LACTATION STUDY BASICS LESSONS LEARNED

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CONFLICT OF INTEREST

- Consultant UCB Bioscience

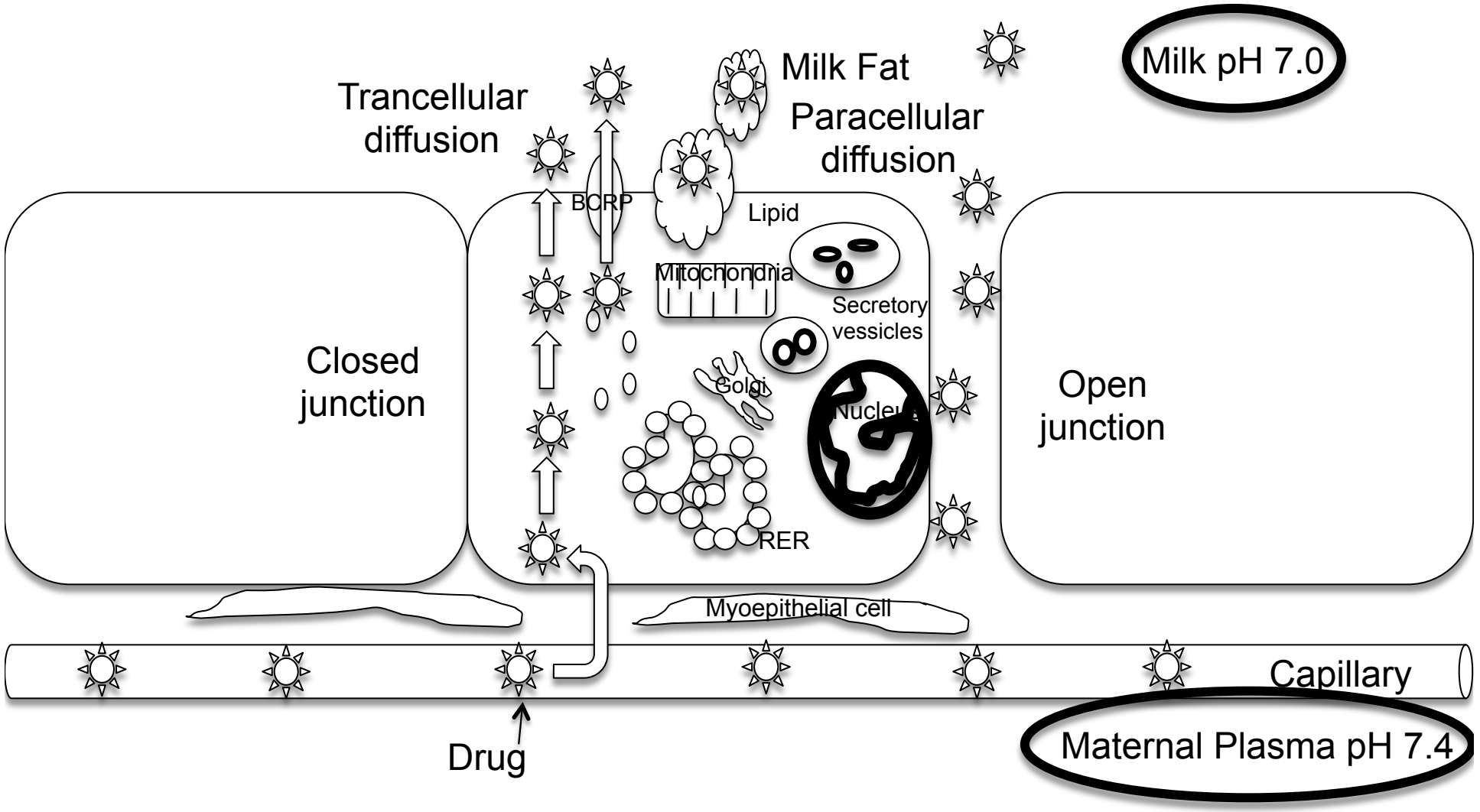
IDEAL STUDY DESIGN

- Intensive sampling maternal pharmacokinetics
- All milk collected every 2-3 hours over dosing interval or 24 hours
- Nursing infant concentrations measured
- Pharmacodynamic outcome measured in nursing infant
- Infant developmental outcomes and other long-term effects (e.g. cancer risk for immunosuppression)

DRUGS WITH VERY LONG HALF-LIVES

- Intensive PK study on day with highest expected infant exposure (i.e. worst case scenario).
- Determination of how long drug is detectable in breast milk (i.e. intermittent samples until drug is cleared)
- When Mom is “Pumping and Dumping”, sometimes can obtain all milk for prolonged period of time.
- Nursing infant sample.
- Infant outcomes.

