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Systematic review

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

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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.

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Background

Low birthweight (LBW) and preterm (PT) births are public health issues with physical, emotional, psychological and financial impact.[1] 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,[2] (b) mechanical trauma to the cervix leading to increased risk of cervical insufficiency[3] and (c) surgical procedures including curettage resulting in scarred tissue that may increase the probability of faulty placental implantation and subsequent placenta previa.[4] 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.

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Thorp *et al.*[5] 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[6] 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 studies[3,46–51] reported no neonatal outcome, seven studies[52–58] reported combined spontaneous and I-TOP data, five studies[59–63] had no comparator group, four reports[5,64–66] were reviews, three studies[67–69] reported on very preterm and moderately preterm data only, two studies[70,71] reported on specific population only, two studies[72,73] had already included data from other reports, one report[74] 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 Lumley[26] 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

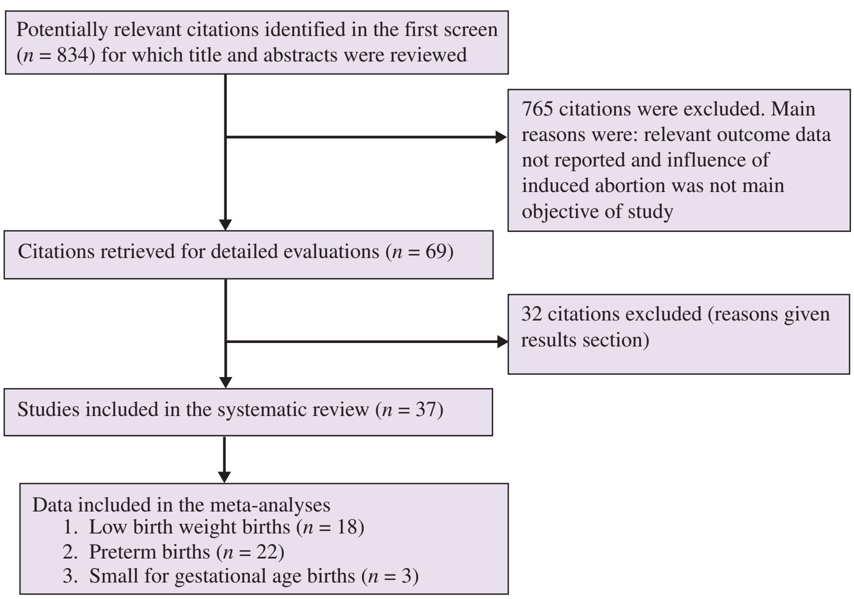


Figure 1. Study selection log.

Table 1. Characteristics of included studies

Author	Year of study	Place of study	Population	Setting	Exposure assessment	Method of abortion	Confounders adjusted	Remarks
Ancel *et al.*[4]	1994–97	10 European Countries	Infants (cases- preterm and control-term births)	Multicentre	Maternal interview at the time of delivery	NR	Maternal age, marital status, social class, smoking, parity and country	
Bracken *et al.*[10]	1980–82	Greater New Haven area, US	Pregnant women residing in the area	Single centre	Delivery record	NR	Ethnicity, age, smoking and exposure to diethylstilbestrol	
Che *et al.*[11]	1993–98	China	Low risk pregnant women	15 centres in China	Interview before 16 weeks	98% vacuum aspiration	Year of recruitment, parental age, occupation, education, contraceptive use, maternal BMI, mode of delivery	Reference cohort more educated and had more white collar jobs
Daling and Emanuel[12]	1965–68	Taipei, Taiwan	Pregnant women in the hospital	Single centre	Maternal history	D & C	None	
Daling and Emanuel[13]	1972–76	Seattle, US	Pregnant women in hospital	Single centre	Medical records	NR	None	
El-Bastawissi *et al.*[14]	1994–95	Seattle, US	Case: preterm births Control: term births	Single centre	Medical records	NR	Maternal age, ethnicity, smoking, Medicaid payment status, parity	
Frank *et al.*[15]	1976–79	England, Scotland and Wales	Cases: Women undergoing induced abortion Controls: No abortion	General practices in Britain	Prospective collection	82% Vacuum aspiration, 6% D & C, 11% instillation of medication	Age, marital status, gestation at entry	Study and control group differed for all three confounders
Harlap and Davies[16]	1966–68	West Jerusalem, Israel	All births in the area and hospital	Single centre/area	Interview and birth certificate	NR	Multiple confounders adjusted	
Henriet and Kaminski[17]	1995	France	Singleton live births	National sample	Medical records and postpartum interviews	NR	Maternal age, parity, past history, pre-pregnancy weight, marital status, education, employment, nationality, smoking, antenatal care	

Table 1. (*Continued*)

