Breastfeeding and Illicit Drug use in Pregnancy

Karen D’Apolito, Ph.D., APRN, NNP-BC
Professor & Director, Neonatal Nurse Practitioner Specialty
Vanderbilt University School of Nursing
Nashville, TN
Objectives

- Identify the incidence of drug use during pregnancy
- Describe the physiology of the production of breast milk
- Identify factors associated with the transfer of drugs to breast milk
- Describe breast feeding recommendations
Statistics 2012-2013

- Pregnant Women Using Illicit Drugs
  - 15-44 YOA: 5.4% (11.4% among non-pregnant women)
  - 15-17 YOA: 14.6%
  - 18-25 YOA: 8.6%
  - 26-44 YOA: 3.2%
  - Lower during 3rd trimester (2.4% compared to first (9%) and second (4.8%))

National Survey on Drug Use & Health, 2013
Illicit Drug Use: Ethnicity

National Survey on Drug Use & Health, 2013
Incidence

- All cultures
- All ethnicity
- All socioeconomic backgrounds
- Also use nicotine and alcohol
Physiology of Breast Milk Development

- Mammary Gland
  - Modified sweat gland
  - Milk production
  - Glandular, fatty and fibrous tissue
  - Part of the skin

Daisy, J. (2010)
Internal Breast Anatomy

- **Glandular Tissue**
  - **Lobes & Lobules**
    - 15-25 lobes that radiate around the nipple
    - Each lobe – 20-40 lobules
    - Lobules are drained by lactiferous ducts
    - Lactiferous duct - 10-100 supporting alveoli (lactiferous sinus)
    - Milk collects in the sinus during nursing and is “let down” by infant sucking
Internal Breast Anatomy

- **Connective tissue**
  - Surrounds the lobes and ducts
  - Supports the breast
  - Cooper’s ligaments – connect breast to the chest wall

- **Blood vessels**
  - Mammary & Axillary Arteries

- **Nerves**
Lactiferous Sinus

- Perfused with capillaries and lymphatic's
- Capillaries
  - Primary source of nutrients
  - Fats
  - Hormones
  - Drugs taken by mother

Pregnancy

- **1st Trimester**
  - Ductal system proliferates and branches – estrogen
  - Lobular system proliferates - progesterone

- **2nd & 3rd Trimesters**
  - Further lobular growth
  - Prolactin stimulates production of colostrum
Pregnancy

- **3rd Trimester**
  - Cells of the alveoli differentiate into secretory cells
  - Capable of producing and releasing milk
  - Breast enlarges – increased secretory cells & distension of alveoli with colostrum

- **Birth**
  - Alveolar epithelial cells increase
  - Increase production of milk
Drug Transfer into Human Milk

- Early stages of lactation
  - Alveoli or lactocytes are small
  - Intracellular spaces are large
  - Substances can easily transfer into milk
    - Drugs
    - Lymphocytes
    - Immunoglobulin's
    - Proteins

Hale, T., 2004
Drug Transfer into Human Milk

- Transition from colostrum to mature milk
  - Changes in the milk
  - Rapid growth of the lactocyte
  - Closing the large gap
  - Tightening the junctions between the cells
  - Result: less transfer of drugs and other maternal proteins into the milk
  - Process starts 36 hrs after delivery and completed by 5 days

Hale, T., 2004
Factors Associated with Drug Transfer

- Molecular weight
- Protein Binding
- pKa (acidity constant)
- Lipid Solubility
- Oral bioavailability

Hale, T., 2004; Anderson, P, 1991
Molecular Weight (MW)

- Amount of drug in breast milk is determined by molecular size or weight
- Drugs with large molecular weight cannot cross a capillary membrane
- Low MW < 500 g/mol diffuse freely across the placenta

\( g/mol = \text{dalton} \)

Molecular Weight (MW)

- MW between 500-1000 g/mol cross less easily
- MW > 1000 g/mol do not cross placental membrane
- Most drugs have molecular weight of less than 500

Sachdeva, et al., 2009
# Molecular Weight

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular Weight (g/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>309</td>
</tr>
<tr>
<td>Marijuana</td>
<td>314</td>
</tr>
<tr>
<td>Alcohol</td>
<td>46</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>504</td>
</tr>
<tr>
<td>Heroin</td>
<td>395</td>
</tr>
<tr>
<td>Crack/Cocaine</td>
<td>303</td>
</tr>
</tbody>
</table>

1 g/mol = 1 daltons

Molecular weight

Hale, 2012
Protein Binding

- Drugs bound to protein (albumin) cannot diffuse through tissue.
- Highly bound drugs remain in the plasma and pass into the milk in low concentrations.
- Drugs not bound to protein are free to enter the breast milk.

