ProLife OB|GYNS
AAPLOG American Association of Pro-life Obstetricians & Gynecologists

PRACTICE BULLETIN

EVIDENCE DIRECTING PRO-LIFE OBSTETRICIANS & GYNECOLOGISTS

Number 5, November 2019

Abortion and Risks of Preterm Birth

Preterm birth (PTB) plagues modern society with over 3 million annual deaths worldwide, and combined with low birth weight, PTBs are estimated to cost over 100 million disability adjusted life-years. The incidence of preterm delivery before 37 completed weeks of gestation ranges from 6 to 8% in Europe, Australia, and Canada to 9 to 12% in Asia, Africa, and the United States (U.S.). There has been no change over the last three decades and in fact some authors believe the trend may be increasing. The purpose of this practice bulletin is to summarize what is known in the medical literature about causes of preterm birth, especially the association between preterm birth and abortion.

Background

Current incidence of preterm birth

Preterm birth (PTB) plagues modern society with over 3 million annual deaths worldwide, and combined with low birth weight, PTBs are estimated to cost over 100 million disability adjusted life-years.[1] The incidence of preterm delivery before 37 completed weeks of gestation ranges from 6 to 8% in Europe, Australia, and Canada[2,3] to 9 to 12% in Asia, Africa, and the United States (U.S.).[4,5] There has been no change over the last three decades and in fact some authors believe the trend may be increasing.[6] In the U.S. the Low Birth Weight (LBW, newborn under 2500 gms) delivery rate in 2002 (with most LBW infants born under 35 weeks gestation) increased to 7.8% from 6.8% in 1985.[7] These findings mark the highest rate in over 30 years.[8] The rate of increase of newborns under 32 weeks gestation, Early Preterm Births (EPB), in singletons increased 5% since the 1980s compared to the overall increase of 15% in preterm deliveries.[9] The majority of the increased EPB appears as a result of multiple gestations due to assisted reproduction.[10] The incidence of newborns under 1500 gms, Very Low Birthweight (VLBW), was 1.46%, which reflected little change from the 1.44% rate of 2001.[11] A recent paper by Magro Malosso et al. 2018 asserted that the preterm delivery rate in the U.S. had decreased from 12.3% in 2003 to 11.5% in 2012.[12] However, this article did not account for lack of linkage in the data and the effects of the aggressive elimination of non-indicated PTB during this same time frame.[13] Therefore, its findings are suspect as to the accuracy of the data presented.

National Academy of Sciences evaluation and neglect of studies demonstrating the association of induced abortion and preterm birth

The recent National Academy of Sciences (NAS) report on the safety of abortion addressed findings pertaining to the association between induced abortion and PTB.[14] The authors posited only five studies met their criteria for inclusion in their

discussion of the abortion PTB link in spite of the 160 statistically significant studies linking PTB to induced abortion.[15] The NAS committee criteria included the following.

- For the study population, there was objective medical record or patient registry documentation of a prior induced abortion (excluding spontaneous abortion or miscarriage).
- The study population (women with a documented abortion) was compared with a control group of women with no documented abortion history.
- The analysis controlled for mental health status prior to the abortion (if assessing the mental health effects of abortion).
- The study was published in 2000 or later and included abortions performed in 1980 or later (to help ensure that reported outcomes reflected contemporary abortion methods).
- The clinical settings and care delivery were similar to those in the United States.

The authors further stated that the studies meriting attention and discussion should control for confounding variables such as smoking, maternal age, type of abortion (surgical or medical), weeks of gestation at abortion, and number of previous abortions. Even if we agree the criteria set forth are sufficient and valid as related to studies after 2000, there are still at least 70 studies that should have been included in the analysis for PTB. No explanation is provided for omitting such a large portion of the literature.

Critique of studies relied upon by NAS

The Woolner et al. 2014 study was the major study utilized by the NAS Committee to make the broad statement regarding no association between induced abortion and PTB in a subsequent pregnancy.[16] However, this study is fraught with significant methodological difficulties including the fact that it analyzes data only from a single site in Scotland.

The study by Woolner et al. 2014 actually contradicts the findings of two other studies by two of the same authors who contributed to the 2014 Woolner study -- S. Bhattacharya and S. Battacharya.

Bhattacharya and Battacharya et al. 2012, using the same Scottish database employed by Woolner et al. 2014, found when examining all the national data from Scotland during the same time frame from 1986 to 2010 an increased risk of PTB among women with an induced surgical abortion compared to women with no abortion [RR: 1.37 [95% CI 1.32-1.42].[17] Their numbers were much larger and the robust sample included 457,477 women without an abortion history and 120,033 with a history of induced abortion. There were 52,560 surgical abortions and 16,702 medical abortions.[18]

Bhattacharya et al. 2012 also noted that smoking data as a comorbidity were not routinely collected prior to 1992 in the Scottish national database, so Woolner et al. 2014 did not have complete smoking data in their sample in spite of the criteria cited above as one of the major cofactors necessary for a credible study. Bhattarya et al. 2012 further controlled for the type of abortion (medical and surgical) performed and utilized known gestational age (i.e. < 13 weeks) to evaluate for risk of PTB on a national level, not a single site as in Woolner.[19] The Woolner et al. 2014 study also mixed the failed medical abortions with the surgical abortion numbers, thereby increasing the PTB risk to the surgical group while lowering the risk for PTB in the medical group, since there is a known increased risk for PTB in a medical abortion requiring surgical completion.[20]

The NAS authors used the 2014 study by Woolner discussed above and the study by Jackson et al. 2007[21] to evaluate the risk of PTB with medical and surgical abortion after 13 weeks. Both of these studies suffer from flaws with the obvious inability to state that later abortions are not related to an increased risk for PTB. Further, Mirmilstein et al. 2009 suggested in a small study of 77 women that

induced abortion with misoprostol in the mid-trimester was in fact a risk factor for PTB.[22]

The authors of the NAS study sought to assign risk for PTB with induced abortion with a shortened inter-pregnancy interval consisting of a conception less than <6 months after previous pregnancy based on one study by Mannisto et al. 2017.[23] However, by their own admission, this finding is inconsistent and may be related to other factors found in other studies.[24,25,26] Finally, the authors of the NAS study do admit that the present data does support the notion that multiple induced abortions increase the risk for PTB demonstrating a dose related effect to induced abortion.[27]

Contrast NAS Opinion with Other Expert Opinion

Dr. Jay Iams is an Associate Editor of the *American Journal of Obstetrics and Gynecology* and editor of 5th, 6th, and 7th editions of Creasy and Resnik's *Maternal Fetal Medicine* text. He was also past president of the Society for Maternal-Fetal Medicine from 2003-04 and of the American Gynecological and Obstetrical Society in 2013. Dr. Iams published in 2010: "Contrary to common belief, population-based studies have found that elective pregnancy terminations in the first and second trimester are associated with a very small but apparently real increase in the risk of subsequent spontaneous preterm birth."[28]

Dr. Phil Steer, editor of the *British Journal of Obstetrics and Gynecology* shared in his editorial on the Shah et al. 2009 meta-analysis analyzing abortion and preterm birth published in the British Journal in 2009: "A key finding is that compared to women with no history of termination, even allowing for the expected higher incidence of socio-economic disadvantage, women with just one TOP (termination of pregnancy) had an increased odds of subsequent preterm birth. However, finding that even one termination can increase the risk of preterm birth means that we should continue to search for ways of making termination less traumatic."[29]

Ethical medical care requires informing women of the most recent and compelling evidence regarding the increased risk of subsequent PTB after a surgical induced abortion. The politically correct pressure to deny such risks, or mitigate them is, however, substantial. No organization in the United States has formally acknowledged the risk with induced abortion for preterm birth. In contrast, the Royal College of Obstetrics and Gynaecology issued a statement which acknowledges the association of induced abortion and PTB. In their 2011 guidelines on "The Care of Women Requesting Induced Abortion," the Royal College shares:

> RECOMMENDATION 5.12: "Women should be informed that induced abortion is associated with a small increase in the risk of subsequent preterm birth, which increases with the number of abortions. However, there is insufficient evidence to imply causality."[30]

Informed consent remains a bedrock of ethical care for surgical and medical interventions. Patients deserve discussion of the risks associated with any procedure.

