Induced termination of pregnancy and low birthweight and preterm birth: a systematic review and meta-analyses

PS Shah, J Zao on behalf of Knowledge Synthesis Group of Determinants of preterm/LBW births*

a Department of Paediatrics, Mount Sinai Hospital and b Department of Paediatrics, University of Toronto, Toronto, ON, Canada

Correspondence: Dr Prakesh S Shah, Department of Paediatrics, Mount Sinai Hospital, 775A—600 University Avenue, Toronto, ON, Canada MSG 1X5. Email pshah@mtsinai.on.ca

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Background

History of induced termination of pregnancy (I-TOP) is suggested as a precursor for infant being born low birthweight (LBW), preterm (PT) or small for gestational age (SGA). Infection, mechanical trauma to the cervix leading to cervical incompetence and scarred tissue following curettage are suspected mechanisms.

Objective

To systematically review the risk of an infant being born LBW/PT/SGA among women with history of I-TOP.

Search strategy

Medline, Embase, CINAHL and bibliographies of identified articles were searched for English language studies.

Selection criteria

Studies reporting birth outcomes to mothers with or without history of induced abortion were included.

Data collection and analyses

Two reviewers independently collected data and assessed the quality of the studies for biases in sample selection, exposure assessment, confounder adjustment, analytical, outcome assessments and attrition. Meta-analyses were performed using random effect model and odds ratio (OR), weighted mean difference and 95% confidence interval (CI) were calculated.

Main results

Thirty-seven studies of low–moderate risk of bias were included. A history of one I-TOP was associated with increased unadjusted odds of LBW (OR 1.35, 95% CI 1.20–1.52) and PT (OR 1.36, 95% CI 1.24–1.50), but not SGA (OR 0.87, 95% CI 0.69–1.09). A history of more than one I-TOP was associated with LBW (OR 1.72, 95% CI 1.45–2.04) and PT (OR 1.93, 95% CI 1.28–2.71). Meta-analyses of adjusted risk estimates confirmed these findings.

Conclusions

A previous I-TOP is associated with a significantly increased risk of LBW and PT but not SGA. The risk increased as the number of I-TOP increased.

Keywords

Birth outcomes, infant-low birthweight, infant-premature, therapeutic termination of pregnancy.


Background

Low birthweight (LBW) and preterm (PT) births are public health issues with physical, emotional, psychological and financial impact. The research to identify relative contribution of various factors leading to preterm births spans several decades. First or even second-trimester-induced termination of pregnancy (I-TOP) are often considered minor and benign procedures; however, some studies report significant consequences to childbearing potentials and possibilities of LBW and PT births. Current theories linking previous I-TOP to PT/LBW births include (a) overt or covert infection following I-TOP, (b) mechanical trauma to the cervix leading to increased risk of cervical insufficiency and (c) surgical procedures including curettage resulting in scarred tissue that may increase the probability of faulty placental implantation and subsequent placenta previa. It is also likely that circumstances that made women to choose I-TOP such as socio-economic status may lead to LBW. Women who chose I-TOP may be inherently different from women who continue pregnancy and may be a risk factor for adverse pregnancy outcomes.
Thorp et al. in a review of 24 studies, stated that in 12 studies that reported on the I-TOP and PT births, the risk ratios for PT births ranged from 1.3 to 2.0. A dose–response relationship was observed in seven studies, with the risk increasing as the number of abortions increased. The remaining 12 studies reported no such association. Cumulative risk was not quantified.

We asked the following questions:
1. Are women with a history of I-TOP at an increased risk of adverse pregnancy outcomes compared to women without such history?
2. Is there an increase in adverse outcomes with increasing number of I-TOP, that is, ‘dose–response gradient’?
3. Is there a difference in the risk of adverse outcomes between different methods of I-TOP?

**Methods**

We followed the Meta-analyses of Observational Studies in Epidemiological Studies (MOOSE) criteria for this meta-analysis. The data were extracted from published manuscripts and thus, no Ethics Board approval was obtained.

**Objectives**

To systematically review the risk of LBW, PT and SGA births among the following:
1. Women with history of one I-TOP versus women without history of I-TOP
2. Women with history of more than one I-TOP versus women without history of I-TOP
3. Women who had I-TOP using different methods of I-TOP

**Criteria for considering studies for this review**

Observational studies that assessed the association between I-TOP and the outcomes of LBW, PT and SGA births were included. A study was included if it provided adequate information on the method of ascertainment of the history of I-TOP and its effects on any of the outcomes of interest. We only included information available from the publications and did not contact primary authors. Studies were included only if there was a comparative cohort. Studies published only as abstracts were not included. Studies or data on spontaneous TOP were not included as they were considered mostly to be beyond women’s control.

