

## Optimising caesarean section use 2



# Short-term and long-term effects of caesarean section on the health of women and children

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A caesarean section (CS) can be a life-saving intervention when medically indicated, but this procedure can also lead to short-term and long-term health effects for women and children. Given the increasing use of CS, particularly without medical indication, an increased understanding of its health effects on women and children has become crucial, which we discuss in this Series paper. The prevalence of maternal mortality and maternal morbidity is higher after CS than after vaginal birth. CS is associated with an increased risk of uterine rupture, abnormal placentation, ectopic pregnancy, stillbirth, and preterm birth, and these risks increase in a dose–response manner. There is emerging evidence that babies born by CS have different hormonal, physical, bacterial, and medical exposures, and that these exposures can subtly alter neonatal physiology. Short-term risks of CS include altered immune development, an increased likelihood of allergy, atopy, and asthma, and reduced intestinal gut microbiome diversity. The persistence of these risks into later life is less well investigated, although an association between CS use and greater incidence of late childhood obesity and asthma are frequently reported. There are few studies that focus on the effects of CS on cognitive and educational outcomes. Understanding potential mechanisms that link CS with childhood outcomes, such as the role of the developing neonatal microbiome, has potential to inform novel strategies and research for optimising CS use and promote optimal physiological processes and development.

### Introduction

Although caesarean section (CS) can be a life-saving intervention for mothers and children, it can also lead to short-term and long-term health consequences. Greater understanding of how the mode of birth can affect longer term health outcomes for women and children is crucial to inform decision making by clinicians, women, and policy makers, considering the very different circumstances and varied risks between low-resource and high-resource settings.

The Right Care Series<sup>1–3</sup> created a framework for understanding overuse and underuse of medical interventions and drivers of poor care around the world. Right care was defined as “care that weighs up benefits and harms, is patient-centred (taking individual circumstances, values, and wishes into account), and is informed by evidence, including cost-effectiveness”.<sup>4</sup> CS is an example of a medical intervention that is underused in some low-resource settings and overused in many parts of the world.<sup>5</sup> The first paper<sup>6</sup> in this Series on Optimising Caesarean Section Use<sup>6,7</sup> showed that, globally, CS use is high and increasing: in 2015, an estimated 29·7 million (21·1%) births occurred by CS, which was almost double the proportion in 2000 (12·1%). WHO has estimated that 6·2 million excess—ie, not medically indicated—CSs are being performed each year, 50% of which are in Brazil and China alone.<sup>8</sup> However, there is ongoing debate around the optimal frequency of CS use.<sup>9</sup>

Previous reviews<sup>10–13</sup> have examined the specific effects of CS for non-medical reasons and for women with

previous CS, preterm birth, and term breech. However, to our knowledge, there is no published overview that has collated and summarised the evidence to include an analysis of the short-term and long-term health effects of CS on women and children. There are benefits of CS for maternal and infant health, but our focus here is instead on the effects of increasing CS use, not on the benefits of CS in regions where it is underused. We have selected important, large, and recent systematic reviews and cohort studies to summarise the effects of CS on short-term and long-term outcomes for both women and children.

### Search strategy and selection criteria

To assess the effects of caesarean section on the health of women, we searched the Cochrane Library, PubMed, and Scopus databases with the search terms “caesarean OR caesarean section AND vaginal delivery”, “benefit OR risk OR complication”, and “long term OR short term”. The first two of these searches were combined, followed by combining all three search terms. We further narrowed the results by searching in the results for the terms “trial of labour”, “planned vaginal birth”, “vaginal birth after caesarean”, “mortality”, “morbidity”, “elective caesarean”, “repeat caesarean”, “caesarean on demand”, and “medically and non-medically indicated caesarean”. We assessed the title and abstract of all records, and we obtained the full text of reviews, prospective studies, and population-based datasets. Only English language articles published between Jan 1, 1993, and Jan 31, 2018, were included. To assess the effects of caesarean section on the health of children, we did the same searches, but with the search terms “caesarean section”, “caesarean section”, “C-section”, and “mode of delivery”, combined with “allergy”, “atopy”, “asthma”, “overweight OR obesity”, “microbiome”, “immune system”, “cardio-vascular”, “behaviour”, “autoimmune disorder”, “diabetes”, and “gastro-intestinal disorder”.

*Lancet* 2018; 392: 1349–57

This is the second in a Series of three papers on optimising caesarean section use

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## Key messages

- Caesarean section (CS) is a life-saving intervention for specific complications during pregnancy and childbirth that should be available to all women in need. CS also confers an increased risk of maternal mortality and severe acute morbidity and a higher risk for adverse outcomes in subsequent pregnancy compared with vaginal birth. Multiple CSs are associated with a higher risk of maternal morbidity and mortality.
- Some benefits of CS, such as less frequent incontinence and urogenital prolapse have been described.
- Infants born by CS have different hormonal, physical, bacterial, and medical exposures (such as intrapartum antibiotics and uterotonins) and are exposed to more short-term risks, which range from altered immune development, allergy, atopy, asthma, and reduced diversity of the intestinal gut microbiome, compared with those born vaginally.
- Emerging research has shown biological mechanisms that underlie the acute and chronic effects of CS on child health and the long-term effects of CS on children, including how these effects might be mitigated.

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## Short-term and long-term effects of CS on women's health

### Limitations to CS studies

Understanding of the short-term and long-term outcomes of CS for women has been restricted by limitations in study design, inadequate power of studies, failure to control for confounders, and inappropriate selection of comparison groups. Additionally, there has been a failure to differentiate between elective and emergency procedures, or to account for obstetric and medical conditions that have prompted the need for CS that could be the underlying cause of increased morbidity and mortality. A summary of the evidence regarding the short-term and long-term effects of CS for the mother, including increased risks of hysterectomy, abnormal placentation, uterine rupture, stillbirth, and preterm birth in the subsequent pregnancy is shown in the appendix. Bleeding, a need for blood transfusion, pelvic adhesions, intraoperative surgical injury, and hysterectomy are more prevalent with increasing number of CSs.

### Maternal mortality

The absolute risk of maternal death associated with CS is known to be low in high-resource settings, and higher in low-resource settings.<sup>14,15</sup> Estimating the exact risk attributed to this mode of birth proves difficult. One review<sup>16</sup> in high-resource countries that included 402 883 women showed in an unadjusted analysis that maternal mortality increased with elective repeat CS compared with labour. Similar results were found in Brazil, with adjusted odds ratios ranging from 1.6 to 7.08.<sup>17</sup> However, an unadjusted cross-sectional study in China of 108 847 births (of which 59 415 births were by CS) showed no difference in the frequency of maternal death associated with antepartum CS without medical indication compared with vaginal birth.<sup>18</sup>

Planned CS confers a lower risk of mortality compared with emergency, intrapartum CS. Although still a rare

event, studies<sup>19–21</sup> have estimated the risk of death from an emergency intrapartum CS to be up to four times higher than from vaginal birth. Further, the risk of maternal death during birth is increased in pregnancies after a CS, due to an increased risk of uterine rupture and abnormal placentation.

