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META-ANALYSIS Early pregnancy

Dilatation and curettage increases the risk of subsequent preterm birth: a systematic review and meta-analysis

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STUDY QUESTION: Could dilatation and curettage (D&C), used in the treatment of miscarriage and termination of pregnancy, increase the risk of subsequent preterm birth?

SUMMARY ANSWER: A history of curettage in women is associated with an increased risk of preterm birth in a subsequent pregnancy compared with women without such history.

WHAT IS KNOWN ALREADY: D&C is one of the most frequently performed procedures in obstetrics and gynaecology. Apart from the acknowledged but relatively rare adverse effects, such as cervical tears, bleeding, infection, perforation of the uterus, bowel or bladder, or Asherman syndrome, D&C has been suggested to also lead to an increased risk of preterm birth in the subsequent pregnancy.

STUDY DESIGN, SIZE, DURATION: In the absence of randomized data, we conducted a systematic review and meta-analysis of cohort and case–control studies.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We searched OVID MEDLINE and OVID EMBASE form inception until 21 May 2014. We selected cohort and case–control studies comparing subsequent preterm birth in women who had a D&C for first trimester miscarriage or termination of pregnancy and a control group of women without a history of D&C.

MAIN RESULTS AND THE ROLE OF CHANCE: We included 21 studies reporting on 1 853 017 women. In women with a history of D&C compared with those with no such history, the odds ratio (OR) for preterm birth <37 weeks was 1.29 (95% CI 1.17; 1.42), while for very preterm birth the ORs were 1.69 (95% CI 1.20; 2.38) for <32 weeks and 1.68 (95% CI 1.47; 1.92) for <28 weeks. The risk remained increased when the control group was limited to women with a medically managed miscarriage or induced abortion (OR 1.19, 95% CI 1.10; 1.28). For women with a history of multiple D&Cs compared with those with no D&C, the OR for preterm birth (<37 weeks) was 1.74 (95% CI 1.10; 2.76). For spontaneous preterm birth, the OR was 1.44 (95% CI 1.22; 1.69) for a history of D&C compared with no such history.

LIMITATIONS, REASONS FOR CAUTION: There were no randomized controlled trials comparing women with and without a history of D&C and subsequent preterm birth. As a consequence, confounding may be present since the included studies were either cohort or case–control studies, not all of which corrected the results for possible confounding factors.

WIDER IMPLICATIONS OF THE FINDINGS: This meta-analysis shows that D&C is associated with an increased risk of subsequent preterm birth. The increased risk in association with multiple D&Cs indicates a causal relationship. Despite the fact that confounding cannot be excluded, these data warrant caution in the use of D&C for miscarriage and termination of pregnancy, the more so since less invasive options are available.

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Key words: miscarriage / termination of pregnancy / dilatation and curettage / preterm birth / expectant management / misoprostol

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Introduction

Dilatation and curettage (D&C) is a frequently performed surgical procedure in obstetrics and gynaecology. It is used in the management of first and second trimester miscarriage as well as for termination of pregnancy. Although the procedure is generally considered to be relatively safe and easy to perform, serious adverse effects may occur. Short-term complications include cervical tears, bleeding, infection and perforation of the uterus, which may sometimes be accompanied by perforation of the bladder or bowel (Kaali *et al.*, 1989; Molin, 1993; Child *et al.*, 2001; Bhattee *et al.*, 2006). A well-known long-term complication is the formation of intrauterine adhesions, also known as Asherman syndrome, which may lead to menstrual disorders and fertility problems (Schenker and Margalioth, 1982; Hooker *et al.*, 2014). Another possible adverse long-term effect of D&C is an increased risk of preterm birth in subsequent pregnancies. Preterm birth, defined as birth before 37 weeks of gestation, is a major concern in perinatology and continues to be the leading cause of perinatal morbidity and mortality in developed countries (Wen *et al.*, 2004; Ananth and Vintzileos, 2006).

Since the legalization of termination of pregnancy in many countries, several articles have been published on a possible relationship between termination of pregnancy and preterm birth in subsequent pregnancies, with contradicting results (Pantelakis *et al.*, 1973; Daling and Emanuel, 1975; Berkowitz, 1985; Frank *et al.*, 1985; Atrash and Hogue, 1990; Lopes *et al.*, 1991; Foix-L'Helias and Blondel, 2000; Ancel *et al.*, 2004; Moreau *et al.*, 2005; Freak-Poli *et al.*, 2009). Several systematic reviews have reported an increased preterm birth rate after termination of pregnancy (Atrash and Hogue, 1990; Thorp *et al.*, 2003; Shah and Zao, 2009; Lowit *et al.*, 2010). In these studies, no distinction has been made between the medical management and surgical management for termination of pregnancy. One might argue that it is not so much the event of a miscarriage or termination of pregnancy, but possibly its surgical management (D&C), which causes the increased risk of preterm birth in these women. More recently, large nationwide studies indeed have reported an increased risk of preterm birth specifically after D&C, be it for miscarriage or termination of pregnancy (Zhou *et al.*, 1999; Virk *et al.*, 2007; Bhattacharya *et al.*, 2012; Mannisto *et al.*, 2013; McCarthy *et al.*, 2013). Several studies which have also assessed preterm birth rates, did so by comparing medical with surgical management (Chen *et al.*, 2004; Virk *et al.*, 2007; Liao *et al.*, 2011; Bhattacharya *et al.*, 2012; Mannisto *et al.*, 2013; McCarthy *et al.*, 2013). The majority of these papers, but not all of them, reported an increased risk of preterm birth in women managed by D&C when compared with those women who received medical treatment.

In view of these results, we performed a systematic review and meta-analysis on the association between D&C for either first trimester miscarriage or termination of pregnancy, and the risk of preterm birth in a subsequent pregnancy.

Materials and Methods

Sources

Since we extracted all data from previously published papers, institutional review board approval was not necessary for this study. This systematic review was conducted according to the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

A clinical librarian (J.L.) performed an electronic search in MEDLINE (OVID) and EMBASE (OVID) from inception to 21 May 2014, using both Subject Headings, such as MeSH (MEDLINE), and words in title, abstract and author keywords. The search consisted of two parts (see Supplementary Table SI). In part I of the search, we combined a search for D&C and synonyms (i.e. surgical abortion, vacuum aspiration), with a broad search for preterm birth, including indirect terms such as 'small for gestational age' and (low) 'birth weight' [PTB broad]. Part II of the search aimed to find articles on the topic not mentioning terms indicative of 'dilatation & curettage' in the abstract. Here we searched for induced, incomplete, spontaneous or recurrent abortion [IIa] or abortion in previous pregnancy [IIb]. This broad search was combined with a narrower search for preterm birth [PTB narrow].

