Abortion and the Risk of Subsequent Preterm Birth

A Systematic Review with Meta-analyses

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OBJECTIVE: To conduct a systematic review and meta-analyses of studies that test the association between induced or spontaneous abortion and subsequent preterm birth.

STUDY DESIGN: International databases were reviewed (1995–2007) using the terms preterm, premature, birth, labor, delivery, abortion, induced abortion, miscarriage *and* spontaneous abortion. *Only studies that met prespecified objective criteria for methodologic design and reporting were included in the meta-analyses.*

RESULTS: Twelve induced and 9 spontaneous abortion studies met inclusion criteria. Common adjusted odds ratios (ORs) for preterm birth following 1 and ≥2 induced abortions were 1.25 (95% confidence interval [95% CI] 1.03–1.48) and 1.51 (95% CI 1.21–1.75), respectively. Four studies provided a common adjusted OR for ≤32 weeks' births of 1.64 (95% CI 1.38–1.91). Meta-regression analysis revealed a previously unrecognized inverse relationship between the ln OR and the control population preterm birth rate, explaining in part the observed heterogeneity among studies. Analysis of spontaneous abortion and subsequent preterm birth revealed a similar common adjusted OR and inverse meta-regression on the control preterm birth rates.

CONCLUSION: Induced and spontaneous abortion are associated with similarly increased ORs for preterm birth in subsequent pregnancies, and they vary inversely with the baseline preterm birth rate, explaining some of the variability among studies. (J Reprod Med 2009; 54:95–108)

Our systematic review with meta-analyses demonstrates that induced and spontaneous abortions are similarly associated with increased ORs for subsequent PTB....

Keywords: abortion, induced; abortion, spontaneous; preterm birth.

Preterm birth (PTB) (delivery at <37 weeks) contributes to infant mortality and childhood morbidity, including chronic lung disease, sensory deficits, cerebral palsy, cognitive impairments and behavioral problems.[1,2] Despite improvements in maternal nutrition, access to prenatal care, early identification of preterm labor and treatment of maternal infections, PTB rates have risen in the United States, from 9.4% in 1981 to 12.8%* in 2006, for a 36% in-

*National Center for Health Statistics preliminary data for 2006.

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crease.[3-7] While much of this increase is attributable to the rise in multiple pregnancies as the result of assisted reproductive technologies and advanced maternal age, singleton PTB rates have risen as well, primarily due to an increase in medically indicated preterm deliveries.[8-11]

Some population-based studies have raised concerns that induced abortions contribute to PTBs.[12-16] However, in 1979 the World Health Organization concluded that vacuum aspiration of the uterus had no observed effect on subsequent PTB.[17] In 1982 Hogue et al conducted a narrative review and concluded that the incidence of shortened gestation after 1 induced abortion was similar to that in first pregnancies.[18] Because 46% of the 1.29 million abortions performed annually in the United States are repeat procedures, whether multiple induced abortions increase the risk of subsequent PTB remains an important unanswered public health question.[19,20] Likewise, because >50% of abortions in the United States are performed on women ≤24 years of age, who are likely to become pregnant again, the question of whether a single abortion affects subsequent PTB also has substantial public health implications.[19]

Prior spontaneous abortion was associated with PTB in some studies.[21,22] Spontaneous abortions are caused by a variety of factors, such as chromosomal abnormalities, prothrombotic states, uterine anomalies, infections, endocrine and immune conditions, which bear no obvious relationship to induced abortions except that both result in a truncated gestation.[23]

We report a systematic review and meta-analyses of recent studies that investigated whether 1 or more induced abortions increases a woman's risk of subsequent PTB. A similar review and meta-analyses were conducted for spontaneous abortion.

Materials and Methods

Search Strategy

We conducted a systematic review of the literature using methodology described by Egger et al to identify epidemiologic studies that investigated the association of induced or spontaneous abortions and subsequent PTB.[24] The Egger methodology begins with a detailed, written study protocol to address a well-formulated review question, followed by a comprehensive search for studies that address the research question. Identified studies are scrutinized for methodologic quality by blinded reviewers using prespecified inclusion and exclusion criteria. Data extraction is conducted in duplicate by independent investigators. Analyses of observational studies focus on sources of heterogeneity between studies and sources of potential bias and confounders. Smaller studies that devote more attention to characterizing the exposure of interest and confounding variables are generally preferred to studies that collect cruder data on a larger number of participants. Systematic reviews present data graphically and are reported such that the review can be reproduced.

In our systematic review the principal investigator (H.S.) worked with a medical reference librarian to identify relevant studies. PubMed, Science Citation Index Expanded, EMBASE and Scopus databases were searched for articles on induced or spontaneous abortion published between January 1, 1995, and October 15, 2007, a period when vacuum aspiration was the predominantly practiced procedure, using Medical Subject Headings terms *preterm, premature, birth, labor, delivery, abortion, induced abortion, miscarriage,* and *spontaneous abortions*. Because null associations are often excluded from titles and abstracts, when a title or abstract suggested that a study might report PTB risk factors, the entire article was examined to determine if the study analyzed the association between induced or spontaneous abortion and PTB. Bibliographies of articles were reviewed to identify studies missed by the database searches. An expert informant, John Thorp, M.D., author of a 2005 narrative review on complications of induced abortion, was consulted regarding any published or unpublished studies missed by the principal investigator's search.[25] Articles published in non-English languages with abstracts that suggested that the studies might be relevant were translated by bilingual faculty with either an M.D. or Ph.D. degree in the language of publication.

