OBSTETRICS

Cesarean section and development of the immune system in the offspring

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This review examines the relation between the mode of delivery and development of the immune system in the offspring. Recent epidemiological studies provide evidence that elective cesarean section (CS) is associated with aberrant short-term immune responses in the newborn infant, and a greater risk of developing immune diseases such as asthma, allergies, type 1 diabetes, and celiac disease. However, it is still unknown whether CS causes a long-term effect on the immune system of the offspring that contributes to compromised immune health. With the dramatic increase in the rate of CS today, a greater emphasis should be placed on the discussion among both professionals and childbearing women on potential consequences of CS on the health of the offspring.

Key words: cesarean section, delivery, immune system, offspring

The worldwide rate of cesarean section (CS) has quadrupled in <2 decades,[1,2] making CS the most common surgical procedure performed in women of childbearing age today. The World Health Organization recommends that in up to 15% of deliveries, CS may be indicated.[3] However, 37 of 60 developed countries currently exceed this recommendation.[4] The rate of CS is currently 25% in the United Kingdom and Canada, 32% in the United States, 40% in China, and 46% in Brazil,[5-7] suggesting that in many settings, women are undergoing prelabor, elective CS without a clear medical indication.

This rapid change in mode of delivery probably reflects the widespread notion that CS is life saving and prevents injury to both the mother[8] and her baby.[9] The rise in parental requests for CS is also boosted by a worrying increase in fear for childbirth[10,11] and at the same time, both professionals and parents tend to choose CS for reasons of convenience and better control over the timing of delivery.[12,13] Finally, financial incentives may promote hospitals and physicians to favor CS at the expense of vaginal delivery.[14]

Currently, the emphasis of discussion and counseling around mode of delivery is on the benefits and potential harms for the pregnant woman herself.[15,16] As for her infant, the risks with vaginal delivery are often underlined, whereas only 2 of 3 women are reported to have discussed neonatal problems after elective CS.[15,16] To date, implications of delivery mode for the future health of the offspring is seldom discussed, mainly due to a lack of existing information. With the increasing number of children and young adults who have been delivered by CS, however, this gap in knowledge needs to be addressed.

Given the established evidence that environmental influences during early life shape the developmental trajectory of the offspring and alter the risk of disease in adulthood,[17,18] it is no longer unintelligible to see how changes from fetal to neonatal life may play a role in future health. The purpose of this review is to explore the evidence for an impact of the mode of delivery on activation and development of the immune system in the offspring. The focus will be on recent epidemiological links between mode of delivery and immune disorders in later life. We will also highlight some of the underlying mechanisms by which the mode of delivery may shape the immune system for life.

Search methods

This review was prepared by conducting a search in MEDLINE to identify relevant English-language articles published before March 2012. Search words included variations of "cesarean section," "delivery," "immune system," "asthma," "allergy," "diabetes," "celiac disease," "skeletal disease," and "cancer." Additional articles were found by a manual search from the references cited in relevant reviews, letters, and editorials.

Observations in human beings

CS and later risk for asthma

A metaanalysis of 23 studies has shown that children and adults born by CS have a 20% higher risk of developing asthma compared to those born vaginally.[19-28] This association remained after adjustment for known confounders such as maternal smoking, low birth weight, and duration of breast-feeding. The overrisk of asthma in children born with CS in 2 studies was confined to those diagnosed age <3-5 years, suggesting that the etiology in early- and late-onset asthma may differ.[20,29] The more difficult neonatal respiratory adaptation after CS–sometimes causing neonatal lung disease[30]–may possibly contribute to these findings,[31] but it is unclear how such maladaptation mediates lung problems beyond the neonatal period.[24]

CS and later risk for allergy

Allergic rhinitis and atopy have been reported to be more prevalent in children born by CS.[26,32] Infants born by CS also

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have a higher risk of food allergy, given that the mother had a history of atopy.[33-35] In contrast, other studies found no association between birth by CS and childhood food allergy.[26,36] In a prospective cross-sectional study, infants born by CS had greater IgE-mediated sensitization when introduced to cow's milk compared to those vaginally born.[37]

CS and later risk for type 1 diabetes mellitus

A metaanalysis summarizing 20 studies has shown that children born by CS have a 23% higher risk of developing childhood-onset type 1 diabetes compared to those vaginally born.[38-43] This association was not altered by adjusting for confounders such as maternal age, birth order, birth weight, gestational age, breast-feeding, maternal diabetes, or family history.

