OBSTETRICS

Cesarean delivery and hematopoietic stem cell epigenetics in the newborn infant: implications for future health?

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OBJECTIVE: Cesarean section (CS) has been associated with a greater risk for asthma, diabetes, and cancer later in life. Although elective CS continues to rise, it is unclear whether and how it may contribute to compromised future health. Our aim was to investigate the influence of mode of delivery on the epigenetic state in neonatal hematopoietic stem cells.

STUDY DESIGN: This was an observational study of 64 healthy, singleton, newborn infants (33 boys) born at term. Cord blood was sampled after elective CS (n = 27) and vaginal delivery. Global deoxyribonucleic acid (DNA) methylation in hematopoietic stem cells (CD34+) was determined by luminometric methylation assay, and genome-wide, locus-specific DNA methylation analysis was performed by Illumina Infinium 450K (Illumina, San Diego, CA), validated by bisulfite-pyrosequencing.

RESULTS: CD34+ cells from infants delivered by CS were globally more DNA methylated (+2%) than DNA from infants delivered vaginally ($P = .02$). In relation to mode of delivery, a locus-specific analysis identified 343 loci with a difference in DNA methylation of 10% or greater ($P < .01$). A majority of the differentially methylated loci in neonatal CD34+ cells (76%) were found to be hypermethylated after vaginal delivery. In these infants, the degree of DNA methylation in 3 loci correlated to the duration of labor. The functional relevance of differentially methylated loci involved processes such as immunoglobulin biosynthetic process, regulation of glycolysis and ketone metabolism, and regulation of the response to food.

CONCLUSION: A possible interpretation is that mode of delivery affects the epigenetic state of neonatal hematopoietic stem cells. Given the functional relevance indicated, our findings may have important implications for health and disease in later life.

Key words: cesarean section, delivery, epigenetics, methylation

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Cesarean section (CS) rates increase rapidly worldwide. Today CS is the most common surgical procedure performed in women of child-bearing age.[1,2] In up to 15% of deliveries, CS may be indicated according to recommendations from the World Health Organization.[3] However, most countries exceed this recommendation, suggesting that many women are undergoing CS without a medical indication.[4] Although short-term outcomes after CS are well characterized,[5] the basis for suggested long-term consequences of this global change in childbirth is mostly unknown.

Recent clinical and epidemiological studies have shown that birth by CS is associated with a greater risk of developing diseases later in life, such as asthma, allergies,[6] type 1 diabetes,[7] celiac disease,[8] obesity,[9] and malignancies.[10-12] Although known confounders have in many of these studies been accounted for, it is still unclear whether and how CS may compromise health in the offspring.[13,14] The lack of appropriate gut colonization and microbiome exposure, the lack of the immune-activating effects of labor, and epigenetic changes that may modify the immune system have all been suggested as mechanisms for CS-related effects on health and disease risk.[12]

We previously found support for altered epigenetic states in blood cells from newborns delivered by elective CS compared with those vaginally born.[15] Epigenetic states provide mechanisms for the functional genome and mediate adaptations to a dynamic environment.[16-18] Epigenetic deoxyribonucleic acid (DNA) methylation may retain its stability for the cells' lifetime, even through divisions. Accordingly, DNA methylation and epigenetic cell memory associated with the mode of delivery could be mechanisms for later differences

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in disease risk, especially if these occur and are propagated in progenitor cells.

Before a more conclusive answer can be given on an epigenetic memory of birth, several important questions remain to be resolved. We hypothesized that DNA methylation in neonatal stem cells differs in relation to mode of delivery and between different genes/gene regions. Data presented herein suggest that CS is associated with altered epigenetic states of neonatal CD34+ hematopoietic stem cells, involving differential DNA methylation of genes/gene regions relevant for later immune-mediated diseases.

TABLE
Subject characteristics of participants (n = 64)

Characteristic	CS (n = 27)	VD (n = 37)	*P* value
Maternal age, y[a]	37 (25–43)	34 (23–41)	.03
Prepregnancy BMI, kg/m^2	22.9 (18.9–33.4)	22.7 (15.9–38.4)	.75
Parity, n	2 (1–4)	2 (1–4)	.19
Gestational age, wks[b]	38.9 (37.7–39.9)	40.3 (37.6–42.0)	< .001
Birthweight, g	3625 (2820–4645)	3675 (2985–4915)	.97
Infant sex, girls/boys	11/16	20/17	.32

Data are presented as median value with interquartile range or as proportion. SI conversion factors: to convert birthweight to kilograms, divide values by 1000.

