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ORIGINAL ARTICLE *Early pregnancy*

Pregnancy loss managed by cervical dilatation and curettage increases the risk of spontaneous preterm birth

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STUDY QUESTION: Do women with a previous miscarriage or termination of pregnancy have an increased risk of spontaneous preterm birth and is this related to previous cervical dilatation and curettage?

SUMMARY ANSWER: A single previous pregnancy loss (termination or miscarriage) managed by cervical dilatation and curettage is associated with a greater risk of SpPTB.

WHAT IS KNOWN ALREADY: Miscarriage affects ~20% of pregnancies and as many as a further 20% of pregnancies undergo termination.

STUDY DESIGN, SIZE, DURATION: We utilized data from 5575 healthy nulliparous women with singleton pregnancies recruited to the Screening for Pregnancy Endpoints (SCOPE) study, a prospective cohort study performed between November 2004 and January 2011.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The primary outcome was spontaneous preterm birth (defined as spontaneous preterm labour or preterm premature rupture of membranes (PPROM) resulting in preterm birth <37 weeks' gestation). Secondary outcomes included PPROM, small for gestational age, birthweight, pre-eclampsia and placental abruption.

MAIN RESULTS AND THE ROLE OF CHANCE: Women with previous pregnancy loss (miscarriage or termination) were compared with those with no previous pregnancy loss. There were 4331 (78%) women who had no previous pregnancy loss, 974 (17.5%) who had one early previous pregnancy loss, 249 (4.5%) who had two and 21 (0.5%) who had three or four losses. Women with two to four previous losses, but not those with a single loss, had an increased risk of spontaneous preterm birth (adjusted OR 2.12; 95% CI 1.55, 2.90) and/or placental abruption (adjusted OR 2.30; 95% CI 1.36, 3.89) compared with those with no previous pregnancy. A single previous miscarriage or termination of pregnancy where the management involved cervical dilatation and curettage was associated with an increased risk of spontaneous preterm birth (adjusted OR 1.64; 95% CI 1.08, 2.50; 6% absolute risk and adjusted OR 1.83; 95% CI 1.35, 2.48; 7% absolute risk, respectively) compared with those with no previous pregnancy losses. This is in contrast with women with a single previous miscarriage or termination managed non-surgically who showed no increase risk (adjusted OR 0.86; 95% CI 0.38, 1.94; 3.4% absolute risk and adjusted OR 0.87; 95% CI 0.69, 1.12; 3.8% absolute risk, respectively).

LIMITATIONS, REASONS FOR CAUTION: Although every effort was made to record accurate previous pregnancy data, it was not feasible to confirm the history and management of previous pregnancy loss by hospital records. This may have introduced recall bias.

WIDER IMPLICATIONS OF THE FINDINGS: This large prospective cohort study of healthy nulliparous women has demonstrated that women with either a previous miscarriage or termination of pregnancy were at increased risk of spontaneous preterm birth if they were managed by procedures involving cervical dilatation and curettage. However, overall, women with a single pregnancy loss did not have an increased risk of

having any other of the adverse pregnancy outcomes examined. In contrast, two to four previous pregnancy losses were associated with an increased risk of having a pregnancy complicated by spontaneous preterm birth and/or placental abruption. Research is required to determine whether non-surgical management of miscarriage or termination of pregnancy should be advocated over surgical treatment.

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Key words: miscarriage / termination of pregnancy / spontaneous preterm birth / adverse pregnancy outcomes

Introduction

Miscarriage affects ~20% of pregnancies (Regan and Rai, 2000), and in some regions including England and Wales as many as a further 20% of pregnancies undergo termination (Department of Health, 2011). Surgical evacuation of uterus with dilatation of the cervix is a common procedure for both spontaneous miscarriage (up to 80% of cases; Hemminki, 1998) and termination of pregnancy (~57–75%; Sedgh *et al.*, 2007, 2012; Pazol *et al.*, 2011).

Currently, women who have had one or two miscarriages or terminations of pregnancy are not considered high risk in subsequent pregnancies and consequently do not receive any altered or increased antenatal surveillance. The current data regarding adverse pregnancy outcomes following previous miscarriage are mixed and often conflicted (Schoenbaum *et al.*, 1980; de Haas *et al.*, 1991; Eskenazi *et al.*, 1991; Ekwo *et al.*, 1993; Basso *et al.*, 1998; Buchmayer *et al.*, 2004; Sheiner *et al.*, 2005; Hammoud *et al.*, 2007; Bhattacharya *et al.*, 2008; van Oppenraaij *et al.*, 2009).

Similar conflicting data exist regarding previous terminations of pregnancy and adverse pregnancy outcomes (Hogue *et al.*, 1983; Pickering and Forbes, 1985; Atrash and Hogue, 1990; Lang *et al.*, 1996; Zhou *et al.*, 1999; Ancel *et al.*, 2004; Moreau *et al.*, 2005; Raatikainen *et al.*, 2006; Smith *et al.*, 2006). No difference in the risk of miscarriage, preterm delivery or small for gestational age (SGA) was observed in women with a previous termination of pregnancy managed by a medical technique or by vacuum aspiration, respectively, in one of the most recent large (11 814 participants) long-term safety studies on termination of pregnancy (Virk *et al.*, 2007). However, the conflicting data possibly reflect differences in study design, lack of control for potential confounders (e.g. body mass index (BMI), smoking, substance abuse and low socio-economic status), inappropriately selected controls and/or a selection of heterogeneous populations including women of varying parities and co-existing medical conditions.

