Austin Journal of Public Health and Epidemiology

Open Access

Austin Publishing Group

Rapid Communication

Pregnancy-Induced Proinflammatory Immunological Tone and Gut Microbiota Profile are not Reversed at the Delivery

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Received: October 08, 2022; **Accepted:** November 02, 2022; **Published:** November 09, 2022

Abstract

Pregnancy is associated with an increased production of pro-inflammatory factors and concomitant modifications in the gut microbiota composition. The persistence of these pregnancy-associated immunologic and gut microbiota profiles was assessed in 43 women. In the postpartum period the gut microbiota composition remained relatively unchanged while the concentrations of the pro-inflammatory cytokines continued to increase.

Keywords: Mode of delivery; Caesarean section; Inflammatory cytokines

Abbreviations

CS Caesarean section, IL-8 interleukin-8, MCP-1 monocyte chemotactic protein-1, TNF- α tumor necrosis factor α.

Introduction

Pregnancy is currently perceived as a critical stage in guiding the adaptation of foetus to the anticipated extrauterine environment and thereby impacting on the metabolic and immunological programming of child health. Carrying the pregnancy until term is ensured by a gradual modulation of the maternal immune system towards tolerance induction [1]. The metabolic features appear beneficial during pregnancy in shunting metabolic fuels to promote foetal growth, while the same profiles epitomize the metabolic syndrome in a non-pregnant situation [2,3]. We have previously demonstrated that the gut microbiota undergoes substantial changes over the course of pregnancy [4]. The precise interconnections between these alterations in gut microbiota composition and the maternal immunological tone remain obscure, as well as their restoration *postpartum*. An important question thus remains whether the delivery, and the delivery modes, reverse the microbial and immune tone to the pre-pregnant situation or does the pregnancy-induced alteration extend beyond the perinatal period.

Material and Methods

Patient Enrolment and Sample Collection

A nested case-control study based on a prospective intervention trial [5] was conducted. Altogether 46 women were studied: 10 women who had delivered by elective Caesarean Section (CS) and 13 women with non-elective CS were selected. and 23 women who delivered vaginally. The latter were chosen as controls and matched for pre-pregnancy body mass index, probiotic intervention during pregnancy as well as antibiotic exposure during pregnancy and labour. Written informed consent was obtained from all participants. The Ethics Committee of the Hospital District of Southwest Finland approved the study. Blood and faecal samples were been collected at the third trimester of pregnancy and one month *postpartum*. The concentrations of the cytokines Interleukin-8 (IL-8), Monocyte Chemotactic Protein-1 (MCP-1) and Tumour Necrosis Factor α (TNF-α) were measured from serum by using the Milliplex assay (Millipore, Billerica, MA) and the Luminex 200 system (Luminex Corporation, Austin, TX) according to manufacturer's instructions. The composition of the gut microbiota was assessed by qPCR as described previously [6] using the ABI 7300 system (Applied Biosystems, Foster city, CA).

Statistical Analyses

The cytokine levels and microbial data are presented in medians and range and because of the skewness of the data. Wilcoxon signed rank test were used for comparison of two time points and Kruskal-Wallis test for the comparison between delivery methods. The statistical analyses were performed by using SAS Software Version 9.4.

Results and Discussion

The clinical characteristics of the women and the neonates in the study are presented in (Table 1a). All the children were born from metabolically healthy term pregnancies. There were no differences in the clinical characteristics among women with different delivery modes. The serum concentrations of IL-8, MCP-1 and TNF-α were significantly higher one month postpartum as compared to the third trimester of pregnancy (Table 1b) irrespective of the mode of delivery. The gut microbiota composition remained unchanged from the third trimester of pregnancy to the situation one month after delivery (Table 1c). However, *Clostridium coccoides* numbers were higher one month postpartum in mothers who had delivered vaginally as compared to those who had delivered by CS (p=0.0001).

Pregnancy is related to profound immunological and metabolic

Citation: Hermansson H, Rautava S, Löyttyniemi E, Salminen S and Isolauri E. Pregnancy-Induced Proinflammatory Immunological Tone and Gut Microbiota Profile are not Reversed at the Delivery. Austin J Public Health Epidemiol. 2022; 9(4): 1135.

Table 1: The results of the study.

