



Full dilatation cesarean section: a risk factor for recurrent second-trimester loss and preterm birth.

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1 **Full dilatation cesarean section: a risk factor for recurrent second-trimester**
2 **loss and preterm birth**

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4 **Running title:** Full dilatation cesarean and recurrent preterm birth.
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25 **Conflicts of Interests Notification:**
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27 The authors declare no conflicts of interest.
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1 Abstract

2 *Introduction:* A previous cesarean section at full dilatation (FDSC) is a risk factor for preterm
3 birth. To provide insight on the risk to subsequent pregnancies, this cohort study compares the
4 outcomes of pregnant women with a previous preterm birth associated either with a prior FDSC
5 or a prior term vaginal delivery. *Material and methods:* We identified women attending two
6 inner-city preterm surveillance clinics (Guy's and St Thomas Hospital and University College
7 London Hospital, London, UK) who had a spontaneous late miscarriage (14^{+0} – 23^{+6} weeks) or
8 sPTB (<37 weeks) following a term pregnancy, and then a further pregnancy for analysis. Cases
9 were those with a prior term FDSC, while controls had a prior term vaginal birth; both before the
10 late miscarriage/sPTB. Main outcomes were gestational age at delivery and delivery <30 weeks
11 in the next (third) pregnancy. *Results:* Over the study period 66 women were identified who had
12 a term delivery followed by a late miscarriage or sPTB, and a subsequent pregnancy. Recurrent
13 sPTB <30 weeks was more common in cases compared to controls (12/29, vs 5/37, $p=0.02$,
14 Fisher's exact test, RR 3.06, 95% CI 1.22-7.71). Median gestation at delivery was significantly
15 lower (249 days (IQR 154, 267) vs 280 days (IQR 259, 280) $p<0.001$). Eleven women in the
16 FDSC group received vaginal cerclage, five of whom delivered <37 weeks. *Conclusion:* In this
17 cohort study we observed that women with a term FDSC and subsequent late miscarriage/sPTB
18 have a higher risk of recurrent sPTB compared to women whose first term delivery was vaginal.

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20 Keywords:

21 Cesarean section, preterm birth, cervix, ultrasound, delivery

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23 List of Abbreviations

24	sPTB	spontaneous preterm birth
25	sLM	spontaneous late miscarriage
26	FDSC	full dilatation cesarean section

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1 **Key message**

- 2 Women with a term cesarean at full dilatation, prior to spontaneous late miscarriage/
- 3 spontaneous preterm birth have a high risk of recurrent spontaneous preterm birth.

For Peer Review

1 **Introduction**

2 Rates of cesarean section, including those at full dilatation (FDCS), are increasing worldwide
3 (1,2). At the same time there has been a decline in operative vaginal delivery, which may be
4 linked to concerns around trauma to the newborn, over-medicalisation and training challenges
5 (3). Cesarean section in the second stage results in greater incidence of morbidity (1,4).
6 Maternal complications include damage to the cervix or high vagina by the uterine incision, as
7 the cervix is drawn into the lower segment (an incidence of 4.4% (5)).

8 Links between spontaneous late miscarriage (>14 weeks) or spontaneous preterm birth (sPTB)
9 (<37 weeks) following FDCS are beginning to emerge in the literature. A retrospective study at
10 one institution evaluated the effect that a cesarean delivery in one pregnancy had on the risk of
11 sPTB in a subsequent pregnancy (6). The study found that women with a second-stage cesarean
12 delivery had a significantly higher than expected rate of subsequent sPTB (13.5%) compared
13 with both the overall US national sPTB rate (7-8%) and to women who had a first-stage cesarean
14 delivery (2.3%). However, we know little of the course of pregnancies which follow the
15 spontaneous late miscarriage or sPTB, and how best to manage the subsequent pregnancy. The
16 aim of our study was to evaluate outcomes for pregnancies that followed spontaneous late
17 miscarriage /sPTB, where we believe the aetiology of the subsequent early delivery is damage to
18 the cervix/vagina during the term FDCS, compared to women without such damage.

