Regional Caesarean Delivery Practices, the Maternal-Infant Microbiome, and Risk for Asthma

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J Obstet Gynaecol Can 2018;40(8):1061–1065

https://doi.org/10.1016/j.jogc.2018.01.025

As caesarean section (CS) rates continue to climb around the globe, Richards et al.[1] have pointed out interesting international differences. CS delivery at early term gestation (37–38 weeks) rose in Canada and several European countries between 2006 and 2014, but it declined in the United States.[1] Clinician-initiated interventions such as labour induction or pre-labour CS were cited as the primary reason for the increasing trends.[1] Both labour induction and pre-labour CS rose for early term births in Canada over the 8-year study period, with the latter showing a slight decline after 2012. In contrast, US rates of both labour induction and pre-labour CS rates in early term gestation declined.[1] Preceded only by repeat CS, CS after failed induction or pre-labour CS makes the second largest contribution to aggregate Canadian CS rates,[2] a contribution that has remained constant in most provinces.[2] Together, these Canadian trends in labour and delivery practice have implications for long-term outcomes in children. We use the example of childhood asthma and its putative association with CS and early term birth to illustrate the impact of these birth interventions on the maternal and neonatal microbiome.

Key Words: Caesarean section, maternal infant microbiome, asthma risk

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Competing interests: See Acknowledgements.

Received on June 20, 2017

Accepted on January 14, 2018

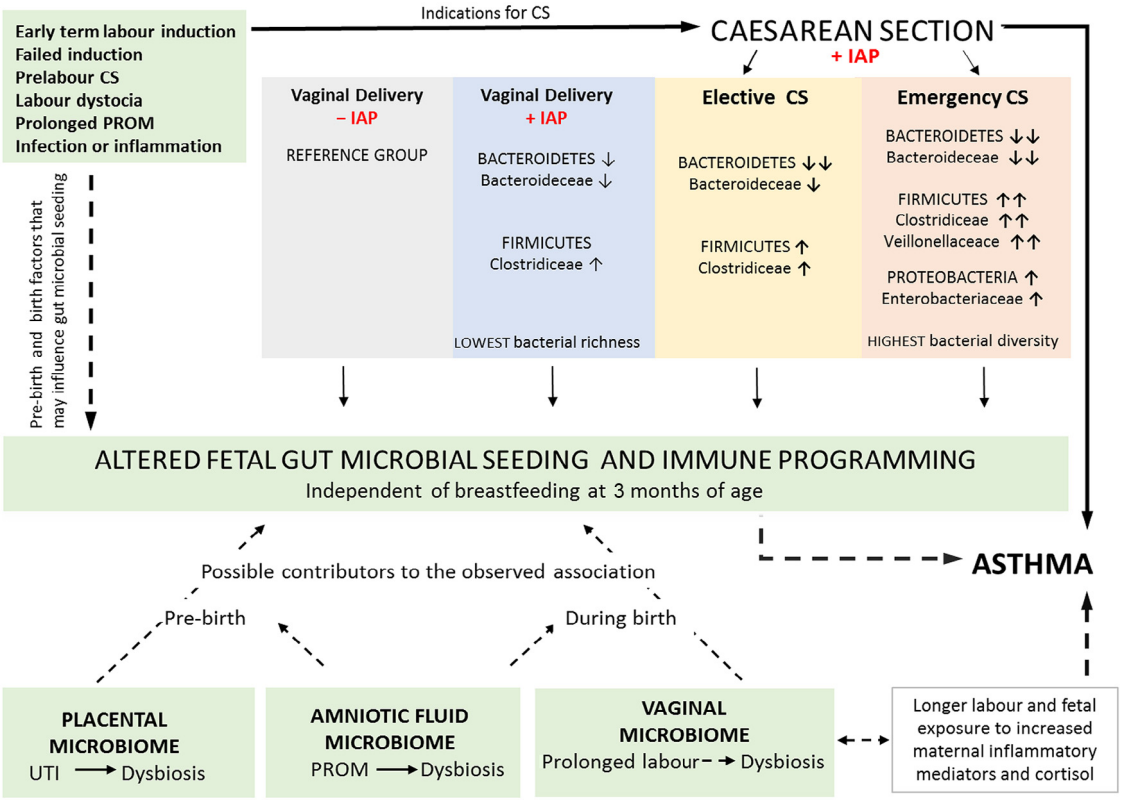
CS, EARLY TERM BIRTH, AND ASTHMA: OVERVIEW AND ISSUES