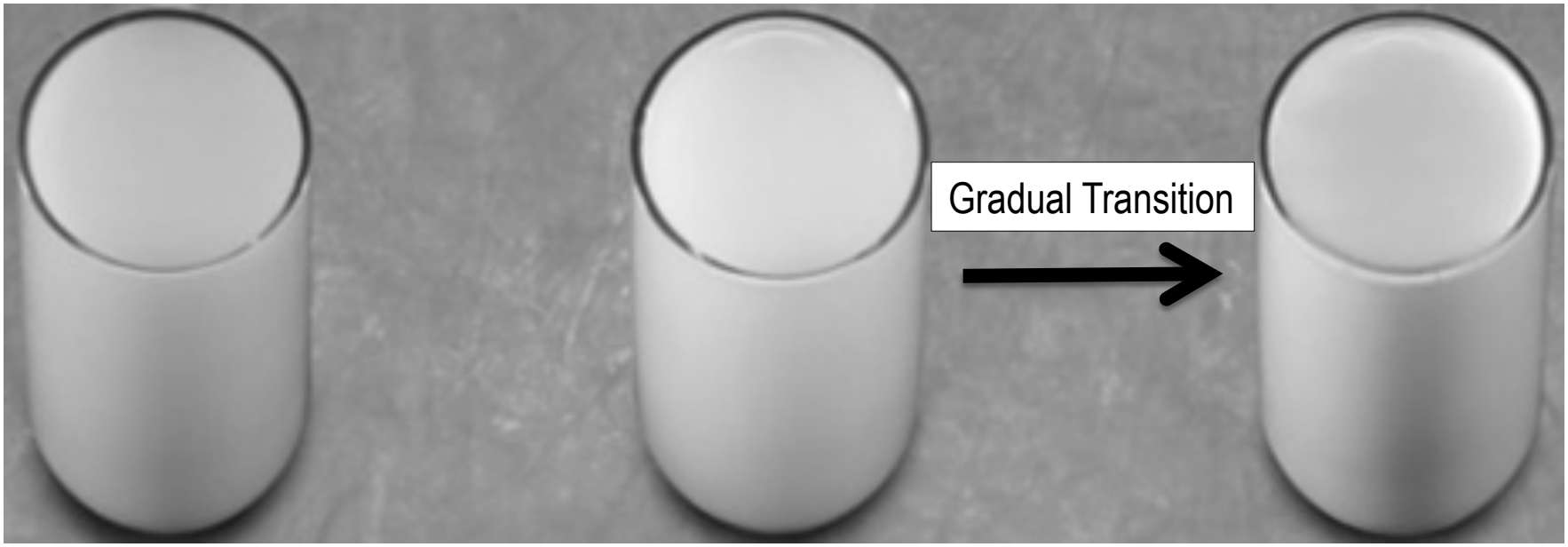
DRUG TRANSFER INTO BREAST MILK



MAMMARY DRUG TRANSPORTERS

- Organic cation
  - OCT1
  - OCT2
  - OCT3
  - OCTN1
  - OCTN2
  - MDR1
  - MDR3
- Organic anion
  - OAT1-4
  - OATP-A
  - OATP-B
  - OATP-C-E
  - MRP1,2,5
  - MRP3,4
- Other
  - BCRP
  - CNT1,3
  - CNT2
  - ENT1,3
  - ENT2
  - SVCT1
  - SVCT2

DOES IT MATTER HOW AND WHEN YOU COLLECT BREAST MILK SAMPLES?



Colostrum

24-48 hours, Teaspoons
Low in Fat, High in Carbohydrates, Protein, and Secretory IgA

Foremilk

Beginning of Feeding, Ounces,
Low in Fat, High in Volume

Hindmilk

End of Feeding,
Higher in Fat

FOREMILK VS HINDMILK

Drug	
Reboxetine	No significant difference in foremilk and hindmilk concentrations (95% CI for difference -1.79 to 0.56 µg/mL, p=0.28)
Paroxetine	Significant gradient effect was observed, with greater paroxetine concentrations found in hindmilk than in foremilk
Sertraline	The breast milk concentrations of sertraline and des-methylsertraline concentrations were lowest in the foremilk and ~2-fold higher in the hindmilk
Imipramine, Amitriptyline, Clomipramine, Dothiepin	Drug concentrations in foremilk, but not in hindmilk, increased in line with its fat content, which was maximal in hindmilk. Foremilk and hindmilk:maternal plasma concentration ratios were 1.0 and 1.5 respectively
Vitamin K_1	Higher vitamin K_1 concentrations in hindmilk than foremilk
Calcium, Magnesium, Sodium, Potassium	No significant differences were found in the mineral concentrations in fore and hindmilk
Selenium	Significantly higher concentration in hindmilk than foremilk, $p<0.05$

Hackett et al. Eur J Clin Pharmacol. 2006 Aug;62(8):633-8. Stowe et al.
Stowe et al. Am J Psychiatry. 1997 Sep;154(9):1255-60. Yoshida et al. J Affect Disord. 1997 May;43(3):225-37.
von Kries et al. Pediatr Res. 1987 Nov;22(5):513-7. Smith et al. Nutr. 1982 Mar;35(3):521-6.

COLOSTRUM VERSUS MATURE MILK

	Energy (measured)		Protein (true protein)		Fat	
	Preterm	**Term**	**Preterm**	**Term**	**Preterm**	**Term**
Colostrum	49	54	2.7	2.0	2.2	1.8
Mature milk	73	63	1.1	1.0	3.3	3.4
Difference	49%	16%	−61%	−52%	50%	93%
p-value	<0.00001*	<0.00001*	<0.00001*	<0.00001*	<0.00001*	<0.00001*

Gidrewica DA et al. BMC Pediatr. 2014 Aug 30;14:216.

META-ANALYSIS SUMMARY ESTIMATES OF BREAST MILK COMPOSITION PER 100 ML

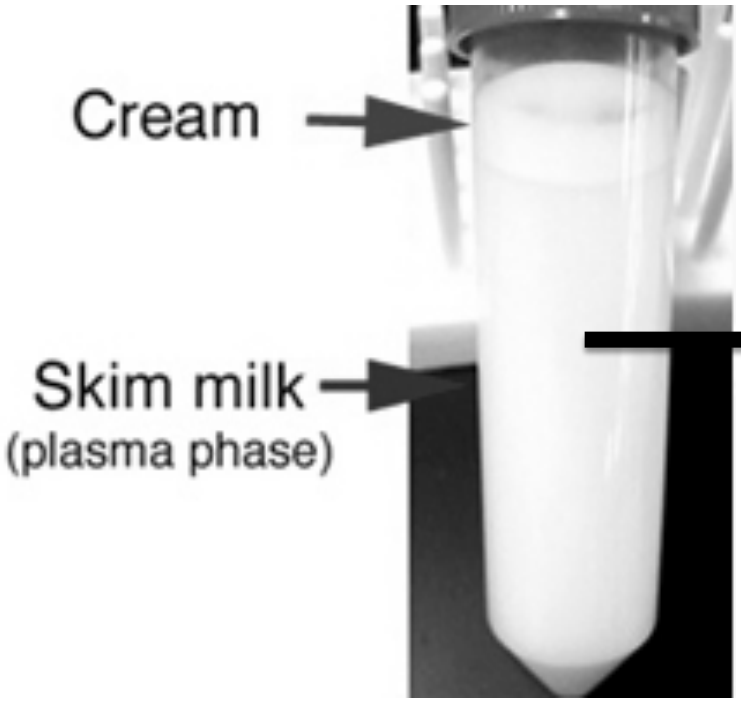
Preterm	Energy (kcal)	Protein (g)	Fat (g)
1st week	60 (45–75)	2.2 (0.3-4.1) *	2.6 (0.5-4.7)*
2nd week	71 (49–94) *	1.5 (0.8-2.3) *	3.5 (1.2-5.7)*
Week 3/4	77 (61–92) *	1.4 (0.6-2.2) *	3.5 (1.6-5.5)
Week 10/12	66 (39–94)	1.0 (0.6-1.4) *	3.7 (0.8-6.5)
Term	**Energy (kcal)**	**Protein (g)**	**Fat (g)**
1st week	60 (44–77)	1.8 (0.4-3.2)	2.2 (0.7-3.7)
2nd week	67 (47–86)	1.3 (0.8-1.8)	3.0 (1.2-4.8)
Week 3/4	66 (48–85)	1.2 (0.8-1.6)	3.3 (1.6-5.1)
Week 10/12	68 (50–86)	0.9 (0.6-1.2)	3.4 (1.6-5.2)