	Vaginal delivery n=23	Non-elective CS n=13	Elective CS n=10	All participants
Table 1a: Clinical characteristics. (expressed as mean and range)				
Maternal age (y)	29.9 (22.8-38.7)	31.7 (28.5-35.2)	31.8 (28.4-38.9)	30.8 (18.4-33.6)
Prepregnancy BMI(kg/m²)	23.6 (18.4-33.6)	24.0 (20.1-28.2)	25.0 (20.2-33.5)	24.0 (18.4-33.6)
GDM	3/23 (13%)	1/13 (7.7%)	1/10(10%)	5/46 (10.9%)
Duration of pregnancy (wk)	40.3 (36-42)	41.2(37-43)	39.9 (39-42)	40.4 (36-43)
Infant's birth weight (g)	3561 (2630-4460)	3848 (2855-4660)	3560 (2910-4030)	3642 (2630-4660)
Table 1b: Maternal serum cytokine levels. (pg/ml) (expressed as medians and range)				
IL-8				
3rd trimester	5.27 (3.3-12.1)	8.4 (3.8-14.8)	4.8 (3.4-22.9)	5.97 (3.3-22.9)
1 mo post partum	10.3 (3.3-116.4)	10.1 (5.5-15)	10.6 (5.2-30.3)	10.22 (3.4-116.4)*
MCP-1				
3rd trimester	362.8 (47.8-664.1)	267.8 (185-447)	400.1 (199-801)	332.9 (47.8-801.7)
1 mo post partum	538.3 (82-1961.8)	426.9 (163-768)	524 (259-744)	483.4 (290)*
TNF-α				
3rd trimester	9.37(5.7-45.8)	8.5 (5.2-13.1)	8.2 (4.5-16.6)	9.1 (4.5-45.8)
1 mo post partum	11.65 (5.7-67.3)	8.6 (-13.5)	8.9 (3.9-93.1)	9.7 (3.9-93.1)*
Table1c: Gut microbiota. (Log cell/g). (expressed as medians and range)				
Bifidobacterium genus				
3rd trimester	10.4 (9.4-10.4)	10.3 (9.7-10.8)	10.5 (9.0-11.5)	10.4 (9.0-11.5)
1 mo post partum	10.3 (8.6-11.5)	9.9 (4.8-11.2)	10.5 (9.6-11.5)	10.2 (4.8-11.5)
Bifidobacterium longum				
3rd trimester	10.0 (8.2-11.1)	9.9 (6.9-10.6)	9.6 (3.3-11.3)	9.9 (3.3-11.3)
1 mo post partum	9.7 (7.8-10.8)	9.8 (7.9-10.7)	9.9 (7.6-10.8)	9.7 (7.6-10.8)
Bifidobacterium catenulatum				
3rd trimester	7.0 (5.1-10.5)	6.6 (5.1-10.1)	7.3 (5.1-10.0)	7.0 (5.1-10.5)
1 mo post partum	6.9 (5.1-10.2)	7.4 (5.1-10.5)	6.8 (5.1-10.7)	7.0 (5.1-10.7)
Bifidobacterium Bifidum				
3rd trimester	6.4 (5.4-10.1)	6.6 (5.4-10.4)	7.3(5.4-10.7)	6.7 (5.4-10.7)
1 mo post partum	6.2 (5.4-9.8)	6.3 (5.1-10.4)	7.5 (5.4-9.8)	6.5 (5.1-10.4)
Bifidobacterium Lactis				
3rd trimester	7.2 (2.9-10.5)	6.9 (2.9-9.7)	7.0 (2.9-10.7)	7.1 (2.9-10.7)
1 mo post partum	6.5 (2.9-9.8)	6.4 (2.9-10.1)	5.4 (2.9-7.7)	6.3 (2.9-10.1)
Bifidobacterium Infantis				
3rd trimester	6.6 (6.5-8.0)	6.5 (6.5-6.9)	7.1 (6.5-9.8)	6.7 (6.5-9.8)
1 mo post partum	6.7 (6.5-9.5)	6.5 (6.5-6.6)	6.7 (6.5-8.2)	6.6 (6.5-9.5)
Bifidobacterium Adolescentis				
3rd trimester	7.1 (5.7-11.1)	6.1 (5.7-9.8)	7.7 (5.7-10.6)	7.0 (5.7-11.1)
1 mo post partum	7.2 (5.7-11.2)	6.6 (5.7-10.3)	7.9 (5.7-11.0)	7.1 (5.7-11.2)
Bifidobacterium Breve				
3rd trimester	5.6 (5.6-6.0)	5.9 (5.6-7.4)	5.9 (5.6-7.2)	5.7 (5.6-7.4)
1 mo post partum	5.7 (5.6-8.3)	6.0 (5.6-8.0)	5.6 (5.6-5.6)	5.8 (5.6-8.3)
Clostridium Coccoides				
3rd trimester	10.1 (9.0-10.6)	10.2 (9.3-10.7)	10.5 (9.8-11.5)	10.2 (9.0-11.5)**
1 mo post partum	11.6 (9.4-12.8)	10.6 (9.7-12.2)	10.8 (10.0-12.3)	11.1 (9.4-12.8)
Clostridium Leptum				
3rd trimester	9.3 (8.4-10.6)	9.5 (8.5-10.0)	9.5 (8.3-10.1)	9.4 (8.3-10.6)
1 mo post partum	9.5 (7.9-10.3)	9.0 (7.3-9.8)	9.4 (9.0-10.0)	9.3 (7.3-10.3)
Clostridium Difficile				
3rd trimester	5.2 (5.2-5.2)	5.3 (5.2-6.8)	5.2 (5.2-5.2)	5.2 (5.2-6.8)
1 mo post partum	5.3 (5.2-8.5)	5.2 (5.2-5.2)	5.2 (5.2-5.2)	5.2 (5.2-8.5)
Akkermansia Muciniphila				
3rd trimester	6.8 (1.9-9.3)	5.7 (1.9-9.2)	7.7 (1.9-9.3)	6.7 (1.9-9.9)
1 mo post partum	6.2 (1.9-9.9)	5.8 (1.9-9.1)	7.0 (1.9-9.4)	6.2 (1.9-9.9)
Staphylococcus Aureus				
3rd trimester	5.0 (4.9-6.7)	5.0 (4.9-6.3)	5.3 (4.9-7.4)	5.1 (4.9-7.4)
1 mo post partum	5.0 (4.9-6.3)	5.0 (4.9-6.2)	4.9 (4.9-4.9)	5.0 (4.9-6.3)
Clostridium Perfringens				
3rd trimester	6.4 (6.3-6.4)	6.4 (6.4-6.4)	6.4 (6.4-6.4)	6.4 (6.3-6.4)
1 mo post partum	6.6 (6.4-8.8)	6.5 (6.4-7.1)	6.4 (6.4-6.4)	6.5 (6.4-8.8)