The search included an iterative process to refine the search strategy through adding search terms as new relevant citations were identified (i.e. via checking of references and citations of relevant trials). No language or any other restrictions were applied. Animal studies were safely excluded (not ((animals/ not humans/) or cattle.ti.). The bibliographic records retrieved were downloaded and imported into Reference Manager ® software (version 12.0) to de-duplicate, store and analyse the search results. No language restriction was applied in the search strategy. For articles published in any other language than English or Dutch, translation was sought. Considered for inclusion were articles published in peer- reviewed or non-peer-reviewed journals, as well as conference abstracts and non-published studies.

Eligibility of the detected studies was assessed based on title and abstract. When a study was potentially eligible, the full article was obtained and reviewed by two researchers (M.L. and M.A.C.V.). When a full article was unavailable, contact with original authors was sought.

Study selection

We considered randomized clinical trials, prospective and retrospective cohort studies, and case–control studies, reporting on surgical management for first trimester miscarriage and/or termination of pregnancy and the prevalence of subsequent preterm birth for inclusion.

Surgical management could consist of dilatation and evacuation, dilatation and curettage (D&C) or vacuum curettage. Studies reporting solely on conservative management of miscarriage or medical evacuation of miscarriage or termination of pregnancy were excluded, as were studies reporting on hysterotomy or saline abortion. Studies reporting on second trimester D&C were excluded; short-term complications are more likely in second trimester D&C which might influence long-term complications and the cervical trauma in these women might lead to a different risk of subsequent preterm birth. Studies without a control group were excluded. We also excluded studies which assessed the relationship between preterm birth and miscarriage or termination of pregnancy without specifying its management (i.e. expectant, medical or surgical). Preterm birth was defined as birth before 37 weeks of gestation. Studies assessing preterm birth by birthweight were excluded. Studies reporting on both term and pre-term birth were excluded if no clear distinction was made between these groups.

Nomenclature

To describe clinical events in early pregnancy, we used the revised terminology as proposed by the ESHRE Special Interest Group of Early Pregnancy (SIGEP) (Farquharson *et al.*, 2005).

First trimester miscarriage was defined as the spontaneous expulsion of products of conception or the disappearance of fetal heart activity on ultrasound or a gestational sac that did not grow in consecutive ultrasound examinations before 14 weeks of gestation.

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Severity of preterm birth

The most common definition of preterm birth is birth before 37 weeks of gestation. To indicate the severity of preterm birth, several terms are used in the literature; mild, moderate and severe preterm birth, or preterm and very preterm birth, thereby indicating decreasing gestational ages. For the purpose of comparison we divided preterm birth into three commonly used categories: birth before 37 weeks of gestation, birth before 32 weeks of gestation and birth before 28 weeks of gestation.

Data extraction and assessment of methodological quality

Two researchers (M.L. and M.A.C.V.) independently extracted the following data on the selected papers: publication year, study design, inclusion and exclusion criteria and patient characteristics. Discrepancies were discussed until mutual agreement was achieved. Subsequently, quality of the included studies and risk of bias was independently assessed by the same researchers (M.L. and M.A.C.V.). The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) combined checklist for observational studies (version4, 2007) was used to report on the methodological quality of included studies. We constructed two-by-two tables comparing a history of D&C and the other treatment modalities as stated earlier, to the presence or absence of subsequent preterm birth. If possible, we noted the number of surgically managed abortions, the duration of pregnancy in gestational weeks at the time of D&C, the type of surgical procedure (i.e. dilatation and evacuation, dilatation and curettage or vacuum curettage), the establishment of gestational age at birth (i.e. first trimester ultrasound, last menstrual period (LMP) or Dubowitz score) and the degree (i.e. <37 weeks, <32 weeks or <28 weeks) and nature (i.e. spontaneous or elective/iatrogenic) of preterm birth.

Outcome measures

Primary outcome was the presence and extent of preterm birth subsequent to a history of curettage. We analysed the risk of any preterm birth <37 weeks, <32 weeks and <28 weeks in women with a history of D&C compared with all possible control groups. In the various studies, control groups consisted of women with a history of medical management for miscarriage or termination of pregnancy, women with a history of spontaneous miscarriage without any intervention or women without a history of miscarriage or termination of pregnancy.

Furthermore, we intended to identify a possible dose–response relationship by comparing women with a history of multiple D&Cs to women without a history of D&C. We analysed the risk of any preterm birth<37 weeks in women with a history of multiple D&Cs compared with all (possible) available control groups.

Sensitivity analyses

In order to explore the robustness of our hypothesis, we assessed the risk of any preterm birth <37 weeks in women with a history of D&C compared with women with a history of medically managed miscarriage or termination of pregnancy, in order to explore whether preterm birth was associated with the previous miscarriage or termination of pregnancy or with the treatment methods used in its management.

Furthermore we performed a subgroup analysis to assess whether D&C is associated with spontaneous birth or iatrogenic preterm birth, or both in order to gain insight into the pathophysiological mechanism behind the association. We did this by assessing the risk of spontaneous preterm birth <37 weeks in women with a history of D&C compared with all possible control groups.

In the final meta-analysis, adjusted odds ratios for the risk of preterm birth <37 weeks subsequent to a history of curettage, from all available studies were compared.

Data analysis

We used Review manager (RevMan) version 5.2 software to conduct the statistical analysis.

For all tests performed, statistical significance was determined at $P < 0.05$. Statistical heterogeneity was assessed using I^2 statistics and χ^2 (chi-squared) test, and considered substantial when I^2 exceeded 50% or when $P > 0.10$. Depending on the heterogeneity, a random or fixed effects model with the inverse variance weighting approach was used for pooling the results of different studies. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Results

Included studies

Our search identified 2110 unique citations. The flow diagram illustrates the selection procedure (Fig. 1). After screening of titles and abstracts, we excluded 1913 papers. Of the remaining 197 papers, 3 full manuscripts could not be retrieved, despite several attempts to contact the authors. After reviewing the 194 complete manuscripts, 130 articles were excluded since it remained unclear whether the miscarriage or termination of pregnancy was managed medically or surgically. Another 23 papers were letters to the editor, narrative or non-systematic reviews. In further 8 papers, preterm birth was not, or not clearly, defined. Another 12 articles were excluded for a variety of other reasons. One of these was excluded because it reported on the same patient data as another (larger) included study (Woolner *et al.*, 2014).