20 **Material and methods**

21 We identified all women presenting to preterm surveillance clinics at two tertiary London
22 hospitals (Guy's and St Thomas NHS Foundation Trust and University College London Hospital
23 NHS Foundation Trust) between April 2012 and November 2016 with a history of spontaneous
24 late miscarriage or sPTB that had been preceded by a term pregnancy. These clinics
25 prospectively collect data for their preterm surveillance clinic databases including
26 contemporaneously obtained outcome. The databases are populated and monitored by research
27 staff trained in Good Clinical Practice. Cases were those with a history of term FDCS before the
28 spontaneous late miscarriage /sPTB while controls were those with a prior term vaginal delivery
29 (spontaneous or assisted). For the purpose of clarification, pregnancies are categorised into A, B
30 and C for each woman, as shown in figure 1.

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3 1 Women with multiple pregnancies in A, B or C were excluded. Women were excluded if they
4 2 had a history of sPTB or spontaneous late miscarriage, or previous cervical/pelvic surgery
5 3 (including cesarean section) prior to pregnancy A. Those with elective or first stage cesarean
6 4 sections in pregnancy A were excluded. Term deliveries prior to pregnancy A and first trimester
7 5 miscarriages (<14 weeks) or terminations of pregnancy (any gestation) were omitted for the
8 6 purposes of analysis.
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16 8 Pregnancy B was defined as the first subsequent spontaneous late miscarriage/sPTB following
17 9 the term delivery. The main outcomes of interest were gestational age at delivery and delivery <
18 10 30 weeks (primary endpoint) in pregnancy C (defined as the next pregnancy following
19 11 pregnancy B). Premature births less than 30 weeks have recently been identified as of particular
20 12 significance by the UK National Institute for Health and Care Excellence (NICE) who advise
21 13 admission, steroids and tocolysis without diagnostic testing for any women in threatened preterm
22 14 labour below this gestation (7). We also reported preterm birth rates prior to 34 and 37 weeks in
23 15 view of their clinical relevance (secondary endpoints).
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32 17 At the clinics, pregnancies are managed according to prespecified protocols using regular
33 18 ultrasound transvaginal cervical length measurement to guide decisions about preventive therapy
34 19 such as cervical cerclage. Vaginal cervical cerclage is offered to women who are found to have a
35 20 short cervical length (<25mm) on ultrasound surveillance. Transabdominal cerclage is usually
36 21 reserved for those who have had a failed vaginal cerclage previously, defined as delivery before
37 22 28 weeks despite having a vaginal cerclage.
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45 24 Variables collected included maternal age, ethnicity, parity, body mass index and smoking
46 25 history. As secondary outcome measures, we collected data on timings and nature of
47 26 interventions aimed to prevent spontaneous late miscarriage and sPTB, such as cerclage (history-
48 27 indicated/ultrasound-indicated/rescue/transabdominal), progesterone or Arabin pessary in
49 28 pregnancy C.
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54 29 Statistical analysis was performed using Stata software Version 14.1 (StataCorp, College Station,
55 30 Texas). Data was skewed so median gestations were compared with a Wilcoxon rank-sum test
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1 and confidence intervals (8). Time to delivery was displayed using a Kaplan-Meier plot.
2 Fisher's exact test was used to compare percentages (sPTB < 30 weeks).

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4 *Ethical approval*

5 The study was conducted according to the principles set forth in the Helsinki Declaration of
6 1975, as revised in 2013. We obtained a waiver of Institutional Review Board approval from the
7 two relevant NHS Health Research Authorities who confirmed that the study was classified as
8 service evaluation and therefore Research Ethics Committee review or Health Research
9 Authority approval was not necessary. Reporting of this study was conducted in accordance with
10 the STROBE Statement.

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13 **Results**

14 Sixty-six women with a spontaneous late miscarriage /sPTB following a term delivery were
15 identified, with a total of 198 pregnancies for analysis. There were 29 women with a prior FDCS
16 who had completed a further pregnancy between April 2012 and November 2016. The
17 remaining 37 who had a prior term vaginal delivery were treated as controls. Cases and controls
18 had similar baseline characteristics (Table 1). There were 6 reported cases of past or present
19 history of Group B Streptococcus in the cases compared to three in the control group. Only one
20 woman (control) reported previous bacterial vaginosis. Three women in the cases reported a
21 history of recurrent urinary tract infections, and one of the controls. No women reported
22 intimate partner violence despite routine screening in both clinics.