Climbing rates of CS have paralleled another public health concern, the rising rates of childhood asthma. In a meta-analysis of 26 cohort studies with minimal heterogeneity, Huang et al.[3] found a 16% increase in childhood asthma risk after CS birth. Because CS is an obstetric intervention performed for maternal or fetal well-being, many published meta-analysis are unable to adjust for potential confounding factors. Hence, it is unclear whether the link between asthma and CS can be attributed predominantly to delivery mode alone or to other pre-birth, birth, and/or early life environmental influences.

Vaginal delivery exposes the newborn to constituent maternal vaginal and fecal bacteria; these seeding opportunities for the newborn gut are bypassed with CS, especially in the absence of labour. A recent systematic review by Rutayisire et al.[4] found CS to be associated with both lower abundance and less diversity of the Actinobacteria and Bacteroidetes, and higher abundance and diversity of the phylum Firmicutes from birth to 3 months of life. As such, many investigators have proposed the "microflora hypothesis" to explain the heightened asthma risk subsequent to CS or antibiotic treatment of the infant or the reduced risk with farm living, dog ownership, and day-care attendance.[5]

Yet many studies examining childhood asthma and CS have not separately considered emergency versus scheduled CS, even though emergency CS usually occurs after labour. In the subgroup meta-analysis by Huang et al.,[3] the likelihood of asthma with emergency CS was marginally higher (OR 1.23; 95% CI 1.9–1.26) than with elective CS (OR 1.21; 95% CI 1.17–1.25). There was considerable heterogeneity among cohorts contributing to the emergency CS summary OR, mainly as a result of the study by Tollanes et al.[3,6] In a

Figure. Pre-birth and birth factors and their role in gut microbial seeding and risk of asthma. IAP: intrapartum antibiotic prophylaxis; PROM: premature rupture of membranes; UTI: urinary tract infection; ↓: low; ↓↓: significantly low; ↑: high; ↑↑: significantly high; solid black arrow: proven association; dashed black arrow: tentative association. Microbiome findings are based on Azad et al.[19].



large, population-based Swedish cohort, Almqvist et al.[7] used a sibling design to account for familial, socioeconomic, and environmental factors. After stratification by emergency CS and scheduled CS, statistical significance was lost for the latter; childhood asthma risk was significantly higher in the emergency CS versus scheduled CS group. In contrast, other population-based analyses (Danish perinatal database and combined European cohorts) have yielded the opposite finding, with a larger risk for childhood asthma secondary to scheduled CS (without labour) than with emergency CS.[8,9]

The literature is more consistent in reporting that early term birth increases the risk for child asthma.[10] These reports, together with new evidence on the presence of bacterial DNA in the amniotic fluid and placenta,[11] point to the possibility of pre-birth microbial influences. New evidence is also emerging on other characteristics of the birth process, such as labour duration,[12] which is discussed in full later. As illustrated in the Figure, emerging trends in labour management in Canada are relevant to pre-labour and labour-related factors that affect the gut microbial and mucosal immune systems of infants. These factors may help explain current or projected unintended health consequences. In this commentary, we explore the contribution of the placenta, duration of labour, and premature rupture of membranes (PROM) in shaping the maternal and/or infant microbiomes, infant immune system, and subsequent risk of childhood asthma.

EARLY TERM AND THE PLACENTA

As a natural interface between the maternal and fetal environment, the placenta plays a key role in regulating exposure to microbes. Recent discovery of a placental microbiome further illustrates this complex role. Using metagenomic sequencing to catalogue bacteria in a US sample, Aagaard et al.[13] reported a unique microbiome in the placenta of normal term pregnancies that consisted of the phyla Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria.[13] *Escherichia coli* was identified as the most abundant species. Collado et al.[11] also detected Enterobacteriaceae in the placental membranes and amniotic fluid of Finnish neonates born by scheduled CS with intact membranes, and detection at a much higher abundance than observed in meconium. The composition of the placental microbiome