Thus, a total of 21 studies were included (Table I): 3 case–control studies (Berkowitz, 1985; Siedlecka and Makowiec-Dabrowska, 1998; Watson *et al.*, 2012), 7 prospective cohort studies (W.H.O. Task Force on Sequelae of Abortion, 1979; Che *et al.*, 2001; Chen *et al.*, 2004; Zou *et al.*, 2004; de Carvalho *et al.*, 2005; Liao *et al.*, 2011; McCarthy *et al.*, 2013) and 11 retrospective cohort studies (Renkielska, 1978; van der Slikke and Treffers, 1978; Meirik *et al.*, 1982; Meirik and Bergstrom, 1983; Krasnodebski *et al.*, 1989; Zhou *et al.*, 1999; Virk *et al.*, 2007; Suzuki, 2010; Bhattacharya *et al.*, 2012; Mannisto *et al.*, 2013; Scholten *et al.*, 2013).

Quality of included studies

The 21 included studies comprised a total of 1 853 017 women of whom 71 231 had a history of at least one D&C in the first trimester of pregnancy. In 66 003 women, D&C had been performed for termination of pregnancy. The control group consisted of 1 781 786 women. Among them were 392 838 nulliparous and 1945 multiparous women, while the parity of 1 363 965 women was not reported. In the control group, 24 977 women had received a medical treatment for either miscarriage or termination of pregnancy, while 1189 had had a spontaneous miscarriage. The remaining women of the control group consisted of a mixture of primi- and multigravida with or without a history of spontaneous miscarriage.

There were 5 register based cohort studies (Zhou *et al.*, 1999; Virk *et al.*, 2007; Bhattacharya *et al.*, 2012; Mannisto *et al.*, 2013; Scholten

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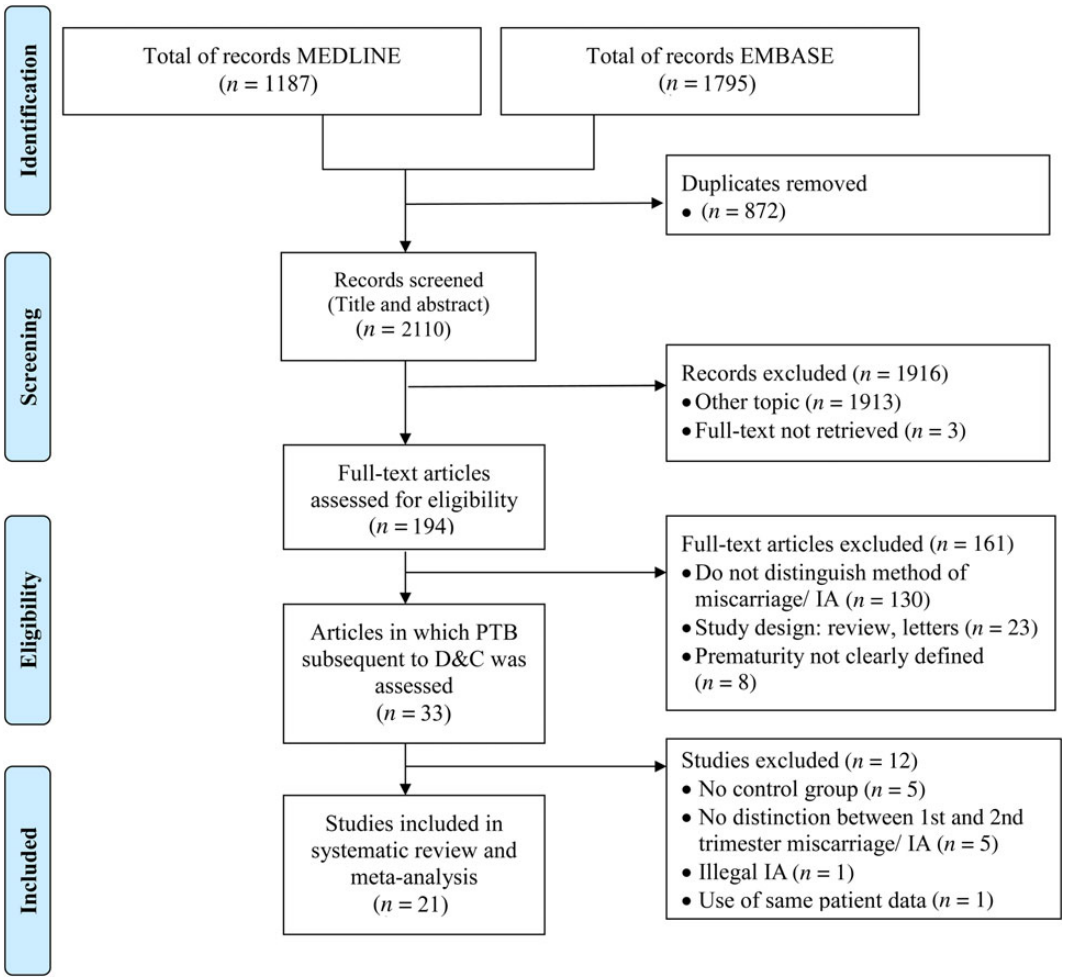

Figure 1 PRISMA flow diagram illustrating the selection procedure of relevant articles.

et al., 2013) performed in different countries (Scotland, Finland, the Netherlands, Denmark and Denmark) reporting on 1 784 707 women (96% of the total).

Preterm birth was defined as spontaneous or induced birth before 37 weeks of gestation in 17 included studies, while 4 studies defined preterm birth as birth <36 (2 studies), <34 (1 study) and <32 weeks (1 study), respectively (Renkielska, 1978; Berkowitz, 1985; Suzuki, 2010; Bhattacharya et al., 2012). Very preterm birth was defined as delivery before <32 weeks and <28 weeks, respectively in seven and five studies (Renkielska, 1978; Krasnodebski et al., 1989; Zhou et al., 1999; Che et al., 2001; Chen et al., 2004; Bhattacharya et al., 2012; Mannisto et al., 2013). In 13 studies, the method for establishing gestational age was not reported, while 3 studies used last menstrual period (LMP) (Che et al., 2001; Chen et al., 2004; Bhattacharya et al., 2012), 3 studies used a combination of LMP and first trimester ultrasound (Che et al., 2001; de Carvalho et al., 2005; Bhattacharya et al., 2012) and 2 studies used a Dubowitz score for the assessment of gestational age at delivery (Renkielska, 1978; Berkowitz, 1985).