Response to the NAS study

In response to the NAS study, a more systematic and thorough analysis of the literature to date (2018) of the known association of PTB with induced abortion is provided in this Practice Bulletin. Previous articles began exploring the association with induced abortion and PTB in 2003.[31,32] Rooney and Calhoun 2003 reviewed studies from 1966-2003 and found 49 studies with a statistically significant risk for PTB after abortion.[33]

Fueled by the overwhelming findings on the medical effects of abortion on the increased incidence of PTB, Calhoun et al. 2007 made the public health argument for the U.S. from the 59 statistically significant studies (up to 2005) that induced abortion increased the incidence of PTB by approximately 31.5%.[34] Calhoun et al. 2007 calculated, based on the 31.5% increased risk

associated with abortion, that the concomitant hospital costs due to prematurity were over $1.2 billion per year in the U.S.[35] McCaffrey, writing in 2017, recalculated the costs of very preterm birth (<2,500 gms) and estimated between $52-57 billion[25] (U.S.) in hospital costs for the 43 years studied (from 1973-2016).[36] These hospital expenses did not include any of the significant costs after discharge to home related to the morbidity of prematurity: cerebral palsy, retinopathy, bronchopulmonary dysplasia, deafness, and early intervention programs. As of June, 2018, no one has yet to dispute these estimates of abortion's associated increased risk for prematurity (31.5%) or the impact on healthcare dollars by induced abortion.

Two of the most powerful meta-analyses were published in 2009, one by Swingle et al. and the other by Shaw.

Swingle Meta-analysis

Swingle et al. 2009 performed a meta-analysis of literature from 1995-2007.[37] The paper's authors included two pro-abortion and two pro-life authors per their admission.[38] They believed this would reduce any bias. They searched 7,891 titles, 349 abstracts, and 130 papers. After reading the papers and using their inclusion criteria for data and obtaining the data from the studies for analysis, the authors found 30 induced abortion and 26 spontaneous abortion (SAB) papers. The authors analyzed data from 12 induced abortion and nine SAB papers. Four of 12 studies on induced abortion had data available for common ORs for calculation for induced abortion < 32 weeks. The common OR for these studies was 1.64 [95% CI 1.38-1.91].[27] The authors therefore demonstrated a 64% increased risk of preterm birth < 32 weeks with just a single induced abortion.[39]

The Swingle et al. 2009 study authors also found an increased risk for PTB with SABs.[40] Out of the nine studies available for common OR for PTB with SABs, seven had data for use in calculations. The authors found that the SAB's OR for preterm delivery < 37 weeks with 1 SAB was an OR of 1.43 [95% CI 1.05-1.66] and with ≥ 2 SABs an OR of 2.27 [95% CI1.98-2.81].[28] These findings regarding SAB and PTB are not unexpected in any such meta-analysis of PTB. Preterm birth with induced abortions is not in any way related to PTB with SABs. It must be noted the etiologies of why women miscarry spontaneously (SAB) are significantly different than those who have induced abortions. The very medical reasons women miscarry spontaneously may also predispose them to PTB. Further, SAB is not an avoidable epidemiological risk factor for preterm birth; it is a tragic outcome of a wanted pregnancy for most women. Therefore, to compare SAB's relationship to PTB as similar to the relationship of PTB with induced abortion is not a proper comparative analysis.

Shah Meta-analysis

The second study from 2009 is the large meta-analysis by Shah et al. 2009.[41] The authors screened 834 papers and excluded 765 for lack of data and objectives. They retrieved 69 citations and again excluded 32 for lack of data. Of the 37 remaining studies, there were 18 studies of Low Birth Weight (LBW), 22 studies for PTB and three studies for small for gestational age (SGA). Out of the 18 studies for low birth weight there were 280,529 patients available to compare no induced abortions versus one abortion prior to first pregnancy. Shah et al. 2009 found an increased risk for PTB with an OR of 1.35 [95% CI 1.20-1.52] demonstrating a 35% increase in the PTB rate in patients with only one abortion.[42] Only 5/18 studies had ≥ 2 induced abortions and included 49,347 patients. The OR for PTB for > 2 induced abortions was 1.72 [95% CI 1.45-2.04] demonstrating a 72% increase in the PTB rate which shows the important epidemiological principle of a dose related effect: the more abortions one has prior to first pregnancy, the higher the risk for PTB.[43]

Examining the 22 studies focusing on PTB exclusively including 268,379 patients, the authors

found an increased risk for PTB with an OR for one induced abortion of 1.36 [95% CI 1.24-1.50] demonstrating a 36% increase in the PTB rate.[44] In the 7/22 studies with ≥2 induced abortions and including 158,421 patients they found an increased risk for PTB with an OR of 1.93 [1.38-2.71] demonstrating a 93% increase in the preterm birth rate.[45] These are striking findings available in a large meta-analysis that allows the inherent confounding variables in the study to be controlled and accounted for in the analysis due to the large numbers of patients in the database. The authors also examined the effects of abortion on SGA and found no influence with either one or more induced abortions.[46]

Other studies of note

Oppenraaij et al. 2009 in their literature review found increased risk of very PTB ≤ 28-32 weeks and PTB ≤ 37 weeks with 1 induced abortion and increasing risk of both very PTB and PTB with ≥ 2 induced abortions.[47] Their study included 13 studies available at the time of the review. In spite of the authors attempts to explain the increased preterm delivery with surgical abortion was related to confounders (smoking, unemployment, socioeconomic status, short inter-pregnancy interval, etc.), they were still forced to admit, "Despite these methodological drawbacks, it can be concluded that a history of TOP [termination of pregnancy] is associated with an increased risk for PPROM, PTD, and VPTD. These risks depend on the number of TOP."[48]

Lowit et al. 2010 reported on data from seven systematic reviews (including four meta-analyses) and 18 primary studies found increased risk of PTB and early PTB ≤ 32 weeks in the studies.[49] There was one prospective study, 12 retrospective studies, and five case control studies in the analysis. The authors again attempt to minimize the association between surgical abortion and preterm delivery by attempting to confuse the appropriate control groups between first pregnancies and abortion, i.e. whether to use someone in a first pregnancy (G1P0) or use a G2P1 since the abortion patients are G2P0 individuals. The authors state in their conclusions that the "effects of IA [induced abortion] on subsequent reproduction is sparse and conflicting."[29] However, the same Lowit et al. 2010 authors are forced to admit, through the careful analysis of their several meta-analyses and systematic reviews in their conclusions on the first page of the article that, "Current evidence also suggests an association between IA [Induced abortion] and pre-term birth."[50]