### Severe acute maternal morbidity

Severe acute maternal morbidity (SAMM) has been used as a proxy measure (defined in several ways) for maternal death. Severe maternal morbidity is defined as the presence of complications such as a haemorrhage, requiring hysterectomy or blood transfusion, any hysterectomy, uterine rupture, complications associated with anaesthetic (including those arising from the administration of a general or local anaesthetic, analgesic, or other sedation during labour and delivery), obstetric shock, cardiac arrest, acute renal failure, assisted ventilation or intubation, puerperal venous thromboembolism, major puerperal infection, in-hospital wound disruption, and haematoma. In large population-based studies, the overall unadjusted frequency of SAMM is consistently greater following CS than vaginal birth. For example, a Canadian population-based study<sup>22</sup> of 2 339 186 births reported that more women in the planned CS group had SAMM (2.7%) than those in the planned vaginal birth group (0.9%). A nationwide prospective cohort Dutch study<sup>23</sup> that used unadjusted data for 371 000 pregnancies found that birth by planned or emergency CS was associated with a five times increased risk of SAMM (risk ratio [RR] 5.2, 95% CI 4.8–5.6). This increased risk also applied to CS without labour (4.6, 4.2–5.0). Another prospective cohort Dutch study<sup>24</sup> of 2552 births found that current and previous CSs increased the risk of SAMM. Compared with planned vaginal birth, the unadjusted incidence of SAMM in the elective CS group was 6.4 events per 1000 births versus 3.9 events per 1000 births (odds ratio [OR] 1.7, 95% CI 1.4–2.0) in the vaginal birth group. CS in a previous pregnancy conferred a three times increased risk for SAMM in the current pregnancy (3.0, 2.7–3.3). The authors reported that emergency intrapartum CS conferred a higher risk for SAMM than elective procedures. In a Finnish register-based retrospective cohort study<sup>25</sup> of 110 000 births, the unadjusted risk of SAMM was greater with elective CS than vaginal birth (RR 2.5, 95% CI 1.9–3.2), and with emergency intrapartum CS compared with vaginal birth (RR 4.9, 95% CI 4.2–5.8).

### Short-term and long-term morbidity

Immediate and delayed intraoperative and postoperative risks associated with planned CS have been well documented.<sup>12,26,27</sup> A 2017 evidence update for the UK's National Institute for Health and Care Excellence (NICE) includes nine prospective studies that compared the outcomes of planned CS with those of planned

vaginal birth (for women with an uncomplicated pregnancy and no previous CS).<sup>28</sup> Planned vaginal birth was associated with reductions in length of hospital stay, the risk of hysterectomy for postpartum haemorrhage, and the risk of cardiac arrest compared with planned CS. However, planned CS was associated with a reduced risk of vaginal injury, abdominal and perineal pain during birth and 3 days postpartum, early postpartum haemorrhage, and obstetric shock compared with planned vaginal birth. Other intra-operative, perioperative, and postoperative risks showed no difference between the modes of birth, or conflicting findings regarding any differences. The quality of these data was noted by NICE to be low or very low, and studies from low-resource settings were excluded. Similarly, a 2006 systematic review<sup>29</sup> of the evidence for the US National Institutes of Health statement on CS showed insufficient evidence to state whether any of these immediate and delayed risks from planned CS were greater or less than those from planned vaginal birth. Advances in improved anaesthetic and surgical techniques, including thromboembolic prevention, antibiotic prophylaxis, and blood conservation, might have minimised the risk of many of these short-term outcomes.

When evaluating risk, it is important to acknowledge that not all attempted vaginal births are successful. Although the risk of some short-term morbidities is slightly increased for planned CS, studies<sup>19,30,31</sup> have documented that maternal morbidity associated with unsuccessful spontaneous birth (either CS in labour [16.3%] or an assisted vaginal delivery with forceps or vacuum extraction [12.9%]) is greater than that with planned CS (7%). Comparing planned CS with planned vaginal birth is thus appropriate in terms of assessing risk.<sup>19,32</sup>

Long-term sequelae of CS include pelvic adhesions, small bowel obstruction, menorrhagia, dysmenorrhoea, chronic pain, sexual dysfunction, subfertility, urinary and faecal incontinence, and pelvic organ prolapse. A 2018 systematic review<sup>33</sup> and meta-analysis found no difference in outcomes between CS and vaginal birth for chronic pain, menorrhagia and dysmenorrhoea, or faecal incontinence. However, compared with vaginal birth, CS was associated with decreased risk of urinary incontinence (OR 0.56, 95% CI 0.47–0.66) and pelvic organ prolapse (0.29, 0.17–0.51). There were conflicting results regarding sexual dysfunction in the form of dyspareunia.

CS is associated with reduced risk of urinary incontinence, but the difference seems to level out with age.<sup>34</sup> A meta-analysis<sup>35</sup> has shown that the odds ratio for anal incontinence is 1.35 (95% CI 1.07–1.7) for vaginal birth compared with CS in the first year postpartum. However, a Cochrane review<sup>36</sup> that compared CS with vaginal birth concluded that prevention of anal incontinence should not be used as a primary criterion for choosing planned CS.

Pelvic adhesions and small bowel obstruction were not addressed in these studies, reviews, and meta-analyses. Development of adhesions after CS is not uncommon, and the prevalence increases with subsequent CSs, to 12–46% after a second CS, and 26–75% after a third CS.<sup>37</sup> The risk of small bowel obstruction due to adhesions is low but does appear to increase with each CS, although the overall risk is small (16.3 events per 10 000 person-years).<sup>38</sup> This finding is in agreement with data from a large Danish national register, which have shown, in a fully adjusted multi-variable analysis, that women requiring a hysterectomy have more perioperative and postoperative complications than women having a vaginal birth (adjusted OR 1.31, 95% CI 1.03–1.68 if one previous CS; and 1.35, 0.96–1.91 if two or more previous CSs). Women were more often likely to need a relaparotomy (OR 1.32, 95% CI 1.03–1.68) later in life if they had previously had a CS than if they previously had a vaginal birth.<sup>39</sup> An increased risk of future subfertility has also been associated with CS.<sup>40,41</sup>

The psychological effects of CS have not been well studied. Women who have given birth by CS have reported less immediate and long-term satisfaction with their birth experience and less positive interactions after birth compared with women who had a vaginal birth.<sup>42</sup> Increased post-traumatic stress symptoms have been documented in women who preferred CS but gave birth vaginally compared with women who both preferred vaginal delivery and delivered vaginally.<sup>43</sup> However, we found a paucity of prospective studies designed to establish causal relationships, and variation in how adjustments were made.

