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PII: S0002-9378(15)02596-X

DOI: 10.1016/j.ajog.2015.12.044

Reference: YMOB 10852

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 10 November 2015

Revised Date: 19 December 2015

Accepted Date: 21 December 2015

Please cite this article as: Saccone G, Perriera L, Berghella V, Prior uterine evacuation of pregnancy as independent risk factor for preterm birth: a systematic review and meta-analysis, *American Journal of Obstetrics and Gynecology* (2016), doi: 10.1016/j.ajog.2015.12.044.

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Prior uterine evacuation of pregnancy as independent risk factor for preterm birth: a systematic review and meta-analysis

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Disclosure: The authors report no conflict of interest.

Financial Support: No financial support was received for this study. This study had no funding source.

Word count: Abstract 499; Text 4035; Tables 5; Figures 14

Key words: miscarriage, abortion, preterm delivery, termination of pregnancy

Obstetrics

Condensation: Prior surgical abortion is an independent risk factor for preterm birth

Short titles: Abortion and risk of preterm birth

ABSTRACT

Background: Preterm birth (PTB) is the number one cause of perinatal mortality. Prior surgery on the cervix is associated with an increased risk of PTB. History of uterine evacuation, by either induced termination of pregnancy (I-TOP) or spontaneous abortion (SAB), which involve mechanical and/or osmotic dilatation of the cervix, has been associated with an increased risk of PTB in some studies, but not in others.

Objective: To evaluate the risk of PTB among women with history of uterine evacuation for I-TOP or SAB.

Data Sources: Electronic databases (MEDLINE, Scopus, ClinicalTrials.gov, EMBASE, Sciencedirect) were searched from their inception until January 2015 with no limit for language.

Study eligibility criteria: We included all studies of women with prior uterine evacuation for either I-TOP or SAB, compared to a control group without history of uterine evacuation, which reported data about the subsequent pregnancy.

Study appraisal and synthesis methods: The primary outcome was the incidence of PTB <37 weeks. Secondary outcomes were incidence of low birth weight (LBW) and of small for gestational age (SGA). We planned to assess the primary and the secondary outcomes in the overall population as well as in studies on I-TOP and SAB, separately. The pooled results were reported as odds ratio (OR) with 95% confidence interval (95% CI).

Results: We included 36 studies in this meta-analysis (1,047,683 women). Thirty-one studies reported data about prior uterine evacuation for I-TOP, while five studies for SAB. In the overall population women with history of uterine evacuation for either I-TOP or SAB had a significantly higher risk of PTB (5.7% vs 5.0%; OR 1.44, 95% CI 1.09 to 1.90), LBW (7.3% vs 5.9%; OR 1.41, 95% CI 1.22 to 1.62) and SGA (10.2% vs 9.0%; OR 1.19, 95% CI 1.01 to 1.42) compared to controls. Out of the 31 studies on I-TOP, 28 included 913,297 women with history of surgical I-TOP, while three included 10,253 women with prior medical I-TOP. Women with prior surgical I-TOP had a significantly higher risk of PTB (5.4% vs 4.4%; OR 1.52, 95% CI 1.08 to 2.16), LBW (7.3% vs 5.9%; OR 1.41, 95% CI 1.22 to 1.62) and SGA (10.2% vs 9.0%; OR 1.19, 95% CI 1.01 to 1.42) compared to controls. Women with prior medical I-TOP had a similar risk

of PTB compared to those who did not have history of I-TOP (28.2% vs 29.5%; OR 1.50, 95% CI 1.00 to 2.25). Five studies, including 124,133 women, reported data about subsequent pregnancy in women with prior SAB. In all of the included studies, the SAB was surgically managed. Women with prior surgical SAB had a higher risk of PTB compared to those who did not have history of SAB (9.4% vs 8.6%; OR 1.19, 95% CI 1.03 to 1.37).

Conclusions: Prior surgical uterine evacuation for either I-TOP or SAB is an independent risk factor for PTB. These data warrant caution in the use of surgical uterine evacuation, and should encourage safer surgical techniques as well as medical methods.

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INTRODUCTION

Preterm birth (PTB) is the number one cause of perinatal mortality in many countries, including the US.[1,2] Defining risk factors for prediction of PTB is an important goal for several reasons. First, identifying women at risk allows initiation of risk-specific treatment.[3,4] Second, it may define a population useful for studying particular interventions. Finally, it may provide important insights into mechanisms leading to PTB.

Prior surgery on the cervix, such as cone biopsy and LEEP procedures, is associated with an increased risk of spontaneous PTB.[5-7] History of uterine evacuation, by either induced termination of pregnancy (I-TOP) or treatment of spontaneous abortion (SAB) by suction dilation and curettage (D&C) or by dilation and evacuation (D&E), which may involve mechanical and/or osmotic dilatation of the cervix, has been associated with an increased risk of PTB in some studies, but not in others.[8-10] Some studies have also postulated that the method of uterine evacuation may influence the association (or not) with PTB.[9,10] Moreover, with recent increases in the use of medications (misoprostol and mifepristone), it would be important to assess outcomes in subsequent pregnancies after medical termination of pregnancy as the element of cervical trauma is minimized with these techniques.[11]

Objective

The aim of this meta-analysis is to evaluate the risk of PTB among women with history of uterine evacuation for either I-TOP or SAB.

METHODS

Search strategy

Electronic databases (i.e. MEDLINE, Scopus, ClinicalTrials.gov, EMBASE, Sciencedirect) were searched from their inception until January 2015 with no limit for language. Search terms used were the following key words: “low birth weight;” “premature birth;” “preterm birth;” “small for gestational age;” “miscarriage;” “pregnancy;” “premature;” “newborn;” “uterine evacuation”; “abortion;” “induced abortion;” “spontaneous abortion;” “termination of pregnancy;”

"curettage;" "first trimester;" "second trimester;" "mifepristone;" "misoprostol;" "laminaria;" "subsequent;" "dilatation and evacuation;" "dilation and curettage;" "spontaneous preterm birth." In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches. The electronic search and the eligibility of the studies were independently assessed by the authors (GS, VB). Differences were resolved by discussion.

Study selection

We included all studies of women with prior uterine evacuation for either I-TOP or SAB, compared to a control group without prior uterine evacuation, which reported data about the subsequent pregnancy. We excluded studies without a control group (e.g. case series) as well as studies about stillbirth.

I-TOP was defined as an intervention to voluntarily terminate a pregnancy (i.e. induced abortion) by either surgical or medical means so it does not result in a live birth. SAB was defined as spontaneous intrauterine pregnancy loss prior to 20 weeks. Surgical uterine evacuation (for either I-TOP or SAB) was defined as a procedure using surgical instruments, either D&E or vacuum aspiration (VA), to remove the fetus and placenta from the uterus. D&E was defined as a procedure that includes mechanical cervical dilatation (usually by using uterine dilators of increasing diameter to stretch the cervix) followed by removal of uterine contents using a combination of suction and instruments (e.g. sharp curette, ring clamp or forceps). VA was defined as evacuation of the uterine contents using an electric vacuum aspirator (EVA) or manual vacuum aspirator (MVA). Medical uterine evacuation (for either I-TOP or SAB) was defined as a non-surgical uterine evacuation in which pharmaceutical drugs are used to empty the uterus. Therefore, we had the potential for different sensitivity analyses according to type of abortion (Table 1).

Primary and secondary outcomes were planned a-priori. The primary outcome was the incidence of PTB (i.e. preterm delivery <37 weeks). Secondary outcomes were neonatal outcomes including incidence of low birth weight (birth weight <2500 grams) and of small for gestational age (birth weight <10th percentile for gestational age). We planned to assess the primary and the secondary outcomes in the overall population as well as in studies on I-TOP and SAB, separately. We also planned several subgroup analyses according to: the number of prior uterine

evacuation; the number of fetuses in the index pregnancy; the gestational age at abortion; the type of the study (either cohort or case-control study) (Table 1). We assessed these subgroup analyses for only the primary outcome (i.e. incidence of PTB) in both surgical and medical I-TOP and SAB, separately and not in the overall combined data (Table 1).

Data extraction and risk of bias assessment

Data abstraction was completed by two independent investigators (GS, VB). Each investigator independently abstracted data from each study separately. Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. Differences were resolved by consensus. Information of confounders adjusted and adjusted risk estimates were collected when available. When possible, all authors were contacted for missing data.

Reviewers (GS, VB) independently assessed the risk of bias of the included studies via the Methodological Index for Non-Randomized Studies (MINORS).[12] Seven domains related to risk of bias were assessed in each study: 1) Aim (i.e. clearly stated aim), 2) Rate (i.e. inclusion of consecutive patients and response rate), 3) Data (i.e. prospective collection of data), 4) Bias (i.e. unbiased assessment of study end points), 5) Time (i.e. follow-up time appropriate), 6) Loss (i.e. loss to follow-up), 7) Size (i.e. calculation of the study size).[4] Review authors' judgments were categorized as "low risk," "high risk" or "unclear risk of bias." Discrepancies were resolved by discussion.

Data analysis

The data analysis was completed independently by two authors (GS, VB) using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014).[13] Discrepancies were resolved by discussion. Heterogeneity across studies was assessed using the Higgins I^2 test.[13] In case of statistically significant heterogeneity (I^2>0%) the random effects model of DerSimonian and Laird was used, otherwise, in case of no inconsistency in risk estimates (i.e. I^2=0%), a fixed effect model was managed. The pooled results were reported as odds ratio (OR) with 95% confidence interval (95% CI). For the outcomes not directly assessed by any of the included studies, an indirect comparison meta-analysis was performed (Table 1).[13] In the indirect comparison meta-analysis, data were combined in a two-stage approach in which outcomes were

analyzed in their original study and then summary statistics combined using standard summary data meta-analysis techniques to give an overall measure of effect (summary RR with 95% CI).[13]

For studies which reported both unadjusted and adjusted risk for confounders statistically proven, we performed meta-analyses using generic inverse variance method in order to obtain the adjusted risk estimate (aOR) of the primary outcome (i.e. incidence of PTB).[13,14] We assessed the aOR only for the primary outcome (i.e. incidence of PTB) in studies on both surgical and medical I-TOP and SAB, separately.[14]

Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No.: CRD42015026482). Therefore, all the analyses and the outcomes were planned a-priori before the data extraction.

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[15]

RESULTS

Study selection and study characteristics

We included 36 studies in this meta-analysis (1,047,683 women).[16-51] The flow of study identification is shown in Figure 1. Risk of publication bias was assessed by visual inspection of funnel plot; the symmetric plot suggested no publication bias (Figure 2). Publication bias, assessed using Begg's and Egger's tests, showed no significant bias (P=0.87 and P=0.71, respectively).

Thirty-one studies reported data about prior uterine evacuation for I-TOP, while 5 studies reported data regarding prior uterine evacuation for SAB (Table 2, Table 3, Table 4).[34,40,42,43,51].

The quality of the studies included in our meta-analysis was assessed by the MINORS' tool for assessing the risk of bias (Figure 3).[12] Nine of the included studies were retrospective cohort;[17-19,21,25,26,33,37,44] while nine were prospective cohort;[22-24,27,29,46,48-50] eleven were case-control study;[16,20,28,31,34,36,38-41,43] seven were large, high-quality population-based study.[30,32,35,42,45,47,51] Majority had low risk of bias in "aim" and "time."

Synthesis of results

UTERINE EVACUATION FOR INDUCED TERMINATION OF PREGNANCY OR SPONTANEOUS ABORTION: COMBINED DATA

In the overall population women with history of uterine evacuation for either I-TOP or SAB had a significantly higher risk of PTB (5.7% vs 5.0%; OR 1.44, 95% CI 1.09 to 1.90; Figure 4A; 34 studies, 1,031,320 women), of low birth weight (7.3% vs 5.9%; OR 1.41, 95% CI 1.22 to 1.62; Figure 4B; 11 studies, 675,197 women) and of small for gestational age (10.2% vs 9.0%; OR 1.19, 95% CI 1.01 to 1.42; Figure 4C; 3 studies, 43,411 women) compared to controls (i.e. women without history of uterine evacuation).

INDUCED TERMINATION OF PREGNANCY

Out of the 31 studies reporting data regarding I-TOP, 28 included 913,297 women with history of surgical I-TOP,[16-33,35-39,41,44-47] while three included 10,253 women with prior medical I-TOP (Table 2, Table 3).[48-50] Women with history of uterine evacuation for I-TOP had a significantly higher risk of PTB (5.5% vs 4.4%; OR 1.52, 95% CI 1.09 to 2.13; Figure 5A, 29 studies, 907,187 women), of low birth weight (7.3% vs 5.9%; OR 1.41, 95% CI 1.22 to 1.62; Figure 5B; 11 studies, 675,197 women) and of small for gestational age (10.2% vs 9.0%; OR 1.19, 95% CI 1.01 to 1.42; Figure 5C; 3 studies, 43,411 women) compared to controls (i.e. women without history of uterine evacuation for I-TOP).

