



Effects of anticipated neonatal surgical intervention on maternal milk cytokine production[☆]



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ABSTRACT

Background: Maternal stress on neonatal outcomes of infants admitted to the NICU is incompletely understood. We previously demonstrated breast milk derived cytokines remain biologically active in the neonatal intestine. We hypothesized that the need for neonatal surgical intervention would be stimulus leading to maternal cytokine production thus affecting neonatal outcome.

Methods: Discarded expressed breast milk (EBM) in the first 3 weeks following delivery was analyzed for IL-23 and IL-10 by ELISA. Variables analyzed included: the need for a pediatric surgical procedure, the need for cardiac surgical procedure, no surgical interventions, and survival. All values are expressed as mean $\pm$ SEM. Statistical analysis utilized Kruskal and Mann-Whitney test.

Results: EBM from mothers whose infants required any surgical procedure ($n = 19$) revealed significant elevation in IL-10 but not IL-23 compared to nonsurgical EBM ($n = 18$). Subdivided by procedure type, there was no difference between those undergoing a cardiac ($n = 9$) versus pediatric surgical ($n = 10$) procedure in both IL-10 and IL-23. Mothers whose infants requiring surgical intervention or whose infants did not survive in the first 3 weeks of life had elevation of IL-10.

Conclusion: Results suggest maternal stress impacts the cytokine profile of breast milk.

Level of evidence: Level III.

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Sources of maternal inflammation leading to secretion of cytokines into breast milk because of maternal stress experienced during neonatal critical diagnosis and treatment have not been definitively identified. Breast milk is a complex mixture of biologically active components that not only differs among women, but also during the lactation period and degree of prematurity from colostrum through transitional to mature milk [1]. Multiple biologically active factors are secreted into milk including growth factors, immunoglobulins, cytokines, proteins, oligosaccharides, and lipids. The breast milk factors promote intestinal health and facilitate the maturation, protection of the intestinal mucosal barrier and immunomodulation [2–4]. Clinical and epidemiological studies indicate that maternal milk plays a protective role in the pathogenesis

of one important neonatal disease, necrotizing enterocolitis (NEC) [5]. However, some investigators have suggested that milk rich in pro-inflammatory, but low in anti-inflammatory cytokines may be associated with NEC or systemic inflammation [6].

Pro-inflammatory cytokines in breast milk exhibit biological variation at different periods of human lactation [7]. We previously demonstrated the highly variable interleukin (IL)-23 expression of in human breast milk [8,9]. IL-23 expression has been shown to be pivotal to the development of clinically relevant inflammation in both rheumatoid arthritis and inflammatory bowel disease (IBD) [10,11]. Blockade of the IL-23 receptor on T cells, natural killer cells, monocytes, and dendritic cells has been shown to decrease intestinal inflammation in a mouse model of IBD illustrating the importance of IL-23 in intestinal inflammation [10]. IL-10 expression in normal pregnancy is thought to help suppress the pro-inflammatory cytokine responses and is important for maintaining a healthy pregnancy [12].

The effect of maternal stress on neonatal outcomes of infants admitted to the NICU is incompletely understood. We hypothesized that the need for neonatal surgical intervention would be a stressful stimulus leading to maternal cytokine IL-23 and IL-10 production and secretion into expressed human milk (EBM). Finally, we examined if prenatal diagnosis as well as involvement of parental support palliative care influenced the cytokines secreted in EBM.

☆ Contributions:

• Study conception and design: J.L.J., M.C. and A.J.W.

• Acquisition of data: J.L.J.

• Analysis and interpretation of data: R.M.R. and J.L.J.

• Drafting of manuscript: R.M.R. and J.L.J.

• Critical revision of manuscript: J.L.J., R.M.R., A.J.W., and D.M.G.

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Table 1

Demographics table. There is no statistical difference between non-surgical and surgical neonates.

	Non-surgical	Surgical	p
Gestational age	33.73 wk $\pm$ 5.29	35.23 wk $\pm$ 4.93	0.36
Birth weight	1.95 kg $\pm$ 1 kg	2.45 kg $\pm$ 1 kg	0.13
Gender (% male)	63.2% male	54.5% male	0.59
Mode of delivery (% vaginal)**	35.3% vaginal	40% vaginal	0.75

** 2 in each group unknown.

1. Materials and methods

1.1. Breast milk and chart review

As described previously [6] following institutional review board approval, discarded breast milk was obtained from the neonatal intensive care unit (NICU) and pediatric cardiac intensive care unit (CICU) at Children's Hospital of Wisconsin. The whey fraction of the milk was isolated by centrifugation at 4000 rpm for 4 min after thawing the milk overnight at 4 °C. Charts were reviewed for need for surgical intervention, palliative care consult and survival to discharge with demographics listed in Table 1.

1.2. Analysis of IL-10 and IL-23

Whole milk was centrifuged (700g for 10 min at 4 °C) and supernatant IL-10 and IL-23 were measured by ELISA as per manufacturer's instructions. A 1:1000 dilution of whey was used to measure the amount of IL-10 and IL-23 in each aliquot of milk. IL-10 ELISA (R&D Systems D1000B, Minneapolis, MN) and IL-23 (R&D Systems D2300B, Minneapolis, MN). A minimum of three samples were used for all of the

experiments. All samples were completed in triplicate and expressed as the mean $\pm$ SEM.

