Medication Abortion and Preterm Birth

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ABSTRACTS: Considerable controversy exists about the effects of medication abortion on the incidence of preterm birth (PTB). Medication abortion of various types continues to be touted as a safe alternative to surgical abortion, and without increased risk for PTB. There is a paucity of evidence regarding medication abortion and PTB, but available papers are reviewed here. There is moderate-quality evidence that medication abortions which require surgical completion increase PTB rates more than surgical abortion alone.

Background

Preterm Birth

Preterm birth (PTB), defined as delivery before 37 weeks of gestation, leads to 3 million annual deaths worldwide, and combined with low birth weight, PTB is estimated to cost over 100 million disability adjusted life-years.[1] The incidences of PTB range from 6-8% in Europe, Australia, and Canada[2,3] to 9-12% in Asia and Africa.[4,5] The rate of PTB in the U.S. was 10.2% in 2019.[6] In the U.S., the rate of delivering a low birth weight (LBW) infant, defined as less than 2500 grams, is 8.3%, with most LBW infants born before 35 weeks.[7] Preterm births before 32 weeks continues to represent 1.4% of singleton births in the U.S.[1]

The increased risk for PTB after surgical abortion is likely due to physical trauma associated from dilation and removal of intrauterine contents

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during pregnancy.[8] The association of PRB with medication abortion has been less actively studied, although medication abortion has been offered as a less traumatic alternative. Medication abortion now represents 53% of all abortions in the United States.[9]

Medication Abortion and PTB

The putative mechanisms by which mifepristone may increase the risk for PTB is not clear but may include decreasing maternal immune defenses (since mifepristone has glucocorticoid effects and is associated with maternal sepsis),[22] or adverse remodeling associated with cervical ripening.[23]

Mifepristone is a powerful progesterone receptor blocker. Its mechanism is thought to be through 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, and that the "long-term impact of such chemically induced cervical changes is unclear."[24]

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.[25]

The long-term effects of biochemical changes in the cervix due to mifepristone, along with genetic upregulation of a number of genes, is unclear. If mifepristone administration causes remodeling, short- or long-term cervical instability may increase the risk for future PTB.

There are few studies assessing the rate of PTB after medication abortion. The largest study included 419,879 nulliparous women in Finland with singleton deliveries between 1996 and 2013.[10] The authors compared women with prior medication abortion, surgical abortion, and no prior abortion. 365,356 women (87%) had no prior abortion, 13,450 (3.2%) had a prior medication abortion, 38,659 (9.2%) had a prior surgical abortion, and 2,414 (0.6%) had prior medical *and* surgical abortions. Authors calculated adjusted odds ratios (aOR) accounting for maternal age, marital status, city dwelling, tobacco use, and year of childbirth.

In this study, preterm birth was more prevalent in women with prior surgical abortion or surgical plus medication abortion, but not in women who had medication abortions alone. Confounders in this study included smoking, a known risk factor for PTB, which was more common among those who had a prior abortion, and birth year of the child after the abortion, which is consistent with trends in improved neonatal care. Prior to 2010, there were also more surgical abortions. This difference in timing means that surgical abortions

happened more often before significant improvements in neonatal care. This could confound outcomes such as neonatal death after preterm birth. This study found the well-known association between surgical abortion and PTB, and re-demonstrated that later gestational age at surgical abortion is associated with more preterm birth, although this effect was not identified for medication abortion. Medication abortion was associated with *lower* odds of PTB before 37 weeks (aOR 0.83, 95% CI 0.74-0.89). The adjusted odds ratio of PTB before 32 weeks and before 28 weeks were not significantly different from the population without prior abortion (aOR 0.83, 95% CI 0.64-1.08 and aOR 0.94, 95% CI 0.68-1.30).

The next largest study was done by Planned Parenthood in China, and included 4,925 women without prior abortion, 4,931 with prior medication abortion, and 4,800 with prior surgical abortion.[11] The rate of PTB before 37 weeks in this study was 3.7% with no self-disclosed abortion history, 2.9% after medication abortion, and 3.0% after surgical abortion.

The rate of PTB after medication abortion before 7 weeks was not significantly different from the rate in women who reported no prior abortion (OR 0.78, 95% CI 0.60-1.01), nor was this different from PTB rates in women who had medication abortion between 7 and 16 weeks (OR 0.77, 95% CI 0.53-1.10).

There was also no difference in PTB rates after medication abortion with curettage, compared to women with no prior abortion (OR 0.94, 95% CI 0.65-1.34), and there was *less* PTB after medication abortion without curettage compared to women with no prior abortions (OR 0.87, 95% CI 0.55-0.93). This study also reported that medication abortions were not associated with higher PTB rates compared to surgical abortion, regardless of whether they were completed with curettage (0.87, 95% CI 0.66-1.14) or not (1.15, 95% CI 0.79-1.67).

These findings cannot be interpreted as equivalent to preterm birth rates in the U.S., however, because all deliveries in this study prior to 28 weeks were termed spontaneous abortions, and no neonates born before 28 weeks were resuscitated. This may falsely depress reported PTB rates since it does not include any births between 20 and 28 weeks, which are counted as preterm births in U.S.

As mentioned above, the study relied on women to self-report their previous abortions status, which could lead to reporting bias given the rigorously-enforced one child policy still in place in the early 2000s. Without confirmation of self-reported abortion in medical records, it is possible that women in the control group of "no prior abortion" had in fact undergone an abortion by some means, and preferred not to report it.