**Types of studies**

Observational cohort studies with matched, unmatched or historical controls; longitudinal studies; and case–control studies were included. Reports of data from National or local Vital Statistics not published as peer-reviewed article were not included.

**Types of participants**

Women who had live births were included (stillbirths were excluded as often their maturity and weight are not accurately recorded).

**Assessment of exposure**

Maternal I-TOP in most instances was elicited during history. Further details on maternal characteristics were ascertained from medical records, hospital records, administrative databases, national databases or vital registers and were included.

**Types of outcome measures**

1. Low birthweight: Defined as birthweight <2.5 kg
2. Preterm birth: Defined as gestational age <37 weeks
3. Small for gestational age: Defined as birthweight <10th centile for gestational age
4. Birthweight in grams
5. Gestational age in weeks

**Search strategy for identification of studies**

Electronic databases (Medline, Embase and CINAHL) were searched from their inception until August 2008 for all published studies in the English language. The search terms were modified according to database requirements. The reference lists of the identified articles were reviewed to locate further eligible studies. The articles were scanned initially based on titles and abstracts by two authors (PS and JZ) using a study relevance form. Selected articles were retrieved in full and were assessed for eligibility by two authors (PS and JZ). Discrepancies were resolved by consensus. Search terms used were: low birthweight; premature birth; small for gestational age; mother; growth, intrauterine; high-risk pregnancy; infant, premature; infant, newborn; pregnancy; abortion; abortion, induced; pregnancy termination; induced labour, first trimester, and second trimester.

**Methods of the review**

**Data extraction**

Data from each eligible study were extracted without modification of original data onto custom-made data collection forms by both authors. Discrepancies were resolved by consensus. For some studies, numbers were calculated from the available information. Information of confounders adjusted and adjusted risk estimates (adjusted odds ratios) were collected when available.

**Assessment of quality of included studies**

The methodological quality of studies was assessed using a pre-defined checklist (Table S1) by two authors (PS and JZ). Discrepancies were resolved by consensus.
Data synthesis
We first included unadjusted data for this review addressing all questions. Traditional with other meta-analyses, no adjustment for multiple analyses was made. Weighting of the studies was calculated based on the inverse variance method. Meta-analytic software (Revman from the Cochrane Collaboration) was used.7 The random effect model was chosen because it accounts for between studies and within studies variability as we expected a degree of clinical and statistical heterogeneity among the studies. For categorical measures, odds ratio (OR) is reported and for continuous measures, weighted mean differences (WMD) were used. Summary estimates with 95% confidence interval (CI) were calculated. If the variable was identified as significant, the population attributable risk (PAR) was calculated.
Some authors have reported both adjusted and unadjusted risks in their population controlling for confounders perceived (or statistically proven) to have effect on the summary estimate. We pooled data from these studies and performed random effects model meta-analyses using generic inverse variance method.8

Heterogeneity and publication bias assessment
Clinical heterogeneity was assessed and reported in the table of included studies. We planned a subgroup analyses based on whether the I-TOPs were performed using vacuum aspiration or were medically induced. Sensitivity analysis was planned by dividing studies in two groups (before and after midway between years of publication). Statistical heterogeneity was assessed and I-squared ($I^2$) values were calculated.9 Funnel plots were assessed to explore the possibility of publication bias.

Results
Description of studies
The results of the search, the study selection log and the number of studies are reported (Figure 1). Thirty-seven studies were included in this review.4,10–45 Thirty-two studies were excluded: Seven studies3,46–51 reported no neonatal outcome, seven studies52–58 reported combined spontaneous and I-TOP data, five studies59–63 had no comparator group, four reports5,64–66 were reviews, three studies67–69 reported on very preterm and moderately preterm data only, two studies70,71 reported on specific population only, two studies72,73 had already included data from other reports, one report74 was a duplicate publication and for one study,75 data were not ascertainable. Baseline characteristics of included studies are reported in Table 1.

Methodological quality of included studies
The results of the quality assessments are reported in Table 2. Most studies had low to moderate risk of bias. Studies were likely to have recall bias or bias because of incorrect information provided by women when asked about reproductive history because of stigma associated with TOP.

