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SARAH J STOCK (Orcid ID: 0000-0003-4308-856X)

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Caesarean birth and risk of subsequent preterm birth: a retrospective cohort study

Carolina Williams¹, Rosalyn Fong¹, Sarah Murray¹, Sarah J Stock^{1,2}

1) Tommy's Centre for Maternal and Fetal Health, University of Edinburgh MRC Centre for Reproductive Health Queen's Medical Research Institute, Edinburgh EH16 4TJ

2) University of Edinburgh Usher Institute, NINE Edinburgh BioQuarter, 9 Little France Road, Edinburgh EH16 4UX

Corresponding Author: Dr Sarah J Stock, Centre for Medical Informatics, Usher Institute, University of Edinburgh, NINE Edinburgh BioQuarter, 9 Little France Road, Edinburgh EH16 4UX. Email: sarah.stock@ed.ac.uk Tel: +44 (0)131 242 2691

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Abstract

Objective

To determine the risk of spontaneous and medically indicated preterm birth associated with mode of birth in previous term born pregnancy.

Design

Retrospective cohort study

Setting

Two UK maternity units

Population or Sample

16340 women with first two consecutive singleton births and the first birth at term

Methods

Retrospective cohort study using routinely collected clinical data.

Main Outcome Measures

Incidence of spontaneous preterm birth and medically indicated preterm birth less than 37 weeks gestation after term birth, in relation to mode of birth in first pregnancy. Subgroup analysis on cervical dilatation at the time of first caesarean birth.

Results

Compared to vaginal birth, emergency caesarean birth at full dilatation was associated with an increase in spontaneous preterm birth (2.3% vaginal birth versus 4.5% full dilatation caesarean; adjusted Odds Ratio [aOR] 3.29 (95% Confidence Interval [CI] 2.02-5.13, p<0.001). Elective, emergency caesarean <4cm, and emergency caesarean 4-9 cm were associated with increased medically indicated preterm birth (0.8% vaginal births versus 1.9 % elective caesarean, 3.3% <4 cm caesarean, 1.3% 4-9 cm caesarean; aOR 2.30 [1.19-4.15], p=0.009; 4.68 [2.98-7.24], p<0.001; and 2.43 [1.43-4.00], p=0.001 respectively).

Conclusions

Term caesarean in the first stage of labour or performed prelabour is associated with medically indicated preterm birth. Term caesarean in the second stage of labour is associated with spontaneous preterm birth.

Funding

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Keywords

Pregnancy; Preterm Labour; Preterm Birth; Caesarean; Mode of Birth

Tweetable abstract

Caesarean in the second stage of labour is associated with spontaneous preterm birth.

Introduction

Preterm birth, defined as birth before completing 37 weeks gestation, is a major public health problem. It is the leading cause of childhood mortality below 5 years of age, ² and associated with short and long-term morbidities. Around two thirds of preterm births are 'spontaneous', being preceded by spontaneous onset of contractions and/or cervical dilatation, or by spontaneous preterm prelabour rupture of membranes. The remaining third of preterm births are indicated preterm birth i.e. initiated by care providers due to complications in the mother or baby when the risks of ongoing pregnancy outweigh the risks of delivery. ³

A number of risk factors have been associated with preterm birth including nulliparity, previous preterm birth, cervical surgery, short interpregnancy interval, social deprivation and smoking. ⁴ Caesarean birth has been associated with preterm birth in a subsequent pregnancy in some ⁵⁻⁷ but not other studies ^{8, 9}. The stage in labour that caesarean is performed may be crucial, with some studies suggesting preterm birth risk is higher if caesarean is carried in the second stage of labour, when the cervix is fully (10 cm) dilated, compared to caesarean before labour onset ^{2, 5, 10-12}. Trauma to the cervix at the time of caesarean, which is more common at full dilatation caesarean birth, may impair the cervical function to retain a pregnancy in a subsequent pregnancy, resulting in spontaneous preterm labour.

Quantifying the risk of subsequent preterm birth associated with index pregnancy mode of birth could have a number of benefits. Firstly, it could help inform decision making around mode of birth in the first pregnancy. Secondly, it could help identify those at risk of preterm birth in a subsequent pregnancy who may benefit from additional screening and interventions to improve neonatal outcome. Thirdly, it could provide better understanding of the potential mechanisms underlying different types of preterm birth and inform preventative strategies.

The objective of this study was to determine the risk of preterm birth in women who have had one singleton term birth; and determine the influence of mode of first birth on spontaneous and indicated preterm birth in the next pregnancy. The distinction between spontaneous and indicated preterm birth is important, due to their different aetiologies.