Breitzka, et al., 1997
Protein Binding

- During pregnancy maternal albumin levels decrease; fetal albumin levels increase
- Proteins in breast milk have a lower affinity for drug binding.
- Result – free (unbound) fraction of the total drug concentration is greater in milk than in plasma

Skopp., et al, 2002; Drugs and Human Performance Facts Sheet, 2012; Berlin, 1981; Breitzka, et al., 1997
## Protein Binding

<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>89%</td>
</tr>
<tr>
<td>Marijuana</td>
<td>97%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>No plasma protein binding</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>96%</td>
</tr>
<tr>
<td>Heroin</td>
<td>Little</td>
</tr>
<tr>
<td>Cocaine</td>
<td>91%</td>
</tr>
</tbody>
</table>

- Once drug enters breast milk only 0.8% to 0.9% is attached to milk protein and consumed by the baby.

pKa

- pKa – pH at which a drug exists equally in ionic and non-ionic state
- Molecules that are electrically charged or ionized do not diffuse through membranes.
- pKa of a drug determines the amount of charge a molecule has at a given pH.

Breitzka, et al., 1997
pKa

- Non ionized weak base molecules diffuse from plasma through breast tissue into an acid milk environment
- Becomes ionized, stays or becomes trapped in the milk
- Drug molecules that become ionized in the breast milk cannot cross back into the plasma

Breitzka, et al., 1997
Drugs that are more basic (have a higher pKa) become charged when in contact with breast milk (pH of 7).

Become trapped in breast milk (pKa > 7.2)

<table>
<thead>
<tr>
<th>Drug</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>8.6</td>
</tr>
<tr>
<td>Marijuana</td>
<td>10.6</td>
</tr>
<tr>
<td>Ethanol</td>
<td>15.9</td>
</tr>
<tr>
<td>Heroin</td>
<td>7.6</td>
</tr>
<tr>
<td>Crack/Cocaine</td>
<td>8.6</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>8.24-9.9</td>
</tr>
</tbody>
</table>
Lipid Solubility

- Determine if drug will dissolve in lipid portion of human milk
- Drugs are trapped in the lipid molecule & do not transfer back into the plasma

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lipid Soluble</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>Yes</td>
</tr>
<tr>
<td>Marijuana</td>
<td>Yes</td>
</tr>
<tr>
<td>Ethanol</td>
<td>No</td>
</tr>
<tr>
<td>Heroin</td>
<td>Yes</td>
</tr>
<tr>
<td>Crack/Cocaine</td>
<td>Yes</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Hale, 2004
Oral Bioavailability

- Amount of drug that is absorbed in the intestine and enters circulation after oral consumption
- Drugs with poor bioavailability in the mother will typically not transfer into breast milk
- Drugs that do transfer the infant’s oral bioavailability determine if drug enters circulation

Ashton, 2001
# Oral Bioavailability

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Bioavailability in Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>41-99%</td>
</tr>
<tr>
<td>Marijuana</td>
<td>6-20%</td>
</tr>
<tr>
<td>Ethanol</td>
<td>100%</td>
</tr>
<tr>
<td>Crack/Cocaine</td>
<td>80%</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>31%</td>
</tr>
<tr>
<td>Heroin</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Don’t know bioavailability in infants
Low bioavailability poor absorption

Diffusion

- Passive or facilitative diffusion
- Free drug on each side of the membrane
- Transfer from a area of high to low concentration
- Drug levels sometimes reach equilibrium between the milk and maternal plasma (M/P ratio = 1)
Ingestion of Drug by Infant

- Concentration of drug in milk
- The frequency of breastfeeding
- Volume of milk consumed
- Drug absorption
- Metabolism
- Typically, baby gets <2% of mother’s dose

(Powers & Slusser, 1997)
M:P Ratio

- Index of amount of maternal dose of a drug that enters breast milk
- Estimate
- Often Inaccurate
- Cautious with interpretation
- Accuracy depends upon several factors

Breitzka, et al., 1997
M:P Ratio

- M:P point ratio vs M:P ACU (area under the curve) ratio
- M:P point ratio – ratio of milk drug concentration to simultaneous plasma drug concentration at a given time
  - When during dosing interval drug concentrations were measured?
  - Peak milk drug concentrations do not coincide with peak plasma concentrations

