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MATERNO-FETAL MEDICINE

Repeated medical abortions and the risk of preterm birth in the subsequent pregnancy

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Abstract
Purpose The aim of this study was to determine the impact of repeated first trimester mifepristone-induced medical abortions on the risk of preterm birth in a subsequent pregnancy.
Methods This is a pregnancy-based cohort study. Clinical data were collected from seven public hospitals in Chengdu, China from January 2006 to December 2009. Pregnant women with one or more first trimester mifepristone-induced medical abortions, and/or one or more surgical abortions, or no previous induced abortions were included in the study. The women were monitored through pregnancy and birth. Samples for analysis included 18,024 singleton births.
Results The risk of preterm birth among women with one or more first trimester mifepristone-induced abortions did not differ significantly from the risk among primigravida women (OR 1.03, 95% confidence interval 0.53–1.63). The risks of preterm birth were higher among women with repeated surgical abortions in comparison to women with repeated medical abortions (OR 1.22, 95% confidence interval 1.03–1.64).
Conclusions 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.

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Keywords Medical abortion · Preterm birth · Repeated induced abortions · Mifepristone

Introduction

Of the estimated 211 million pregnancies that occur each year worldwide, about 46 million are terminated by induced abortions [1]. Approximately 9 million induced abortions are performed annually in the medical settings of China in recent years [2].

Currently, the use of medical abortion to terminate an early pregnancy is increasing worldwide. The reported proportions of medical abortions in the total number of induced abortions are 40–50% in China [3], 46.5% in Norway [4], 69% in Finland [5], 30% in the United Kingdom [6], and 13% in the United States [7]. As an alternative to surgical evacuation, the efficacy, acceptance, and safety of medical abortion are well identified. In countries with limited health resources and poorly developed health care systems, the medical procedure has made legal abortions safer and more accessible.

Repeated abortions also account for a large portion among early pregnancy terminations. The reported occurrence of repeated induced abortions is 35% in China [8]. The corresponding figures are 30–38% in Northern Europe [9], approximately 50% in the USA [10], and 35.5% in Canada [11]. Repeated abortion seekers are often young, unmarried, and with desires for future fertility [12]. It is important to understand the long-term impact of previous abortions on subsequent pregnancy.

Preterm delivery is a leading cause of perinatal morbidity and mortality, and is also a major cost burden to health care systems worldwide. Over the past decades, studies have shown the association between previous abortions and

subsequent preterm delivery. Previous spontaneous abortions and missed abortions have been found to be related to increased risks of preterm birth [13–15]. And the risk of preterm delivery increases with the number of previous induced abortions [16]. A recent systematic review demonstrated that a history of one induced abortion was associated with increased odds of preterm birth (OR 1.36, 95% CI 1.24–1.50), and more than one induced abortions was associated with an even higher risk of preterm birth (OR 1.93, 95% CI 1.28–2.71) [17].

The majority of studies relating abortions and preterm birth combine medical and surgical abortion without a classification for abortion types. Other studies concerning this issue analyze pregnancy outcome after one medical abortion (gravidity 1 parity 0 or gravidity 1 parity 1). Compared with surgical abortion, a history of one previous medical abortion is not related to a higher risk of ectopic pregnancy, preterm birth, low birth weight (LBW), or prolonged third stage labor in subsequent pregnancies [3, 18, 19]. However, until recently little is known about the effects of repeated medical abortions on subsequent pregnancy outcomes; clear conclusions are lacking.

Given the widely increasing trend of medical abortion and repeated abortions in an even younger population worldwide, studying the effects of multiple medical abortions on subsequent pregnancy complications has essential public health importance. This study was conducted to determine the impact of repeated first trimester mifepristone-induced abortions on the risk of preterm birth in a subsequent pregnancy.

Materials and methods

Data source

This pregnancy-based cohort study was conducted in six public hospitals in Chengdu, China over a period of 4 years from January 2006 to December 2009. Women were enrolled at their first antenatal care before 20 gestational weeks in their current pregnancy. All the subjects were followed up until 6 weeks after delivery. The gestational age was estimated on the basis of the last menstrual period (LMP), and corrected by the ultrasound estimates.