While there may be causative factors related to early pregnancy loss and complications in a subsequent pregnancy, the method of management of the pregnancy loss may also be influential. The traditional management of first trimester miscarriage or termination is cervical dilatation and curettage but in the absence of any strong evidence, women who have received surgical management are not generally informed of any potential risks in subsequent pregnancies nor do they usually receive altered antenatal care in subsequent pregnancies.

The aims of this study were 2-fold. First, we sought to clarify whether previous miscarriage or termination of pregnancy was associated with subsequent adverse pregnancy outcomes in a prospective cohort of nulliparous women. Secondly, we investigated whether any association was mediated by procedures involving cervical dilatation and curettage.

Methods

SCOPE (Screening for Pregnancy Endpoints) is a prospective, multicentre cohort study with the primary aim of developing screening tests to predict pre-eclampsia, SGA infants and spontaneous preterm birth. In this study, data from the SCOPE study were used to assess the risks associated with previous pregnancy loss. SCOPE participants were healthy nulliparous women with singleton pregnancies recruited between November 2004 and January 2011 in Auckland, New Zealand, Adelaide, Australia, Cork, Ireland, and Manchester, Leeds and London, UK. Women were recruited at 15 ± 1 -week gestation through hospital antenatal clinics, obstetricians, general practitioners, community midwives, self-referral in response to advertisements or recommendations of friends, as previously described (McCowan *et al.*, 2009; North *et al.*, 2011). Women were excluded if they were considered to be at high risk of pre-eclampsia, SGA babies or spontaneous preterm birth due to underlying medical conditions or gynaecological history, if they had experienced three or more previous miscarriages or three or more terminations of pregnancy, or if they had received interventions, such as aspirin, that might modify pregnancy outcome.

Ethical approval was obtained from local ethics committees [New Zealand AKX/02/00/364, Australia REC 1712/5/2008, London, Leeds and Manchester 06/MRE01/98 and Cork ECM5(10)05/02/08] and all women provided written informed consent.

SCOPE participants were interviewed and examined by SCOPE research midwives at 15 ± 1 and 20 ± 1 weeks' gestation. At the time of the interview, data were entered on an internet-accessed central database with a complete audit trail (MedSciNet). Participants were followed up prospectively, with pregnancy outcome data being collected by research midwives. Each participant's data was individually checked. Data entry errors in the lifestyle questionnaire were checked manually and a customized software program was used to detect any systematic data entry errors. The primary

outcome was spontaneous preterm birth. Secondary outcomes included preterm premature rupture of membranes (PPROM) resulting in spontaneous birth, SGA, pre-eclampsia, placental abruption and birthweight.

Pregnancy loss was defined as a combination of one or two previous miscarriages and/or one or two previous terminations of pregnancy. Miscarriage was defined as spontaneous pregnancy loss <20 weeks' gestation. Previous miscarriage was further classified as having occurred by 10 weeks' or after 10 weeks' gestation. Gestation of miscarriage or termination was defined as the number of weeks when a previous pregnancy miscarried or ended surgically or non-surgically. Medical management was defined as management of termination or miscarriage involving any of 'misoprostol (Cytotec®), gemeprost (Cervagen®), Mifeprix or ru486 (mifepristone) or prostaglandin f2a. For missed miscarriage, the estimated time of demise was recorded. The management of previous miscarriage and/or termination of pregnancy was also recorded as either involving cervical dilatation and curettage or not involving any form of cervical dilatation, i.e. non-surgical management only. The estimated date of delivery was calculated from a certain last menstrual period (LMP) date. The estimated date of delivery was only adjusted if either a scan at <16 weeks' gestation found a difference of 7 or more days between the scan gestation, when calculated by the LMP, or at a 20-week scan, a difference of 10 or more days was found between the scan gestation, when calculated from the LMP. If the LMP date was uncertain, scan dates were used to calculate the estimated date of delivery.

Spontaneous preterm birth was defined as spontaneous onset of labour (<37 weeks' gestation) resulting in preterm birth at <37 weeks' gestation. This included women with PPROM. PPROM was also examined as its own distinct outcome and was defined as spontaneous preterm birth where the woman presented with confirmed rupture of membranes in the absence of labour, and the time between the rupture of membranes to delivery was at least 6 h greater than the duration of established labour (i.e. duration of first stage + duration of the second stage), i.e. rupture of membranes occurred at least 6 h before the onset of established labour. SGA was defined as birthweight below the 10th customized centile adjusted for maternal weight, height, parity, ethnic group and infant sex (www.gestation.net; Gardosi JFA, 2007). Placental abruption was defined by evidence of retroplacental clot at delivery and finally, pre-eclampsia was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least two occasions 4 h apart after 20 weeks' gestation but before the onset of labour or post-partum, with proteinuria (24 h urinary protein ≥300 mg, or spot urine protein to creatinine ratio ≥30 mg/mmol creatinine, or urine dipstick protein ≥2+) or any multisystem complication of pre-eclampsia (Brown *et al*., 2000).