Methods

Ethics and Reporting

Results are reported according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines. ¹³ A National Research Ethics Service tool was completed, which indicated that full ethical review was not required (IRAS number 283966). Local registration was granted by NHS Lothian and the University of Edinburgh (Lothian R&D Project No: 2020/0102 Sponsor Reference: AC20076) in line with local clinical governance procedures.

Core outcome set

This is a retrospective cohort study of routine data with the primary aim of exploring the relationship between mode of birth and subsequent preterm birth. We have used (as far as was possible within the constraints of routinely collected data) the minimum data set required for studies into preterm birth ¹⁴, but no other relevant core outcome set exists for this non-interventional study.

Parental and patient involvement

As our study aims to determine a risk factor for preterm birth it aligns with the number one research priority for preterm birth "Which interventions (including diagnostic tests) are most effective to predict or prevent preterm birth?" identified by a James Lind Alliance Stakeholder priority Setting Partnership that included parents and preterm born adults. ¹⁵ As the study was a data analysis project, parents were not involved in the conduct of the research. However, we have strong links with Tommy's the baby charity who supported this work. Tommy's will be consulted on further dissemination of findings, and we anticipate using their large parental network to leverage this.

Funding

There was no specific funding for this work. SJS is supported by a Wellcome Trust Clinical Career development fellowship (209560/Z/17/Z). The work was carried out at the MRC Centre for Reproductive Health (MR/N022556/1). Infrastructure support was provided through Tommy's (registered charity in Scotland SC039280).

Study design, setting and population

This was a retrospective cohort study at two UK maternity units: the Royal Infirmary of Edinburgh (a tertiary referral centre with approximately 6500 births per year) between 1st January 2009 and

31st December 2018 and St John's Hospital Livingston (a district general hospital with approximately 3500 births per year) between 1st July 2009 and 31st December 2018.

Inclusion criteria

Women were included if they i) had maternity care for their first two consecutive births (i.e. their parity = 0 and parity = 1 pregnancy) in either hospital, and ii) their first birth was at term (37-43+6 weeks gestation). Women were excluded if the first birth was a stillbirth, they had a midtrimester loss preceding their first term birth, there was uncertainty about the gestational age at birth in either pregnancy, either pregnancy was a multiple pregnancy, or if mode of birth in the first pregnancy was not recorded.

Data source

The study was a secondary analysis of data extracted from clinical maternity records for service evaluation. Data was extracted from the TrakCare (InterSystems, Cambridge, MA, USA) electronic maternity record that is used to record all antenatal, intrapartum and postnatal care across the two hospital sites. Search criteria to identify women were based on parity, to identify first two consecutive pregnancy records (Figure 1). Women generally book for maternity care 9-11 weeks gestation. Pregnancies ending before this are not captured. Most outcomes and covariates were directly extracted from structured data fields within the maternity record. All structured variables are reported in national birth records (Scottish Morbidity Report 02), and so are quality assured and have high completeness. ¹⁶ Structured data were supplemented by hand searching of records to verify i) cervical dilatation at the time of caesarean in women who had an emergency caesarean birth (3,308 records) and ii) onset of preterm birth in women who had a preterm birth (507 records). An anonymised extract of data was provided identified by a randomly generated study identifier. To preserve anonymity, all dates within pregnancy were converted to gestation (days) and the interpregnancy interval converted to days (calculated from the birth-tobirth interval minus the gestational age of the second birth). Scottish Index of Multiple Deprivation (SIMD) quintile was derived from postcode, based on the most recent version of SIMD available prior to the year of birth. ¹⁷ All data were stored and analysed on password protected University servers.

Exposures

The exposure was mode of birth in first pregnancy. This was categorised as vaginal birth (spontaneous vertex deliveries and vaginal breech deliveries), assisted vaginal birth (forceps and ventouse deliveries), planned caesarean birth (scheduled caesarean), prelabour/early labour emergency caesarean birth (cervical dilation <4cm), emergency caesarean birth in first stage of labour (cervical dilation 4-9cm), and emergency caesarean birth in second stage of labour (at full dilatation [10cm]). Cervical dilatation data was taken from findings of the last vaginal examination before birth. If an emergency caesarean was performed without preceding vaginal examination and there were no signs of labour documented (e.g. no contractions), birth was be categorised as prelabour/early labour emergency caesarean birth (cervical dilatation 0cm). In two cases cervical dilatation was missing, but first stage of labour was documented. These two cases were categorised as emergency caesarean birth in first stage of labour for the primary analysis.

