

ANALYSIS



Time to consider the risks of caesarean delivery for long term child health

Jan Blustein and Jianmeng Liu examine the evidence linking caesarean delivery with childhood chronic disease and say that guidelines on delivery should be reviewed with these risks in mind

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Caesarean delivery can improve maternal and child health, and even save lives. But the past two decades have brought a sharp growth in caesareans in many nations, raising concerns about unnecessarily high rates. Caesarean delivery on maternal request is relatively rare in the UK (1-2% of births) and US (3% of births). But in some middle income countries the rate is high and growing (20% of births in southeastern China in 2006), making it an emerging global public health concern. Another contributor to the rising rates is repeat caesarean. Although this is not necessarily medically indicated in women with otherwise low obstetrical risk, among US births to women with prior caesarean in 2006, over 90% were caesarean deliveries.

Prospective parents want a delivery that is safe for the baby.¹ In emergencies, or when a fetal or maternal indication is present, the choice is clear. But in cooler moments, such as repeat or maternal choice of caesarean, it makes sense to consider the risks and benefits of caesarean versus vaginal delivery, just as we would for other medical treatments. Both modes of delivery are associated with well known acute risks. For the neonate, for example, a caesarean is associated with increased risk of admission to a neonatal intensive care unit and vaginal delivery with a greater likelihood of cephalohaematoma. To date, concerns around long term child health have largely focused on neurological impairment. But recent research points to latent risks for chronic disease: children delivered by caesarean have a higher incidence of type 1 diabetes, obesity, and asthma. We argue that a detailed assessment of these risks should be taken into account in guidelines for caesarean delivery.

Evidence on childhood chronic disease

Much of the evidence linking caesarean delivery to chronic disease is observational. Because caesarean delivery does not occur at random, plausible studies rely on careful stratification and adjustment for clinical confounders that are associated both with caesarean delivery and the outcomes of interest. Meta-analyses of cohort and case-control studies find a positive

association with type 1 diabetes (based on 20 studies),² asthma (23 studies),³ and obesity (nine studies).⁴ We did not find any meta-analyses that reported no association with these outcomes.

The combined cohort and case-control evidence for type 1 diabetes is particularly compelling because many of the studies used detailed sets of well characterised clinical confounders (birth weight, gestational age, maternal age, birth order, maternal diabetes, and breast feeding). Authors of the meta-analysis were able to assemble individual patient data from most component studies and calculate a pooled risk estimate, adjusting for known confounders. The fully adjusted analysis found that caesarean delivery increased the relative risk of type 1 diabetes by 19%²; similar increases were found in the meta-analyses of asthma and obesity.

The absolute rates derived from these relative increases depend on many assumptions, including local rates of caesarean and disease prevalence. For example, using the US caesarean rate of 32.7% and an overall childhood obesity rate of 17%, the estimated rate of obesity is 15.8% among children delivered vaginally and 19.4% among children delivered by caesarean. With an overall childhood asthma rate of 8.4%, the rate of asthma among children delivered vaginally is estimated at 7.9% compared with 9.5% in those delivered by caesarean. And an overall childhood type 1 diabetes rate of 1.9/1000 translates to rates of 1.79/1000 children delivered vaginally and 2.13/1000 children delivered by caesarean.

Applicability to non-essential caesareans

The meta-analyses included studies in which caesarean was conducted for a variety of indications. So how relevant are the data to non-essential caesarean and how much are studies still potentially confounded by maternal, fetal, or obstetric characteristics associated with the outcomes? The answers vary among studies. Detailed information about indication for caesarean is generally not captured in clinical data. In some

studies surgery is classified as elective or emergent, but rarely as emergent, urgent, scheduled, or elective,⁵ or as before or after labour starts. Maternal request is not routinely coded in Western clinical data, although it is in China. Some studies consider only full term normal weight babies; this presumably avoids confounding by key factors such as low birth weight and being small for gestational age. Others statistically adjust for birth weight and gestational age. Some studies exclude mothers with conditions that may precipitate caesarean, such as pre-eclampsia and gestational diabetes.

We believe that these limitations mean the evidence on risks needs to be assessed by looking at individual studies. That said, some of the cohort studies are quite focused. For instance, a recently published prospective study based on detailed clinical data compared caesarean at maternal request with vaginal delivery and found an increased risk of childhood overweight.⁶ This is certainly not the last word, and we applaud efforts such as the Royal College of Obstetricians and Gynaecologists's clinical indicators project,⁷ which aims to capture better obstetric data in future in order to improve clinical practice and strengthen the evidence base.