Student's *t*-test or Mann–Whitney *U*-test was used to compare continuous variables and χ^2 was used to compare categorical variables in relation to previous pregnancy loss(s), previous miscarriage(s) only and previous termination(s) only. In all the statistical tests, women with no previous pregnancy represented the reference group. Logistic regression and linear regression were used to analyse the binary (all outcomes excluding birthweight) and continuous (birthweight) outcome measures, respectively. Logistic regression models were adjusted for maternal age, smoking, alcohol consumption, ethnicity, BMI, infant sex, marital status and income. The logistic models were further adjusted for any clustering effect of SCOPE centres using the 'cluster' option in STATA which specifies that the standard errors allow for intragroup correlation, relaxing the usual requirement that the observations be independent. That is, the observations are independent across groups (centres) but not necessarily within groups. Models were also examined for the potential confounding effects of maternal and sister history of miscarriage but the results were not changed materially. The linear regression for birthweight was adjusted for the same variables as the logistic models in addition to gestational age at delivery.

The initial analyses examined the overall effects of previous pregnancy loss on adverse pregnancy outcomes. Previous pregnancy loss was represented in the analyses as a three-category variable: (i) no pregnancy loss, (ii) one previous pregnancy loss and (iii) two to four previous pregnancy losses.

Subgroup analyses were performed to assess the effect of previous miscarriages on adverse pregnancy outcomes. This was done by generating a three-category variable: (i) no previous pregnancy, (ii) one previous pregnancy ending in miscarriage and (iii) two previous pregnancies ending in miscarriages. Women who had previous terminations of pregnancy were excluded from the miscarriage analyses. Similar subgroup analyses were performed to assess the effect of terminations of pregnancy on adverse pregnancy outcome. This was done by generating a three-category variable: (i) no previous pregnancy, (ii) one previous pregnancy ending in termination and (iii) two previous pregnancies ending in terminations. Women who had previous miscarriages were excluded from the termination analyses.

The secondary aim of the study was to investigate the effect of pregnancy-loss management method on the risk of adverse pregnancy outcomes. Previous cervical dilatation and curettage was represented in the analyses as a three-category variable: (i) no previous cervical dilatation and curettage, (ii) one previous cervical dilatation and curettage and (iii) two or three previous cervical dilatations and curettage.

To investigate the effect of pregnancy loss management method on the risk of spontaneous preterm birth, the previous miscarriage models and the previous termination models were repeated for (i) no cervical dilatation and curettage and (ii) women managed by cervical dilatation and curettage. In all models, the reference group consisted of women with no previous recognized pregnancies. These analyses were restricted to women with only either one previous miscarriage or one previous termination of pregnancy. To examine whether there was a significant difference in the risk of preterm birth between women managed surgically compared with women managed non-surgically, two further analyses were performed. First, women with one previous miscarriage managed non-surgically were compared with women with one previous miscarriage managed surgically by restricting the logistic regression models to women with one previous miscarriage only. Secondly, women with one previous termination managed non-surgically were compared with women with one previous termination managed surgically by restricting the logistic regression models to women with one previous termination only.

A final subgroup analysis was performed to investigate the impact of cervical length on the observed increased risk of spontaneous preterm birth. A binary variable was generated indicating whether cervical length was >30 or ≤30 mm. This variable was included in the spontaneous preterm birth models to assess whether cervical length may partly explain any observed associations.

All statistical analyses were performed in STATA 10.0.

Results

Of the 5690 women who were recruited to the SCOPE study, 5575 (98%) were included in this study (Fig. 1). There were 4331 women (78%) who had no history of miscarriage or termination, 974 (17.5%) who had one previous pregnancy loss, 249 (4.5%) who had two previous pregnancy losses and 21 (0.5%) who had three or four previous pregnancy losses. Women with previous pregnancy losses tended to be older, more likely to be overweight, more likely to have a family history of miscarriage, and less likely to have consumed alcohol in pregnancy but more likely to be smokers compared with those with no previous pregnancy loss (Table I).

Whilst a single pregnancy loss was not associated with a statistically significant increase in adverse pregnancy outcomes, women with two to four previous pregnancy losses were at significant increased risk of spontaneous preterm birth (adjusted OR 2.12; 1.55, 2.90) and/or placental

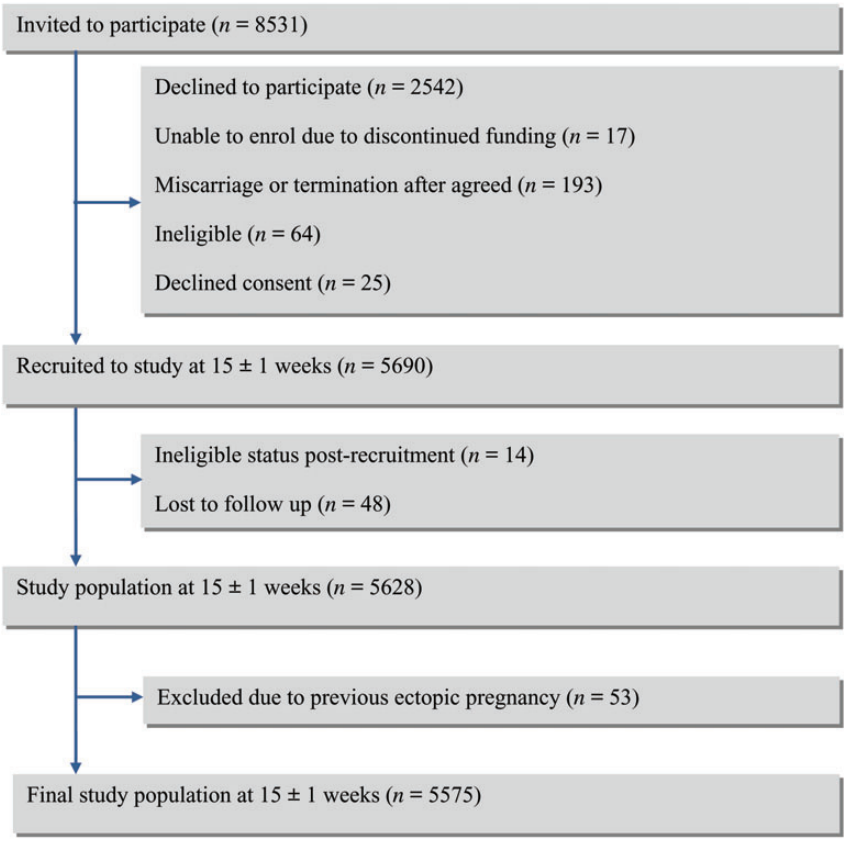

Figure 1 Recruitment of participants.