Data from individual studies
Data from the study by Lumley26 were presented in graphical format only; thus, they are not included in any of the meta-analyses. Lumley reported with increasing risk of preterm births at 20–27 weeks, 28–31 weeks and 32–36 weeks GA with increasing number of I-TOPs. The incidences of LBW, PT, SGA and mean birthweight and mean gestational
<table>
<thead>
<tr>
<th>Author</th>
<th>Year of study</th>
<th>Place of study</th>
<th>Population</th>
<th>Setting</th>
<th>Exposure assessment</th>
<th>Method of abortion</th>
<th>Confounders adjusted</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancel et al.4</td>
<td>1994–97</td>
<td>10 European Countries</td>
<td>Infants (cases- preterm and control-term births)</td>
<td>Multicentre</td>
<td>Maternal interview at the time of delivery</td>
<td>NR</td>
<td>Maternal age, marital status, social class, smoking, parity and country</td>
<td></td>
</tr>
<tr>
<td>Bracken et al.10</td>
<td>1980–82</td>
<td>Greater New Haven area, US</td>
<td>Pregnant women residing in the area</td>
<td>Single centre</td>
<td>Delivery record</td>
<td>NR</td>
<td>Ethnicity, age, smoking and exposure to diethylstilbestrol</td>
<td></td>
</tr>
<tr>
<td>Che et al.11</td>
<td>1993–98</td>
<td>China</td>
<td>Low risk pregnant women</td>
<td>15 centres in China</td>
<td>Interview before 16 weeks</td>
<td>98% vacuum aspiration</td>
<td>Year of recruitment, parental age, occupation, education, contraceptive use, maternal BMI, mode of delivery</td>
<td>Reference cohort more educated and had more white collar jobs</td>
</tr>
<tr>
<td>Daling and Emanuel12</td>
<td>1965–68</td>
<td>Taipei, Taiwan</td>
<td>Pregnant women in the hospital</td>
<td>Single centre</td>
<td>Maternal history</td>
<td>D &amp; C</td>
<td>D &amp; C</td>
<td>None</td>
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<tr>
<td>Daling and Emanuel13</td>
<td>1972–76</td>
<td>Seattle, US</td>
<td>Pregnant women in hospital</td>
<td>Single centre</td>
<td>Medical records</td>
<td>NR</td>
<td>Maternal age, ethnicity, smoking, Medicaid payment status, parity</td>
<td></td>
</tr>
<tr>
<td>Frank et al.15</td>
<td>1976–79</td>
<td>England, Scotland and Wales</td>
<td>Cases: Women undergoing induced abortion Controls: No abortion</td>
<td>General practices in Britain</td>
<td>Prospective collection</td>
<td>82% Vacuum aspiration, 6% D &amp; C, 11% instillation of medication</td>
<td>Age, marital status, gestation at entry</td>
<td>Study and control group differed for all three confounders</td>
</tr>
<tr>
<td>Harlap and Davies16</td>
<td>1966–68</td>
<td>West Jerusalem, Israel</td>
<td>All births in the area and hospital</td>
<td>Single centre/area</td>
<td>Interview and birth certificate</td>
<td>NR</td>
<td>Multiple confounders adjusted</td>
<td></td>
</tr>
<tr>
<td>Henriet and Kaminski17</td>
<td>1995</td>
<td>France</td>
<td>Singleton live births</td>
<td>National sample</td>
<td>Medical records and postpartum interviews</td>
<td>NR</td>
<td>Maternal age, parity, past history, pre-pregnancy weight, marital status, education, employment, nationality, smoking, antenatal care</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year of study</td>
<td>Place of study</td>
<td>Population</td>
<td>Setting</td>
<td>Exposure assessment</td>
<td>Method of abortion</td>
<td>Confounders adjusted</td>
<td>Remarks</td>
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<tr>
<td>Hogue</td>
<td>1968–69</td>
<td>Macedonia, Yugoslavia</td>
<td>Case: Previous abortion Control: Previous term pregnancy</td>
<td>Single centre</td>
<td>Hospital records and interviews</td>
<td>54% vacuum aspiration, 20% D &amp; C, 5% saline administration, 6% combination and 16% unknown</td>
<td>Income, smoking</td>
<td></td>
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<tr>
<td>Koller and Eikhom</td>
<td>1972–74</td>
<td>Begen, Norway</td>
<td>Women with history of previous abortion compared with women with previous live births</td>
<td>Single centre</td>
<td>Medical records</td>
<td>Dilatation and curettage, aspiration and hypertonic saline (numbers unknown)</td>
