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

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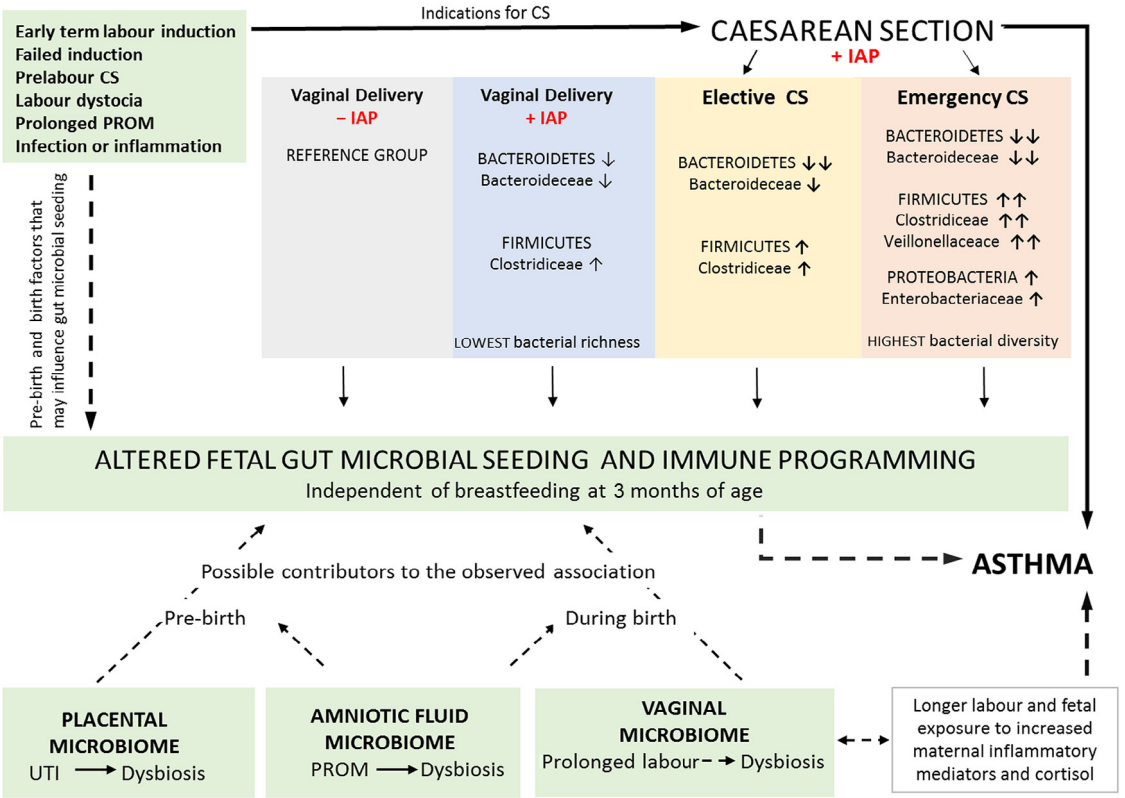
CS, EARLY TERM BIRTH, AND ASTHMA: OVERVIEW AND ISSUES

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

is reportedly influenced by GA, birth weight, and frequency of maternal urinary tract infection in pregnancy.[13] Put together, fetal exposure to bacteria and bacterial DNA could well begin in utero before delivery as a function of maternal health.

Conversely, newer literature in this area suggests that microbes detected in placental samples are the result of contamination. In a US study, Lauder et al.[14] evaluated placental samples from an uncomplicated term pregnancy to a find a microbial signature undistinguishable from that of control samples obtained from unused sterile swabs and blank swabs waved in the air of the laboratory. It is then interesting that the placental microbiome is shaped by the same factors that elevate risk for childhood asthma. such as early-term Caesarean birth,[6] low birth weight,[10] and maternal history of urinary tract infection.[10]

LABOUR INDUCTION AND DURATION

Evidence that labour may mediate child health comes from older reports in the literature of associations between prolonged labour and asthma development.[15] Although these associations seem counter to the notion that prolonged contact with vaginal microbiota improves seeding opportunities, the birth process initiates inflammatory responses, such as the release of C-reactive protein, the serum levels of which have been associated with childhood wheeze.[16] In the study by Logan et al.[17] of German newborns, cord blood levels of high sensitivity C-reactive protein were lowest in newborns delivered by scheduled CS (no labour), intermediate after unassisted or assisted vaginal birth, and highest after emergency CS. Independent of labour duration, induction of vaginal delivery was also associated with elevated fetal high sensitivity C-reactive protein levels.

Labour also has direct effects on newborn immunity. Thysen et al.[12] found the immune cell profile of cord blood in Danish newborns to be modified by scheduled CS (absence of labour), such that dendritic cells, T-regulatory cells, and $CD4^+$ T cells were higher, whereas neutrophils and monocytes were reduced, compared with profiles of newborns after vaginal birth. These immune profile differences (ie, lower monocyte and higher T-regulatory cell levels) were more often seen at early term in scheduled CSs. Cord immune cell profiles were similar between vaginal birth (spontaneous or induced) and emergency CS. The importance of labour in galvanizing immune cells during birth was similarly noted in an Australian birth cohort.[18] Evaluating data from newborns at term, Zhang et al.[18] observed the ratio of monocyte or $CD4^+$ T-helper cells in cord blood to be elevated with an extended duration of labour. This positive correlation was evident only among infants in whom food sensitization developed; details were not provided on whether labour was induced or assisted or whether it ended in CS.