abruption (adjusted OR 2.30; 95% CI 1.36, 3.89) compared with those with no previous pregnancy losses (Table II).

A single pregnancy loss (miscarriage or termination of pregnancy) managed by cervical dilatation and curettage was associated with a 60% increased risk of spontaneous preterm birth (adjusted OR 1.66; 95% CI 1.14, 2.42) and/or placental abruption (adjusted OR 1.83; 95% CI 0.98, 3.42) compared with those with no previous pregnancy. Two previous pregnancy losses managed by cervical dilatation and curettage were associated with more than a two-fold increased risk of spontaneous preterm birth (adjusted OR 2.32; 95% CI 1.88, 2.88) compared with those with no previous pregnancy. Numbers were insufficient to examine women with two or three previous cervical dilation and curettages (Table III).

Overall, women with one previous miscarriage alone were not at a significantly increased risk of adverse pregnancy outcomes (Table IV). Women with two previous miscarriages were at increased risk of having a pregnancy complicated by either spontaneous preterm birth (adjusted OR 3.14; 95% CI 2.36, 4.20) or PPROM (adjusted OR 3.31; 95% CI 2.34, 4.69; Table IV). Women with one previous termination of pregnancy had a significantly increased risk of spontaneous preterm birth (adjusted OR 1.48; 95% CI 1.04, 2.10), but the number of women with two previous terminations and spontaneous preterm birth were too small for a conclusion to be drawn (Table V). There was little evidence to suggest an association between one previous termination of pregnancy and PPROM, SGA or pre-eclampsia (Table V).

As spontaneous preterm birth was the primary outcome, the association between spontaneous preterm birth, cervical dilatation and curettage, previous miscarriage and previous termination was examined in separate analyses (Table VI). Women with one previous miscarriage or termination managed by cervical dilatation and curettage had an increased risk of having a pregnancy complicated by spontaneous preterm birth (adjusted OR 1.64; 95% CI 1.08, 2.50 and adjusted OR 1.83; 95% CI 1.35, 2.48, respectively) compared with women with no previous pregnancy loss (Table VI). In contrast, women with one previous miscarriage or termination not managed by cervical dilatation and curettage did not have an increased risk of having a pregnancy complicated by spontaneous preterm birth (adjusted OR 0.86; 95% CI 0.38, 1.94 and adjusted OR 0.87; 95% CI 0.69, 1.12, respectively) compared with women with no previous pregnancy loss.

To examine whether there were significant differences between women managed surgically compared with those women managed non-surgically, we restricted the analyses first to women with one previous miscarriage only, i.e. allowing us to compare the effect of one miscarriage managed surgically with one miscarriage managed non-surgically on the risk of spontaneous preterm birth. The crude OR from this analysis was 1.82 (95% CI 1.02, 3.24), suggesting that curettage increases the risk of spontaneous preterm birth compared with women who had a miscarriage without curettage. However, when we adjusted the logistic model for the same variables as in Table VI, the estimate changed marginally and became statistically not significant (OR 1.75; 95% CI 0.83,

Table I Characteristics of participants and pregnancy outcomes by number of pregnancies and mode of pregnancy loss.