<td>None</td>
<td>Younger women in abortion group</td>
</tr>
<tr>
<td>Lao and Ho</td>
<td>1993–96</td>
<td>Hong Kong</td>
<td>Teenage singleton pregnant women</td>
<td>Single centre</td>
<td>Medical records</td>
<td>Suction and evacuation in first trimester and prostaglandin pessaries in second trimester (numbers unknown)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Lekea-Karanika et al.</td>
<td>1983</td>
<td>Greece</td>
<td>All births</td>
<td>National</td>
<td>Maternal interview</td>
<td>NR</td>
<td>Previous miscarriage, bleeding during pregnancy</td>
<td></td>
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<tr>
<td>Lekea-Karanika and Tzoumaka-Bakoula</td>
<td>1983</td>
<td>Greece</td>
<td>All births</td>
<td>National</td>
<td>Maternal interview</td>
<td>NR</td>
<td>Previous miscarriage, bleeding during pregnancy</td>
<td></td>
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<tr>
<td>Linn et al.</td>
<td>1977–80</td>
<td>Boston, US</td>
<td>Postpartum women</td>
<td>Single centre</td>
<td>Maternal interview</td>
<td>NR</td>
<td>Age, ethnicity, smoking, economic status, parity</td>
<td>None</td>
</tr>
<tr>
<td>Lopes et al.</td>
<td>1985–89</td>
<td>Hong Kong</td>
<td>Cases: Women who had ≥2 abortions Control: Primipara</td>
<td>Single centre</td>
<td>Medical records</td>
<td>NR</td>
<td>None</td>
<td></td>
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<tr>
<td>Lumley</td>
<td>1982–83</td>
<td>Victoria, Australia</td>
<td>All first singleton births</td>
<td>Multicentre</td>
<td>Medical records</td>
<td>NR</td>
<td>Maternal age</td>
<td>None</td>
</tr>
<tr>
<td>Lumley</td>
<td>1983–92</td>
<td>Victoria, Australia</td>
<td></td>
<td>State-wide</td>
<td>State-wide surveillance data</td>
<td>NR</td>
<td>None</td>
<td></td>
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<tr>
<td>Mandelin and Karjalainen</td>
<td>Can’t tell</td>
<td>Helsinki</td>
<td>Singleton, gravidity ≤3, known last menstrual date, no medical complications</td>
<td>Multicentre</td>
<td>History, delivery records</td>
<td>50% vacuum aspiration, 35% D&amp;C, 8% hysterotomy, 7% saline or prostaglandin</td>
<td>None</td>
<td></td>
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<tr>
<td>Author</td>
<td>Year of study</td>
<td>Place of study</td>
<td>Population</td>
<td>Setting</td>
<td>Exposure assessment</td>
<td>Method of abortion</td>
<td>Confounders adjusted</td>
<td>Remarks</td>
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<tr>
<td>Mandelson et al.28</td>
<td>1984–87</td>
<td>Washington, US</td>
<td>White women, sampled for no history of abortion and history of one abortion and all women with &gt;1 abortion</td>
<td>Multicentre</td>
<td>Birth record</td>
<td>NR</td>
<td>Maternal age, marital status, smoking, income, trimester of initiation of prenatal care</td>
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<tr>
<td>Martius et al.29</td>
<td>1994</td>
<td>Bavaria</td>
<td>All singleton births in the country</td>
<td>Multicentre</td>
<td>National surveillance data</td>
<td>NR</td>
<td>Gravity, previous abortion, uterine surgery, medical complications, type of work, urinary tract infection, hypotension</td>
<td></td>
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<tr>
<td>Meirik et al.30</td>
<td>1970–75</td>
<td>Uppsala County, Sweden</td>
<td>Cases: First birth after a notified legal abortion in first trimester in parous women Controls: matched for parity, hospital and year of birth</td>
<td>Single centre</td>
<td>Birth register</td>
<td>All vacuum aspiration</td>
<td>Marital status, smoking</td>
<td></td>
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<tr>
<td>Meirik and Bergstrom31</td>
<td>1970–75</td>
<td>Uppsala, Sweden</td>
<td>Cases: First birth after a notified legal abortion in first trimester in nulliparous women Controls: Two controls matched for parity, hospital and year of birth</td>
<td>Single centre</td>
<td>Birth register</td>
<td>All vacuum aspiration</td>
<td>Marital status, smoking</td>
<td></td>
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<tr>