Author	Year of study	Place of study	Population	Setting	Exposure assessment	Method of abortion	Confounders adjusted	Remarks
Hogue[18]	1968–69	Macedonia, Yugoslavia	Case: Previous abortion Control: Previous term pregnancy	Single centre	Hospital records and interviews	54% vacuum aspiration, 20% D & C, 5% saline administration, 6% combination and 16% unknown	Income, smoking	
Koller and Eikhom[19]	1972–74	Begen, Norway	Women with history of previous abortion compared with women with previous live births	Single centre	Medical records	Dilatation and curettage, aspiration and hypertonic saline (numbers unknown)	None	Younger women in abortion group
Lao and Ho[20]	1993–96	Hong Kong	Teenage singleton pregnant women	Single centre	Medical records	Suction and evacuation in first trimester and prostaglandin pessaries in second trimester (numbers unknown)	None	
Lekea-Karanika *et al.*[21]	1983	Greece	All births	National	Maternal interview	NR	Previous miscarriage, bleeding during pregnancy	
Lekea-Karanika and Tzoumaka-Bakoula[22]	1983	Greece	All births	National	Maternal interview	NR	Previous miscarriage, bleeding during pregnancy	
Linn et al.[23]	1977–80	Boston, US	Postpartum women	Single centre	Maternal interview	NR	Age, ethnicity, smoking, economic status, parity	
Lopes *et al.*[24]	1985–89	Hong Kong	Cases: Women who had ≥2 abortions Control: Primipara	Single centre	Medical records	NR	None	
Lumley[25]	1982–83	Victoria, Australia	BW >500 g	Multicentre	Medical records	NR	Maternal age	
Lumley[26]	1983–92	Victoria, Australia	All first singleton births	State-wide	State-wide surveillance data	NR	None	
Mandelin and Karjalainen[27]	Can't tell	Helsinki	Singleton, gravidity ≤3, known last menstrual date, no medical complications,	Multicentre	History, delivery records	50% vacuum aspiration, 35% D&C, 8% hysterotomy, 7% saline or prostaglandin	None	

Table 1. *(Continued)*

Author	Year of study	Place of study	Population	Setting	Exposure assessment	Method of abortion	Confounders adjusted	Remarks
Mandelson *et al.*[28]	1984–87	Washington, US	White women, sampled for no history of abortion and history of one abortion and all women with >1 abortion	Multicentre	Birth record	NR	Maternal age, marital status, smoking, income, trimester of initiation of prenatal care	
Martius *et al.*[29]	1994	Bavaria	All singleton births in the country	Multicentre	National surveillance data	NR	Gravidity, previous abortion, uterine surgery, medical complications, type of work, urinary tract infection, hypotension	
Meirik *et al.*[30]	1970–75	Uppsala County, Sweden	Cases: First birth after a notified legal abortion in first trimester in parous women Controls: matched for parity, hospital and year of birth	Single centre	Birth register	All vacuum aspiration	Marital status, smoking	
Meirik and Bergstrom[31]	1970–75	Uppsala, Sweden	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	Single centre	Birth register	All vacuum aspiration	Marital status, smoking	
Meirik and Nygrn[32]	1970–75	Uppsala, Sweden	Cases: First birth after a notified legal abortion in second trimester Controls: matched for parity, hospital and year of birth	Single centre	Birth register	All—Instillation of saline or prostaglandin followed by D & C	Parity	
Obel[33]	1974–75	Denmark	All women registered for delivery	Two-centres	Maternal interview	79% vacuum aspiration, 9% D & C and 12% other methods	Age, socioeconomic status and parity	

Table 1. (*Continued*)

Author	Year of study	Place of study	Population	Setting	Exposure assessment	Method of abortion	Confounders adjusted	Remarks
Pantelakis *et al.*[34]	1966–68	Athens, Greece	All women admitted for delivery	Single centre	Maternal survey at admission to delivery	NR	None	
Papaevangelou *et al.*[35]	1969–70	Athens, Greece	Singleton, >24 weeks GA and >500 g BW	Single centre	History and medical records	NR	None	
Park *et al.*[36]	1979–81	Hang Kwa Island, Korea	Women registered with family health workers	Three cities	Pregnancy and household records	NR	Parity, education, contraceptive use	
Pickering and Forbes[37]	1980–81	Scotland	Cases: History of ≥1 induced abortion Controls: No history of abortion	Multicentre	Medical register	NR	Maternal age, height, sex of infant, marital status and social class	Study group women were older
Raatikainen *et al.*[38]	1989–01	Kuopio, Finland	All singleton pregnancies without significant fetal anomaly	Single centre	Maternal interview and delivery record	94% Vacuum aspiration followed by D & C, 6% Misoprostol or mifepristone	Maternal age, weight, marital status, education, employment, smoking, alcohol consumption, parity, use of intrauterine device, uterine surgery, diabetes, toxaemia, and gravidity	Women in study group more overweight, smoked and used alcohol, high parity, higher use of intrauterine devices
Roht and Aoyama[39]	1971	Kochi prefecture, Japan	Women of 20–44 years of age	Single centre	Survey, interview and delivery record	NR	None	Groups differ in age and duration of marriage
Schoenbaum *et al.*[40]	1975–76	Boston, US	All pregnant women	Single centre	Medical record	NR	None	Induced abortion had more black, single, and younger, women, had less formal education and delayed prenatal care
Seidman *et al.*[41]	1974–76	Jerusalem, Israel	All singleton pregnant women	Multicentre	Postpartum interviews	NR	Multiple demographic factors adjusted	
Van der Slikke and Treffers[42]	1972–76	Amsterdam	Singleton pregnant without fetal anomaly	Multicentre	Maternal history and new born examination	NR	None	
W.H.O.Task Force[43]	Can't tell	Eight European cities	Singleton, uncomplicated pregnancy with live birth	Multicentre	Maternal history	65% D & C, 35% vacuum aspiration	None	Cities were clustered depending upon method of abortion