A subgroup analysis was performed, including only women who had emergency caesarean birth, with the exposure being cervical dilatation (cm). If cervical dilatation was recorded as being in between two integers it was rounded down, and if it was recorded as a "rim" it was categorised 9cm. Two cases included in the primary analysis were excluded from the subgroup analysis on cervical dilatation due to missing data on cervical dilatation (with only first stage of labour recorded).

Outcomes

The primary outcomes were spontaneous and indicated preterm birth less than 37 weeks gestation. Spontaneous preterm birth was defined as preterm birth after spontaneous onset of contractions and/or cervical dilatation, or preceded by preterm prelabour rupture of membranes. Indicated preterm birth was defined as elective (planned) caesarean birth, emergency prelabour caesarean birth, or induction of labour (in the absence of prelabour rupture of membranes). Gestation was determined by first trimester ultrasound scan. Secondary outcomes were spontaneous and indicated early preterm birth less than 34 weeks gestation. Gestation of birth (weeks) of second pregnancy was also considered as a continuous variable in time-to-event analysis.

Covariables

Data on clinically plausible potential confounding factors that were assumed to be associated with the mode of birth of the first pregnancy and preterm birth were prespecified and included as risk adjustment factors. Gestational age of the first birth (weeks), birthweight centile of the first baby (calculated using the Intergrowth Newborn size centiles ¹⁸ with the centile for 42+6 weeks used if gestation of birth was ≥42+6 weeks) and interpregnancy interval were included as continuous variables.

Potential maternal confounders were extracted from the second pregnancy record. Maternal age at second birth was included as a continuous variable. The SIMD quintile was used as an indicator of social deprivation with 1 indicating highest deprivation and 5 indicating lowest deprivation (referent). ¹⁷ Maternal smoking status at pregnancy booking was categorised as current smoker or non-smoker. Maternal body mass index (BMI kg/m²) was categorised according to World Health Organisation Definitions as underweight (<18.5), normal (18.5-24.9; referent), overweight (25-29.9), and obese (≥30). ¹⁹ Where data were not available for BMI, SIMD and smoking, they were categorised as "Unknown" and included in the analysis to prevent loss of information within models (Table S1). Maternal ethnicity was initially categorised as recommended by Information Services Division Scotland Ethnic Group (White, Mixed or multiple ethnic groups, Asian, Asian Scottish or Asian British, African, Caribbean or Black, Other ethnic group, Refused/Not provided, Not known). ²⁰ However, due to high proportion of the cohort being white (93%), with very low proportions of individual non-white ethnicities (0.2 - 4%), we collapsed maternal ethnicity into three categories, White, Other ethnic group and Unknown.

Statistical Analysis

To maximise the power of the study to detect differences between groups we included all eligible births available in the service improvement dataset from January 2009 to December 2018 for Royal Infirmary of Edinburgh births, and July 2009 to December 2018 for St John's Hospital Livingston births. TrakCare was implemented in the Royal Infirmary of Edinburgh in 2008, and in St John's Hospital Livingston in 2009.

All analyses were carried out in R (Version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria).

Summary statistics were derived and stratified by first birth mode of birth (Vaginal birth, Assisted vaginal birth, Elective caesarean birth, Emergency caesarean prelabour or early labour, Emergency caesarean birth in first stage of labour, Emergency caesarean birth in second stage of labour). All hypothesis tests were two-sided, and statistical significance assumed at p < 0.05. Univariable comparisons of categorical data were performed using χ^2 . The relationship between having a spontaneous or indicated preterm birth in the second pregnancy and mode of birth in the

first pregnancy was assessed by multiple logistic regression using potential confounders adjustment variables as fixed effects, with unadjusted and adjusted Odds Ratio and 95% confidence intervals (CI) presented. All potential confounders that were pre-specified (gestation of first birth, birthweight centile of first birth, interpregnancy interval, maternal age, ethnicity, BMI category, smoking status and deprivation index) were included in logistic regression models. In a supplementary analysis we compared patterns seen in logistic regression models (with preterm birth as a binary outcome and presentation of OR and 95% CI) with patterns seen in Cox proportional hazards models (time-to-event analysis for duration of pregnancy and presentation of Hazard ratios [HR] and 95% CI). Kaplan-Meier curves (unadjusted) were plotted for gestation of spontaneous preterm birth and gestation of indicated preterm birth (in weeks), categorised by the mode of birth of first birth. We right censored for indicated preterm birth in the spontaneous preterm birth plot, and right censored for spontaneous preterm birth plot. As survival curves converge at term we also censored at 37 weeks gestation. A subgroup analysis was performed for the binary outcome of spontaneous preterm birth (less than 37 weeks gestation), in women who had caesarean in labour, with the exposure being cervical dilatation (cm) considered as a continuous variable.

