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The long-term effects of birth by caesarean section: The case for a randomised controlled trial

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ABSTRACT

Birth by caesarean section is rising rapidly around the world and is associated with a range of adverse short and long-term outcomes in offspring. The latter include features of the metabolic syndrome, type-1 diabetes, and asthma. Though there are several plausible candidate biological mechanisms, evidence of a causal relationship between mode of delivery and long-term outcomes remains lacking. Here we review the evidence to date, and examine ways in which future studies might advance understanding. We conclude that a randomised controlled trial of mode of delivery for the healthy term, cephalic pregnancy, is neither unethical nor unfeasible and should be seriously considered as the optimum means of addressing a question of great relevance to public health.

1. Introduction

In 2011 the UK National Institute for Health and Clinical Excellence (NICE) guidelines [1] were modified to support offering caesarean section (CS) to women who, after discussion with a mental health expert, feel unwilling to accept a vaginal delivery (VD). This guideline is likely to fuel further increase in an already high and rapidly rising CS delivery rate worldwide.

The reasons for the exponential rise in CS deliveries are complex. Whilst maternal choice is often considered the major factor, many studies suggest otherwise [2]. Both pre-labour CS (PLCS) and in-labour CS (ILCS) [3] are on the rise, suggesting clinicians may play a significant role. Indeed, pregnant women may accept higher risks to give birth by VD, than obstetricians [4]. A meta-analysis of women's preference for CS delivery (38 studies; n = 19403) gave a pooled preference for CS of 15.6% [95% confidence-intervals (95% CI) 12.5–18.9] [5]; but this was lower in women who had not previously given birth by CS (10.1 [95% CI 7.5–13.1]), compared to women who had (29.4 [95% CI 24.4–34.8]). A randomised controlled trial (RCT) of standard care, compared to decisional aids, to inform women who had had a previous CS delivery about birth choices for subsequent pregnancies, showed that use of decisional aids increased VD [6]. These data suggest that standard care may not adequately empower mothers to make an informed decision about birthing choices, possibly increasing the CS rate. The authors concluded that use of appropriate decisional aids in antenatal clinics could substantially reduce the rate of CS in the UK. We believe that understanding the long-term impact of CS on the offspring is vital to reassessment of the increasing role of CS in the obstetric population. We will review current evidence of long-term outcomes following CS, and consider possible research strategies to test causality and advance understanding of underlying biological mechanisms.

2. Long term health outcomes of CS delivery

Many studies have suggested that CS affects long-term health. These can be loosely grouped into conditions associated with the metabolic syndrome, the immune system, dentition, malignancies, and the nervous system. We will review each of these in turn.

2.1. Features of the metabolic syndrome

The term "metabolic syndrome" is used to describe a constellation of features, namely abdominal adiposity, hypertension, dyslipidaemia and insulin resistance, that are associated with type-2 diabetes and cardiovascular disease.

2.1.1. Increased BMI and obesity

Several studies report on the relationship between CS and greater body mass index (BMI) or obesity in offspring; these are contradictory. In the USA, a prospective cohort study of 1255 mother–child pairs, showed no association between CS and risk of overweight at age 3 after adjustment for maternal age, education, ethnicity, pre-pregnancy BMI, and offspring birth weight, age at measurement and sex (OR 1.24 [95% CI 0.86, 1.77]) [7], although an increased risk of obesity following CS (OR 2.10 [95% CI 1.36, 3.23]) and a 0.20 unit increase in BMI

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z-score [95% CI 0.07–0.33] were noted. These data may indicate a non-normal data distribution. In sub-group analyses there was no difference between types of CS (planned-CS OR 2.32 [95% CI 1.18–4.55] and unplanned-CS OR 2.42 [95% CI 1.52–3.83]), comparing each against VD, although after adjustment, only unplanned-CS was significantly associated with increased obesity (OR 2.19 [95% CI 1.34–3.55]). A cohort study of nearly 200,000 adolescents (15–19 years) applying for driving licences in Utah, USA, showed those born by CS were 1.4 times more likely to be overweight than those born by VD [8].

A case–control study in China of 162 pre-school children, produced an adjusted OR of 5.23 [95% CI 1.24–22.04] for obesity following CS compared to VD [9]. In Brazil, a study measuring BMI at 4, 11, 15 and 23 years of age, reported increased obesity prevalence in CS compared to VD offspring up to 15 years, but not at 23 years [10]. When adjusted for covariates, obesity prevalence was reduced and there were no differences between the birth groups at any age excepting the 4 year old males (OR 2.03 [95% CI 1.20, 3.42] following CS). However, another Brazilian cohort ($n=2057$) of 23–25 year olds demonstrated increased obesity prevalence following CS compared to VD (prevalence ratio: 1.46 [95% CI 1.15, 1.85]); the prevalence ratio remained significant after adjusting for covariates (1.58 [95% CI 1.23, 2.02]) [11].

Most differences in obesity following CS delivery are reported in children. Importantly, a recent estimate suggests that >10,000 individuals would be required to achieve 80% power to detect differences in obesity between offspring born by CS or VD [12]. The study of 28,354 Danish children aged 7, by Ajslev et al. [13], reported an unadjusted association between CS and childhood overweight (OR 1.15 [95% CI 1.02–1.29]) [13], but after adjustment for maternal and infant factors (e.g. maternal BMI, birth weight and breastfeeding) the association was attenuated (OR 1.01 [95% CI 0.82–1.24]).