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24 Median gestation was significantly lower (35^{+4} weeks (interquartile range 22^{+0} , 38^{+1}) vs 40^{+0}
25 weeks days (interquartile range 37^{+0} , 40^{+0}) $p < 0.001$) in the cases compared to controls. For
26 women with a prior term FDCS and subsequent late miscarriage/sPTB in pregnancy A and B
27 respectively, the relative risk of recurrent sPTB less than 30 weeks in pregnancy C was 3.06
28 (95% CI 1.22-7.71) compared to women with prior term vaginal delivery and subsequent late
29 miscarriage /sPTB (12/29 vs 5/37 $p = 0.02$, Fisher's exact test). The absolute risk of recurrent
30 sPTB in pregnancy C for women with a previous term FDCS was 28% (95% CI 7%-49%). The

1 incidence of sPTB less than 34 weeks was 12/29 vs 5/37 ($p=0.02$, Fisher's exact test), and the
2 incidence before 37 weeks was 16/29 vs 7/37 ($p=0.0038$ Fisher's exact test). This was in spite of
3 a higher rate of intervention (17/29 vs 6/37 received intervention in cases compared to controls).
4 Kaplan-Meier "Survival" estimates depict the proportion of women undelivered at each
5 gestational week according for cases and controls (figure 2)

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7 In order to exclude possible effects of intervention on outcome, we compared sPTB rates in
8 women without intervention in each group. In women who received no intervention in
9 pregnancy C, cases had a higher rate of sPTB relative to controls (10/12 vs 4/34, $p<0.0001$
10 Fisher's exact test). A description of the interventions received in pregnancy C and their sPTB
11 rates are provided in Table 2.

12 13 **Discussion**

14 Caesarean section at full dilatation is increasingly common. However counselling women who
15 have a FDCS followed by a late miscarriage or sPTB is challenging because the incidence of
16 sPTB following any term delivery is low (9). This unique study analyses the subsequent
17 pregnancies of this group. It demonstrates that women with a prior history of term FDCS and
18 subsequent late miscarriage/sPTB have a threefold increased relative risk of recurrent sPTB
19 compared to those women with a history of term vaginal delivery and subsequent late
20 miscarriage/sPTB.

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22 In this study, management decisions whilst guided by ultrasound surveillance, varied according
23 to clinician preference. Conservative management in pregnancies that followed late
24 miscarriage/sPTB was associated with higher recurrence of sPTB in women with a prior history
25 of FDCS compared to a vaginal delivery. More women with a history of term FDCS received an
26 intervention than those delivering vaginally at term, but in spite of this, their overall outcomes
27 were worse. In this small cohort, transabdominal cerclage appeared the most effective treatment
28 but a larger sample would be required to demonstrate whether this is a true finding.

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1 The high recurrent sPTB risk is consistent with a previously observed 6-fold increased odds of
2 having an sPTB following a FDACS, relative to a first stage cesarean (adjusted odds ratio 5.8;
3 95% CI 1.08-30.8; P =0.04) (6). Alternative physiological mechanisms that result in premature
4 birth may account for the excess risk. In three cases an anterior cervical defect was clearly seen
5 on ultrasound. This is likely to be associated with incision at the time of cesarean section, which
6 may be inadvertently too low (figure 2). It is worth noting however that a caesarean section
7 defect was not systematically looked for in all cases, and the rate of anterior cervical defects may
8 be higher than this. Whilst cervical defects may not be apparent in every case, the optimum
9 management of this subset of women needs to be established. If transabdominal cerclage
10 supports the cervix above a defect caused by a low FDACS incision, it may provide a more logical
11 rationale for this intervention and offer the best chance of a term pregnancy for these women. A
12 potential increase in gestation at birth, however, needs to be balanced against the risks of major
13 surgery.

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15 Spontaneous preterm birth or late miscarriage following term pregnancies is relatively rare and
16 this is a unique cohort of 66 women with longitudinal data. Another strength of the study is that
17 the data is from pregnancies that were followed in two clinics sharing common protocols for
18 management of recurrent sPTB.

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20 The sample size and detailed information were restricted by the need to examine three
21 pregnancies in each woman, the first two of which may have occurred over many years and in
22 different hospitals or countries. For example, data on the indication for the FDACS and whether an
23 instrumental delivery was attempted, might further the understanding of the sPTB recurrence
24 risk. Data on serial cervical length and fetal fibronectin values for each pregnancy might have
25 enabled us to make more specific recommendations regarding management of future pregnancies
26 in these women. Increasing awareness of the risk of recurrent late miscarriage/sPTB following
27 FDACS is likely to facilitate future data collection. The low numbers of diverse interventions
28 women received mean that whilst trends were observed, statistical significance was not reached
29 on data that could suggest best management strategies.