Post hoc analyses

A number of changes to the analyses pre-specified in the protocol were made in response to feedback from reviewers. Maternal age, gestation of first birth, birthweight centile and interpregnancy interval were included in models as continuous variables rather than categorised. Time-to-event analyses were included as supplementary analyses, to increase confidence in the findings from logistic regression models. Elective caesarean births were excluded from the subgroup analyses exploring the relationship between cervical dilatation and spontaneous preterm birth (i.e. this analysis was confined to women having emergency caesarean). Cervical dilation was considered as a continuous variable in this subgroup analysis.

Results

Participant characteristics

16343 women (of 67735 women with any pregnancy record during the study period) had records for their first two consecutive singleton births, with the first birth (i.e. when they were Parity = 0) a livebirth at term gestation (Figure 1). 3 women were excluded from the analysis as data on the gestation of the first birth was missing.

Characteristics of the cohort, stratified by mode of first birth, are shown in Table S1. Of the 16340 women included in the analysis, 7743 (47.4%) had a vaginal birth, 4580 (28.0%) had an assisted vaginal birth, 709 (4.3%) had an elective caesarean birth, 1042 (6.4%) had an emergency caesarean birth before or in the early stages of labour, 1755 (10.7%) had an emergency caesarean birth in the first stage of labour, and 511 women (3.1%) emergency caesarean birth in the second stage of labour.

In the second pregnancy (i.e. when women were Parity = 1), after having one previous term birth, 15833 women (96.9%) had another term birth, 333 (2.0%) of women had a spontaneous preterm birth less than 37 weeks gestation and 174 (1.1%) had an indicated preterm birth less than 37 weeks gestation. Rates of early preterm birth were low, with 77 (0.5%) of women having a spontaneous preterm birth less than 34 weeks gestation and 40 (0.2%) women having an indicated preterm birth less than 34 weeks gestation.

Mode of birth and risk of subsequent spontaneous or medically indicated preterm birth less than 37 weeks

Associations between mode of birth and spontaneous preterm birth and medically indicated preterm birth at less than 37 weeks are shown in Table 1. Full model details are provided in Tables S2 and S3.

Compared to vaginal birth, emergency caesarean birth in the second stage of labour was associated with a three-fold increase in spontaneous preterm birth (adjusted OR 3.29 [2.02-5.13], p<0.001) after adjustment for confounders. Other modes of birth were not independently associated with risk of subsequent spontaneous preterm labour.

A different relationship was seen between mode of birth and subsequent medically indicated preterm birth. Compared to vaginal birth (unadjusted risk 0.8%), an increased risk of indicated preterm birth was seen in association with elective (adjusted OR 2.30 [1.19-4.15], p=0.009) prelabour/early labour emergency (adjusted OR 4.68 [2.98-7.24], p<0.001) and first stage of labour emergency caesarean (adjusted OR 2.43 [1.43-4.00], p=0.001) on multivariable analysis adjusting for confounders. Second stage caesarean (unadjusted risk 1.0%) was not associated with an increased risk of medically indicated preterm birth compared to vaginal birth.

Time to event analyses showed similar relationships between mode of birth and subsequent preterm birth as seen in logistic regression analysis. Figure 2 shows Kaplan-Meier curves of spontaneous preterm births (panel a) and indicated preterm births (panel b) in second pregnancy, stratified by mode of birth of the first birth. Hazard Ratios (HRs) for spontaneous preterm birth and indicated preterm births are shown in Tables S4 and S5 respectively. Multivariable time-to-event analysis again indicated an independent effect of second stage caesarean birth on subsequent spontaneous preterm birth compared to vaginal birth (adjusted HR 3.10 [1.99-4.84], p<0.001). Other modes of birth were not associated with spontaneous preterm birth, when compared to vaginal birth. In contrast, elective (HR 2.31 [1.25-4.26], p=0.008), prelabour/early labour emergency (HR 4.51 [2.93-6.95], p<0.001), and first stage emergency caesarean (HR 2.39 [1.434-3.96], p=0.001), but not second stage caesarean, were independently associated with medically indicated preterm birth in the subsequent pregnancy, when compared to vaginal birth.

Mode of birth and risk of subsequent spontaneous or medically indicated preterm birth less than 34 weeks

Associations between mode of birth and spontaneous early preterm birth and medically indicated early preterm birth at less than 34 weeks are shown in Tables S6 and S7.