Variable	First pregnancy (n = 4331)	One pregnancy loss (n = 974)	Two to four pregnancy losses (n = 270)	P-value[a]	One miscarriage (n = 559)	Two miscarriages (n = 94) [c]	P-value[a]	One TOP (n = 415) [b,c]	Two TOP (n = 66) [b,c]	P-value[a]
Maternal age (SD)	28.4 (5.4)	29.2 (5.6)	29.8 (6.1)	<0.001	29.6 (5.5)	30.5 (5.5)	<0.001	28.6 (5.5)	28.9 (5.2)	0.14
Ethnic origin				0.08			0.38			0.02
White	3910 (90)	872 (90)	231 (85)		517 (92)	82 (87)		355 (85)	59 (89)	
Indian	106 (3)	20 (2)	8 (3)		9 (2)	3 (3)		11 (3)	1 (2)	
Other	315 (7)	82 (8)	31 (12)		33 (6)	9 (10)		49 (12)	6 (9)	
Married/cohabitating	3901 (90)	897 (92)	242 (90)	<0.001	525 (94)	90 (96)	0.003	372 (89)	55 (83)	0.19
Body mass index, n (%)				0.006			0.008			0.04
≤18.5	69 (2)	11 (1)	4 (1)		8 (1)	2 (2)		3 (1)	0	
18.6–24.9	2452 (57)	507 (52)	132 (50)		283 (51)	41 (44)		224 (53)	28 (42)	
25–29.9	1185 (27)	301 (31)	77 (28)		182 (33)	28 (30)		119 (29)	21 (32)	
>35	625 (14)	155 (16)	57 (21)		86 (15)	23 (24)		69 (17)	17 (26)	
Mother with history of miscarriage	183 (4)	37 (4)	21 (8)	0.056	21 (4)	7 (8)	0.26	16 (4)	3 (5)	0.27
Sister with history of miscarriage	433 (10)	121 (13)	44 (16)	<0.001	73 (13)	17 (18)	0.004	48 (12)	6 (9)	0.57
Income				0.11			0.37			0.20
<25 k	436 (10)	82 (8)	24 (9)		49 (9)	7 (8)		33 (8)	8 (12)	
25–74 k	1386 (32)	352 (36)	97 (36)		189 (34)	39 (41)		163 (39)	21 (31)	
75–124 k	1602 (37)	328 (34)	92 (34)		191 (34)	28 (29)		137 (33)	26 (40)	
>124 k	488 (11)	118 (12)	25 (9)		75 (13)	11 (12)		43 (10)	5 (8)	
Unknown	419 (10)	94 (10)	32 (12)		55 (10)	9 (10)		39 (10)	6 (9)	
Alcohol[d]				0.15			0.06			0.94
No alcohol in pregnancy	1647 (38)	400 (41)	119 (44)		237 (42)	45 (47)		163 (39)	25 (38)	
Quit in first trimester	2333 (52)	483 (50)	124 (46)		277 (50)	41 (44)		206 (50)	33 (50)	
Continued to drink	451 (10)	91 (9)	27 (10)		45 (8)	8 (9)		46 (11)	8 (12)	
Smoking[d]				<0.001			0.03			<0.001
Never smoked	3329 (77)	710 (73)	184 (68)		415 (74)	77 (82)		295 (71)	30 (46)	
Quit in pregnancy	583 (13)	138 (14)	35 (13)		70 (13)	6 (6)		68 (16)	16 (24)	
Continued to smoke	419 (10)	126 (13)	51 (19)		74 (13)	11 (12)		52 (13)	20 (30)	
Pregnancy outcomes										
Spontaneous preterm birth	160 (4%)	49 (5%)	23 (9%)	<0.001	25 (5%)	11 (12%)	<0.001	24 (6%)	4 (6%)	0.07
PPROM	75 (2%)	21 (2%)	9 (3%)	0.13	8 (1%)	6 (6%)	<0.05	13 (3%)	2 (3%)	0.10

Continued

Table I *Continued*

Variable	First pregnancy (n = 4331)	One pregnancy loss (n = 974)	Two to four pregnancy losses (n = 270)	P-value[a]	One miscarriage (n = 559)	Two miscarriages (n = 94)[c]	P-value[a]	One TOP (n = 415)[b,c]	Two TOP (n = 66)[b,c]	P-value[a]
SGA	466 (11%)	129 (13%)	32 (12%)	0.07	75 (13%)	15 (16%)	0.55	54 (13%)	7 (11%)	0.36
Placental abruption	27 (1%)	8 (1%)	6 (2%)	0.01	6 (1%)	1 (1%)	0.43	2 (1%)	3 (5%)	<0.001
Pre-eclampsia	212 (5%)	47 (5%)	13 (5%)	0.99	26 (5%)	6 (6%)	0.78	21 (5%)	3 (5%)	0.98

Data are mean (SD) or number in %. *P* values are for comparisons between the groups using Student's *t*-test or χ^2-test, $P < 0.05$. PPROM, preterm premature rupture of membranes; SGA, small for gestation age.
[a]Women in the first pregnancies were the reference group.
[b]TOP, termination of pregnancy.
[c]Women with both miscarriages and TOP were excluded.
[d]At 15 ± 1 weeks.

3.69). On examining the variables that we adjusted for, maternal age stood out as the main variable which adjusted the estimate from being significant to non-significant. In this post-hoc analysis, we explored this further by fitting an interaction term between curettage and maternal age and we found that curettage was associated with an increased risk of spontaneous preterm birth in women aged 25 years or older (OR 3.22; 95% CI 1.27, 8.20) but not in younger women ($P = 0.02$ for interaction).

A similar analysis was performed for termination allowing us to compare women with one previous termination managed surgically with women with one previous termination managed non-surgically. This model showed a non-significant crude estimate (OR 1.89; 95% CI 0.93, 3.84) and a significant adjusted estimate (OR 1.85; 95% CI 1.15, 2.99), suggesting that one previous termination managed with curettage was associated with an increased risk of spontaneous preterm birth of 85% compared with women with one previous termination managed non-surgically, i.e. with no curettage. The difference between the crude and adjusted OR was not related to adjustment of a specific variable.

To examine whether the observed increased risk of spontaneous preterm birth was related to the gestational age at which the previous miscarriage or termination occurred, we restricted our analyses to those women with a previous miscarriage or termination that occurred $<$10 weeks' gestation. The results were unchanged.

Sensitivity analysis was performed to investigate the impact of cervical length on the observed increased risk of spontaneous preterm birth. Approximately 50% of women in the study cohort had transvaginal cervical length measurements at 19–21 weeks' gestation. This analysis was then restricted to SCOPE participants from Auckland and Adelaide where ~85% of participants had transvaginal cervical length measurements. A binary cervical length variable was generated where participants were divided in to those with a cervical length $<$30 or $\geq$30 mm. This variable was added to the previously described adjusted models. None of the results were changed materially, i.e. the present findings cannot be explained by shortened cervical lengths.