There were 6 studies comparing D&C to medical management for miscarriage or termination of pregnancy, published between 1999 and 2013 and analysing 59 442 women (3.2% of total) (Chen et al., 2004; Virk et al., 2007; Liao et al., 2011; Bhattacharya et al., 2012; Mannisto et al., 2013; McCarthy et al., 2013), and these were considered of high quality with a mean score of 23.3 (range 19–28). Studies published after 2000 were generally of higher quality (mean 22.3 range 9–29) than those studies published before 2000 (mean 15.1 range 7–23). Results of the assessment of the methodological quality of the included studies using the STROBE checklist are reported in Supplementary Table SII. In general the quality of the included studies varied substantially. The included items had a mean quality score of 19.3 (range 7–29).

In order to assess the possibility of publication bias a funnel plot was constructed (Fig. 2). A symmetrical distribution is displayed around the estimated effect, therefore publication bias seems unlikely.

Analyses

The risk of preterm birth <37 weeks was increased in women with D&C, as compared with women without a history of D&C for miscarriage or termination of pregnancy (21 studies, 1 853 017 women, pooled OR 1.29 (95% CI 1.17; 1.42) (Figs 3 and 4A). Figure 3 also shows the results for prospective cohort studies, retrospective cohort studies, and case–control studies.

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Table I Study characteristics.

Author	Year	Design	Period	Patient characteristics—study group	Patient characteristics—control group	Patients	All PTB/SPTB	Definition of PTB	Gestational age
Berkowitz	1985	CCS	1977–1978	Patients with preterm birth	Patients with term birth	498	SPBT	<37 weeks	Dubowitz score
Bhattacharya	2012	RCS	1981–2007	Patients with a live birth after surgical TOP	Primiparous patients without TOP or after medical TOP	342 817	SPBT	<37 weeks (<32 weeks, <28 weeks)	NM
Che	2001	PCS	1993–1998	Pregnant patients with a history of surgical TOP	Primigravid patients	2707	All PTB	<37 weeks	LMP
Chen	2004	PCS	1998–2001	Pregnant patients with a history of surgical TOP	Pregnant patients without history of abortion and pregnant patients with a history of medical TOP	13 928	All PTB	<37 weeks	LMP
de Carvalho	2005	PCS	1998–2001	Pregnant patients with a history of surgical TOP or miscarriage	Pregnant patients without a history surgical TOP or miscarriage	1958	SPBT	<37 weeks	LMP + US
Krasnodebski	1989	RCS	1980–1984	Patients with a live birth after surgical miscarriage	Patients with a live birth without a history of miscarriage	357	NM	<37 weeks	NM
Liao	2011	PCS	2006–2009	Pregnant patients with a history of surgical TOP	Pregnant patients without history of abortion and pregnant patients with a history of medical TOP	18 024	All PTB	<37 weeks (<32 weeks, <28 weeks)	LMP + US
McCarthy	2013	PCS	2004–2011	Pregnant patients with a history of surgical TOP or miscarriage	Nulliparous pregnant patients without TOP or miscarriage, with spontaneous miscarriage or with medical TOP or miscarriage	5575	SPTB	<37 weeks	LMP + US
Meirik	1983	RCS	1970–1975	Patients with a live birth after surgical TOP	Primiparous patients without TOP	1979	NM	<37 weeks	LMP
Meirik	1982	RCS	1970–1975	Patients with a live birth after surgical TOP	Multiparous patients without TOP	1491	NM	<37 weeks	NM
Männistö	2012	RCS	2000–2009	Patients with a live birth after surgical TOP	Patients with a live birth after medical TOP	8294	NM	<37 weeks (<32 weeks, <28 weeks)	NM
Renielska	1978	RCS	1976	Patients with a live birth after surgical TOP	Patients with a live birth without TOP	324	NM	<36 weeks	NM
Scholten	2013	RCS	2000–2007	Patients with a live birth after surgical TOP	Patients with a live birth without TOP	1 357 894	SPBT	<37 weeks (<32 weeks, <28 weeks)	NM
Siedlecka	1998	CCS	1992–1994	Patients with preterm birth	Patients with term birth	286	NM	<37 weeks	NM
Suzuki	2010	RCS	2002–2007	Patients with a live birth after surgical TOP or miscarriage	Patients with a live birth without surgical TOP or miscarriage	5815	All PTB	<37 weeks (<32 weeks, <28 weeks)	NM
van der Slikke	1978	RCS	1972–1976	Patients with a live birth after surgical TOP or miscarriage	Patients with a live birth without TOP, or with spontaneous miscarriage	878	All PTB	<36 weeks (<32 weeks, <28 weeks)	Dubowitz score
Virk	2007	RCS	1999–2004	Patients with a live birth after surgical TOP	Patients with a live birth after medical TOP	8577	All PTB	<37 weeks	NM

Continued

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Table I *Continued*

Author	Year	Design	Period	Patient characteristics—study group	Patient characteristics—control group	Patients	All PTB/SPTB	Definition of PTB	Gestational age
Watson	2011	CCS	2002–2004	Patients with preterm birth	Patients with term birth	1377	All PTB and SPTB	<32 weeks	NM
WHO	1979	PCS	NM	Pregnant patients with a history of surgical TOP	Primigravid pregnant patients, pregnant patients with history of spontaneous miscarriage pregnant patients with history of life birth	12 813	All PTB	<37 weeks	NM
Zhou	1999	RCS	1980–1982	Patients with a live birth after surgical TOP	Primiparous patients without TOP	67 125	All PTB	<37 weeks	NM
Zou	2004	PCS	NM	Pregnant patients with a history of surgical TOP	Pregnant patients with a history of medical TOP	300	NM	<37 weeks	NM

CCS, case–control study; NM, not mentioned; RCS, retrospective cohort study; LMP, last menstrual period; PCS, prospective cohort study; US, ultrasound.

There were seven studies which reported on very preterm birth. All of these reported on birth <32 weeks of gestation, and showed an OR of 1.69 (95% CI 1.20; 2.38) for those with a history of D&C compared with those with no such history (Fig. 4B). Five studies reported on birth <28 weeks of gestation, and demonstrated an OR of 1.68 (95% CI 1.47; 1.92) after D&C compared no D&C (Fig. 4C).

Three studies reported on multiple D&Cs for a miscarriage or termination of pregnancy in relation to the risk of preterm birth in a subsequent pregnancy. These studies reported on 2157 women who underwent more than one D&C procedure while the control group consisted of women with a history of either a medically managed miscarriage or termination of pregnancy, or no miscarriage or termination of pregnancy at all. These showed an OR of 1.74 (95% CI 1.10; 2.76) for preterm birth (Fig. 4D). There was only one study (Zhou *et al.*, 1999) comparing women with one D&C or two D&Cs or three D&Cs, to women without a history of D&C. In this study the ORs for preterm birth were 1.89 (95% CI 1.70; 2.10) after one D&C, 2.66 (95% CI 2.09; 3.37) after two D&Cs and 2.18 after three D&Cs (95% CI 1.31; 3.64).