At enrollment, trained interviewers administered a structured questionnaire on demographic and socioeconomic characteristics, marital status, employment, lifestyle, reproductive history, previous operations, illnesses, obstetric history, contraceptive use, smoking and alcohol consumption before and during pregnancy and details on the previous induced abortion. Information on pregnancy complications, duration of gestation, labor and delivery complication, the vital status, sex, and birth weight of the infant and the presence of any malformations was based on clinical records. Errors and inconsistencies were corrected by reinterviewing the women. Approval was obtained from the regional ethics committee, and all women were provided written informed consents.

Eligibility and group assignments

Nulliparous women who had undergone one or more first trimester mifepristone-induced abortions, and/or first trimester surgical abortions for nonmedical reasons, or had no prior induced abortions were eligible. During the study period, 19,527 eligible pregnant women were identified. Among those eligible, 18,323 (93.8%) were successfully recruited, with approximately 2% lost due to patient refusal, 2% due to an inability to make contact at the time of their clinic visit, 1% due to physician refusal, and 1% for other reasons.

The rate of women lost to follow-up was 0.49% (89/18,328). After excluding those lost to follow-up, 98.9% (7,478 of 7,558), and 98.7% (10,546 of 10,681) of the pregnancies resulted in singleton live or stillbirths in the abortion cohort and non-abortion cohort, respectively. The results reported here for pregnancy duration were based on 18,024 singleton births. A flow-chart of the study population is shown in Fig. 1.

According to previous induced abortion, the study population was divided into an abortion cohort ($n = 7,478$) and a non-abortion (NA) cohort ($n = 10,546$). The abortion cohort was further divided into three sub-cohorts: a surgical abortion (SA) cohort, a medical abortion (MA) cohort, and a surgical and medical abortion (SA + MA) cohort. SA and MA cohorts consisted of women with a history of one or more MAs or SAs, respectively. The SA + MA cohort consisted of women with a reported history of both medical and surgical abortions. According to the presence of previous spontaneous abortion, we further divided the NA cohort into two sub-cohorts: a spontaneous abortion (SpA) cohort ($n = 451$) and a primigravida cohort ($n = 10,095$).

In the abortion cohort, 4,669 women reported one prior induced abortion (62.4%) and 2,809 women have had at least two prior induced abortions (37.6%). The rate of women who reported at least two previous MAs was 3.07% (553/18,024) in the study sample. In the NA cohort, 332 women had one prior spontaneous abortion (3.15%), 78 had two spontaneous abortions (0.74%) and 41 had at least three spontaneous abortions (0.39%).

The following definitions were used to record pregnancy risk factors and outcomes: preterm delivery is defined as delivery at less than 37 completed weeks (259 days) of gestation. Very preterm is defined as birth at less than 32