Inclusion and Exclusion Criteria

Cohort and case-control studies, but not case reports, case series, or cross-sectional surveys, which lack controls, were reviewed. Articles that failed to distinguish between spontaneous and induced abortions or that analyzed both abortion types together were excluded. Prior to the review the authors agreed to exclude studies that failed to specify study objectives, study population, sampling method, inclusion and exclusion criteria, use of appropriate controls, geographic location, study dates or appropriate statistical analysis. To be included in the meta-analysis, studies also had to address possible confounders by using either matching or stratification in the study design or multivariate analysis or stratification in the statistical analysis. Although studies had to adjust for confounders to be included, we computed common unadjusted outcomes as well as the adjusted outcomes because studies varied in the confounders they controlled for.

Data Extraction and Quality Assessment

Data extraction was conducted independently using a 2-step process. Initially 2 reviewers (F.M. and T.C.) were given only the methods section of 31 articles addressing induced abortion and 26 addressing spontaneous abortion, with journal of publication and authors' names removed, and were asked to evaluate study design objectively using Tooth's checklist of quality indicators for observational research.[26] Checklist criteria address recruitment, data collection, biases, data analysis and descriptive issues relevant to study rationale, study population and generalizability, factors that are threats to the internal and external validity of observational studies. The masked reviewers were subsequently given the entire articles, again with journal and authorship information obscured. To test for masking, reviewers were asked if they recognized each paper. The third reviewer (H.S.), who had compiled the articles, was not masked. For critiques lacking unanimity, each author discussed his or her rationale for inclusion or exclusion. After discussion, if 2 investigators concluded that a study should be included, the paper was retained and incorporated into the statistical analysis.

Statistical Analysis

The linear mixed model using approximate likelihood was applied in these meta-analyses to estimate the effects of induced and spontaneous abortion on the incidence of PTB.[27] The SAS 9.1 MIXED procedure (Cary, North Carolina) was used to fit a random effects model to obtain maximum likelihood estimates of the mean log-odds ratio and the between-study variance, with 95% profile likelihood-based CIs computed for these 2 statistics.[28] A random effects model was chosen because we assumed that the effect of induced abortions performed by variably skilled providers in ethnically diverse populations in multiple geographic areas would vary around an overall average treatment effect. Graphic displays of the results from individual studies plotted using a common scale—i.e., forest plots—were constructed showing the mean OR with 95% CI and the common OR estimates.

For cohort studies, meta-regression was performed to examine the relationship of log-odds ratio for PTB with incidence of PTB in the no-abortion cohort. This was also done by linear mixed model using approximate likelihood, as described above.[27]

To test for publication bias, a simple weighted linear regression with ln (OR) as the dependent variable and the inverse of the total sample size as the independent variable was used. This minor modification of Macaskill's test,[29] with the total sample size as the independent variable, was proposed by Peters et al[30] as an alternative to Egger's regression test.[31] The Meta-analysis of Observational Studies in Epidemiology group checklist and the Cochrane Collaboration guidelines were used in drafting this manuscript.[32,33]

Results

Search Results

We screened 7,891 titles, 349 abstracts and 130 articles. For induced abortion, 31 papers were identified, which report 30 studies that met criteria for review.[12-15,34-60] For spontaneous abortion, 26 papers met criteria for review.[13,14,21-23,36,37,39-43,46,48-50,54-57,59-64] None of the reviewed studies were identified by bibliography review.

Quality Assessment

Among the 30 studies on induced abortion, we unanimously agreed to include 10 and exclude 10 based on our independent checklist assessments. After discussion, the consensus was that 2 additional studies should be included, while the remaining 8 should be excluded. Among the 26 articles that investigated spontaneous abortion, initially we agreed to include 8 and exclude 16. After discussion, the remaining 2 papers were excluded. (See Tables I and II in the Appendix for a summary of excluded studies. Table III in the Appendix provides the data sources for the studies included in the meta-analyses.)

Qualitative Findings

Among the 30 induced abortion studies, 17 were conducted in Europe, 6 in Asia, 3 each in North America and Africa, and 1 in Australia. Individual study populations ranged from 206 to 456,890 subjects. Among the studies included in the meta-analysis, 8 were cohort studies, and 4 were case-control (Table I). Characteristics of the studies

Table I *Studies Included in the Meta-analysis of Induced Abortion*

Study	Design	Country	n	Dose response[a]	Confounders controlled for
Martius et al (1998)	Cohort	Germany	106,345	Yes	Age, occupation, parity, previous adverse pregnancy outcomes, medical and surgical risk factors
Zhou et al (1999)	Cohort	Denmark	61,753	No	Age, residence, gravidity, previous adverse pregnancy outcomes, interpregnany interval, number of previous preterm births
Doyle et al (2000)	Cohort	Taiwan	6,485	No	Parental education, parity, maternal age, previous spontaneous abortions, prior stillbirths, smoking, VDRL, maternal hypertension, antepartum hemorrhage, prepregnancy weight, maternal height
Foix-l'Hélias et al (2001)[b]	Cohort	France	13,318	NA	Age, parity, previous adverse pregnancy outcomes, employment, marital status, education, nationality, smoking, prepregnancy weight
Henriet et al (2001)	Cohort	France	12,336	Yes	Age, parity, previous adverse pregnancy outcomes, prepregnancy weight, marital status, education, employment, nationality, smoking, antenatal care
El-Bastawissi et al (2003)	Case-control	United States	736	No	Age, parity, Medicaid payment status, race, smoking
Ancel et al (2005)	Case-control	Multiple countries[c]	7,719	Yes	Age, nulliparity, marital status, social class, previous preterm birth, smoking
Nguyen et al (2005)	Cohort	Vietnam	1,709	No	Age, income, maternal height, weight gain, prenatal care, vaginal bleeding < 20 weeks' gestation
Moreau et al (2005)[d]	Case-control	France	2,837	Yes	Age, parity, previous preterm births, marital status, education, employment, prepregnancy weight, smoking
Raatikainen et al (2006)	Cohort	Finland	26,976	No	Age, primiparity, previous adverse pregnancy outcomes, marital status, education, employment, smoking, alcohol consumption, medical and surgical risk factors
Smith et al (2006)	Cohort	Scotland	84,391	Yes	Age, marital status, smoking, body mass index, socioeconomic status, previous miscarriages
Selo-Ojeme et al (2006)	Case-control	United Kingdom	206	No	Previous preterm birth, short interpregnancy interval, early pregnancy bleeding, prelabor spontaneous rupture of membranes