Breitzka, et al., 1997
M:P Ratio

- M:P AUC ratio – time integrated average
- Ratio of area under the milk drug concentration curve to the area under the plasma drug concentration curve
- More accurate however factors can influence this value
  - Postpartum time
  - Physiologic changes

Breitzka, et al., 1997
Factors Influencing M:P AUC

- Physiologic changes
  - Increased volume of distribution
  - Drugs less protein bound
  - Increased clearance
  - Normalize by 3 months postpartum
  - M/P ratio calculated soon after delivery is inaccurate

Breitzka, et al., 1997
Factors Influencing M:P AUC

- Changes in breast milk composition
  - Protein – Highest first 15 days postpartum; remains lower than plasma, net changes not significant
  - Fat
    - Increases throughout first month until reaches plateau
    - M/P ratio’s at delivery will underestimate amount of lipophilic drug in breast milk

Breitzka, et al., 1997
Factors Influencing M:P AUC

- **Time of Day**
  - Fat content highest in morning; reaches nadir at 6-10 in evening

- **Duration of Feeding**
  - Fat content varies over duration of feeding
  - Hindmilk contains 4-5 X as much as foremilk

Breitzka, et al., 1997
A ratio < 1 is low and suggests a small amount of drug has entered the breast milk.

<table>
<thead>
<tr>
<th>Drug</th>
<th>M:P Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>0.68</td>
</tr>
<tr>
<td>Marijuana</td>
<td>8</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1</td>
</tr>
<tr>
<td>Crack/Cocaine</td>
<td>?</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>1.7</td>
</tr>
<tr>
<td>Heroin</td>
<td>2.45</td>
</tr>
</tbody>
</table>

Hale, 2012
## Hale Classification of Drugs by Risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>1.3</td>
</tr>
<tr>
<td>Heroin</td>
<td>1.5</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>1.2</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.3</td>
</tr>
<tr>
<td>Crack/Cocaine</td>
<td>1.5</td>
</tr>
<tr>
<td>Marijuana</td>
<td>1.5</td>
</tr>
</tbody>
</table>

1.1 – Safest  
1.2 – Safer  
1.3 – Probably safe  
1.4 – Possibly hazardous  
1.5 - Hazardous  

Hale, 2012
Maternal Drug Use & Breastfeeding

- AAP Committee on Drugs 2001
  - Cocaine – intoxication
  - Marijuana – transfer found in human milk (Perez et al, 1982)
  - Alcohol – 1 gm daily inhibits milk ejection
  - Nicotine – Present in concentrations 1.5 to 3 times simultaneous maternal plasma level
Breastfeeding & Methadone

- AAP Committee on Drugs
- 1994
- None if maternal dose \( \leq 20 \text{ mg/day} \)
- Case Reports – minimal transmission of into breast milk regardless of mother’s methadone dose (Geraghty, et al, 1997)
Study by Begg et al, (2001)
- Blood & milk samples
- 2.8% of mother’s methadone dose gets to infant through breast milk

Study by McCarthy & Posey, (2000)
- Maternal dose & milk samples
- Range maternal dose – 25 to 180 mg/day
- Mean Level of methadone in milk – 95 mcg/L (27 to 260 mcg/L)
- Methadone ingestion based on infant consumption of 475 ml/day of breast milk – 0.05mg/day
Other Studies from 1974 to 1997

- Report a range of 10 to 570 mcg/L – baby getting 0.01 to 0.27 mg/day
8 Breastfeeding mothers

- Methadone doses between 50 – 105 mg/day
- Measured breast milk methadone levels on day of life 1,2,3,4,14 & 30
- Collected foremilk at the feeding before mother’s methadone dose (peak)
- Hindmilk – 3 hrs after dose (trough)

- Results:
  - Examined milk days 1-4, 14 & 30
  - Average amount of methadone in breast milk ingested by infant was small across sampling periods and was < 0.2 mg/day at day 30 despite maternal methadone dose.