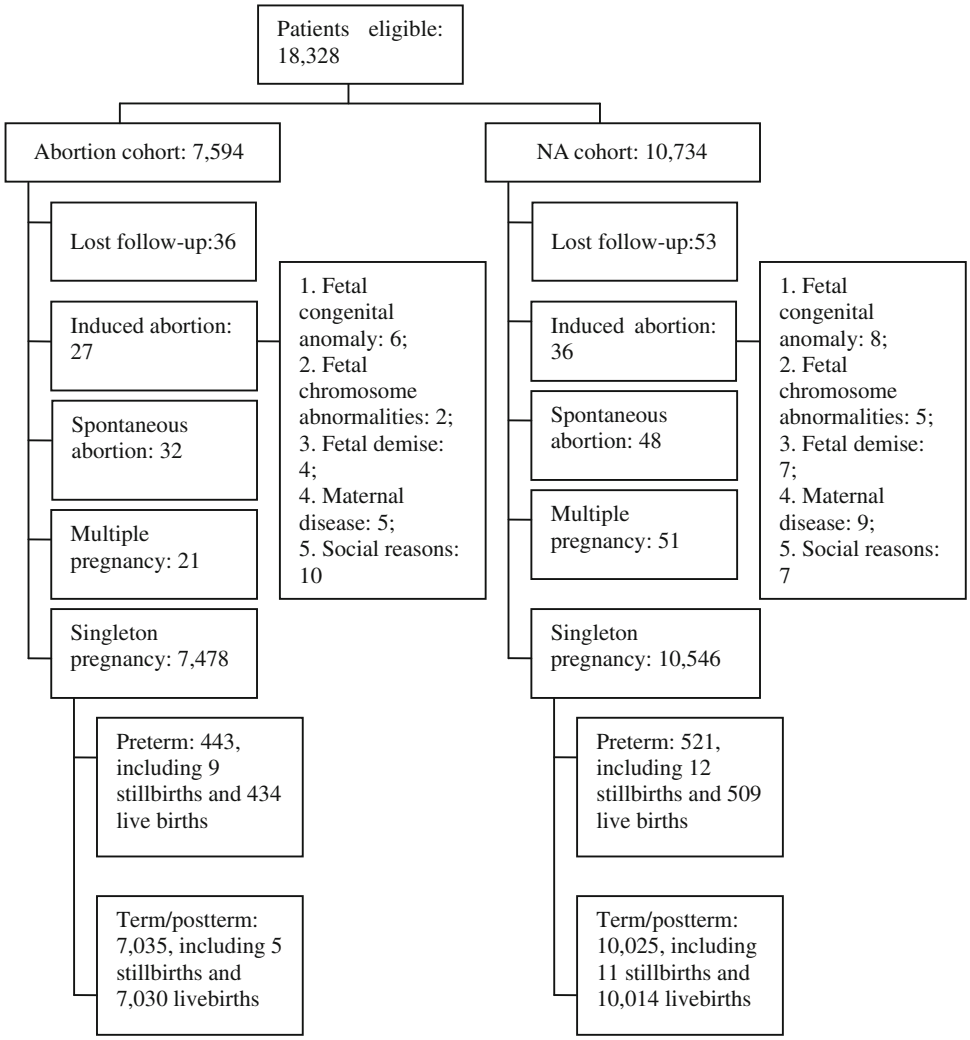

Fig. 1 Flow chart of the study population

weeks of gestation. Spontaneous abortion is defined as the spontaneous loss of a fetus or embryo before 20 completed weeks of gestation or weighing less than 500 g. The post-abortion interpregnancy interval (PAII) is defined as the time elapsed between the day of the prior induced abortion and the first day of the LMP for the index pregnancy. The first trimester is defined as the period from conception to 12 completed weeks of gestation.

Medical abortion regimens

The regimens for mifepristone abortion in China were: (1) 200 mg administered orally in a single dose, (2) 50 mg taken twice daily for 2 days, (3) one 50-mg dose and one 25-mg dose taken daily for 2 days, (4) one 50-mg dose and one 25-mg dose taken for the first day, one 25-mg dose taken twice daily for the next day and one 25-mg dose taken for the third day. 48 h after the first dose of mifepristone was administered, misoprostol (0.6 mg) was given orally.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 13.0 (SPSS, Chicago, IL, USA). At the comparison of pregnant women with MA or SA during the study pregnancy, Student's *t* test was used for quantitative and Chi-square test for categorical variables. $P < 0.05$ was considered to be statistically significant. Logistic regression analyses were performed to estimate the effects of abortion on preterm birth. Several factors (e.g. maternal age, educational level, employment) that have been proved to be risk factors for preterm birth in previous studies were included in all adjusted multivariate analyses of pregnancy outcome. Other categorical covariates were marital status,

family income, contraceptive use, smoking, alcohol drinking, and chronic disease history, gestational age at abortion, medication use, pre-pregnancy weight and interpregnancy interval. Multivariable analysis was performed stepwise, leaving only the significantly associated confounders to the final models. Confidence intervals (CI) were evaluated at 95%.

Results

Demographic background

Women who reported a history of multiple SAs were mostly 30 years old or older (42.5 vs. 32.9%, $P < 0.01$), unemployed (17.5 vs. 9.7%, $P < 0.001$), with lower educational levels (e.g., primary or middle school) (76.7 vs. 65.9%, $P < 0.05$) than the women with repeated MAs (Table 1). PAII of less than 6 months were often seen in women with at least two previous MAs, but this difference did not show statistical significance ($P > 0.05$).

Type of and gestational age at previous abortion

More women reported a history of abortion beyond 7 completed weeks of pregnancy in the SA cohort than the MA cohort (67.5 vs. 17.1%, $P < 0.01$). The mean gestational weeks at abortion were 6.1 ± 4.5 and 8.2 ± 4.7 weeks in the MA and SA cohort, respectively ($P < 0.05$). Surgical abortions in the study population were mainly performed by vacuum aspiration (Table 2).