Surgically induced termination of pregnancy

Table 2 shows the characteristics of the included studies on surgical I-TOP. [16-33,35-39,41,44-47] 913,297 women from 28 studies with at least one prior surgical I-TOP were included. Seventeen studies reported information on confounders and adjusted risk estimates.[24-33,35,37-39,45-47] Ten studies included only singleton gestations.[17-21,23,32,35,44,46] The vast majority (27 out of the 28) stratified data for number of prior I-TOP, while one did not report informative data about it.[36] Most of the studies had incidence of PTB as primary outcome. Regarding the method of abortion five studies defined the procedure as only VA,[24,26,37,44,45] five studies defined the procedure as only D&E,[19,27,36,46,47] while the others used both methods. One study reported the use of prostaglandins followed by D&E.[27]

Women with prior surgical I-TOP had a significantly higher risk of PTB (5.4% vs 4.4%; OR 1.52, 95% CI 1.08 to 2.16; Figures 6A; 27 studies, 906,297 women), of low birth weight (7.3% vs 5.9%; OR 1.41, 95% CI 1.22 to 1.62; Figure 6B; 11 studies, 675,197 women) and of small for gestational age (10.2% vs 9.0%; OR 1.19, 95% CI 1.01 to 1.42; Figure 6C; 3 studies, 43,411 women) compared to controls (i.e. women without history of uterine evacuation for I-TOP). The risk of PTB was still significantly higher after adjusting for confounders statistically proven, including marital status, smoking, age, ethnicity, economic status, parity, maternal height, race, social class, gestational age at entry, gravidity, parity, parental age, education, BMI, uterine surgery, type of work, alcohol consumption, urinary tract infection and sex of infant (aOR 1.25, 95% CI 1.13 to 1.38; Figure 7; 16 studies, 874,080 women).

- **Subgroup analysis: method of abortion**

Comparing the women with prior surgical I-TOP with those who did not, both VA (3.6% vs 3.1%; OR 1.20, 95% CI 1.16 to 1.24; Figure 8; 5 studies, 609,912 women) and D&E (5.5% vs 4.3%; OR 1.39, 95% CI 1.08 to 1.80; Figure 9; 5 studies, 68,679 women) were associated with an increased risk of PTB. Moreover, by using an indirect comparison meta-analysis we found that women who received D&E had a significantly higher risk of PTB compared to those who received VA (5.5% vs 3.6%; OR 1.54, 95% CI 1.38 to 1.73).

- **Subgroup analysis: number of prior I-TOP**

Women with only one prior surgical I-TOP had a significantly higher risk of PTB compared to those who did not have any prior I-TOP (5.1% vs 4.4%; OR 1.53, 95% CI 1.02 to 2.31; Figure 10A; 23 studies, 875,356 women). Women with more than one prior surgical I-TOP had significantly higher risk of PTB compared to those without any prior I-TOP (23.4% vs 8.6%; OR 1.98, 95% CI 1.46 to 2.68; Figure 10B; 9 studies, 165,085 women). Moreover, by using an indirect comparison meta-analysis we found that women with more than one prior surgical I-TOP had a significantly higher risk of PTB compared to those who had only one prior surgical I-TOP (23.4% vs 5.1%; OR 5.65, 95% CI 5.10 to 6.25).

- **Subgroup analysis: number of fetuses**

In subgroup analysis of studies in which only singleton gestations in the index pregnancy where enrolled, women with history of surgical I-TOP had a significantly higher risk of PTB compared to controls (9.6% vs 6.6%; OR 1.45, 95% CI 1.27 to 1.65; Figure 11; 10 studies, 152,668). No separate data about multiple gestations were reported in any studies.

- **Subgroup analysis: type of study**

Out of 28 included studies (Table 2), [16-33,35-39,41,44-47] nine were case-control, [16,20,28,31,32,36,38,39,41] while 19 were cohort studies.[17-19,21-27,29,30,33,35,37,44-47] Comparing I-TOP group with controls, women with prior surgical I-TOP had a significant higher risk of PTB in the subgroup analysis of only case-control studies (15.7% vs 8.2%; OR 1.52, 95% CI 1.31 to 1.75; 9 studies, 145,193 women), while the risk was similar in the subgroup analysis of only cohort studies (4.7% vs 3.7%; OR 1.55, 95% CI 0.90 to 2.68; 18 studies, 761,104 women).

- **Subgroup analysis: gestational age at abortion**

Only seven studies reported data regarding gestational age at abortion.[24,26,27,29,33,35,44] In subgroup analysis of studies which included only women with prior first trimester (<14 weeks) surgical I-TOP,[24,26,27,33,44] there was no statistically significant difference in the risk of PTB comparing I-TOP group with controls (17.5% vs 4.5%; OR 2.36, 95% CI 0.39 to 14.11; Figure 12; 5 studies 94,096 women).

Medically induced termination of pregnancy

Only three studies, including 10,253 women, reported data about subsequent pregnancy in women with prior medical I-TOP (Table 3).[48-50]

One study enrolled women with prior first-trimester mifepristone I-TOP,[48] one enrolled women with prior mid-trimester misoprostol I-TOP,[49] while the other one enrolled women with prior misoprostol and mifepristone I-TOP in either first or mid-trimester.[50] All of the three studies were prospective cohort and enrolled only women with just one prior medical I-TOP.

One study reported only data about placental complications as outcomes,[48] and so only two studies with 890 women were included in the pooled results for the primary outcome.

Women with prior medical I-TOP had a similar risk of PTB compared to those who did not have a prior medical I-TOP (28.2% vs 29.5%; OR 1.50, 95% CI 1.00 to 2.25; Figure 13; 2 studies, 890 women). No data were available regarding secondary outcomes. Due to limited data, assessing subgroup and sensitivity analyses were not feasible. None of the included studies adjusted the incidence of PTB for confounders statistically proven and so assessed the aOR by using generic inverse variance method was not feasible.

SPONTANEOUS TERMINATION OF PREGNANCY

Five studies, including 124,133 women, reported data about subsequent pregnancy in women with prior SAB.[42,43,51] In all of the included studies the SAB was surgically managed. Two of them were large population-based study,[42,51] while the others were case-control study (Table 4). Women with prior surgical management of SAB had a higher risk of PTB compared to those who did not have history of SAB (9.4% vs 8.6%; OR 1.19, 95% CI 1.03 to 1.37; Figure 14; 5 studies, 124,133 women). Due to limited data, assessing subgroup and sensitivity analyses were not feasible. None of the included studies adjusted the incidence of PTB for confounders statistically proven and so assessed the aOR by using generic inverse variance method was not feasible.

Spontaneous abortion vs induced termination of pregnancy

By using an indirect comparison meta-analysis we found that women who had history of uterine evacuation for SAB had a significantly higher risk of PTB compared to those who had history of uterine evacuation for I-TOP (9.4% vs 5.5%; OR 1.80, 95% CI 1.68 to 1.92).

COMMENT

Main findings

This meta-analysis evaluated the effect of prior uterine evacuation on future PTB risk. We found that prior surgical uterine evacuation, for either I-TOP or SAB, was independent risk factor for PTB. Summary of our findings is reported in Table 5. Women with at least one prior surgical I-TOP had significantly higher risk of PTB, low birth weight and small for gestational age

compared to those who did not have any prior surgical I-TOP. Women with more than one prior surgical I-TOP had a significantly higher risk of PTB compared to those who had only one prior surgical I-TOP. Subgroup analyses revealed higher risk of PTB for both VA and D&E. The risk of PTB was significantly higher in the D&E group compared to VA group. Data about medical I-TOP and about SAB were limited. However, we did not find an increased risk of PTB in women with history of medical I-TOP The clinical significance of a higher rate of PTB associated with uterine evacuation for SAB versus uterine evacuation for I-TOP is of unclear clinical significance, and requires further study. (Table 5).

Comparison with existing literature

One other meta-analysis has evaluated the risk of PTB in women with prior surgical I-TOP.[10] Shah et al showed that a previous surgical I-TOP was associated with an increased risk of PTB.[10] However, it did not include all currently available studies, outcomes considered were different, subgroup and sensitivity analyses were not performed, the number of included women was lower and medical I-TOP and SAB were not analyzed.[10]

Strengths and limitations

Our study has several strengths. To our knowledge, no prior meta-analysis on this issue is as large, up-to-date or comprehensive. The number of the included women is large. Most of the included studies had incidence of PTB as the primary outcome. We planned several subgroup and sensitivity analyses in order to reduce the heterogeneity between the studies and to have higher quality data.

Limitations of our study are inherent to the limitations of the included studies. Most of the studies did not report mechanism of surgical abortion, and did not control appropriately for confounders. Only six studies included parity, an important determinant of preterm delivery, as a potential confounder.[25,27,32,35,38,44] Women who have induced abortions typically have a lower socioeconomic status, are more likely to smoke, and generally have other risk factors for PTB.[1-4] In all of the included studies, cervical dilatation was performed mechanically using uterine dilators; none of them used balloon catheter or laminaria. No studies reported size or type of dilators used for surgical I-TOP in order to analyze the effect of cervical trauma related to size of dilators. Most of the included studies did not report gestational age of prior surgical TOP to

analyze whether late surgical TOP has different effect than early surgical TOP. Some studies compared women with prior surgical TOP to nulliparous, while others to multiparous. Half of more than 1,000,000 women included in this meta-analysis were drawn from a single national register-based cohort study.[45] In this study, Bhattacharya et al. reported that data regarding smoking was frequently missing and that the inter-pregnancy interval was much shorter in the I-TOP group compared to controls.[45] Moreover, the specific methods of abortion were not well described.[45] Bhattacharya et al. found no increased risk of PTB after the first I-TOP.[45] There were no randomized controlled trials included in the meta-analysis and no studies comparing prior medical with prior surgical uterine evacuation. Data about medical I-TOP and about SAB were limited. Search strategies for retrieving studies in electronic databases are limited and this could have influenced our findings. Study on surgical I-TOP did not report data regarding previous cervical preparation with cervical ripener, which could lead into less cervical injury; only one study reported the use of prostaglandins before D&E.[27] None of the included studies reported data about type of VA, if EVA or MVA. Since women face stigma when reporting induced abortion, women in the case or control group could have omitted I-TOP from their medical history, which would lead to under-reporting of abortion in the control group, and under-reporting of number of abortions in the case group. This recall bias has the potential to dramatically impact the risk of PTB associated with uterine evacuation procedures, particularly if abortion were under-reported in the control group. Data regarding PTB referred to both spontaneous and indicated as etiology of PTB. Most outcomes had very high statistically heterogeneity and this was a major shortcoming of the meta-analysis. Notably, the PTB rate in the control group ranged widely from about 4% to about 29%. While most of the comparisons are statistically significant (Table 5), their clinical significance may be valued by some clinicians and patients as less compelling; for example, the difference in the incidence of PTB in women with prior uterine evacuation is just 0.7% higher in absolute numbers (5.7%) than in women without prior uterine evacuation (5.0%).

Implications

The are many methods of abortion.[52-61] The procedure used depends largely upon the stage of pregnancy and the size of the fetus.[52] Dilatation of the cervix is required during surgical methods of abortion.[52] In contrast to normal birth, where the dilation occurs slowly over a period of many

hours, during a surgical abortion the cervix is usually mechanically stretched.[53] This stretching of the cervix may results in permanent physical injury to the cervix.[53] Osmotic dilators are often used to reduce the need for mechanical dilation. Osmotic dilators are inserted into the cervix prior to the procedure, they absorb water and swell, gradually stretching the cervix open.[54] VA or suction dilation and curettage may be used to evacuate the uterus up to 16 weeks gestation. This is the most common way to evacuate the uterus in the developed world.[55,56] In gestations above 8-12 weeks misoprostol is often used in combination with mechanical dilation to prepare the cervix prior to evacuation.[57] General and/or local anesthesia is given to the pregnant women and her cervix is quickly dilated. Surgical evacuation with the added insertion of a spoon shaped scraper (curette) is not the preferred method to evacuate the uterus as it is associated with more complications.[52] Compared to labor-induction abortion, surgical uterine evacuation offers more predictable timing of evacuation and greater cost savings.[52] Moreover, this surgical procedure also allows women to avoid the labor-like process of a medical induction. Medical abortion is effective throughout the first and the second trimester, however in randomized trials has been shown to have greater complications when compared to surgical uterine evacuation.[58] It is the termination of pregnancy by stimulation of labor-like contractions that cause eventual expulsion of the fetus and placenta from the uterine cavity.[59] The combination of mifepristone and misoprostol is the most effective and fastest regimen.[60] Typically, mifepristone 200 mg is followed by use of misoprostol 24-48 hours later.[61]

The biological plausibility to explain the higher risk of PTB in women with history of uterine evacuation is not completely clear. However, three main hypotheses can be made. Previous studies have suggested that infectious diseases following surgical uterine evacuation account for the increased risk of PTB.[62,63] The increased risk of PTB could result from the overt or covert infection following surgically uterine evacuation,[62] as well as from mechanical trauma to the cervix leading to increased risk of cervical insufficiency.[5,6,8] The greater mechanical dilation of the cervix obtained during the D&E compared to VA,[58-59] could explain the higher risk of PTB in women with prior D&E compared to those with history of VA. Moreover, surgical procedures including curettage during D&E may result in scar tissue that may increase the probability of faulty placental implantation. Indeed, same studies reported an association between prior D&E and subsequent complications such as preeclampsia, pregnancy loss, placenta previa and placenta accreta.[41,45-47,64,65] Data about medical I-TOP are very limited.[48-50] However, studies

comparing medical I-TOP with surgical I-TOP in the first trimester, showed that medical I-TOP was probably safer than surgical one with respect to the influence on subsequent pregnancy,[66,67] and is not associated with placental complications.[48] So, provided there is no contraindication, medical I-TOP may be the preferred choice for evacuating the uterus in the first trimester, especially for those women without a child and for those who wish to avoid surgery and anaesthesia.[66,68,69] Furthermore, medical abortion is associated with higher acceptability.[68,69]

Conclusions

In summary, this meta-analysis found that prior surgical evacuation of the uterus may be an independent risk factor for PTB. These data warrant caution in the use of standard surgical evacuation for either I-TOP or SAB, and should encourage better surgical methods perhaps with cervical ripening before evacuation as well as medical and minimally invasive methods for mechanical cervical dilation such as osmotic dilators). However, patient preference for the type of abortion experience should drive the decision-making. Women should be given the choice between a surgical and medical procedure and should also be informed realistic and accurate risk of the procedures and the risk in the subsequent pregnancy. Due to the limitations of the studies included in our meta-analysis it is difficult to definitively recommend that surgical abortion should be avoided and that medical methods should be preferentially offered. To be able to make a definitive statement regarding risk of PTB associated with medical and surgical abortion, more research is needed. Particularly there is a need for randomized controlled trials that investigate if technical interventions (e.g. cervical preparation before uterine evacuation) diminish the risk of PTB associated with surgical uterine evacuation, and for randomized trials comparing surgical and medical evacuation of the uterus.