Saccone et al. 2016 evaluated 36 studies for a systematic review and meta-analysis with 31 studies for termination of pregnancy and five for SAB with D&C with 1,047,683 women.[51] The authors carefully controlled for bias by using two authors to independently extract data, assess for bias via the Methodological Index for Non-Randomized studies, and used the Higgins test to test for heterogeneity across studies. Finally, the authors planned all their analyses and outcomes a priori to data extraction. Women with termination had increased risk of PTB at 37 weeks with OR of 1.52 [1.08-2.16], low birth-weight with OR of 1.41 [1.22-1.62], and SGA OR of 1.19 [1.01-1.42].[30] The authors concluded, "In summary, this meta-analysis found that prior surgical evacuation of the uterus may be an independent risk factor for PTB [preterm birth]."[52]

Finally, Lemmers et al. 2016 confirmed the association between PTB and surgical induced abortion. Lemmers et al. 2016 reviewed 21 studies reported on 1,853,017 with dilation and curettage (D&C) on either termination of pregnancy or completion of miscarriage.[53] Women with a history of a D&C compared to those with no history, had an AOR for preterm birth was 1.29 [1.17;1.42], while the risk for VPTB the AOR was 1.69 [1.20-2.38]. For women with a history of multiple D&Cs compared with those with no D&C, the OR for preterm birth was 1.74 [1.10-2.76]. Thus, women with a previous D&C, for whether miscarriage or termination of pregnancy in the first trimester, are at increased risk for PTB and most notably VPTB. Lemmers concluded, "This meta-analysis shows

that D&C is associated with an increased risk of subsequent preterm birth. The increased risk in association with multiple D&Cs indicates a causal relationship. Despite the fact that confounding cannot be excluded, these data warrant caution in the use of D&C for miscarriage and termination of pregnancy, the more so since less invasive options are available."[54]

Abortion Study Review for Deliveries ≤ 37 weeks

A rubric was utilized to evaluate the quality of the studies linking abortion history with PTB ≤ 37 weeks (Table 1). It includes nine criteria: sample size, generalizability, consent to participate rate, abortion concealment, attrition rate, control for potentially confounding variables, inclusion of a control group, strength of measures or preterm birth, and prospective data collection (longitudinal studies only). Each criterion was worth 0-4 points for a total of 36 points. Significant studies are ranked via these criteria in Table 2: Preterm Birth less than 37 weeks, and Table 3: Very Preterm Birth less 28 weeks to 32 weeks.

Ancel et al. 2004 in a case control study of 2,938 PTBs and 4,781 controls at term from 10 European countries found that the risk for VPTB ≤ 28 weeks with one abortion with OR of 1.34 [1.08-1.68] and increased risk of PTB with ≤2 abortions with OR of 1.82 [1.34-2.49].[55] The evaluation of the quality of this study was 21 out of a possible 36 points.

Voigt et al. 2009 evaluated eight German federal states in a retrospective cohort study of 247,593 primiparous women with increased risk of PTB ≤ 36 weeks and ≤ 31 weeks.[33] The rate of PTB for women with one induced abortion was 7.8% and for ≥ 2 abortions 8.5%.[56] This is in contrast to the risk of 6.5% in the control population reaching statistical significance of P=0.015. The biggest weakness is that the data regarding previous termination of pregnancies was obtained by interview from patients at the initial obstetrical visit. However, this would only strengthen the association since underreporting would only decrease the association through a decrease in the number of exposed pregnancies prior to preterm delivery/birth. The evaluation of the quality of this study was 29 out of a possible 36 points.

Freak-Poli et al. 2009 used data from South Australia from 1998-2003 (to include maternal smoking history data) encompassing 42,269 singletons with 39,191 term births and 3,078 PTBs.[57] They demonstrated an increased risk of PTB ≤ 37 weeks and with induced abortion with adjusted OR (aOR) of 1.63 [1.28-2.08] and a risk of PTB with ≥ 2 with a OR of 1.35 [1.08-1.68] [increasing numbers of induced abortions]. One of the key strengths of the study was the internal validation of the perinatal database with the actual patient records regarding socioeconomic status, race, previous pregnancy outcomes, gestational age, hypertension, IUGR, and antepartum hemorrhage (See Table 2). The evaluation of the strength of this study was 33 out of a possible 36.

There were three informative studies on PTB ≤ 37 weeks and induced abortion in 2011, one data base linked (Di Renzo)[58] and two cohort studies.[59] [60] We will concentrate on the database-linked study.

Di Renzo et al. 2011 is a database-linked study which was a multicenter, observational, retrospective and cross-sectional study of PTB and vaginal deliveries in nine centers in Italy. Di Renzo eliminated cesarean section deliveries in their sample analysis due to the inability to control for heterogeneity for performing cesarean delivery in disparate regions of the country. The records were linked to outcomes for the patient outcomes at each center within the central database registry. The investigators properly performed a power analysis prior to beginning the research to determine the number of patients needed to reach statistical significance in their particular population. They estimated they needed 6,000 women with vaginal deliveries to determine a difference in the PTB rate in their population. Di Renzo utilized a baseline PTB rate of 5% utilizing 20 variables in their multivariate regression analysis of their delivering patients. Their sample included 7,634 women

delivering vaginally from September-December 2008 at the nine medical centers. Analysis of the data included 15 confounding variables evaluated as co-factors for PTB including: BMI, age, medical co-morbidities, tobacco abuse, previous cesarean section, and abortion. The authors did not separate out when the abortions occurred with regard to the incident pregnancy studied (i.e. prior pregnancy/ pregnancies all ending in abortion or abortion after full-term pregnancy), or by the numbers of abortions each woman might have experienced. What Di Renzo found was an increased odds ratio (OR) risk for PTB of 1.954 (1.162-3.285) or a 95% increase in the preterm birth rate with any previous abortion(s) no matter when the abortions occurred in the patients' reproductive histories.[61] Interestingly, they also found in the study an independently increased risk of PTB, unrelated to abortion, with either a: BMI >25 with an OR of 1.662 (1.033-2.676) and a previous cesarean with an OR of 2.904 (1.66-7.910). The evaluation of the quality of this study was 33 out of a possible 36 points.

The strengths of the 2011 Di Renzo study include:

- large, linked data base with power/multivariate analysis;
- found increased PTB risk in *all* patients with previous abortions as an independent risk factor regardless of when the abortion occurred in relation to the incident pregnancy, i.e. found no "protective effect" of a previous term birth prior to the incident pregnancy studied.

The weaknesses of the 2011 Di Renzo study include:

- did not separate out abortion timing prior to incident pregnancy;
- did not do analysis for multiple abortions so unable to discuss "dose effect."