Table 1. (*Continued*)

Author	Year of study	Place of study	Population	Setting	Exposure assessment	Method of abortion	Confounders adjusted	Remarks
Zhou *et al.*[44]	1980–82	Denmark	Aged 15–44, all primigravida	Multicentre	Medical birth register	92% vacuum aspiration, 7% D & C, <1% had other methods	None	Younger maternal age in abortion cohort
Zhou *et al.*[45]	1995	Denmark	Singleton, uncomplicated pregnancy	Multicentre	National register	92% vacuum aspiration, 7% D & C, <1% had other methods	Maternal age, residence, inter-pregnancy interval, fetal sex	Study groups were younger

BMI, body mass index; D & C, dilatation and curettage; PTB, preterm birth; NR, not reported.

age for individual studies are reported in tables in the Supporting Information.

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 birthweight (6 studies, 6306 participants, WMD 23 g, 95% CI −21, 66 g, I^2=51%,) or mean gestational age (seven studies, 5162 participants, WMD −0.07 week, 95% CI −0.21, 0.07 week, I^2=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, I^2=22%, Table S5) or mean gestational age (3 studies, 2077 participants, WMD 0.01 week, 95% CI −0.23, 0.26 week, I^2=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,[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,[4,11,14,15,17,21,23,29–31,37,38,44] 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,[17,23,28,38,45] OR 1.47, 95% CI 1.24, 1.73; Figure 4), PT births (7 studies,[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.[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.[15,27,33,38] Compared to women with no history

Table 2. Quality assessments of included studies

Author year	Type of study	Selection bias	Exposure assessment bias	Outcome assessment bias	Confounding factor bias	Attrition bias	Analytical bias	Overall risk of bias
Ancel *et al.*[4]	Case–control study	Low	None	None	None	None	Moderate	Moderate
Bracken *et al.*[10]	Cohort study with unmatched concurrent controls	None	None	None	Low	Low	Low	Low
Che *et al.*[11]	Cohort study with unmatched concurrent controls	None	None	None	None	None	Low	Low
Daling and Emanuel[12]	Case–control study	None	Can't tell	Can't tell	Moderate	Low	Moderate	Moderate
Daling and Emanuel[13]	Case–control study	Low	None	None	Moderate	Low	Moderate	Moderate
El-Bastawissi *et al.*[14]	Case–control study	None	None	None	None	None	Low	Low
Frank *et al.*[15]	Cohort study with unmatched concurrent controls	None	None	None	Low	Moderate	Low	Low
Harlap and Davies[16]	Cohort study with unmatched concurrent controls	Low	None	None	Moderate	Moderate	Low	Moderate
Henriet and Kaminski[17]	Cohort study with unmatched concurrent controls	None	None	None	None	Low	Low	Low
Hogue[18]	Cohort study with unmatched concurrent controls	Low	Moderate	None	Moderate	Moderate	Low	Moderate
Koller and Eikhom[19]	Cohort study with unmatched concurrent controls	None	None	None	Moderate	None	Low	Moderate
Lao and Ho[20]	Case–control Study	Low	None	None	Moderate	None	Low	Moderate
Lekea-Karanika[21]	Cohort study with unmatched concurrent controls	Low	None	None	Low	Moderate	Moderate	Moderate
Lekea-Karanika and Tzoumaka-Bakoula[22]	Cohort study with unmatched concurrent controls	Low	None	None	Low	Moderate	Moderate	Moderate
Linn *et al.*[23]	Cohort study with unmatched concurrent controls	Moderate	None	None	None	None	Low	Low
Lopes *et al.*[24]	Case–control study	Low (exposure)	None	None	Moderate	None	Low	Moderate
Lumley[25]	Cohort study with unmatched concurrent controls	None	None	None	Moderate	None	Low	Moderate
Lumley[26]	Cohort study with unmatched concurrent controls	None	None	None	Moderate	None	Low	Moderate
Mandelin and Karjalainen[27]	Cohort study with matched concurrent controls	Low	None	None	Moderate	Low	Low	Moderate

