Brief report

Maternal Fasting or Fluid Abstention Does Not Significantly Affect the Macronutrient Composition of Human Milk: Clinical and Clinical Research Relevance

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Abstract: There are guidelines on lactation following maternal analgo-sedative exposure, but these do not consider the effect of maternal fasting, nor fluid abstention on human milk macronutrient composition. We therefore performed a structured search (PubMed) on 'human milk composition' and screened title, abstract and full paper on 'fasting' or 'abstention' and 'macronutrient composition' (lactose, protein, fat, solids, triglycerides, cholesterol). This resulted in 6 papers and one abstract related to religious fasting (n=129 women) and observational studies in lactating women (n=23, healthy volunteers, fasting). These data reflect two different 'fasting' patterns: an acute (18-25h) model in 71 (healthy volunteers, Yom Kippur/Ninth of Av) women and a chronic fasting (Ramadan) model in 81 women. Changes were most related to electrolytes and were moderate, with almost no changes in macronutrients during acute fasting. We therefor conclude that neither short term fasting nor fluid abstention (18-25h) affect human milk macronutrient composition, so that women can be reassured when this topic were raised during consulting. Besides the nutritional relevance, this also matters as clinical research samples – especially to estimate analgo-sedative exposure by lactation - are commonly collected after maternal procedural sedation, associated with maternal fasting and physiology-based pharmacokinetic (PBPK) models assume stable human milk composition.

Keywords: lactation; physiology-based lactation models; drug exposure prediction; fasting; drug safety; newborn; infant; human milk

1. Introduction

Breastfeeding results in improved infant and maternal health outcome in both the industrialized and developing world, and is recognized as an important public health issue as mentioned in the aims and scope of this journal. Consequently, women also want to breastfeed shortly following analgo-sedation for surgery or diagnostic procedures. To further facilitate this practice, guidelines are provided by different associations [1,2,3]. We also recently summarized the available knowledge on lactation during or after exposure to commonly prescribed analgesics, narcotics or sedatives (opioids, intravenous and inhalational anesthetics, benzodiazepines, non-opioid analgesics, and local anesthetics) following surgery, diagnostic procedures or medical indications. We proposed that the use of systemic non-opioid analgesics, local anesthetics, inhalational or intravenous anesthetics is safe when mothers are nursing. When systemic opioids are used, we recommend care providers to consider clinical monitoring of the infant for sedation. Furthermore, we suggested that the duration of maternal exposure (> 4 days) and the presence of maternal signs of somnolence hereby served as additional 'red flags' [4]. Such information is useful for lactating women and their care providers when planning analgo-sedation related to surgery or diagnostic interventions.

Following discussions with different colleagues and anesthesia associations during the development of (perioperative) guidelines on lactation following sedation and clinical consulting with individual lactating women, we realized that we only had focused on drugs or compounds 'temporarily ***added***' to the maternal diet, and not on the nutritional or fluid intake 'temporarily ***removed***' from the maternal diet as these women are commonly requested to abstain from enteral nutritional intake, enteral fluid intake, sometimes even including water. We therefore felt that a structured search on the available evidence on the effects of maternal fasting or water abstention on the macronutrient composition of human milk is valuable to enable counseling based on the available evidence.

Along the same line, such a structured search is also of clinical relevance as these mothers are sometimes invited to provide paired plasma and human milk samples to quantify exposure to these analgo-sedatives as part of clinical research programs. Such samples are used to develop and explore the performance of physiology-based pharmacokinetic (PBPK) lactation models, hereby assuming that human milk macro-nutrient composition remains stable during maternal fasting. As recently discussed by Yeung et al., PBPK models have the ability to provide *in silico* estimates of drug exposure given the proper parameterization with host physiology and drug properties [5]. In order to fully exploit the utility of PBPK models in quantifying drug uptake in breastfed neonates, an accurate measure of infant feeding parameters, volume and frequency of maternal milk intake are needed [6]. Human milk composition is another of these needed parameters [5,6].

As clinical research samples - especially for analgo-sedatives - are commonly collected after maternal procedural sedation and because these procedures are associated with maternal fasting, it is of relevance to ensure that macronutrient composition of human milk is not different from non-fasting settings so that data can be extrapolated to other populations and clinical settings and that *in silico* estimates of drug exposure related to lactation remain useful.