The last study included in Table 2 is **Liao** et al. 2011.[62] Liao purported to evaluate the effects of repeated first trimester medical abortions with mifepristone on preterm birth in subsequent pregnancies. It was a cohort study from seven hospitals in Chendu, China, including four years of study from January 2006-December 2009. The study was interview based with delivery outcomes available in 18,323 (93.8%) women out of the 19,527 originally enrolled in the study group to analyze for PTB. The women were then stratified further into the two groups with regard to whether or not they had an abortion, or abortions, prior to the incident pregnancy to evaluate for PTB. The evaluation of the quality of this study was 21 out of a possible 36 points. Review of the study's data reveals:

- 7,478 women with complete follow up in the abortion group out of original 7,558 (98.9%);
- 10,546 women with complete follow up in the no abortion group out of original 10,681 (98.9%).

The nulliparous women with abortions were then divided into three subsequent comparison groups for PTB with a further division by the type of abortion (medical or surgical), versus, no abortions:

- nulliparous women with one or more first trimester medical abortions (mifepristone);
- nulliparous women with surgical elective abortions;
- nulliparous women with no previous abortions.

Within the two abortion groups (abortion/no abortion groups) the following numbers of women with abortion groups were found for analysis:

- In the no abortion group of women there were 332 spontaneous abortions 332/10,546 or 3.15%. No data or information was available in the paper on management of these spontaneous abortions: i.e. whether the spontaneous the abortions were managed without any therapy (totally spontaneous); medical therapy alone; surgical therapy alone; or combined medical/ surgical therapy.
- In the abortion group of women there were:
  - 1,769 women with one medical abortion: 1,769/7,468 (24%);
  - 2,900 women with one surgical abortion: 2,900/7,468 (38%);

- 553 women with >1 medical abortion: 553/7,468 (7.4%)
- 1,088 women with >1 surgical abortion: 1,088/7,468 (15%)
- 1,168 women with medical/surgical abortions: 1,168/7,468 (16%).

There was a fairly even distribution of all types of abortions found in the population experiencing abortion as well as significant numbers of abortions overall in the study population. The findings regarding PTB with surgical and/or combined surgical-medical abortions were as follows:

- OR 1.4 (1.1-1.8) demonstrating a 40% increase in the PTB rate with 1 surgical abortion;
- OR 1.62 (1.27-3.42) demonstrating a 62% increase in the PTB rate ≥ 3 surgical abortions (dose effect);
- OR 2.18 (1.51-4.42) demonstrating a 218% increase in the PTB rate with medical & surgical abortions.

These clinical findings demonstrate that surgical abortion prior to the first incident pregnancy are associated with PTB, but, most importantly that multiple surgical abortions show a concomitant increase in PTB rates demonstrating a "dose effect" by multiple surgical abortions. Finally, that a history of combined surgical-medical abortion is even more serious in its association with an increased PTB risk of over 200%.

The strengths of the Liao et al. 2011 paper include:

- large group of patients (18,323);
- large numbers of abortions in several categories (surgical/medical/both);
- demonstrated an increased risk of PTB with surgical abortions and combined surgical/medical abortions.

The weaknesses of the Liao et al. 2011 paper include::

• Not sharing the most startling clinical findings regarding abortion in this paper:

* **OR 1.4 (1.1-1.8) demonstrating a 40% increase in the PTB rate with 1 surgical abortion**;
* **OR 1.62 (1.27-3.42) demonstrating a 62% increase in the PTB rate ≥3 surgical abortions (dose effect);**
* **OR 2.18 (1.51-4.42) demonstrating a 218% increase in the PTB rate with medical & surgical abortions**

• **The need for surgical curettage in 20% medical abortions to complete the abortions with an:**

* **OR 1.69 (1.02-3.16) demonstrating a 69% increased PTB risk in women with medical abortion < 7 weeks *with curettage!***
* ***AND* risk for < 32 week delivery OR was 3.61 (1.43-4.93) demonstrating a 361% increased PTB risk in women with < *7 week medical abortion with curettage (20% of patients!)***

• Interview study and not data linked.

In spite of these significant clinical findings, Liao et al. 2011 abstract failed to report one of the most important outcomes of the study. The abstract blandly states: "*A history of multiple first trimester mifepristone-induced abortions is not associated with a higher risk of preterm delivery among singleton births in the first subsequent pregnancy*."

The authors' statement hides the most startling of the findings of the Liao et al. 2011 paper which were:

• the authors burying in the article that ***20.3% of patients with medical abortion needed a post-abortion surgical suction curettage to complete the abortion process;***

• the increased OR of 1.69 (1.02-3.16) or increased risk of 69% in the PTB risk in women with medical abortion < 7 weeks *with curettage!*

• and the increased risk for < 32 week delivery of over 360% with an OR of 3.61 (1.43-4.93) with < 7 week medical abortion with curettage (20% of patients).

The authors did not report either of these findings in abstract.

Abortion Study Review for Very-Low Birth-weight /Very Preterm Birth (≤ 28 weeks or ≤ 1,500 gms)

The same rubric was utilized to evaluate studies on very preterm birth (≤28-32 weeks) (See Table 3). It included nine criteria: sample size, generalizability, consent to participate rate, abortion concealment, attrition rate (longitudinal studies only), control for potentially confounding variables, inclusion of a control group, strength of measures or PTB, and prospective data collection. Each criterion was worth 0-4 points for a total of 36 points.

Levin et al. 1980 compared pregnancy loss/PTB ≤ 28 weeks with those who delivered at term (≥ 37 weeks).[63] Women who had ≥ 2 induced abortions had 2-3 fold risk of PTD ≤ 28 weeks. The evaluation of the quality of this study was 25 out of a possible 36 points.

Lumley 1998 primarily analyzed data from all first singleton births from 1983 to 1992 (243,679 births) in the State of Victoria, Australia.[64,38] Relative risk and 95% confidence interval was calculated for each of gestational categories (20-27, 28-31, and 32-36 weeks) by the number and type of previous pregnancy (none, spontaneous abortion(s) only, induced abortion(s) only, both spontaneous and induced abortions). The control group consisted of women whose first birth was also their first pregnancy. The secondary analysis included all women whose reproductive history contained no spontaneous or induced abortions. Lumley 1998 demonstrated an increased risk of VPTB ≤ 28 weeks and PTB ≤ 32 weeks with induced abortion and a dose effect noted with increasing risk of PTB with increasing numbers of induced abortions. Weaknesses of the study included possible confounding with regard to maternal age, marital status, birth defect, tobacco, socioeconomic status, and possible alcohol use. In spite of this, Lumley notes, "*The data meet four of the criteria for causality. The temporal sequence is clear: the abortions preceded the preterm birth. The association is a strong one. There is a dose-response relationship: the greater the number of prior pregnancies the higher the relative risk. The association is plausible: possible mechanisms exist…*"[65] The evaluation of the quality of this study was 33 out of a possible 36 points.

Moreau et al. 2005 evaluated VPTB (22-32 weeks of gestation) in nine French regions (EPIPAGE study).[66] The study sample was from a regionally defined population in France. The study encompassed 1,943 VPTBs (<33 weeks), 276 moderate PTBs (33-34 weeks) and 618 unmatched term controls (39-40 weeks). The study strength was its control for confounding variables in the linked data (previous PTB, education, socioeconomic status, smoking, and marital status, etc.). The study found an Odds Ratio of 1.8 for 22-27 week delivery and 1.7 for 28-32 week delivery with induced abortion. The evaluation of the quality of this study was 28 out of a possible 36 points.