<td>Meirik and Nygrn32</td>
<td>1970–75</td>
<td>Uppsala, Sweden</td>
<td>Cases: First birth after a notified legal abortion in second trimester Controls: matched for parity, hospital and year of birth</td>
<td>Single centre</td>
<td>Birth register</td>
<td>All—Instillation of saline or prostaglandin followed by D &amp; C</td>
<td>Parity</td>
<td></td>
</tr>
<tr>
<td>Obel33</td>
<td>1974–75</td>
<td>Denmark</td>
<td>All women registered for delivery</td>
<td>Two-centres</td>
<td>Maternal interview</td>
<td>79% vacuum aspiration, 9% D &amp; C and 12% other methods</td>
<td>Age, socioeconomic status and parity</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year of study</td>
<td>Place of study</td>
<td>Population</td>
<td>Setting</td>
<td>Exposure assessment</td>
<td>Method of abortion</td>
<td>Confounders adjusted</td>
<td>Remarks</td>
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<tr>
<td>Pantelakis et al.</td>
<td>1966–68</td>
<td>Athens, Greece</td>
<td>All women admitted for delivery</td>
<td>Single centre</td>
<td>Maternal survey at admission to delivery</td>
<td>NR</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Papaevangelou et al.</td>
<td>1969–70</td>
<td>Athens, Greece</td>
<td>Singleton, &gt;24 weeks GA and &gt;500 g BW</td>
<td>Single centre</td>
<td>History and medical records</td>
<td>NR</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Park et al.</td>
<td>1979–81</td>
<td>Hang Kwa Island, Korea</td>
<td>Women registered with family health workers</td>
<td>Three cities</td>
<td>Pregnancy and household records</td>
<td>NR</td>
<td>Parity, education, contraceptive use</td>
<td></td>
</tr>
<tr>
<td>Pickering and Forbes</td>
<td>1980–81</td>
<td>Scotland</td>
<td>Cases: History of ≥1 induced abortion Controls: No history of abortion</td>
<td>Multicentre</td>
<td>Medical register</td>
<td>NR</td>
<td>Maternal age, height, sex of infant, marital status and social class</td>
<td>Study group women were older</td>
</tr>
<tr>
<td>Raatikainen et al.</td>
<td>1989–01</td>
<td>Kuopio, Finland</td>
<td>All singleton pregnancies without significant fetal anomaly</td>
<td>Single centre</td>
<td>Maternal interview and delivery record</td>
<td>94% Vacuum aspiration followed by D &amp; C, 6% Misoprostol or mifepristone</td>
<td>Maternal age, weight, marital status, education, employment, smoking, alcohol consumption, parity, use of intrauterine device, uterine surgery, diabetes, toxoaemia, and gravity</td>
<td>Women in study group more overweight, smoked and used alcohol, high parity, higher use of intrauterine devices</td>
</tr>
<tr>
<td>Roht and Aoyama</td>
<td>1971</td>
<td>Kochi prefecture, Japan</td>
<td>Women of 20–44 years of age</td>
<td>Single centre</td>
<td>Survey, interview and delivery record</td>
<td>NR</td>
<td>None</td>
<td>Groups differ in age and duration of marriage Induced abortion had more black, single, and younger, women, had less formal education and delayed prenatal care</td>
</tr>
<tr>
<td>Schoenbaum et al.</td>
<td>1975–76</td>
<td>Boston, US</td>
<td>All pregnant women</td>
<td>Single centre</td>
<td>Medical record</td>
<td>NR</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Seidman et al.</td>
<td>1974–76</td>
<td>Jerusalem, Israel</td>
<td>All singleton pregnant women</td>
<td>Multicentre</td>
<td>Postpartum interviews</td>
<td>NR</td>
<td>Multiple demographic factors adjusted</td>
<td></td>
</tr>
<tr>
<td>Van der Slikke and Treffers</td>
<td>1972–76</td>
<td>Amsterdam</td>
<td>Singleton pregnant without fetal anomaly</td>
<td>Multicentre</td>
<td>Maternal history and newborn examination</td>
<td>NR</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>W.H.O.Task Force</td>
<td>Can’t tell</td>
<td>Eight European cities</td>
<td>Singleton, uncomplicated pregnancy with live birth</td>
<td>Multicentre</td>
<td>Maternal history</td>
<td>65% D &amp; C, 35% vacuum aspiration</td>
<td>None</td>
<td>Cities were clustered depending upon method of abortion</td>
</tr>
</tbody>
</table>
Women with a history of one previous I-TOP versus women without such history