#### Adverse outcomes for women in subsequent pregnancy

After a CS, subsequent pregnancies show increased risks of hysterectomy, abnormal placentation, uterine rupture, stillbirth, and preterm birth.<sup>33,41</sup> A higher frequency of bleeding, need for blood transfusion, adhesions, intra-operative surgical injury, and hysterectomy occurred with increasing number of CSs.<sup>16,44,45</sup> Evidence regarding the association of CS with subsequent incidence of miscarriage is conflicting.<sup>46</sup>

A Dutch study<sup>47</sup> found a risk of one event in 25 000 pregnancies for hysterectomy due to abnormal placentation in women without previous CS, which increased to one event in 500 pregnancies for women with one previous CS, and to one event in 20 pregnancies for women with three or more previous CSs. In a large US study,<sup>48</sup> a similar prevalence of hysterectomies was found after the first prelabour CS (0.65%, which was attributed to placenta accreta in about half of these cases). This study also showed a progressive increase in hysterectomy with increasing CSs; after the third subsequent CS, the risk was 2.4%. In cases of placenta praevia, the risk for placenta accreta increased from 3% in the first subsequent CS, to 11% for the second, 40% for the third,

60% for the fourth, and 67% for the fifth (or more) subsequent CSs.

The overall risk of a uterine rupture is about 0·5–1%. The risks of uterine rupture, abnormal invasive placenta, and severe postpartum haemorrhage are higher after a previous CS.<sup>49</sup> The risk of these adverse events depends on the time interval between pregnancies and is highest for an interval under 6 months. Induction of labour, especially with prostaglandins, increases the risk of a uterine rupture,<sup>50</sup> which causes much higher mortality in low-resource settings than in high-resource settings. Given the risks of a uterine rupture, a planned vaginal birth after CS should only take place in facilities with high-quality emergency obstetrical care.<sup>51,52</sup>

There might be an increased risk of stillbirth in a subsequent pregnancy in women with a previous CS.<sup>33,46</sup> Three studies<sup>53–55</sup> have shown an increase in spontaneous preterm delivery after term CS.<sup>53</sup> In one study,<sup>54</sup> this finding was restricted to one pregnancy after a second-stage term CS and, in another, to multiple repeat CSs.<sup>55</sup>

### Short-term and long-term outcomes for infants and children

#### Intrauterine effects on infant health

CSs can save infants' lives and prevent perinatal mortality and severe morbidity, such as intrapartum asphyxia; however, it should be recognised that severe neurological morbidities can originate during the antenatal period, not only in the intrapartum period.<sup>9</sup> Additionally, many clinicians perform planned CSs before 39 weeks of gestation. Such planned early birth could increase the risk of respiratory problems and hypoglycaemia.<sup>56,57</sup>

Intrauterine exposures have far-reaching effects on the lifelong health of infants. Evidence is emerging that the birth process and intrapartum interventions can also affect normal physiological or pathophysiological development. Infants born by CS are subject to different hormonal, physical, bacterial, and medical interventions (such as intrapartum antibiotics and uterotonins). These factors have the potential to subtly alter physiology. The short-term and long-term consequences of CS on infants are summarised in the appendix. The short-term risks include altered immune development, allergy, atopy, asthma, and reduced intestinal gut microbiome diversity.<sup>56</sup> The persistence of these early childhood effects into later life is less well investigated. Data from individual studies have highlighted an association between birth by CS and features of metabolic syndrome, including adiposity, increased blood pressure, type 1 diabetes, asthma, increased body mass, changes to liver function, immune-related conditions, neurological and stress-related problems, and autoimmune gastrointestinal disease in childhood. However, a 2018 meta-analysis<sup>33</sup> only identified increased risks of obesity up to age 5 years and asthma up to age 12 years in children born by CS. These divergent findings might be because myriad childhood exposures obfuscate associations;

larger-scale longitudinal studies are needed to establish causality.

Studies on the effects of CS on emotional and behavioural outcomes have predominantly focused on autistic spectrum disorders and attention deficit hyperactivity disorder. In a sibling-controlled adjusted model<sup>58</sup> that used population-level data (in >2000000 people; Swedish National Registers), no association was found between CS and attention deficit hyperactivity disorder for planned or emergency CS. Similarly, no association between planned CS and autistic spectrum disorders was found in a UK cohort of 13 141 children.<sup>59</sup> The longer-term effects of CS on cognitive and educational outcomes is an area that is understudied. Conflicting data from two similarly sized Australian cohorts (appendix) illustrates the need for more research.<sup>60,61</sup>

#### How does mode of birth affect infant and child health outcomes?

Mode of birth—ie, spontaneous, induced, augmented, or instrumental vaginal birth (or a combination of these) versus CS—could affect neonatal development and future health, and understanding these potential links could inform interventions. There are three biological mechanisms that have been hypothesised to explain how mode of birth could affect clinical outcomes in children.<sup>62</sup>

The first of these hypotheses is that inadequate transfer of the maternal microbiome to infants born by CS leads to altered immunological development. Although mode of birth is only one aspect that determines the infant's microflora composition (such as on the skin and in the intestinal tract), data suggest that the reduced exposure to the maternal microbiota of infants born by CS could be important in the first weeks of life.<sup>63</sup> It has been proposed that the effect of mode of birth on the infant's gut microbiota can persist for several years after birth,<sup>64</sup> but this suggestion is still under considerable debate.<sup>63,65</sup>

In addition to a potential effect of the microbial composition of the infant's gut on the risk of obesity and metabolic disease, aberrant colonisation of the intestinal tract can also affect the development and differentiation of their immune system. Some of these immune effects can persist into adulthood, altering susceptibility to certain diseases.<sup>66–71</sup> For example, persistently increased numbers of invariant natural killer cells can only be prevented by colonisation of the microbiota in the neonatal period.<sup>66</sup> Further, components of the microflora that drive regulatory T cell generation are essential to control inflammation.<sup>67–71</sup> The gut microbiome also drives secretion of IgA<sup>72</sup> and determines inflammatory cytokine profiles.<sup>73</sup> Immune disturbances driven by altered microbial colonisation in early life therefore provide a plausible mechanism that could underpin an increased risk of cardiometabolic and autoimmune disorders in babies born by CS.