Estimates as +/– 2 standard deviations assumed no skew. Energy values were bomb calorimeter measured values except for 10–12 weeks, which were calculated values. Protein values are true measured protein, not based on total nitrogen content.

*Significantly different than term.

Gidrewica DA et al. BMC Pediatr. 2014 Aug 30;14:216.

MILK FRACTIONS



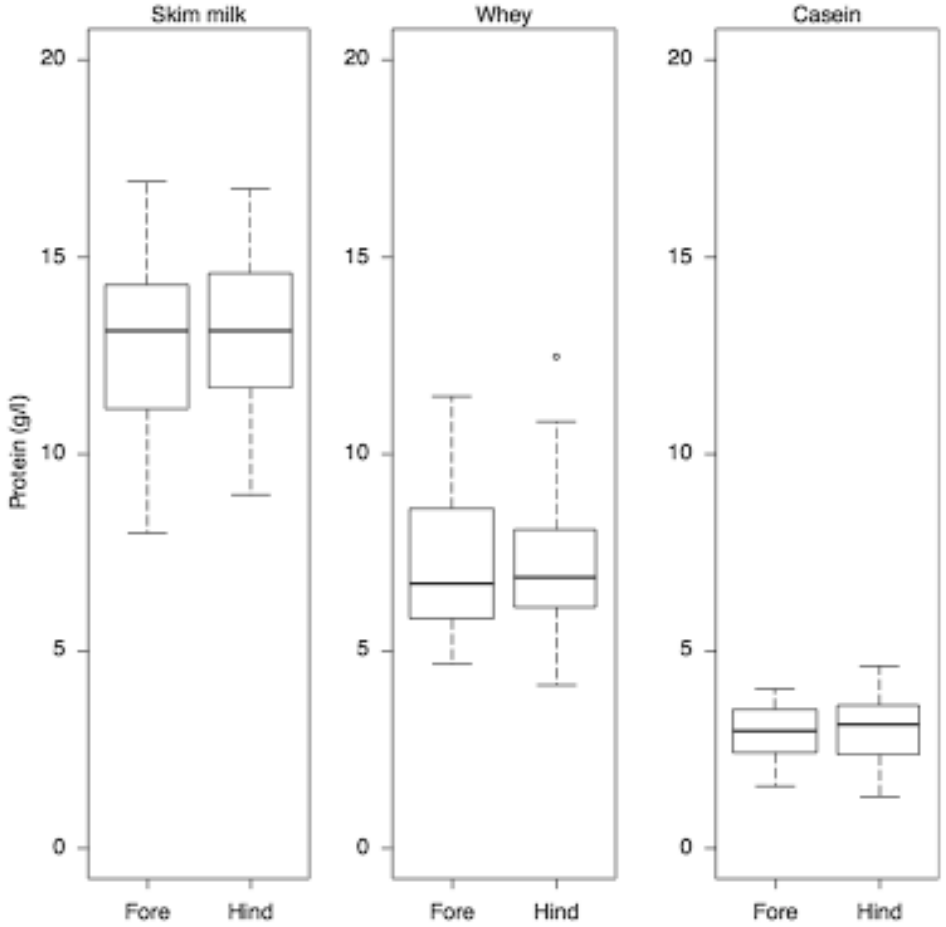
High speed
Centrifugation

Casein
(Curd)

Whey
(Supernatant)