Table 2. (*Continued*)

Author year	Type of study	Selection bias	Exposure assessment bias	Outcome assessment bias	Confounding factor bias	Attrition bias	Analytical bias	Overall risk of bias
Mandelson *et al.*[28]	Case–control study	Low	None	None	None	Low	Low	Low
Martius *et al.*[29]	Cohort study with unmatched concurrent controls	None	None	Low	None	Low	Low	Low
Meirik *et al.*[30]	Case–control study	None	None	None	Low	Low	Low	Low
Meirik and Bergstrom[31]	Case–control study	None	None	None	Low	Low	Low	Low
Meirik and Nygren[32]	Case–control study	None	None	None	Low	Low	None	Low
Obel[33]	Cohort study with matched concurrent controls	None	None	None	Moderate	Moderate	Low	Moderate
Pantelakis *et al.*[34]	Cohort study with unmatched concurrent controls	None	None	None	Moderate	None	Low	Moderate
Papaevangelou *et al.*[35]	Cohort study with unmatched concurrent controls	None	None	None	Moderate	None	Low	Moderate
Park *et al.*[36]	Cohort study with unmatched concurrent controls	None	None	None	Moderate	None	Low	Moderate
Pickering and Forbes[37]	Cohort study with unmatched concurrent controls	None	None	None	None	None	Low	Low
Raatikainen *et al.*[38]	Cohort study with unmatched concurrent controls	Low	None	None	None	None	Low	Low
Roht and Aoyama[39]	Cohort study with unmatched concurrent controls	None	Low	None	Low	Moderate	Low	Moderate
Schoenbaum *et al.*[40]	Cohort study with unmatched concurrent controls	None	None	None	Moderate	Moderate	Low	Moderate
Seidman *et al.*[41]	Cohort study with unmatched concurrent controls	None	Can't tell	None	None	None	Low	Low
Van der Slikke and Treffers[42]	Cohort study with matched concurrent controls and cohort study with unmatched concurrent controls	None	Can't tell	None	Moderate	Low	Low	Moderate
W.H.O.Task Force[43]	Case–control Study	None	None	None	Moderate	Moderate	Low	Moderate
Zhou *et al.*[44]	Cohort study with unmatched concurrent controls	Moderate	Low	Low	Moderate	Low	Low	Moderate
Zhou *et al.*[45]	Cohort study with unmatched concurrent controls	None	None	Low	None	Moderate	Low	Moderate

Table 3. Results of association of induced abortion and LBW/PT/SGA births

Infant status	Results	History of one induced abortion versus no history of induced abortion	History of >1 induced abortions versus no history of induced abortions
LBW	Number of studies	18	5
	Participants	280 529	49 347
	Risk in exposed (%)	6.4	7.9
	Risk in non-exposed (%)	4.9	5.0
	UAOR (95% CI)	1.35 (1.20, 1.52)	1.72 (1.45, 2.04)
	PAR (%)	3.8	N/A
PT	Number of studies	22	7
	Participants	268 379	158 421
	Risk in exposed (%)	8.7	21.8
	Risk in non-exposed (%)	6.8	7.8
	UAOR (95% CI)	1.36 (1.24, 1.50)	1.93 (1.38, 2.71)
	PAR (%)	3.2	N/A
SGA	Number of studies	3	2
	Participants	38 835	35 422
	Risk in exposed (%)	9.8	5.3
	Risk in non-exposed (%)	8.8	8.8
	UAOR (95% CI)	0.87 (0.69, 1.09)	1.06 (0.84, 1.33)

UAOR, unadjusted odds ratio.

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.

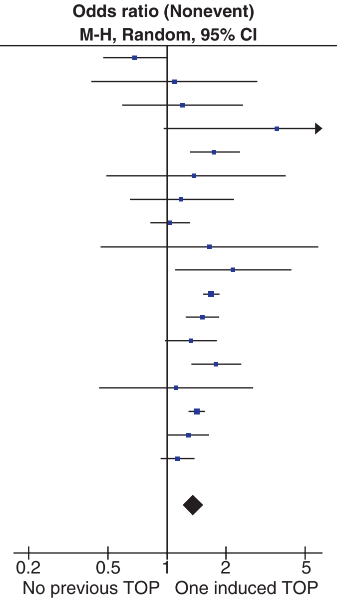
Discussion

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.

