Review Article

NON-INDICATED SCHEDULED CAESAREAN DELIVERIES IN LOW-RISK PREGNANCIES HAVE HARMFUL EFFECTS ON GENE EXPRESSION AND IMMUNE FUNCTION

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ABSTRACT
Medicalised birth is increasing on a global scale. Scheduled caesarean deliveries have become the most common delivery mode in the South African private sector despite evidence that a vaginal delivery is the safest delivery mode in low risk pregnancies. Interventions at childbirth occur at a critical time for epigenetic influence, the assembly of the neonatal microbiome and downstream immune development. The perinatal events that may affect epigenetic influence include iatrogenic premature delivery, distress, bypassing of the vagina, separation of the mother-infant dyad, formula feeds, admission to a neonatal intensive care unit and antibiotics. Caesarean section delivery is associated with a list of long-term immune consequences. A scheduled caesarean section delivery often represents the initial event that will precipitate a domino-effect of altered early life exposures. The purpose of this review is to emphasise the roles of the fetal epigenome and microbiome in long term health and to highlight the harmful effects of a scheduled caesarean delivery on their integrity.

Keywords: scheduled caesarean section delivery, early life exposures, epigenome, microbiome, immune consequences

INTRODUCTION

Medicalised birth is increasing on a global scale. Questions are being raised about excessive interventions at childbirth as the perinatal period represents a critical time for epigenetic influence, the assembly of the neonatal microbiome and downstream immune development. The International Federation of Gynaecology and Obstetrics (FIGO) recently expressed discontent about a 'caesarean section epidemic' – a global increase in the caesarean section rate from approximately 6% in 1990 to 19% in 2014 – and warned specifically about its overuse in developing economies.[1] The South African private sector is at the forefront with the highest global caesarean delivery (CD) rate of more than 90% in most private healthcare facilities.[2]

Scheduled caesarean section deliveries (SCD) have become the most common delivery mode in the South African private sector despite evidence that a vaginal delivery is the safest delivery mode in low-risk pregnancies. Three out of four healthy women are transformed into surgical patients (by iatrogenic intervention), which sets the scene for an alternative early-life environment in their newborn infants. These include separation, formula feeds, admission to a neonatal intensive care unit (NICU) and the use of antibiotics. Three out of four infants are at risk of developing short- and long-term negative health consequences that could have been prevented by a safe vaginal delivery. In fact, no foetus – as the initiator of labour – anticipates a *prelabour* delivery which bypasses its orchestrated survival strategies initiated *in utero*. These ensure a seamless fetal–neonatal transition and the immediate availability of colostrum followed by effective lactation. Caesarean deliveries also bypass the vaginal passage, interrupt assembly of the microbiome and initiate *intrapartum* epigenetic processes that result in unfavourable fetal epigenomic modelling, which is perpetuated and has a harmful effect on the developing immune system. When a prelabour caesarean-delivered toddler develops immune dysregulation and dysbiosis presenting as repeated, prolonged episodes of a 'noisy chest' and a wet cough which interrupt activities and wake family members at night, the role of the delivery mode is ignored. Instead, multiple diagnoses such as bronchitis, upper-airway infection and asthmatic bronchitis are made with poor response to costly treatment. Sadly, the problem will most likely recur in the next pregnancy, because it will inevitably end in another SCD – because once a CD, usually always a CD.

The aim of this article is to emphasise the roles of the fetal epigenome and microbiome in long-term health and to highlight the harmful effects of a SCD as an early-life event on their integrity.

THE ARRIVAL OF THE 'OMICS' AND A BETTER UNDERSTANDING OF EARLY-LIFE EFFECTS ON THE ASSEMBLY OF A FAVOURABLE MICRIBIOME AND EPIGENOME

The genome of the fetus undergoes epigenetic remodelling in the form of DNA methylation and histone modifications throughout pregnancy and early life. In the absence of deleterious intrauterine stimuli such as smoking and alcohol, it becomes a predominantly favourable epigenome and it is responsible for gene expression independently of the underlying DNA sequence.

In the past decade, modern gene-sequencing technology and the development of a parallel mass-sequencing capability (such as metagenomics) have advanced the study of the genome, epigenome, microbiome and its molecular background on a cellular level. This encompasses genomics (gene detection), transcriptomics (transcription of mRNA) and proteomics (expression of proteins) in specific biologic samples. The science of these so-called 'omics' informs on the mechanisms that alter phenotypic expression without altering the underlying DNA sequence (epigenetic influence) and the reasons for it. Importantly, the 'omics' have enabled us to understand the epigenetic mechanisms by which peripartum events such as the induction of labour by synthetic oxytocin, the mode of delivery, the assembly of the microbiome and other early-life events may influence gene transcription to alter phenotypic expression and disease phenotypes.