Smith et al. 2006 analyzed risk with induced abortion and spontaneous PTB in 84,391 first births in Scotland between 1992 and 2001.[67] The major strength of the study is the use of Cox modeling and proportional hazards model to determine whether or not the relative risk of spontaneous preterm birth is associated with a given factor with regard to prematurity. The authors found, using their Cox and hazard modeling, an increased risk of PTB at 24-32 weeks with a Hazard Risk (HR) of 1.19 with one abortion and a Hazard Risk of 1.90 with ≥ 2 induced abortions. The evaluation of the quality of this study was 33 out of a possible 36 points.

Klemetti et al. 2012 in a registry study from Finland compared the singleton birth registry from 1996-2008 (300,858 women) with the abortion registry women from 1983-2008.[68] Among first-time mothers, the authors found 31,083 single

abortions, 4,513 with two abortions, and 93 had three or more abortions. They found increased risk of VPTB ≤ 28 weeks with unadjusted OR of 1.22 for 1 abortion, 1.86 for 2 abortions, and 3.38 with ≥ 3 abortions. Adjusted ORs reveled increased risk with ≥2 abortions. The study's strength was its completeness of records with linkages among all the datasets and points. There was no recall bias or lack of reporting since all medical encounters are reported to the central database. The authors only comment on weakness was, "Observational studies like ours, however large and well-controlled, will not prove causality." The same assertion may be made regarding tobacco with regard to lung and oral cancers as well as vascular diseases. The evaluation of the quality of this study was 34 out of a possible 36 points.

Bhattacharya et al. 2012 in a registry study from Scotland from 1981-2007 followed outcomes in a second pregnancy after induced abortion, live birth, and miscarriage.[69] There were 120,033 women with induced abortion, 457,477 women with live birth, and 47,355 women with miscarriage, respectively. The weaknesses of the study were the differences in recorded data, changes in clinical practice, unrecorded/missing data and reliability of parity of patients during the epoch. Strengths were the large numbers of patients for comparison and controlling for significance by using a 1% significance level in the analysis. In spite of the limitations, the authors noted, "Women with a previous IA [induced abortion] face increased risks of antepartum hemorrhage and spontaneous preterm birth."

Bhattacharya et al. 2012 found that women with previous abortion (medical or surgical) had increased risk of PTB < 37 weeks with adjusted RR of 2.30 [2.27-2.33]. There was missing smoking data on 50% patients and in 25% of cases, the abortion type was not listed (i.e. surgical/ medical), and estimates were used for sample size.[11] The evaluation of the quality of this study was 27 out of a possible 36 points.

Scholten et al. 2013 used national registry study from the Netherlands from 2000-2007 investigating preterm delivery after pregnancy termination.[70] https://bmjopen.bmj.com/content/bmjopen/3/5/e002803.full.pdf They used a sample size of 16,000 women with previous pregnancy termination prior to next delivery. A weakness of the study was its interview base for individual abortions, not registry derived data. PTB ≤ 32 weeks was increased by adjusted OR of 1.52 [1.26-1.85] and ≤ 28 weeks by adjusted OR of 1.67 [1.30-2.15]. The authors concluded, "***Women who have had a termination of pregnancy have an increased risk of preterm delivery, cervical incompetence treated by cerclage, placental problems, and PPH [postpartum hemorrhage]***."[71] The evaluation of the strength of the quality of the study was 27 out of a possible 36 points.

Hardy et al. 2013 utilized registries from a Canadian database looking at deliveries <32, 28, and 26 weeks with induced abortions.[72] The population study was from April 2001 to March 2006 using the McGill Obstetric and Neonatal Database. The study included 17,916 women with 2,276 (13%) having undergone one prior induced abortion and 862 having undergone ≥ 2 induced abortions. A limitation of the study was self-report to disclose a history of induced abortion. However, failure to disclose would tend to bias in favor of the null hypothesis and not increase risk, since women would tend to not disclose rather than vice versa. A second limitation was whether the abortion was performed surgically or medically and whether done in the first or second trimester. In spite of these limitations, the adjusted ORs for increased risk of PTB were 1.45 < 32 weeks [1.11-1.90], 1.71 < 28 weeks [1.21-2.42; and < 26 weeks 2.17 [1.41-3.35] respectively. The evaluation of the quality of this study was 25 out of a possible 36 points.

Zhou et al. 2014 performed a population-based prospective study in 14 cities in China from 1 January 2001 to 31 January 2012 to evaluate

preterm premature rupture of membranes (PPROM).[73] The population included 117,330 women who attended routine prenatal clinics that were enrolled with 112,439 included in the analysis. A total of 3,077 (2.7%) had PPROM. The strength of the study is the ability to control for smoking, alcohol, medical history comorbidities, a family history of medical diseases, history of spontaneous miscarriage, fetal death, and fetal abnormalities. Zhou et al. 2014 found increased risk of preterm premature rupture of membranes (PPROM) ≤ 28 weeks with increased OR of 2.75 [1.66-4.56] of PPROM with induced abortion. The evaluation of the quality of this study was 34 out of a possible 36 points.

Usynina et al. 2016 using registry data from all births (52,806 live births) in a Russian county from 2006-2011 found adjusted increased adjusted ORs for PTB <28 weeks 1.96 [1.32-2.91] and increased adjusted ORs 28-32 weeks of 1.36 [1.06-1.76].[74] The strengths of the study were the ability to control for the morbidities of educational level, marital status, alcohol abuse, and diabetes and the large size. Limitations include possible under-reporting of alcohol abuse, pre-pregnancy BMI, and the lack of separation of induced and spontaneous miscarriages. However, including spontaneous miscarriages in the data would tend to move toward the null hypothesis with a lessening of induced abortion impact, since spontaneous miscarriages would be represented in the preterm delivery numbers and dilute the effects of induced abortion. The evaluation of the quality of this study was 32 out of a possible 36 points.

Situ et al. 2017 in a study from Finland from 1996 to 2003 including 419,879 first-time mothers with a single birth demonstrated significantly increased risk of extremely preterm birth ≤ 28 weeks with OR of 1.51 [1.03-2.23].[75] Strengths of the study include the large number of first-time mothers with singleton births over an 18-year time frame, use of national registry linked data, and ability to analyze for induced abortions in multiple categories. Limitations of the study include lack of data on inter-pregnancy intervals and socioeconomic status. The authors were able to use smoking as a proxy to control for socioeconomic status in Finland thereby controlling for socioeconomic status. The evaluation of the quality of this study was 34 out of a possible 36 points.

Finally, **Magro Malosso et al**. 2018 performed a study of abortion from 2003 to 2012 from U.S. databases (which are not linked) from National Vital Statistics Reports and Center of Disease and Prevention which found increased risk for preterm birth with surgical abortion and decreased preterm birth rates with medical abortion.[76] However, the study suffered from lack of linkage of the data and correlation coefficients as a quantitative assessment. The correlation coefficient only assesses the co-variation as opposed to causation. Also, the authors did not address the issues of efforts to decrease preterm births operative during the study period. Professional societies, like ACOG, produced committee opinions to aggressively decrease the incidence of late PTB (34 0/7-36 6/7 weeks) and this could bring bias into the data collected as a result of changes in practice not related to induced abortion.[77] Finally, the study did not look at very preterm birth ≤ 28-32 weeks. The evaluation of the quality of this study was 22 out of a possible 36 points.

