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

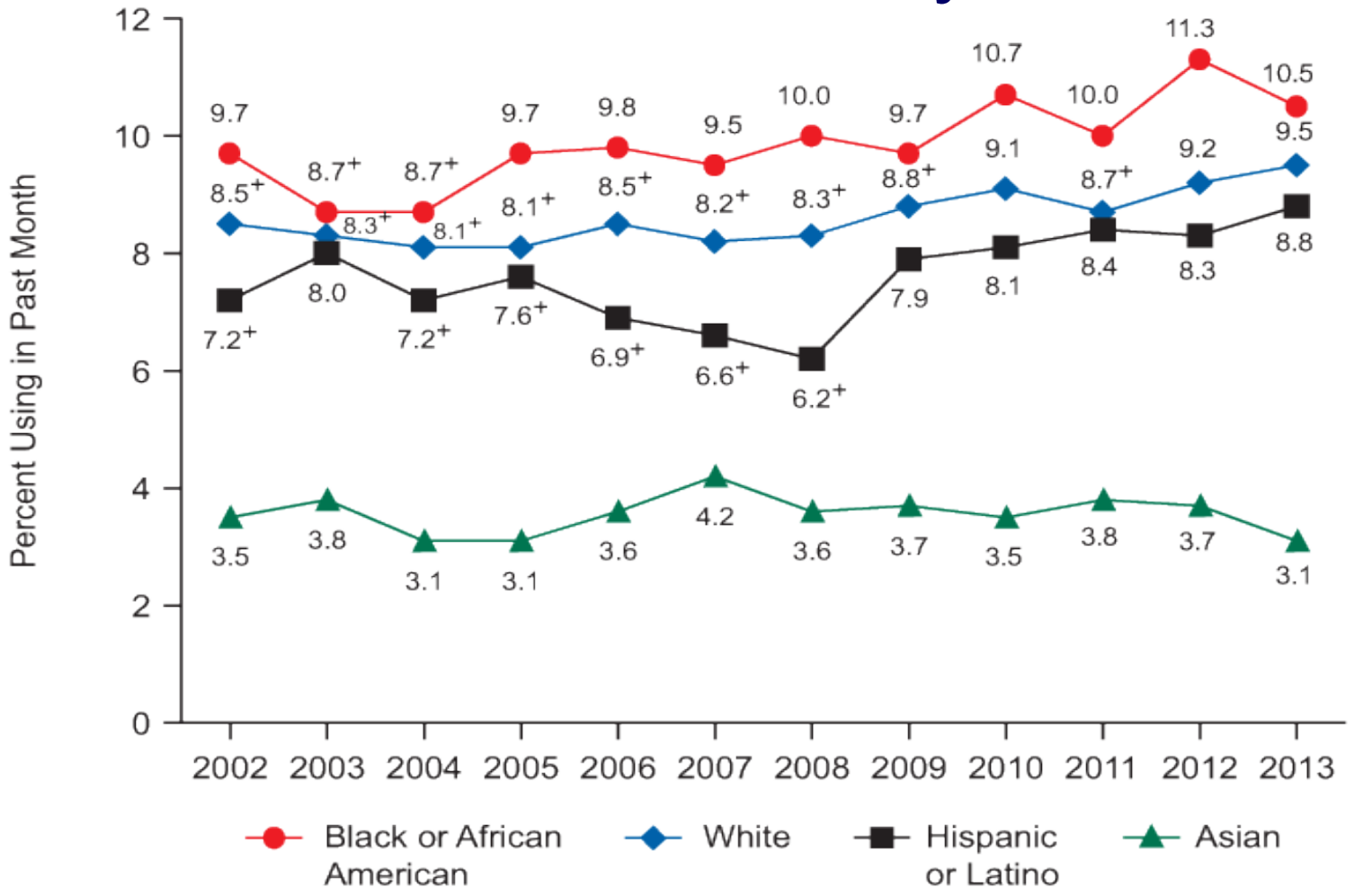
Statistics 2012-2013

- 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

National Survey on Drug Use & Health, 2013

Illicit Drug Use: Ethnicity



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

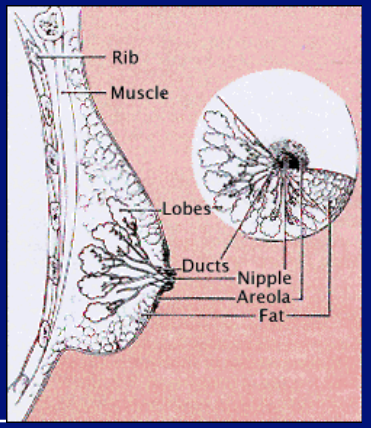
Daisy, J. (2010)

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

Hale, T., (2004)

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

Blackburn, S. (2007)

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 = dalton

Breitzka, et al., 1997; Hale, 2012; Sachdeva, et al, 2009

Molecular Weight (MW)

- MW between 500-1000g/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

Drug	Molecular Weight (g/mol)
Methadone	309
Marijuana	314
Alcohol	46
Buprenorphine	504
Heroin	395
Crack/Cocaine	303

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

Drug	Protein Binding
Methadone	89%
Marijuana	97%
Alcohol	No plasma protein binding
Buprenorphine	96%
Heroin	Little
Cocaine	91%

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

Skopp., et al, 2002; Drugs and Human Performance Facts Sheet, 2012; Berlin, 1981; Cohn, et al, 1994

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

pKa

- 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)

Drug	pKa
Methadone	8.6
Marijuana	10.6
Ethanol	15.9
Heroin	7.6
Crack/Cocaine	8.6
Buprenorphine	8.24-9.9

Hale, 2004, Manallack, 2007

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

Drug	Lipid Soluble
Methadone	Yes
Marijuana	Yes
Ethanol	No
Heroin	Yes
Crack/Cocaine	Yes
Buprenorphine	Yes

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