The assembly of the microbiome starts *in utero* and spans labour and the vaginal passage to attain bacterial diversity characterised by large numbers. Integrity is maintained by immediate skin-to-skin contact, colostrum ingestion and exclusive breastfeeding. The cornerstone of assembly is the vaginal passage, where and when vaginal and colonic microbes are ingested. Within minutes of a vaginal birth, microbial colonisation of the infant's skin, nasopharynx and gastrointestinal tract (GIT) resembles that of the mother's vagina. The resulting favourable microbiome is maintained by the exclusive intake of breast milk.

The microbiome has a key influence on the immune function of a neonate. It is an essential component of the innate immune system and by promoting pathways of naïve T-cells, facilitates immune tolerance and the development of adaptive immunity.[3]

But the resulting epigenome is affected not only by a favourable microbiome. Labour and birth are characterised by surges of stress hormones such as cortisol, adrenocorticoids and oxytocin to facilitate a healthy stress response ('eustress') and a favourable epigenetic effect. A similar profile of stress hormones is understandably absent in a SCD, which leads to epigenetic effects because of 'dys-stress' and the physiological unpreparedness of the mother and infant for extra-uterine existence.[4]

SCHEDULED CAESAREAN DELIVERY AND HARMFUL EFFECTS

SCD is often the initial iatrogenic intervention that will initiate a downstream 'domino effect' of altered early-life exposures. SCD is performed before the spontaneous onset of labour. It interrupts organ maturation, physiological preparedness and passage through the vagina, and it may precipitate a host of downstream effects that have a further impact on the early microbiome and epigenome.

A SCD deprives the fetus of using its preparatory armamentarium for successful extra-uterine life. This includes labour onset, which announces organ maturity and perpetuates maturational–physiological processes that prevent, inter alia, hypothermia and hypoglycaemia, and clear lung fluid.[5] Instead, a newborn infant is delivered whose vulnerability demands medical interventions – analogous to denying someone a parachute prior to their jumping from an aeroplane. The end-result of vulnerability may indeed be fatal, as happens in some cases of persistent pulmonary hypertension in the neonate (PPHN) after an SCD.

Iatrogenic interventions which start with a SCD in a low-risk pregnancy may then have immeasurably harmful effects on the epigenome and microbiome apart from being undesirable, dangerous and potentially fatal.

DELIVERY OF A PREMATURE INFANT (<37 WEEKS)

In the presence of high rates of SCDs, the risk of delivering a premature infant 'unintentionally' prevails because of dating errors and changing the expected date of delivery during the pregnancy.

Infants face conditions which will affect their microbiome adversely. These include a harmful microbial environment induced by an NICU, non-maternal caregivers, antibiotics, alternative feeding strategies, medications and many more.

ADMISSION TO AN NICU

Up to 17.8% of infants born by an SCD – performed between 37 and 38 weeks and six days of pregnancy – require admission to an NICU[6] for respiratory distress, oxygen augmentation, hypoglycaemia and hyperbilirubinaemia. These conditions are a reflection of inadequate organ maturity because physiological preparedness is not in place.[7] These admissions are significantly more prevalent when SCDs are performed before 39 weeks of pregnancy.[7] NICU admission also has an adverse impact on skin-to-skin care and breastfeeding, and increases antibiotic exposure and 'dys-stress'.

ANTIBIOTICS

A CD is associated with a five- to tenfold increased risk of postpartum infection[8] and prophylactic antibiotics (cefazolin) should be administered 30–60 minutes before skin incision. This implies high antibiotic blood levels in a normal fetus before delivery. The price paid includes an association between prenatal antibiotic use and downstream obesity and asthma.[9]

DELAYED ROOMING IN

A CD is categorised as major abdominal surgery and has a six times higher risk for severe maternal morbidity compared to a vaginal delivery (aOR 5.93; 95% CI 3.88–9.05).[10] Post-operative pain and complications will have a negative impact on skin-to-skin care, breastfeeding and bonding ('dys-stress').