NA = not available.
[a]Dose response defined as OR for ≥2 induced abortions greater than for 1 induced abortion.
[b]Data from 1995, but not 1981, included in the meta-analysis.
[c]Germany, Finland, Scotland, Sweden, Italy, Czech Republic, Slovenia, Romania, Russia and Hungary.
[d]Burguet et al (2004) also reported data from this study.

included in the meta-analysis of spontaneous abortion are shown in Table II. All of the studies included in the meta-analyses for induced and spontaneous abortion restricted their analyses to singleton births.

Quantitative Findings for Induced Abortion

Induced abortion was associated with an increased risk of subsequent PTB as indicated by both crude and variably adjusted ORs (Figure 1), which in fact were similar. Moreover, common ORs for case-control studies were similar to common ORs for cohort studies. The common adjusted ORs for PTB following 1, ≥1 and ≥2 induced abortions were 1.25 (95% CI 1.03–1.48), 1.32 (95% CI 1.11–1.53) and 1.51 (95% CI 1.21–1.75), respectively, suggesting in-

Table II *Studies Included in the Meta-analysis of Spontaneous Abortion*

Study	Design	Country	n	Confounders controlled for
Basso et al (1998)	Cohort	Denmark	55,201	Age, social status, interpregnancy interval
Martius et al (1998)	Cohort	Germany	106,345	Age, occupation, parity, previous adverse pregnancy outcomes, medical and surgical risk factors
Doyle et al (2000)	Cohort	Taiwan	6,485	Parental education, parity, maternal age, previous induced abortions, prior stillbirths, smoking, VDRL, maternal hypertension, antepartum hemorrhage, prepregnancy weight, maternal height
El-Bastawissi et al (2003)	Case-control	United States	736	Age, parity, Medicaid payment status, race, smoking
Buchmayer et al (2004)	Cohort	Sweden	601,883	Age, smoking, marital status, nationality, birth year
Nguyen et al (2004)	Cohort	Vietnam	1,709	Age, income, maternal height, weight gain, prenatal care
Heaman et al (2005)	Case-control	Canada	684	Age, previous adverse pregnancy outcomes, marital status, education, height, weight gain, smoking, prenatal care, physical abuse, perceived stress, medical risk factors
Selo-Ojeme et al (2006)	Case-control	United Kingdom	206	Previous preterm birth, short interpregnancy interval, early pregnancy bleeding, prelabor spontaneous rupture of membranes
Smith et al (2006)	Cohort	Scotland	84,391	Age, marital status, smoking, body mass index, socioeconomic status, previous miscarriages

creased risk of PTB with multiple induced abortions. Four studies provided data for more marked PTB, variably defined as birth at <28 to ≤ 32 weeks, which resulted in a common adjusted OR of 1.64 (95% CI 1.38–1.91).

The test for heterogeneity among the 12 studies demonstrated that all studies were not homogeneous. Importantly, meta-regression analysis of 8 cohort studies revealed an inverse relationship between ln OR and the rate of PTB in the control population; i.e., studies in populations with lower baseline preterm birth rates had higher ORs for PTB following induced abortion than did studies in populations with higher PTB rates (Figure 2).

We excluded from the analysis a study by Che et al[58] because the reported data were suspect, with 54.2% of the infants in the control cohort male, which suggested the likelihood of unreported abortions of female fetuses or unreported dropouts in the reference group. Because exclusion of this study was not based on failure to meet 1 of our prespecified inclusion criteria, we conducted a sensitivity analysis with the study included. The common ORs varied little whether the Che study was included or excluded; e.g., the common unadjusted OR for ≥ 1 induced abortion was 1.31 (95% CI 1.13–1.48) with inclusion vs.s 1.32 (95% CI 1.13–1.50) with exclusion.

Quantitative Findings for Spontaneous Abortion

Nine studies on spontaneous abortion met methodologic criteria for inclusion in a meta-analysis. Data were available from only 8 studies for calculating the common unadjusted OR and from 7 studies for calculating the common adjusted OR. Two studies reported that previous spontaneous abortion was not associated with PTB but did not provide the OR and 95% CI.[14,59] The common adjusted OR for PTB after 1 previous spontaneous abortion was 1.43 (95% CI 1.05–1.66). The common adjusted OR for PTB after >1 spontaneous abortion was 2.27 (95% CI 1.98–2.81) (Figure 3). As we found for induced abortion, meta-regression analysis revealed an inverse relationship between the ln OR and the baseline PTB rate for studies of PTB following 1 spontaneous abortion (Figure 2).