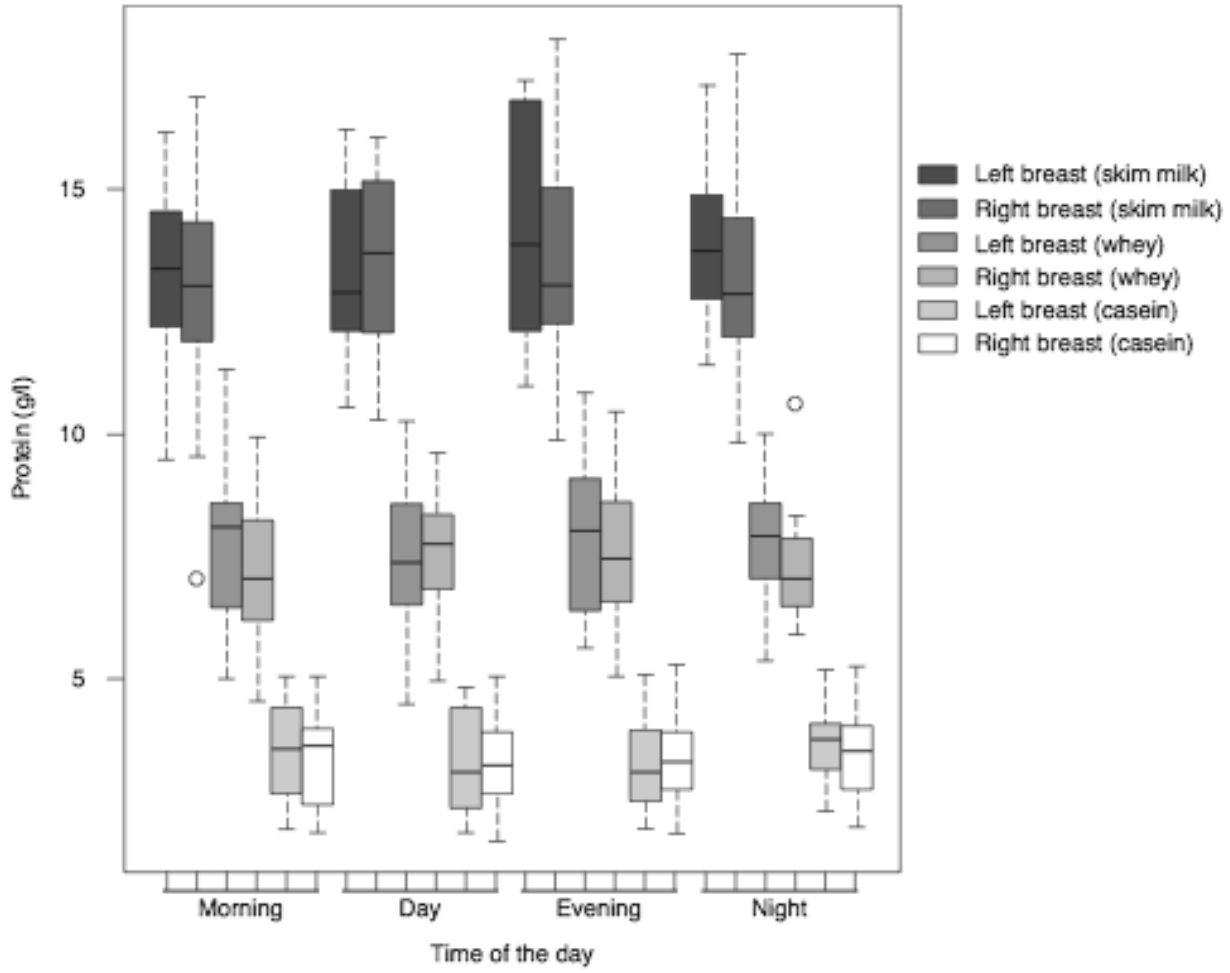
Water, lactose and
Non-casein proteins

PROTEIN CONCENTRATIONS IN FOREMILK AND HINDMILK



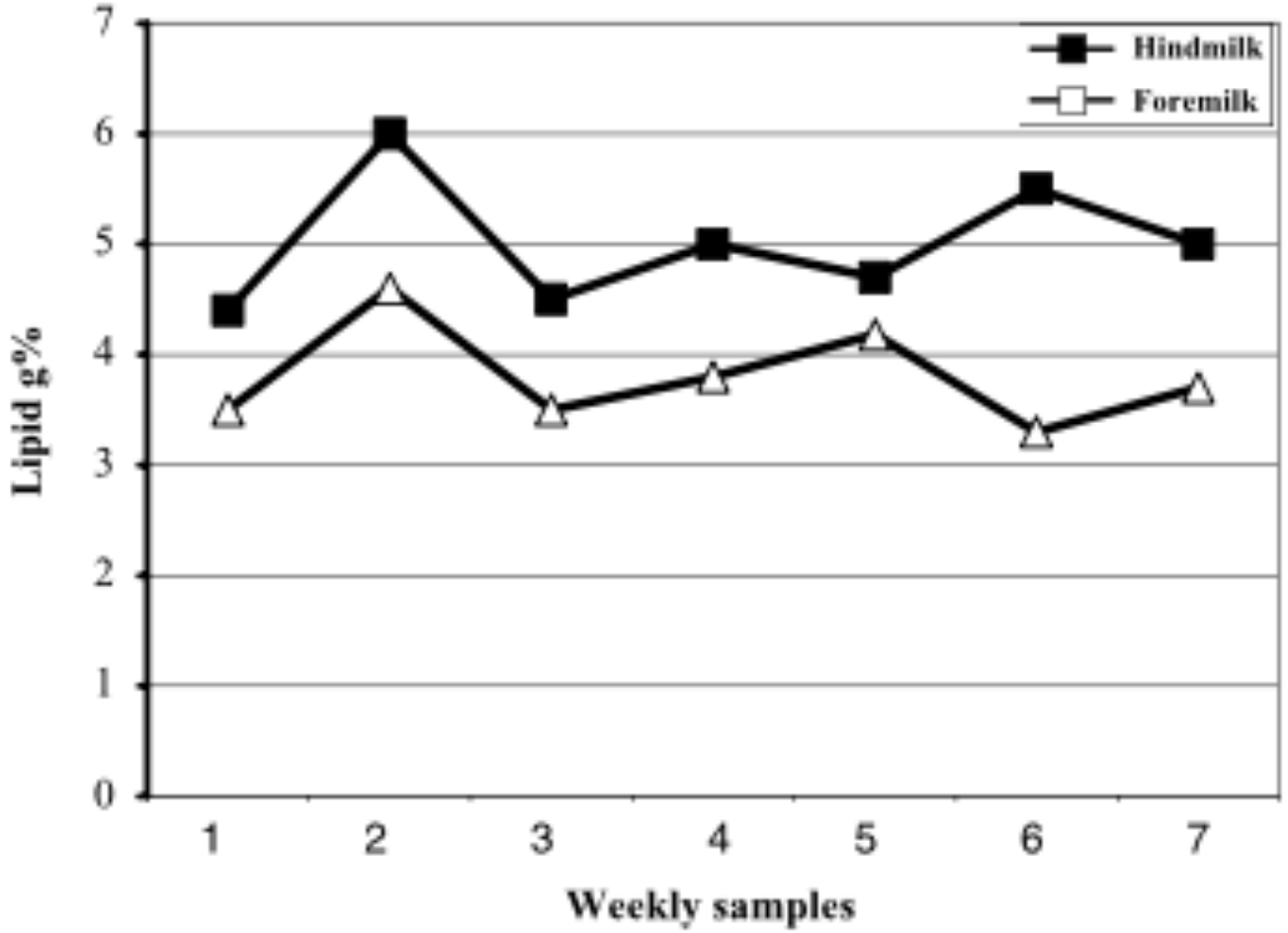
Distribution of protein concentration of skim, whey, and casein fractions in fore and hindmilk collected during breast expression. Values are shown by box plots illustrating median (indicated by the bold line), quartiles (box), range (error bars), and outliers (o). No significant differences were found.
Kahn S et al. J Pediatr Gastroenterol Nutr. 2012 Aug;55(2):136-41.