The additional exposure of infants born by CS to prophylactic antibiotics in preparation for the procedure could also be a contributory confounder to aberrant microbial colonisation of the infant gut and possible increased susceptibility to metabolic disease in later life.<sup>74</sup>

The second hypothesis is that reduced intrapartum exposure to mechanical forces and stress hormones during CS bypasses many important physiological stimuli initiated by vaginal birth. Exposure to maternal stress hormones and the physical forces of labour and passage through the birth canal provide important development cues for the fetus in preparation of extra-uterine life. For example, increased concentrations of stress hormones are thought to be important signals in the infant for development of the hypothalamic–pituitary–adrenal axis, maturation of the immune system, lung and organ maturation, and neurogenesis. In infants born by CS, the absence of these triggers during this crucial window of development might be further compounded by the typically shorter gestation lengths present in planned CSs that occur before 40 weeks' gestation.<sup>62</sup> Some commentators have suggested that there are indications for women planning a CS to consider a curtailed labour, to allow optimal neonatal transition.<sup>75</sup> Data suggest that impaired cytokine concentrations later in life are not only affected by CS, but also by whether the mother was in active labour (more than 6-cm dilated) before CS.<sup>76</sup>

The final hypothesis is that different epigenetic modification of gene expression between methods of birth affects future infant health. The Epigenetic Impact of Childbirth research collaboration postulates that intrapartum use of synthetic oxytocin, antibiotics, or CS has several effects on the neonatal epigenome remodelling processes that have consequences for health of the offspring.<sup>77</sup> This hypothesis has yet to be fully investigated, and there are inadequate data to support this hypothesis. Stem cells have more DNA methylation in infants born by CS than those born vaginally,<sup>78</sup> and global DNA methylation in white blood cells obtained from cord blood is increased in newborns delivered by CS without labour compared with those born vaginally.<sup>79</sup> The biological significance of these changes is not immediately apparent, but could have implications for gene expression that are compounded by environmental exposures later in life. However, a 2012 study<sup>80</sup> found no evidence of global methylation changes associated with CS versus vaginal birth in a larger sample size study. Methodological differences in methylation assay and adjustment for maternal factors, such as age and smoking history, might account for the disparity between these studies. An experimental study in rats<sup>81</sup> of neonatal stress has shown that epigenetic alterations in DNA methylation of glucocorticoid receptors in the adult hippocampus is associated with increased stress reactivity in later life. Further studies of this hypothesis are needed.

### Can targeting biological mechanisms improve outcomes for infants born by CS?

Given that CS is often clinically indicated and necessary, understanding the potential biological mechanisms linking CS and childhood outcomes has a theoretical potential to inform novel strategies to minimise the negative effects of CS and optimise normal physiological processes. Mimicking some aspects of physiological birth during CS, for example, has been suggested. Based on data from animal and human studies,<sup>82</sup> some viable options would be to include deliberate slowing down of the birth at CS, skin-to-skin contact, and including a so-called physical squeeze to activate cortisol responses in the neonate. Although there is insufficient evidence at this time to support administration of antenatal corticosteroids before planned CS at term,<sup>83</sup> this is a potential area of future research.<sup>84,85</sup> There are also concerns about administration of corticosteroids in low-income and middle-income countries: neonatal mortality might not necessarily be reduced and there could be increased risk of maternal infection.<sup>86</sup> Another option would be to avoid use of planned CS before 39 weeks' gestation, to reduce the risk of respiratory distress syndrome. There are potential associations between mode of delivery and early-life microbial colonisation of the skin and gut<sup>63–65</sup> and the effects of this microbial colonisation on clinical outcomes, such as risk of asthma,<sup>87</sup> and there is a growing interest in the concept of microbiome seeding, to improve neonatal health. Vaginal swabbing as a potential route to seeding of the neonatal skin and gut after CS has been proposed,<sup>88</sup> however, this approach is unlikely to promote appropriate colonisation of the gut<sup>62</sup> and it carries inherent risks associated with group B streptococcal transfer.<sup>89</sup>

Alternative ways of seeding the neonatal gut microbiome are emerging.<sup>90</sup> Breastfeeding is fundamental to the developing neonatal gut microbiome<sup>63</sup> and is beneficial for babies born by CS, but it relies on appropriate intestinal colonisation of the infant at the time of birth.<sup>91</sup> In the absence of exposure to appropriate maternal gut bacteria (due to mode of delivery, hygiene practices, or low maternal colonisation with key bacteria), it is possible that probiotic supplementation, in tandem with promotion and intensive support of breastfeeding, could assist with adequate development of the intestinal microbiome and immune responses.<sup>91,92</sup> These alternative ways of seeding the microbiome will require further research before any clinical recommendations can be made.

### Implications in low-resource settings

The balance of risk and benefit must also be considered in relation to whether settings are high-resource or low-resource. In 2013, a WHO analysis<sup>93,94</sup> considered maternal near-miss or maternal death by mode of birth and showed that, in 29 African, Asian, Latin American, and Middle Eastern countries, 62·5% of women had a severe maternal outcome after CS, compared with

37·5% for vaginal birth. By contrast, a Finnish register-based retrospective cohort study of 110 000 births—ie, a high-resource setting—found a frequency of SAMM of 5·2 events per 1000 women for spontaneous vaginal deliveries, 12·1 events per 1000 women for planned CSs, and 27·2 events per 1000 women for emergency CSs.<sup>25</sup>

In low-resource settings, where fewer women receive all four of the recommended antenatal visits, there are minimal opportunities to provide information and plan a birth in a health facility. Studies<sup>94,95</sup> from Tanzania and Burkina Faso indicate that many women often reacted with fear and shock to their provider's decision when informed that they needed a CS,<sup>96</sup> felt guilty because they could not give birth vaginally, and they worried about the cost and risks of poor outcomes and poor quality of care. Consequently, in subsequent labours, women can be reluctant to present to a health facility, which again increases their risk of morbidity and mortality.<sup>96,97</sup>

Birth outcomes in low-resource settings are likely to be considerably worse than those in high-resource settings because of lower availability, accessibility, and affordability of comprehensive obstetric health services; inadequate operative infrastructure and access to water and poor sanitation; long distances to travel between rural areas and hospitals; and shorter intervals between pregnancies due to poor access to modern contraceptives and safe abortion services. Although the proportion of births with skilled birth attendants in 56 low-resource settings has increased from 52% in 2005 to 75% in 2017, use of these professionals is lower in many regions within countries.<sup>98,99</sup> A 2017 survey<sup>95</sup> of five referral public maternity hospitals in east, central, and southern Africa found that none of these health facilities had all the necessary equipment and staff for CS (according to minimum defined standards of care), and only 7% had adequate anaesthesiology staff. The availability of blood and capacity of expert surgical facilities is usually compromised in low-resource settings, and most women are unable to have more than 4–6 units of transfusion blood per case.<sup>100</sup> Additionally, the surgical expertise and logistical support required for safer CS in cases of abnormal placentation is less likely to be available in low-resource settings, especially in more rural settings. Careful case management can mitigate these risks; however, plans for safe CS can often be thwarted by inadequate capacity.

