Mifepristone-induced Early Abortion and Outcome of Subsequent Wanted Pregnancy

Aimin Chen1,5, Wei Yuan1, Olav Meirik2, Xianmi Wang3, Shi-Zhong Wu4, Lifeng Zhou1, Lin Luo4, Ersheng Gao1, and Yimin Cheng3

1 Key Laboratory of Contraceptive Drug and Device Research, Department of Reproductive Epidemiology and Social Science, Shanghai Institute of Planned Parenthood Research, Shanghai, China.
3 Department of Reproductive Epidemiology and Social Science, National Research Institute for Family Planning, Beijing, China.
4 Department of Reproductive Epidemiology, Chengdu Donghua Reproductive Health Research Institute, Sichuan, China.
5 Current address: Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC.

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Follow-up information on subsequent pregnancies after mifepristone (RU486)-induced abortion is scarce. The authors examined whether one mifepristone-induced first-trimester abortion affects the outcome of a subsequent wanted pregnancy. In a study conducted in 1998–2001 at antenatal clinics in Beijing, Chengdu, and Shanghai, China, the authors enrolled 4,925 women with no history of induced abortion, 4,931 women with one previous mifepristone-induced abortion, and 4,800 women with one previous surgical abortion and followed them through pregnancy and childbirth. The adjusted odds ratio for preterm delivery in women with one mifepristone abortion compared with women with no abortion was 0.77 (95% confidence interval: 0.61, 0.98). Although the mean birth weight of infants born to women with mifepristone abortion was 33 g (95% confidence interval: 17, 49) higher than that of infants born to women with no abortion, the frequencies of low birth weight and mean lengths of pregnancy were similar. There were no significant differences in risk of preterm delivery, frequency of low birth weight, or mean infant birth weight in the comparisons of women with previous mifepristone abortion and women with surgical abortion. This study suggests that one early abortion induced by mifepristone in nulliparous women has no adverse effects on the outcome of a subsequent pregnancy.

abortion, induced; infant, low birth weight; labor, premature; mifepristone; pregnancy outcome

Abbreviations: CI, confidence interval; SD, standard deviation.

Mifepristone, also referred to as RU486, was first registered for induction of early first-trimester abortion in China and France in 1988 (1, 2). It is now widely registered for use in numerous countries, including several countries in the European Union and the United States (3). By the year 2000, more than three million women had used mifepristone for pregnancy termination, including 620,000 in Europe (2, 3).

While the effects of surgical first-trimester abortion (vacuum aspiration, dilation and curettage) on subsequent, wanted pregnancies have been well documented (4), no such information is available for abortion induced in early pregnancy by mifepristone and a prostaglandin. Thus, we investigated whether a mifepristone-induced early abortion in nulliparous women affects the outcome of subsequent wanted pregnancies. We did this by following cohorts of nulliparous pregnant women with histories of one mifepristone-induced abortion, one surgically induced abortion, and no induced abortion through pregnancy and childbirth.
MATERIALS AND METHODS

Subjects and follow-up

Women visiting antenatal clinics before 16 completed weeks of pregnancy in Beijing (18 clinics), Chengdu (34 clinics), and Shanghai (31 clinics), China, between June 1998 and March 2001 were eligible for study if they were aged 20–34 years; were nulliparous; had a history of one first-trimester mifepristone-induced abortion, one first-trimester surgical abortion, or no induced abortion; and were willing and able to give informed consent. Exclusion criteria were a history of spontaneous abortion or a history of severe heart, liver, kidney, or lung disease. Women with no previous abortion or with one previous surgical abortion were frequency-matched by age in 5-year bands (20–24, 25–29, and 30–34 years) to women with one previous mifepristone abortion in each clinic. Since relatively few women with a history of surgical abortion met the age criterion, age matching for them was expanded soon after initiation of enrollment to include a neighboring age band within the age range 20–34 years. Women in the study were followed up at 28–30 weeks of pregnancy, at delivery, and 4–6 weeks after delivery.