Individual data from studies on LBW and PT are described in Tables S2–S4. The results of the adjusted and unadjusted meta-analyses of LBW and PT are described in Table 3 and Figures 2 and 3. The results of meta-analyses of SGA birth (Table 3 and Figure S1), mean BW (Table S5, Figure S2) and mean GA (Table S6, Figure S2). There was no significant difference in the mean birth-weight (6 studies, 6306 participants, WMD 23 g, 95% CI –21, 66 g, I²=51%) or mean gestational age (seven studies, 5162 participants, WMD –0.07 week, 95% CI –0.21, 0.07 week, I²=0%) of infants born to women with a history of one I-TOP compared to women without such history.

Women with a history of more than one previous I-TOP versus women without a history of previous I-TOP

The results of the adjusted and unadjusted meta-analyses are reported in Table 3 and Figures 4 and 5. The results of meta-analyses of SGA birth (Table 3 and Figure S3), mean BW (Table S4, Figure S4) and mean GA (Table S5, Figure S4). There was no significant difference in the mean birthweight (4 studies, 2957 participants, WMD –15 g, 95% CI –81, 52 g, I²=22%, Table S5) or mean gestational age (3 studies, 2077 participants, WMD 0.01 week, 95% CI –0.23, 0.26 week, I²=0%, Table S6) of infants born to women with a history of >1 I-TOP compared to women without a history of I-TOP.

Meta-analyses of adjusted data

Compared to women with no history of I-TOP, women who had a history of one I-TOP had higher odds of LBW births, but confidence limit included 1 (10 studies,\textsuperscript{11,15,17,22,23,28,30,32,38,45} OR 1.24, 95% CI 1.00, 1.53; Figure 2), increased odds of PT births (13 studies,\textsuperscript{4,11,14,15,17,21,23,37,38,44} OR 1.27, 95% CI 1.12, 1.44; Figure 3). Compared to women with no history of I-TOP, women who had a history of more than one I-TOP had higher odds of LBW births (5 studies,\textsuperscript{17,23,28,37,45} OR 1.47, 95% CI 1.24, 1.73; Figure 4), PT births (7 studies,\textsuperscript{4,14,17,23,37,38,44} OR 1.62, 95% CI 1.27, 2.07; Figure 5). Meta-analyses results of SGA births are reported in Figures S1 and S3.

Subgroup and sensitivity analyses

Thirteen reports provided data on different methods of I-TOP.\textsuperscript{11,12,15,18,27,30–33,38,43–45} Of these, four provided data on the methods of I-TOP but did not correlate them with outcomes.\textsuperscript{15,27,33,38} Compared to women with no history of one I-TOP, women who had a history of more than one I-TOP had higher odds of LBW births (5 studies,\textsuperscript{17,23,28,37,45} OR 1.47, 95% CI 1.24, 1.73; Figure 4), PT births (7 studies,\textsuperscript{4,14,17,23,37,38,44} OR 1.62, 95% CI 1.27, 2.07; Figure 5). Meta-analyses results of SGA births are reported in Figures S1 and S3.
Table 2. Quality assessments of included studies

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of I-TOP, women who had I-TOP following vacuum aspiration had higher odds of LBW births (3 studies, 18,43,45 OR 1.69, 95% CI 1.22, 2.33; I^2=43%) but not PT births (5 studies, 11,30,31,43,45 OR 1.24, 95% CI 0.89, 1.74; I^2=77%). Compared to women with no history of I-TOP, women who had I-TOP following dilatation and curettage had higher odds of LBW births (3 studies, 18,32,43 OR 1.95, 95% CI 1.45, 2.62; I^2=0%) but not PT births (4 studies, 12,32,43,44 OR 1.35, 95% CI 0.88, 2.06; I^2=81%). No study has compared two methods directly. Sensitivity analyses revealed no difference in the risk associated with I-TOP when studies published before 1984 (OR 1.19 for LBW and OR 1.34 for PT birth) or after 1984 were pooled (OR 1.45 for LBW and OR 1.37 for PT birth).

Heterogeneity assessment and publication bias

Clinical heterogeneity among studies is described in Table 1. Moderate statistical heterogeneity was identified in the meta-analyses (I^2=69% for LBW, 64% for preterm births, 63% for SGA births in analyses involving history of one I-TOP), which remained even after dividing studies in two era (before and after 1984). Funnel plot assessment revealed that most of the studies had effect estimates slightly lower or significantly higher than one (Figure S5). Analyses of funnel plots revealed that there is the potential of missing small sample-sized studies of higher risk of adverse outcomes associated with no history of I-TOP.