PROTEIN CONCENTRATIONS BETWEEN BREAST AND EFFECTS OF TIMING



Comparison of protein concentration between breasts in skim, whey, and casein fractions across 4 time points of the day. Box plots represent median (indicated by the bold line), quartiles (box), range (error bars). Kahn S et al. J Pediatr Gastroenterol Nutr. 2012 Aug;55(2):136-41.

LIPID CONTENT IN FOREMILK AND HINDMILK



Charpak N et al. Acta Paediatr. 2007 Dec;96(12):1755-9.

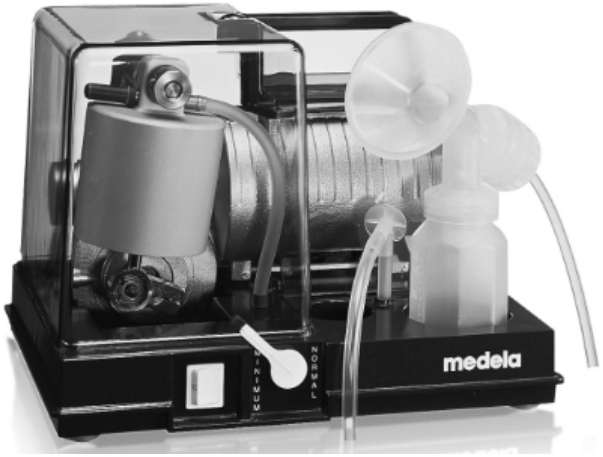
BREAST MILK DURING WEANING

- Longer duration between nursing -> lower fat content in milk
- Lower total milk volume during weaning