There is some evidence for CS differences in infant gut microbiota in the presence of labour (emergency CS) and in its absence (scheduled CS). Examining the gut microbiota of 3-month-old Canadian infants born at term, Azad et al.[19] reported a striking lack of the Bacteroidetes in all CS-delivered infants. After emergency CS, Proteobacteria were overrepresented, as were *Enterococcus* and *Clostridium* species; the latter persisted at 1 year of age when infants were not exclusively breastfed for at least 3 months. Fewer microbial changes occurred in infants delivered by scheduled CS, and they did not persist. In a US study, Chu et al.[20] observed that meconium (first) microbiota of neonates born by emergency CS after labour was similar in composition to maternal fecal microbiota, whereas the microbial composition of meconium in infants born by CS without labour was similar to maternal cutaneous microbiota. Put together, the emerging evidence suggests that labour, its presence or duration, may influence microbial colonization and composition of the infant gut. As we learn more about how fetal immune cells communicate with placental or amniotic fluid microbiota,[21] and the role of changes to maternal vaginal and fecal microbiota that occur towards the end of gestation,[22] the importance of labour will be better understood and appreciated.

PRE-LABOUR MEMBRANE RUPTURE AND AMNIOTIC FLUID

Many studies overlook the potential significance of membrane rupture as an explanation for asthma risk relating to emergency CS. To assess the impact of PROM rigourously, Tollanes et al.[6] included a control group of Norwegian infants with cephalopelvic disproportion who were delivered by scheduled CS without membrane rupture. Compared with spontaneous vaginal birth, this group with cephalopelvic disproportion (with intact membranes) had the lowest asthma risk, followed by infants delivered by scheduled CS with potentially ruptured membranes. The risk for childhood asthma was highest for infants delivered by emergency CS (hazard ratio 1.59; 95% CI 1.44–1.75); this risk was further elevated with lower GA.[6] Although one cannot rule out prenatal factors in emergency CS, the stronger association with scheduled CS under the different conditions of membrane rupture points to the existence of a PROM effect. The duration of membrane rupture also may play a role. Keski-Nisula et al.[23] found that if the duration of membrane rupture was between 156 and 343 minutes before labour onset, compared with less than 45 minutes, there was

a strong association with childhood wheeze at 18 months among Dutch children, independent of many indicators of fetal distress.

A long-standing assumption has been that preterm and term PROM permits invasion of pathogenic microbes into the sterile amniotic cavity to cause infection and inflammation. Finding a unique microbiota in the amniotic fluid of healthy, full-term Finnish infants,[11] the study by Collado et al. offered another perspective on dysbiotic mechanisms in PROM. Comparable to the infants with cephalopelvic disproportion in the study by Tollanes et al.,[6] the infants in the study by Collado et al.[11] were delivered by scheduled CS without rupture of membranes or signs of maternal infection to minimize contamination of the samples. The genera *Escherichia or Shigella*, *Propionibacterium,* and *Lactobacillus* were detected both in amniotic fluid and in newborn meconium, thereby identifying amniotic fluid as a potential source for in utero colonization of the gut.[11] Hence, it is possible to speculate that dysbiotic changes in amniotic fluid microbiota provoke PROM. Fetal swallowing of the dysbiotic amniotic fluid and subsequent seeding of the gut may introduce susceptibility to atopic disease in later life.

Because amniotic fluid is alkaline, PROM can modify vaginal microbial composition by raising vaginal pH. The vaginal microbiota of healthy pregnant women is dominated by lactobacilli that produce lactic acid and support the growth of vaginal commensals. Key to shaping the development of infant gut microbiome, the vertical transmission of *Lactobacillus*-rich vaginal bacteria from mother to newborn may be modified by the alkalinity of amniotic fluid. In their study of *Lactobacillus* transmission to the neonatal oral cavity during birth, Keski-Nisula et al.[24] observed lowered transmission in the presence of PROM. *Lactobacillus* transmission was significantly less likely when membranes were ruptured between 2 and 9 hours before labour onset and was almost non-existent when rupture of membranes exceeded 9 hours.

SUMMARY

The development of the infant gut microbiome is multifactorial, and the method of delivery is a key early life event to influence its maturation. Rising rates of early term CS and induced labour before CS bring to the forefront the potential long-term impact of labour and delivery decisions in Canada. In light of these emerging trends, we present a focused examination of the evidence on the risk for asthma associated with CS delivery, with a lens on pre-labour and labour events in relation to the maternal and infant gut microbiome. Our review considers the influence of early term birth, PROM, and duration of labour on the microbiomes of the placenta, amniotic fluid, and vagina. From compositional changes in the placental or amniotic fluid microbiome with early gestation to the alkalinization of vaginal microbiota with PROM, all of these factors may affect initial seeding of infant gut microbiota and elevate the risk for future asthma. The labour process may additionally affect gut microbial colonization of the newborn by influencing the maternal transfer of immune cells and C-reactive protein. To conclude, a genuine possibility exists that pre-labour and labour factors affect maternal, fetal, and infant microbiomes. With rising rates of early term birth and birth without labour, several of these risk factors may gain prominence. As new information surfaces on trends for obstetric practices involving labour,[1] a deeper scrutiny of their impact on the newborn microbiome is required.

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