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3 1 There may be a degree of selection bias in the cases as we have only recently become aware of
4 2 FDCS as a risk factor, so the details of a preceding caesarean section may not have been actively
5 3 sought for all women presenting at these clinics. However cases we have selected genuinely have
6 4 this history. To minimise bias and because preterm birth after term delivery is rare, we selected
7 5 all cases and controls in the timeframe, rather than matching. The baseline characteristics are
8 6 comparable.

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16 8 We believe our results are generalisable as these cases were referred by many units to these
17 9 specialist services. However, as the insult is likely to be iatrogenic, obstetric practice could
18 10 influence risk (i.e. threshold of when to do cesareans and technique of incision), so these
19 11 findings should also be confirmed in other clinical settings (e.g. outside the UK).

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25 13 Recurrent spontaneous late miscarriage or sPTB has a major impact for a woman and her family
26 14 and our findings are therefore relevant to all women who are delivered by cesarean at full
27 15 dilatation and clinicians who are evaluating management options in the second stage. The
28 16 recurrence risk and management challenges we have demonstrated, highlight the need for early
29 17 specialist referral and the inadequacy of a conservative approach. Given the persistent risk that
30 18 a FDSC poses to a small but increasing number of women, future trials may explore preventative
31 19 strategies at the time of FDSC, such as high incisions in the lower segment, and best
32 20 management of subsequent pregnancies, which may include transabdominal cervical cerclage in
33 21 the presence of an anterior cervical defect. Observational imaging and biomarker studies may
34 22 also help determine the aetiology and optimum management of this problem.

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45 24 *Conclusion*

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47 25 Spontaneous preterm birth and late miscarriage following FDSC are associated with poor
48 26 outcomes and these women require specialist surveillance and management in subsequent
49 27 pregnancies. Women should be counselled regarding these implications following cesarean
50 28 delivery in the second stage. Clinicians should be aware of FDSC as a risk factor.

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45 2 **Legends**
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8 3 Figure 1. Description of analysed pregnancies.
910 4 Figure 2. Kaplan-Meier "Survival" estimates depicting the proportion of women
11 undelivered in Pregnancy C at each gestational week according for cases and controls.
12 5
13 6 sPTB, spontaneous preterm birth.
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16 7 Table 1. Baseline characteristics of cases and controls.
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19 8 Table 2: Interventions and outcome in pregnancy C (pregnancy following spontaneous late
20 miscarriage/ spontaneous preterm birth).
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Figure 1: Description of analysed pregnancies