MUST HAVE RESOURCES FOR MOTHER AND BABY

BREAST PUMPS

HOSPITAL GRADE DOUBLE ELECTRIC VS MANUAL



Medela Classic

Medela Symphony

Medela

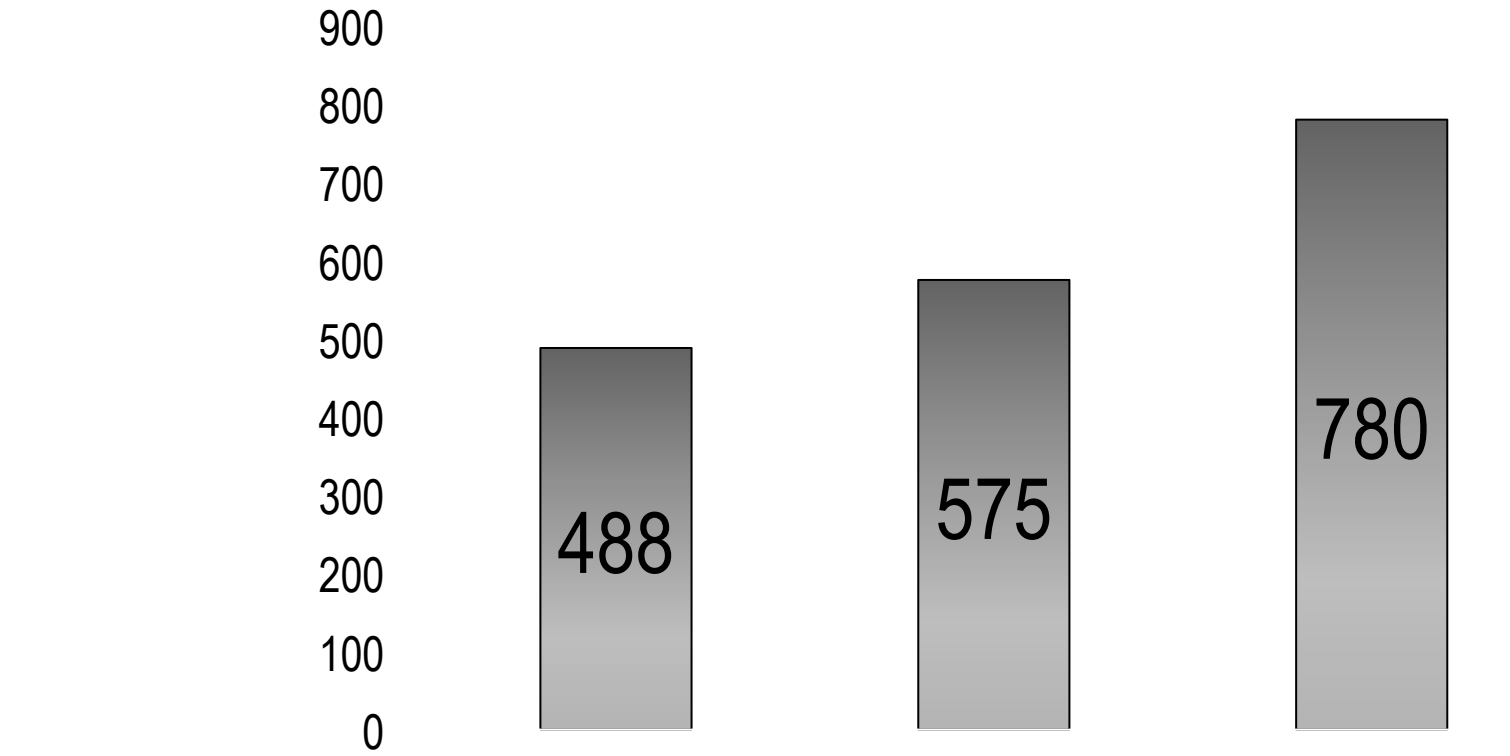
Nuk Expressive

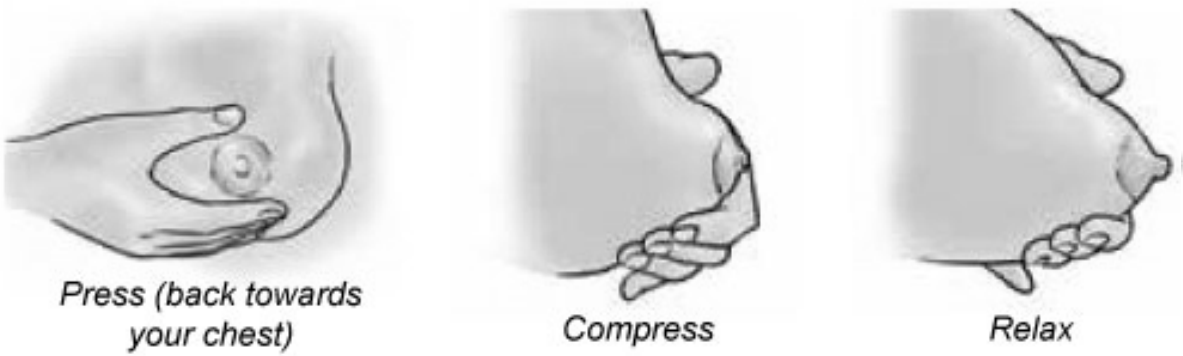
Spectra Dew 350

Evenflo

Avent

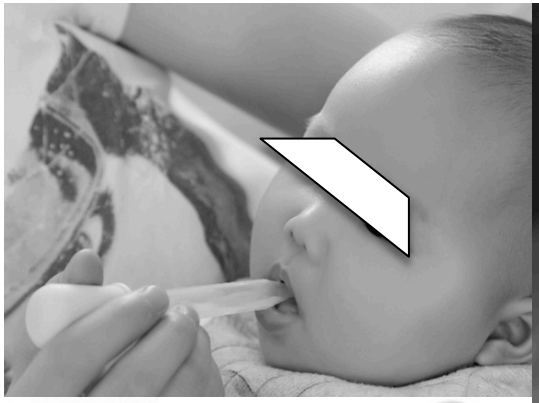
COMPARING PUMP-ALONE TO PUMP-PLUS-HAND-EXPRESSION: MILK VOLUME IN ML/DAY AT 2 WEEKS POSTPARTUM





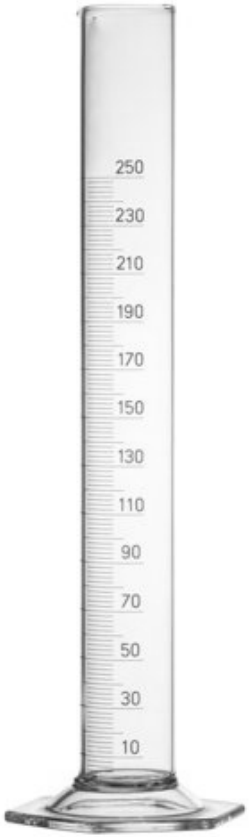
Meier 2012, Morton 2009

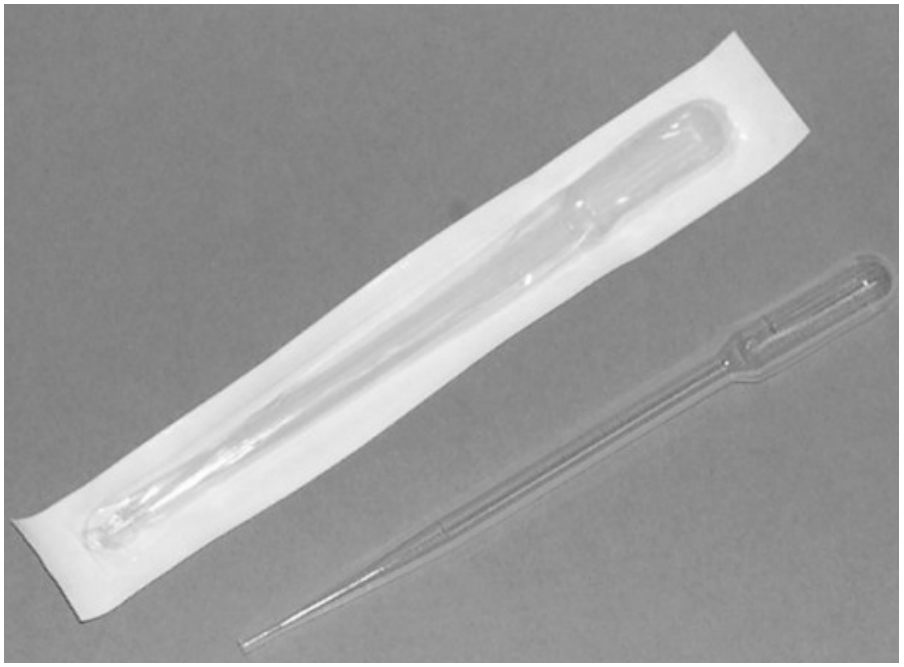
TRICKS OF THE LACTATION NURSES WHEN NURSING NOT ALLOWED