Drug	Oral Bioavailability in Mother
Methadone	41-99%
Marijuana	6-20%
Ethanol	100%
Crack/Cocaine	80%
Buprenorphine	31%
Heroin	Poor

Don’t know bioavailability in infants
Low bioavailability poor absorption

Hale, 2004; 2012; http://drug.addictionblog.org/do-you-get-high-if-you-eat-weed/

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

M:P Ratio

- A ratio < 1 is low and suggests a small amount of drug has entered the breast milk

Drug	M:P Ratio
Methadone	0.68
Marijuana	8
Ethanol	1
Crack/Cocaine	?
Buprenorphine	1.7
Heroin	2.45

Hale, 2012

Hale Classification of Drugs by Risk

Drug	Classification
Methadone	1.3
Heroin	1.5
Buprenorphine	1.2
Alcohol	1.3
Crack/Cocaine	1.5
Marijuana	1.5

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 ≤ 20 mg/day
- Case Reports – minimal transmission of into breast milk regardless of mother's methadone dose (Geraghty, et al, 1997)

Breastfeeding & Methadone

- 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

- Kreek,,M., et al, (1974). Analysis of methadone and other drugs in maternal and neonatal body fluids. Use in evaluation of symptoms in a neonate of mother maintained on methadone. American Journal of Drug & Alcohol Abuse, I, 409-419.
- Blinick, G., et al, (1975). Methadone assays in pregnant women and progeny. American Journal of Obstetrics & Gynecology, 121, 617-621.
- Wojnar-Horton, R., et al., (1997). Methadone distribution and excretion into breast milk of clients in a methadone maintenance program. British Journal of Clinical Pharmacology 44, 543-547.
- Geraghty, B.,et al., (1997). Methadone levels in breast milk. Journal of Human Lactation 13, 227-230.