Risk of preterm birth (PTB)

The overall risk of PTB was 5.3%, while the risk was 4.9% among primigravid women. The incidences for PTB were 5.4 and 6.0%, respectively, in women with single and at least two induced abortions.

Table 1 Demographic and clinical characteristics of the study population ($n = 18{,}024$)

Variable	Number of prior abortions					
	None [($n = 10{,}546$), %]	One		Two or more		
		MA [($n = 1{,}769$), %]	SA [($n = 2{,}900$), %]	MA [($n = 553$), %]	SA [($n = 1{,}088$), %]	MA + SA [($n = 1{,}168$), %]
Maternal age (years)						
<20	1.2	1.7	1.4	0.4	0.7	1.5
20–24	35.4	37.3	36.2	25.4	15.7	25.4
25–29	40.7	36.2	37.2	41.3	41.1	33.5
30–35	18.6	17.5	16.3	28.6	31.0	24.4
>35	4.1	7.3	8.9	4.3	11.5	15.2
Education						
Primary school	19.7	28.6	30.3	27.4	29.5	26.9
Middle school	57.7	53.4	49.8	38.5	47.2	41.1
University and higher	22.6	18.0	19.9	34.1	23.3	32.0
Residence						
Rural	27.4	31.8	28.6	47.4	38.6	36.2
Urban	72.6	68.2	71.4	52.6	61.4	63.8
Employment during pregnancy						
Yes	82.4	89.4	87.1	90.3	82.5	86.4
No	17.6	10.6	12.9	9.7	17.5	13.6
Weight before pregnancy <45 kg						
Yes	3.1	4.8	5.2	3.4	2.8	4.5
No	96.9	95.2	94.8	96.6	97.2	95.5
PAII (months)						
<6	_	3.8	4.2	5.4	4.8	5.5
6–12	_	16.5	16.8	9.6	11.4	7.3
12–36	_	43.9	52.7	41.3	57.2	69.2
>36	_	35.8	26.3	43.7	26.6	18.0

PAII postabortion interpregnancy interval

Table 2 Distribution of methods of previous SAs (SA cohort only, $n = 3{,}988$)

Number of previous IAs and methods	*n* (%)
One SA ($n = 2{,}903$)	
One vacuum aspiration	2,659 (91.6)
One evacuation	125 (4.3)
Uncertain	119 (4.1)
Two SAs ($n = 686$)	
Two vacuum aspirations	614 (89.5)
Two evacuations	13 (1.9)
One vacuum + one evacuation	25 (3.7)
Uncertain	34 (4.9)
Three SAs ($n = 343$)	
Three vacuum aspirations	299 (87.3)
Two vacuums + one evacuation	11 (3.2)
Others	8 (2.3)
Uncertain	25 (7.2)
More than three SAs ($n = 56$)	
All vacuums	43 (76.8)
Others	3 (5.6)
Uncertain	10 (17.6)

Risk of PTB in relation to previous spontaneous abortions

Women with one prior spontaneous abortion had a 5.1% risk for PTB; for women with two prior spontaneous abortions, this risk increased to 6.4%; for women with three previous spontaneous abortions, the risk increased to 7.3% ($P < 0.05$).

Risk of PTB according to the number and methods of previous abortions

Women with a history of induced abortion (IA) were at higher risks of PTB than those without such history (OR 1.4, 95% CI 1.1–1.8), especially those with one or more SAs (OR 1.29, 95% CI 1.02–2.43). The risk of PTB in women with one or more MAs did not differ significantly from those without prior abortions (OR 1.03, 95% CI 0.53–1.63).

The risk of PTB increased with the number of previous surgically induced abortions ($P < 0.05$). Three or more SAs were associated with the highest risk of PTB (OR 1.62, 95% CI 1.27–3.42). The risk of PTB among women with multiple MAs did not differ significantly from the risk among primigravida women (OR 1.13, 95% CI 0.72–1.43). The risks of PTB according to the number and types of previous abortions are shown in Fig. 2.