Absolute risks of early preterm birth were very low, at less than 1% for all modes of birth; except for second stage caesarean birth, which was associated with an absolute risk of 2% (10/493) for spontaneous early preterm birth. Compared to vaginal birth, caesarean birth in the second stage of labour was associated with early spontaneous preterm birth less than 34 weeks gestation (adjusted OR 7.55 [3.42-15.41], p<0.001). Compared to vaginal birth, emergency caesarean in the first stage of labour was associated with increased risk of early indicated preterm birth (unadjusted risk 0.2% for vaginal birth and 0.7% for pre/early labour caesarean; adjusted OR 4.16 [1.55-10.09], p=0.002).

Cervical dilatation and risk of spontaneous preterm birth

Figure 3 shows the relationship between spontaneous preterm birth less than 37 weeks gestation, and cervical dilatation in women with emergency caesarean births in their first pregnancy. The full model is shown in Table S8. Dilation at the time of first emergency caesarean was independently associated with risk of subsequent spontaneous preterm birth, such that every cm of dilatation was associated with increased odds of subsequent spontaneous preterm birth with an adjusted OR 1.15 (1.07-1.24, p<0.001) on multivariable analysis.

Discussion

Main Findings

Compared with vaginal birth, caesarean birth in the second stage of labour is associated with increased rates of subsequent spontaneous preterm birth at less than 37 weeks gestation, and early spontaneous preterm birth at less than 34 weeks gestation. Caesarean birth in the first stage of labour is not associated with an increase in spontaneous preterm birth. In contrast, pre, early or first stage caesarean birth, but not second stage caesarean birth, is associated with increased risk of subsequent medically indicated preterm birth.

Strengths and Limitations

Strengths of our study are that it is a large cohort study using routinely collected data with high completeness, analysed according to a predefined protocol; the outcomes of all second pregnancies booked at the maternity units were included (including mid trimester losses); and we provide absolute estimates of the risk of preterm birth. In our analysis we adjusted for a number of recognised confounding factors including interpregnancy interval and gestation of first term birth that have not been included in other studies. However, despite including more than 16000 women with first two consecutive singleton pregnancies, the numbers of early preterm births (less than 34 weeks) were low, and so there are wide confidence intervals around some estimates, particularly for medically indicated early preterm birth. These data must therefore be interpreted with caution. The study was based in two hospitals in the same regions, where there are relatively high rates of assisted vaginal birth (28% of all term births), thus the findings may not be generalisable to some other settings. Due to the observational design of the study, causation cannot be inferred. Despite adjusting for potential confounding effects, residual confounding may be an influence results.

Interpretation

Caesarean birth could be linked to subsequent spontaneous and medically indicated preterm birth by different mechanisms. Trauma to the cervix at the time of caesarean may impair the cervical function predisposing to spontaneous preterm labour. Myometrial scarring might predispose to disorders of placental implantation (e.g. placenta previa, placenta accreta spectrum, vasa previa, and velamentous cord insertion), which are indications for indicated preterm birth. Alternatively, conditions that indicate caesarean birth in the first pregnancy (e.g. maternal medical disorders or placental insufficiency) may worsen and increase rates of indicated preterm birth in a subsequent pregnancy.

Our findings are consistent with those of a previous large Canadian cohort study by Wood et al, linking second stage caesarean birth with subsequent spontaneous preterm labour less than 32 weeks gestation. 11 A secondary analysis of a cohort study found that second stage caesarean was associated with a higher risk of spontaneous preterm birth when compared to first stage caesarean birth, but the increase in spontaneous preterm birth was not statistically significant when compared to vaginal birth, although numbers were small (37 second stage caesarean births) at term. ¹⁰ A US retrospective cohort study of women with the first two consecutive singleton deliveries did not find any association between caesarean birth and subsequent medically indicated or spontaneous preterm birth, after using propensity score analysis to adjust for confounders. 8 However, propensity score matching could only be performed on a subset of eligible pregnancies (approximately one third), meaning the generalisability of the findings to the whole cohort of women having caesarean birth may be limited, as well as having limited power to detect differences in preterm birth rates. A Dutch population study but found that overall caesarean birth at term was associated with a small increased risk in preterm birth, compared to vaginal birth, and this was mainly driven by an increase in spontaneous preterm birth. However, the study did not differentiate between the stage of labour that caesarean was performed at 7

Caesarean birth is increasingly used for operative birth in the second stage of labour, with an accompanying reduction in attempted and successful assisted vaginal births. ²¹⁻²³ A large US study found that nearly one-quarter of primary caesarean births in 2000 were in the second stage of labour. ²³ Recognition that assisted vaginal birth is associated with more than a 4-fold lower risk of subsequent preterm birth than second stage caesarean birth may help influence future decisions around mode of birth in the second stage.