Conclusions to NAS rebuttal

The most remarkable finding to date (June 2018) are the 160 published peer review articles all documenting increased risk for PTB with induced abortion.[78]

This review of papers (as of May 2018) demonstrates the overwhelming evidence to support the association between induced abortion and preterm birth. Multiple papers, including multiple meta-analyses demonstrate risk for preterm birth is significantly increased by induced abortion. The paper by Liao et al. 2011 highlights the problems in interpreting the medical abortion and preterm birth literature. The authors buried the most important clinical and statistical findings in

the paper about medical abortions. **Liao et al. 2011 did not report the *startling OR of 3.61 (1.43-4.93)* for PTB with < 7 week medical abortion with curettage (20% of patients!). This over 360% increase in the risk for 20% of the women who underwent a medical abortion and needed a surgical procedure to complete the abortion was simply not reported in the abstract.** The bias in not reporting this extremely important finding is staggering and represents the duplicity in how abortion complications are reported.

Finally, the NAS study ignores the substantial body of literature (160 papers at last count June 2018) regarding induced abortion and its association with PTB. Critical evaluation of the NAS references finds them lacking and limited in both number and significance. Whole bodies of literature (some 70 studies from 2000 onward per their own criteria) are ignored with biased selection and arbitrary criteria (which the authors appear to ignore for part of their evaluation, particularly with Woolson et al. 2014).

Abortion and Very Preterm Birth Mortality

Our review precludes a detailed review of abortion mortality and cerebral palsy but conservative estimates over the last 43 (1973-2018) years detail approximately 102,056 deaths associated with VPTB and abortion.[79] Of these deaths 46,268 (45%) were in the Black community even though Blacks comprise only 15-16% of population.[80] As McCaffrey notes, this is "equal to the number of lives that would lost if 88 fully loaded 747 airliners crashed."[81] Also, Gissler et al. 2004 found an almost three times increased risk for all-cause mortality after abortion compared to a live birth.[82]

With regard to cerebral palsy, Calhoun et al. 2007 calculated an estimated 1,096 cases of cerebral palsy each year attributable to induced surgical abortion and very preterm birth.[83] To date, no one has refuted or discounted these estimates.

Pathophysiology of Induced Abortion and Preterm Birth

The putative mechanisms by which surgical induced abortion may increase the risk for PTB include the following:

- cervical trauma and injury with use of surgical instruments to forcibly dilate the cervix;
- induction of or predisposing to inflammation with surgery with introduction of infection with the procedure;
- chronic maternal stress with increased production of stress hormones leading to PTB;
- other unknown factors that may contribute to PTB such as socioeconomic or lifestyle issues.

The literature has shown for some time the increasing risk for PTB with surgical abortion. The association with medical abortion has been less actively studied. Researchers, including Oliver-Williams et al. 2013 have shared that the traumatic injury from surgical abortion is the reason that surgical abortion increases PTB risk.[84] Medical abortion has been offered as a less traumatic alternative, but data from studies is lacking. Further, as of the most recent data in the U.S. in 2011, 77% of abortions in the U.S. are surgical.[85] Therefore, most of the induced abortions were surgical and thus the overwhelming majority of the women who have had a prior induced abortion have been exposed to surgical abortion, which is known to elevate risk for future PTB.

Mifepristone Abortion and the Cervix

Assertions have been made and theories advanced, based on limited research, that medical abortion eliminates the preterm birth risk. May this statement be made with certainty? We should consider the pharmacology of mifepristone.

Mifepristone (RU-486) is a powerful progesterone receptor blocker. Its abortive mechanism is thought to be mainly due to its effects on the decidua of the endometrium, but it also blocks progesterone receptors throughout the entire body, including the cervix. Animal studies have also revealed effects

regarding inflammatory cytokines. Denison et al. 2000 noted, "Animal research demonstrates that a fall in the effect of local progesterone in the cervix appears to up-regulate Metal Metalloprotein-9 (MM-9) release, which would degrade vascular basement membrane. This, in conjunction with release of chemokines, including MCP-1 and IL-8, favors accumulation of infiltrating leukocytes, specifically neutrophils, monocytes, and mast cells. These inflammatory cells release collagenases MMP-1 and MMP-8 by stromal cells promoting remodeling and loosening cervical connective stroma…The long-term impact of such chemically induced cervical changes is unclear."[86]

Animal studies in mice revealed that the sudden loss of progesterone function involved premature activation of the term ripening in the mouse along with partial activation of resident neutrophils and macrophages similar to the post-partum repair phase of cervical remodeling. Further, mifepristone up-regulates genes Chi313 Ptgs1, and Cox 1 as well.[87]

The long-term effects of mifespristone's biochemical changes in the cervix, along with genetic upregulation of a number of genes, is unclear at best. If mifepristone administration causes reordering, remodeling, and rearranging of cervical collagen bundles, there is a potential that long-term cervical instability may be the result, increasing the risk for future PTB.

Association of Abortion, Infection, Chronic Inflammation, and Preterm Birth

The association of chorioamnionitis with PTB is well-established. Infection causes the release of inflammatory factors, which influence cervical ripening and cervical dilation. The ascending infection into the reproductive tract also may elicit premature cervical ripening. Further, some researchers believe that prior abortion leads to an increased risk for infection, which may mediate the risk of preterm birth. [88,89,90,91,92] Muhlemann et al. 1996 found a triple elevation in the risk of chorioamnionitis both induced and spontaneous abortion.[93] Finally Krohn et al. 1998 found that women with elective induced abortion increased risk of infection by 2.7 to 5.8 (CI 95%).[94]

Association and Causality: Comparing Smoking and Prior Abortion with Subsequent Preterm Birth

Objective review of the obstetrical literature clearly shows there is substantial evidence for an association between induced abortion and PTB. The evidence for the abortion-PTB link is extensive and more robust than that for smoking and preterm birth. This is not to denigrate the association for smoking, but if an association is recognized for tobacco abuse, an unprejudiced reviewer would have to agree there is also an abortion-PTB association.

Generally, public health officials' duty is to warn their constituents of demonstrated associations and causal factors which may impact individual health and wellbeing. How do we make such determinations? How do we determine causality in medicine?

Causality in Medicine: Bradford Hill Causation Criteria

Professor Bradford Hill, in his Presidential Address to the Royal Society of Medicine in 1965 shared the following nine conditions that give evidence of a causal inference for an observed association in medicine:

- Strength of the association--does the effect meet statistical and/or clinical significance;
- Consistency--does the effect provide consistent results or outcomes;
- Specificity--is the effect specific to the outcome or result;
- Temporality--does the effect occur prior or during the given item under study;
- Dose Response--does the effect increase with increasing exposure;
- Plausibility--does the effect meet criteria for biologically reasonableness;
- Coherence--does the effect make sense with the outcome specified or found;

• Experiment--is the effect experimentally reproducible in multiple experiments with diverse authors and/or populations;
• Analogy--is the effect similar (analogous) to other effects found experimentally or clinically.