The risks of PTB after one MA did not differ significantly from the risks after one SA (OR 0.93, 95% CI 0.52–1.74). However, the incidences of PTB were higher among women with multiple SAs than women with multiple MAs (OR 1.22, 95% CI 1.03–1.64). The incidence of very PTB was even higher among women with multiple SAs or both MAs and SAs than women who had multiple MAs (OR 2.18, 95% CI 1.51–4.42; OR 1.35, 95% CI 1.05–1.82). A higher risk of very PTB was also found among women with at least two prior spontaneous abortions than those with multiple medical abortions (Table 3). The incidence of PTB increased slightly with the increasing number of previous MAs; however, no statistically significant trend was detected ($P = 0.16$).

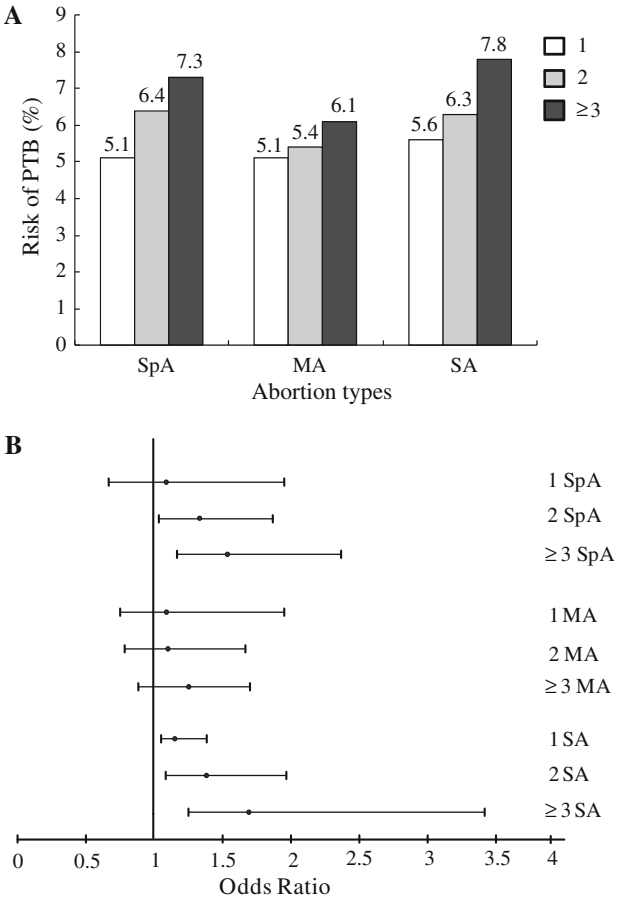

Fig. 2 **a** Risks of PTB according to the number and type of previous abortions. Data were derived from 16,856 women (not included women who had both MA and SA). **b** Odds ratios (with 95% confidence intervals) of the risk of PTB according to number and methods of previous abortions. Data were derived from 16,856 women (not included women who had both MA and SA)

Risk of PTB in relation to postabortion curettage in medical abortions

Overall, 20.3% of the patients in the medical cohort received a postabortion suction curettage. Patients with a history of previous SA had a higher incidence of postabortion

Table 3 Preterm birth among singleton births (n = 2,918) in women with multiple abortions

Pregnancy outcome	Abortion group				Comparison		
	SpA (n = 119)	MA (n = 552)	SA (n = 1,083)	MA + SA (n = 1,164)	SpA versus MA AOR[a] (CI)	SA versus MA AOR[b] (CI)	MA + SA versus MA AOR[c] (CI)
PTB	8 (6.7)	31 (5.6)	74 (6.8)	64 (5.5)	1.18 (0.93–1.36)	1.22 (1.03–1.64)*	0.99 (0.69–1.84)
Very PTB	2 (1.7)	5 (0.9)	21 (1.9)	14 (1.2)	1.95 (1.68–3.79)*	2.18 (1.51–4.42)**	1.35 (1.05–1.82)*

Values are presented as n (%), unless otherwise indicated

SpA spontaneous abortion, *AOR* adjusted odds ratio, *CI* adjusted 95% confidence interval

* $P < 0.05$, ** $P < 0.01$

[a] Adjusted for age, education, residence, occupational status

[b] Adjusted for age, education, residence, pre-pregnancy weight, occupational status and postabortion interpregnancy interval (PAII)

[c] Adjusted for age, education, residence, occupational status and postabortion interpregnancy interval (PAII)

Table 4 Pregnancy outcome according to the presence of postabortion curettage after MA, stratified with the gestational weeks (MA cohort only, n = 2,322)