- Mean plasma: milk ratio was between 0.36 and 0.49 (Hale 0.68)
- Levels in infant plasma DOL 14 – 2.2 to 8.1 mcg/L
- No differences between maternal methadone doses and infant plasma methadone concentrations
Ideal Situation

- High MW > 500 g/mol
- Low pKa (<7.2)
- High protein binding
- Low bioavailability
- Low M:P ratio
- Low lipid solubility
## Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>MW</th>
<th>pKa</th>
<th>Protein Binding</th>
<th>Lipid Solu.</th>
<th>M/P Ratio</th>
<th>Oral Bio</th>
<th>Hale Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>309</td>
<td>8.6</td>
<td>89%</td>
<td>Yes</td>
<td>0.68</td>
<td>41-99%</td>
<td>1.3</td>
</tr>
<tr>
<td>Marijuana</td>
<td>314</td>
<td>10.6</td>
<td>99.9%</td>
<td>Yes</td>
<td>8</td>
<td>6-20%</td>
<td>1.5</td>
</tr>
<tr>
<td>Alcohol</td>
<td>46</td>
<td>15.9</td>
<td>None</td>
<td>No</td>
<td>1</td>
<td>100%</td>
<td>1.3</td>
</tr>
<tr>
<td>Bup</td>
<td>504</td>
<td>8-10</td>
<td>96%</td>
<td>Yes</td>
<td>1.7</td>
<td>31%</td>
<td>1.2</td>
</tr>
<tr>
<td>Heroin</td>
<td>396</td>
<td>7.6</td>
<td>Little</td>
<td>Yes</td>
<td>2.5</td>
<td>Poor</td>
<td>1.5</td>
</tr>
<tr>
<td>Crack/Cocaine</td>
<td>303</td>
<td>8.6</td>
<td>91%</td>
<td>Yes</td>
<td>?</td>
<td>80%</td>
<td>1.5</td>
</tr>
</tbody>
</table>

MW – All <500 g/mol  
pKa – all >7.2  
Protein binding – All except heroin and alcohol have potential high protein binding  
Lipid solubility – Most are soluble in fat  
M:P ratio – Methadone has lowest  
Oral bioavailability – based on adults  
Hale class - ??
Summary

- Methadone – Recommended
  - Low pKa
  - Lipid soluble however limited amounts in milk fat due to low Pka
  - Infant consumed <0.2mg of methadone despite maternal dose (research)
  - M:P ratio 0.68 (documented as low as 0.36)
  - MW > 500 g/mol
Summary

- Marijuana & Cocaine – Not recommended
  - Both are lipid soluble & can be trapped in breast milk if maternal dose is more than what can be bound to maternal plasma protein (can’t specifically be determined).
  - M:P ratio of cannabis is 8

- Buprenorphine – Recommended ?? (no studies)
  - 96% protein bound
  - M:P ratio 1.7
  - pKa 8.2-9.92
Summary

- **Ethanol – Not recommended**
  - High Pka
  - No lipid binding
  - 100% bioavailable
  - Does not attach to maternal plasma protein
  - Diffuses in and out of breast milk based on maternal dose
Infant Drug Clearance

- Infants
  - 24-28 weeks – 5%
  - 28-34 weeks – 10%
  - 34-40 weeks – 33%
  - 40-44 weeks – 50%
  - 44-48 weeks – 66%
  - ≥ 68 weeks – 100%

Hale, 2004
Other Factors

- Infant metabolism
- Classification system of drug exposure:
  - Low risk – 6-18 months of age
  - Moderate risk - < 6 months with medical problems (GI, inadequate feeding)
  - High risk – Preterm, unstable, poor renal output

Hale, 2004
Breastfeeding

• OK, providing mother is being monitored in a methadone or buprenorphine treatment program
• Small amounts of the drug are transferred to the breast-milk
• Suggested that breastfeeding may decrease the severity of withdrawal signs however more research is needed
Maternal Drug Use & Breastfeeding

- Marijuana, cocaine, heroin, amphetamines, alcohol use should not breastfeed
- Pump & Dump
  - Alcohol – 24 hrs
  - Marijuana – 48 hrs
  - Cocaine – 72 hours
- Not Useful

Maternal Drug Use & Breastfeeding

- AAP Committee on Drugs 2001
  - Cocaine – intoxication
  - Marijuana – transfer found in human milk (Perez et al, 1982)
  - Alcohol – 1 gm daily inhibits milk ejection
  - Nicotine – Present in concentrations 1.5 to 3 times simultaneous maternal plasma level
Maternal Drug Use & Breastfeeding

- Academy of Breastfeeding Medicine
  - Abstain from use for 90 days before delivery
  - Enrolled in substance abuse treatment program
  - Negative drug screen at delivery
  - Consistent prenatal care
  - No other contraindications for breastfeeding
Breastfeeding & Methadone

- AAP Committee on Drugs
- 1994
- None if maternal dose ≤ 20 mg/day
- Case Reports – minimal transmission into breast milk regardless of mother’s methadone dose (Geraghty, et al, 1997)
References

References

References

Breastfeeding

- OK, providing mother is being monitored in a methadone or buprenorphine treatment program