Discussion

Our meta-analyses indicate that there is an increased risk of PTB after either spontaneous or induced abortion in both case-control and cohort studies. Unadjusted and adjusted outcomes yield similar ORs for subsequent PTB following 1 or more induced abortions, suggesting that the various potential confounding variables used for adjustment in those studies do not have much effect on the outcome. Adjusted OR for PTB after >1 spontaneous abortion is greater than the adjusted OR for PTB after only 1 spontaneous abortion, suggesting increased risk after multiple spontaneous abortions.

Moreover, the risk of PTB following 1 or more induced abortions (adjusted OR 1.32 [1.11, 1.53]) is

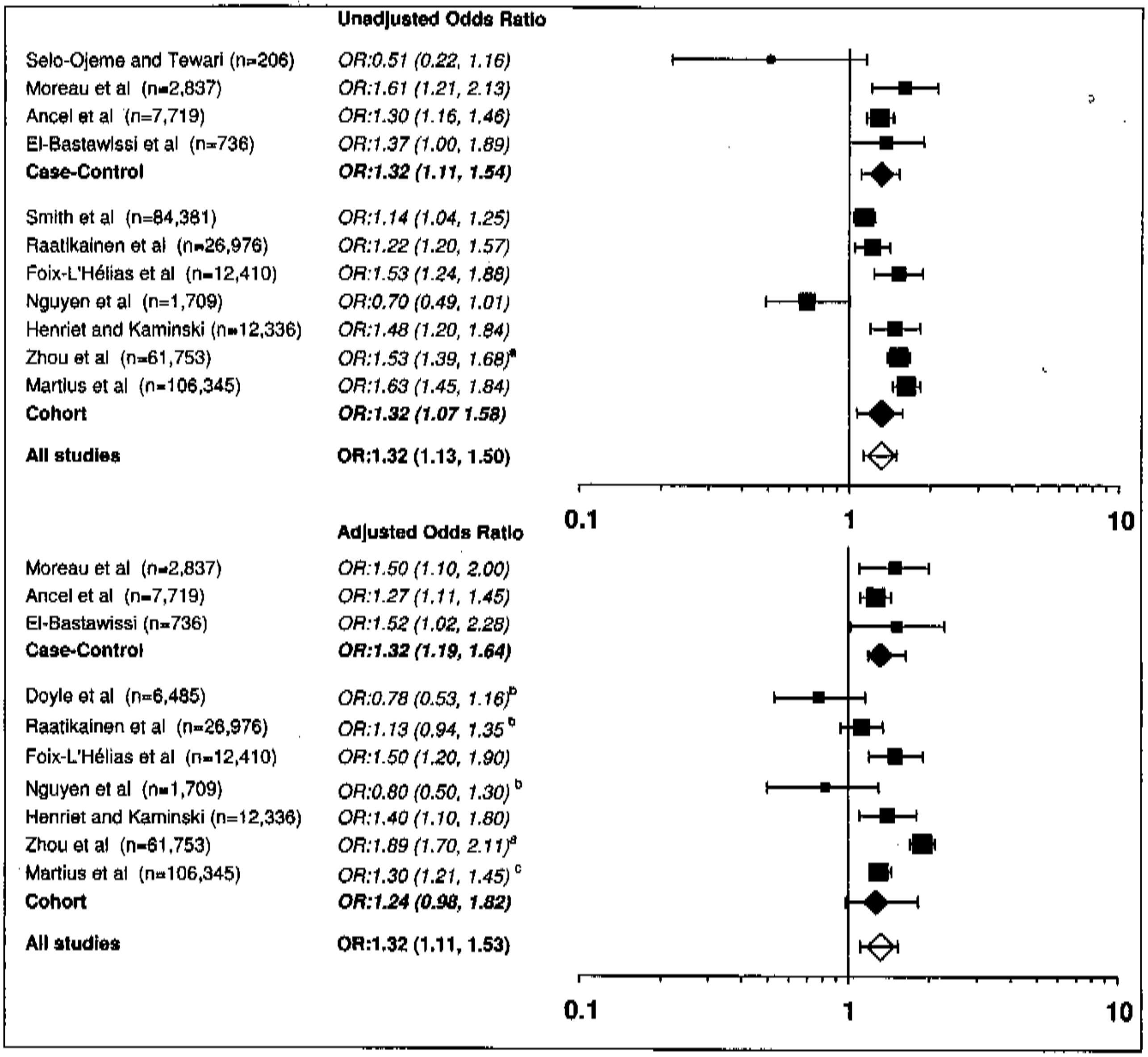

Figure 1 Forest plots for unadjusted and adjusted ORs for preterm birth following ≥1 induced abortion. [a]Unadjusted OR was computed for women on second gravida (n=52,156; 11,394 in abortion cohort and 40,758 in control cohort), and adjusted OR is reported for women with 1 previous induced abortion (n=12,972) vs. no previous induced abortion (n=46,026). [b]Adjusted OR is reported for women with 1 previous induced abortion vs. no previous induced abortion for Doyle et al (n=1,572 with 1 abortion and n=4,234 no abortion), Raatikainen et al (n=2,364 with 1 abortion and n=24,248 no abortion), and Nguyen et al (n=281 with 1 abortion and n=1,274 no abortion). [c]Adjusted OR is per 1 increase in number of previous induced abortions.

similar to the risk of PTB following 1 spontaneous abortion (adjusted OR 1.43 [1.05, 1.66]. Our interpretation of these findings is that early termination of a pregnancy, whether spontaneous or induced, incurs a modest risk of PTB in a subsequent pregnancy. Interruption of pregnancy may expand the "physiological regression hypothesis" that was constructed to explain the effect of interpregnancy interval on preterm birth.[65]

Finally, the meta-regression analyses for both types of abortion cohort studies reveal that the adjusted OR for subsequent PTB is related to the PTB rate in the control population, an important factor that explains some of the difference in outcomes of individual studies. This observation, which has not been previously reported, suggests that modest risk factors for preterm birth may be obscured in populations with higher preterm birth rates.