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REFERENCES

1. Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2013. Natl Vital Stat Rep, 2015; 64:1-68
2. Patel RM, Kandefer S, Walsh MC et al. Causes and timing of death in extremely premature infants from 2000 through 2011. N Engl J Med, 2015; 372:331-40
3. Spong CY. Prediction and prevention of recurrent spontaneous preterm birth. Obstet Gynecol, 2007; 110:405-415
4. Mercer BM, Goldeberg RL, Moawad AH et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Networks. Am J Obstet Gynecol, 1999; 181:1216-21
5. Simoens C, Goffin F, Simon P et al. Adverse obstetrical outcomes after treatment of precancerous cervical lesions: a Belgian multicenter study. BJOG, 2012; 119:1247-55
6. Jakobsson M, Gissler M, Sainio S et al. Preterm delivery after surgical treatment for cervical intraepithelial neoplasia. Obstet Gynecol, 2007; 109:309-13
7. Watson LF, Rayner JA, King J, Jolley D, Forster D. Intracervical procedures and the risk of subsequent very preterm birth: a case-control study. ACTA Obstet Gynecol Scand, 2012; 91:204-10
8. Oliver-Williams C, Fleming M, Wood A, Smith G. Previous miscarriage and the subsequent risk of preterm birth in Scotland, 1980-2008: a historical cohort study. BJOG, 2015 Jan 28. doi: 10.1111/1471-0528.13276
9. Woolner A, Bhattacharya S, Bhattacharya S. The effect of method and gestational age at termination of pregnancy on future obstetric and perinatal outcomes: a register-based cohort study in Aberdeen, Scotland. BJOG, 2014; 121:309-18
10. Shah PS, Zao J; Knowledge Synthesis Group of Determinants of preterm birth/LBW birth. Induced termination of pregnancy and low birthweight and preterm birth: a systematic review and meta-analyses. BJOG, 2009; 116:1425-42
11. Murray S, Muse K. Mifepristone and first trimester abortion. Clin Obstet Gynecol, 1996; 39:474-85

12. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (MINORS). Development and validation of a new instrument. ANZ J Surg, 2003; 73:712-6
13. Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions, version 5.1.0 (update March 2011). The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org. (Accessed January 15, 2014).
14. Peters J, Mengersen K. Selective reporting of adjusted estimates in observational epidemiology studies: reasons and implications for meta-analyses. Eval Health Prof, 2008; 31:370-89
15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; 62:1006-12
16. Pantelakis SN, Papadimitriou GC, Doxiadis SA. Influence of induced and spontaneous abortions on the outcome of subsequent pregnancies. Am J Obstet Gynecol, 1973; 116:799-805
17. Papaevangelou G, Vrettos AS, Papadatos C, Alexiou D. The effect of spontaneous and induced abortion on prematurity and birth weight. J Obstet Gynecol Br Commonw, 1973; 80:418-22
18. Daling JR, Emanuel I. Induced abortion and subsequent outcome of pregnancy. A matched cohort study. Lancet, 1975; 2:170-3
19. Daling JR, Emanuel I. Induced abortion and subsequent outcome of pregnancy in a series of American women. N Engl J Med, 1977; 297:1241-5
20. Van der Slikke JW, Treffers PE. Influence of induced abortion on gestational duration in subsequent pregnancies. Br Med J, 1978; 1:270-2
21. W.H.O. Task Force. Gestation, birth weight and spontaneous abortion in pregnancy after induced abortion. Report of Collaborative Study by W.H.O. Task force on sequelae of abortion. Lancet, 1979; 1:142-5
22. Obel EB. Pregnancy complications following legally induced abortion. Acta Obstet Gynecol Scand, 1979; 58:485-90
23. Mandelin M, Karjalainen O. Pregnancy outcome after previous induced abortion. Ann Chir Gynaecol, 1979; 6:147-54

24. Meirik O, Nygren KG, Bergstrom R, Gynsjo A. Outcome of delivery subsequent to induced vacuum-aspiration abortion in parous women. Am J Epidemiol, 1982; 116:415-29
25. Linn S, Schoenbaum SC, Monson RR, Rosner B, Stubblefield PG, Ryan KJ. The relationship between induced abortion and outcome of subsequent pregnancies. Am J Obstet Gynecol, 1983; 146:136-40
26. Meirik O, Bergstrom R. Outcome of delivery subsequent to vacuum aspiration abortion in nulliparous women. Acta Obstet Gynecol Scand, 1983; 62:499-509
27. Meirik O, Nygren KG. Outcome of first delivery after 2nd trimester two-stage induced abortion. A controlled historical cohort study. Acta Obstet Gynecol Scand, 1984; 63:45-50
28. Park TK, Strauss LT, Hogue CJ, Kim IS. Previous experience of induced abortion as a risk factor for fetal death and preterm delivery. Int J Gynaecol Obstet, 1984; 22:195-202
29. Frank PI, Kay CR, Lewis TL, Parish S. Outcome of pregnancy following induced abortion. Report from the joint study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists. Br J Obstet Gynecol, 1985; 92: 308-16
30. Pickering RM, Forbes JF. Risks of preterm delivery and small-for-gestational age infants following abortion: a population study. Br J Obstet Gynecol, 1985; 92:1106-12
31. Lekea-Karanika V, Tzoumaka-Bakoula C, Golding J. Previous obstetric history and subsequent preterm delivery in Greece. Eur J Obstet Gynecol Reprod Biol, 1990; 37:99-109
32. Martius JA, Steck T, Oehler MK, Wulf KH. Risk factors associated with preterm (<37+0 weeks) and early preterm birth (<32+0 weeks) univariate and multivariate analysis of 106 345 singleton births from the 1994 statewide perinatal survey of Bavaria. Eur J Obstet Gynecol Reprod Biol, 1998; 80:183-9
33. Zhou W, Sorensen HT, Olsen J. Induced abortion and subsequent pregnancy duration. Obstet Gynecol, 1999; 94:948-53
34. Doyle P. Influence of maternal risk factors of low birth weight, preterm delivery and small for gestational age. A prospective cohort study of pregnancy. Chin J Public Health, 2000; 19:192-202

35. Henriet L, Kaminski M. Impact of induced abortions on subsequent pregnancy outcome: the 1995 French national perinatal survey. BJOG, 2001; 108:10366-42
36. Fox-Helias L, Blondel B. Changes in risk factors of preterm delivery in France between 1982 and 1995. Paediatr Perinat Epidemiol, 2000; 14:314-323
37. Che U, Zhou W, Gao E, Olsen J. Induced abortion and prematurity in a subsequent pregnancy: a study from Shanghai. J Obstet Gynaecol, 2001; 21:270-3
38. El-Bastawissi AY, Sorensen TK, Akafomo CK, Frederick IO, Xiao R, Williams MA. History of fetal loss and other adverse pregnancy outcomes in relation to subsequent risk of preterm delivery. Matern Child Health J, 2003; 7:53-8
39. Ancel PY, Lelong N, Papiernik E, Saurel-Cubizolles MJ, Kaminski M. History of induced abortion as a risk factor for preterm birth in European countries: results of the EUROPOP survey. Human Reprod, 2004; 19:734-40
40. Nguyen N, Savitz DA, Thorp JM. Risk factors for preterm birth in Vietnam. Int J Gynaecol Obstet, 2004; 86:70-8
41. Moreau C, Kaminski M, Ancel PY et al. Previous induced abortions and the risk of very preterm delivery: results of the EPIPAGE study. Br J Obstet Gynaecol, 2005; 112:430-7
42. Smith GC, Shah I, White IR et al. Maternal and biochemical predictors of spontaneous preterm birth among nulliparous women: a systematic analysis in relation to the degree of prematurity. Int J Epidemiol, 2006; 35:1169-77
43. Selo-Ojeme DO, Tewari R. Late preterm (32-36 weeks) birth in a North London hospital. J Obstet Gynaecol, 2006; 26:6246
44. Raatikainen K, Heiskanen N, Heinone S. Induced abortion: not an independent risk factor for pregnancy outcome, but a challenge for health counseling. Ann Epidemiol, 2006; 16:587-92
45. Bhattacharya S, Lowit A, Bhattacharya S et al. Reproductive outcomes following induced abortion: a national register-based cohort study in Scotland. BMJ Open, 2012; 2
46. McCarthy FP, Khashan AS, North RA et al. Pregnancy loss managed by cervical dilatation and curettage increases the risk of spontaneous preterm birth. Hum Reprod, 2013; 28:3197-206

ACCEPTED MANUSCRIPT

47. Woolner A, Bhattacharya S, Bhattacharya S. The effect of method and gestational age at termination of pregnancy on future obstetric and perinatal outcomes: a register-based cohort study in Aberdeen, Scotland. BJOG, 2014; 121:309-18
48. Zhu QX, Gao Es, Chen AM et al. Mifepristone-induced abortion and placental complications in subsequent pregnancy. Human Reprod, 2009; 24:315-9
49. Mirmilstein V, Rowlands S, King JF. Outcomes for subsequent pregnancy in women who have undergone misoprostol mid-trimester termination of pregnancy. Aust N Z J Obstet Gynaecol, 2009; 49:195-7
50. Winer N, Resche-Rigon M, Morin C et al. Is induced abortion with misoprostol a risk factor for late abortion or preterm delivery in subsequent pregnancies? Eur J Obstet Gynecol Reprod Biol, 2009; 145:53-6
51. Freak-Poli R, Chan A, Tucker G, Street J. Previous abortion and risk of pre-term birth: a population study. J Maternal Fetal Neonatal Med, 2009; 22:1-7
52. Kulier R, Fekih A, Hofmeyer GJ, Campana A. Surgical methods for first trimester termination of pregnancy. Cochrane Database Syst Rev, 2001; 4:CD002900
53. Renner RM, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care? A systematic review. BJOG, 2013; 120:23-31
54. Newmann SJ, Dalve-Endres A, Diedrich JT, Steinauer JE, Meckstroth K, Drey EA. Cervical preparation for second trimester dilation and evacuation. Cochrane Database Syst Rev, 2010; 8:CD007310
55. Iyengar K, Iyengar SD. Elective abortion as a primary health service in rural India: experience with manual vacuum aspiration. Reprod Health Matters, 2002; 10:54-63
56. Sedgh G, Henshaw S, Singh S, Ahman E, Shah IH. Induced abortion: estimated rates and trends worldwide. Lancet, 2007; 370:1338-45
57. World Health Organization Task Force on the Use of Prostaglandins for the Regulation of Fertility. Prostaglandins and abortion. III. Comparison of single intra-amniotic injections of 15-methyl prostaglandin F2alpha and prostaglandin F2alpha for termination of second-trimester pregnancy: an international multicenter study. Am J Obstet Gynecol, 1977; 129:601-6

ACCEPTED MANUSCRIPT

58. Bryant AG, Grimes DA, Garret JM, Stuart GS. Second-trimester abortion for fetal anomalies or fetal death: labor induction compared with dilation and evacuation. Obstet Gynecol, 2011; 117:788-92
59. Blumenthal PD, Castleman LD, Jain JK. Abortion by labor induction. In: Paul M, Lichtenberg ES, Borgotta L, Grimes DA, Stubblefield PG, eds. A Clinician's Guide to Medical and Surgical Aobrtion. Churchill Livingston, New York, 1999
60. Shaw KA, Topp NJ, Shaw JG, Blumenthal PD. Mifepristone-misoprostol dosing interval and effect on induction abortion times: a systematic review. Obstet Gynecol, 2013; 121:1335-47
61. Grimes DA, Smith MS, Witham AD. Mifepristone and misoprostol versus dilation and evacuation for midtrimester abortion: a pilot randomized controlled trial. BJOG, 2004; 111:148-53
62. Muhlemann K, Germain M, Krohn M. Does an abortion increase the risk of intrapartum infection in the following pregnancy? Epidemiology, 1996; 7:194-8
63. Sturchler D, Menegoz F, Daling J. Reproductive history and intrapartum fever. Gynecol Obstet Invest, 1986; 21:182-6
64. Hung TH, Hsieh CC, Hssu JJ et al. Risk factors for placenta previa in an Asian population. Reprod Sci, 2007; 14:59-65
65. Zhou W, Nielsen GL, Larsen H, Olsen J. Induced abortion and placenta complications in the subsequent pregnancy. Acta Obstet Gynecol Scand, 2001; 80:115-20
66. Zou Y, Luo J, Xiao YF et al. Study on the influence of medical abortion and surgical abortion on subsequent pregnancy. Sichuan Da Xue Bao Yi Xue Ban, 2004; 35:543-5
67. Gan C, Zou Y, Wu S, Li Y, Liu Q. The influence of medical abortion compared with surgical abortion on subsequent pregnancy outcome. Int J Gynaecol Obstet, 2008; 101:231-8
68. Prased S, Kumar A, Divya A. Early termination of pregnancy by single-dose 800 microg misoprostol compared with surgical evacuation. Fertil Steril, 2009; 91:28-31
69. Ashok PW, Kidd A, Flett GM et al. A randomized comparison of medical abortion and surgical vacuum aspiration at 10-13 weeks gestation. Human Reprod, 2002; 17:92-8