1.3. Statistical analysis

Using STAT software (ver. 14; StataCorp LP, College Station, TX), comparisons were made between treatment groups. Means and standard errors (SE) are reported for normally distributed data and groups were compared using a t-test. Medians and inter-quartile ranges were reported for skewed data and groups were compared using a Mann–Whitney test. Differences were considered statistically significant if the *p*-value was ≤ 0.05 . All tests were conducted as two-tail tests.

2. Results

2.1. IL-10 is elevated in EBM of mothers whose infants underwent surgical intervention

Milk expressed in the first 6 weeks of life was evaluated for concentrations of IL-23 and IL-10. The mean concentration of IL-23 in EBM from mothers whose infants underwent surgery was 70.37 pg/mL $\pm$ 9.49 (*n* = 22) versus 68.18 pg/mL $\pm$ 6.24 (*n* = 19) in those who did not require an operation (Fig. 1A). There was a significant elevation in the concentration of IL-10 from EBM of surgical infants when compared to nonsurgical infants (9.89 pg/mL $\pm$ 1.14 vs 6.41 pg/mL $\pm$ 0.84 *p* = 0.022, Fig. 1B).

Given the perceived greater risks involved in cardiac versus general or neurosurgical procedures shortly after birth, these groups were subdivided and analyzed. There was no difference in EBM IL-23 or IL-10 concentrations in those undergoing a cardiac surgical procedure when compared to another surgical procedure (Fig. 1C, D).

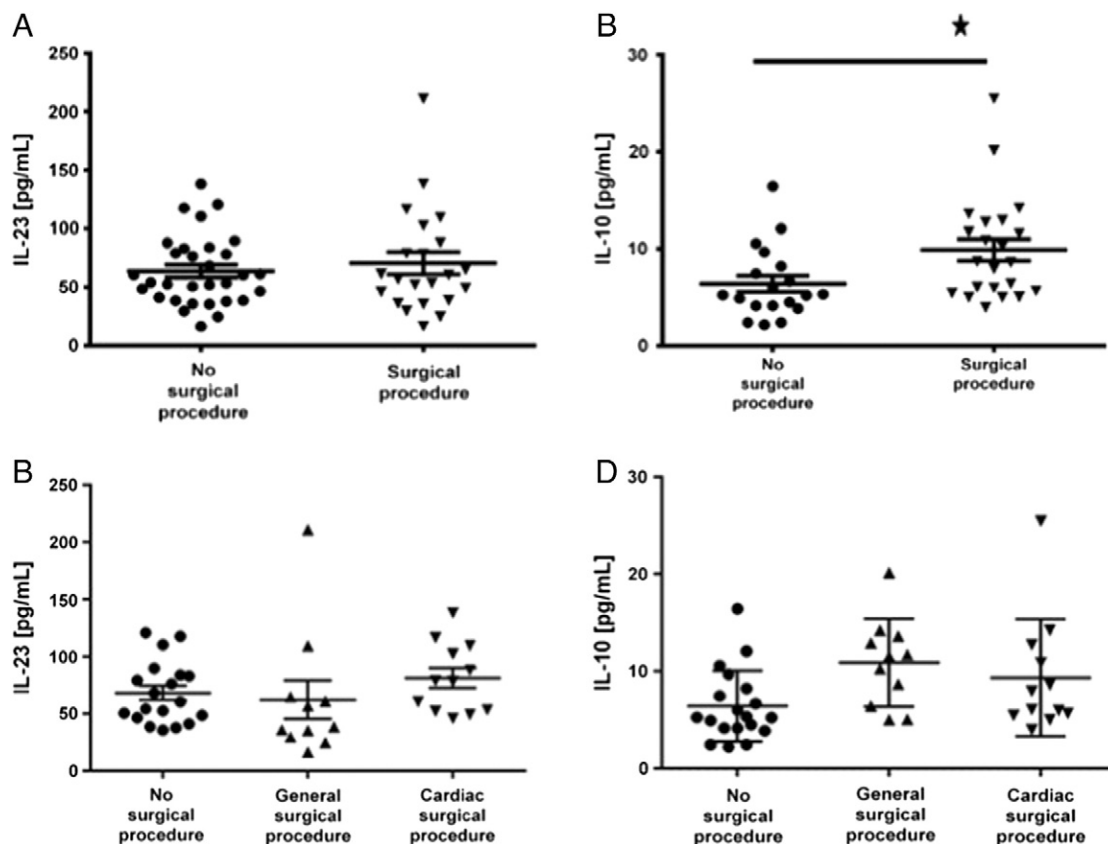


Fig. 1. Concentrations of IL-23 and IL-10 in EBM from surgical and non-surgical infants. A. There is no difference in IL-23 concentration between the two groups. B. IL-10 was significantly higher in surgical infants (*p* = 0.022). Concentrations of IL-23 and IL-10 in EBM from non-surgical, cardiac surgical and other surgical infants. C. There is no difference in IL-23 or D. IL-10 concentrations between the two groups. Data are expressed as mean; error bars represent SEM.

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