At enrollment, trained interviewers administered a structured questionnaire on demographic and socioeconomic characteristics, lifestyle, reproductive history, medical history, current pregnancy, and, for women who had undergone one, details on the previous induced abortion. The women also provided information on their last menstrual period and whether their menstrual cycle was regular. At recruitment, obstetricians estimated gestational age on the basis of the last menstrual period, pregnancy signs and symptoms, physical examination, and sometimes ultrasonography. At the first follow-up at 28–30 weeks of pregnancy, information on medical conditions and events, including interval spontaneous abortion, was collected from interviews and medical records. At the second follow-up, immediately after delivery, information was collected from interviews and medical records regarding the third trimester of pregnancy, the course and type of delivery, the duration of labor, and the vital status, sex, and birth weight of the infant and the presence of any malformations. At the third follow-up 4–6 weeks postpartum, the mothers were interviewed about their infants’ health.

Upon completion of the questionnaires, the interviewers checked them for completeness and consistency. Supervisors at each study center subsequently checked the questionnaires as well. Errors and inconsistencies were corrected—if necessary, by reinterviewing the woman over the telephone. Each center coded and entered data with Epi Info, version 6.04c (Centers for Disease Control and Prevention, Atlanta, Georgia), using double data entry and validation. After the data checks were completed at each center, a logic check and statistical analyses were conducted at the Shanghai center.

The study was approved by the institutional review board at each center in China and by the Scientific and Ethical Review Group of the Special Programme of Research, Development, and Research Training in Human Reproduction, World Health Organization (Geneva, Switzerland).

Statistical analyses

The main outcome variables were length of gestation and birth weight among singleton livebirths. We also investigated spontaneous abortion, malformations detected at birth, stillbirth, and neonatal death. Gestational age was calculated on the basis of the last menstrual period unless there was a difference of more than 1 week between the obstetrician’s estimate at enrollment and the estimate based on the last menstrual period, in which case the obstetrician’s estimate was used. Accordingly, the date of the last menstrual period was revised for 2.9 percent of the women. Preterm delivery was defined as delivery between 28 and 37 completed weeks (196–258 days) of gestation. Low birth weight was defined as a birth weight less than 2,500 g. Full-term low birth weight was defined as low birth weight in infants born at or after 37 completed weeks of gestation. Spontaneous abortion was defined as spontaneous termination of pregnancy with a dead fetus before 28 completed weeks of gestation. Stillbirth was defined as the death of a fetus after the 28th week of pregnancy. Neonatal death was defined as the death of a live-born infant within 28 days of birth (5). Season of conception was categorized as spring (March–May), summer (June–August), autumn (September–November), or winter (December–February). Interpregnancy interval was defined as the number of days between termination of the previous pregnancy and the last menstrual period of the current pregnancy.

We compared pregnancy outcome in women with one previous mifepristone abortion with pregnancy outcome in women with no previous abortion and women with one previous surgical abortion. Risks of preterm delivery, low birth weight, and other adverse events were compared using logistic regression models; duration of gestation and birth weight were compared using linear regression models. Study center, age, education, occupation, and residence, grouped as shown in table 1, were included in all adjusted multivariate analyses of pregnancy outcome. Other categorical covariates were marital status, income, room size, body mass index, smoking, alcohol drinking, regularity of the menstrual cycle, contraceptive use, chronic disease history, gestational age at recruitment, season of conception, accordance of the last menstrual period with the obstetrician’s estimate of gestational age, reproductive tract infections, other infections,