Study by Jansson, et al, 2008

- 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)

Study by Jansson, et al, 2008

- **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.**

Jansson, L., et al, 2008.

Study by Jansson, et al, 2008

- 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

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

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

Wilton, J. (1992); Anderson, 1991

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

Academy of Breastfeeding Medicine, 2009

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

- Academy of Breastfeeding Medicine. (2009). Guidelines for Breastfeeding and the Drug-Dependent Woman.
- Anderson, P., (1991). Drug use during breastfeeding. Clinical Pharmacology 10, 694-606.
- Ashton, C. H. (2001). Pharmacology and effects of cannabis: A brief review. The British Journal of Psychiatry 178 (2), 101-106.
- Berlin, C. (1981). Pharmacologic considerations of drug use in the lactating mother. Obstetrics & Gynecology 58 (supplement 5), 17s-23s
- Blackburn, S., (2007). Postpartum Period and Lactation Physiology. In Maternal, Fetal & Neonatal Physiology: A Clinical Perspective. St. Louis, MI: Saunders, pp. 157-169., (2001). The transfer of drugs and other chemicals into human milk. Pediatrics 108, 776-789.
- Cohn, G., et al., (1997). Heroin and morphine binding with human serum protein and red blood cells. Experimental Biologic Medicine 147(3), 664-666.
- Committee on Drugs, (1997) . The transfer of drugs and other chemicals into human milk. Pediatrics 93(1), 137-150.

References

- Committee on Drugs, (2001) . The transfer of drugs and other chemicals into human milk. Pediatrics 108(3), 776-789.
- Daisy, J., (2010). Anatomy and physiology of the mammary glands. http://nursingcrib.com/anatomy-and-physiology-of-mammary-gland
- Drugs and Human Performance Facts Sheet (2012). https://www.google.com/?gws_rd=ssl#q=Drugs+and+Human+Performance+Facts+Sheet%2C+2012
- Geraghty, B., et al., (1997). Methadone levels in breast milk. Journal of Human Lactation 13(3), 227-230.
- Hale, T., (2004, 2012). Medications and mothers milk. Hale Publishing, Amarillo, TX.
- Hale, T., (2004). Pharmacology Review: Drug Therapy and Breastfeeding Pharmacokinetics, Risk Factors and Effects on Milk Production. NeoReviews 5, e164-e172

References

- Jansson,. L., et al., (2008). Methadone Maintenance and Breastfeeding in the Neonatal Period. Pediatrics 121, 121-1182
- Manallack, D. (2007). The pKa distribution of drugs: Applicaton to drug discovery. Perspect Med Chem 1, 25-38
- McCarthy, J., & Posey, B. (2000). Methadone levels in human milk. Journal of Human Lactation 16(2), 115-120.
- National Survey on Drug Use and Health, (2013). US Department of Health and Human Services. http://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.htm#2.6
- Perez-Reges, M., et al., (1982). Presence of tetrahydrocannabinol in human milk. New England Journal of Medicine 307, 819-820.
- Patrick, S., Schumacher, R., Benneyworth, B., Krans, E., et al, (2012). Neonatal Abstinence and Associated Health Care Expenditures: US 2000-2009. JAMA 307(18), 1934-1940

References

- Powers, N. & Slusser, W., (1997). Breastfeeding Update 2: Clinical Lactation Management. Pediatrics in Review 18(5), 147-161.
- Sachdeva, P., et al., (2009). Drug Use in Pregnancy: A point to ponder. Indian Journal of Pharmaceutical Sciences 71(1), 1-7.
- Skopp, G., et al., (2002). Partition Coefficient, blood to plasma ratio, protein binding and short-term stability of 11-nor-carboxy tetrahydrocannabinol glucuronide. Forensic Science International 126, 17-23
- Wilton, J. (1992). Breastfeeding and the Chemically Dependent Woman. NAACOG's Clinical Issues 3(4), 667-671.

Breastfeeding

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