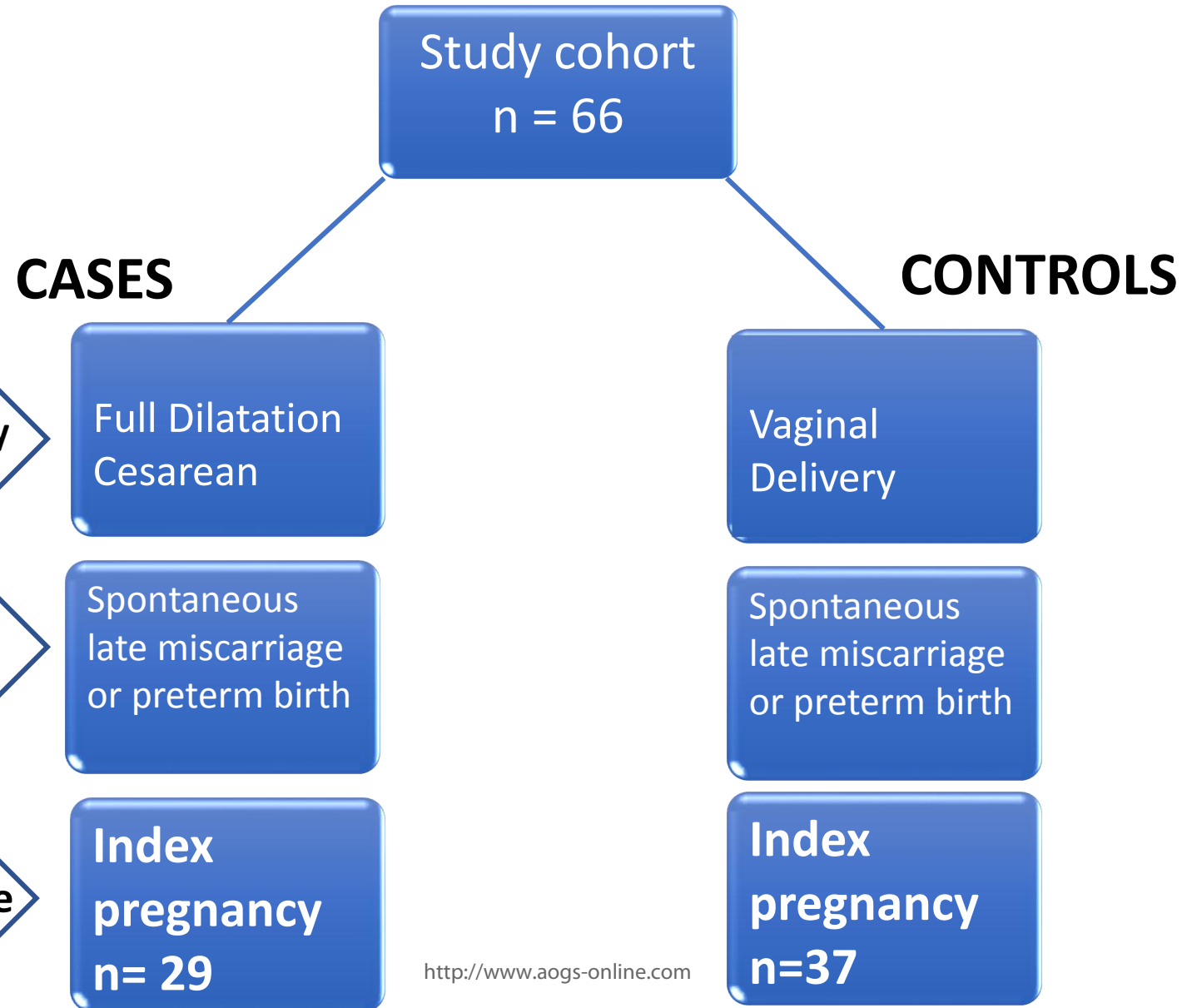
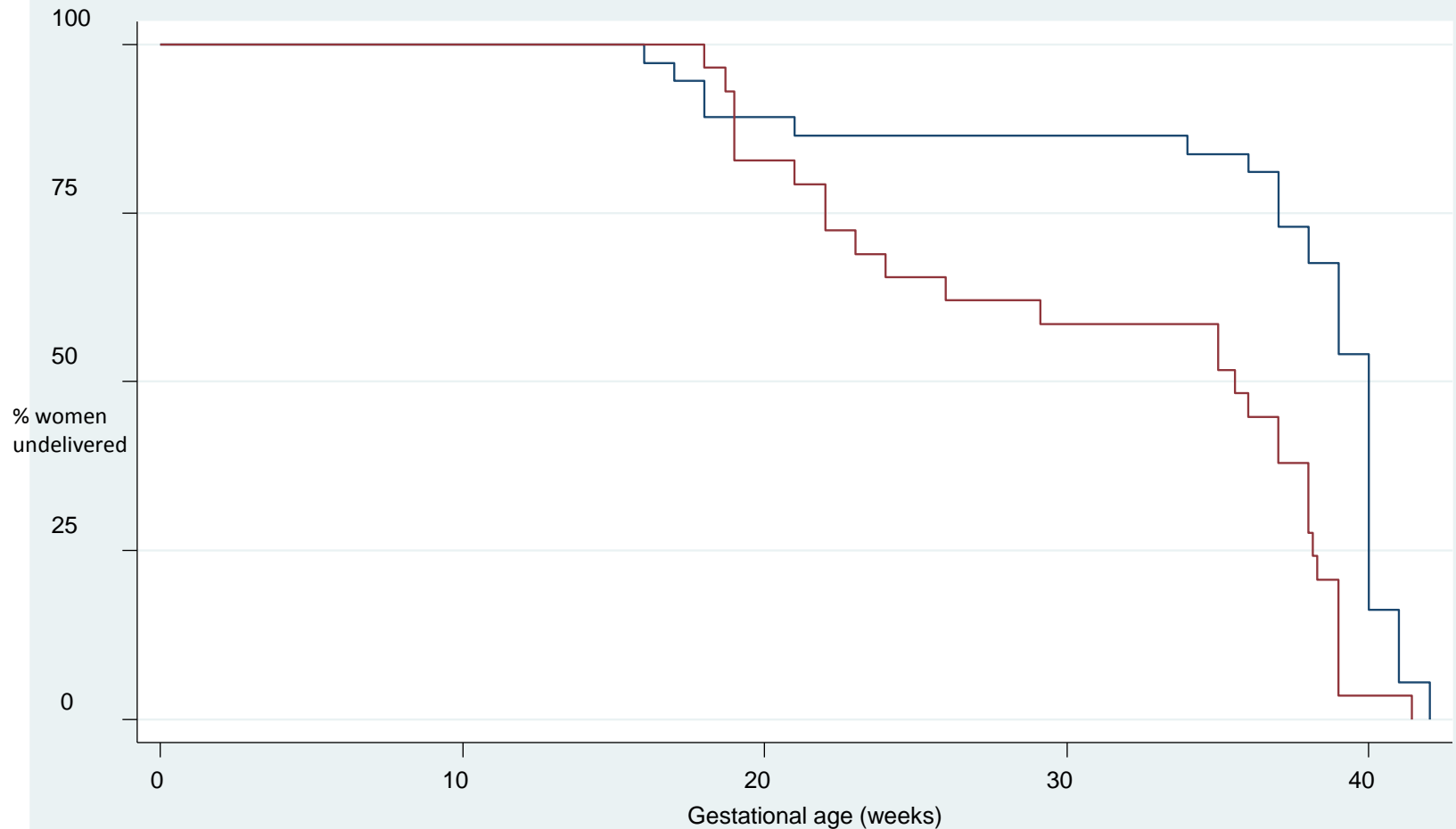