Nevertheless, the absolute risk of preterm birth following term caesarean birth in the second stage of labour is relatively low, being 4.5% for spontaneous preterm birth less than 37 weeks gestation and 2% for spontaneous preterm birth less than 34 weeks gestation. Current NHS England guidance is that all women who have had a second stage caesarean birth should have a single cervical length scan in a subsequent pregnancy. ²⁴ However, this is not based on any evidence that cervical length is an effective or cost-effective screening strategy for preterm birth in this population, or that preventative treatments that might be used such as cervical cerclage work. A small case-control study suggested that women with a previous second stage caesarean at term were more likely to have recurrent preterm birth than women with a previous term vaginal birth. ²⁵ Further research is required to confirm the association between second stage caesarean and early spontaneous preterm birth and confirm appropriate management strategies.

Conclusion

Caesarean birth in the second stage of term labour is associated with increased risk of subsequent spontaneous preterm birth, whilst caesarean birth in early or first stage of labour is associated with subsequent medically indicated preterm birth, compared with vaginal birth.

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Disclosure of Interests

SJS receives grant funding (paid to the institution) from Wellcome Trust, National Institute of Healthcare Research, and Chief Scientist Office Scotland. The authors declare no conflicts of interest. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to Authorship

SJS conceived the study. CW, RF and SJS wrote the protocol. SJS and SM performed the analysis. CW drafted the manuscript. All authors commented and edited the manuscript.

Details of Ethical Approval

A National Research Ethics Service tool was completed, which indicated that full ethical review was not required (IRAS number 283966). Local registration was granted by NHS Lothian and the University of Edinburgh (ACCORD, R&D No: 2020/0102) in line with local clinical governance procedures.

Funding

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References

- 1. NICE. National Institute of Health and Care Excellence NG25: Preterm labour and birth. London; 2015.
- 2. Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000-15: an updated systematic analysis with implications for the Sustainable Development Goals. Lancet. 2016;388(10063):3027-35.
- 3. Norman JE, Morris C, Chalmers J. The effect of changing patterns of obstetric care in Scotland (1980-2004) on rates of preterm birth and its neonatal consequences: perinatal database study. PLoS Med. 2009;6(9):e1000153.
- 4. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84.
- 5. Wong LF, Wilkes J, Korgenski K, Varner MW, Manuck TA. Risk factors associated with preterm birth after a prior term delivery. BJOG. 2016;123(11):1772-8.
- 6. Williams CM, Asaolu I, Chavan NR, Williamson LH, Lewis AM, Beaven L, et al. Previous cesarean delivery associated with subsequent preterm birth in the United States. Eur J Obstet Gynecol Reprod Biol. 2018;229:88-93.
- 7. Visser L, Slaager C, Kazemier BM, Rietveld AL, Oudijk MA, de Groot C, et al. Risk of preterm birth after prior term cesarean. BJOG. 2020;127(5):610-7.
- 8. Vahanian SA, Hoffman MK, Ananth CV, Croft DJ, Duzyj C, Fuchs KM, et al. Term cesarean delivery in the first pregnancy is not associated with an increased risk for preterm delivery in the subsequent pregnancy. Am J Obstet Gynecol. 2019;221(1):61 e1- e7.
- 9. Keag OE, Norman JE, Stock SJ. Long-term risks and benefits associated with cesarean delivery for mother, baby, and subsequent pregnancies: Systematic review and meta-analysis. PLoS Med. 2018;15(1):e1002494.
- 10. 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(3):360 e1-7.
- 11. Wood SL, Tang S, Crawford S. Cesarean delivery in the second stage of labor and the risk of subsequent premature birth. Am J Obstet Gynecol. 2017;217(1):63 e1- e10.