LACTATION FAILURE

All women who deliver by CD, but particularly those who have a SCD, are at high risk of impaired lactation performance.[11] The absence of the hormonal opulence associated with labour and parturition impair lactation, attachment and the ability to nurse and 'feel good' after delivery. The results of a systematic review and meta-analysis comprising 553 306 women revealed that up to 83% of mothers (OR 0.83; CI 95% 0.80–0.86) who did not go into labour before their CD will fail successful initiation of and sustained breastfeeding by the time of discharge from hospital.[12] The deprived microbiome associated with CD can, however, be restored partially by exclusive breastfeeding compared to mixed feeding.[13]

FORMULA SUPPLEMENTATION

Lactation failure, neonatal hypoglycaemia and reduced infant alertness necessitate supplementary feeds, which should comprise donor breast milk. However, because of its short supply, formula is administered, and that violates a basic human right of an infant to receive human milk. Independent associations exist six weeks after birth between the character of the stool microbiome for caesarean-delivered and vaginally delivered infants, and for breastfed and formula-fed infants.[14] The stool microbiome of infants who received both formula and breastmilk after birth resembled that of exclusively formula-fed infants. The promotion of exclusive breastfeeding after a CD is therefore paramount.

INCREASED RISK OF INFECTION OR ANTIBIOTIC USE

Caesarean-delivered infants are more likely to receive antibiotics for a presumed bacterial infection during the first years of life. In a Danish cohort of 1 921 children, the adjusted incidence rate ratio for hospitalisations because of infection in children born by SCD was 1.45 (95% CI; 1.16–1.80; p = 0.001) compared to vaginal birth at a mean age of 3.5 years.[15]

MEDIUM- AND LONG-TERM IMMUNE CONSEQUENCES ASSOCIATED WITH CAESAREAN DELIVERY

The absence of specific physiological processes during the antenatal, perinatal and neonatal periods and new insights into dysbiosis, altered early-life 'immune learning' and downstream immune consequences led to modifications to Strachan's[16] initial hygiene hypothesis. As an example, Rook[17] suggested that the neonatal gut acquires flora that have been inherited across generations and that a co-dependency has developed between these organisms and the human immune system. The assembly of these 'old friends' depends on the specific physiological processes during the antenatal, perinatal and neonatal periods.

When compared to vaginal birth, CD has been associated with chronic immune disorders such as asthma (aIRR 1.23; 95% CI, 1.21–1.25), systemic connective-tissue disorders (aIRR 1.22; 95% CI, 1.04–1.19), juvenile arthritis (aIRR 1.10; 95% CI, 1.02–1.18), inflammatory bowel disease (aIRR 1.2; 95% CI, 1.06–1.36) and leukaemia (aIRR 1.17; 95% CI, 1.00–1.36). A significantly higher risk for immune deficit and the recurrence of infections (aIRR 1.46; 95% CI, 1.32–1.62) is also noted.[18] Alternative colonisation of the infantile airway shows a significant association with later acute severe exacerbation of wheeze (HR 2.99; 95% CI, 1.66–5.39), persistent wheeze (HR 2.4; 95% CI, 1.45–3.99), hospitalisation for wheeze (HR 3.85; 95% CI, 1.90–7.79) and asthma diagnosis at five years of age (33% vs 10%).[19] The risk for asthma is reduced with a CD performed after the rupture of membranes,[20] whereas the risk for allergy increases twofold with a repeat CD – when the membranes are more likely to be still intact.[21]

The Global Initiative for Asthma (GINA) advice on the primary prevention of asthma includes the elimination of tobacco smoke during pregnancy and after birth, vaginal birth where possible, support for exclusive breastfeeding and the avoidance of broad-spectrum antibiotics during the first year of life.[22]

A low-risk pregnancy has indeed been transformed into a minefield of potential risks to the long-term health of both the infant and their mother; driven by multiple pathways and epigenetic effects which follow on from the initial falling domino that is the SCD.

CONCLUSIONS

The caesarean section rate in the South African private sector is unprecedented globally[2] and is not supported by reliable outcome data for both mothers and their infants.[23] While a fear of litigious circumstances may drive the practice, women with low-risk pregnancies are not fully informed about the short- and long-term consequences of a SCD, which in itself creates a litigious risk.[24] A low-risk pregnancy terminated by a pre-labour SCD can be transformed into a minefield of short- and long-term health effects via epigenetic pathways related to the genome and microbiome of which the mother and the obstetrician may not be aware. The decision to perform a non-indicated SCD should not be taken lightly if its hidden epigenetic effects are to be avoided.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

This article has been peer reviewed.

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