Abortion regimens

The regimens for mifepristone abortion in the mid-1990s in China were: 1) 200 mg administered orally in a single dose; 2) 50 mg taken twice daily for 2 days; 3) 150 mg administered in one dose; 4) one 50-mg dose and one 25-mg dose taken daily for 2 days; and 5) three 25-mg doses taken daily for 2 days (1). Forty-eight hours after the first dose of mifepristone, a prostaglandin was given. The prostaglandins used were prostaglandin F₂α (1 mg), which was usually given vaginally, and (more often) misoprostol (0.6 mg), which was usually given orally. Vacuum aspiration was used for most first-trimester surgical abortions; prostaglandins for cervical ripening were not used during the period in which the surgical abortions studied here occurred.
medication use, sexual intercourse during pregnancy, abdominal injury, vacation, physical labor, toxicant exposure, occupational hazards during pregnancy, and interpregnancy interval for the comparisons between previous medical and surgical abortion. If data on any of these covariates differed (Cochran-Mantel-Haenszel statistics stratified by center; \( p < 0.05 \)) between women with mifepristone abortion and reference women (no abortion or past surgical abortion) and were associated with the outcome (preterm delivery or low birth weight) in either reference group (\( p < 0.05 \)), the covariate was considered a potential confounder and was adjusted for in the final model. All statistical tests were two-tailed, with a significance level of 0.05. Statistical analyses were carried out using SAS, version 8.1 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

A total of 14,656 pregnant women were enrolled in the study and had a baseline interview at their first antenatal visit. Table 1 shows the characteristics of the enrollees.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No abortion</th>
<th>Medical abortion</th>
<th>Surgical abortion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. or mean</td>
<td>%</td>
<td>No. or mean</td>
</tr>
<tr>
<td>Study center</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beijing</td>
<td>1,710</td>
<td>35</td>
<td>1,691</td>
</tr>
<tr>
<td>Shanghai</td>
<td>1,613</td>
<td>33</td>
<td>1,638</td>
</tr>
<tr>
<td>Chengdu</td>
<td>1,602</td>
<td>32</td>
<td>1,602</td>
</tr>
<tr>
<td>Education*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle school or below</td>
<td>1,278</td>
<td>26</td>
<td>1,204</td>
</tr>
<tr>
<td>High school</td>
<td>1,815</td>
<td>37</td>
<td>2,024</td>
</tr>
<tr>
<td>College or above</td>
<td>1,832</td>
<td>37</td>
<td>1,703</td>
</tr>
<tr>
<td>Occupation*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctor/teacher/researcher, administration</td>
<td>1,980</td>
<td>40</td>
<td>1,983</td>
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<tr>
<td>Industrial worker, service worker</td>
<td>1,530</td>
<td>31</td>
<td>1,458</td>
</tr>
<tr>
<td>Farmer, other</td>
<td>1,415</td>
<td>29</td>
<td>1,490</td>
</tr>
<tr>
<td>Area of residence†</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>City</td>
<td>3,631</td>
<td>74</td>
<td>3,656</td>
</tr>
<tr>
<td>Town</td>
<td>599</td>
<td>12</td>
<td>665</td>
</tr>
<tr>
<td>Countryside</td>
<td>695</td>
<td>14</td>
<td>610</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>12</td>
<td>0.2</td>
<td>26</td>
</tr>
<tr>
<td>Mean age (years)‡</td>
<td>25.6 (2.6)§</td>
<td></td>
<td>25.7 (2.4)</td>
</tr>
<tr>
<td>Mean maternal weight (kg)‡</td>
<td>51.6 (6.9)</td>
<td></td>
<td>51.7 (6.9)</td>
</tr>
<tr>
<td>Mean week of gestation at recruitment‡</td>
<td>10.4 (2.9)</td>
<td></td>
<td>10.4 (3.0)</td>
</tr>
</tbody>
</table>

* Comparison of the medical abortion group with the surgical abortion group: \( p < 0.01 \).
† Comparison of the medical abortion group with the no-abortion group: \( p < 0.01 \).
‡ Comparison of the medical abortion group with the surgical abortion group: \( p < 0.05 \).
§ Numbers in parentheses, standard deviation.

Similar numbers of women were admitted at the three study centers. Women with a previous surgical abortion were older and less educated than women with a previous mifepristone abortion, and fewer of them had skilled jobs. No such differences were observed between women with no previous abortion and women with a history of mifepristone abortion. More women with no abortion history lived in rural areas.