- 12. Cong A, de Vries B, Ludlow J. Does previous caesarean section at full dilatation increase the likelihood of subsequent spontaneous preterm birth? Aust N Z J Obstet Gynaecol. 2018;58(3):267-73.
- 13. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med. 2007;4(10):e297.
- 14. Myatt L, Eschenbach DA, Lye SJ, Mesiano S, Murtha AP, Williams SM, et al. A standardized template for clinical studies in preterm birth. Reprod Sci. 2012;19(5):474-82.
- 15. Oliver S, Uhm S, Duley L, Crowe S, David AL, James CP, et al. Top research priorities for preterm birth: results of a prioritisation partnership between people affected by preterm birth and healthcare professionals. BMC Pregnancy Childbirth. 2019;19(1):528.
- 16. Assessment of SMR02 (Maternity Inpatient and Day Case) Data; Scotland 2017-2018. NHS National Services Scotland; 2019.
- 17. Scottish Index of Multiple Deprivation 2020: Scottish Government; [Available from: https://www.gov.scot/collections/scottish-index-of-multiple-deprivation-2020/.
- 18. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014;384(9946):857-68.
- 19. Global Strategy on Diet, Physical Activity and Health [Available from: https://www.who.int/dietphysicalactivity/childhood_what/en/.
- 20. https://www.ndc.scot.nhs.uk/Dictionary-A-Z/Definitions/index.asp?Search=E&ID=243&Title=Ethnicity%20Code
- 21. Loudon JA, Groom KM, Hinkson L, Harrington D, Paterson-Brown S. Changing trends in operative delivery performed at full dilatation over a 10-year period. J Obstet Gynaecol. 2010;30(4):370-5.
- 22. Corry EMA, Ramphul M, Rowan AM, Segurado R, Mahony RM, Keane DP. Exploring full cervical dilatation caesarean sections-A retrospective cohort study. Eur J Obstet Gynecol Reprod Biol. 2018;224:188-91.
- 23. Alexander JM, Leveno KJ, Rouse DJ, Landon MB, Gilbert S, Spong CY, et al. Comparison of maternal and infant outcomes from primary cesarean delivery during the second compared with first stage of labor. Obstet Gynecol. 2007;109(4):917-21.
- 24. Saving Babies' Lives Version Two: A care bundle for reducing perinatal mortality. 2019.

25. Watson HA, Carter J, David AL, Seed PT, Shennan AH. Full dilation cesarean section: a risk factor for recurrent second-trimester loss and preterm birth. Acta Obstet Gynecol Scand. 2017;96(9):1100-5.

Tables

Table 1: Univariable and Multivariable Logistic Regression of spontaneous preterm birth and medically indicated preterm birth <37 weeks gestation by mode of birth of first pregnancy

)ependent:								
spontaneous Preterm			Spontaneous		OR	Indicated		OR
3irth <37 weeks		Term Birth	Preterm Birth	OR (univariable)	(multivariable)	Preterm Birth	OR (univariable) (multivariable)	(multivariable)
Node of Birth	Vaginal Birth	7510 (97.7)	174 (2.3)	ı	1	59 (0.8)	ı	ı
	Assisted Birth	4472 (98.5)	67 (1.5)	0.65 (0.48-0.85, p=0.003)	0.85 (0.63-1.13, p=0.263)	41 (0.9)	1.17 (0.78-1.74, p=0.449)	1.44 (0.96-2.16, p=0.077)
	Elective CS	681 (97.8)	15 (2.2)	0.95 (0.53-1.57, p=0.853)	0.89 (0.50-1.49, p=0.680)	13 (1.9)	2.43 (1.27-4.31, p=0.004)	2.30 (1.19-4.15, p=0.009)
	Emergency CS <4cm	986 (97.8)	22 (2.2)	0.96 (0.60-1.47, p=0.869)	1.00 (0.61-1.55, p=0.999)	34 (3.3)	4.39 (2.84-6.69, p<0.001)	4.68 (2.98-7.24, p<0.001)
	Emergency CS 4-9cm	1701 (98.2)	32 (1.8)	0.81 (0.55-1.17, p=0.283)	1.45 (0.96-2.13, p=0.064)	22 (1.3)	1.65 (0.99-2.65, p=0.047)	2.43 (1.43-4.00, p=0.001)
	Emergency CS 10cm	483 (95.5)	23 (4.5)	2.06 (1.28-3.14, p=0.001)	3.29 (2.02-5.13, p<0.001)	5 (1.0)	1.32 (0.46-2.99, p=0.556)	1.76 (0.61-4.05, p=0.234)

Multivariable models include gestational age at first birth, birthweight centile, interpregnancy interval, maternal age, maternal ethnicity, maternal BMI category and maternal deprivation index. Full models are shown in table S2 and S3. For the spontaneous preterm birth model: Number in dataframe = 16166, Number in model = 16164, Missing = 2, AIC = 3026.7, C-statistic = 0.733, H&L = Chi-sq(8) 3.16 (p=0.924). For the indicated preterm birth model: Number in dataframe = 16007, Number in model = 16005, Missing = 2, AIC = 1837.6, C-statistic = 0.716, H&L = Chi-sq(8) 7.80 (p=0.453)