In Papua New Guinea, for example, only 40% of women have any level of supervision at birth, and this proportion is lower in rural areas, where the distance to a health facility is often more than a day's walk. For these reasons, and because many women are likely to have larger families, a primary CS places a woman at higher risk of abnormal placentation because of potential exposure to a greater number of CSs over her reproductive lifetime.<sup>101</sup> Because of evidence-based policies and concerns about the risk of CS in the next pregnancy, CS use in hospitals in Papua New Guinea has remained

infrequent (6% at the public hospital in Port Moresby, and between 5% and 12% in hospitals in the provincial capitals).<sup>102</sup> Nevertheless, the perinatal mortality rates in these hospital settings (19–40 deaths per 1000 live births) are lower than those in sub-Saharan Africa, where hospital perinatal mortality rates typically range from 50–100 deaths per 1000 live births.<sup>15</sup> The situation in Papua New Guinea would seem to indicate that it is possible to maintain low CS use and still achieve relatively low perinatal mortality rates.

By contrast, a study<sup>103</sup> in Tanzania found a concurrent increase in maternal near-miss and mortality with CS in low-risk births. It is unclear whether this was due to distance that mothers are required to travel, financial barriers for the mothers, or that CSs were being done too late, with an inadequate infrastructure and inexperienced healthcare workers.<sup>104</sup> Another study<sup>105</sup> in Tanzania showed that previous CS was not a risk factor for impaired maternal outcome, possibly because these women had a planned CS in subsequent pregnancies. As with mortality, discussion on morbidity must not be limited to the first pregnancy, but should also consider future pregnancies and reproductive health consequences across a woman's reproductive lifespan.

## Conclusions

Almost every woman who has a CS increases her risk of certain morbidities in her subsequent pregnancies. The axiom once a caesarean, always a caesarean is not evidence-based, but once a caesarean, always a scar reinforces the maxim that women with a previous CS should be considered to be at increased risk of obstetric complications and poorer outcomes for mother and baby. The discussed evidence shows the complexity in achieving an initially favourable result from an operative intervention and, consequently, potentially severe complications in subsequent pregnancies.

There is a need to consider the long-term outcomes for women and children when planning the mode of birth in high-resource and low-resource settings. We have identified evidence about CS and its effects on short-term maternal and infant outcomes compared with vaginal birth, but more evidence is needed from low-resource settings. The evidence regarding outcomes of CS for women, infants and children is complex, often of poor quality, and carries uncertainty in establishing causality over the longer term. In parallel with the strengthening of this evidence base, interventions after birth that are aimed at improving lifelong health for CS infants and children should be developed and evaluated.

The application of the principles of Right Care<sup>1-3</sup> provides a basis for the assessment of national and global interventions to address variation in the use of CS globally while considering cost-effectiveness and women-centred care. The final paper<sup>7</sup> in this three-part Series<sup>6,7</sup> analyses the drivers of CS and the multifaceted strategies that might be needed to address its overuse.

### Contributors

JS, RMT, and MT conceptualised the paper. JS and RMT wrote a first draft and all authors contributed to revisions. LA did the searches and constructed the tables on women's outcomes, with contributions from JS, GM, GHAV, and HK. RMT led the outcomes for children, on which NMK did related searches and constructed the tables, with contributions from CSEH, DG, and PT. HPK contributed to review and editing of the paper. All authors had full access to the papers drawn upon. JS edited and revised the final draft with assistance from Markus MacGill and had responsibility for submission of the manuscript. All authors contributed to writing, and reviewed and approved the final manuscript.

### Declaration of interests

RMT has research interests in the role of the microbiome and infant health and is funded to undertake a randomised controlled trial of probiotic supplementation (2017–21) for promotion of a healthy gut microbiome in elective caesarean section arrivals (PROMESA; ISRCTN11690200) by Evolve Biosystems. NMK is employed as a research assistant on this study. All other authors declare no competing interests.

### Acknowledgments

The authors would like to thank Markus MacGill of Green Ink for editorial assistance. JS is supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust. CSEH is supported by the Australian National Health and Medical Research Council as a Principal Research Fellow. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR, or the Department of Health and Social Care (UK).

