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The impact of delivery mode on epigenetic changes in newborns and their health outcomes

Vplyv spôsobu pôrodu na epigenetické zmeny u novorodencov a ich zdravotné následky

Z. Turcsányiová, P. Gašparová, Z. Ballová, E. Dosedla

Department of Gynaecology and Obstetrics, Faculty of Medicine, Pavol Jozef Safarik University in Košice, Hospital AGEL Košice-Šaca Inc., Slovak Republic

Summary: Recent decades have seen a notable increase in cesarean section rates. Although lifesaving, cesarean delivery is associated with an elevated risk of adverse health outcomes in newborns, including respiratory diseases, atopic disorders, obesity, diabetes, and severe autoimmune conditions. The exact mechanisms underlying these associations remain elusive; however, epigenetic modifications have emerged as a plausible molecular basis linking perinatal factors with future disease susceptibility. This review summarizes current literature, revealing that the delivery method may influence epigenetic markers in neonates, primarily through alterations in global DNA methylation and gene-specific methylation patterns.

Key words: epigenetics – DNA methylation – cesarean section

Súhrn: V posledných desaťročiach sme zaznamenali výrazný nárast počtu cisárskych rezov. Hoci je pôrod cisárskym rezom život zachraňujúci, je spojený so zvýšeným rizikom nepriaznivých zdravotných následkov u novorodencov, vrátane respiračných a atopických ochorení, obezity, cukrovky a závažných autoimunitných ochorení. Presné mechanizmy, ktoré sú základom týchto spojitostí zostávajú nepochopené; epigenetické modifikácie sa však ukázali ako pravdepodobný molekulárny základ spájajúci perinatálne faktory s budúcou náchylnosťou na ochorenie. Tento prehľad spája súčasnú literatúru a odhaľuje, že spôsob pôrodu môže ovplyvniť epigenetické markery u novorodencov, predovšetkým prostredníctvom zmien globálnej metylácie DNA a génovo špecifických metylačných vzorcov.

Kľúčové slová: epigenetika – metylácia DNA – cisársky rez

Introduction

In recent decades, the incidence of cesarean sections (C-sections) has surged globally, becoming the most frequent surgical intervention among women. According to a report by The Lancet, the global rate of C-sections increased from 12.2% in 2000 to approximately 21.1% by 2015 [1]. Notably, countries such as Brazil, Cyprus, and the Dominican Republic have reported C-section rates exceeding 50%, with more than 26 countries worldwide surpassing the 30% mark [2]. This upward trend can be attributed to a combination of anatomical and evolutionary changes, including a rise in cephalopelvic disproportion, genetic factors, and significant environmental shifts over the years. Improved living conditions and maternal nutrition have contributed to an increase in maternal body mass index (BMI) and the age at which women have their first child. These factors are associated with a higher prevalence of diabetes with diabetic fetopathy, fetal macrosomia, and maternal hypertensive disorders [3,4].

The escalating prevalence of C-sections has sparked considerable scientific interest in examining the procedure's implications for children's health and development. While C-sections can be lifesaving, they significantly alter the physiological processes inherent to spontaneous vaginal birth. Newborns delivered via C-section are exposed to a variety of hormonal, physical, bacterial, and medical interventions, including intrapartum antibiotics and uterotonics, which can subtly influence physiological outcomes [5]. A critical aspect of C-sections is the marked reduction in childbirth-related stress [6]. Elective C-sections, performed before labor onset, interrupt the natural release of catecholamines, potentially leading to immune system maladaptation [7]. Immediate consequences for the newborn

may include altered immune reactivity, diminished inflammatory marker expression, and an elevated risk of developing hypersensitivity, skin atopy, asthma [8–10], and decreased intestinal microbiome diversity [11–14]. The long-term persistence of these risks is not well-understood [5]. Numerous epidemiological studies have identified an association between C-section delivery and an increased risk of autoimmune responses later in life, including type 1 diabetes [15,16], inflammatory bowel diseases, celiac disease [17], allergies [18], metabolic syndrome, obesity [19–23], arterial hypertension, and certain malignancies such as leukemia [24,25] and neuroblastoma [26,27] in childhood and adolescence.

The mechanisms by which delivery mode impacts the development of immunity and the incidence of immune-related diseases in children are not fully elucidated. Specifically, the reduction in childbirth stress associated with C-sections, which may result in immune system maladaptation, has been linked to epigenetic alterations in gene expression regulating white blood cells. Such alterations are referred to as epigenetic changes when they occur at the gene expression level. Epigenetic mechanisms, which include DNA methylation, histone modification, and the activity of non-coding RNA molecules, regulate gene expression without altering the DNA sequence, leading to changes in gene activity or function due to epimutations. Studies suggest that the mode of delivery may trigger epigenetic modifications that influence immunological processes in children during the postnatal period [28–34]. Among the various epigenetic control mechanisms, DNA methylation is the most extensively studied. Unlike true genetic mutations, which are generally random and irreversible, epigenetic changes are often reversible and modifiable. Nonetheless, epigenetic DNA methylation can remain stable throughout a cell's life and across cell divisions. DNA methylation and the epigenetic cellular memory associated with the mode of delivery could constitute a molecular mechanism for later development of immune-related diseases, particularly if DNA methylation occurs in progenitor cells [30]. Epigenetic programming is most active during the fetal period and extends from conception until the child reaches two years of age, making the first 1,000 days critical [35,36].