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590 **TABLES**

591 **Table 1**. Potential overall, sensitivity and subgroup analyses planned

Intervention group	**Control group**
Overall analysis	
Prior uterine evacuation (I-TOP and SAB)	No prior uterine evacuation
Planned sensitivity analyses in women with prior uterine evacuation for I-TOP	
Prior I-TOP	No prior I-TOP
Prior surgical (either D&E or VA) I-TOP	No prior I-TOP
Prior surgical I-TOP by D&E	No prior I-TOP
Prior surgical I-TOP by VA	No prior I-TOP
Prior surgical I-TOP by D&E	Prior surgical I-TOP by VA*
Prior medical I-TOP	No prior I-TOP
Planned sensitivity analyses in women with prior uterine evacuation for SAB	
Prior SAB	No prior SAB
Prior surgical (either D&E or VA) SAB	No prior SAB
Prior surgical SAB by VA	No prior SAB
Prior surgical SAB by D&E	No prior SAB
Prior surgical SAB by D&E	Prior surgical SAB by VA*
Prior medical SAB	No prior SAB
Planned sensitivity analyses comparing I-TOP with SAB	
Prior uterine evacuation for I-TOP	Prior uterine evacuation for SAB*
Planned subgroup analyses in study on I-TOP and in study on SAB, separately	
Only one prior uterine evacuation	No prior uterine evacuation
More than one prior uterine evacuation	No prior uterine evacuation
More than one prior uterine evacuation	Only one prior uterine evacuation*

Prior uterine evacuation in singletons	No prior uterine evacuation in singletons
Prior uterine evacuation in multiple gestations	No prior uterine evacuation in multiple gestations
Prior uterine evacuation in cohort studies	No prior uterine evacuation in cohort studies
Prior uterine evacuation in case-control studies	No prior uterine evacuation in case-control studies
According to gestational age at uterine evacuation	-

I-TOP, induced termination of pregnancy; SAB, spontaneous abortion; VA, vacuum aspiration; D&E, dilation and evacuation

**Since that, none of the included studies evaluated this outcome we used an indirect comparison meta-analysis to assess this outcome.*

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Table 2. Characteristics of the included studies on surgically induced termination of pregnancy

	Study location	**Type of study**	**Number of included women**	**Method of abortion**	**GA at abortion**	**Confounders adjusted**	**Primary outcome**
Pantelakis 1973[16]	Greece	Case-control	4,779	Surgical	N/A	None	PTB
Papaevangelou 1973[17]	Greece	Retrospective cohort	3,467	Surgical	N/A	None	PTB
Daling 1975[18]	Taiwan	Retrospective cohort	1,516	Surgical	N/A	None	PTB
Daling 1977[19]	USA	Retrospective cohort	553	D&E	N/A	None	PTB
Van der Slikke 1978[20]	Netherlands	Case-control	3,432	Surgical	N/A	None	GA at delivery
WHO 1979[21]	Europe	Retrospective cohort	3,352	Surgical	N/A	None	GA at delivery
Obel 1979[22]	Denmark	Prospective cohort	497	Surgical	N/A	None	Placental complications
Mandelin 1979[23]	Finland	Prospective cohort	696	Surgical	N/A	None	Birth weight

Meirik 1982[24]	Sweden	Prospective cohort	1,442	Vacuum	<13 weeks	Marital status, smoking	Birth weight
Linn 1983[25]	USA	Retrospective cohort	9,823	Surgical	N/A	Age, ethnicity, smoking, economic status, parity	Birth weight
Meirik 1983[26]	Sweden	Retrospective cohort	1,292	Vacuum	<13 weeks	Marital status, smoking	PTB
Meirik 1984[27]	Sweden	Prospective cohort	269	Prostaglandins followed by D&E	<13 weeks	Parity	PTB
Park 1984[28]	Korea	Case-control	681	Surgical	None	N/A	PTB
Frank 1985[29]	United Kingdom	Prospective cohort	1,545	Surgical	<22 weeks	Age, marital status, gestational age at entry	LBW
Pickering 1985[30]	United Kingdom	Population-based cohort study	7,000	Surgical	N/A	Maternal age, height, sex of infant, marital status, social class	PTB
Lekea-Karanika 1990[31]	Greece	Case-control	4,391	Surgical	N/A	Race, smoking	PTB
Martius	Germany	Population-	106,124	Surgical	N/A	Gravidity, uterine	PTB

1998[32]		based case-control study				surgery, type of work, urinary tract infection	
Zhou 1999[33]	Denmark	Retrospective cohort	64,125	Surgical	<14 weeks	Maternal age	PTB
Henriet 2001[35]	French	Population-based cohort study	12,336	Surgical	<22 weeks	Maternal age, parity, education, smoking	SGA
Foix-Helias 2001[36]	French	Case-control	17,411	D&E	N/A	None	PTB
Che 2001[37]	China	Retrospective cohort	2,707	Vacuum	N/A	Parental age, occupation, education, maternal BMI	PTB
El-Bastawissi 2003[38]	USA	Case-control	654	Surgical	N/A	Maternal age, race, smoking, parity	PTB
Ancel 2004[39]	Europe	Case-control	7,721	Surgical	N/A	Maternal age, marital status, social class, smoking, parity	PTB
Moreau 2005[41]	French	Case-control	2,561	Surgical	N/A	None	PTB

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Raatikainen 2006[44]	Finland	Retrospective cohort	26,967	Vacuum	<14 weeks	Maternal age, weight, marital status, education, smoking, alcohol consumption, parity, uterine surgery	N/A
Bhattachary a 2012[45]	Scotland	Population-based cohort study	577,510	Vacuum	N/A	Maternal age, weight, smoking	PTB
McCarthy 2013[46]	Multicenter	Prospective cohort	4,812	D&E	N/A	Maternal age, weight, smoking	PTB
Woolner 2014[47]	Scotland	Population-based cohort study	45,631	D&E	N/A	Smoking, social class	PTB

GA, gestational age; N/A, data not reported in the original study; PTB, preterm birth; SGA, small for gestational age; D&E, dilatation and evacuation; Surgical abortion, both dilatation and evacuation and vacuum; LBW, low birth weight; SGA, small for gestational age

Table 3. Characteristics of the included studies on medically induced termination of pregnancy.

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	Study location	**Type of study**	**Number of included women**	**Method of abortion**	**GA at abortion**	**Confounders adjusted**	**Primary outcome**
Zhu 2009[48]	China	Prospective cohort	9,363	200 mg Mifepristone	<14 weeks	None	Placental complications
Mirmilstein 2009[49]	Australia	Prospective cohort	154	400 µg Misoprostol	14-24 weeks	None	PTB
Winer 2009[50]	France	Prospective cohort	736	200 mg Mifepristone followed by 400 µg Misoprostol	<22 weeks	None	PTB

GA, gestational age; PTB, preterm birth

Table 4. Characteristics of the included studies on spontaneous abortion

	Study location	Type of study	Number of included women	Method of abortion	GA at abortion	Confounders adjusted	Primary outcome
Doyle 2000[34]	Taiwan	Case-control	12,273	Surgical	N/A	None	PTB
Nguyen 2004[40]	Vietnam	Case-control	1,709	Surgical	N/A	None	PTB
Smith 2006[42]	Scotland	Population-based case-control	84,391	Surgical	N/A	None	PTB
Selo-Ojeme 2006[43]	United Kingdom	Case-control	206	Surgical	N/A	None	PTB
Freak-Poli 2009[51]	Australia	Population-based case-control study	25,554	Surgical	<20 weeks	None	N/A

GA, gestational age; N/A, data not reported in the original study; PTB, preterm birth; D&E, dilatation and evacuation; Surgical abortion, either dilatation and evacuation or vacuum; LBW, low birth weight; SGA, small for gestational age

Table 5. Summary of the pooled results for the risk of preterm birth

Intervention group	Control group	Results** n (%)	OR, 95% CI
Overall analysis			-
Women with prior uterine evacuation (both I-TOP and SAB)	Women with no prior uterine evacuation	9,170/160,143 (5.7%) vs 43,750/871,177 (5.0%)	OR 1.44, 95% CI 1.09 to 1.90*
Planned sensitivity analyses in women with prior uterine evacuation for I-TOP			-
Women with prior I-TOP (either surgical or medical)	Women with no prior I-TOP	8,159/149,395 (5.5%) vs 34,034/757,792 (4.4%)	OR 1.52, 95% CI 1.09 to 2.13*
Women with prior surgical (either D&E or VA) I-TOP	Women with no prior I-TOP	8,110/149,221 (5.4%) vs 33,823/757,076 (4.4%)	OR 1.52, 95% CI 1.08 to 2.16*
Women with prior surgical I-TOP by VA	Women with no prior I-TOP	4,553/125,554 (3.6%) vs 15,063/484,358 (3.1%)	OR 1.20, 95% CI 1.16 to 1.24*
Women with prior surgical I-TOP by D&E	Women with no prior I-TOP	342/6,232 (5.5%) vs 2,657/62,447 (4.3%)	OR 1.39, 95% CI 1.08 to 1.80*
Women with prior surgical I-TOP by D&E	Women with prior surgical I-TOP by VA	342/6,232 (5.5%) vs 4,553/125,554 (3.6%)	OR 1.54, 95% CI 1.38 to 1.73*

Women with prior medical I-TOP	Women with no prior I-TOP	49/174 (28.2%) vs 211/716 (29.5%)	OR 1.50, 95% CI 1.00, 2.25
- Planned subgroup analyses in women with prior uterine evacuation for I-TOP			
Women with only one prior surgical (either D&E or VA) I-TOP	Women with no prior I-TOP	7,336/142,543 (5.1%) vs 32,578/732,813 (4.4%)	OR 1.53, 95% CI 1.02 to 2.31*
Women with more than one prior surgical (either D&E or VA) I-TOP	Women with no prior I-TOP	518/2,209 (23.4%) vs 14,022/162,876 (5.1%)	OR 1.98, 95% CI 1.46 to 2.68*
Women with more than one prior surgical (either D&E or VA) I-TOP	Women with only one prior surgical (either D&E or VA) I-TOP	518/2,209 (23.4%) vs 7,336/142,543 (5.1%)	OR 5.65, 95% CI 5.10 to 6.25
Women with prior surgical (either D&E or VA) I-TOP with singleton gestation in the index pregnancy	Women with no prior surgical (either D&E or VA) I-TOP with singleton gestation in the index pregnancy	1,129/11,766 (9.6%) vs 10,058/151,492 (6.6%)	OR 1.45, 95% CI 1.27 to 1.65*
Women with prior surgical (either D&E or VA) I-TOP with multiple gestation in the index pregnancy	Women with no prior surgical (either D&E or VA) I-TOP with multiple gestation in the	-	Not feasible

	index pregnancy		
Women with prior surgical (either D&E or VA) I-TOP in only cohort studies	Women with no prior surgical (either D&E or VA) I-TOP in only cohort studies	6,568/139,372 (4.7%) vs 22,714/621,732 (3.7%)	OR 1.55, 95% CI 0.90 to 2.68
Women with prior surgical (either D&E or VA) I-TOP in only case-control studies	Women with no prior surgical (either D&E or VA) I-TOP in only case-control studies	1,542/9,849 (15.7%) vs 11,109/135,344 (8.2%)	OR 1.52, 95% CI 1.31 to 1.75*
Women with prior surgical (either D&E or VA) I-TOP in the first trimester (<14 weeks)	Women with no prior surgical (either D&E or VA) I-TOP in the first trimester (<14 weeks)	1,063/6,083 (17.5%) vs 3,947/88,013 (4.5%)	OR 2.36, 95% CI 0.39 to 14.11
Planned sensitivity analyses in women with prior uterine evacuation for SAB			-
Women with prior surgical (either D&E or VA) SAB	Women with no prior SAB	1,011/10,748 (9.4%) vs 9,716/113,385 (8.6%)	OR 1.19, 95% CI 1.03 to 1.37*
Women with prior surgical SAB by VA	Women with no prior SAB	-	Not feasible
Women with prior surgical SAB by D&E	Women with no prior SAB	-	Not feasible
Women with prior surgical SAB by D&E	Women with prior surgical SAB by VA	-	Not feasible
Women with prior	Women with no	-	Not feasible

medical SAB	prior SAB		
- Planned subgroup analyses in women with prior uterine evacuation for SAB			
Women with only one prior SAB	Women with no prior SAB	-	Not feasible
Women with more than one prior SAB	Women with no prior SAB	-	Not feasible
Women with more than one prior SAB	Women with only one prior SAB	-	Not feasible
Women with prior SAB with singleton gestation in the index pregnancy	Women with no prior SAB with singleton gestation in the index pregnancy	-	Not feasible
Women with prior SAB with multiple gestation in the index pregnancy	Women with no prior SAB with multiple gestation in the index pregnancy	-	Not feasible
Women with prior SAB in only case-control studies	Women with no prior SAB in only case-control studies	-	Not feasible
Women with prior SAB in only cohort studies	Women with no prior SAB in only cohort studies	-	Not feasible
Subgroup analysis according to gestational age at prior uterine evacuation for SAB		-	Not feasible