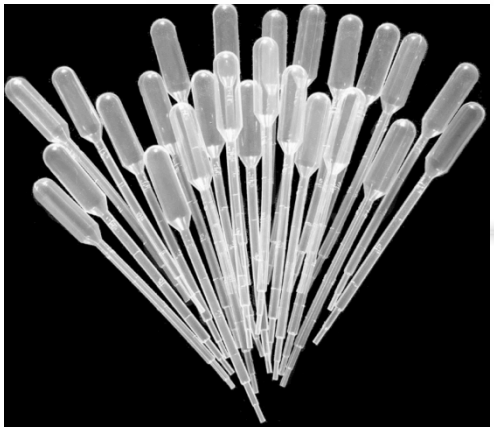
BPA-Free Bottles

CLEAN AND STERILIZED

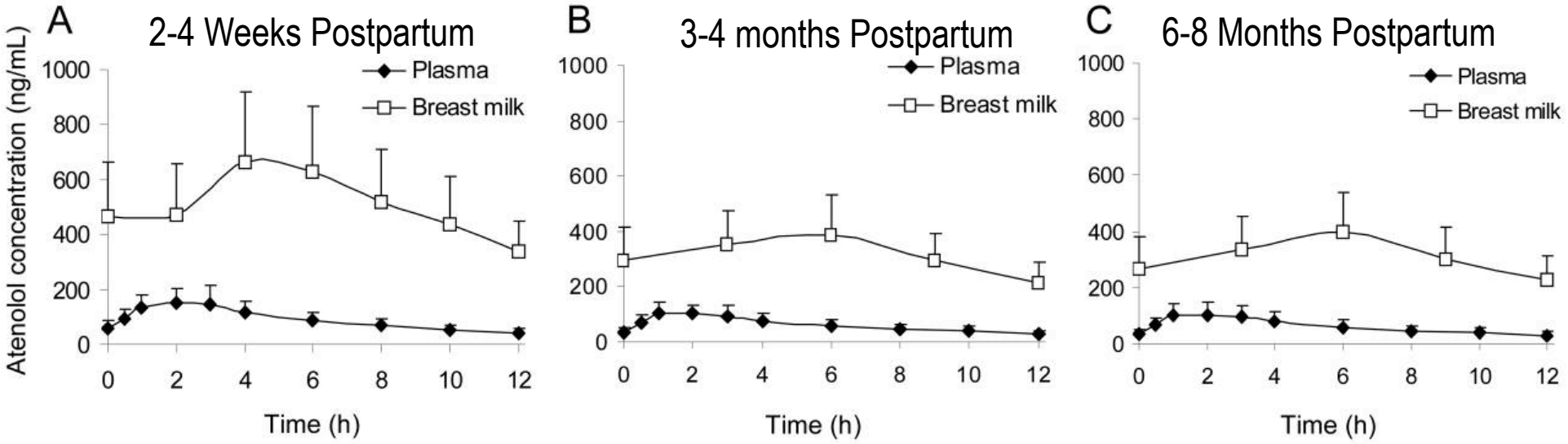




CONSIDER DRUG BINDING TO COLLECTION EQUIPMENT



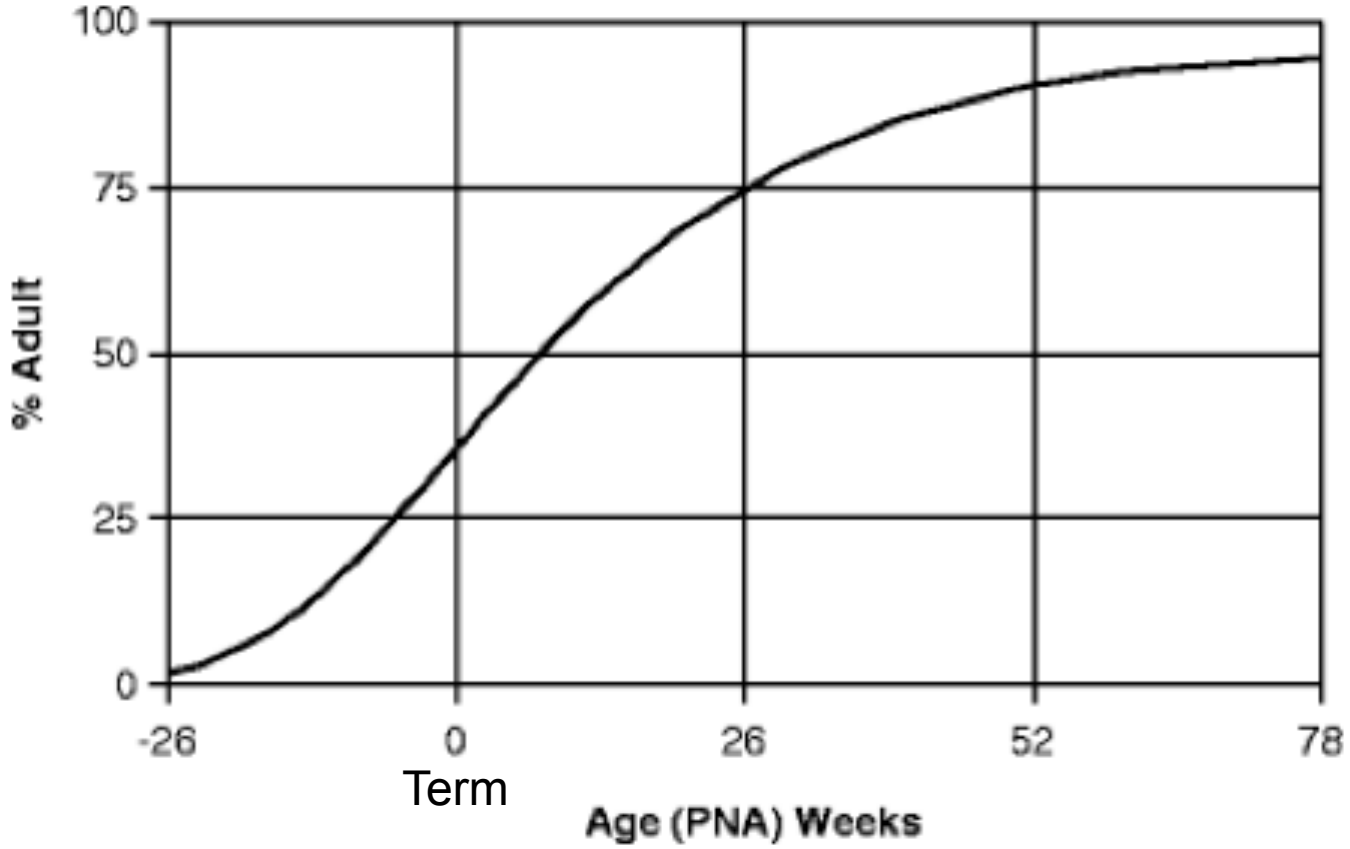
MATERNAL AND BREAST MILK ATENOLOL CONCENTRATIONS