For the purpose of sensitivity analysis, we identified six studies that reported only on spontaneous preterm birth in women with a history of D&C for miscarriage or termination of pregnancy, compared with those with no history of D&C. These showed an OR of 1.44 (95% CI 1.22; 1.69) (Fig. 4E).

There were six studies which compared the risk of subsequent preterm birth (<37 weeks) between D&C and medical management for miscarriage or termination of pregnancy: OR 1.19 (95% CI 1.10; 1.28) (Fig. 4F). Only one study assessed the risk of spontaneous preterm birth (<37 weeks) in women with a history of D&C for termination of pregnancy compared with women with medical termination of pregnancy (OR 1.18 (95% CI 1.05; 1.34) adjusted OR 1.25 (95% CI 1.07; 1.45)) (Bhattacharya *et al.*, 2012). One study assessed the risk of preterm birth subsequent to either vacuum aspiration or evacuation as surgical method used for termination of pregnancy. A history of one vacuum aspiration (OR 1.82 (95% CI 1.63; 2.04)) led to a significant lower risk of subsequent preterm birth compared with a history of surgical dilatation and evacuation (OR 2.27 (95% CI 1.71; 3.01)). This difference was even more substantial in cases of two vacuum aspirations (OR 2.45 (95% CI 1.90; 3.17)) compared with two surgical evacuations (OR 12.55 (95% CI 5.14; 30.64)).

When comparing women with and without a history of D&C for miscarriage or termination of pregnancy and the risk of subsequent preterm birth, the majority of studies presented confounder-adjusted ORs. Adjustments were made for various confounders including maternal age, parity, smoking status, use of alcohol, BMI, socio-economic status, residence, co-habitation status, inter pregnancy intervals and season of conception (Zhou *et al.*, 1999; Che *et al.*, 2001; Chen *et al.*, 2004; Virk *et al.*, 2007; Liao *et al.*, 2011; Bhattacharya *et al.*, 2012; Watson *et al.*, 2012; Mannisto *et al.*, 2013; McCarthy *et al.*, 2013; Scholten *et al.*, 2013). With these adjustments included, the reported risks for preterm (<37 weeks) and very preterm birth (<32 weeks and <28 weeks) were OR 1.43 (95% CI 1.25; 1.64), OR 1.49 (95% CI 1.26; 1.76) and OR 1.61 (95% CI 1.40; 1.84), respectively. These risks did not differ significantly from the unadjusted analyses with crude numbers.

For all except one analyses, statistical heterogeneity was substantial with $I > 50\%$ or $P > 0.10$ and therefore random effect models were used to pool the overall effect. Clinical heterogeneity was also relevant in these analyses mostly due to the different control groups used in the

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selected studies. Both statistical and clinical heterogeneity were low when comparing women with D&C to women with medical treatment for miscarriage or termination of pregnancy for the risk of subsequent preterm birth <37 weeks. In this particular analysis, we used a fixed effect model.

Discussion

Main findings

Our meta-analysis indicates that women with a previous D&C, for miscarriage or termination of pregnancy in the first trimester, are at increased risk for preterm and especially very preterm birth, in comparison to women without a previous D&C.

The increased risk on preterm birth remained statistically significant when we limited the analysis to women who had medical management in the control group, indicating that D&C itself is an important risk factor for preterm birth. The odds ratio was greater for very preterm birth. The risk of preterm birth increased in case of multiple previous D&C procedures, which suggests a dose–response effect. All analyses showed the same tendency towards a higher risk of preterm birth after D&C, which indicates the consistency of these results. Arguably, these findings suggest that surgical management, rather than the actual miscarriage or termination, is the decisive factor which increases risk of preterm birth in the following pregnancy.

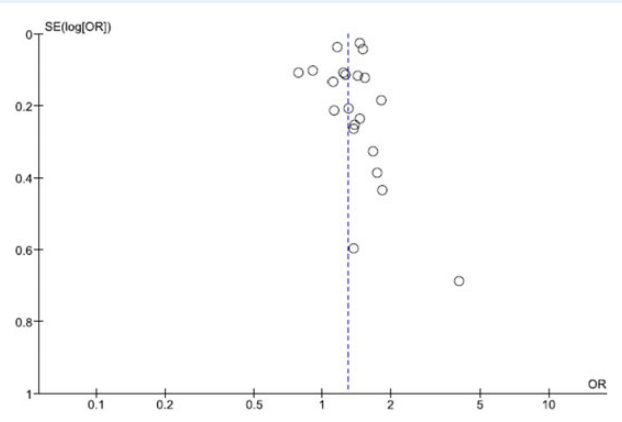

Figure 2 Funnel plot for identification of publication bias.

Strengths and limitations

This is the first systematic review and meta-analysis addressing the association between D&C and preterm birth. The search strategy for this study was comprehensive. We did not exclude any studies based on language restrictions, while two independent researchers assessed all eligible abstracts and papers. Inclusion and exclusion criteria were clearly formulated beforehand. Sensitivity analyses, where the exposure was limited to a control group of women who were medically managed, or where the outcome was limited to spontaneous preterm birth, confirmed the robustness of our findings.

There were no randomized controlled trials that met the inclusion criteria. We included prospective and retrospective cohort studies or case–control studies. The quality of selected studies varied substantially, with STROBE scores ranging from 7 to 29. Sensitivity analysis of high quality studies comparing D&C to medical management for miscarriage or termination of pregnancy and subsequent preterm birth <37 weeks (STROBE score mean 23.5 range 13–28) showed a similar OR for preterm birth when compared with the pooled OR of all included studies. Similarly, subgroup analysis excluding papers with STROBE scores <15 did not significantly change the OR for preterm birth in pregnancies subsequent to D&C (analysis not shown).

Our meta-analyses included five population-based cohort studies (Zhou *et al.*, 1999; Virk *et al.*, 2007; Bhattacharya *et al.*, 2012; Mannisto *et al.*, 2013; Scholten *et al.*, 2013). In these studies, the databases were reported to be about 95% accurate. The approximate 5% missing or incorrect data probably included both women with or without D&C and/or preterm birth and bias, therefore, seems unlikely.