Discussion

This large prospective cohort study of healthy nulliparous women with singleton pregnancies has demonstrated that women with previous pregnancy loss were at increased risk of spontaneous preterm birth, if they were managed by procedures involving cervical dilatation and curettage. Furthermore, a greater association between women with a history of two or three procedures involving cervical dilatation and curettage and spontaneous preterm birth, compared with women with only one previous cervical dilatation and curettage, was demonstrated (adjusted OR 2.32; 95% CI 1.88, 2.88 versus adjusted OR 1.66; 95% CI 1.14, 2.42). Overall, women with a single pregnancy loss did not have an increased risk of having any other of the adverse pregnancy outcomes examined. In contrast, two to four previous pregnancy losses were associated with an increased risk of having a pregnancy complicated by spontaneous preterm birth and/or placental abruption.

We then separated fetal loss into miscarriage and termination of pregnancy. Although one previous miscarriage overall was not associated with an increased risk of spontaneous preterm birth, when women were managed with procedures involving cervical dilatation and curettage, a significant risk of spontaneous preterm birth was observed. Women with one previous termination of pregnancy had an overall increased risk of spontaneous preterm birth but again this risk was

Table II Association between previous pregnancy loss (miscarriage and/or termination of pregnancy) and adverse pregnancy outcomes.

	One previous pregnancy loss ($n = 974$)			Two to four previous pregnancy losses ($n = 270$)		
	N	Estimate (95% CI)	Adjusted estimate (95% CI)[a]	*N*	Estimate (95% CI)	Adjusted estimate (95% CI)[a]
Spontaneous preterm birth	49	1.38 (0.94, 2.04)	1.31 (0.85, 2.00)	23	2.45 (1.85, 3.24)	2.12 (1.55, 2.90)
PPROM	21	1.25 (0.76, 2.06)	1.24 (0.71, 2.17)	9	1.98 (1.13, 3.45)	1.57 (0.93, 2.64)
SGA	129	1.27 (1.03, 1.58)	1.20 (0.95, 1.52)	32	1.13 (0.81, 1.57)	0.97 (0.68, 1.38)
Birthweight (g)	974	−45 (−84, −5)	−20 (−62, 22)	270	−93 (−192, 6)	24 (−80, 128)
Placental abruption	8	1.32 (0.80, 2.18)	1.17 (0.74, 1.87)	6	3.66 (2.00, 6.69)	2.30 (1.36, 3.89)
Pre-eclampsia	47	0.99 (0.69, 1.40)	0.94 (0.67, 1.33)	13	1.00 (0.69, 1.43)	0.90 (0.67, 1.19)

[a]All end-points, except for birthweight, were analysed using logistic regression and presented as odds ratios (95% CI). Birthweight was analysed using linear regression with robust estimation and is presented as adjusted mean differences (95% CI). The reference group was primigravid women (no previous pregnancy losses). All regression models were adjusted for maternal age, smoking, alcohol consumption, ethnicity, BMI, infant sex, marital status and income. All analyses were adjusted for potential clustering effect of SCOPE centres. Birthweight also adjusted for gestational age at delivery. PPROM, preterm premature rupture of membranes; SCOPE, screening for pregnancy endpoints; SGA, small for gestation age.

Table III Association between previous cervical dilatation and curettage and adverse pregnancy outcomes.

	One previous cervical dilatation and curettage ($n = 579$)			Two-third of previous cervical dilatation and curettages ($n = 95$)		
	N	Estimate (95% CI)	Adjusted estimate (95% CI)[a]	*N*	Estimate (95% CI)	Adjusted estimate (95% CI)[a]
Spontaneous preterm birth	37	1.72 (1.19, 2.44)	1.66 (1.14, 2.42)	9	2.61 (2.07, 3.31)	2.32 (1.88, 2.88)
PPROM	18	1.80 (1.04, 3.10)	1.83 (0.98, 3.42)	1	One case	One case
SGA	72	1.14 (0.95, 1.38)	1.05 (0.85, 1.29)	13	1.27 (0.68, 2.38)	1.00 (0.50, 2.05)
Birthweight (g)	579	−15 (−75, 45)	−1 (−35, 33)	95	−89 (−232, 54)	10 (−70, 90)
Placental abruption	5	1.19 (0.51, 2.77)	1.04 (0.43, 2.47)	2	Two cases	Two cases
Pre-eclampsia	29	1.01 (0.78, 1.32)	0.94 (0.72, 1.22)	4	0.84 (0.47, 1.51)	0.72 (0.42, 1.21)

[a]All end-points, except for birthweight, were analysed using logistic regression and presented as odds ratios (95% CI). Birthweight was analysed using linear regression with robust estimation and is presented as adjusted mean differences (95% CI). The reference group was primigravid women (no previous pregnancy losses). All regression models were adjusted for maternal age, smoking, alcohol consumption, ethnicity, BMI, infant sex, marital status and income. All analyses were adjusted for potential clustering effect of SCOPE centres. Birthweight also adjusted for gestational age at delivery. PPROM, preterm premature rupture of membranes; SCOPE, screening for pregnancy endpoints; SGA, small for gestation age.

Table IV Association between previous miscarriage only and adverse pregnancy outcomes.