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Planned analysis in women with prior uterine evacuation for SAB vs women with prior uterine evacuation for I-TOP			
Women with prior SAB	Women with prior I-TOP	1,011/10,748 (9.4%) vs 8,159/149,395 (5.5%)	OR 1.80, 95% CI 1.68 to 1.92*

I-TOP, induced termination of pregnancy; SAB, spontaneous abortion; VA, vacuum aspiration; D&E, dilation and evacuation; OR, odds ratio; CI, confidence interval

**Statistically significant*

*** Data are presented as number in the intervention group versus number in the control group (with percentages).*

FIGURES

Figure 1. Flow diagram of studies identified in the systematic review. *PTB, preterm birth; I-TOP, induced termination of pregnancy; SAB, spontaneous abortion*

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Figure 2. Funnel plot for assessing publication bias. *OR, odds ratio; SE, standard error*

Figure 3. Assessment of risk of bias. *Aim, clearly stated aim; Rate, inclusion of consecutive patients and response rate; Data, prospective collection of data; Bias, unbiased assessment of study end points; Time, follow-up time appropriate; Loss, loss to follow-up; Size, calculation of the study size.* (A) Summary of risk of bias for each study. *Plus sign, low risk of bias; minus sign, high risk of bias; question mark, unclear risk of bias.* (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

Figure 4. Forest plot for primary outcome (i.e. risk of preterm birth) and for secondary outcomes (i.e. low birth weight, small for gestational age) in overall women with history of uterine evacuation for either induced termination of pregnancy or spontaneous abortion. *M-H, Mantel-Haenszel test; CI, confidence interval; PTB, preterm birth; LBW, low birth weight; SGA, small for gestational age. A, risk for PTB; B, risk for LBW; C, risk for SGA.*

Figure 5. Forest plot for primary outcome (i.e. risk of preterm birth) and for secondary outcomes (i.e. low birth weight, small for gestational age) in women with history of uterine evacuation for induced termination of pregnancy. *M-H, Mantel-Haenszel test; CI, confidence interval; PTB, preterm birth; LBW, low birth weight; SGA, small for gestational age; I-TOP, induced termination of pregnancy. A, risk for PTB; B, risk for LBW; C, risk for SGA.*

Figure 6. Forest plot for primary outcome (i.e. risk of preterm birth) and for secondary outcomes (i.e. low birth weight, small for gestational age) in women with history of uterine evacuation for surgically induced termination of pregnancy. *M-H, Mantel-Haenszel test; CI, confidence interval; PTB, preterm birth; LBW, low birth weight; SGA, small for gestational age; I-TOP, induced termination of pregnancy. A, risk for PTB; B, risk for LBW; C, risk for SGA.*

Figure 7. Adjusted estimates forest plot for primary outcome (i.e. risk of preterm birth) in women with history of surgically induced termination of pregnancy. *IV, independent variable; SE, standard error; CI, confidence interval.*

Figure 8. Forest plot for primary outcome (i.e. risk of preterm birth) in women with history of surgically induced termination of pregnancy with vacuum aspiration. *M-H, Mantel-Haenszel*

test; CI, confidence interval; PTB, preterm birth; I-TOP, induced termination of pregnancy; VA, vacuum aspiration.

Figure 9. Forest plot for primary outcome (i.e. risk of preterm birth) in women with history of surgically induced termination of pregnancy with dilatation and evacuation. *M-H, Mantel-Haenszel test; CI, confidence interval; PTB, preterm birth; I-TOP, induced termination of pregnancy; D&C, dilatation and evacuation.*

Figure 10. Forest plot for primary outcome (i.e. risk of preterm birth) according to number of prior termination of pregnancy in women with history of surgically induced termination of pregnancy. *M-H, Mantel-Haenszel test; CI, confidence interval; PTB, preterm birth; I-TOP, induced termination of pregnancy. A, women with only one prior surgical I-TOP; B, women with more than one prior surgical I-TOP*.

Figure 11. Forest plot for primary outcome (i.e. risk of preterm birth) in singleton gestations with history of surgically induced termination of pregnancy. *M-H, Mantel-Haenszel test; CI, confidence interval; PTB, preterm birth; I-TOP, induced termination of pregnancy.*

Figure 12. Forest plot for primary outcome (i.e. risk of preterm birth) in women with history of first trimester (<14 weeks) surgically induced termination of pregnancy. *M-H, Mantel-Haenszel test; CI, confidence interval; PTB, preterm birth; I-TOP, induced termination of pregnancy*

Figure 13. Forest plot for primary outcome (i.e. risk of preterm birth) in women with history of medically induced termination of pregnancy. *M-H, Mantel-Haenszel test; CI, confidence interval; PTB, preterm birth; I-TOP, induced termination of pregnancy*

Figure 14. Forest plot for primary outcome (i.e. risk of preterm birth) in women with history of spontaneous abortion. *M-H, Mantel-Haenszel test; CI, confidence interval; PTB, preterm birth; SAB, spontaneous abortion*

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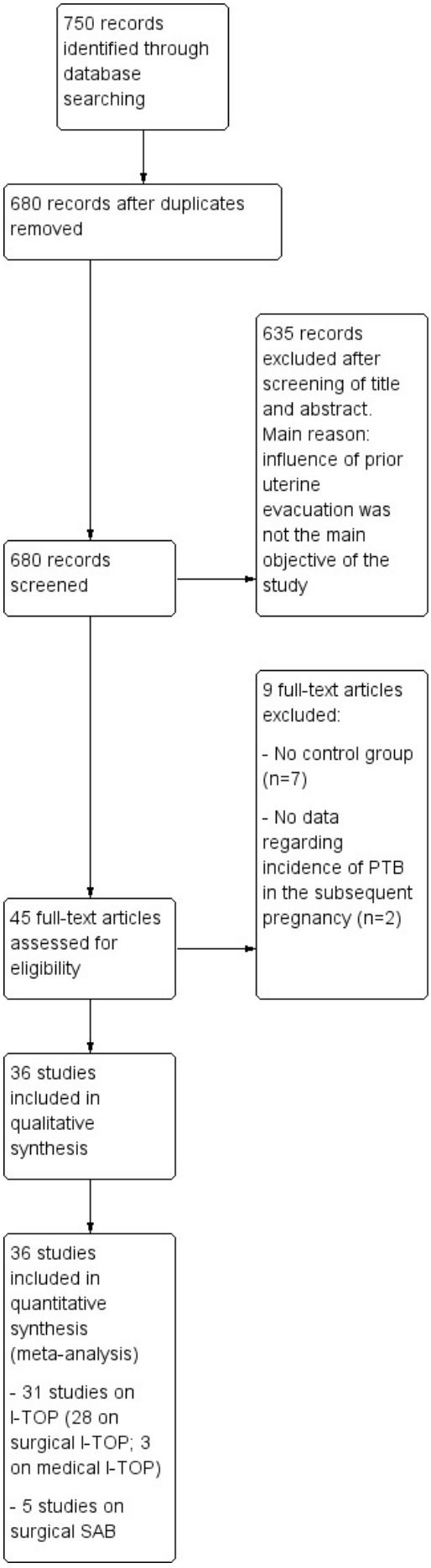

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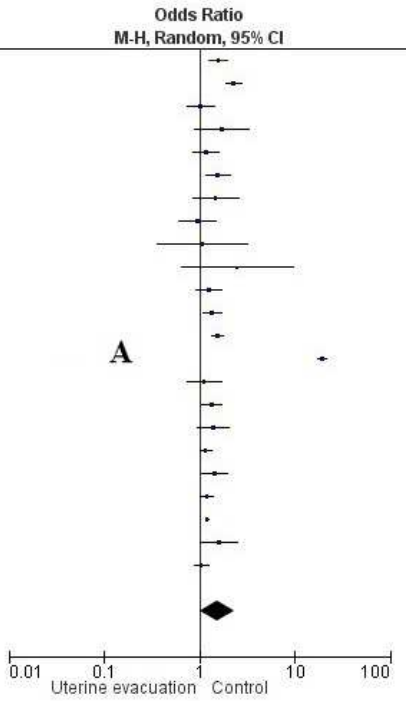
Study or Subgroup	I-TOP Events	I-TOP Total	No I-TOP Events	No I-TOP Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Papaevangelou 1973	133	731	314	2550	4.5%	1.58 [1.27, 1.98]	1973
Pantelakis 1973	251	1508	261	3271	4.5%	2.30 [1.91, 2.77]	1973
Daling 1975	83	758	81	758	4.4%	1.03 [0.74, 1.42]	1975
Daling 1977	25	271	16	285	4.1%	1.71 [0.89, 3.28]	1977
Van der Slikke 1978	53	265	555	3167	4.5%	1.18 [0.86, 1.61]	1978
WHO 1979	109	1407	99	1945	4.5%	1.57 [1.18, 2.07]	1979
Mandelin 1979	26	269	29	427	4.2%	1.47 [0.84, 2.55]	1979
Meirik 1983	40	670	39	622	4.3%	0.95 [0.60, 1.50]	1983
Park 1984	4	107	20	574	3.5%	1.08 [0.36, 3.21]	1984
Meirik 1984	8	142	3	127	3.1%	2.47 [0.64, 9.51]	1984
Frank 1985	70	470	131	1075	4.5%	1.26 [0.92, 1.72]	1985
Lekea Karanika 1990	125	1407	199	2984	4.5%	1.36 [1.08, 1.72]	1990
Martius 1998	251	2532	6858	103245	4.6%	1.55 [1.35, 1.77]	1998
Zhou 1999	774	1775	2377	62350	4.6%	19.51 [17.61, 21.61]	1999
Che 2001	48	1356	43	1351	4.4%	1.12 [0.73, 1.70]	2001
Henriet 2001	83	1487	443	10536	4.5%	1.35 [1.06, 1.71]	2001
El-Bastawissi 2003	64	133	209	521	4.4%	1.38 [0.94, 2.03]	2003
Ancel 2004	389	964	2335	6324	4.6%	1.16 [1.01, 1.33]	2004
Moreau 2005	238	294	1644	2199	4.5%	1.43 [1.06, 1.95]	2005
Raatikainen 2006	173	2364	1503	24248	4.5%	1.19 [1.01, 1.41]	2006
Bhattacharya 2012	4224	120033	13453	457477	4.6%	1.20 [1.16, 1.25]	2012
McCarthy 2013	24	415	160	4331	4.3%	1.60 [1.03, 2.49]	2013
Woolner 2014	141	3185	1806	42446	4.5%	1.04 [0.87, 1.24]	2014
Total (95% CI)		**142543**		**732813**	**100.0%**	**1.53 [1.02, 2.31]**	
Total events	7336		32578				

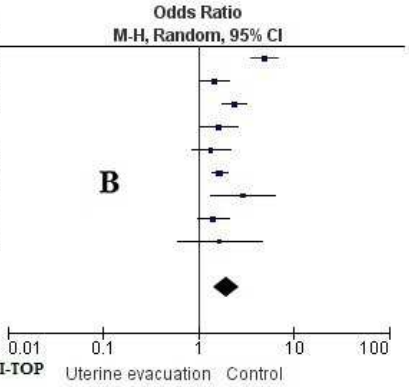
Heterogeneity: Tau² = 0.97; Chi² = 2664.60, df = 22 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.03 (P = 0.04)



Risk of PTB in women with only one prior surgical I-TOP

Study or Subgroup	I-TOP Events	I-TOP Total	No I-TOP Events	No I-TOP Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Papaevangelou 1973	63	186	314	3350	12.8%	4.95 [3.58, 6.86]	1973
Linn 1983	34	359	536	8122	12.3%	1.48 [1.03, 2.13]	1983
Martius 1998	50	347	6858	103245	13.1%	2.37 [1.75, 3.20]	1998
Henriet 2001	21	313	443	10536	11.3%	1.64 [1.04, 2.58]	2001
El-Bastawissi 2003	39	82	209	521	11.1%	1.35 [0.85, 2.16]	2003
Ancel 2004	215	433	2355	6324	14.1%	1.66 [1.37, 2.02]	2004
Moreau 2005	61	68	1644	2199	7.5%	2.94 [1.34, 6.47]	2005
Raatikainen 2006	31	355	1503	24248	12.2%	1.45 [1.00, 2.10]	2006
McCarthy 2013	4	66	160	4331	5.6%	1.68 [0.60, 4.68]	2013
Total (95% CI)		**2209**		**162876**	**100.0%**	**1.98 [1.46, 2.68]**	
Total events	518		14022				

Heterogeneity: Tau² = 0.16; Chi² = 44.70, df = 8 (P < 0.00001); I² = 82%
Test for overall effect: Z = 4.38 (P < 0.0001)