Unadjusted estimates

Study or subgroup	No previous induced TOP Events	No previous induced TOP Total	One induced TOP Events	One induced TOP Total	Weight	Odds ratio (Nonevent) M-H, Random, 95% CI	Year
Roht 1974	161	2252	39	779	5.8%	0.68 [0.48, 0.98]	1974
Hogue 1975	38	719	5	87	1.3%	1.09 [0.42, 2.85]	1975
Daling 1977	16	285	18	271	2.3%	1.20 [0.60, 2.40]	1977
Koller 1977	3	121	10	119	0.8%	3.61 [0.97, 13.46]	1977
WHO 1979	93	2157	110	1513	7.2%	1.74 [1.31, 2.31]	1979
Obel 1979	8	217	7	139	1.2%	1.39 [0.49, 3.91]	1979
Schoenbaum 1980	64	1095	14	205	3.0%	1.18 [0.65, 2.15]	1980
Linn 1983	569	8122	97	1342	8.6%	1.03 [0.83, 1.29]	1983
Meirik 1984	4	127	7	139	0.8%	1.63 [0.47, 5.71]	1984
Bracken 1986	22	880	15	286	2.5%	2.16 [1.10, 4.22]	1986
Lumley 1986	6042	111453	679	7759	11.7%	1.67 [1.54, 1.82]	1986
Seidman 1988	817	14857	145	1791	9.6%	1.51 [1.26, 1.82]	1988
Mandelson 1992	85	1941	111	1944	7.1%	1.32 [0.99, 1.77]	1992
Lekea-Karanika 1994	123	3357	94	1487	7.4%	1.77 [1.35, 2.34]	1994
Lao 1998	10	118	11	118	1.5%	1.11 [0.45, 2.72]	1998
Zhou 2000	2271	62360	698	13775	11.7%	1.41 [1.29, 1.54]	2000
Henriet 2001	456	10608	81	1494	8.1%	1.28 [1.00, 1.63]	2001
Raatikainen 2006	1140	24248	125	2364	9.4%	1.13 [0.94, 1.37]	2006
Total (95% CI)		**244917**		**35612**	**100.0%**	**1.35 [1.20, 1.52]**	
Total events	11922		2266				

Heterogeneity: $Tau^2 = 0.03$; $\chi^2 = 53.99$, df = 17 ($P < 0.00001$); $I^2 = 69\%$
Test for overall effect: $Z = 5.05$ ($P < 0.00001$)



Adjusted estimates

Study or subgroup	Log[Odds ratio]	SE	Weight	Odds ratio IV, Random, 95% CI	Year
Meirik 1982	–0.4429	0.387445	5.1%	0.64 [0.30, 1.37]	1982
Linn 1983	–0.07257	0.116865	12.5%	0.93 [0.74, 1.17]	1983
Meirik 1984	–0.04082	0.274111	7.5%	0.96 [0.56, 1.64]	1984
Frank 1985	0.329304	0.269672	7.7%	1.39 [0.82, 2.36]	1985
Mandelson 1992	0.182322	0.130313	12.0%	1.20 [0.93, 1.55]	1992
Lekea-Karanika 1994	0.593327	0.139117	11.8%	1.81 [1.38, 2.38]	1994
Zhou 2000	0.641854	0.092578	13.2%	1.90 [1.58, 2.28]	2000
Henriet 2001	0.09531	0.112712	12.6%	1.10 [0.88, 1.37]	2001
Che 2001	0.530628	0.361496	5.5%	1.70 [0.84, 3.45]	2001
Raatikainen 2006	0.029559	0.127842	12.1%	1.03 [0.80, 1.32]	2006
Total (95% CI)			**100.0%**	**1.24 [1.00, 1.53]**	

Heterogeneity: $Tau^2 = 0.08$; $\chi^2 = 41.71$, df = 19 ($P < 0.00001$); $I^2 = 78\%$
Test for overall effect: $Z = 1.96$ ($P = 0.05$)

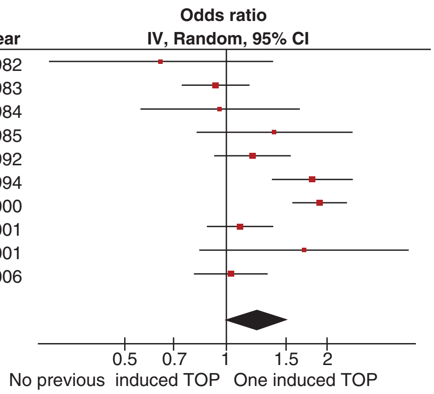


Figure 2. Unadjusted and adjusted estimates of Low birthweight births among women with a history of one previous induced abortion versus no history of induced abortions.

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[18] reported 63% of women denied past history of abortion when checked against hospital records, whereas Kline *et al.*[76] reported only 1.6% of women, both in cases and controls, denied previous abortion.

