposed

Riley et al, J Womens Health (Larchmt) 14:401, 2005
Hardy et al, Pharmacoepidemiology and Drug Safety, 15:555-564, 2006

Methods to Ethically Collect Pharmacokinetic Data in Women

- Trials of women on hormonal contraceptives
- Pharmacokinetic and pharmacogenetic studies in pregnant and breast feeding women
  - Drugs prescribed for recognized indications
  - Study non-human primates
  - Use unplanned pregnancies seeking termination
  - Indemnify manufacturer and investigator
  - Prolong patent protection
- Well designed informed consent

Methods to Ethically Collect Pharmacokinetic Data in Women

- Cross sectional, longitudinal, or blinded
  - Population pharmacokinetic studies at 4 time points to identify candidate drugs for longitudinal studies
  - Simultaneous pharmacogenetic studies (e.g. high throughput SNPs)

Methods to Ethically Collect Pharmacokinetic Data in Women

- Better use of post marketing data- many women already use these drugs
- Systematic surveillance projects
  - Current Registries used as models (17 covering >50 drugs)
  - Use CDC or CROs for surveillance
  - Target Pharmacies / Prescriptions / Specialists
  - Determine threshold signal for intervention
  - Regular reporting of cumulative experience

Prescribing Sources of Information

- Relatively few published or unpublished trials that even include much less focus on pregnant or lactating women
- Even fewer studies of milk pharmacokinetics of neonatal drug levels
- Isolated case reports or small uncontrolled series
- In the past, these were scattered across the medical literature, but there has been a clear increases lately

Prescribing Sources of Information

- Detail men- don’t believe everything you hear
  - US sales force has more than doubled in less than 10y; $20 billion spent in 2018 to schmooze healthcare personnel

Hensley, S. Wall Street Journal, June 18, 2003

- Advertisements- don’t believe everything you read
  - Consumer direct spending went from $2.1 B in 1997 to $9.6 B in 2016, of which $6 B was for marketing prescription drugs
  - Trade: promotional claims are frequently misleading and or cite studies either not retrievable or fail to back-up particular claims

Prescribing Sources of Information

- Reference texts
  - Do they contain the needed information?
  - How often are they updated?
  - Categorization; e.g. FDA

What do you need to know to assist your clients?

- Maternal considerations
- Breast feeding considerations

Drug Categorizations

- Don’t reveal how pregnancy or lactation may alter the response to pharmacotherapy
- The assigned category is typically stagnant, based on information available when the drug is first approved in that country
- Only 25% of 236 drugs common to the US, Australia and Sweden were placed into the same risk category


LactMed (TOXNET Database)

Drug Levels and Effects

- Summary of Use during Lactation:
  - Drug Levels
    - Maternal Levels
    - Infant Levels
- Effects in Breastfed Infants
- Effects on Lactation and Breastmilk
- Alternate Drugs to Consider
- Reference
Before prescribing drugs to lactating women

- Is the drug really necessary? If yes, a discussion between the pediatrician and the mother’s physician may be the most useful way to determine an alternative.
- Chose the safest option e.g. acetaminophen vs. aspirin.
- If there is a possibility a drug presents a risk to the infant, consider measuring the blood concentration in the nursing infant.
- Drug exposure to the nursing infant may be minimized by applying knowledge of milk levels.

Breast Feeding Considerations

- Puerperal changes in clearance- $t/2$, AUC:
  - Increased cardiac output maintained for about a week
  - GFR increased until the puerperal diuresis finishes
  - Changes in breast milk
- Availability of trial data to support on and off label indications
- Drug interactions; e.g. low dose aspirin
- Breastfeeding triggers its own physiologic adaptations
- Great variability

Breast Feeding Considerations

- Transfer to breast milk:
  - More than M/P ratios- concentration is necessary to understand potential neonatal dose
  - Relationship to timing of maternal dose
  - Fore and hind milk
  - Change over time