BMI, body mass index; *CS*, cesarean section; *SI*, International System of Units; *VD*, vaginal delivery.

[a] Maternal age higher in the CS group ($P = .03$); [b] Gestational age shorter in the CS group ($P < .001$).

Almgren. Epigenetics in stem cells after cesarean section. Am J Obstet Gynecol 2014.

Materials and Methods

Participants

Pregnant women were recruited at the delivery units at Danderyd Hospital in Stockholm, Sweden. Multiple pregnancies, maternal diabetes or gestational diabetes, maternal hypertension, preeclampsia, smoking during the index pregnancy, preterm delivery (gestational age <37 weeks), small-for-gestational-age infants (birthweight ≥2 SD below the mean for a Swedish reference population,[19] neonatal asphyxia (Apgar score <7 at 1 and 5 minutes), malformations, chromosomal disorders, or congenital infection were all exclusion criteria. No pregnancy resulting from assisted reproductive technology was included in the study.

For measurement of global DNA methylation by luminometric methylation assay (LUMA) in cord blood stem cells, we included 40 infants (18 girls) to women delivered by elective CS before the start of labor and under spinal analgesia, and as reference group, 49 infants (22 girls) born after spontaneous, nonassisted vaginal delivery (VD) were included. After cell separation and DNA extraction from stem cells (see the following text), 43 samples (18 CS and 25 VD) contained sufficient DNA (>500 ng DNA) for methylation analyses.

In the VD group, the start of labor was defined as the time point at which the pregnant woman for the first time perceived regular (3-4 per 10 minutes) and painful uterine contractions. When admitted to the hospital, all women were asked about the time point (hours and minutes) for the start of labor. If labor had not started before admission, the start of labor was noted by the attending midwife. Deliveries with induction of labor were not included in this study.

Indications for CS included maternal request, previous CS, breech position, or pelvic disproportion. In the VD group, the median duration of labor was 14.5 hours (range, 1–53 hours), and the median duration of ruptured membranes was 4 hours (range, 0–17 hours).

Because of exhausted blood samples from the first group, a second group of infants was recruited. Cord blood from 12 infants (6 CS) was used to fill 1 Illumina 450K array (Illumina, San Diego, CA) to measure genome-wide, locus-specific DNA methylation. The DNA content in 9 of these blood samples was sufficient for subsequent validation analysis using bisulfite pyrosequencing. To increase the numbers and power of the validation analysis, we recruited an additional 10 infants (4 CS) to the second study group. There were no differences in maternal characteristics, gestational age (GA), sex distribution, or birthweight between the first and second study groups.

In the whole cohort of 64 mothers, the median maternal age was 35 years (range, 23–43), the body mass index (BMI) was 22.8 kg/m^2 (range, 15.9–38.4), and 17 of 64 mothers were primigravida. The GA was 39.2 (range, 37.6–42) weeks, and all infants had birthweights appropriate for gestational age (3667 g; range, 2820–4915 g).

Mothers in the CS group (n = 27) were older compared with mothers in the VD group (n = 37) (37 [range, 25–43] vs 34 [range, 23–41] years; $P = .03$), and GA was shorter in the CS group compared with the VD group (38.9 [range, 37.7–39.9] vs 40.3 [range, 37.6–42.0] weeks; $P < .001$). Maternal and infant characteristics by mode of delivery for LUMA, Illumina, and bisulfite pyrosequencing groups are presented in the Table.

The regional ethical review board approved the study protocol and informed consent was obtained from parents before birth (number 2010/440-31/4; 2012/1029/32).

Blood sampling and preparation of hematopoietic stem cells

In all participating infants, 15-20 mL blood was sampled in EDTA tubes from the umbilical cord directly after cord clamping. The cord was clamped after 30 seconds to obtain the targeted volume of cord blood. Blood cells were sorted with commercially available tools (Dynabeads positive isolation kit; Invitrogen by Life Technologies Corp, Carlsbad, CA) to separate CD34+ stem cells from other DNA-containing cells. DNA in stem cells was extracted using Illustra DNA extraction (GE Healthcare

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