### References

- Brownlee S, Chalkidou K, Doust J, et al. Evidence for overuse of medical services around the world. *Lancet* 2017; **390**: 156–68.
- Glasziou P, Straus S, Brownlee S, et al. Evidence for underuse of effective medical services around the world. *Lancet* 2017; **390**: 169–77.
- Saini V, Garcia-Armesto S, Klemperer D, et al. Drivers of poor medical care. *Lancet* 2017; **390**: 178–90.
- Kleinert S, Horton R. From universal health coverage to right care for health. *Lancet* 2017; **390**: 101–02.
- Miller S, Abalos E, Chamillard M, et al. Beyond too little, too late and too much, too soon: a pathway towards evidence-based, respectful maternity care worldwide. *Lancet* 2016; **388**: 2176–92.
- Boerma T, Ronsmans C, Melesse DY et al. Global epidemiology of use of and disparities in caesarean sections. *Lancet* 2018; **392**: 1341–48.
- Pilar Betrán A, Temmerman M, Kingdon C, et al. Interventions to reduce unnecessary caesarean sections in healthy women and babies. *Lancet* 2018; **392**: 1358–68.
- Gibbons L, Belizán JM, Lauer JA, Betrán AP, Meriáldi M, Althabe F, for WHO. The global numbers and costs of additionally needed and unnecessary caesarean sections performed per year: overuse as a barrier to universal coverage. 2010. <http://www.who.int/healthsystems/topics/financing/healthreport/30C-sectioncosts.pdf> (accessed Sept 15, 2018).
- Betran AP, Torloni MR, Zhang J, et al. What is the optimal rate of caesarean section at population level? A systematic review of ecologic studies. *Reprod Health* 2015; **12**: 57.
- Lavender T, Hofmeyr GJ, Neilson JP, Kingdon C, Gyte GM. Caesarean section for non-medical reasons at term. *Cochrane Database Syst Rev* 2012; **3**: CD004660.
- Dodd JM, Crowther CA, Huertas E, Guise JM, Horey D. Planned elective repeat caesarean section versus planned vaginal birth for women with a previous caesarean birth. *Cochrane Database Syst Rev* 2013; **12**: CD004224.
- Alfirevic Z, Milan SJ, Livio S. Caesarean section versus vaginal delivery for preterm birth in singletons. *Cochrane Database Syst Rev* 2012; **6**: CD000078.
- Hofmeyr GJ, Hannah M, Lawrie TA. Planned caesarean section for term breech delivery. *Cochrane Database Syst Rev* 2015; **7**: CD000166.
- Litorp H, Kidanto HL, Nystrom L, Darj E, Essén B. Increasing caesarean section rates among low-risk groups: a panel study classifying deliveries according to Robson at a university hospital in Tanzania. *BMC Pregnancy Childbirth* 2013; **13**: 107.
- Mola G. Port Moresby General Hospital, Division of Obstetrics and Gynaecology, annual reports–2016. Port Moresby, Papua New Guinea: Port Moresby General Hospital, National Department of Health, 2017.
- Guise JM, Denman MA, Emeis C, et al. Vaginal birth after caesarean: new insights on maternal and neonatal outcomes. *Obstet Gynecol* 2010; **115**: 1267–78.
- Fahmy WM, Crispin CA, Cliffe S. Association between maternal death and caesarean section in Latin America: a systematic literature review. *Midwifery* 2018; **59**: 88–93.
- Hou L, Hellerstein S, Vitonis A, et al. Cross sectional study of mode of delivery and maternal and perinatal outcomes in mainland China. *PLoS One* 2017; **12**: e0171779.
- Gregory KD, Jackson S, Korst L, Fridman M. Caesarean versus vaginal delivery: whose risks? Whose benefits? *Am J Perinatol* 2012; **29**: 7–18.
- Harper MA, Byington RP, Espeland MA, Naughton M, Meyer R, Lane K. Pregnancy-related death and health care services. *Obstet Gynecol* 2003; **102**: 273–78.
- Deneux-Tharaux C, Carmona E, Bouvier-Colle MH, Bréart G. Postpartum maternal mortality and caesarean delivery. *Obstet Gynecol* 2006; **108**: 541–48.
- Liu S, Liston RM, Joseph KS, Heaman M, Sauve R, Kramer MS. Maternal mortality and severe morbidity associated with low-risk planned caesarean delivery versus planned vaginal delivery at term. *CMAJ* 2007; **176**: 455–60.
- Zwart JJ, Richters JM, Ory F, de Vries JI, Bloemenkamp KW, van Roosmalen J. Severe maternal morbidity during pregnancy, delivery and puerperium in the Netherlands: a nationwide population-based study of 371,000 pregnancies. *BJOG* 2008; **115**: 842–50.
- van Dillen J, Zwart JJ, Schutte J, Bloemenkamp KW, van Roosmalen J. Severe acute maternal morbidity and mode of delivery in the Netherlands. *Acta Obstet Gynecol Scand* 2010; **89**: 1460–65.
- Pallasmaa N, Ekblad U, Gissler M. Severe maternal morbidity and the mode of delivery. *Acta Obstet Gynecol Scand* 2008; **87**: 662–68.
- Mylonas I, Frieke K. Indications for and risks of elective caesarean section. *Dtsch Arztebl Int* 2015; **112**: 489–95.
- D'Souza R. Caesarean section on maternal request for non-medical reasons: putting the UK National Institute of Health and Clinical Excellence guidelines in perspective. *Best Pract Res Clin Obstet Gynaecol* 2013; **27**: 165–77.
- National Institute of Health and Care Excellence. Caesarean section: clinical guideline CG132. August, 2012. <https://www.nice.org.uk/guidance/cg132> (accessed Sept 15, 2018).
- National Institutes of Health. National Institutes of Health state-of-the-science conference: caesarean delivery on maternal request. March 27–29, 2006. *Obstet Gynecol* 2006; **107**: 1386–97.
- Wax JR. Maternal request caesarean versus planned spontaneous vaginal delivery: maternal morbidity and short term outcomes. *Semin Perinatol* 2006; **30**: 247–52.
- Allen VM, O'Connell CM, Liston RM, Baskett TF. Maternal morbidity associated with caesarean delivery without labor compared with spontaneous onset of labor at term. *Obstet Gynecol* 2003; **102**: 477–82.
- Vadnais M, Sachs B. Maternal mortality with caesarean delivery: a literature review. *Semin Perinatol* 2006; **30**: 242–46.
- Keag OE, Norman JE, Stock SJ. Long-term risks and benefits associated with caesarean delivery for mother, baby, and subsequent pregnancies: systematic review and meta-analysis. *PLoS Med* 2018; **15**: e1002494.
- Rørtveit G, Hannestad YS. Association between mode of delivery and pelvic floor dysfunction. *Tidsskr Nor Lægeforen* 2014; **134**: 1848–52.
- Pretlove SJ, Thompson PJ, Toozs-Hobson PM, Radley S, Khan KS. Does the mode of delivery predispose women to anal incontinence in the first year postpartum? A comparative systematic review. *BJOG* 2008; **115**: 421–34.
- Nelson RL, Furner SE, Westercamp M, Farquhar C. Caesarean delivery for the prevention of anal incontinence. *Cochrane Database Syst Rev* 2010; **2**: CD006756.