CS and later risk for gastrointestinal disease

Increased hospitalization for gastroenteritis in infancy has been linked to birth by CS.[23] In addition, an increased risk for celiac disease has been reported in children born by CS compared to vaginal delivery.[44,45] However, the risk of inflammatory bowel disease was not affected by mode of delivery.[44] These findings indicate that CS may impact the gastrointestinal function in the offspring in later life.

CS and later risk for skeletal disease

Birth by CS has been associated with a 36% overrisk for later aseptic necrosis of the femoral head (Legg-Calvé-Perthes disease) in childhood, even after adjusting for breech presentation of the fetus at the time of delivery.[46]

CS and later risk for cancer in the young

There are some indications for an increased risk for cancer (leukemia, neuroblastoma, testicular cancer) in children and young adults born by CS compared to vaginal delivery[47-49] although these associations have been unconfirmed or contradicted in other studies.[50-52] It is possible that the discrepancy in results is due to various maternal factors such as vitamin intakes[53] and smoking status[54,55] during pregnancy, although this was accounted for in 1 study.[47]

Strengths and limitations of the epidemiological evidence

Several of the observational studies in human beings are of high quality being prospective, population-based, and sufficiently large for multivariate analyses, adjusting for known confounders. Still, the strength of the epidemiological evidence should be considered with some caution. Epidemiological findings suggesting a long-term impact of CS on the risk of developing immune disease may be limited due to heterogeneity of study results stemmed from confounding variables that are difficult to control for, such as use of anesthetic agents and antibiotics during CS, diet, hospital environment, as well as genetic diversity of study populations.[31,56]

Anesthetic drugs used during CS are thought to cross the placental barrier and alter the immune system of the offspring.[57] Although the physical response of anesthetics on immune markers in newborns delivered by CS is not clear, previous reports have shown that general anesthesia lowers neutrophil respiratory burst test of cord blood compared to regional anesthesia.[58] Given that general anesthesia has long since been abandoned in many countries in favor of regional (spinal or epidural) anesthesia in both elective and emergency CS, it is unlikely that adverse effects of general anesthesia on the immune system could be the sole explanation for long-term health effects in the offspring.

Many studies conducted to date do not distinguish between prelabor elective CS and emergency CS after onset of labor, performed in deliveries that are complicated by fetal distress. In studies that have separated the 2 types of CS, an increased risk for later immune disease was confined to those delivered by prelabor CS.[45] Assuming that this would be valid also for other outcomes, mixing prelabor and emergency CS would introduce a conservative bias and underestimate any effect of prelabor CS on later health outcomes.

Mode of delivery and immune biomarkers

Several studies have identified differences in blood biomarkers following CS compared to vaginal birth.[59] Infants born by prelabor CS have been found to have a lower leukocyte count[60] as well as lower subpopulation counts of neutrophil, monocyte, and natural killer (NK) cells in cord blood.[61,62] Furthermore, cord blood leukocytes of babies born by CS had lower in vitro transmigration ability and expression of cell surface adhesion molecule CD11b/CD18,[63,64] and reduced levels of NK ($CD3^-/16^+/56^+$) cells compared to those vaginally delivered.[65] In addition, the activity of leukocytes[63,64] as well as their proinflammatory cytokine release such as interleukin (IL)-4r, IL-1β, IL-6, and tumor necrosis factor (TNF)-α[66,67] were lower after CS compared to vaginal delivery, thereby hampering immune cell functions.[68,69] However, these results are inconsistent with no difference observed in fecal human β-defensin 2 and TNF-α concentrations of infants born by CS compared to vaginal delivery.[70]

Higher risk of immune-related disorders following delivery by CS may be due to persisting differences in immune components.[31] In line with this suggestion, 1-year-old infants born by CS have been found to contain a greater number of immune cells secreting IgA and IgG compared to those vaginally born.[59] The atopic responder type has been characterized by an increased production of immunoglobulins,[71] providing a possible link between CS and compromised immune health.

Experimental evidence

CS and altered gene expression in the immune system

Investigation into the role of CS in immune development using animal models is limited. The paucity of experimental data may be due to the lack of appropriate animal models or strains to study effects of mode of delivery. In the piglet liver, prelabor CS resulted in lower gene expression of interferon (IFN)-γ, NKp80, and C-reactive protein.[72] Although serum concentrations of inflammatory markers in piglets born by CS did not

differ significantly compared to those vaginally born, there was a trend for lower levels of IFN-γ and higher levels of TNF-α[73] and a reduced activation of proinflammatory cytokine IL-6.[56] These findings suggest that mode of delivery can alter gene expression with a functional significance for the innate immune system.