The epigenome's responsiveness to environmental factors, including the conditions of delivery, suggests that altered fetal or neonatal epigenetic modifications may influence susceptibility to diseases later in life [37–39]. Global DNA methylation pattern measurements serve as a practical approach for detecting different epigenetic effects in neonates. This review aims to provide a comprehensive overview of studies focusing on changes in DNA methylation in the newborns' blood, depending on the mode of delivery.

DNA methylation changes

The earliest documentation of a correlation between elective cesarean section and elevated DNA methylation levels at birth compared to vaginal delivery was introduced by Schlinzig et al. in 2009 [28]. This foundational study included 37 healthy newborns, comprising 21 spontaneous vaginal deliveries and 16 elective cesarean sections. By analyzing DNA extracted from white blood cells in umbilical cord blood immediately after birth and again during the third to fifth round of routine newborn screening, they discovered significantly higher global DNA methylation levels in the cesarean section group at birth. However, these levels stabilized in newborns delivered vaginally when assessed from birth to 3–5 days postnatally. Although the cesarean section group experienced a reduction in DNA methylation levels by days 3–5, making them comparable to vaginal delivery levels, the epigenetic adaptation observed post-cesarean did not achieve the physiological benchmarks observed in vaginal deliveries, indicating a potential deviation in epigenetic activity. The study, however, was limited by its small sample size [28].

Expanding on this work, Virani et al. (2012) [40] assessed global methylation in a larger cohort (408 births), exploring the association between delivery type and epigenetic alterations. This study differentiated between spontaneous vaginal, elective cesarean, and emergency cesarean deliveries post-labor onset. Using DNA isolated from cord blood, the study employed two global methylation measurement techniques – Luminometric Methylation Assay (LUMA) and LINE-1 methylation assay – to enhance result reliability. The findings indicated significantly lower DNA methylation levels in cesarean deliveries, both planned and total, compared to vaginal deliveries. However, these associations dissipated after adjusting for maternal age, smoking, and infant gender, suggesting that while delivery mode may influence health outcomes, global genomic methylation might not be the underlying mechanism. This study also noted limitations, including the lack of adjustment for critical perinatal and maternal factors potentially influencing fetal epigenetic modifications.

A Polish study by Słabuszewska-Jóźwiak (2020) [31] involved 111 pregnant women identifying notably lower DNA methylation levels in elective cesarean deliveries compared to vaginal and intrapartum cesarean deliveries. This study was unique in its examination of global DNA methylation levels in placental tissue, rather than in cord or peripheral infant blood, unveiling the impact of uterine contractions prior to cesarean delivery on DNA methylation levels [31,40] and demonstrating sexual dimorphism in placental global DNA methylation. As an ongoing pilot study, the outcomes of neonatal follow-up promise further insights.

Franz et al. (2014) [32] conducted a prospective pilot study with 41 neonates, comparing global methylation and methylation of 96 individual genes between spontaneous and elective cesarean deliveries. This investigation found no significant differences in global methylation based on delivery mode but identified specific genes with hypermethylation patterns. Notably, genes related to T cell activation and inflammatory responses exhibited lower methylation in vaginally born infants, suggesting enhanced gene activity [32]. Despite its strengths, including stringent inclusion criteria and a well-characterized cohort, the study's small sample size was a limitation.

In China, where cesarean delivery rates are among the highest globally [41], a study compared DNA methylation in cord blood following maternal-request cesarean deliveries without medical indications to spontaneous vaginal deliveries [33]. Analyzing 70 cases each, through both Illumina Infinium Human Methylation 450 K BeadChip and targeted bisulfite sequencing, the study identified 165 differentially methylated positions associated with immune system development. After adjusting for cell type proportions, significant differences in DNA methylation between groups were minimal, aligning with prior research findings [33].

A recent Turkish study found no significant differences in global DNA methylation between delivery modes [34]. However, it reported a significant increase in global DNA methylation levels associated with maternal age over 30 in both mothers and infants. Focusing on the PTEN gene, known for its role in cellular functions and epigenetic diseases [42–45], the study observed higher methylation rates in the cesarean delivery group, suggesting potential implications for disease susceptibility.

An observational study [30] examining the effect of delivery mode on neonatal hematopoietic stem cell epigenetics identified differential DNA methylation patterns that could influence lifelong disease susceptibility. The study highlighted the modulation of genes related to immunoglobulin biosynthesis and metabolic regulation, suggesting that labor duration and the delivery mode significantly impact DNA methylation.

Further expanding on this research, Schlinzig et al. (2017) [29] analyzed immune deficiency markers in 6014 newborns, adjusting for perinatal and maternal factors. The study suggested that elective cesarean sections might affect the formation of new T- and B-lymphocytes, a hypothesis requiring further exploration for its immunological implications.