- 37 Berghella V. Cesarean delivery: postoperative issues. July 12, 2018. <http://www.uptodate.com/contents/cesarean-delivery-postoperative-issues> (accessed Sept 14, 2018).
- 38 Abenhaim HA, Tulandi T, Wilchesky M, et al. Effect of cesarean delivery on long-term risk of small bowel obstruction. *Obstet Gynecol* 2018; **131**: 354–59.
- 39 Lindquist SAI, Shah N, Overgaard C, et al. Association of previous cesarean delivery with surgical complications after a hysterectomy later in life. *JAMA Surg* 2017; **152**: 1148–55.
- 40 Gurol-Urganci I, Bou-Antoun S, Lim CP et al. Impact of caesarean section on subsequent fertility: a systematic review and meta-analysis. *Hum Reprod* 2013; **28**: 1943–52.
- 41 O'Neill SM, Kearney PM, Kenny LC, et al. Caesarean delivery and subsequent pregnancy interval: a systematic review and meta-analysis. *BMC Pregnancy Childbirth* 2013; **13**: 165.
- 42 DiMatteo MR, Morton SC, Lepper HS, et al. Cesarean childbirth and psychosocial outcomes: a meta-analysis. *Health Psychol* 1996; **15**: 303–14.
- 43 Garthus-Niegel S, von Soest T, Knoph C, Simonsen TB, Torgersen L, Eberhard-Gran M. The influence of women's preferences and actual mode of delivery on post-traumatic stress symptoms following childbirth: a population-based, longitudinal study. *BMC Pregnancy Childbirth* 2014; **14**: 191.
- 44 Marshall NE, Fu R, Guise JM. Impact of multiple cesarean deliveries on maternal morbidity: a systematic review. *Am J Obstet Gynecol* 2011; **205**: 262.
- 45 Azam S, Khanam A, Tirapur S, Khan K. Planned caesarean section or trial of vaginal delivery? A meta-analysis. *Curr Opin Obstet Gynecol* 2014; **26**: 461–68.
- 46 O'Neill SM, Kearney PM, Kenny LC, et al. Caesarean delivery and subsequent stillbirth or miscarriage: systematic review and meta-analysis. *PLoS One* 2013; **8**: e54588.
- 47 Kwee A, Bots ML, Visser GHA, Bruinse HW. Emergency peripartum hysterectomy: a prospective study in The Netherlands. *Eur J Obstet Gynecol Reprod Biol* 2006; **124**: 187–92.
- 48 Silver RM, Landon MB, Rouse DJ, et al. Maternal morbidity associated with multiple repeat cesarean deliveries. *Obstet Gynecol* 2006; **107**: 1226–32.
- 49 Colmorn LB, Petersen KB, Jakobsson M, et al. The Nordic Obstetric Surveillance Study: a study of complete uterine rupture, abnormally invasive placenta, peripartum hysterectomy, and severe blood loss at delivery. *Acta Obstet Gynecol Scand* 2015; **94**: 734–44.
- 50 Rossi AC, Prefumo F. Pregnancy outcomes of induced labor in women with previous cesarean section: a systematic review and meta-analysis. *Arch Gynecol Obstet* 2015; **291**: 273–80.
- 51 Bujold E, Goyet M, Marcoux S, et al. The role of uterine closure in the risk of uterine rupture. *Obstet Gynecol* 2010; **116**: 43–50.
- 52 Thisted DLA, Mortensen LH, Hvidman L, Krebs L. Operative technique at caesarean delivery and risk of complete uterine rupture in a subsequent trial of labour at term. A registry case-control study. *PLoS One* 2017; **12**: e0187850.
- 53 Di Renzo GC, Giardina I, Rosati A, Clerici G, Torricelli M, Petraglia F. Maternal risk factors for preterm birth: a country-based population analysis. *Eur J Obstet Gynecol Reprod Biol* 2011; **159**: 342–46.
- 54 Levine LD, Sammel MD, Hirshberg A, Elovitz MA, Srinivas SK. Does stage of labor at time of cesarean delivery affect risk of subsequent preterm birth? *Am J Obstet Gynecol* 2015; **212**: 360.
- 55 Cook JR, Jarvis S, Knight M, Dhanjal MK. Multiple repeat caesarean section in the UK: incidence and consequences to mother and child. A national, prospective, cohort study. *BJOG* 2013; **120**: 85–91.
- 56 Tita AT, Landon MB, Spong CY, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *N Engl J Med* 2009; **360**: 111–20.
- 57 Wilmink FA, Hukkelhoven CW, Lunshof S, Mol BW, van der Post JA, Papatsonis DN. Neonatal outcome following elective cesarean section beyond 37 weeks of gestation: a 7-year retrospective analysis of a national registry. *Am J Obstet Gynecol* 2010; **202**: 250.
- 58 Curran EA, Dalman C, Kearney PM, et al. Association between obstetric mode of delivery and autism spectrum disorder. *JAMA Psychiatry* 2015; **72**: 935–42.
- 59 Curran EA, Cryan JF, Kenny LC, et al. Obstetrical mode of delivery and childhood behavior and psychological development in a British cohort. *J Autism Dev Disord* 2016; **46**: 603–14.
- 60 Polidano C, Zhu A, Bornstein JC. The relation between cesarean birth and child cognitive development. *Sci Rep* 2017; **7**: 11483.
- 61 Smithers LG, Mol BW, Wilkinson C, Lynch JW. Implications of caesarean section for children's school achievement: a population-based study. *Aust NZ J Obstet Gynaecol* 2016; **56**: 374–80.
- 62 Tribe RM, Taylor PD, Kelly NM, Rees D, Sandall J, Kennedy HP. Parturition and the perinatal period: can mode of delivery impact on the future health of the neonate? *J Physiol* 2018; published online March 13. DOI:10.1113/JP275429.
- 63 Hill CJ, Lynch DB, Murphy K, et al. Evolution of gut microbiota composition from birth to 24 weeks in the INFANTMET Cohort. *Microbiome* 2017; **5**: 4.
- 64 Jakobsson HE, Abrahamsson TR, Jenmalm MC, et al. Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. *Gut* 2014; **63**: 559–66.
- 65 Chu S, Chen Q, Chen Y, Bao Y, Wu M, Zhang J. Cesarean section without medical indication and risk of childhood asthma, and attenuation by breastfeeding. *PLoS One* 2017; **12**: e0184920.
- 66 Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* 2005; **122**: 107–18.
- 67 Olszak T, An D, Zeissig S, et al. Microbial exposure during early life has persistent effects on natural killer T cell function. *Science* 2012; **336**: 489–93.
- 68 Atarashi K, Tanoue T, Oshima K, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. *Nature* 2013; **500**: 232–36.
- 69 Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* 2013; **504**: 451–55.
- 70 Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature* 2013; **504**: 446–50.
- 71 Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* 2013; **341**: 569–73.
- 72 Hapfelmeier S, Lawson MA, Slack E, et al. Reversible microbial colonization of germ-free mice reveals the dynamics of IgA immune responses. *Science* 2010; **328**: 1705–09.
- 73 Schirmer M, Smeekens SP, Vlamakis H, et al. Linking the human gut microbiome to inflammatory cytokine production capacity. *Cell* 2016; **167**: 1125–36.
- 74 Mueller NT, Whyatt R, Hoepner L, et al. Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity. *Int J Obes (Lond)* 2015; **39**: 665–70.
- 75 Sinha A, Bewley S, McIntosh T. Myth: babies would choose prelabour caesarean section. *Semin Fetal Neonatal Med* 2011; **16**: 247–53.
- 76 Martikainen MV, Keski-Nisula L, Jakupović H, et al. The lack of natural processes of delivery and neonatal intensive care treatment lead to impaired cytokine responses later in life. *Am J Reprod Immunol* 2017; **77**: e12621.
- 77 Dahlen HG, Kennedy HP, Anderson CM, et al. The EPIIC hypothesis: intrapartum effects on the neonatal epigenome and consequent health outcomes. *Med Hypotheses* 2013; **80**: 656–62.
- 78 Almgren M, Schlinzig T, Gomez-Cabrero D, et al. Cesarean delivery and hematopoietic stem cell epigenetics in the newborn infant: implications for future health? *Am J Obstet Gynecol* 2014; **211**: 502.
- 79 Schlinzig T, Johansson S, Gunnar A, Ekstrom TJ, Norman M. Epigenetic modulation at birth—altered DNA-methylation in white blood cells after caesarean section. *Acta Paediatr* 2009; **98**: 1096–99.
- 80 Virani S, Dolinoy DC, Halubai S, et al. Delivery type not associated with global methylation at birth. *Clin Epigenetics* 2012; **4**: 8.
- 81 Weaver IC, Cervoni N, Champagne FA, et al. Epigenetic programming by maternal behavior. *Nat Neurosci* 2004; **7**: 847–54.
- 82 McCallie KR, Gaikwad NW, Castillo Cuadrado ME, et al. Skin-to-skin contact after birth and the natural course of neurosteroid levels in healthy term newborns. *J Perinatol* 2017; **37**: 591–95.
- 83 Sotiriadis A, Makrydimas G, Papatheodorou S, Ioannidis JP. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. *Cochrane Database Syst Rev* 2009; **4**: CD006614.