Dr. Hill made the follow observations on his criteria:

> *What I do not believe and this has been suggested--is that we can usefully lay down some hard-and-fast rules of evidence that must be observed before we accept cause and effect. None of my viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua on. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question--is there another way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect? All Scientific work is incomplete--whether it be observed or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time. Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on the 8:30 next day.*[95]

Applying the Bradford Hill Criteria to Abortion, Smoking and Preterm Birth

In 1964, the U.S. Surgeon General applied the emerging Bradford Hill criteria for causality to studies evaluating the smoking-PTB link, and chose to warn the public of a potential causal effect. Analyzing the comparison between smoking and prior induced surgical abortion to PTB, there appears to be a similar relationship found in the literature. This is despite the fact that many "experts" still will not acknowledge the latter; but where do these two factors rate with regard to meeting the requirements of Hill for not only association, but causality?

With regard to timing, both a prior abortion and smoking occur either before or during a pregnancy, which may result in PTB. There is a known dose effect demonstrated for the risk of PTB and very pre-term (VPTB) birth increasing with a greater number of induced surgical abortions.[96] [97] No such increased risk has been demonstrated with smoking and PTB. There is consistency of the effects of prior surgical induced abortion, but inconsistency with smoking.[98] Some studies show a protective effect of smoking.[99] No study shows any protective effect on induced abortion and PTB. Induced abortion has a very strong effect of association with a specific escalating rate of PTB and VPTB consistent with dose effect and causation.[100,101] Biologic plausibility for prior surgical abortion as a cause for future preterm birth is thought to be the result of either trauma or inflammation mediated.[102,103,104,105] There may even be a biologic plausibility for medical abortion and preterm birth, but better clinical studies and further research are necessary. The logical conclusion drawn from the published literature that linked tobacco abuse and lung cancer is almost exactly the same as the logical conclusion drawn from the published literature linking induced surgical abortion and PTB.

The lack of scholarly rigor for the issue of induced abortion and PTB casts serious doubts on the NAS study and its questionable findings. Preterm birth, based on the data in over 160 studies in the published peer reviewed medical literature, is significantly associated with induced abortion. These findings stand in stark contrast to the NAS study with its lack of association. It is also remarkable that the American College of Obstetricians and Gynecologists (ACOG) in their on-line Compendium for 2011 refused to acknowledge (June 2018) the increased associated risk for PTB or acknowledge the substantial body of literature raising this concern.[106]

Clinical Considerations and Recommendations

The following recommendations are made for patients who have been exposed to either surgical, medical or medical abortions completed by surgical procedures.

Q *What care options are available to patients with previous abortions?*

Patients with previous abortions will necessitate enhanced prenatal care similar to patients who have a history of preterm delivery, history of cervical procedures, uterine anomalies, or multiple gestations.[107] This consists of the following:

- Confirmation of gestational age
- Treat previous preterm birth patients with 250 mg of IM 17-hydroxyprogesterone weekly with cervical lengths
- Weekly cervical length ultrasound by standard procedure beginning 16-18 weeks until 24-26 weeks.
    - * Includes measuring cervix from internal os to external os without any vaginal or abdominal pressure
    - * Obtain at least three measurements and utilize the shortest measurement for the cervical length
- If cervical length is < 2.0 cm in patient without history of PTB (asymptomatic cervical shortening) < 24 weeks, consider vaginal progesterone therapy by either 90 gms of 8% vaginal progesterone gel nightly or 200 mg vaginal progesterone suppositories nightly
- If cervical length is < 2.5 cm, with history of PTB with IM progesterone therapy, and less than 24 weeks gestation, consider cervical cerclage
- If cervical length is <2.5 cm with progesterone therapy (in previous abortion patients without PTB) and less than 24 weeks gestation with prior PTB < 34 weeks, consider cervical cerclage.[108]
- Discontinue progesterone (weekly IM or daily vaginal progesterone) at 34-36 weeks.
- Removal of cerclage at 37 weeks.

Q *What clinical outcomes are typically seen with patients who have undergone previous induced abortion?*

Patients with surgical abortion resemble those with historical risk factors for cervical cerclage (i.e. cone biopsy, LEEP procedures, 2nd trimester losses with painless dilation and delivery). Therefore, there are likely decreased PTB rates in abortion patients with cerclage who have had a history of PTB < 34 weeks with cervical length ≤ 2.5 cm. [109]

Summary of Recommendations and Conclusion

The following recommendations are based on good and consistent scientific evidence (Level A):

1. Women with termination of pregnancy are at increased risk for PTB.
2. Women with termination of pregnancy are at least at 30% increased risk for PTB with one abortion and almost double the risk (200%) increased risk for PB with ≥ 2 abortions.
3. Women with termination of pregnancy with history of PTB < 34 weeks and cervical length ≤2.5 cm are candidates for cervical cerclage.
4. Tests, such as fetal fibronectin screening, bacterial vaginosis testing, and home uterine activity monitoring, are not recommended as screening strategies.

The following recommendations are based on limited and inconsistent scientific evidence (Level B):

1. PTB rates may be decreased with progesterone therapy.
2. Cervical cerclage is controversial in prevention of preterm in multiples or patients with uterine anomalies.
3. Progesterone therapy with cervical cerclage in patients with history of PTB may help prevent PTB.

The following recommendations are based primarily on consensus and expert opinion (Level C):

1. Medical abortions are at increased risk for PTB, particularly when being completed by surgical abortion.
2. Progesterone is controversial in prevention of PTB in multiple gestations and uterine anomalies.
3. Cervical cerclage in patients with cervical lengths <2.5 cm in multiple gestations and uterine anomalies is controversial in prevention of PTB.

Committee on Practice Bulletins: The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Table 1: Rubric for Coding Preterm Birth Studies

Criterion	0	1	2	3	4
Sample size "S"	50 or fewer	51-199	200-399	400-999	1000 or more
Generalizable "G"	Restricted to one city, self-selected, clinical, or convenience sample.	2 to 4 cities within 200 miles of each other	5 or more cities in different geographical locations, over 200 miles apart with no evidence the sample represents the population.	5 or more cities in different geographical locations, over 200 miles apart with evidence the sample somewhat approximates the population.	5 or more cities/ nationally representative/population based/ large international study including 3 or more nations.
Consent to participate rate "CP"	Not available or under 20%	20%-39%	40%-59%	60%- 79%	80% or greater/population based
Abortion concealment "C"	Includes women prone to concealment (minors, victims of domestic violence, highly religious or conservative family back-ground).	Concealment rates equivalent to typical studies on abortion.	Methodology employed some effort to reduce concealment.	Methodology employed extensive strategies to reduce concealment.	No concealment/ record-based data/ data secured at an abortion clinic.
Attrition rate (longitudinal studies only) "A"	High: 44% or less of sample retained.	Moderately high 45-59% of sample retained.	Moderate 60-74% of sample retained	Moderately low 75-89% of sample retained.	Low: 90-100% of sample retained.
Control for confounding variables "CF"	No controls for potential confounds.	5 or fewer demographic control variables.	6 or more controls for several potential confounds not restricted to demographic factors.	6 or more controls for several potential confounds, not restricted to demographic factors and including prior PTB	6 or more controls for several potential confounds, not restricted to demographic factors and including prior PTB and pregnancy intendedness.
Inclusion of a control group "CG"	No comparison group or different forms of abortion (chemical vs. surgical or early vs. late) comparison of women's to partner's responses.	Women with no reproductive event or women from the general population.	Women who gave birth without intendedness identified.	Other form of perinatal loss (miscarriage, stillbirth, adoption placement).	Unintended pregnancy delivered with or without women having actively considered abortion.
Strength of measures or preterm birth "PTB"	Variables measured with under 10 self- report measures of outcomes associated with PTB	Use of self-report measures with under 10 or fewer items per variable and some evidence of PTB association	Use of multiple item self-report measures (10 or more) with extensive well - established associations with PTB.	Use of multiple item self-report measures (10 or more) with extensive well- established association with PTB and another form of data other than self- report.	PTB diagnosed by a trained professional using a well-developed linkage of data or protocol.
Prospective data collection "PD"	One post-abortion assessment or retrospective.	Two or more post-abortion assessments.	Two or more assessments, with the first occurring between the time of abortion or within 6 month of the procedure.	Pre and post- abortion assessments with one or more post- abortion assessment(s) extending up to a year after the procedure.	Pre-abortion assessment(s) and extensive post-abortion assessments, extending from at least a month before to more than a year after the procedure.