Maternal factors affecting drug transfer

- The maternal serum drug concentration
- Drugs: protein binding, lipid solubility, molecular weight and ionization:
  - Transfer is greatest with
    - low protein binding high lipid solubility
    - low molecular weight
    - weakly basic drugs
- Milk composition:
  - Hindmilk contains more fat than the foremilk and therefore concentrate fat-soluble drugs

Breast Feeding Considerations - Neonate

- Condition of the infant- Greater precaution for premature or compromised infants or in their first week of life than for older, healthy infants
- The amount of breast milk consumed by the infant
- Neonatal oral absorption- i.e., bioavailability
- The pharmacologic activity of the drug:
  - absorption, distribution, metabolism and elimination by the infant

Age of infant:

- Early postpartum, large gaps between mammary alveolar cells allow many drugs to pass; these gaps close by the 2nd week of lactation.
- Premature babies and infants <1 month have a different capacity to absorb and excrete drugs than older infants.

Hence the extra caution indicated for these infants.
Transfer of Drugs into Breast Milk

- Nearly all drugs transfer into breast milk to some extent
- Notable exceptions are molecules too large to cross biological membranes - e.g. heparin, insulin and ‘biologicals’
- Drug transfer from maternal plasma to milk is, with rare exceptions, by passive diffusion across biological membranes

Infant Exposure to Drugs

Relative infant dose (RID, mg/kg): weight corrected % maternal dose ingested by the unsupplemented 3kg neonate and the resulting neonatal blood level

\[ D_{\text{infant}}(\text{mg/kg/day}) = C_{\text{maternal}}(\text{mg/L}) \times \frac{M}{\text{PAUC}} \times \frac{V_{\text{infant}}}{L_{\text{infant}}(\text{L/kg/day})} \]

- \(C_{\text{maternal}}\) = maternal plasma concentration
- \(M/\text{PAUC}\) ratio = milk to plasma concentration ratio (AUC)
- \(V_{\text{infant}}\) = volume of milk ingested (commonly estimated as 150 mL/kg/day).

An arbitrary cut-off of 10% is used as a guide for the safe use of drugs during lactation.

Minimizing Potential Risk to Nursing Infants from Maternal Medications

General considerations

- Use topical therapy when possible
- Drugs that are safe for the nursing infant’s age are generally safe for the breast-feeding mother
- Drugs that are safe in pregnancy are not always safe in breast-feeding mothers (nursing infant must independently metabolize and excrete the medication)

Medication selection

- Choose medications with the shortest t/2 and highest protein-binding ability
- Choose medications that are well-studied in infants if available
- Choose medications with the poorest oral absorption
- Choose medications with the lowest lipid solubility

Medication dosing

- Administer single daily-dose drugs just before the longest sleep interval for the infant, usually after the bed-time feeding
- Breast-feed infant immediately before medication dose when multiple daily doses are needed

WHO Classification of Drugs during Breastfeeding (2002)

1. Compatible with breastfeeding
2. Compatible with breastfeeding (occasional mild side effects); monitor infant for side effects
3. Avoid if possible (significant side effects); monitor infant for side-effects
4. Avoid if possible (may inhibit lactation); monitor for amount of milk
5. Contraindicated (dangerous side effects)
WHO Classification Drugs during Breastfeeding (2002)

1. Compatible with breastfeeding

There are no known or theoretical contraindications for their use, and it is considered safe for the mother to take the drug and continue to breastfeed.

2. Compatible with breastfeeding (occasional mild side-effects): monitor infant for side-effects

If side-effects: stop the drug, and find an alternative.

If the mother cannot stop the drug, consider stopping breastfeeding and substitute formula / donor milk until her treatment is completed.

3. Avoid if possible (significant side-effects): monitor infant for side-effect

Chloramphenicol, tetracycline, metronidazole (Flagyl), quinolones (e.g. Cipro)

4. Avoid if possible (often may inhibit lactation)
   - Estrogen or estrogen analogs
   - Thiazides
   - Prolactin inhibitors

If a mother requires one of these drugs for a short period, she can offset the possible decrease in milk production by encouraging her baby to suckle more frequently.