We limited our systematic review to publications between 1995 and 2007 for 3 reasons. First, studies published in this interval collected data during a period when vacuum aspiration was the predominantly used abortion procedure in the United States, Western Europe and elsewhere.[58,66-68] Some previous reviews conclude that dilatation and curettage, but not vacuum aspiration, increased the risk of PTB,[17,18,66] and more recent data similarly suggest that vacuum aspiration is associated with a lower risk of subsequent preterm birth than other procedures.[15] Vacuum aspiration was the predominantly used procedure among all studies in our meta-analysis. Second, studies in this era have reported outcomes 1–2 decades after legalization of elective abortion,[20] and thus we speculated that these studies might have less underreporting of prior abortions than older studies. Last, newer studies more often attempt to control for confounders using multivariate analysis. Our study protocol excluded studies that did not differentiate between induced and spontaneous abortions because induced and spontaneous abortions differ in social and medical risk factors,[12,19,53] and adjustments for these differences may not have been made.

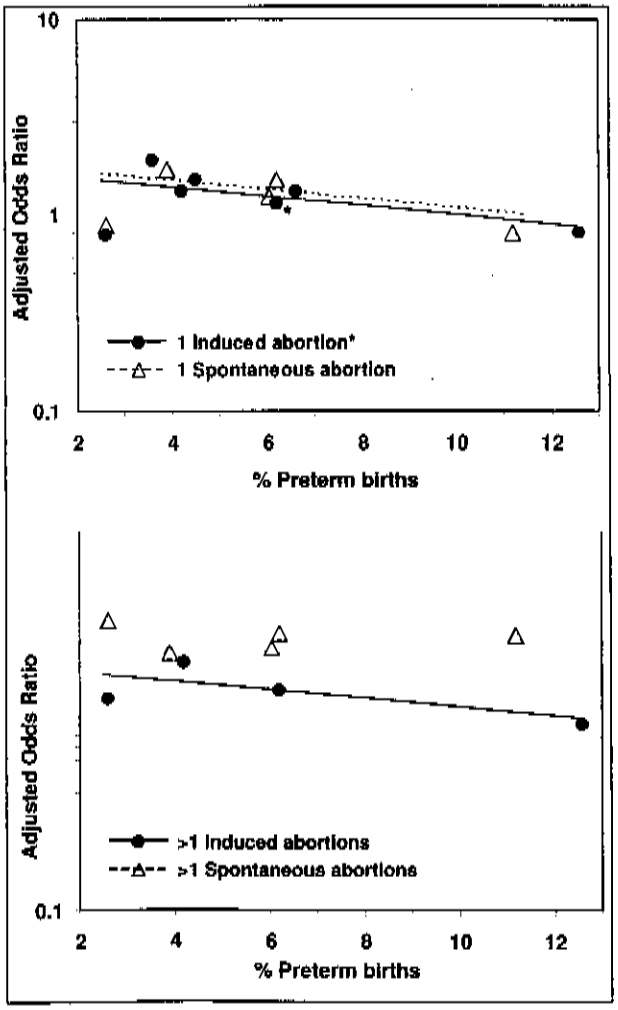

Figure 2 Meta-regression of adjusted ORs on PTB rate in control cohort after 1 (top) and >1 (bottom) induced or spontaneous abortion. *Eight cohort studies are depicted in the graph for induced abortion; 2 points overlap.

Biologically plausible hypotheses proposed for PTB may also be pathophysiologic mechanisms leading to preterm delivery following pregnancy termination by either induced or spontaneous abortion.[4,10,18,69,70] Women who undergo elective abortions have more acute and chronic psychosocial stress resulting from poverty, unsafe neighborhoods, lack of partner and social supports, domestic violence or racism, which could activate the maternal or fetal hypothalamic-pituitary-adrenal (HPA) axis.[12,53,71] Induced abortion may be a marker for these life stressors. Conversely, induced or spontaneous abortions per se may result in stress,[72] activating the HPA pathway in subsequent pregnancies. Surgical procedures, such as vacuum aspiration or dilatation and curettage after miscarriage, might result in cervical trauma and later cervical incompetence.[18] These procedures also may alter cervicovaginal flora. In support of an infectious etiology, Krohn et al found that women who had induced abortions were 4 times more likely to have intraamniotic infections in subsequent pregnancies.[73] Late pregnancy bleeding and placenta previa are increased following induced abortion, implicating hemorrhage as a mechanism leading to PTB in some women.[35,74] Abortions may contribute to nutritional deficiencies, such a low maternal cholesterol, which are associated with preterm birth.[65,75] Last, an increase in medically indicated preterm deliveries following both spontaneous abortion and multiple induced abortions has been reported.[48,51]

For a public health perspective, the effect of smoking during pregnancy may be compared. A meta-analysis of 22 prospective studies of cigarette