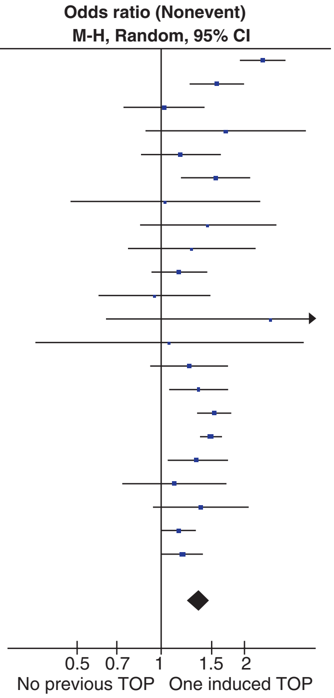
Second, it has been identified that women with a history of I-TOP were unmarried, young and from socio-economically disadvantaged group.[11,15,19,38,40,44,45,72] These confounders differ for different timing of seeking abortion (first or second trimester). Certain studies controlled for confounders, whereas other studies failed to do so (Table 1). Even the confounders controlled in studies varied. As suggested by Peters and Mengersen,[8] 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.

Unadjusted estimates

Study or subgroup	No previous induced TOP Events	No previous induced TOP Total	One induced TOP Events	One induced TOP Total	Weight	Odds ratio (Nonevent) M-H, Random, 95% CI	Year
Pantelakis 1973	261	3271	251	1508	6.9%	2.30 [1.91, 2.77]	1973
Papaevangelou 1973	314	2550	133	731	6.2%	1.58 [1.27, 1.98]	1973
Daling 1975	81	758	83	758	4.4%	1.03 [0.74, 1.42]	1975
Daling 1977	16	285	25	271	1.7%	1.71 [0.89, 3.28]	1977
Van der Slikke 1978	555	3167	53	265	4.6%	1.18 [0.86, 1.61]	1978
WHO 1979	99	1945	109	1407	5.1%	1.57 [1.18, 2.07]	1979
Obel 1979	12	217	16	280	1.3%	1.04 [0.48, 2.24]	1979
Mandelin 1979	29	427	26	269	2.2%	1.47 [0.84, 2.55]	1979
Meirik 1982	25	666	37	776	2.4%	1.28 [0.76, 2.16]	1982
Linn 1983	536	8122	102	1342	6.2%	1.16 [0.93, 1.45]	1983
Meirik 1983	39	622	40	670	2.9%	0.95 [0.60, 1.50]	1983
Meirik 1984	3	127	8	142	0.5%	2.47 [0.64, 9.51]	1984
Park 1984	20	574	4	107	0.7%	1.08 [0.36, 3.21]	1984
Frank 1985	131	1075	70	470	4.6%	1.26 [0.92, 1.72]	1985
Lekea Karanika 1990	199	2984	125	1407	5.9%	1.36 [1.08, 1.72]	1990
Martius 1998	6858	103245	251	2532	7.9%	1.55 [1.35, 1.77]	1998
Zhou 1999	2377	62350	774	1775	8.7%	1.50 [1.38, 1.63]	1999
Henriet 2001	443	10536	83	1487	5.8%	1.35 [1.06, 1.71]	2001
Che 2001	43	1351	48	1356	3.3%	1.12 [0.73, 1.70]	2001
El-Bastawissi 2003	209	521	64	133	3.7%	1.38 [0.94, 2.03]	2003
Ancel 2004	2335	6324	389	964	7.8%	1.16 [1.01, 1.33]	2004
Raatikainen 2006	1503	24248	173	2364	7.3%	1.19 [1.01, 1.41]	2006
Total (95% CI)		**235365**		**33014**	**100.0%**	**1.36 [1.24, 1.50]**	
Total events	16088		2864				

Heterogeneity: $Tau^2 = 0.02$; $\chi^2 = 59.12$, df = 21 ($P < 0.00001$); $I^2 = 64\%$
Test for overall effect: $Z = 6.45$ ($P < 0.00001$)



Adjusted estimates

Study or subgroup	Log[odds ratio]	SE	Weight	Odds ratio IV, Random, 95% CI	Year
Meirik 1982	0.198851	0.364233	2.4%	1.22 [0.60, 2.49]	1982
Linn 1983	0.067659	0.113136	8.7%	1.07 [0.86, 1.34]	1983
Meirik 1983	–0.05129	0.233748	4.6%	0.95 [0.60, 1.50]	1983
Frank 1985	0.122218	0.183201	6.0%	1.13 [0.79, 1.62]	1985
Pickering 1985	0.300105	0.077208	10.2%	1.35 [1.16, 1.57]	1985
Lekea-Karanika 1990	0.307485	0.118715	8.5%	1.36 [1.08, 1.72]	1990
Martius 1998	0.262364	0.046159	11.3%	1.30 [1.19, 1.42]	1998
Zhou 1999	0.636577	0.055117	11.0%	1.89 [1.70, 2.11]	1999
Henriet 2001	0.262364	0.135364	7.8%	1.30 [1.00, 1.69]	2001
Che 2001	0	0.233748	4.6%	1.00 [1.63, 1.58]	2001
El-Bastawissi 2003	0.405465	0.212477	5.1%	1.50 [0.99, 2.27]	2003
Ancel 2004	0.139762	0.075314	10.3%	1.15 [0.99, 1.33]	2004
Raatikainen 2006	0.122218	0.092342	9.6%	1.13 [0.94, 1.35]	2006
Total (95% CI)			**100.0%**	**1.27 [1.12, 1.44]**	