2.1.2. Adiposity

A study in which skinfold measurements in 1255 American 3 year olds were measured reported a 0.94 mm [95% CI 0.36. 1.51] increase in the sum of skinfolds in CS compared to VD children [7]. However, there was no association between mode of delivery and subscapular: triceps skinfold ratio, a measure of central adiposity (β −0.18 [95% CI −2.30, 1.94]).

2.1.3. Possible mechanisms driving increased BMI in CS delivered infants

There are several postulated mechanisms that might link CS and increased offspring BMI [14]. In animals, alterations in metabolism, in particular preferential storage of fat and lower gluconeogenic flux, following PLCS birth may drive increased BMI and adiposity [15]. Alternatively, in our meta-analysis, including over half a million subjects, of breast feeding following CS [16], we showed that the OR for breast feeding initiation following CS compared to VD was 0.57 [95% CI 0.50–0.64]. Significantly, this association only held when comparing PLCS with VD (OR 0.83 [95% CI 0.80–0.86]) and not when comparing ILCS with VD (OR 1.00 [95% CI 0.97–1.04]). Differences in breast feeding consequent upon mode of delivery may contribute to later-life obesity [17]. Differences in circulating concentrations of orexigenic peptides in early life may also programme appetite regulation [18]. The infant microbiome, which is known to differ according to mode of delivery, may also drive obesity, with certain microbial species being associated with altered energy harvesting and consequently with a risk of obesity [13].

2.1.4. Interaction between maternal BMI and mode of delivery

Several confounding factors may account for the association between CS and offspring BMI, especially maternal BMI which is closely associated with increased risk of CS delivery. We reported that infant intrahepatocellular lipid (IHCL) is associated with maternal pre-pregnancy BMI, but the association is dependent on the mode of delivery (mode of delivery $p=0.025$, maternal BMI $p=0.030$, interaction between mode of delivery and maternal BMI $p=0.022$). Maternal BMI is associated with a significant increase in IHCL in PLCS infants (32% increase [95% CI 10%, 59%] per kg/m^2 increase in maternal BMI); but has no effect in ILCS infants (6% [95% CI −17%, 35%] per kg/m^2 increase in maternal BMI) or infants born by VD (0.4% [95% CI −6%, 7%] per kg/m^2 increase in maternal BMI) [19]. In 3 year old American children, the association between CS and obesity was reduced in offspring of obese mothers (BMI≥25 kg/m^2; OR 2.97 [95% CI 1.58, 5.60]) compared to normal weight mothers (<25 kg/m^2; OR 1.61 [95% CI 0.88, 2.96]) [7].

2.1.5. Blood pressure

There are reports of lower neonatal blood pressure following CS, [20–24], including the suggestion that these differences persist up to three months of age [21]. In children aged 7–9 years, born preterm ($n=756$), systolic blood pressure was lower if born by CS compared to VD (CS: 99.3 ± 10.0 (mean ± SD), VD: 104.4 ± 9.4 mm Hg; $p=0.003$) [25], whilst in the term born control cohort ($n=166$) there was no difference in blood pressure between children born by CS or VD, even after adjustment for sex, gestational age, age at measurement and height [25]. These data suggest that blood pressure may be affected by a complex interaction between gestational age and mode of delivery, although mechanisms driving this are unknown. In the short-term reduced plasma concentrations of renin [26] and angiotensin II [27] in CS neonates, possibly driven by higher cord blood pH [28], could conceivably drive altered blood pressure between CS and VD infants [26].

2.2. Dentition

A study of 102 Spanish children (51% low-birth weight (LBW)) assessed at age 4–5, showed that CS delivered infants had increased risk of enamel hypoplasia compared to VD infants ($p=0.024$) [29]. The number of LBW infants in the cohort may be a confounder; LBW infants have ≈4 four times more hypoplasia than normal-birth weight children, and LBW is an independent risk factor for CS. However, a study of the width of the neonatal line in primary tooth enamel, suggested it was altered by birth experience (11.9 ± 4.8 μm (mean ± SD) in children born by normal VD; 18.6 ± 5.7 μm in children born by "difficult operative delivery"; 7.6 ± 1.5 μm in children born by CS) [30]. Perinatal stress, can determine the size of the neonatal line [31]. Another study showed no significant difference between the neonatal line in children born by CS compared to VD [32].

2.3. Immune related conditions

2.3.1. Type-1 diabetes

Infants born by CS have greater incidence of type-1 diabetes mellitus (T1DM). A meta-analysis (20 independent data-sets; 2,133,236 subjects; 205,941 delivered by CS and 9938 cases of T1DM), showed higher incidence of T1DM in children born by CS compared to VD (OR 1.23 [95% CI 1.15, 1.32] $p\leq0.001$; random effects model; heterogeneity: $I^2=0\%$, $p=0.54$) [33].

In a German cohort study of 1650 children born to a parent with T1DM, the association between CS delivery and increased risk of T1DM in childhood was confirmed (Hazard ratio 2.5 [95% CI 1.4, 4.3]) [34]. However, CS was not associated with increased islet autoantibodies ($p=0.6$), but there was an association with a faster progression to symptoms of T1DM after the first identification of islet autoantibodies in CS compared to VD children ($p=0.015$). Additionally there were interactions between mode of delivery and genetic susceptibility; T1DM and expression of the interferon-induced helicase-1 gene were only associated in CS delivered children. In another study, CS appeared to protect against the association between T1DM and expression of the gene *PTPN22* [35]. Altered gut microflora, the hygiene hypothesis and perinatal stress have been postulated as plausible mechanisms linking CS and T1DM [36].