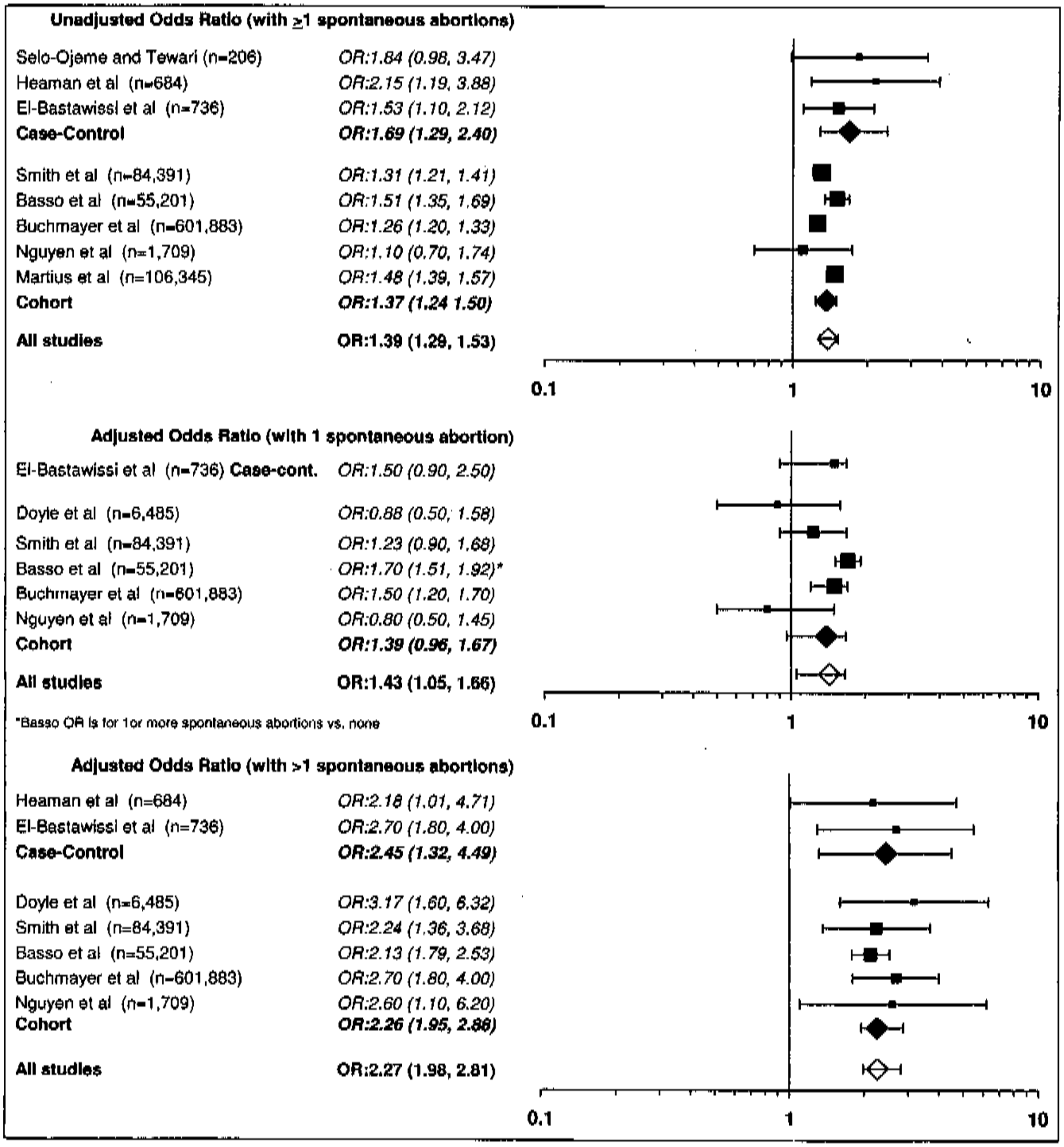

Figure 3 Forest plots for unadjusted and adjusted ORs for PTB following spontaneous abortion.

smoking during pregnancy found smoking increases the risk of PTB 1.27-fold (CI 1.21–1.33) and heavy smoking—i.e., ≥1 pack/d—1.31-fold (CI 1.19–1.45).[76] More pregnant women in the United States have had a prior induced or spontaneous abortion than smoke heavily during pregnancy, and the ORs for abortions as a predictor of PTB are similar to the OR for smoking.

A narrative review of the English-language literature linking induced abortion to subsequent PTB reports an increase in early PTB of 31.5% following induced abortion.[77] Those authors estimated an excess of >22,000 early PTBs and an annual excess cost of > $1.2 billion in initial neonatal hospital costs as a consequence of induced abortion.

Our analyses of the world literature indicate that prior induced and spontaneous abortions are associated with an increased risk of PTB. Such associations may be causal or due to chance, bias or confounding variables. Based on the power of the studies reviewed, chance is an unlikely explanation for the observed associations. Bias and/or confounding variables, however, are possible explanations. Low socioeconomic status, higher gravidity, high-risk sexual behaviors, smoking and illicit drug use, prior adverse pregnancy outcomes, being single with poor social support, and black race are more common among women with prior induced abortions than controls.[12,19,53] Women who have had spontaneous abortions, similarly, differ in medical risk factors.[73] If future studies find that induced abortions are causally related to preterm delivery, public health efforts should be directed to educating women about these risks, and alternative forms of birth control should be more aggressively promoted.

Limitations

This analysis has limitations. Among the induced abortion studies reviewed, 29 relied upon maternal recall, and only 1 used provider records for abortion data.[15] Studies have consistently demonstrated underreporting of induced abortions.[78,79] In the 1995 U.S. National Survey of Family Growth, Fu et al estimated that only 6 of every 10 prior abortions were reported.[79] In France the annual incidence of induced abortion is 6.9 per 1,000 women based on self-reports but 15 per 1,000 based on national statistics.[78] Nondifferential underreporting of abortions skews any association with PTB towards the null. However, 3 studies included in our meta-analysis obtained data in the postpartum period and, thus, potentially could have differential reporting of abortion, which could skew the observed association in the opposite direction.[12,45,53]

Our meta-analyses are by necessity limited to observational studies, which vary in their study designs. For example, the study by Zhou et al[15] included all primigravidas in Denmark from 1980 to 1982, and all subsequent deliveries in the abortion or control cohorts through 1994 were reviewed for PTB. The study by Foix-l'Hélias, in contrast, recorded all births in France over a 1-week period in February 1995 and thus addressed only 1 subsequent pregnancy per subject.[45] For the studies on spontaneous abortions, none provided data on the medical or surgical management.