	One previous miscarriage only ($n = 559$)			Two previous miscarriages only ($n = 94$)		
	N	Estimate (95% CI)	Adjusted estimate (95% CI)[a]	*N*	Estimate (95% CI)	Adjusted estimate (95% CI)[a]
Spontaneous preterm birth	25	1.22 (0.73, 2.06)	1.16 (0.64, 2.10)	11	3.44 (2.56, 4.64)	3.14 (2.36, 4.20)
PPROM	8	0.82 (0.32, 2.11)	0.80 (0.31, 2.02)	6	3.86 (2.79, 5.34)	3.31 (2.34, 4.69)
SGA	75	1.29 (1.06, 1.56)	1.23 (0.99, 1.54)	15	1.57 (0.84, 2.92)	1.42 (0.76, 2.65)
Birthweight (g)	559	−28 (−74, 18)	−13 (−49, 22)	94	−99 (−285, 86)	10 (−90, 110)
Placental abruption	6	1.73 (0.79, 3.79)	1.47 (0.65, 3.33)	1	One case	One case
Pre-eclampsia	26	0.94 (0.66, 1.37)	0.93 (0.61, 1.41)	6	1.32 (0.88, 1.99)	1.12 (0.70, 1.80)

[a]All end-points, except for birthweight, were analysed using logistic regression and presented as odds ratios (95% CI). Birthweight was analysed using linear regression with robust estimation and is presented as adjusted mean differences (95% CI). The reference group was primigravid women (no previous pregnancy losses). All regression models were adjusted for maternal age, smoking, alcohol consumption, ethnicity, BMI, infant sex, marital status and income. All analyses were adjusted for potential clustering effect of SCOPE centres. Birthweight also adjusted for gestational age at delivery. PPROM, preterm premature rupture of membranes; SCOPE, screening for pregnancy endpoints; SGA, small for gestation age.

Table V Association between previous termination of pregnancy only and adverse pregnancy outcomes.

	One previous termination ($n = 415$)			Two previous terminations ($n = 66$)		
	N	Estimate (95% CI)	Adjusted estimate (95% CI)[a]	*N*	Estimate (95% CI)	Adjusted estimate (95% CI)[a]
Spontaneous preterm birth	24	1.60 (1.20, 2.14)	1.48 (1.04, 2.10)	4	1.71 (0.70, 4.16)	1.11 (0.53, 2.39)
PPROM	13	1.84 (1.01, 3.32)	1.86 (0.92, 3.75)	2	1.80 (0.35, 9.15)	0.91 (0.16, 5.13)
SGA	54	1.25 (0.95, 1.63)	1.16 (0.86, 1.57)	7	1.01 (0.33, 3.10)	0.78 (0.25, 2.45)
Birthweight (g)	415	−67 (−98, −40)	−29 (−104, 47)	66	−117 (−329, 95)	31 (−103, 165)
Placental abruption	2	Two cases	Two cases	3	Three cases	Three cases
Pre-eclampsia	21	1.03 (0.69, 1.55)	0.98 (0.69, 1.38)	3	0.95 (0.40, 2.26)	0.82 (0.31, 2.21)

[a]All end-points, except for birthweight, were analysed using logistic regression and presented as odds ratios (95% CI). Birthweight was analysed using linear regression with robust estimation and is presented as adjusted mean differences (95% CI). The reference group was primigravid women (no previous pregnancy losses). All regression models were adjusted for maternal age, smoking, alcohol consumption, ethnicity, BMI, infant sex, marital status and income. All analyses were adjusted for potential clustering effect of SCOPE centres. Birthweight also adjusted for gestational age at delivery. PPROM, preterm premature rupture of membranes; SCOPE, screening for pregnancy endpoints; SGA, small for gestation age.

Table VI Association between pregnancy loss, cervical dilatation and curettage and spontaneous preterm birth.

	One previous miscarriage	One miscarriage managed without cervical dilatation and curettage	One miscarriage managed by cervical dilatation and curettage	One previous termination	One termination managed without cervical dilatation and curettage	One termination managed by cervical dilatation and curettage
N with spontaneous preterm birth	25	11	14	24	6	18
Absolute risk (%)	4.9	3.4	6.0	5.8	3.8	7.0
Crude odds ratio (95% CI)	1.22 (0.73, 2.06)	0.91 (0.42, 1.97)	1.67 (1.21, 2.30)	1.60 (1.19, 2.13)	1.03 (0.60, 1.79)	1.96 (1.50, 2.55)
Adjusted odds ratio (95% CI)[a]	1.19 (0.66, 2.15)	0.86 (0.38, 1.94)	1.64 (1.08, 2.50)	1.55 (1.14, 2.11)	0.87 (0.69, 1.12)	1.83 (1.35, 2.48)

[a]Logistic regression analysis adjusted for maternal age, smoking, alcohol consumption, ethnicity, BMI, infant sex, marital status and income. All analyses were adjusted for potential clustering effect of SCOPE centres. The reference group was women with no previous pregnancy losses ($n = 4331$, of whom 160 had spontaneous preterm birth). SCOPE, screening for pregnancy endpoints.

restricted to when the previous termination of pregnancy was managed surgically. These associations were not gestation dependent, because the results remained unchanged when analyses were confined to <10 weeks' gestation.

Women with two previous miscarriages were at an increased risk of either spontaneous preterm birth or PPROM. This may reflect an increased incidence of undiagnosed medical problems associated with recurrent miscarriage such as anti-phospholipid syndrome (Rai *et al.*, 1997) or reflect an underlying predisposition towards poor placentation (Bose *et al.*, 2006).