Obviously, all retrospective cohort and case–control studies that we used may have been susceptible to selection and recall bias. Analysis of prospective cohort studies which are not susceptible for these types of bias, however, showed similar results. There were several possible confounding factors, such as maternal age, parity, smoking status, use of alcohol, BMI, socio-economic status, residence, co-habitation status, inter pregnancy intervals and season of conception which were adjusted for in most albeit not all studies. Two studies also corrected for

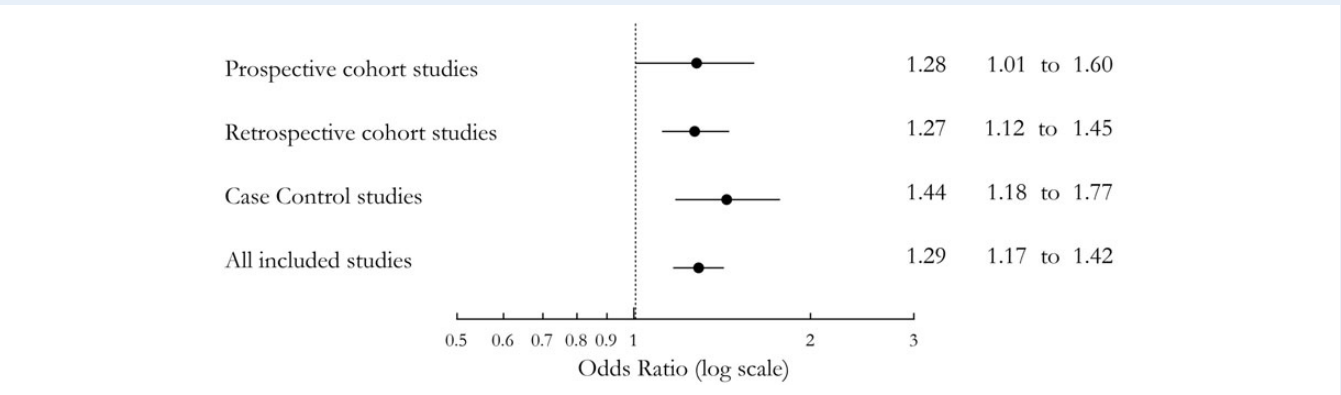

Figure 3 Risk of preterm birth (<37 weeks gestation) in women with a history of D&C compared with those with no D&C. Odds ratios (ORs) are shown, followed by 95% confidence intervals.

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gestational age at time of TOP (Virk et al., 2007; Mannisto et al., 2013). The four other studies which compared D&C to medical management for either TOP or miscarriage did not mention a difference in gestational age at time of TOP or miscarriage for women receiving either D&C or medical treatment.

For the purpose of sensitivity analysis, a meta-analysis with the adjusted odds ratios were compared with unadjusted analysis with crude numbers. There was no statistically significant difference between these analyses. Since the included studies were either cohort or case–control studies, it is quite possible there are other confounding factors, for instance uterine abnormalities, trombophilia or uterine fibroids. Since these factors might influence the occurrence of a miscarriage as well as the decision on which treatment is used (medical or surgical), these factors could have biased our results. Women undergoing medical management for miscarriage or TOP might need an additional curettage when initial medical treatment is unsuccessful and the evacuation of the uterus is incomplete. Apart from one study (Mannisto et al., 2013), none of the papers mentioned correcting for additional surgical procedures. Mannisto et al. performed a subgroup analysis of women needing a second intervention after initial medical or surgical treatment for first trimester TOP. The risk of preterm birth in a subsequent pregnancy was still higher, though not significantly higher, in women with initial medical management.

The control groups in the various included studies consisted of primigravid or multigravid women, either with or without a history of spontaneous or medically managed miscarriage or termination of pregnancy. It is questionable if primigravid women are a valid control group since these women did not have the chance to have had a D&C procedure in their