**Discussion**

In this systematic review and meta-analyses of 37 studies, we identified significantly increased unadjusted and adjusted odds of LBW and PT births among women with a history of I-TOP compared to women without such a history. The risks of LBW and PT births increased with increasing numbers of I-TOPs. Subgroup analyses revealed higher unadjusted odds of LBW for both vacuum aspiration and dilatation and curettage methods of I-TOP; however, the number of studies reporting this information was small. There were clinical heterogeneities among the studies included in this review for exposure assessment (self-reporting, interview or database), setting (single institution based study versus national sample) and adjustment for confounders. Overall assessment of clinical characteristics of the included studies revealed a common underlying theme (assessment of risk of outcomes following one or more I-TOPs) in all studies and thus meta-analysis was justified. The impact on SGA births, birthweight and gestational age were explored only in few studies, which revealed no statistically significant difference, likely because of lack of power. The research spans more than three decades; however, the studies suggesting association and lack thereof between I-TOP and LBW or PT were identified both during early and late years.
There were heterogeneities among studies included in this systematic review (detailed in Table 1). First, for majority of these studies, a history of I-TOP was obtained by maternal self-reporting. Stigma associated with abortion or social acceptance in different countries could have resulted in underreporting. Hogue reported 63% of women denied past history of abortion when checked against hospital records, whereas Kline et al. reported only 1.6% of women, both in cases and controls, denied previous abortion.

Second, it has been identified that women with a history of I-TOP were unmarried, young and from socio-economically disadvantaged group. These confounders differ for different timing of seeking abortion (first or second trimester). Certain studies controlled for confounders, whereas other studies failed to do so (Table 1). Even the confounders controlled in studies varied. As suggested by Peters and Mengersen, we pooled unadjusted and adjusted data for all outcomes. Marginally lower than unadjusted estimates were identified; however, the results remained clinically significant. This may not be the ideal way of combining data as different studies adjusted for different factors; however, it provides an indication regarding some degree of robustness.

Third, we identified lack of small studies of either nonsignificance or of adverse effects of I-TOP. This method for assessment of publication bias is exploratory and indirect and may be the result of location of literature, language of publication, citation issues and sample size of the study. No adjustment for publication bias was made in the analyses.

Figure 2. Unadjusted and adjusted estimates of Low birthweight births among women with a history of one previous induced abortion versus no history of induced abortions.
of cervical trauma can be minimised with these techniques.

assess outcomes in subsequent pregnancies as the element

Figure 3. Unadjusted and adjusted estimates of Preterm births among women with a history of one previous induced abortion versus no history of induced abortions.

Fourth, the methods used for abortion could vary in different studies. Subgroup analyses of vacuum aspiration and dilatation and curettage revealed a similar risk for LBW with either method. The risk for PT birth was not higher in subgroup analyses; however, only five studies reported outcomes based on the method of I-TOP. With recent changes in the use of medications (misoprostol and mifepristone),38 laminaria tents77 etc; it would be important to assess outcomes in subsequent pregnancies as the element of cervical trauma can be minimised with these techniques.

Studies have not reported size of dilators used for I-TOP to analyse the effect of cervical trauma related to size of dilators. Studies have also not reported GA at which I-TOP were carried out to analyse whether early I-TOP has different effect than late I-TOP.

Fifth, time following an I-TOP before the next pregnancy may be important.74 The complications rates may be higher following early subsequent pregnancy than late pregnancies.36 From the available studies, we were not able to ascertain this aspect.
Finally, certain studies compared women with a history of I-TOP with women who had never been pregnant and other studies compared them with women who had previous live births. The rates of complications may be different in both comparisons; however, biological rationale of damage following previous I-TOP does not change in either comparison. Additionally, a previous review indicated that I-TOP was not protective for risk of LBW associated with primiparity; that is, the risk of LBW was higher for women with a history of I-TOP compared with women who had never been pregnant.26 The results of our review differ from previous reviews mainly because this is the first attempt to quantify results reported in various studies. We are aware that the major critique of our review is suitability of studies for combining their results. We included studies in which the primary aim was to explore the relationship between a history of I-TOP and adverse pregnancy outcomes; thus, we felt meta-analyses were appropriate. We perceive that the strengths of this systematic review include a focused question, extensive literature search, large total sample size of the studied population, robust effect size, quantification of adjusted effects and narrow confidence intervals.