Recall, selection and publication biases, as well as a cohort effect, could affect our results. However, our analysis failed to detect publication bias. (See Figure 1 in the Appendix.) Another limitation is the fact that no checklists for observational studies, including the Tooth checklist, which we used, have been validated.[80] Furthermore, failure of the studies in the meta-analyses to adjust for the same covariates (maternal age was the only covariate universally controlled for), to conduct subtype analyses of spontaneous vs. medically induced preterm delivery and to restrict subjects exclusively to those who had undergone vacuum aspiration or to terminations during a defined period of gestation limit our study's conclusions. None of the studies investigated periodontal disease, which has recently been shown to be a significant risk factor for PTB.[81] Last, Hogue et al have argued that parity rather than gravidity should be controlled for in studies investigating PTB.[18] Among the 12 studies in our meta-analysis of the induced abortion studies, 8 controlled for parity and 1 for gravidity, and 3 did not control for either.

The results of our study are generalizable only to developed countries where abortion is legal and vacuum aspiration is routinely used.

Interpretation

Our systematic review with meta-analyses demonstrates that induced and spontaneous abortions are similarly associated with increased ORs for subsequent PTB and that these associations vary inversely with the baseline rate of PTB in the populations studied, a relationship not previously recognized.

Potential Conflicts of Interest

None of the authors have financial or other conflicts of interest other than the potential conflicts from their respective views of induced abortion. In this regard, 2 of the authors oppose induced abortion, and 2 do not.

Appendix

Table I *Studies Excluded from the Meta-analysis of Induced Abortion*

Study	Design	Country	n	Association Induced AB with PTB	Analysis	Principal reason(s) for exclusion
Kristensen (1995)	Cohort	Denmark	51,851	NA	Univariate	No OR or analysis relative to term birth cohort given.
Lang (1996)	Cohort	United States	9,490	Yes	Multivariate	Preterm labor rather than PTB used as end point. No. who delivered preterm not given.
Velonakis (1997)	Cohort	France	2,040	No	Multivariate	Method of sampling not described.
Lumley (1998)	Cohort	Australia	456,890	Yes	Univariate	No confounders examined.
Nondonfaz (1998)	Cohort	Belgium	778	No	Univariate	Method of sampling not defined.
Lao (1998)	Case-control	China	236	No	Univariate	Preterm labor rather than PTB used as end point. No. who delivered preterm not given.
Andriamady (1999)	Case-control	Madagascar	7,717	NA	Univariate	Only maternal age was compared between cases and controls. Report is essentially a case series.
Che (2001)	Cohort	China	2,953	No	Multivariate	Dataset is suspect due to 54.2% male infants in the reference (nonabortion) cohort, suggesting the likelihood of unreported abortions of female fetuses or unreported dropouts in the reference group.*
Monaghan (2001)	Cohort	Ukraine	3,023	No	Multivariate	Large amount of missing data. Preterm birth and spontaneous abortion redefined retrospectively.
Carlini (2002)	Case-control	Italy	1,508	No	Multivariate	Method of case selection not described.
Balaka et al (2003)	Case-control	Togo	558	Yes	Univariate	Did not define sampling method.
Sun (2003)	Cohort	China	2,953	Yes	Multivariate	Same dataset as Che et al.
Ezechi (2003)	Case-control	Nigeria	309	Unclear	Multivariate	Several inconsistencies noted. Not prospective as stated. Twins not excluded.
Chen (2004)	Cohort	China	14,656	No	Multivariate	Method of sampling not described. No live births <33 weeks' gestation suspect. Unexplained cesarean section rates.
Grjibovski (2005)	Cohort	Russia	1,103	No	Univariate	No adjustment for confounders. "Previous PTB . . . poorly recorded in medical files."
Coleman (2005)	Cohort	United States	1,020	Yes	Multivariate	Large amount of missing data.
Kyrklund-Blomberg (2005)	Case-control	Sweden	490	Yes	Univariate	No adjustment for confounders.
Poikkeus (2006)	Case-control	Finland	628	No	Multivariate	Study enrolled only assisted reproductive patients, an a priori different population.

AB = abortion, NA = not available.
*The likelihood that 54.2% of the infants from 3,335 births would be male, if due to chance alone, is <0.001.