Pregnancy outcome [n (%)]	GA < 7 weeks				GA ≥ 7 weeks			
	Curettage (n = 295)	Non-curettage (n = 1,569)	Adjusted OR[a]	95% CI	Curettage (n = 177)	Non- curettage (n = 281)	Adjusted OR[a]	95% CI
PTB	21 (7.1)	76 (4.8)	1.69	1.02–3.16*	9 (5.1)	16 (5.7)	0.84	0.39–1.86
Very PTB	8 (2.7)	13 (0.8)	3.61	1.47–4.93**	3 (1.7)	3 (1.1)	1.72	0.61–3.85

* $P < 0.05$, ** $P < 0.01$

[a] Adjusted for age, education, residence, pre-pregnancy weight, occupational status and postabortion interpregnancy interval

suction curettage after medical abortion than women without such history (OR 1.78, 95% CI 1.12–2.85). The incidences of PTB following one MA were, respectively, 6.36 and 4.98% in women with and without postabortion. After adjustment for maternal characteristics, the results indicated no statistical difference ($P > 0.05$).

The incidence of PTB in women with a history of MA at 7 gestational weeks or later did not differ from the incidence in women who underwent MA earlier than 7 weeks (OR 1.05, 95% CI 0.48–2.15). Compared to women without postabortion curettage, women with a history of MA earlier than 7 completed weeks and postabortion curettage were at an increased risk of PTB (OR 1.69, 95% CI 1.02–3.16); and the risk was even higher for very PTB (OR 3.61, 95% CI 1.43–4.93) (Table 4).

Discussion

In the present study, we found that a history of multiple first trimester mifepristone-induced abortions was not associated with a statistically significant higher risk of PTB among singleton births compared with women without previous induced abortions. The risks of PTB were higher after multiple surgical abortions than after multiple medical abortions.

The main advantages of this study are large size and cohort design as well as the classification made between surgical and medical procedures. This is one of the first studies to explore the risk of PTB after multiple medical abortions. It would be helpful to understand the impact of MA on future pregnancies, especially for women with repeated abortion procedures.

Several potential limitations need to be kept in mind to interpret the results of this study. First, the abortion procedures were not restricted to be performed within a specified institute. It was therefore difficult to assess the exact gestation ages at termination and procedure details such as types of surgical procedure performed (dilation and evacuation or vacuum aspiration). The criteria for candidates of postabortion curettage could also differ across institutes. In addition, based on the self-reporting questionnaire, the recall bias or underreporting could not be ruled out, as with most other studies concerning this issue. Second, by excluding multiple pregnancies and multipara, the rate of PTB would be underestimated in both medical and surgical cohorts. The interactions between abortions and the confounding factor of parity could not be fully assessed. Third, based on the study population, the sample size was smaller in the MA cohort than the SA cohort. Meanwhile, risks of PTB were lower following MAs than SAs. From a statistical viewpoint, however, such difference in the cohort size would be

expected to weaken the ability to detect the effects of MA on subsequent PTB. Finally, spontaneous PTB was not distinguished from induced PTB. The association between abortion and the risks of idiopathic preterm delivery, preterm following preterm rupture of membrane (PROM) or iatrogenic preterm complicated with pregnancy-induced hypertension, placenta abnormalities, and other complications were not identified. Though unavailable in the present study, the hypothesis that multiple induced abortions (surgical or medical) possibly related with a certain cause of PTB could be evaluated in the future.

Currently, mifepristone-induced medical abortion and vacuum aspiration in the first trimester comprise the majority of voluntary early pregnancy terminations performed in China. Mifepristone has been produced in China in the 1990s and now mifepristone combined with misoprostol is widely used in hospitals and clinics. Early medical abortion is recommended up to 7 weeks of pregnancy in China; vacuum aspiration is restricted up to 10 weeks of pregnancy; Dilation and evacuation (D&E) is used in pregnancy between 10 and 14 weeks. However, D&E is now seldom performed in early pregnancy termination in clinical practice for the severe surgical complications including heavy bleeding and uterine or cervical injury. In comparison to surgical abortion, medical abortion provides significant advantages in the management of "high-risk induced abortions", for instance, IAs following multiple SAs or caesarean deliveries; abortions during the lactation periods; in women with cervical or pelvic malformations or with high level of anxiety to the surgical procedures. A total of 19.7% of the study population is consisted of women with a history of MA at 7 gestational weeks or later. This phenomenon would be partly due to the clinical practice that a few "high-risk induced abortions" (as mentioned above) beyond 7 gestational weeks are performed with medical methods based on the balance of both side effects and safety considerations.