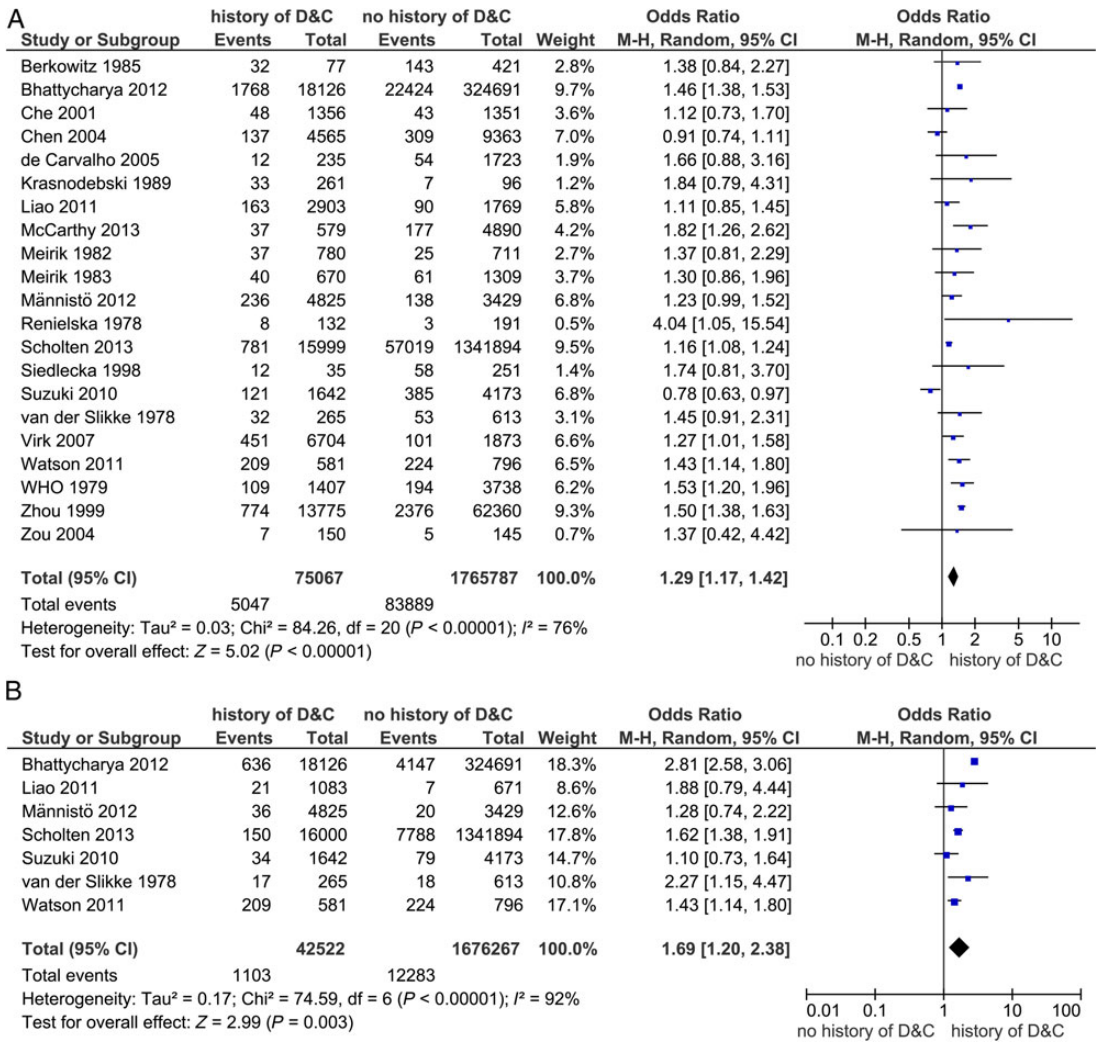

Figure 4 Various meta-analyses of the risk of preterm birth in women with a history of D&C. (**A**) Risk of preterm birth (<37 weeks gestation) in women with a history of D&C compared with those with no D&C. (**B**) Risk of very preterm birth (<32 weeks gestation) in women with a history of D&C compared with those with no D&C. (**C**) Risk of very preterm birth (<28 weeks gestation) in women with a history of D&C compared with those with no D&C. (**D**) Risk of preterm birth (<37 weeks gestation) in women with a history of multiple D&Cs compared with those with no D&C. (**E**) Risk of only spontaneous preterm birth (<37 weeks gestation) in women with a history of D&C compared with those with no D&C. (**F**) Risk of preterm birth (<37 weeks gestation) in women with a history of D&C compared with those with medical management for miscarriage or termination of pregnancy.

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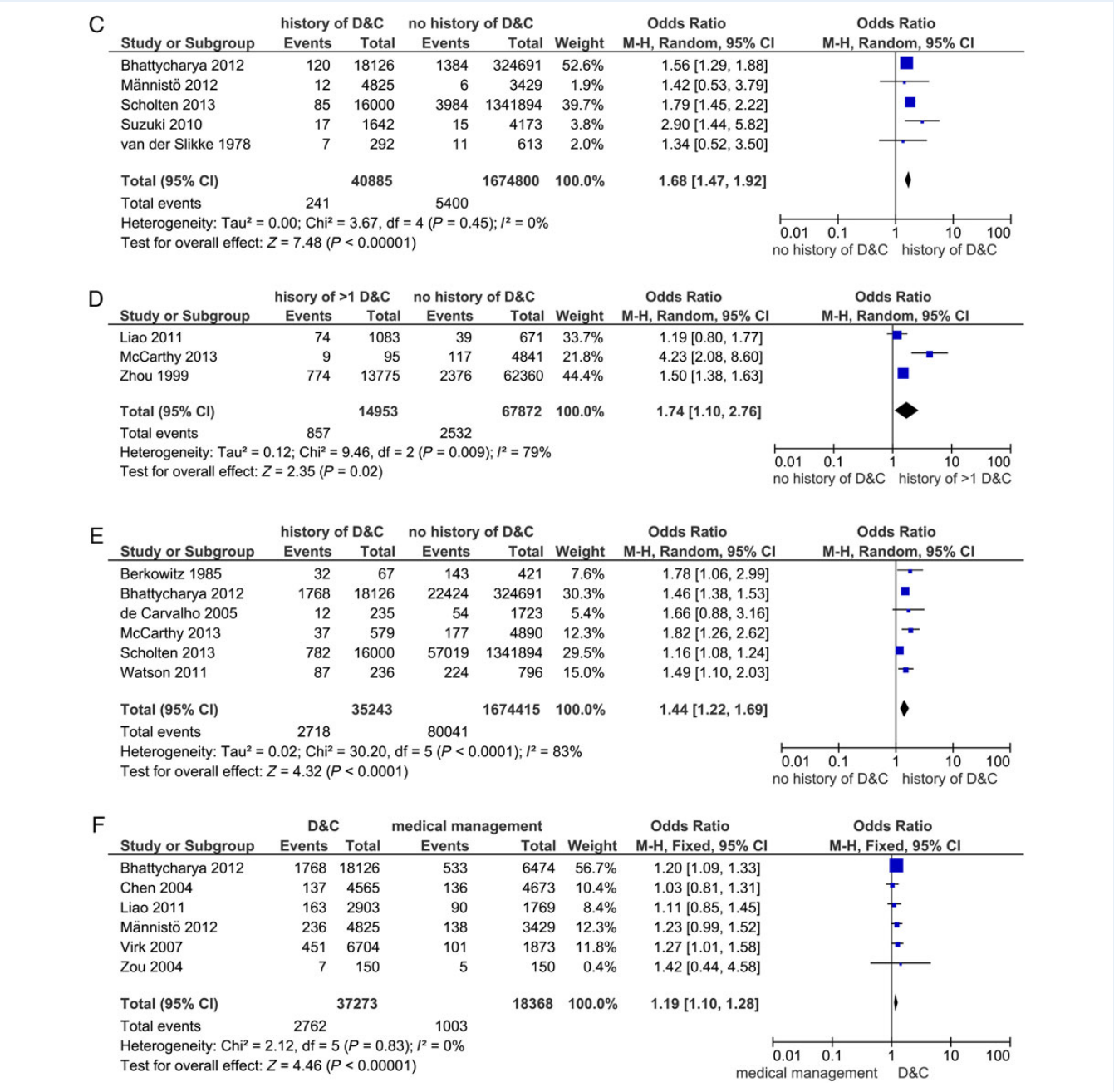

Figure 4 *Continued*

obstetric history. On the other hand since preterm birth is more likely to occur in nulliparous women, excluding them from analysis might bias the results.

In this meta-analysis, we studied the effect of D&C for either termination of pregnancy or miscarriage. We could have limited the meta-analysis to studies reporting on D&C for termination of pregnancy only. However we tried to analyse the possible damage of the D&C procedure in general. It is possible that populations differ in case of miscarriage or termination of pregnancy, and this might have biased the results. There was only one study reporting solely on D&C for miscarriage (Krasnodebski *et al.*, 1989) and seven studies reporting on both miscarriage and termination of pregnancy (van der Slikke and Treffers, 1978; Berkowitz, 1985; Siedlecka and Makowiec-Dabrowska, 1998; de Carvalho *et al.*, 2005; Suzuki, 2010; Watson *et al.*, 2012; McCarthy *et al.*, 2013). The proportion of women with a miscarriage in the various study populations was unclear. We were therefore unable to perform a subgroup analysis on women with a D&C for miscarriage. Heterogeneity between all included studies was substantial, since various types of control groups were used, e.g. women with a medically managed miscarriage or termination of pregnancy, women with no miscarriage or abortion, and women with or without a previous birth. We therefore used a random effect model for statistical analysis. In order to assess the

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robustness of our findings, we compared women with a D&C for miscarriage or termination of pregnancy to women with medical treatment for miscarriage or termination of pregnancy on the risk of subsequent preterm birth <37 weeks. Heterogeneity was low in this subgroup analysis and random, and a fixed effect models showed similar odd ratios, which indicates that the results are indeed robust.