Risk of PTB in women with more than one prior surgical I-TOP

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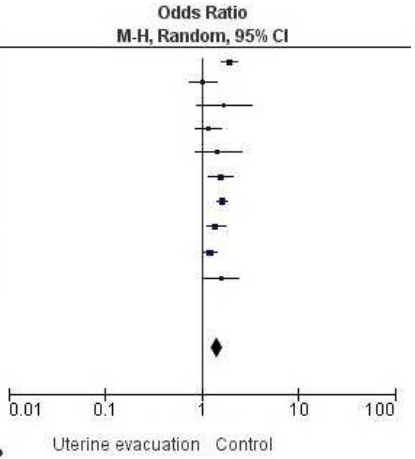
Study or Subgroup	I-TOP Events	I-TOP Total	No I-TOP Events	No I-TOP Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Papaevangelou 1973	196	917	314	2550	13.4%	1.94 [1.59, 2.36]	1973
Daling 1975	83	758	81	758	8.8%	1.03 [0.74, 1.42]	1975
Daling 1977	25	271	16	285	3.3%	1.71 [0.89, 3.28]	1977
Van der Slikke 1978	53	265	555	3167	9.1%	1.18 [0.86, 1.61]	1978
Mandelin 1979	26	269	29	427	4.3%	1.47 [0.84, 2.55]	1979
WHO 1979	109	1407	99	1945	10.2%	1.57 [1.18, 2.07]	1979
Martius 1998	301	2879	6858	103245	16.5%	1.64 [1.45, 1.85]	1998
Henriet 2001	104	1800	443	10536	12.5%	1.40 [1.12, 1.74]	2001
Raatikainen 2006	204	2719	1503	24248	15.3%	1.23 [1.05, 1.43]	2006
McCarthy 2013	28	481	160	4331	6.6%	1.61 [1.07, 2.44]	2013
Total (95% CI)		**11766**		**151492**	**100.0%**	**1.45 [1.27, 1.65]**	
Total events	1129		10058				

Heterogeneity: Tau² = 0.02; Chi² = 23.40, df = 9 (P = 0.005); I² = 62%
Test for overall effect: Z = 5.57 (P < 0.00001)



Risk of PTB in singleton gestations with history of surgical I-TOP

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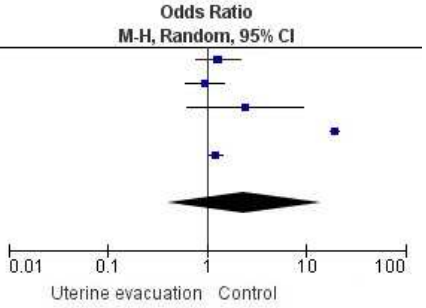
Study or Subgroup	I-TOP Events	I-TOP Total	No I-TOP Events	No I-TOP Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Meirik 1982	37	776	25	666	20.2%	1.28 [0.76, 2.16]	1982
Meirik 1983	40	670	39	622	20.3%	0.95 [0.60, 1.50]	1983
Meirik 1984	8	143	3	127	18.4%	2.45 [0.64, 9.44]	1984
Zhou 1999	774	1775	2377	62350	20.5%	19.51 [17.61, 21.61]	1999
Raatikainen 2006	204	2719	1503	24248	20.5%	1.23 [1.05, 1.43]	2006
Total (95% CI)		**6083**		**88013**	**100.0%**	**2.36 [0.39, 14.11]**	
Total events	1063		3947				

Heterogeneity: Tau² = 4.05; Chi² = 1145.63, df = 4 (P < 0.00001); I² = 100%

Test for overall effect: Z = 0.94 (P = 0.35)



Risk of PTB in women with history of first trimester surgical I-TOP

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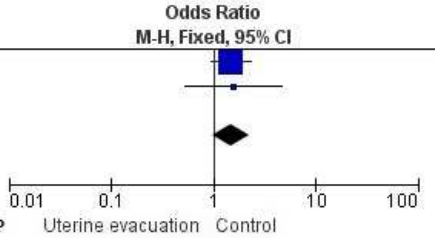
Study or Subgroup	I-TOP Events	I-TOP Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Winer 2009	40	97	205	639	85.7%	1.49 [0.96, 2.30]	2009
Mirmilstein 2009	9	77	6	77	14.3%	1.57 [0.53, 4.64]	2009
Total (95% CI)		**174**		**716**	**100.0%**	**1.50 [1.00, 2.25]**	
Total events	49		211				

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%

Test for overall effect: Z = 1.95 (P = 0.05)



Risk of PTB in women with history of medical I-TOP

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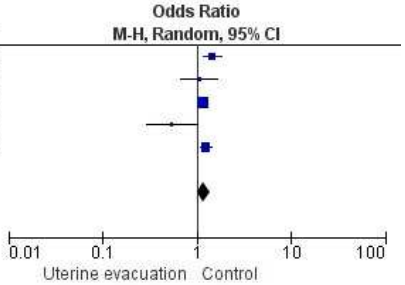
Study or Subgroup	Spontaneous TOP Events	Spontaneous TOP Total	No TOP Events	No TOP Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Doyle 2000	104	1738	443	10535	21.0%	1.45 [1.16, 1.81]	2000
Nguyen 2004	24	197	176	1512	8.1%	1.05 [0.67, 1.66]	2004
Smith 2006	575	5275	7549	79116	35.6%	1.16 [1.06, 1.27]	2006
Selo-Ojeme 2006	21	103	33	103	4.6%	0.54 [0.29, 1.02]	2006
Freak-Poli 2009	287	3435	1515	22119	30.7%	1.24 [1.09, 1.41]	2009
Total (95% CI)		**10748**		**113385**	**100.0%**	**1.19 [1.03, 1.37]**	
Total events	1011		9716				

Heterogeneity: Tau² = 0.01; Chi² = 9.95, df = 4 (P = 0.04); I² = 60%

Test for overall effect: Z = 2.35 (P = 0.02)



Risk of PTB in women with history of SAB

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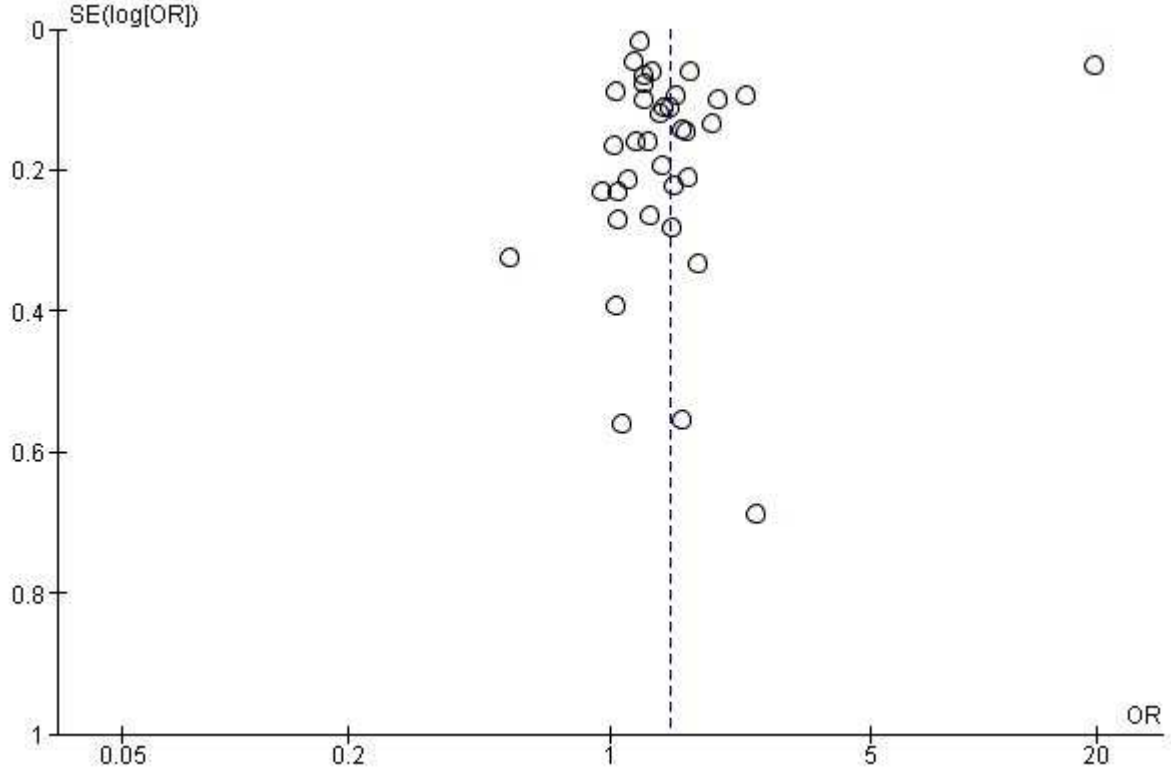

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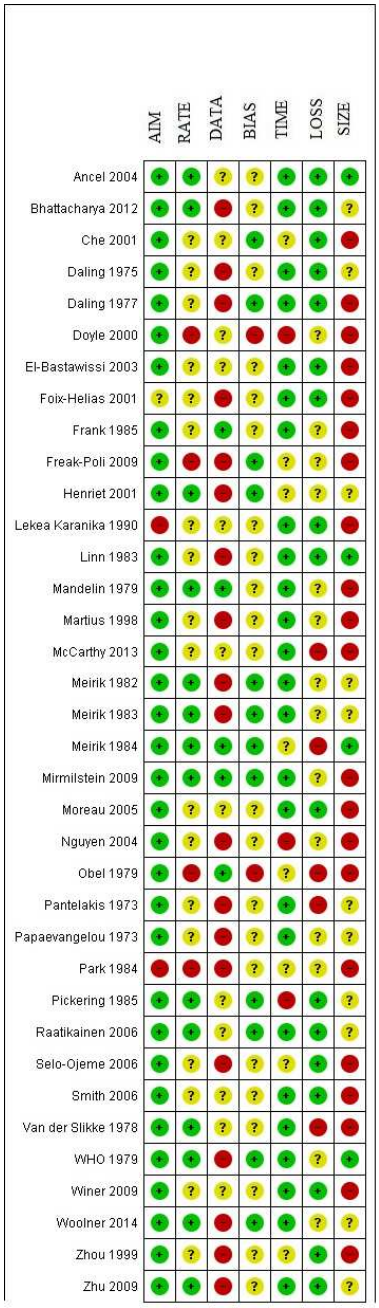
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RATE
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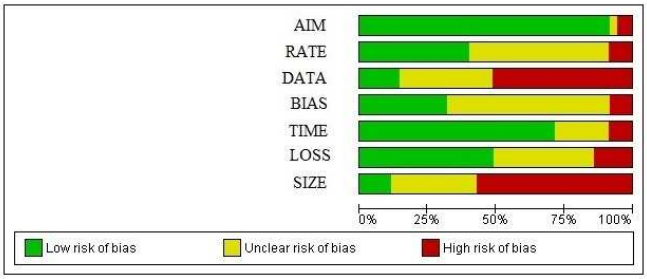
Ancel 2004
Bhattacharya 2012
Che 2001
Daling 1975
Daling 1977
Doyle 2000
El-Bastawissi 2003
Foix-Helias 2001
Frank 1985
Freak-Poli 2009
Henriet 2001
Lekea Karanika 1990
Linn 1983
Mandelin 1979
Martius 1998
McCarthy 2013
Meirik 1982
Meirik 1983
Meirik 1984
Mirmilstein 2009
Moreau 2005
Nguyen 2004
Obel 1979
Pantelakis 1973
Papaevangelou 1973
Park 1984
Pickering 1985
Raatikainen 2006
Selo-Ojeme 2006
Smith 2006
Van der Slikke 1978
WHO 1979
Winer 2009
Woolner 2014
Zhou 1999
Zhu 2009

A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0%
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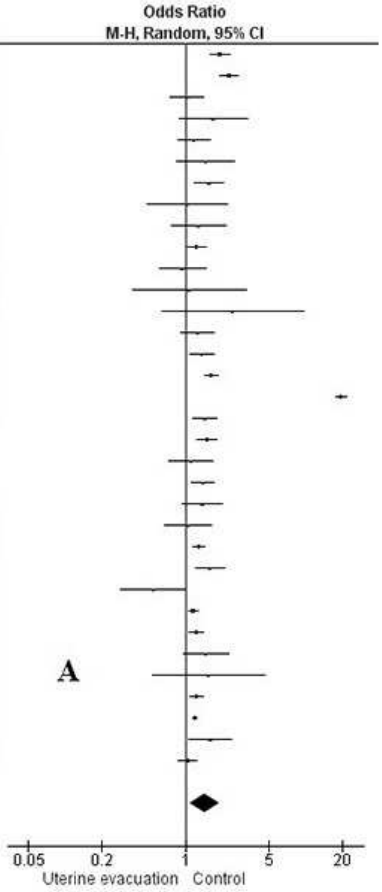
100%
Low risk of bias
Unclear risk of bias
High risk of bias