5. Contraindicated (Dangerous side-effects)

There are very few drugs in this category apart from anticancer drugs and radioactive substances.

If they are essential: Stop breastfeeding until treatment is completed; if treatment is to be prolonged, she may need to stop breastfeeding altogether.
• Amiodarone (RID up to 50%) should be avoided due to high infant exposure and potential for significant toxicity
• Lithium - many sources do not consider it contraindicated, especially in infants over 2m exposed to monotherapy. Numerous infants reports without of no toxicity or developmental problems, most fed from birth and some up to 1y. Toxicity may be more likely with impaired elimination (e.g. dehydration or premi).
• The cut-off of 10% is too high for drugs with inherent toxicity and breastfeeding is contraindicated
  - Ergotamine-quality studies suggest little risk especially pp
  - Gold salts-neonatal drug levels appear low to undetectable
  - Immunosuppressives
  - Isotretinoin-absolutely no data; topical use likely safe

### Oncology

#### Breastfeeding

• Busulfan
  — No human breast milk; considering the terminal t1/2 is 2.5h suggests withholding breastfeeding for at least 24h may be sufficient

• Doxorubicin
  — RID estimated on limited study to be about 2% during the first 72h after administration
  — Breastfeeding success rates are significantly reduced

• Fluorouracil
  — Limited information indicates the milk levels are undetectable after a maternal iv infusion (200 mg/m^2); Monitoring of the infant's complete blood count and differential is advised.

### Opiates

#### Breastfeeding

<table>
<thead>
<tr>
<th>Drug</th>
<th>Breast Milk</th>
<th>Neonatal Blood</th>
<th>RID</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Undetectable to 25 mcg/L</td>
<td>15 mcg/L</td>
<td>0.3%</td>
<td>Trivial amounts after epidural admin; sedation up to 2-3mg for sedation and respiratory depression.</td>
</tr>
<tr>
<td>Methadone</td>
<td>Undetectable to 50 mcg/L</td>
<td>10 mcg/L</td>
<td>1-6%</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Undetectable to 100 mcg/L</td>
<td>5 mcg/L</td>
<td>0.3%</td>
<td>Low bioavailability; sedation up to 2-3mcg/kg for sedation and respiratory depression.</td>
</tr>
<tr>
<td>Codeine</td>
<td>Undetectable to 10 mcg/L</td>
<td>5 mcg/L</td>
<td>0.86%</td>
<td>Not a reason to discontinue breastfeeding</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Undetectable to 10 mcg/L</td>
<td>5 mcg/L</td>
<td></td>
<td>No information</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Undetectable to 10 mcg/L</td>
<td>5 mcg/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Antidepressants / Antianxiety

- **Fluoxetine**
  - Maternal serum & peak breast milk levels of fluoxetine and norfluoxetine predict infant's serum norfluoxetine level
  - RID: 1.6-14.6%
  - Neonatal serum levels typically low in women taking <20mg/d
  - Symptoms of fussiness, colic and crying reported
  - Sertraline, escitalopram better choices

- **Paroxetine**
  - Highest concentrations in the hind milk
  - No breast fed child studied has had clinically relevant levels

- **Sertraline**
  - Concentrations affected by milk fraction sampled, the time after maternal dose (max 7-10h), and daily dose
  - Mean maximum calculated nursing infant dose of sertraline, 0.67mg/d, and desmethylsertraline, 1.44mg/d, represent 0.54% of the maternal daily dose
  - Neonatal serum concentration is usually below detection

- **Diazepam**
  - Maximum neonatal exposure = 3% of the maternal dose
  - Problems may arise with prematurity, or the maternal dose particularly high