Finally, the rate of curettage after medication abortion in this population (25.3% by patient report) exceeds the rate of surgical completion of medication abortion in the U.S. (usually below 6% before 70 days), which may relate to

the late gestational age up to 16 weeks of medication abortion in this study.[12] This high rate of curettage muddies the distinctions between medication and surgical abortion groups, and the multiple challenges with external validity make this study difficult to generalize to a U.S. population.

Subsequently, another study out of China, by Liao *et al* evaluated the effects of repeated first trimester medication abortions with mifepristone on preterm birth in subsequent pregnancies in a cohort of 19,527 women from seven hospitals between 2006 and 2009.[13] The study was interview-based with delivery outcomes available in 18,323 women (94%). 7558 reported a prior abortion, of whom 7478 had complete follow-up (99%). Of 10,681 who denied a prior abortion, 10,546 had complete follow-up (99%).

Nulliparous women with abortions were divided into three groups by the type of abortion (medication, surgical, or medication requiring surgical completion), and compared to controls without prior abortion history for rate of PTB. Of the women with a prior abortion, 24% had one medication abortion, 7.4% had more than one medication abortion, and 16% had medication abortions completed surgically. The rate of curettage after medication abortion was 20.3% in this study, similarly elevated far beyond U.S. rates. In this population, a history of one or multiple successful first trimester medication abortions was *not* associated with a higher risk of PTB in singleton subsequent pregnancies.

Medication abortions completed surgically was associated with *increased* odds of subsequent PTB before 37 weeks (OR 2.18, 95% CI 1.51-4.42), which correlates to a relative risk (RR) of 1.9. If this relative risk was applicable to the U.S. population, then medication abortion completed surgically would increase a woman's baseline risk of PTB from 10.2% to 19.8%.

Medication abortion completed surgically was also associated with increased odds of delivery before 32 weeks (OR 3.61, 95% CI 1.43-4.93), corresponding to a relative risk of 2.9 and an increase in the baseline risk of PTB from 10.1% to 29.1%.

Focusing on medication abortions before 7 weeks completed surgically, there was still increased odds of PTB (OR 1.69, 95% CI 1.02-3.16), which corresponds to a RR of 1.6 and an increase in PTB risk from 10.2% to 16.1% if applicable to a U.S. population.

Like the previously mentioned study by Chen *et al*, this study was interview-based, not linked with medical records, meaning that reporting and recall bias may affect the data quality. Family size practices in China during this study were similar to that during the previous study. Of the two studies with very different findings, it is not clear which is superior or which can be applied to the U.S.

Medication Abortion and LBW

Zafran *et al* analyzed an Israeli database to examine PTB rates in women with prior medication abortion, prior surgical abortion, and no prior abortion.

There was *no increased* risk of PTB and LBW in patients with medication abortion compared to patients without abortions (OR 2.4, 95% CI 0.4-12.6).[14] This study involved 70 women with medication abortion and 210 controls. According to their calculations, they had sufficient power to be able to discern a 10% difference between their baseline of 5% PTB and medication abortion. This 10% difference, which is larger than the baseline prevalence of the outcome, indicates that the sample size in this retrospective study is too small to detect small or moderate (but real) differences in PTB rates that would impact clinical practice or policy.

Männistö *et al* compared PTB rates after medication abortions to those after surgical abortions in Finnish women, and found no difference in risk of PTB (OR 0.87, 95% CI 0.68-1.13), or LBW (OR 0.90, 95% CI 0.68-1.19).[15] Since surgical abortion is a well-known risk factor for PTB, this may not be reassuring. The same authors later compared the rates of PTB after first- and second-trimester medication abortions; rates were similar (aOR 0.97, 95% CI 0.57–1.66).[16]

Virk *et al* 2007 used Danish data to compare rates of PTB and LBW after medication abortion compared to surgical abortion.[17] The rate of PTB after medication abortion was 5.45%, and after surgical abortion, 6.7%. These were not significantly different (RR 0.88, 95% CI 0.66-1.18). There was also no difference in LBW (RR 0.82, 95% CI, 0.61-1.11), which suggests that medication abortion may be associated with an increase in PTB like the increase related to surgical abortion.

Conclusions

There is contradictory evidence on the effect of medication abortion and risk of subsequent PTB. Available papers suggest that the rate of PTB after medication abortion is lower than that is. The heterogeneity of data may be due to varying rates or techniques for curettage. Sharp curettage, compared with vacuum aspiration causes more pain[18] and is associated with more complications in some studies.[19,20] Second trimester surgical abortions, which are less common than first trimester surgical abortions, can lead to even further trauma related to fetal dismemberment and maternal internal laceration.[21]

In addition to these unmeasured differences in the background of studies comparing medication abortion and surgical abortion, unexpected effects in the data suggest that confounders are not completely controlled for. For example, curettage after failed medication abortion causing less PTB than no curettage at all in China suggests that control groups with no prior abortion may include women with undisclosed curettage procedures in the past. These factors prompt caution when interpreting the limited data available.

Summary of Recommendations and Conclusion

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

1) Women with a history of medication abortion may be at increased risk of preterm birthif surgical completion was required.

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

2) Further systematic study of preterm birth rates in populations who have a history of medication abortion is needed.

3) Studies may be limited if medication abortions are reported as spontaneous miscarriages, if they are dependent on voluntary patient disclosure about medical and surgical abortions, or if curettage is subsequently performed.

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