A step further, we would like to mention that this strong association meets several of the criteria suggested by Professor Hill regarding causation such as temporal relationship, biological plausibility, strength of association, dose–response effect (increased risk with increasing number of abortion), consistency (reported by several studies) and coherence (matching with current theory of knowledge). The criteria of an alternate explanation (accounting for other confounders/reasons for the outcome) could be considered satisfied. Two criteria for causation are not satisfied: Specificity (I-TOP is the only cause of LBW/PT births) and alteration of outcome with an opposite experiment are not satisfied. We must caution readers that we have restricted ourselves to explore the association of I-TOP and pregnancy outcomes. Several biomedical, social, environmental, lifestyle-related, genetic and other factors contribute to a preterm and/or LBW births and this needs to be kept in mind in interpreting our results. We caution interpretation being causal as confounding effects of socioeconomic factors, which are important, were considered in very few studies only. Discussion regarding downsides of I-TOP are incomplete without discussing downside of unwanted pregnancies as they are also at risk of adverse outcomes. From pragmatic viewpoint, future studies should assess benefits and risks in both situations.

**Implications for practice**

This information is important from public and health practitioners’ point of view. Estimates in the 1970s indicated...
that more than a million abortions are performed in the US per year. Of these, more than 75% of women wish or get pregnant again. These women should know the risks associated with I-TOP not only for their health but also for their future reproductive potential. A properly obtained consent legally mandates explanation of these risks to women and ensuring their understanding. Potential areas for knowledge transfer include education of girls and women enrolled at schools or colleges, during routine visits to family doctors or specialists and finally when counselling women seeking abortion.

Implication for research

It is important to realise that we need to advance our understanding in this area rather than repeating similar studies. Further studies are needed to assess the impact of newer techniques, to identify the safest method of pregnancy termination in the first and second trimester, or adverse outcomes in subsequent pregnancies. Other questions that need answers include: Does increased knowledge and awareness about risks associated with I-TOP among women reduce the incidence of I-TOPs? What supports are effective for women with a history of I-TOP to improve pregnancy outcomes? However, despite unanswered questions, action should be taken to address what is known.

Reviewers’ conclusions

I-TOP is associated with significantly increased risks of LBW/PT births. Further prospective research to identify safer methods of pregnancy termination in the first and second trimester and effective interventions for pregnant women with history of I-TOP is needed.

Conflict of interest

None for any authors.

Disclosure of interest

No conflict of interest for any authors.
Contribution to authorship
All members of the group were involved in grant concept and design. P.S. Shah and members of the group contributed to the study concept and design. P.S. Shah and J. Zhao were involved in acquisition of data. P.S. Shah and J. Beyene undertook the analysis and interpretation of data. P.S. Shah drafted the manuscript. P.S. Shah and members of the group contributed to the critical revision of the manuscript for important intellectual content.

Details of ethics approval
Not required as this is a meta-analyses of published manuscripts.

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We would sincerely like to thank Elizabeth Uleryk, Chief Librarian at the Hospital for Sick Children, Toronto, for her contribution in developing search strategy and running searches on a periodic basis.

Supporting information
The following supplementary materials are available for this article:

Figure S1. Unadjusted and adjusted estimates of Small-for-gestational-age births among women with a history of one previous I-TOP versus no history of I-TOP.

Figure S2. Meta-analyses of Birthweight and gestational age among women with a history of one previous I-TOP versus no history of I-TOP.

Figure S3. Unadjusted and adjusted estimates of Small-for-gestational-age births among women with a history of more than one previous I-TOP versus no history of I-TOP.

Figures S4. Meta-analyses of Birthweight and gestational age among women with a history of more than one previous I-TOP versus no history of I-TOP.

Figure S5. Funnel plot of publication bias for the outcome of preterm birth.

Table S1. Assessment of quality of included studies
Table S2. Data on low birthweight births
Table S3. Data on preterm birth
Table S4. Data on small for gestational age
Table S5. Data on birthweight in grams
Table S6. Data on gestational age in weeks

Additional Supporting Information may be found in the online version of this article.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author.

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Induced termination of pregnancy and birth outcomes

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subsequent to induced vacuum-aspiration abortion in parous
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Appendix

Prakesh Shah, University of Toronto, Toronto, Canada
Arne Ohlsson, University of Toronto, Canada
Vibhuti Shah, University of Toronto, Toronto, Canada
Kellie E Murphy, University of Toronto, Canada
Sarah D McDonald, McMaster University, Hamilton, Canada
Eileen Hutton, McMaster University, Hamilton, Canada
Christine Newburn-Cook, University of Alberta, Edmonton, Canada
Corine Frick, University of Calgary, Calgary, Canada
Fran Scott, University of Toronto, Toronto, Canada
Victoria Allen, Dalhousie University, Halifax, Canada
Joseph Beyene, University of Toronto, Toronto, Canada