Heterogeneity: $Tau^2 = 0.03$; $\chi^2 = 55.61$, df = 12 ($P < 0.00001$); $I^2 = 78\%$
Test for overall effect: $Z = 3.76$ ($P = 0.0002$)

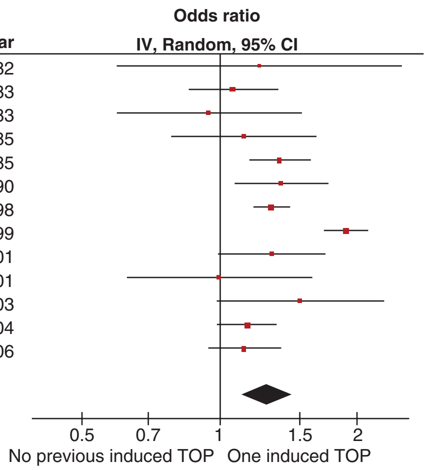


Figure 3. Unadjusted and adjusted estimates of Preterm births among women with a history of one previous induced abortion versus no history of induced abortions.

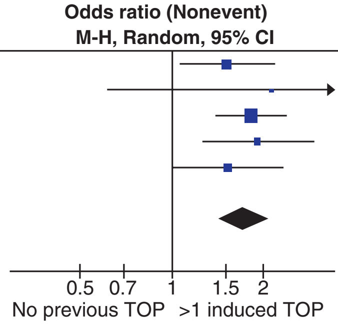
Fourth, the methods used for abortion could vary in different studies. Subgroup analyses of vacuum aspiration and dilatation and curettage revealed a similar risk for LBW with either method. The risk for PT birth was not higher in subgroup analyses; however, only five studies reported outcomes based on the method of I-TOP. With recent changes in the use of medications (misoprostol and mifepristone),[38] laminaria tents[77] 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.

Unadjusted estimates

Study or subgroup	No induced TOP Events	No induced TOP Total	>1 induced TOP Events	>1 induced TOP Total	Weight	Odds ratio (Nonevent) M-H, Random, 95% CI	Year
Linn 1983	569	8122	37	359	23.3%	1.53 [1.07, 2.17]	1983
Bracken 1986	22	880	3	58	1.9%	2.13 [0.62, 7.33]	1986
Mandelson 1992	85	1941	190	2461	41.5%	1.83 [1.40, 2.38]	1992
Henriet 2001	456	10608	25	315	16.3%	1.92 [1.26, 2.92]	2001
Raatikainen 2006	1140	24248	25	355	17.0%	1.54 [1.02, 2.32]	2006
Total (95% CI)		**45799**		**3548**	**100.0%**	**1.72 [1.45, 2.04]**	
Total events	2272		280				

Heterogeneity: Tau^2 = 0.00; χ^2 = 1.32, df = 4 (P < 0.86); I^2 = 0%
Test for overall effect: Z = 6.27 (P < 0.00001)



Adjusted estimates

Study or subgroup	Log[odds ratio]	SE	Weight	Odds ratio IV, Random, 95% CI	Year
Linn 1983	0.223144	0.181135	22.2%	1.25 [0.88, 1.78]	1983
Mandelson 1992	0.405465	0.152509	31.3%	1.50 [1.11, 2.02]	1992
Zhou 2000	0.641854	0.186451	20.9%	1.90 [1.32, 2.74]	2000
Henriet 2001	0.336472	0.239354	12.7%	1.40 [0.88, 2.24]	2001
Raatikainen 2006	0.231112	0.236957	13.0%	1.26 [0.79, 2.00]	2006
Total (95% CI)			**100.0%**	**1.47 [1.24, 1.73]**	

Heterogeneity: Tau^2 = 0.00; χ^2 = 3.18, df = 4 (P = 0.53); I^2 = 0%
Test for overall effect: Z = 4.49 (P < 0.00001)

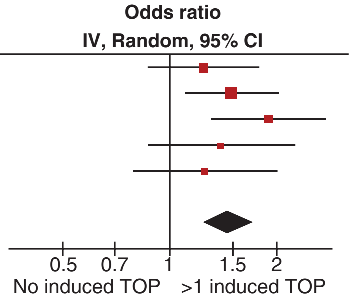


Figure 4. Unadjusted and adjusted estimates of Low birthweight births among women with a history of more than one previous induced abortion versus no history of induced abortions.