Evidence from studies with other designs

Studies of non-twin sibling pairs have also been used to estimate risk of childhood asthma and diabetes by comparing cases in which one sibling has been delivered vaginally and another by caesarean.⁸⁻¹⁰ In all three studies, between sibling point estimates of association were generally (but not invariably) closer to zero than those found in cohort analyses. Attenuation like this is commonly understood to show that the cohort estimates are spuriously biased upward, and some authors of these studies have advanced this interpretation. However, estimates drawn from sibling pairs are inherently less precise, and for the small effect sizes found for caesarean this was problematic.⁸⁻¹⁰ Moreover, recent work in epidemiology¹¹ shows that sibling pair estimates of association may be more biased than cohort estimates because siblings who are dissimilar in exposure are not typical sibling pairs. This means that compared with cohort estimates, sibling pair estimates are more vulnerable to measurement error and thus biased toward zero. They are also more vulnerable to bias by unmeasured confounders, which may result in bias in either direction. In sum, the recent sibling pair evidence is important but should be interpreted cautiously. What about randomised studies? Of the six trials comparing caesarean with vaginal delivery in term healthy pregnancies,¹² only the Term Breech Trial tracked children beyond the perinatal period.¹³ At age 2 years, children in the planned caesarean group had had significantly more medical problems in the past several months (20.8% in the caesarean group versus 14.8% in the vaginal delivery group had upper respiratory, gastrointestinal, ear, skin, allergic, or other problems by parental report; $P=0.02$). Although this evidence does not link caesarean to any particular adverse outcome, it is striking and was unexpected in a randomised study. Unfortunately, there was no further follow up of the cohort.

Understanding the link

The past decade has brought a wealth of new understanding about how delivery shapes early child development. Some of the most intriguing research focuses on the colonisation of the infant gut microbiome, which has a key role in energy uptake and immune function. For vaginally born babies, intestinal colonisation follows from exposure to maternal vaginal and faecal flora; elective caesarean bypasses this. Other research

explores the epigenetic consequences of the physical stress of delivery. Putative links between exposure and disease can in turn be tested in epidemiological data.

Some recent work distinguishes between modes of caesarean (elective versus emergent) and vaginal (operative versus unassisted) delivery, which may reflect different degrees of intrapartum fetal stress and exposure to vaginal microflora. When a caesarean is done after labour has started it may be preceded by rupture of membranes, with exposure to maternal microflora. The risks to long term child health might then vary between caesareans done before and after labour has started. Similarly, intrapartum stress may be higher in emergency caesarean and instrumental vaginal delivery than in unassisted vaginal delivery. Comparing outcomes in various settings allows a test of the relative importance of stress versus caesarean delivery itself. These (and other) more nuanced approaches may lead to better understanding of the dynamics underlying risk. This in turn may lead to clinical approaches to mitigating risk.

No mention in recent guidelines

As we have noted, knowledge about chronic disease risks could affect decision making in non-essential caesarean. The American College of Obstetrics and Gynecology¹⁴ and the UK's National Institute for Health and Care Excellence¹⁵ recently issued consensus statements on caesarean delivery at maternal request. Based on evidence about maternal and perinatal outcomes, both groups concluded that a pregnant woman requesting caesarean should have that choice, if she still desires it after discussion of the risks and benefits of the procedure. Importantly, neither group acknowledged the long term risk of chronic disease.

It is not clear why these risks weren't included. The consensus statements were published in 2011 and 2013; two of the meta-analysis cited above appeared in 2008, although one was published in 2013. Strength of evidence also does not seem to be a reason for exclusion. Much of the evidence on maternal and perinatal outcomes cited in both consensus statements seems to be on par methodologically with the evidence linking delivery mode to chronic disease outcomes (again this requires expert review). A final explanation is that we are not accustomed to considering long term child health in the context of caesarean, beyond neurological impairment. It is disconcerting to consider that an operation that yields an apparently healthy baby could put that child at increased risk of future chronic disease. But exposures in utero and in early infancy have long been known to alter the lifelong risk of cardiovascular disease.¹⁶

Moving forward

Fuller knowledge of risks and benefits may help reduce the growth in rates of caesareans. For example, a recent study offered decision aids to pregnant women who had already had a caesarean and found an increased rate of vaginal birth.¹⁷

In medical decision making, we rarely have the ideal evidence set; we act on the best available current evidence. Today's knowledge is never the last word. There have been calls for a randomised trial of caesarean versus vaginal delivery in healthy singleton pregnancies.^{12 18} We applaud these proposals, and note concerns that have been voiced around ethics and logistics. Randomised trials in other settings (breech, repeat caesarean) have also been advocated. All of these seem worthy investments, even if evidence on long term effects would take decades to emerge. But even then, we might not have the last word. Learning from evidence requires inference across clinical settings. Would evidence on child health from a randomised

trial in breech presentations apply to repeat caesareans? Would findings from a trial in repeat caesarean be accepted as relevant to primiparous women considering requesting a caesarean?

Some have suggested locating the children born to mothers in the six previous randomised trials. This would take a commitment by past investigators, and significant funding from agencies that may be unaccustomed to supporting this sort of long term work. Nonetheless, retrieving the data could give us a sharper estimate of the effect of caesarean delivery on child health.

We acknowledge the importance of caesarean in maternal and child health. But we live in a world where caesarean rates cannot be explained by compelling medical indications. In that world, we all have a stake in a thorough discussion of the risks of caesarean for long term child health.

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Summary points

Rates of caesarean section are rising, with maternal request and repeat caesarean accounting for a large proportion in some countries

Caesarean delivery has been linked to increased risk of childhood obesity, asthma, and type 1 diabetes

The evidence on these risks has not been reviewed in clinical guidelines

Knowing about child health risks could change decisions when caesarean is not a medical necessity