Antidepressants / Antianxiety

- **THC/Cannabis**
  - Limited information; THC is highly fat soluble & slowly released over days to weeks, depending on use.
  - 50 women used cannabis prior 14d. THC was detected in 63% of samples with a median of 9.5 mcg/L (range 1.3-8.6 mcg/L). Only 5 samples had measurable 11-OH-THC (range 1.3 to 12.8 mcg/L) and 5 had measurable cannabinol (range 1.3 to 8.6 mcg/L). Samples at least 140h after use contained <1 mcg/L. Of the 34 milk samples from mothers who reported using cannabis, the half-life of THC in milk was estimated to average about 27 hours. The median RID of THC would be 1.4 mcg/kg daily.
  - 68 infants exposed during breastfeeding were compared to 68 matched control infants; majority were breastfeed for 3 months and received <16 ounces of formula daily. Motor development was slightly reduced in a dose-dependent manner at 1y, especially among those who smoked >15d/mo during the 1st month. No effect was found on mental development.

Antihistamine

- **Chlorpheniramine**
  - Non sedating antihistamines preferred alternatives.
  - 2 or 4 mg occasional doses acceptable; higher doses or prolonged use might effect the infant or decrease milk, especially before lactation was well established or combined with pseudoephedrine (true for all antihistamines)
  - Single dose after last feed best to minimize potential for side effects

- **Terfenadine (parent compound of fexofenadine)**
  - Based on drug passage into breastmilk and the typical serum levels found after fexofenadine, the RID< 0.1%

- **Loratadine**
  - Not be expected to adversely effect breastfed infants due to its lack of sedation and low milk levels; it is a preferred choice (10mg) [ RID 0.3 - 1.3%]

- **Pseudoephedrine**
  - RID 4.7%; may cause irritability occasionally; single dose of may decrease milk production abruptly and repeated use seems to interfere with lactation

Antiviral

- Breast-feeding is contraindicated in HIV infected nursing women where formula is available to reduce the risk of neonatal transmission

- But is this true in women with an undetectable viral load?

Cholesterol Lowering

- **Simvastatin (Zocor) and Lovastatin (Altocor; Lofacol; Mevacor)**
  - Not safe according to package insert based on the theoretic risk of it disrupting infant lipid metabolism
  - Unknown whether enters human breast milk
Cholesterol Lowering
Breastfeeding

- **Atorvastatin**
  - Unknown whether enters human breast milk; 6 women breastfed 11 infants after restarting statins postpartum. The statin used by these women was not reported; most were using atorvastatin, either 40 or 80 mg, daily. Early child development was normal in all. No learning difficulties were reported.

- **Pravastatin**
  - 11 women not breastfeeding were given 20mg bid for 2.5d. Samples were taken after the 5th dose. Peak milk levels averaged 3.9 mcg/L suggesting that negligible levels were excreted into breast milk. Using peak levels, the RID would be a maximum of 1.4% sage.

- **Gemfibrozil, simvastatin**
  - Unknown whether enters human breast milk

Epilepsy
Breastfeeding

- **Common**: 1.1 million US women have epilepsy of which 40% are of childbearing age

- **Women with epilepsy unable to stop AED**
  - Increases risk of seizures
  - Injury
  - Developmental delay
  - Loss of Job or Driving Privileges
  - Risk of cognitive decline

Safety of New AED?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancies Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felbamate</td>
<td>?</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>100</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>119</td>
</tr>
<tr>
<td>Topiramate</td>
<td>5+</td>
</tr>
<tr>
<td>Ticarcinoline</td>
<td>231</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>5+</td>
</tr>
<tr>
<td>Tegretol</td>
<td>12+</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>26+</td>
</tr>
</tbody>
</table>