Figure 2: Kaplan-Meier “Survival” estimates depicting the proportion of women undelivered in Pregnancy C at each gestational week according for cases and controls



— Vaginal Delivery preceding late miscarriage/sPTB — Fully Dilated Caesarean Section preceding late miscarriage/sPTB

Table 1. Baseline characteristics of cases and controls.

Characteristic	Pregnancy C: Index Pregnancy	
	CASES* n=29 (%)	CONTROLS† n=37 (%)
Mean age (years) (SD)	33 (4.1)	36 (5.3)
Mean gestation pregnancy B (weeks) (+/-SD)	21 (6.2)	22 (5.7)
Median gestation pregnancy B (IQR)	20 (18.0, 23.0)	20 (18.0, 25.0)
Ethnicity (%)		
<i>Black</i>	8 (28)	13 (35)
<i>White</i>	18 (62)	22 (59)
<i>Other (Asian/Middle-Eastern)</i>	3 (10)	2 (6)
Reported smoking history		
Current	0 (0)	9 (24)
Ex-smoker	3 (12)	0
Never	23 (88)	28 (76)
Mean Body Mass Index	30.1	29.1
BMI < 20	0	3

* Cases: term full dilatation cesarean section prior to spontaneous late miscarriage or spontaneous preterm birth.

† Controls: term vaginal delivery prior to spontaneous late miscarriage or spontaneous preterm birth.

SD, standard deviation; IQR, interquartile range; BMI, body mass index.

Table 2: Interventions and outcome in pregnancy C (pregnancy following spontaneous late miscarriage/ spontaneous preterm birth).

	CASES (term FDCS prior to sLM or sPTB) n= 29		CONTROLS (term VD prior to sLM or sPTB) n=37	
Pregnancy C Management	No. of women receiving this intervention	No. of women delivered <37 weeks	No. of women receiving this intervention	No. of women delivered <37 weeks
No intervention ^a	12	10	31	4
History indicated cerclage	7	3	2	2
Ultrasound indicated cerclage	2	0	2	1
Rescue cerclage	2	2	2	0
Transabdominal cerclage	4	1	0	0
Arabin pessary	1	0	0	0
Progesterone	1	0	0	0

^ap<0.0001 (Fisher's exact test)

FDCS, full dilatation cesarean section; sLM, spontaneous late miscarriage; sPTB, spontaneous preterm birth; VD, vaginal delivery.