Repeated IA is considered to be an important public health issue. A recent study from the United Kingdom reported a radical increase of 68% repeated abortions over 17 years from 1991 to 2007 [20]. Young age, being parous, and a history of prior abortion emerge as the risk factors for repeated abortions [9].

Until now, little is known about the effects of repeated MA on subsequent pregnancy outcomes, although the relationship between a history of induced abortion and a risk of PTB is well documented. Zhou et al. [21] found an association with ORs of PTB of 1.89, 2.66, and 2.03, following one, two, or more induced abortions, respectively. A population-based study enrolling 12,432 women suggested that a history of IA increased the risk of PTB particularly for women who have had repeated IAs [22]. Moreau [23] found that the strength of association between previous IA and an increased risk of very PTB increased with decreasing gestational age. Furthermore, a history of induced abortions significantly increases the risk of PTB after idiopathic preterm labor, PROM, and ante-partum hemorrhage, but not PTB after maternal hypertension [16]. In the present study, a significantly higher risk of PTB was found to be confined to women with multiple SAs with a dose response to the number of procedures. The risks for PTB after MA did not differ significantly from the risks after SA. Similar results have been reported by Virk [18]. In addition, a history of two or more electively early medical abortions is not related to a higher risk for PTB. It can be explained by the avoidance of instrumentation which is related to potential uterine and cervical trauma during the procedures of a vast majority of medical terminations.

In the present study, an increased risk of PTB was detected in women with an increasing number of spontaneous abortions. These findings confirm studies on the relationship between previous spontaneous abortions and PTB, which demonstrate that a history of spontaneous abortion is a risk factor for subsequent PTB [15, 24].

Prolonged vaginal bleeding and an incomplete abortion are the main adverse events of medical abortion. A history of previous curettage, advanced maternal age, and high parity are regarded as risk factors for postabortion curettage. In the study population, there was an overall postabortion curettage rate of 20.3% which was higher than the reported incidence of 2.6% by Allen [25]. The postabortion curettage rate in the present study is comparable to that reported by other trials from the USA (18.3%) and China (25.3%) [26, 27]. Such difference is likely explained by the clinical practice of performing curettage for minor abortion-related complications (i.e. bothersome vaginal bleeding), despite the absolute indications were ongoing pregnancy and incomplete pregnancy. In China, a postabortion curettage would be performed if the client continues to have vaginal bleeding 2 weeks after administration of mifepristone or has an excessive vaginal bleeding twice as much as menstrual bleeding.

There were no statistical differences in PTB risks between women who had MAs before 7 completed gestational weeks and women who had MAs after 7 weeks in the present study. Similar results have been reported by Chen and colleagues [27] who analyzed the effect of previous IA among women. In addition, the relationship between a higher risk of PTB and a history of postabortion suction curettage was confined to women who had MA earlier than 7 weeks of gestation. A study by Liang [28], enrolling 4,931 women with one previous MA, suggested that a history of postabortion curettage was related to a higher risk for placenta abruption, placenta accrete, or increta and postpartum hemorrhage among women who experienced abortion earlier than 7 gestational weeks. These findings might

be explained by the possibility that a postabortion curettage earlier than 7 weeks would be related to a greater chance for trauma and chronic inflammation to both the cervix and endometrium.

In conclusion, a history of multiple first trimester mifepristone-induced abortions is not associated with a higher risk of PTB among singleton births in subsequent pregnancies. Among women with at least two previous induced abortions, the risks of PTB after surgical abortions are significantly higher than the risks after medical abortions. Medical abortion is the preferred option for women without children and female adolescents to terminate unwanted pregnancies. Family planning, counseling, and antenatal care for women with previous artificial abortions should be administered with careful regard to the effect of abortion on future pregnancy complications.

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Conflict of interest The authors have no conflicts of interest. There is no financial relationship with the organization that sponsored the research. We have had full control of all primary data and that we agree to allow the journal to review our data if requested.

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