Lastly, experimental studies [45] on neonatal stress in rats have linked DNA methylation changes in glucocorticoid receptors to increased stress reactivity, underscoring the need for continued investigation into the epigenetic impacts of birth mode on health outcomes.

Discussion

The correlation between the increasing prevalence of cesarean deliveries and the incidence of immune-related disorders is an area of growing concern and investigation. The hypothesis that variations in DNA methylation between individuals born via cesarean section versus those born vaginally may explain the potential long-term health effects of cesarean sections is particularly compelling. Aberrant DNA methylation patterns are linked to a range of immune deficiencies and autoimmune diseases, highlighting the importance of understanding the epigenetic consequences of birth modes [46].

Although several studies have explored the relationship between DNA methylation changes and delivery methods, inconsistencies in their findings – attributable to diverse research methodologies – offer a complex but intriguing picture. Current literature, after adjusting for confounding variables, generally shows no significant differences in global DNA methylation between cesarean and vaginal delivery groups [28,32,34,40]. However, Almgren et al.'s analysis of CD34+ hematopoietic stem cells stands out, revealing a notable impact of delivery mode on global DNA methylation patterns, with cesarean-delivered newborns exhibiting higher levels of DNA methylation compared to vaginally delivered infants [30]. This discrepancy highlights the importance of cellular context in epigenetic studies, as Almgren et al.'s focus on CD34+ cells may account for their distinct findings.

Moreover, global methylation assessments do not preclude variations at the single-gene level. For instance, Franz et al. [32] detected hypermethylation in specific genes – *FOXP3, CD7, ELA2,* and *IRF1* – regardless of delivery mode, with notable differences in ELA2 and IRF1 methylation between cesarean and vaginal deliveries. This suggests that vaginal birth may activate these genes more effectively. Such genetic alterations have implications for various diseases [47–49], underscoring the necessity of examining methylation at both global and gene-specific levels.

In gene-targeted analyses, disparities in methylation patterns have been linked to immune system development and potential autoimmune disease risks. For example, Chen et al. [34] identified genes with significant implications for immune response development in newborns. Furthermore, Uslu Yuvaci et al. [34] found higher PTEN gene methylation rates in the cesarean delivery group, correlating with the concept of the "DNA methylation clock," which may be influenced by maternal age [50,51].

Almgren et al. also reported methylation changes related to glucose metabolism regulation, suggesting possible links to the increased risk of obesity and diabetes in individuals delivered by cesarean section [52–54]. Additionally, Schlinzig's work suggests that cesarean

delivery may affect the formation of T- and B-lymphocytes, potentially impacting future immunological functions [29].

In summary, while the mode of delivery is associated with later health outcomes, global genomic methylation might not be the sole mechanism involved. The complexity of epigenetic modifications, including those influenced by perinatal and maternal factors, highlights the need for a nuanced understanding of how delivery methods impact epigenetic programming and subsequent health risks.

Conclusion

The synthesis of findings across diverse studies highlights the complexity of comparing outcomes due to varied methodologies employed in assessing DNA methylation. A critical limitation across the board is the absence of longitudinal epigenetic assessments post-delivery. Since methylation patterns are dynamic over time, longitudinal data could significantly enrich the field of epigenetic epidemiology by providing insights into the temporal nature of these changes. Consequently, there is an imperative need for large-scale studies that monitor methylation profiles at various life stages to ascertain whether the influence of delivery mode on the epigenome emerges or persists later in life.

The existing body of research opens promising avenues for future investigations into the correlations between DNA methylation variations and health outcomes across the lifespan, particularly during adolescence and adulthood. It is crucial for subsequent studies to meticulously control for potential confounders, acknowledging that numerous environmental factors – ranging from tobacco exposure [55–57] and dietary habits to maternal stress [58] and pre-pregnancy obesity [59] – can influence both global and gene-specific methylation patterns.

Future research should pivot towards gene-specific analyses, particularly focusing on genes implicated in immune-related diseases. Exploring diverse gene panels may uncover additional genes that undergo aberrant methylation in newborns delivered via cesarean section as compared to vaginal delivery. Comprehensive evaluations of these genes in large cohorts are essential to determine if differential methylation levels are associated with distinct long-term health outcomes post-cesarean section. Continuous follow-up is necessary to conclusively determine whether cesarean delivery impacts DNA methylation in a manner that predisposes to disease later in life, including during childhood, adolescence, and adulthood.

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ORCID authors

Z. Turcsányiová 0000-0002-6376-0790
P. Gašparová 0000-0002-6354-6911
Z. Ballová 0000-0002-0605-948X
E. Dosedla 0000-0001-8319-9008

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Assoc. Prof. Erik Dosedla, MD, PhD, MBA
Department of Gynaecology and Obstetrics
Faculty of Medicine
Pavol Jozef Safarik University
Hospital AGEL Košice-Šaca Inc.
Lúčna 57
040 15 Košice-Šaca
Slovak Republic
erik.dosedla@nke.agel.sk