CS, dopamine, and immune function in the rat

Studies using the rat have demonstrated that the mode of delivery impacts the central nervous system,[74,75] which may alter immune function of the offspring in later life. Rats born by CS had greater dopamine D1 receptor binding in limbic areas of the brain compared to those born by vaginal delivery.[76] Although no study using rodent models has directly related alterations of dopamine receptor in the brain to the immune system, dopamine is known to be involved in the regulation of lymphocyte and T-cell activities.[77] Furthermore, dopamine may be involved in lymphocyte activation at birth, suggested by its association with the level of IFN-γ.[63] Accordingly, CS may alter the normal developmental trajectory of dopamine receptors and progressively increase their binding pattern in adulthood, which may modulate immune function.[76]

Mechanisms

Mode of delivery is thought to influence the development of the immune system in the offspring by several pathways, which include: (1) variation in bacterial colonization of the intestinal tract; (2) different levels of adaptive stress of being born; and (3) altered epigenetic regulation of gene expression (Figure).

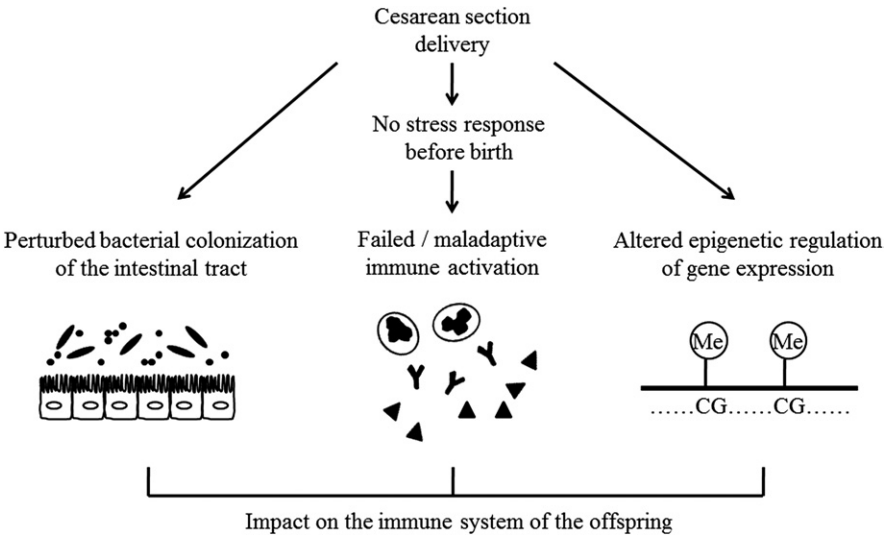
Mode of delivery and bacterial colonization of the gut–the hygiene hypothesis

The hygiene hypothesis proposes that improper bacterial exposure in early life contributes to a greater risk of developing immune diseases.[78] It is thought that the bacteria that newborns are first exposed to may alter their immune development.[79] Newborns delivered vaginally are colonized by bacteria from the mother's birth canal and perianal region, whereas those born by prelabor CS are predominantly colonized by bacteria originating from the hospital environment and nonmaternal skin.[80-82] CS infants more often have longer hospital stays and spend more time separated from their mothers, resulting in delayed breast-feeding[83] compared to those born vaginally, all of which alter the bacterial colonization and growth in the neonatal gut.[84,85]

Neonatal intestinal bacterial colonization primes the immune system and changes the balance between T-helper type 1 and 2 cells.[78] The deviant intestinal colonization of infants born by CS may prolong postnatal immunological immaturity, prevent appropriate immunological priming, and thereby increase the risk for later immune disease.[86] Cross-sectional and longitudinal studies have demonstrated that allergic children are characterized by lower intestinal colonization of bifidobacteria and *Bacteroides species* and higher colonization of clostridia compared to nonallergic children.[87] Interestingly, several reports have suggested that children born by CS have a similar pattern of bacterial colonization as those with atopic dermatitis.[82,88,89]

Prelabor CS decreased bacterial diversity and density in piglets, compared to vaginal delivery.[56] Infants born by CS had a lower total count of gut bacteria at 1 month of age[59] and the gut bacterial flora remained disturbed for up to 6 months.[82] CS was associated with altered composition of intestinal microbes even 7 years after birth, compared to vaginal delivery.[90] Accordingly, there is growing evidence that the intestinal microflora plays an essential role in the development of the immune system.[91] The influence of CS on bacterial colonization of the gut may, however, be incompletely understood using fecal samples as a surrogate measure for the entire gut bacterial population.[92] Moreover, variations in gestational age at birth and differences in postnatal diets also make interpretations difficult.[56] Finally, it is important to note that both the mother undergoing CS and her infant are more likely to be treated with antibiotics. As antibiotics can perturb the intestinal microflora for