2. Materials and Methods

As part of a more extensive effort to explore interspecies differences in milk composition to support interspecies pharmacokinetic prediction models of drug excretion through milk with PBPK models (IMI ConcePTION project, WP3) [7,8], we conducted an additional, independent search on 'human milk composition' within PubMed on October, 29 2019. As side-project and to retrieve an answer on the impact of maternal fasting or fluid abstention on the macronutrient (lactose, protein, fat, solids, triglycerides, cholesterol) composition of human milk, the same search was screened for title, abstract and finally full papers related to 'fasting' or 'abstention' by the first author (KA). Retained papers were screened for references (published paper) and citations (PubMed + Google Scholar). The second author (AS) also screened the list and cases of uncertainty were discussed.

3. Results

The initial search ('human milk composition') resulted in 3100 PubMed hits. Following the search strategy, and screening for citations and references, this resulted in 6 papers and one abstract, mainly related to religious fasting (n=129, Ramadan, Yom Kippur/Ninth of Av), or describing observational studies in lactating women (n=23, healthy volunteers, fasting) (**Table 1**) [9-15].

Table 1: Summary on study characteristics and the impact of acute (18-25 h) or chronic fasting (during Ramadan) on the macronutrients and electrolytes in human milk (chronologically) [9-15].

reference	study model	most relevant findings, human milk
Prentice et al, 1984 [9]	10 lactating women, 2nd-4th week during vs 2 weeks after Ramadan; *morning and evening* samples. 10 non-lactating controls for maternal characteristics (morning *vs* evening, lactating *vs* non-lactating: higher weight loss (during the day); more dehydration; higher water turnover, likely due to higher water intake at night) in lactating women.	during Ramadan *vs* before: osmolarity (+3%), sodium (+25%); lactose (-14%); potassium (-18%). during *vs* after: osmolarity (+3%); sodium (+30%); lactose (-9%); potassium (-5%). during morning *vs* evening, osmolarity (-3%); lactose (-12%); sodium (+55%); potassium (unchanged).
Neville et al, 1987 +1993 [10,11]	23 women. Fasting after evening meal, non-caloric containing fluids allowed for 18-20 h. Repeated human milk sampling over the fasting period.	throughout fasting: milk glucose, protein, fat and lactose remained constant, despite maternal insulin and glucose decrease.
Bener et al, 2001 [12]	26 women, 2nd-4th week during *vs* 2 weeks after Ramadan. *Morning* sampling after nursing, so more a 'chronic' model.	during *vs* after: no differences in macronutrients (lactose, protein, fat, solids, triglycerides, cholesterol).
Rakicioglu et al, 2006 [13]	21 women, 2nd week during *vs* 2 weeks after Ramadan. *Morning* sampling after nursing, so more a 'chronic' model.	during *vs* after: no differences in macro-nutrients; potassium (-25%); dry mass (-22%). Magnesium (-12%); Zinc (-16%)
Zimmerman et al, 2009 [14]	48 women, nursing healthy infants (1-6 months) during a 24 h religious fasting period. Paired sampling human milk 2 days before, just after fasting, and 24-25 h later (10 ml milk before nursing).	just after *vs* before: sodium (+16%); calcium (+17%); protein (+9%); phosphorus (-19%); lactose (-6%); fat unchanged. 24 h later *vs* before: protein (+9%); lactose (-3%).
Salah et al, 2016 [15]	24 women, paired sampling during (100 ml) *vs* 2 weeks after Ramadan. *Morning* sampling after nursing, so more a 'chronic' model.	during *vs* after: lactose (-6%); protein (-6%); sodium (-28%); potassium (-18%); calcium (-7%); phosphorus (-14%) (fat unreported).

In essence, there are data on two different 'fasting' patterns, with an acute fasting (18-25 h) model in 71 (healthy volunteers, Yom Kippur/Ninth of Av) women, or a more chronic fasting (during Ramadan) model in 81 women. However, even in the chronic Ramadan model, the changes were mainly related to electrolytes and classified as moderate, while there were almost no changes in macronutrients (lactose, protein, fat, solids, triglycerides, cholesterol) in the acute fasting setting.

4. Discussion

In essence, we found data on two different 'fasting' patterns, with an acute model <24 h in 71 women [10,11,14], or a more chronic fasting (during Ramadan) model in 81 women [9,12,13,15]. In our assessment, the acute model is likely very similar to the interruption of caloric intake as part of analgo-sedation related to surgery or diagnostic interventions [1-3, 10,11,14]. Based on the data we retrieved, the impact of chronic fasting during Ramadan and breast milk are moderate, although there remains a call for further focused research on this topic, be it that this is out of scope of the current research question [16]. We were unable to retrieve data on human milk composition immediately following surgical interventions or medical procedures, but still feel that the pooled data in **Table 1** [9-15] are useful for extrapolation as there is likely a major burden to conduct such studies in an immediate postoperative setting.