The strengths of our study are that detailed information about pregnancy outcomes were collected prospectively with pregnancy outcome data available in 99% of participants. Pregnancy outcome was assigned according to pre-specified criteria and stringent data monitoring protocols ensured the quality of the data. Although every effort was made to record accurate previous pregnancy loss information and management by the trained SCOPE midwives using a detailed pregnancy loss proforma, it was not feasible to confirm the history and management of previous pregnancy loss by hospital records. This may have introduced recall bias. As pregnancy loss is such an important event for mothers, it is unlikely that this information would be prone to recall bias (Hewson and Bennett, 1987; Githens *et al.*, 1993; Yawn *et al.*, 1998). Furthermore, previous pregnancy loss data were recorded at 15 weeks' gestation prior to the occurrence of any of the observed adverse pregnancy outcomes. The mechanisms to explain the association between cervical dilatation/curettage and spontaneous preterm birth are unknown. Postulated mechanisms include damage to cervical tissues by artificial dilatation of the cervix or alteration in the expression of genes involved in collagenolysis and inflammation following disruption of the endometrium/ myometrium during curettage (Sooranna *et al.*, 2005). As women with three or more miscarriages or three or more terminations of pregnancy were excluded from the SCOPE study due to an accepted assumption of increased risk and therefore increased surveillance, this study cannot assess the potential 'dose' effect beyond two losses but the data suggest that an increased risk is already present after two pregnancy losses (termination of pregnancy or miscarriage) and comparable with the increased risk reported with higher degrees of loss (Thom *et al.*, 1992). In this study, we conducted analyses of

multiple exposures, including the analysis of interaction terms, to examine several outcomes in this cohort. Given the multiple comparisons, there is the possibility of rejecting null hypotheses incorrectly. Non-surgical methods of management of miscarriage and termination of pregnancy would have included medical methods as described in the methods section or occasionally expectant management. As management was classified simply as surgical or non-surgical, we were unable to explore whether any differences occurred between those women managed expectantly or medically.

Published data regarding the association between previous pregnancy loss and adverse pregnancy outcomes in subsequent pregnancies are limited, with conflicting results (van Oppenraaij *et al*., 2009; Virk *et al*., 2007). Some studies have reported that miscarriage is associated with an increased risk of preterm delivery and PPROM (Swingle *et al*., 2009; Buchmayer *et al*., 2004) and SGA (Basso *et al*., 1998; Bhattacharya *et al*., 2008), whereas others have not (Schoenbaum *et al*., 1980; de Haas *et al*., 1991; Ekwo *et al*., 1993; Hammoud *et al*., 2007). Similarly, conflicting evidence exists regarding previous termination of pregnancy and subsequent adverse pregnancy outcomes (Hogue *et al*., 1983; Pickering and Forbes, 1985; Atrash and Hogue, 1990; Lang *et al*., 1996; Zhou *et al*., 1999; Ancel *et al*., 2004; Moreau *et al*., 2005; Raatikainen *et al*., 2006). Few studies have examined whether the mode of management of miscarriage or termination of pregnancy is relevant (Lohmann-Bigelow *et al*., 2007; Virk *et al*., 2007).

Prospective, well-conducted studies are lacking and many of the retrospective studies have small numbers and are of poor quality with a significant bias making definitive conclusions and comparisons difficult. In our study, the association between one previous miscarriage and spontaneous preterm birth was confined to women managed surgically. Our study does not support an association between one previous miscarriage and other pregnancy complications as shown by others (Buchmayer *et al*., 2004; Bhattacharya *et al*., 2008) but concurs with a previously reported association between two previous miscarriages and an increased risk of spontaneous preterm delivery (Buchmayer *et al*., 2004) and PPROM but not SGA, as demonstrated in other studies (Basso *et al*., 1998; Buchmayer *et al*., 2004). Our results differ from those reported by Lohmann-Bigelow *et al.* who found no association between previous dilatation and curettage and preterm delivery, pre-eclampsia and placental abruption and miscarriage in their retrospective study. These findings may be explained by the heterogeneous population of multiparous women included in this study or the fact that pregnancy outcomes were obtained retrospectively, in contrast with the prospective nature of the SCOPE cohort of nulliparous women (Lohmann-Bigelow *et al*., 2007). Whilst this study is consistent with those that have found an association between women with one previous termination of pregnancy and an increased risk of preterm delivery, we did not confirm the previously reported association with PPROM (Ancel *et al*., 2004). The SCOPE database allowed us to access many potential confounding factors such as drug use. Women recruited to the SCOPE cohort were healthy nulliparous women with no known medical conditions thought to influence the risk of preterm birth, SGA or pre-eclampsia. Nonetheless, there is the possibility that undiagnosed medical conditions such as untested thyroid abnormalities may act as further potential confounding factors.

In conclusion, women with either one previous miscarriage or previous termination managed non-surgically were not significantly associated with an increased risk of spontaneous preterm birth. In contrast, when management of miscarriage or termination included cervical dilatation and curettage, a significant association was demonstrated for spontaneous preterm birth. A significant association between women with multiple (two to four) pregnancy losses and spontaneous preterm birth and/or placental abruption was also demonstrated. Despite demonstrating a significant association between pregnancy loss managed by dilatation and curettage and spontaneous preterm birth, an interpretation of any causal effect of dilatation and curettage is not possible and further studies are needed to examine this. Further research is also required to confirm our findings in other populations and to determine whether non-surgical management of miscarriage or termination of pregnancy should be advocated over surgical treatment.

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Authors' roles

F.M.C. is the guarantor. All authors had a role in the conception and design of the study. F.M.C., A.K. and L.K. interpreted the data. All authors took part in drafting the article or revising it for critically important intellectual content and all gave final approval of the version to be published.

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Conflict of interest

None declared.

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