Table II *Studies Excluded from Meta-analysis of Spontaneous Abortion*

Study	Design	Country	n	Association spontaneous AB with PTB	Analysis	Principal reason(s) for exclusion
Fourn (1995)	Case-control	Republic of Benin	2,155	No	Multivariate	Cases and controls were improperly assembled.
Kristensen (1995)	Cohort	Denmark	51,851	NA	Univariate	No OR or analysis relative to term birth cohort given.
Lang (1996)	Cohort	United States	9,490	NA	Multivariate	Preterm labor rather than PTB used as end point. No. who delivered preterm not given.
Velonakis (1997)	Cohort	France	2,040	No	Multivariate	Method of sampling not described.
Lumley (1998)	Cohort	Australia	456,890	Yes	Univariate	No confounders examined.
Nondonfaz (1998)	Cohort	Belgium	778	No	Univariate	Method of sampling not defined.
Jivraj (2001)	Case-control	United Kingdom	24,861	Yes	Univariate	Limited statistical analysis. Medical records not available for 9% of cases. Cases consisted of women with history of ≥3 spontaneous abortions.
Monahan (2001)	Cohort	Ukraine	3,023	No	Multivariate	Large amount of missing data. PTB and spontaneous abortion redefined retrospectively.
Carlini (2001)	Case-control	Italy	1,508	No	Multivariate	Method of case selection not described.
Ezechi (2003)	Case-control	Nigeria	309	Yes	Multivariate	Several inconsistencies noted. Not prospective as stated. Twins not excluded.
Burguet (2004)	Case-control	France	1,431	Yes	Univariate	No adjusted OR for a multivariate regression for PTB as outcome and spontaneous abortion as predictor variable
Kyrklund-Blomberg (2005)	Case-control	Sweden	590	No	Univariate	No adjusted OR for a multivariate regression for PTB as outcome and spontaneous abortion as predictor variable
Grjibovski (2005)	Cohort	Russia	1,103	No		"Previous preterm birth and weight gain . . . were poorly recorded in the medical files."
Coleman (2005)	Cohort	United States	1,020	Yes	Multivariate	Large amount of missing data.
Kim (2005)	Cohort	Korea	2,645	Yes	Multivariate	Unable to determine how cohort was formed.
Poikkeus (2006)	Case-control	Finland	628	No	Multivariate	Study enrolled only assisted reproductive patients, an a priori different population.
Kashanian (2006)	Cohort	Iran	300	No	Univariate	No adjusted OR for a multivariate regression for PTB as outcome and spontaneous abortion as predictor variable.

AB = abortion, NA = not available.

Table III *Data Sources of Induced and Spontaneous Abortion Studies*

Induced abortion studies	Data source
1. Martius et al (1998)	Bavarian Perinatal survey
2. Zhou et al (1999)	Danish National Registries, Medical Birth Registry, Hospital Discharge Registry and the Induced Abortion Registry
3. Doyle et al (2000)	Taipei Municipal Maternal and Child Hospital records
4. Foix-l'Hélias et al (2001)	All public and private maternity units in France
5. Henriet et al (2001)	All public and private maternity units in France
6. El-Bastawissi et al (2003)	Health care provider network of Swedish Medical Center
7. Ancel et al (2005)	EUROPOP study, surveys completed in 60 maternity units from 17 European countries
8. Nguyen et al (2005)	Hanoi Obstetrics and Gynecology Hospital records
9. Moreau et al (2005)	EPIPAGE study, all maternity wards in 9 French regions
10. Raatikainen et al (2006)	Kupio University Hospital records
11. Smith et al (2006)	Scottish Morbidity Record, Scottish Stillbirth and Infant Death Enquiry registry
12. Selo-Ojeme et al (2006)	Chase Farm Hospital records
Spontaneous abortion studies	
1. Basso et al (1998)	Medical Birth Registry of Denmark, Danish National Registry of Patients, Fertility Database
2. Martius et al (1998)	Bavarian Perinatal survey
3. Doyle et al (2000)	Taipei Municipal Maternal and Child Hospital records
4. El-Bastawissi et al (2003)	Health care provider network of Swedish Medical Center
5. Buchmayer et al (2004)	Swedish Medical Birth Register, In-Patient Register of the national Board of Health and Welfare
6. Nguyen et al (2004)	Hanoi Obstetrics and Gynecology Hospital records
7. Hearnan et al (2005)	Hospital records of 2 tertiary care hospitals in Winnipeg, Manitoba, Canada
8. Selo-Ojeme et al (2006)	Chase Farm Hospital records
9. Smith et al (2006)	Scottish Morbidity Record, Scottish Stillbirth and Infant Death Enquiry registry

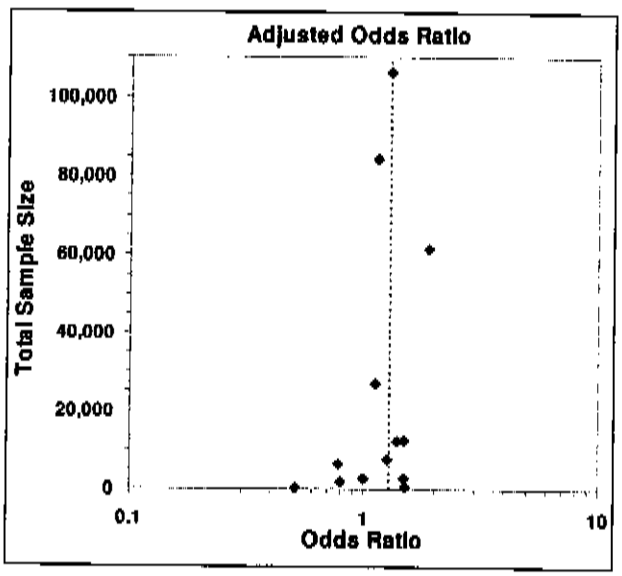

Figure 1 Funnel plot of OR with sample size on the Y-axis. To test for publication bias, a simple weighted linear regression with ln (OR) as the dependent variable and the inverse of the total sample size as the independent variable was used. Applying this analysis on the 13 studies, the regression of the adjusted ln (OR) on the inverse of the total sample size for the 9 studies showed no significant result ($p = 0.44$), suggesting no publication bias. For 2 studies where the adjusted OR was not available, the unadjusted OR was used in the analysis.

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