Finally, certain studies compared women with a history of I-TOP with women who had never been pregnant[26] 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 carried to full-term.[64]

The results of our review differ from previous reviews;[5,10,64,66] 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.

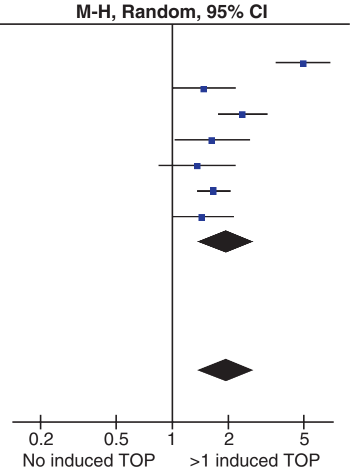
A step further, we would like to mention that this strong association meets several of the criteria suggested by Professor Hill[78] regarding causation such as temporal relationship, biological plausibility, strength of association, dose–response effect (increased risk with increasing number of abortion), 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 socio-economic 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

Unadjusted estimates

Study or subgroup	No induced TOP Events	No induced TOP Total	>1 induced TOP Events	>1 induced TOP Total	Weight	Odds ratio (Nonevent) M-H, Random, 95% CI	Year
Papaevangelou 1973	314	3350	63	186	14.7%	4.95 [3.58, 6.86]	1973
Linn 1983	536	8122	34	359	14.2%	1.48 [1.03, 2.13]	1983
Martius 1998	6858	103245	50	347	15.0%	2.37 [1.75, 3.20]	1998
Henriet 2001	443	10536	21	313	13.0%	1.64 [1.04, 2.58]	2001
El-Bastawissi 2003	209	521	39	82	12.8%	1.35 [0.85, 2.16]	2003
Ancel 2004	2355	6324	215	433	16.1%	1.66 [1.37, 2.02]	2004
Raatikainen 2006	1503	24248	31	355	14.1%	1.45 [1.00, 2.10]	2006
Subtotal (95% CI)		**156346**		**2075**	**100.0%**	**1.93 [1.38, 2.71]**	
Total events	12218		453				
Heterogeneity: $Tau^2 = 0.17$; $\chi^2 = 43.72$, df = 6 ($P < 0.00001$); $I^2 = 86\%$							
Test for overall effect: $Z = 3.81$ ($P < 0.00001$)							
Total (95% CI)		**156346**		**2075**	**100.0%**	**1.93 [1.38, 2.71]**	
Total events	12218		453				
Heterogeneity: $Tau^2 = 0.17$; $\chi^2 = 43.72$, df = 6 ($P < 0.00001$); $I^2 = 86\%$							
Test for overall effect: $Z = 3.81$ ($P = 0.0001$)							



Adjusted estimates

Study or subgroup	Log[odds ratio]	SE	Weight	Odds ratio IV, Random, 95% CI	Year
Linn 1983	0.270027	0.186451	14.9%	1.31 [0.91, 1.89]	1983
Pickering 1985	0.239017	0.310442	9.4%	1.27 [0.69, 2.33]	1985
Zhou 1999	0.978326	0.121875	18.4%	2.66 [2.09, 3.38]	1999
Henriet 2001	0.641854	0.216147	13.4%	1.90 [1.24, 2.90]	2001
El-Bastawissi 2003	0.182322	0.267812	11.0%	1.20 [0.71, 2.03]	2003
Ancel 2004	0.48858	0.111737	18.9%	1.63 [1.31, 2.03]	2004
Raatikainen 2006	0.300105	0.20342	14.0%	1.35 [0.91, 2.01]	2006
Total (95% CI)			**100.0%**	**1.62 [1.27, 2.07]**	
Heterogeneity: $Tau^2 = 0.07$; $\chi^2 = 19.44$, df = 6 ($P = 0.003$); $I^2 = 69\%$					
Test for overall effect: $Z = 3.87$ ($P = 0.0001$)					

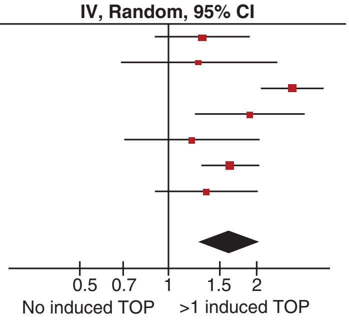


Figure 5. Unadjusted and adjusted estimates of Preterm births among women with a history of more than one previous induced abortion versus no history of induced abortions.

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.[79] 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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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.

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