Based on this structured, focused search, we conclude that neither fasting nor fluid abstention significantly affect the macronutrient composition (lactose, protein, fat, solids, triglycerides, cholesterol) of human milk, so that women can be reassured on this aspect when this topic is raised during consulting. Furthermore and relevant to PBPK model development programs, this also means that - as parameter to be used in PBPK model efforts - it is reasonable to assume similar macronutrient composition of human milk in the immediate postoperative setting during fasting and fluid abstention [5-8].

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References

1. Martin, E.; Vickers, B.; Landau, R.; Reece-Stremtan S. ABM clinical protocol #28, peripartum analgesia and anesthesia for the breastfeeding mother. *Breastfeed. Med.* **2018**, *13*, 164–171. doi 10.1089/bfm.2018.29087.ejm.
2. Smathers, A.B.; Collins, S.; Hewer, I. Perianesthetic considerations for the breastfeeding mother. *J. Perianesth. Nurs.* **2016**, *31*, 317-329. doi 10.1016/j.jopan.2014.09.006.
3. Oliveira, M.R.E.; Santos, M.G.; Aude, D.A.; Limar, R.M.E.; Módolo, N.S.P.; Navarro, L.H. Should maternal anesthesia delay breastfeeding? A systematic review of the literature. *Rev. Bras. Anestesiol.* **2019**, 69, 184-196. doi 10.1016/j.bjan.2018.11.006.
4. Allegaert, K.; van den Anker, J.N. Maternal analgosedation and breastfeeding: guidance for the pediatrician. *J. Pediatr. Neonat. Individual. Med.* **2015**, *4*, e040117. doi 10.7363/040117.

5. Yeung, C.H.T.; Fong, S.; Malik, P.R.V.; Edginton, A.N. Quantifying breast milk intake by term and preterm infants for input into paediatric physiologically based pharmacokinetic models. *Matern. Child. Nutr.* **2020**, 16, e12938. doi 10.1111/mcn.12938.
6. Maharaj, A.R.; Edginton, A.N. Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. *CPT. Pharmacometrics. Syst. Pharmacol*. **2014**, *3*, e150. doi 10.1038/psp.2014.45.
7. Ventrella, D.; Forni, M.; Bacci, M.L.; Annaert, P. Non-clinical models to determine drug passage into human breast milk. *Curr. Pharm. Des*. **2019**, 25, 534-548. doi 10.2174/1381612825666190320165904.
8. IMI Conception. Available online: www.imi-conception.eu/work, accessed 25 March, 2020.
9. Pentrice, A.M.; Lamb, W.H.; Prentice, A.; Coward, W.A. The effect of water abstention on milk synthesis in lactating women. *Clin Sci.* **1984**, *66*, 291-298. doi 10.1042/cs0660291.
10. Neville, M.C.; Jensen, R.G.; Lutes, V.; Hay, W.W. Effects of fasting, insulin and glucose on milk lipid secretion in lactating women [abstract]. *FASEB Proceedings* **1987**, *46*, 409a.
11. Neville, M.C.; Sawicki, V.S.; Hay, W.W. Jr. Effects of fasting, elevated plasma glucose and plasma insulin concentrations on milk secretion in women. *J. Endocrinol.* **1993**, *139*, 165-173. doi 10.1677/joe.0.1390165.
12. Bener, A.; Galadari, S.; Gillett, M.; Osman, N.; Al-Taneiji, H.; Al-Kuwaiti, M.H.H.; Al-Sabosy, M.M.A. Fasting during the holy month of Ramadan does not change the composition of breast milk. *Nutr. Res.* **2001**, *21*, 859-864. doi 10.4103/aam.aam_63_17.
13. Rakicioglu, N.; Samur, G.; Topçu, A.; Topçu, A.A. The effect of Ramadan on maternal nutrition and composition of breast milk. *Pediatr. Int*. **2006**, *48*, 278-283. doi 10.1111/j.1442-200X.2006.02204.x.
14. Zimmerman, D.R.; Goldstein, L.; Braunstein, R.; Stahi, D.; Bar-Haim, A.; Berkovitch, M. Effect of a 24+ hour fast on breast milk composition. *J. Hum. Lact.* **2009**, *25*, 194-198. doi 10.1177/0890334409331505.
15. Salah, E.T.; Malik, N.M.E.; Hassan, M.S.; Mohammed, I.A.; Mohamed, M.; Mohamed, M.O.; Elmadhoun, W.M. How does the fasting of Ramadan affect breast milk constituents. *Sudan JMS*. **2016**, *11*, 17-22.
16. Rashid, H. Ramadan fasting and breast milk. *Breastfeed. Med*. **2007**, *2*, 59-60. doi 10.1089/bfm.2006.0021.