Due to a lack of data, we were not unable to study the effect of cervical priming prior to D&C for miscarriage or termination of pregnancy, nor could we study any differences between various types of surgical procedures. Also were we unable to assess the possible contribution of the length of gestation, more specifically than 'first trimester', at the time of D&C on the risk of subsequent preterm birth.

Interpretation of the findings and clinical implications

Several systematic reviews assessing preterm birth and termination of pregnancy have reported an increased preterm birth rate in women with a previous miscarriage (Atrash and Hogue, 1990; Thorp *et al.*, 2003; Shah and Zao, 2009; Lowit *et al.*, 2010). In these studies, however, no distinction has been made between the medical and surgical treatment modalities that had been used. Arguably, our findings suggest the surgical procedure to play an unmistakable role in increasing the risk of subsequent preterm birth, rather than the miscarriage or termination as such.

The mechanism as to how D&C might increase the risk for preterm birth remains speculative. Cervical dilatation may damage the cervix, which hypothetically directly increases the risk of spontaneous preterm birth in subsequent pregnancies by cervical incompetence. This hypothesis is supported by the evidence that other intra-cervical procedures such as cervical biopsy, LEEP, conisation or cauterization, may also cause an increased risk of subsequent preterm birth (Watson *et al.*, 2012). It has been suggested that cervical damage might impair the anti-microbial defence mechanism thereby facilitating ascending microbial colonization, a known cause of preterm birth (Svare *et al.*, 1992).

Another theory is that the curettage damages the endometrial lining which might cause abnormal placentation in a subsequent pregnancy, thus increasing the risk of placental abruption, pre-eclampsia, placenta praevia and intrauterine growth restriction (Watson *et al.*, 2012). Whenever these complications occur, this could lead to preterm induction of labour or Caesarean section. Iatrogenic preterm birth and spontaneous preterm birth combined showed a similar increased risk after D&C, compared to when the analysis was limited to spontaneous preterm birth only.

Several risk factors for preterm birth have been generally acknowledged for many years, with previous preterm birth being the most uncontroversial. Most guidelines recommend intensified obstetrical care for these women, including monitoring of early signs and symptoms of threatened preterm birth. Odds ratios for future preterm birth after conisation or LEEP range from 1.5–2.0 (McManemy *et al.*, 2007; Bruinsma and Quinn, 2011), which is quite similar to the risk of an earlier D&C as found in the present meta-analysis. Based on these results, intensified obstetric care should be considered in women with a history of D&C for miscarriage or termination of pregnancy. Since the pathophysiological mechanism behind D&C and subsequent preterm birth remains unclear, it is unsure whether cervical shortening will occur prior to preterm birth. It is doubtful that ultrasound screening will help prevent preterm birth in these women.

Future cases of preterm birth could potentially be prevented by avoiding unneeded D&C. Non-invasive management options, i.e. expectant management or medical management in case of miscarriage, and medical management in case of termination of pregnancy, have been proven to be a good alternative. In case of miscarriage, expectant management leads to complete expulsion in 50% of the women within 2 weeks (Wieringa-de Waard *et al.*, 2002; Graziosi *et al.*, 2004; Ankum, 2008). Medical management (i.e. misoprostol) is effective in 50–85% of the women. (Bagratee *et al.*, 2004; Zhang *et al.*, 2005; Neilson *et al.*, 2006; Trinder *et al.*, 2006; Shankar *et al.*, 2007; Prasad *et al.*, 2009). A recently performed randomized controlled trial showed that in cases of an initial incomplete evacuation after misoprostol treatment, 5 out of 6 women have an empty uterus after expectant management (unpublished data). Medical treatment is also considered cost-effective. (Hughes *et al.*, 1996; Graziosi *et al.*, 2005; You and Chung, 2005; Petrou *et al.*, 2006; Rausch *et al.*, 2012). Quality of life is similar in women either treated expectantly, or with medical or surgical management in case of a miscarriage (Lee *et al.*, 2001; Shelley *et al.*, 2005; Kong *et al.*, 2013).

The largest studies included in this meta-analysis were European. Arguably the D&C procedure would have similar effects on European as it would have on women in other continents. Since medical TOP in the US for instance is only common up to 9 weeks of gestation possibly larger proportions of women are exposed to D&C procedures. In the US, the preterm birth rate is higher than in Europe. It is possible that a history of D&C contributes to this (Chang *et al.*, 2013).

A recent Scottish nationwide study showed a previous termination of pregnancy to be a risk factor for spontaneous PTB in the 1980s and 1990s. However, that association progressively weakened and disappeared altogether by 2000. These changes were paralleled by the increasing use of medical termination of pregnancy and cervical pretreatment prior to surgical termination of pregnancy (Oliver-Williams *et al.*, 2013).

We are well aware that observational studies in general are considered to be of lower quality due to their susceptibility to several types of bias as mentioned above. However for the purpose of this systematic review, we accumulated all available evidence on the risk of preterm birth subsequent to D&C and it therefore represents the best available evidence at this moment.

In view of the association that we found between D&C and preterm birth, we plead for a restrained use of D&C for miscarriage and termination of pregnancy. Only when more and better data have become available, indicating that cervical priming does indeed prevent the increased risk of preterm birth, could D&C possibly be applied more liberally once again, as it used to be.

Conclusion

This systematic review demonstrates that D&C for miscarriage or termination of pregnancy to be associated with an increased risk of subsequent preterm birth. The result of this meta-analysis raises questions about use of D&C as first option in the management of women with a miscarriage and those seeking termination of pregnancy, particularly since other non-invasive options are easily available and well tolerated.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

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Authors' roles

B.W.M.M. and M.L. were responsible for designing the study. M.A.C.V., A.B.H., J.A.F.H. and W.M.A. participated in the study design and provided expert knowledge during the analysis and writing of the paper. J.L. performed the literature search. M.L. and M.A.C.V. performed the data abstraction and analysis and B.C.O. performed the statistical (meta) analysis. The first draft of the manuscript was written by M.L. All authors critically revised the manuscript, contributed to the final draft and approved the version for publication.

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Conflict of interest

None of the authors declared a conflict of interest. All authors are independent from the funder ZonMW.

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