Type of and gestational age at previous abortion

Among women with a history of mifepristone abortion, 98.4 percent said they had had the abortion with orally administered mifepristone and prostaglandin, another 1.3 percent had had the prostaglandin administered vaginally, and 0.3 percent were uncertain of the route of administration of the prostaglandin. Of the women with a previous surgical abortion, 93.1 percent stated that they had undergone vacuum aspiration, 4.4 percent had undergone dilation and curettage, and 2.5 percent were uncertain of the procedure used. Of women who had had a mifepristone abortion, 27.6 percent said they had had their abortion beyond 7 completed
weeks of pregnancy; for women with a surgical abortion, this proportion was 61.7 percent ($p < 0.01$). One fourth (25.3 percent) of the women in the mifepristone abortion group said they had undergone subsequent uterine curettage because of incomplete abortion or excessive bleeding.

**Follow-up**

Outcomes of pregnancies and loss to follow-up for all enrolled women are shown in figure 1. Seventy women were lost before the first follow-up, and an additional 48 were lost before the second; the overall loss to follow-up was less than 1 percent. There were no livebirths before the 28th week of gestation. Results reported here for duration of gestation and birth weight are based on 13,928 singleton livebirths.

**Length of gestation**

Among women with singleton livebirths, the proportions of preterm delivery in women with no previous abortion, one mifepristone abortion, and one surgical abortion were 3.7, 2.9, and 3.0 per 100 singleton births, respectively (table 2). Women with a history of medical or surgical abortion were less likely to have a preterm birth than women with no history of abortion; the risks were not statistically different in those with medical abortion and those with surgical abortion (table 2). There was no interaction between study center and medical abortion ($p > 0.1$). The risk of preterm birth for women with a mifepristone abortion compared with women with no abortion was the same regardless of whether the abortion occurred before (odds ratio = 0.78, 95 percent confidence interval (CI): 0.60, 1.01) or after (odds ratio = 0.77, 95 percent CI: 0.53, 1.10) 7 weeks of gestation. Compared with women with no history of abortion, women with and without curettage after mifepristone abortion had adjusted odds ratios for preterm birth of 0.94 (95 percent CI: 0.65, 1.34) and 0.72 (95 percent CI: 0.55, 0.93), respectively. There was no significant interaction between medical abortion and curettage. The adjusted odds ratios for preterm delivery for women with one past mifepristone abortion with and without postabortion curettage as compared with women with surgical abortion were 0.87 (95 percent CI: 0.66, 1.14) and 1.15 (95 percent CI: 0.79, 1.67), respectively.

The mean durations of singleton pregnancies resulting in livebirths were very similar irrespective of mode of delivery (figure 2): For the group with no history of abortion, the mean duration of pregnancy was 278 days (standard deviation (SD), 10); for the mifepristone abortion group, it was 278 days (SD, 10); and for the surgical abortion group, it was 279 days (SD, 10). Adjustment for study center, age, education, occupation, and residence made no difference in the comparison of women with mifepristone abortion and women with no abortion. Women with a previous surgical abortion had a slightly longer duration of gestation (~1 day) than women with a previous mifepristone abortion ($p = 0.044$). The proportion of women whose infants were delivered by cesarean section was high in all three groups (44.2 percent, 45.9 percent, and 46.9 percent in women with no abortion, women with a medical abortion, and women with a surgical abortion, respectively). Separate analyses of risk of preterm birth and duration of pregnancy stratified by cesarean and vaginal delivery gave results (not shown) almost identical to those given above, in table 2, and in figure 2.
Birth weight