*P=0.05. Cytokine concentration was significantly higher in 1 mo samples as compared to 3rd trimester samples.

**P<0.05. The amount of Clostridium coccoides was higher vaginal delivery group.

changes which ensure the growth and development of the foetus. These also affect the maternal microbiota composition and activity, or *vice versa*. The net result at the end of pregnancy is a gut microbiota profile of elevated Proteobacteria and Actinobacteria and reduced bacterial richness [4]. Furthermore, the concentrations of serum pro-inflammatory cytokines vary throughout the pregnancy; the first and third trimester of pregnancy manifest as a proinflammatory state, whereas the second trimester as an anti-inflammatory state. The

balance between proinflammatory and anti-inflammatory tones is crucial for a successful pregnancy, as excessive inflammation during pregnancy is linked to adverse maternal conditions, such as pre-eclampsia, and preterm birth [7].

We report for the first time that the pregnancy-related immunological and microbiota changes remained unrecovered during the postnatal period, reflecting an extended adaptation period which is not dependent on the mode of delivery. We therefore interpret our data to suggest that the increase in serum pro-inflammatory cytokines observed one-month *postpartum* results from an enduring proinflammatory tone of the gut microbiota, inviting the idea that the immunological and microbiota changes typifying the healthy pregnancy may be interrelated. Perhaps, the key resilience is breast feeding, as breast milk represent as a source of beneficial microbes and their growth factors with ample anti-inflammatory potential [8].

Conclusion

The role of the maternal gut microbiota composition during pregnancy and especially in the *postpartum* period remain poorly understood; particularly from the child's perspective. As aberrancies in the mother's microbiota composition and activity may be transferred to the infant by different routes: during pregnancy, at delivery, and close contact between the mother and the newborn after delivery, the mechanisms of the persistence of the inflammatory signals after the perinatal period and potential link to the risk on non-communicable disease call for further research.

Acknowledgements

We want to thank the participating families and Satu Tölkkö for the valuable contribution in microbiota analysis. The study was supported by grants from The Finnish Foundation for Paediatric research and Turku University Foundation. The author have no conflicts of interests.

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