Table 2. Application of Criteria to Published Studies from 2004 to 2018 Preterm Birth < 37 weeks											
	Synopsis	S	G	CP	C	A	CC	CG	PTB	PDC	Total
Ancel, et al 2004[51]	Case control study from 10 European countries finding that the risk for very PTB ≤ 28 weeks with 1 abortion with OR of 1.34 [1.08-1.68] and increased risk of PTB with . 2 abortions with OR of 1.82 [1.34-2.49]	4	4	0	2	2	1	3	1	4	21
Voigt, et al 2009[50]	Evaluation of 8 German federal states in a retrospective cohort study with increased risk of PTB ≤ 36 weeks and ≤ 31 weeks.	4	4	4	2	3	3	3	3	3	29
Freak-Poli, et al 2009[549]	Data from South Australia demonstrating increased risk of preterm birth ≤ 37 weeks and with induced abortion with adjusted OR (aOR)) of 1.63 [1.28-2.08] and a risk of PTB with with ≥ 2 with aOR of 1.35 [1.08-1.68] [increasing numbers of induced abortions]	4	4	4	4	4	3	4	2	4	33
Di Renzo et al, 2011[52]	Data base-linked study was a multicenter, observational, retrospective and cross-sectional study of PTB and vaginal deliveries in 9 centers in Italy. increased odds ratio (OR) risk for preterm birth of 1.954 (1.162-3.285) or a 95% increase in the preterm birth rate with any previous abortion(s) no matter when the abortions occurred in the patients' reproductive history.	4	4	4	3	4	3	4	3	4	33
Liao et al, 2011[12]	Cohort study from 7 hospitals in Chendu, China including 4 years of study from January 2006-December 2009. OR 1.4 (1.1-1.8) demonstrating a 40% increase in the preterm birth rate with 1 surgical abortion. OR 1.62 (1.27-3.42) demonstrating a 62% increase in the preterm birth rate ≥3 surgical abortions (dose effect). OR 2.18 (1.51-4.42) demonstrating a 218% increase in the preterm birth rate with medical & surgical abortions	4	0	4	2	1	3	1	2	4	21

Table 3. Application of Criteria to Published Studies from 1980 to 2018 for Very Preterm Birth ≤28-32 weeks											
Study	Synopsis	S	G	CP	C	A	CC	CG	PTB	PDC	Total
Levin, et al 1980	Compared pregnancy loss/preterm birth ≤ 28 weeks with those who delivered at term (≥ 37 weeks). Women who had ≥ 2 induced abortions had 2-3 fold risk of PTD ≤ 28 weeks	2	0	4	3	3	4	3	3	3	25
Lumley, 1998[55]	Data from State of Victoria, Australia demonstrating increased risk of very preterm birth ≤ 28 weeks and PTB ≤ 32 weeks with induced abortion and a dose effect noted with increasing risk of PTB with increasing numbers of induced abortions	4	4	4	4	4	3	3	3	4	33
Moreau, et al 2005[56]	Evaluated very preterm birth (22-32 weeks of gestation) in 9 French regions. The study found an Odds Ratio of 1.8 for 22-27 week delivery and 1.7 for 28-32 week delivery with induced abortion	4	4	1	3	3	3	3	3	4	28
Smith, et al 2006[57]	Analyzed risk of spontaneous PTB with induced abortion. Found risk of PTB at 24-32 weeks increased of PTB with Hazard Risk (HR) of 1.19 with one abortion 1.90 with ≥ 2 induced abortions		4	4							33
Klemtti, et al, 2012[58]	Registry study from Finland comparing birth outcomes after induced abortion. Found increased risk of very preterm birth ≤ 28 weeks with unadjusted OR of 1.22 for 1 abortion, 1.86 for 2 abortions, and 3.38 with ≥ 3 abortions. Adjusted ORs found increased risk with ≥2 abortions.	4	4	4	4	3	3	4	4	4	34
Bhattacharya, et al, 2012[11]	Registry study from Scotland investigating outcomes in women with induced abortion. Found that women with previous abortion (medical or surgical had increased risk of PTB < 37 weeks with adjusted RR of 2.30 [2.27-2.33]. Missing smoking data on 50% patients and 25% of abortion type not listed (i.e. surgical/medical) Used estimates for sample size.	4	4	4	3	2	2	3	3	2	27
Scholten, et al 2013[59]	National registry study from the Netherlands investigating preterm delivery after pregnancy termination. Interview based and individual abortions not in registry by women. PTB ≤ 32 weeks was increased by adjusted OR of 1.52 [1.26-1.85] and ≤ 28 weeks by adjusted OR of 1.67 [1.30-2.15]	4	4	4	2	4	3	4	2	4	27
Hardy, et al 2013[33]	Registry from Canadian database looking at deliveries <32, 28, and 26 weeks with induced abortions. Adjusted ORs were 1.45 < 32 weeks [1.11-1.90], 1.71 < 28 weeks [1.21-2.42; and < 26 weeks 2.17 [1.41-3.35].	4	1	4	2	3	2	2	3	4	25
Zhou, et al 2014[31]	Population –based prospective study in 14 cities in China looking at preterm premature rupture of membranes (PPROM) ≤ 28 weeks with increased OR of 2.75 [1.66-4.56] PPROM of induced abortion	4	4	4	4	4	3	4	3	4	34
Usynina, et al 2016[60]	Registry of all births in a Russian County found adjusted increased adjusted ORs for PTB <28 weeks 1.96 [1.32-2.91] and increased adjusted ORs 28-32 weeks of 1.36 [1.06-1.76]	4	4	4	3	3	3	4	3	4	32
Situ KC, et al 2017[61]	Study from Finland demonstrating significantly increased risk of extremely preterm birth ≤ 28 weeks with OR of 1.51 [1.03-2.23].	4	4	4	4	3	3	4	4	4	34
Magro Malosso, et al 2018[7]	Study of abortion from 2003-2012 from US databases (which are not linked and suspect) from National Vital Statistics Reports and Center of Disease and Prevention which found increased risk for PTB with surgical abortion and decreased PTB rates with medical abortion.	4	4	2	2	3	2	2	1	2	22

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