B

Study or Subgroup	Uterine evacuation Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Papaevangelou 1973	196	917	314	2550	3.1%	1.94 [1.59, 2.36]	1973
Pantelakis 1973	251	1508	261	3271	3.1%	2.30 [1.91, 2.77]	1973
Daling 1975	83	758	81	758	3.0%	1.03 [0.74, 1.42]	1975
Daling 1977	25	271	16	285	2.7%	1.71 [0.89, 3.28]	1977
Van der Slikke 1978	53	265	555	3167	3.1%	1.18 [0.86, 1.61]	1978
Mandelin 1979	26	269	29	427	2.8%	1.47 [0.84, 2.55]	1979
WHO 1979	109	1407	99	1945	3.1%	1.57 [1.18, 2.07]	1979
Obel 1979	16	280	12	217	2.5%	1.04 [0.48, 2.24]	1979
Meirik 1982	37	776	25	666	2.9%	1.28 [0.76, 2.16]	1982
Linn 1983	136	1701	536	8122	3.1%	1.23 [1.01, 1.50]	1983
Meirik 1983	40	670	39	622	2.9%	0.95 [0.60, 1.50]	1983
Park 1984	4	107	20	574	2.1%	1.08 [0.36, 3.21]	1984
Meirik 1984	8	142	3	127	1.8%	2.47 [0.64, 9.51]	1984
Frank 1985	70	470	131	1075	3.1%	1.26 [0.92, 1.72]	1985
Lekea Karanika 1990	125	1407	199	2984	3.1%	1.36 [1.08, 1.72]	1990
Martius 1998	301	2879	6858	103245	3.2%	1.64 [1.45, 1.85]	1998
Zhou 1999	774	1775	2377	62350	3.2%	19.51 [17.61, 21.61]	1999
Doyle 2000	104	1738	443	10535	3.1%	1.45 [1.16, 1.81]	2000
Foix-Helias 2001	140	2153	672	15258	3.1%	1.51 [1.25, 1.82]	2001
Che 2001	48	1356	43	1351	3.0%	1.12 [0.73, 1.70]	2001
Henriet 2001	104	1800	443	10536	3.1%	1.40 [1.12, 1.74]	2001
El-Bastawissi 2003	64	133	209	521	3.0%	1.38 [0.94, 2.03]	2003
Nguyen 2004	24	197	176	1512	2.9%	1.05 [0.67, 1.66]	2004
Ancel 2004	604	1397	2335	6324	3.2%	1.30 [1.16, 1.46]	2004
Moreau 2005	299	362	1644	2199	3.1%	1.60 [1.20, 2.14]	2005
Selo-Ojeme 2006	21	103	33	103	2.7%	0.54 [0.29, 1.02]	2006
Smith 2006	575	5275	7549	79116	3.2%	1.16 [1.06, 1.27]	2006
Raatikainen 2006	204	2719	1503	24248	3.2%	1.23 [1.05, 1.43]	2006
Winer 2009	40	97	205	639	2.9%	1.49 [0.96, 2.30]	2009
Mirmilstein 2009	9	77	6	77	2.1%	1.57 [0.53, 4.64]	2009
Freak-Poli 2009	287	3435	1515	22119	3.2%	1.24 [1.09, 1.41]	2009
Bhattacharya 2012	4224	120033	13453	457477	3.2%	1.20 [1.16, 1.25]	2012
McCarthy 2013	28	481	160	4331	3.0%	1.61 [1.07, 2.44]	2013
Woolner 2014	141	3185	1806	42446	3.1%	1.04 [0.87, 1.24]	2014
Total (95% CI)		**160143**		**871177**	**100.0%**	**1.44 [1.09, 1.90]**	
Total events	9170		43750				

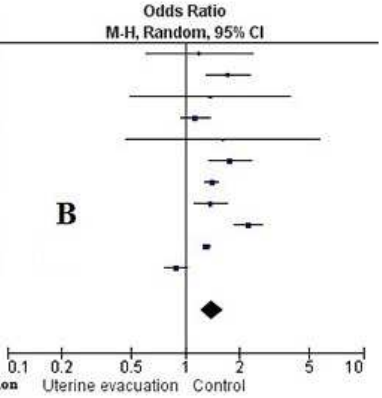
Heterogeneity: Tau² = 0.62; Chi² = 2718.40, df = 33 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.60 (P = 0.009)



Risk of PTB in overall women with history of uterine evacuation

Study or Subgroup	Uterine evacuation Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Daling 1977	18	271	16	285	3.3%	1.20 [0.60, 2.40]	1977
WHO 1979	110	1513	93	2157	9.3%	1.74 [1.31, 2.31]	1979
Obel 1979	7	139	8	217	1.7%	1.39 [0.49, 3.91]	1979
Linn 1983	134	1701	569	8122	11.5%	1.14 [0.93, 1.38]	1983
Meirik 1984	7	139	4	127	1.2%	1.63 [0.47, 5.71]	1984
Lekea Karanika 1990	94	1487	123	3357	9.5%	1.77 [1.35, 2.34]	1990
Zhou 1999	698	13775	2271	62360	13.8%	1.41 [1.29, 1.54]	1999
Henriet 2001	106	1809	456	10608	10.9%	1.39 [1.11, 1.72]	2001
Raatikainen 2006	150	1495	1140	24248	11.9%	2.26 [1.89, 2.70]	2006
Bhattacharya 2012	3104	38278	28735	457477	14.4%	1.32 [1.27, 1.37]	2012
Woolner 2014	202	3186	3004	42446	12.6%	0.89 [0.77, 1.03]	2014
Total (95% CI)		**63793**		**611404**	**100.0%**	**1.41 [1.22, 1.62]**	
Total events	4630		36419				

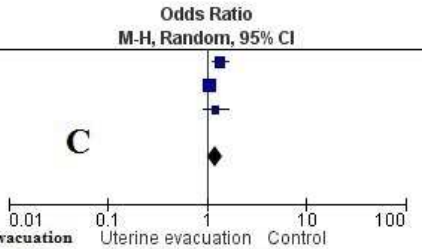
Heterogeneity: Tau² = 0.04; Chi² = 75.22, df = 10 (P < 0.00001); I² = 87%
Test for overall effect: Z = 4.68 (P < 0.00001)



Risk of LBW in overall women with history of uterine evacuation

Study or Subgroup	I-TOP Events	Total	No I-TOP Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Henriet 2001	143	1478	767	10509	34.8%	1.36 [1.13, 1.64]	2001
Raatikainen 2006	236	2364	2304	24248	42.5%	1.06 [0.92, 1.22]	2006
McCarthy 2013	62	481	466	4331	22.7%	1.23 [0.92, 1.63]	2013
Total (95% CI)		**4323**		**39088**	**100.0%**	**1.19 [1.01, 1.42]**	
Total events	441		3537				

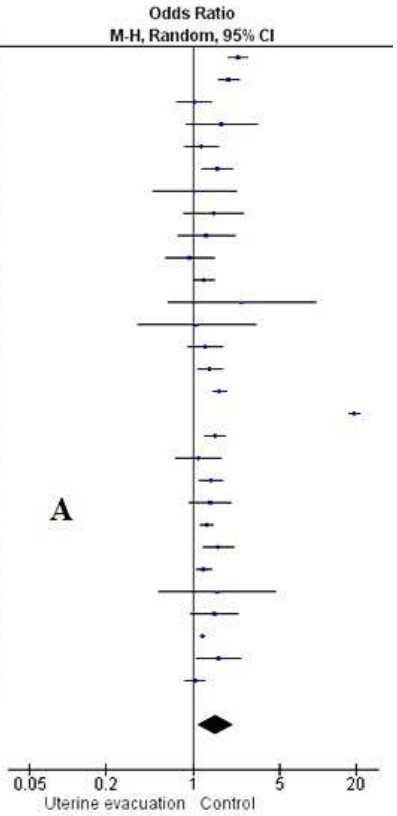
Heterogeneity: Tau² = 0.01; Chi² = 4.62, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 2.02 (P = 0.04)



Risk of SGA in overall women with history of uterine evacuation

Study or Subgroup	Uterine evacuation Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Pantelakis 1973	251	1508	261	3271	3.7%	2.30 [1.91, 2.77]	1973
Papaevangelou 1973	196	917	314	2550	3.6%	1.94 [1.59, 2.36]	1973
Daling 1975	83	758	81	758	3.6%	1.03 [0.74, 1.42]	1975
Daling 1977	25	271	16	285	3.2%	1.71 [0.89, 3.28]	1977
Van der Slikke 1978	53	265	555	3167	3.6%	1.18 [0.86, 1.61]	1978
WHO 1979	109	1407	99	1945	3.6%	1.57 [1.18, 2.07]	1979
Obel 1979	16	280	12	217	3.1%	1.04 [0.48, 2.24]	1979
Mandelin 1979	26	269	29	427	3.4%	1.47 [0.84, 2.55]	1979
Meirik 1982	37	776	25	666	3.4%	1.28 [0.76, 2.16]	1982
Meirik 1983	40	670	39	622	3.5%	0.95 [0.60, 1.50]	1983
Linn 1983	136	1701	536	8122	3.6%	1.23 [1.01, 1.50]	1983
Meirik 1984	8	142	3	127	2.3%	2.47 [0.64, 9.51]	1984
Park 1984	4	107	20	574	2.7%	1.08 [0.36, 3.21]	1984
Frank 1985	70	470	131	1075	3.6%	1.26 [0.92, 1.72]	1985
Lekea Karanika 1990	125	1407	199	2984	3.6%	1.36 [1.08, 1.72]	1990
Martius 1998	301	2879	6858	103245	3.7%	1.64 [1.45, 1.85]	1998
Zhou 1999	774	1775	2377	62350	3.7%	19.51 [17.61, 21.61]	1999
Foix-Helias 2001	140	2153	672	15258	3.7%	1.51 [1.25, 1.82]	2001
Che 2001	48	1356	43	1351	3.5%	1.12 [0.73, 1.70]	2001
Henriet 2001	104	1800	443	10536	3.6%	1.40 [1.12, 1.74]	2001
El-Bastawissi 2003	64	133	209	521	3.5%	1.38 [0.94, 2.03]	2003
Ancel 2004	604	1397	2335	6324	3.7%	1.30 [1.16, 1.46]	2004
Moreau 2005	299	362	1644	2199	3.6%	1.60 [1.20, 2.14]	2005
Raatikainen 2006	204	2719	1503	24248	3.7%	1.23 [1.05, 1.43]	2006
Mirmilstein 2009	9	77	6	77	2.7%	1.57 [0.53, 4.64]	2009
Winer 2009	40	97	205	639	3.5%	1.49 [0.96, 2.30]	2009
Bhattacharya 2012	4224	120033	13453	457477	3.7%	1.20 [1.16, 1.25]	2012
McCarthy 2013	28	481	160	4331	3.5%	1.61 [1.07, 2.44]	2013
Woolner 2014	141	3185	1806	42446	3.7%	1.04 [0.87, 1.24]	2014
Total (95% CI)		**149395**		**757792**	**100.0%**	**1.52 [1.09, 2.13]**	
Total events	8159		34034				

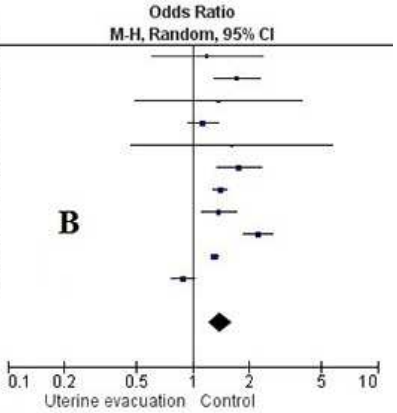
Heterogeneity: Tau² = 0.79; Chi² = 2665.25, df = 28 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.46 (P = 0.01)



Risk of PTB in women with history of I-TOP

Study or Subgroup	Uterine evacuation Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Daling 1977	18	271	16	285	3.3%	1.20 [0.60, 2.40]	1977
WHO 1979	110	1513	93	2157	9.3%	1.74 [1.31, 2.31]	1979
Obel 1979	7	139	8	217	1.7%	1.39 [0.49, 3.91]	1979
Linn 1983	134	1701	569	8122	11.5%	1.14 [0.93, 1.38]	1983
Meirik 1984	7	139	4	127	1.2%	1.63 [0.47, 5.71]	1984
Lekea Karanika 1990	94	1487	123	3357	9.5%	1.77 [1.35, 2.34]	1990
Zhou 1999	698	13775	2271	62360	13.8%	1.41 [1.29, 1.54]	1999
Henriet 2001	106	1809	456	10608	10.9%	1.39 [1.11, 1.72]	2001
Raatikainen 2006	150	1495	1140	24248	11.9%	2.26 [1.89, 2.70]	2006
Bhattacharya 2012	3104	38278	28735	457477	14.4%	1.32 [1.27, 1.37]	2012
Woolner 2014	202	3186	3004	42446	12.6%	0.89 [0.77, 1.03]	2014
Total (95% CI)		**63793**		**611404**	**100.0%**	**1.41 [1.22, 1.62]**	
Total events	4630		36419				

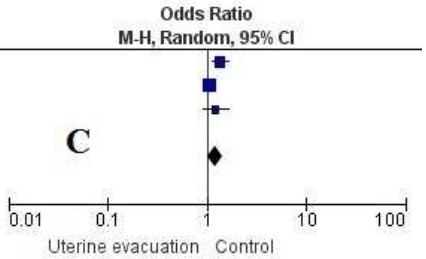
Heterogeneity: Tau² = 0.04; Chi² = 75.22, df = 10 (P < 0.00001); I² = 87%
Test for overall effect: Z = 4.68 (P < 0.00001)