AED Kinetics in Plasma & Breast Milk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Breast Milk/Plasma</th>
<th>Elimination Half-life (hour)</th>
<th>Adult</th>
<th>Neonate</th>
<th>% Prot Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>0.4 - 0.6</td>
<td>8 - 25</td>
<td>8 - 28</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>0.9</td>
<td>40 - 60</td>
<td>40</td>
<td>&lt; 10</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0.4 - 0.6</td>
<td>75 - 126</td>
<td>45 - 50</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>0.2 - 0.4</td>
<td>12 - 50</td>
<td>15 - 105</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>0.7 - 0.9</td>
<td>4 - 12</td>
<td>7 - 60</td>
<td>&lt; 20</td>
<td></td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>0.01</td>
<td>6 - 18</td>
<td>30 - 60</td>
<td>90</td>
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AED Kinetics “New AED”

<table>
<thead>
<tr>
<th>Drug</th>
<th>Breast Milk Plasma</th>
<th>Concentration Ratio</th>
<th>Adult</th>
<th>Neonate</th>
<th>% Prot Bound</th>
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<tbody>
<tr>
<td>Felbamate</td>
<td>?</td>
<td>14 - 22</td>
<td>24 - 35</td>
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<tr>
<td>Gabapentin</td>
<td>?</td>
<td>5 - 8</td>
<td>0</td>
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<td>0.4 - 0.7</td>
<td>24</td>
<td>55</td>
<td></td>
<td></td>
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<tr>
<td>Levetiracetam</td>
<td>?</td>
<td>6 - 8</td>
<td>&lt; 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>0.5</td>
<td>8 - 10</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td>?</td>
<td>4.5 - 13</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>&lt; 1</td>
<td>19 - 23</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>0.9</td>
<td>50 - 60</td>
<td>?</td>
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### Immune Mediated Disorders

#### Monoclonal Antibodies

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<th>RID%</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>Typically (~10 mcg/L)</td>
<td>Undetectable</td>
<td>---</td>
<td>Minimaly excreted into breastmilk; large protein (MW 148,000); likely destroyed in the infant's GI tract. No adverse outcomes with long term F/U.</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Undetectable</td>
<td>----</td>
<td>---</td>
<td>Minimally excreted into breastmilk; large protein (MW 148,000); likely destroyed in the infant's GI tract. However, no long term F/U.</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Undetectable</td>
<td>----</td>
<td>---</td>
<td>No long term F/U</td>
</tr>
<tr>
<td>Infliximab</td>
<td>24 women provided samples at 1, 2, 24, and 48h, and some at 50, 99, 120 and 168h. 19 women had detectable levels (0.001 mg/L). Peak levels occurred at 24h ranging from 0.15 to 0.74 mg/L. 17 had detectable levels 48h with a mean of 0.2 mg/L; 5 of 8 tested at 168h had detectable levels. Samples obtained 5d after maternal dosing when the infant was 15d and 43d after the mother's dose at 57 days of age. Usually either undetectable in breastmilk or detected at very low levels. Bioavailability is minimal. Normal follow up.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Unstable in breastmilk; up to a 26% decrease in concentration when stored for 24h at room Temp. One woman treated 7w pp with a 390mg loading dose iv, then 90 mg every 8 weeks. At 16w, the level was 3.2 mg/L. After the 3rd dose, the level was 0.82 mg/L the first day after, 0.18 mg/L at 3w and 0.16 mg/L at 4w. No data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Undetectable in 2 women 1h after 200mg q2w and in one at 4h</td>
<td>No data</td>
<td>---</td>
<td>Limited published information. Usually either undetectable in breastmilk or detected at very low levels. Absorption is unlikely because it is probably destroyed in the infant's GI tract. If required by the mother, it is rare a reason to discontinue breastfeeding and some experts consider it a good choice in nursing women with psoriasis.</td>
</tr>
</tbody>
</table>

### Summary

- Drug prescribing during pregnancy and lactation is not business as usual
- There is still a huge amount of missing information; as a result, provider logic frequently fails
- Fortunately, the gaps are shrinking; either review the literature yourself or check a reliable reference regularly before you either prescribe or withhold a drug
- As maternal healthcare providers, you have a unique opportunity to help fill in the missing information by conducting simple but essential translational research