- 84 Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. *BMJ* 2016; **355**: i5044.
- 85 Srinivasjois R, Silva D. Antenatal steroid administration in medically uncomplicated pregnancy beyond 37 weeks of gestation for the prevention of neonatal morbidities prior to elective caesarean section: a systematic review and meta-analysis of randomised controlled trials. *J Matern Fetal Neonatal Med* 2017; **30**: 1151–57.
- 86 Althabe F, Belizán JM, McClure EM, et al. A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: the ACT cluster-randomised trial. *Lancet* 2015; **385**: 629–39.
- 87 Arrieta MC, Stiemsma LT, Dimitriou PA, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med* 2015; **7**: 307ra152.
- 88 Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat Med* 2016; **22**: 250–53.
- 89 Cunnington AJ, Sim K, Deierl A, Kroll JS, Brannigan E, Darby J. “Vaginal seeding” of infants born by caesarean section. *BMJ* 2016; **352**: i227.
- 90 Moya-Pérez A, Luczynski P, Renes IB, et al. Intervention strategies for caesarean section-induced alterations in the microbiota-gut-brain axis. *Nutr Rev* 2017; **75**: 225–40.
- 91 Frese SA, Hutton AA, Contreras LN, et al. Persistence of supplemented *Bifidobacterium longum* subsp. *infantis* EVC001 in breastfed infants. *mSphere* 2017; **2**: e00501–17.
- 92 Smilowitz JT, Moya J, Breck MA, et al. Safety and tolerability of *Bifidobacterium longum* subspecies *infantis* EVC001 supplementation in healthy term breastfed infants: a phase I clinical trial. *BMC Pediatr* 2017; **17**: 133.
- 93 Souza JP, Gülmezoglu AM, Vogel J, et al. Moving beyond essential interventions for reduction of maternal mortality (the WHO Multicountry Survey on Maternal and Newborn Health): a cross-sectional study. *Lancet* 2013; **381**: 1747–55.
- 94 Gebhardt GS, Fawcus S, Moodley J, Farina Z. Maternal death and caesarean section in South Africa: results from the 2011–2013 Saving Mothers Report of the National Committee for Confidential Enquiries into Maternal Deaths. *S Afr Med J* 2015; **105**: 287–91.
- 95 Epiu I, Tindimwebwa JV, Mijumbi C, et al. Challenges of anesthesia in low- and middle-income countries: a cross-sectional survey of access to safe obstetric anesthesia in East Africa. *Anesth Analg* 2017; **124**: 290–99.
- 96 Harrison MS, Goldenberg RL. Caesarean section in sub-Saharan Africa. *Matern Health Neonatol Perinatol* 2016; **2**: 6.
- 97 Sanda G, Chipkao R, Harissou A, Soumana A, Tassiou EM. Les fistules uro-génitales iatrogènes: à propos de 62 cas et revue de la littérature. *Afr J Urol* 2016; **22**: 55–60 (in French).
- 98 Countdown to 2030 Collaboration. Countdown to 2030: tracking progress towards universal coverage for reproductive, maternal, newborn, and child health. *Lancet* 2013; **391**: 1538–48.
- 99 Irani M, Deering S. Challenges affecting access to caesarean delivery and strategies to overcome them in low-income countries. *Int J Gynaecol Obstet* 2015; **131**: 30–34.
- 100 Sumigama S, Itakura A, Ota T, et al. Placenta previa increta/percreta in Japan: a retrospective study of ultrasound findings, management and clinical course. *J Obstet Gynaecol Res* 2007; **33**: 606–11.
- 101 Angstmann T, Gard G, Harrington T, Ward E, Thomson A, Giles W. Surgical management of placenta accreta: a cohort series and suggested approach. *Am J Obstet Gynecol* 2010; **202**: 38.
- 102 Mola GDL, Unger HW. Strategies to reduce perinatal mortality in low-income settings—findings from a four-decade cross-sectional study of assisted vaginal birth from Papua New Guinea. *Aust NZ J Obstet Gynaecol* 2018; published online Sept 13. DOI:10.1111/ajo.12876.
- 103 Litorp H, Kidanto HL, Nystrom L, Darj E, Essén B. Increasing caesarean section rates among low-risk groups: a panel study classifying deliveries according to Robson at a university hospital in Tanzania. *BMC Pregnancy Childbirth* 2013; **13**: 107.
- 104 Litorp H, Kidanto HL, Rööst M, Abeid M, Nyström L, Essén B. Maternal near-miss and death and their association with caesarean section complications: a cross-sectional study at a university hospital and a regional hospital in Tanzania. *BMC Pregnancy Childbirth* 2014; **14**: 244.
- 105 Litorp H, Rööst M, Kidanto HL, Nyström L, Essén B. The effects of previous caesarean deliveries on severe maternal and adverse perinatal outcomes at a university hospital in Tanzania. *Int J Obstet Gynecol* 2016; **133**: 183–87.

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