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Figure 1: Study flow chart showing inclusions and exclusions in analyses

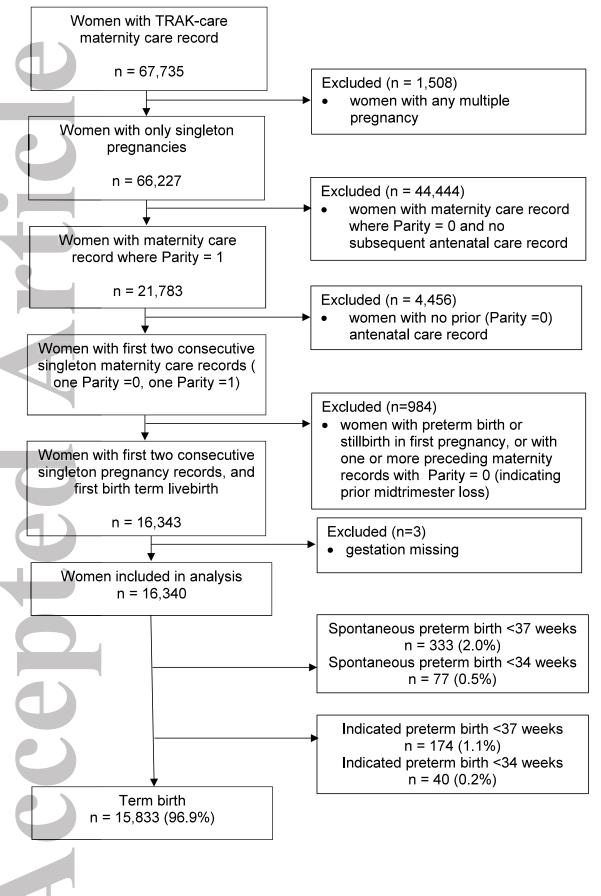
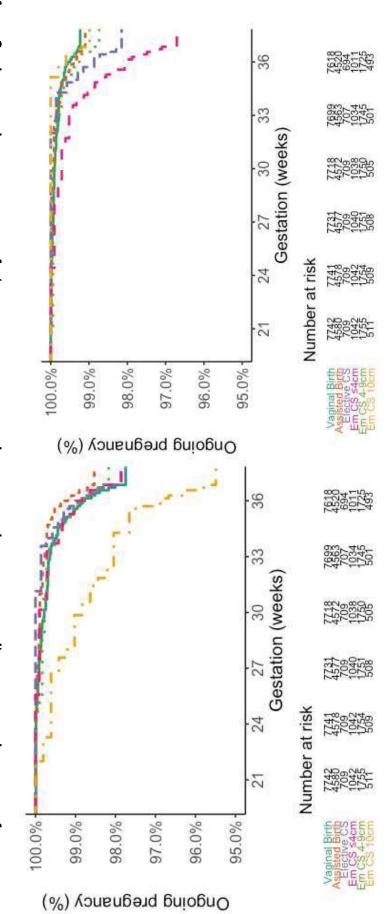
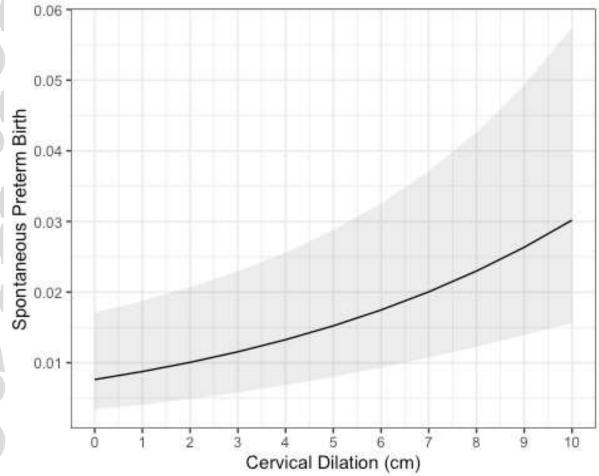


Figure 2: Kaplan-Meier (unadjusted) curves of spontaneous preterm birth (panel a- with medically indicated preterm births censored) and medically indicated preterm birth (panel b – with spontaneous preterm births censored) by mode of birth in previous pregnancy.



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Figure 3: Spontaneous preterm birth (%) by cervical dilation at the time of first emergency caesarean birth



Multivariable model includes gestational age at first birth, birthweight centile, interpregnancy interval, maternal age, maternal ethnicity, maternal BMI category and maternal deprivation index. Full model is shown in Table S8.