Risk of LBW in women with history of I-TOP

Study or Subgroup	I-TOP Events	Total	No I-TOP Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Henriet 2001	143	1478	767	10509	34.8%	1.36 [1.13, 1.64]	2001
Raatikainen 2006	236	2364	2304	24248	42.5%	1.06 [0.92, 1.22]	2006
McCarthy 2013	62	481	466	4331	22.7%	1.23 [0.92, 1.63]	2013
Total (95% CI)		**4323**		**39088**	**100.0%**	**1.19 [1.01, 1.42]**	
Total events	441		3537				

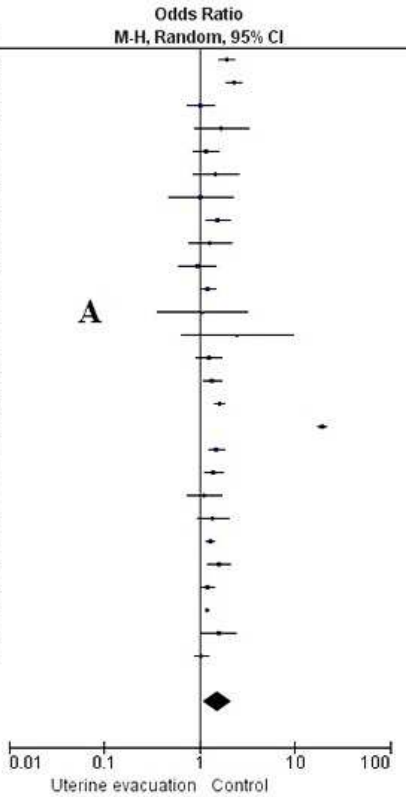
Heterogeneity: Tau² = 0.01; Chi² = 4.62, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 2.02 (P = 0.04)



Risk of SGA in women with history of I-TOP

Study or Subgroup	I-TOP Events	I-TOP Total	No I-TOP Events	No I-TOP Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Papaevangelou 1973	196	917	314	2550	3.9%	1.94 [1.59, 2.36]	1973
Pantelakis 1973	251	1508	261	3271	3.9%	2.30 [1.91, 2.77]	1973
Daling 1975	83	758	81	758	3.8%	1.03 [0.74, 1.42]	1975
Daling 1977	25	271	16	285	3.5%	1.71 [0.89, 3.28]	1977
Van der Slikke 1978	53	265	555	3167	3.8%	1.18 [0.86, 1.61]	1978
Mandelin 1979	26	269	29	427	3.6%	1.47 [0.84, 2.55]	1979
Obel 1979	16	280	12	217	3.3%	1.04 [0.48, 2.24]	1979
WHO 1979	109	1407	99	1945	3.8%	1.57 [1.18, 2.07]	1979
Meirik 1982	37	776	25	666	3.6%	1.28 [0.76, 2.16]	1982
Meirik 1983	40	670	39	622	3.7%	0.95 [0.60, 1.50]	1983
Linn 1983	136	1701	536	8122	3.9%	1.23 [1.01, 1.50]	1983
Park 1984	4	107	20	574	2.8%	1.08 [0.36, 3.21]	1984
Meirik 1984	8	142	3	127	2.5%	2.47 [0.64, 9.51]	1984
Frank 1985	70	470	131	1075	3.8%	1.26 [0.92, 1.72]	1985
Lekea Karanika 1990	125	1407	199	2984	3.9%	1.36 [1.08, 1.72]	1990
Martius 1998	301	2879	6858	103245	3.9%	1.64 [1.45, 1.85]	1998
Zhou 1999	774	1775	2377	62350	3.9%	19.51 [17.61, 21.61]	1999
Foix-Helias 2001	140	2153	672	15258	3.9%	1.51 [1.25, 1.82]	2001
Henriet 2001	104	1800	443	10536	3.9%	1.40 [1.12, 1.74]	2001
Che 2001	48	1356	43	1351	3.7%	1.12 [0.73, 1.70]	2001
El-Bastawissi 2003	64	133	209	521	3.8%	1.38 [0.94, 2.03]	2003
Ancel 2004	604	1397	2335	6324	3.9%	1.30 [1.16, 1.46]	2004
Moreau 2005	299	362	1644	2199	3.8%	1.60 [1.20, 2.14]	2005
Raatikainen 2006	204	2719	1503	24248	3.9%	1.23 [1.05, 1.43]	2006
Bhattacharya 2012	4224	120033	13453	457477	3.9%	1.20 [1.16, 1.25]	2012
McCarthy 2013	28	481	160	4331	3.7%	1.61 [1.07, 2.44]	2013
Woolner 2014	141	3185	1806	42446	3.9%	1.04 [0.87, 1.24]	2014
Total (95% CI)		**149221**		**757076**	**100.0%**	**1.52 [1.08, 2.16]**	
Total events	8110		33823				

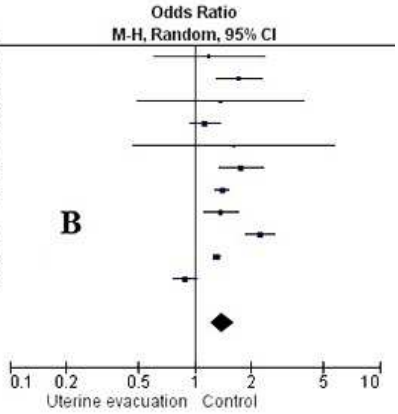
Heterogeneity: Tau² = 0.80; Chi² = 2665.34, df = 26 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.37 (P = 0.02)



Risk of PTB in women with history of surgical I-TOP

Study or Subgroup	Uterine evacuation Events	Uterine evacuation Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Daling 1977	18	271	16	285	3.3%	1.20 [0.60, 2.40]	1977
WHO 1979	110	1513	93	2157	9.3%	1.74 [1.31, 2.31]	1979
Obel 1979	7	139	8	217	1.7%	1.39 [0.49, 3.91]	1979
Linn 1983	134	1701	569	8122	11.5%	1.14 [0.93, 1.38]	1983
Meirik 1984	7	139	4	127	1.2%	1.63 [0.47, 5.71]	1984
Lekea Karanika 1990	94	1487	123	3357	9.5%	1.77 [1.35, 2.34]	1990
Zhou 1999	698	13775	2271	62360	13.8%	1.41 [1.29, 1.54]	1999
Henriet 2001	106	1809	456	10608	10.9%	1.39 [1.11, 1.72]	2001
Raatikainen 2006	150	1495	1140	24248	11.9%	2.26 [1.89, 2.70]	2006
Bhattacharya 2012	3104	38278	28735	457477	14.4%	1.32 [1.27, 1.37]	2012
Woolner 2014	202	3186	3004	42446	12.6%	0.89 [0.77, 1.03]	2014
Total (95% CI)		**63793**		**611404**	**100.0%**	**1.41 [1.22, 1.62]**	
Total events	4630		36419				

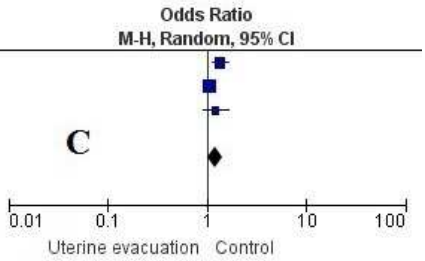
Heterogeneity: Tau² = 0.04; Chi² = 75.22, df = 10 (P < 0.00001); I² = 87%
Test for overall effect: Z = 4.68 (P < 0.00001)



Risk of LBW in women with history of surgical I-TOP

Study or Subgroup	I-TOP Events	I-TOP Total	No I-TOP Events	No I-TOP Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Henriet 2001	143	1478	767	10509	34.8%	1.36 [1.13, 1.64]	2001
Raatikainen 2006	236	2364	2304	24248	42.5%	1.06 [0.92, 1.22]	2006
McCarthy 2013	62	481	466	4331	22.7%	1.23 [0.92, 1.63]	2013
Total (95% CI)		**4323**		**39088**	**100.0%**	**1.19 [1.01, 1.42]**	
Total events	441		3537				

Heterogeneity: Tau² = 0.01; Chi² = 4.62, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 2.02 (P = 0.04)



Risk of SGA in women with history of surgical I-TOP

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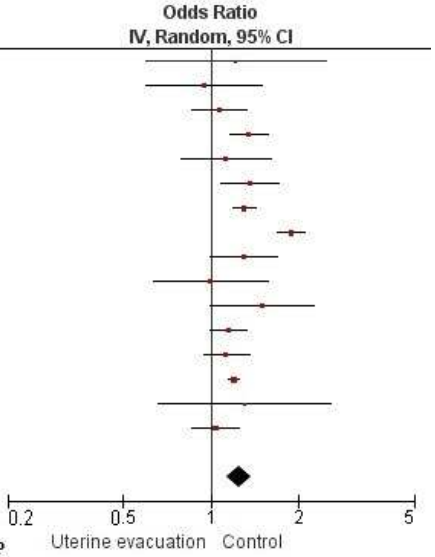
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
Meirik 1982	0.198851	0.364233	1.6%	1.22 [0.60, 2.49]	1982
Meirik 1983	-0.05129	0.233748	3.2%	0.95 [0.60, 1.50]	1983
Linn 1983	0.067659	0.113136	6.9%	1.07 [0.86, 1.34]	1983
Pickering 1985	0.300105	0.077208	8.5%	1.35 [1.16, 1.57]	1985
Frank 1985	0.122218	0.183201	4.4%	1.13 [0.79, 1.62]	1985
Lekea Karanika 1990	0.307485	0.118715	6.7%	1.36 [1.08, 1.72]	1990
Martius 1998	0.262364	0.046159	9.8%	1.30 [1.19, 1.42]	1998
Zhou 1999	0.636577	0.055117	9.5%	1.89 [1.70, 2.11]	1999
Henriet 2001	0.262364	0.135364	6.0%	1.30 [1.00, 1.69]	2001
Che 2001	0	0.233748	3.2%	1.00 [0.63, 1.58]	2001
El-Bastawissi 2003	0.405465	0.212477	3.7%	1.50 [0.99, 2.27]	2003
Ancel 2004	0.139762	0.075314	8.6%	1.15 [0.99, 1.33]	2004
Raatikainen 2006	0.122218	0.092342	7.9%	1.13 [0.94, 1.35]	2006
Bhattacharya 2012	0.182321	0.022959	10.5%	1.20 [1.15, 1.26]	2012
McCarthy 2013	0.264898	0.349489	1.7%	1.30 [0.66, 2.59]	2013
Woolner 2014	0.039221	0.094387	7.8%	1.04 [0.86, 1.25]	2014
Total (95% CI)			**100.0%**	**1.25 [1.13, 1.38]**	

Heterogeneity: Tau² = 0.02; Chi² = 72.92, df = 15 (P < 0.00001)
Test for overall effect: Z = 4.43 (P < 0.00001)



Adjusted estimates forest plot for risk of PTB in women with history of I-TOP

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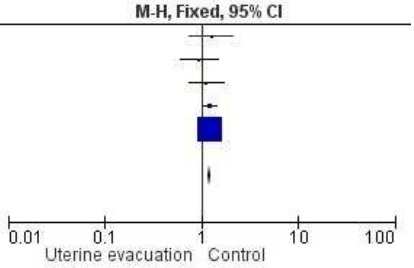
Study or Subgroup	I-TOP Events	I-TOP Total	No I-TOP Events	No I-TOP Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Meirik 1982	37	776	25	660	0.4%	1.27 [0.76, 2.14]	1982
Meirik 1983	40	670	39	622	0.6%	0.95 [0.60, 1.50]	1983
Che 2001	48	1356	43	1351	0.7%	1.12 [0.73, 1.70]	2001
Raatikainen 2006	204	2719	1503	24248	5.0%	1.23 [1.05, 1.43]	2006
Bhattacharya 2012	4224	120033	13453	457477	93.4%	1.20 [1.16, 1.25]	2012
Total (95% CI)		**125554**		**484358**	**100.0%**	**1.20 [1.16, 1.24]**	
Total events	4553		15063				

Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 4 (P = 0.87); I² = 0%

Test for overall effect: Z = 10.67 (P < 0.00001)



Risk of PTB in women with history of I-TOP with VA

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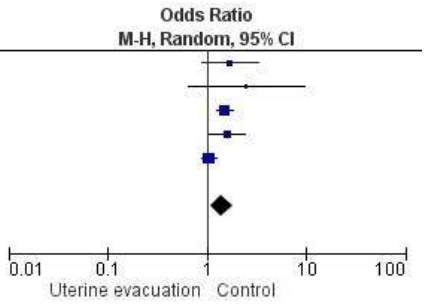
Study or Subgroup	I-TOP Events	I-TOP Total	No I-TOP Events	No I-TOP Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Daling 1977	25	271	16	285	11.2%	1.71 [0.89, 3.28]	1977
Meirik 1984	8	142	3	127	3.3%	2.47 [0.64, 9.51]	1984
Foix-Helias 2001	140	2153	672	15258	32.6%	1.51 [1.25, 1.82]	2001
McCarthy 2013	28	481	160	4331	19.6%	1.61 [1.07, 2.44]	2013
Woolner 2014	141	3185	1806	42446	33.3%	1.04 [0.87, 1.24]	2014
Total (95% CI)		**6232**		**62447**	**100.0%**	**1.39 [1.08, 1.80]**	
Total events	342		2657				

Heterogeneity: Tau² = 0.04; Chi² = 11.10, df = 4 (P = 0.03); I² = 64%

Test for overall effect: Z = 2.52 (P = 0.01)



Risk of PTB in women with history of I-TOP with D&E

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