FIGURE
Mechanisms by which mode of delivery may influence immune system



Cesarean delivery may affect immune system of offspring by: (1) perturbing bacterial colonization of gut; (2) mounting poor and maladaptive stress response; and (3) altering epigenetic regulation of gene expression through DNA methylation on cytosine-phosphate-guanine (CpG) dinucleotides. Stress is also thought to influence epigenome.

Me, methylated; *CG,* cytosine-guanine.

Cho. Cesarean section and immune system of offspring. Am J Obstet Gynecol 2012.

years,[93,94] antibiotic treatment in conjunction with delivery by CS could be a confounding factor in many epidemiological studies.

The stress of being born and later immune function

Another mechanism that may underlie the differences in immune responses between CS and vaginal delivery may be altered levels of stress hormones at birth. Contraction of the uterus and fetal hypoxia during vaginal delivery normally stimulate a significant stress response, as reflected by very high catecholamine and cortisol concentrations in neonates.[95] In contrast, infants delivered by CS before the onset of labor lack this surge of stress hormones.[96] It is well established that elevated circulating cortisol at birth is an indicator of hypothalamic-pituitary-adrenal axis activation.[97] Vaginal delivery and its effects on elevating glucocorticoids have been associated with increased maturation of the organs, including the gut.[56] With already shortened gestational length (elective CS is typically performed ≤39 weeks of gestation), a lack of stress hormone surge and poor activation of hypothalamic-pituitary-adrenal axis consequently result in a less mature immune system than after vaginal delivery. Furthermore, stress experienced at birth is immediate in infants delivered by prelabor CS, whereas it evolves gradually for those born by vaginal delivery. This difference in timing could also contribute to a maladaptive immune response after CS, which may affect the immune system in later life.[31]

Mode of delivery and epigenetics

Adverse prenatal and perinatal stress may permanently alter neuroendocrine and behavioral responses.[98] A novel mechanism for such adaptive responses is epigenetic regulation, in which early gene expression can be modified in response to environmental exposure without altering the DNA sequence.[99] The best studied epigenetic control mechanism is DNA methylation, which has been shown to play a crucial role during fetal development and to be one of the determinants of health and disease in the offspring in later life.[100,101]

Experimental studies on the effects of adverse neonatal stress have demonstrated epigenetic alterations via DNA methylation of glucocorticoid receptors in the hippocampus of mature offspring, resulting in higher stress sensitivity that extends into adulthood.[102] Furthermore, human infants delivered by prelabor CS had higher global DNA methylation in cord blood cells at birth compared to those born by vaginal delivery.[103] These results suggest that the epigenome of a newborn and developing infant is sensitive to experiences at birth. It has been suggested that early adverse gene methylation may be involved in silencing the pathway that regulates the balance between T-helper type 1 and 2 cells, which could contribute to a greater risk of developing immune diseases.[104] However, the role of epigenetic changes by CS in the development of the immune system and immune disorders still remains speculative.

Conclusion

Birth may be a critical time point that determines immune health of the offspring in later life. Existing data suggest that prelabor CS is associated with aberrant short-term immune responses such as reduced expression of inflammatory markers in the newborn infant. Children born by prelabor CS also face a greater risk of developing immune diseases such as asthma, allergies, type 1 diabetes, and celiac disease. However, it is still unknown whether CS causes a long-term effect on the immune system of the offspring that contributes to compromised immune health.

The potential mechanisms by which CS can impact the development of the immune system may work at the level of intestine by altering bacterial colonization, or may be related to an adverse birth stress response and epigenetic modification of gene expression in the immune system.

As for the clinical significance of these findings, we should not discontinue an everyday procedure that in an emergency can be truly life saving, and in many circumstances, constitutes a preventive measure with clear and sound cost-benefit ratio. However, it is time to leave the sometimes 1-sided perspective that seems to drive and justify the current epidemic of CS. A higher awareness among both professionals and childbearing women about the associations between elective CS and adverse health of their offspring is warranted. CS should not be recommended without a clear medical indication, or without a solid evaluation of harms and benefits, both for the mother and her baby. In such evaluation, both short- and long-term consequences for the infant and the child should carry a greater weight than what is considered today. ■

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