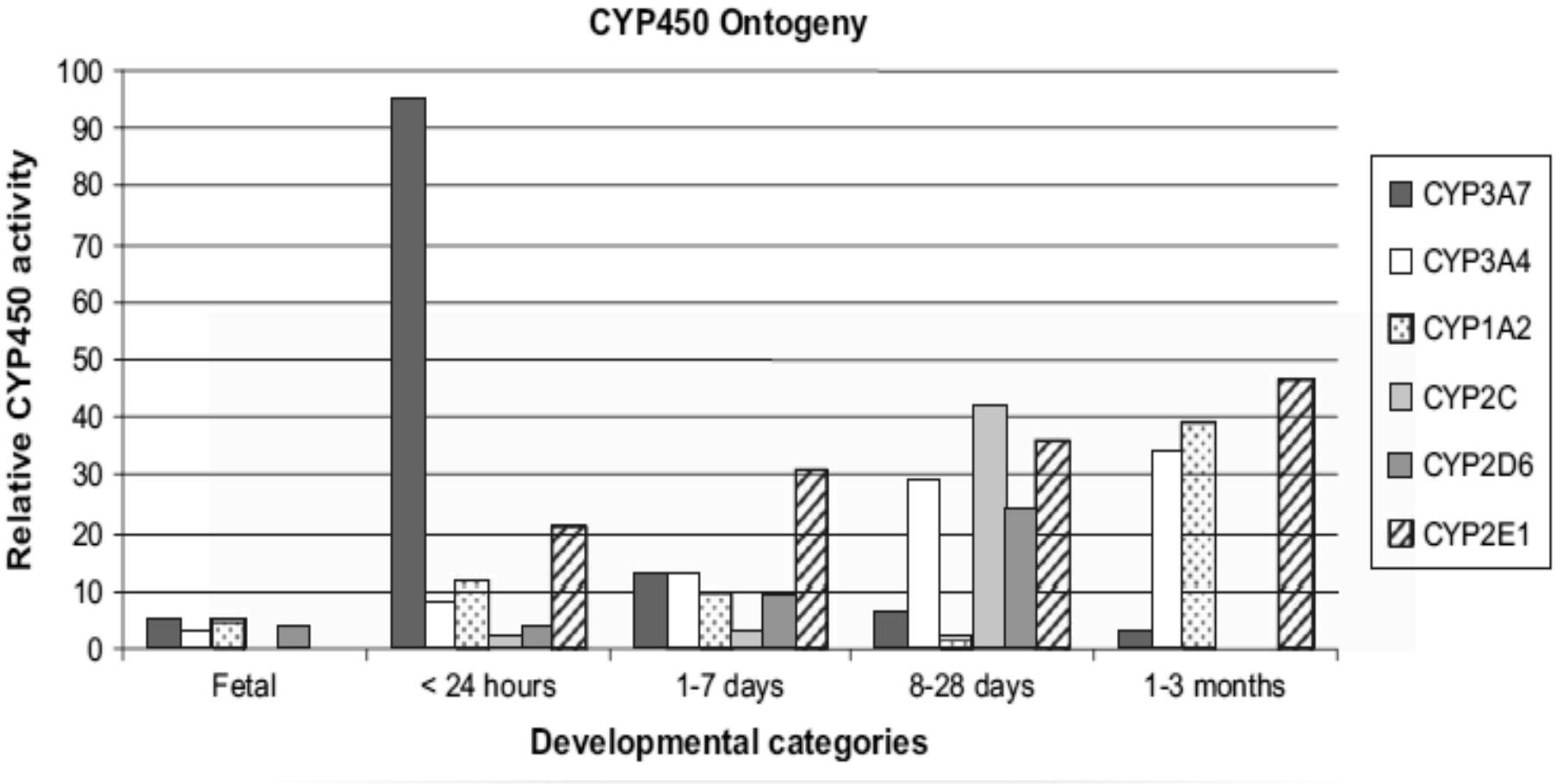
- peak concentrations are later and higher than maternal peak.
- Mammary clearance higher 2-4 weeks postpartum that 3-8 months postpartum.
- All breastfeeding infant concentrations at 3-4 months postpartum are below limit of quantification for assay (<10 ng/mL).

Eyal S et al. J Clin Pharmacol. 2010 Nov;50(11):1301-9.

MATURATION OF GFR SHOWING THE PREDICTIONS OF THE SIGMOID HYPERBOLIC FUNCTION.



P450 ENZYME ONTOGENY



Blake et al. Seminars in Fetal & Neonatal Medicine 2005;10:123-38.

SUMMARY-STUDY DESIGN MATTERS

- Need to accommodate mother and infant on research unit
- No nursing during study
  - Returning milk to infant
- How breast milk is collected
  - Colostrum vs. Foremilk vs. Hindmilk
  - Breast pump vs. Manual vs. Both
  - Glass vs. Plastic
  - Frequency of collections
- When breast milk is collected
  - 2-4 weeks vs. 3-8 months postpartum
  - Peak maternal concentrations not necessarily the same as peak breast milk concentrations

SUMMARY – INFANT CONSIDERATIONS

- Just because a drug is excreted into breast milk does not mean that breastfeeding is contraindicated
- Infant outcomes
  - Value of breast milk vs. risks of drug exposure
- Infant concentrations dependent on:
  - Premature vs. Term Infant
  - Total drug excretion in breast milk
  - Oral bioavailability
  - Infant renal function
  - Enzyme ontogeny

THANK YOU FOR YOUR ATTENTION