The mean birth weights of singleton live newborns in the groups of women with no previous abortion, previous mifepristone abortion, and previous surgical abortion were 3,324 g (SD, 431), 3,360 g (SD, 430), and 3,367 g (SD, 438), respectively. The birth weight distributions are shown in figure 3. After adjustment for study center, age, education, occupation, residence, maternal weight before pregnancy, gestational age, and sex of the newborn, the mean birth weight of infants of women with a previous mifepristone abortion was 33 g (95 percent CI: 17, 49) higher than that of infants of women with no previous abortion. Separate comparative analyses of women with mifepristone abortion conducted according to gestational age at abortion (<7 weeks of pregnancy vs. ≥7 weeks), according to whether or not the women had had curettage after abortion, and excluding women with cesarean section delivery did not materially change these findings (not shown). The birth weight of infants of women with a previous mifepristone abortion was not statistically different from that of infants of women with a previous surgical abortion. There was no statistically significant difference in the proportions of low birth weight infants overall or low birth weight infants in full-term pregnancies between the women with a previous mifepristone abortion and women from either comparison group (table 2).

Other outcomes

Rates of spontaneous abortion among women with no previous abortion, previous mifepristone abortion, or previous surgical abortion were 2.7, 2.4, and 2.3 per 100 pregnant women, respectively. Taking into consideration gestational age at recruitment, logistic models (spontaneous abortion or not) and Cox survival models (time to sponta-
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neous abortion) showed no statistically significant difference in adjusted odds ratios or hazard ratios for spontaneous abortion between women with mifepristone abortion and women in either comparison group. The rates of stillbirth in women with a singleton pregnancy were 4.2, 6.0, and 5.0 per 1,000 births among women with no previous abortion, women with previous mifepristone abortion, and women with previous surgical abortion, respectively. Rates of neonatal death for the same groups were 2.8, 2.1, and 2.0 per 1,000 livebirths, respectively. None of these rates were significantly different from each other. The prevalence of malformation detected at birth among live singleton infants born to women with no previous abortion, women with previous mifepristone abortion, and women with previous surgical abortion was 0.6, 0.5, and 0.6 per 100 births, respectively, and the incidence of a diagnosis of preeclampsia was 0.4, 0.3, and 0.4 per 100 women in the three groups, respectively. None of these rates were statistically different from each other.

DISCUSSION

In this study, the outcome of pregnancy for nulliparous women with a history of one first-trimester mifepristone abortion was similar to that of women with no history of previous abortion or women with a history of one first-trimester surgical abortion. Overall, women with one previous mifepristone-induced abortion had a lower rate of preterm delivery and their infants tended to be heavier at birth in comparison with women with no previous abortion. These differences were not seen between women with a previous mifepristone-induced abortion and women with a previous surgical abortion. More than 98 percent of women with mifepristone abortion reported that the drugs used for the abortion were administered orally, which is consistent with use of the prostaglandin misoprostol in addition to mifepristone.

The comparison of women with one previous induced abortion and women with no previous abortion implies a comparison of women of gravidities 1 and 0, and gravidity by itself can affect the outcome of pregnancy (6). Therefore, the findings of higher birth weight and fewer preterm deliveries among nulliparous women with previous mifepristone abortion than among women with no abortion were not unexpected and can be ascribed to the effect of gravidity. Similar results have been reported by Meirik and Bergstrom (7) and Tan et al. (8), who found higher birth weights in infants born to nulliparous women with previous first-trimester vacuum aspiration abortion than in infants born to women with no previous induced abortion. However, other studies have reported associations between surgical first-trimester induced abortion and preterm delivery or low birth weight in subsequent pregnancy (9).

Approximately one fourth of women with a mifepristone abortion said they underwent postabortion curettage. This proportion is larger than that reported from trials of early mifepristone abortions in Western countries (10) and is likely to stem from the clinical practice in China of performing curettage if the client continues to have vaginal bleeding 2 weeks after administration of mifepristone. Some practitioners even choose to perform curettage earlier (11).

The lower risk of preterm delivery among women with a previous mifepristone abortion compared with women with no abortion was confined to women who had mifepristone abortions without postabortion curettage. There were no differences in risk of preterm delivery between women who had their mifepristone abortion before 7 completed weeks of pregnancy and women who had it after 7 weeks. Mifepristone acts by blocking the effects of progesterone on the
decidua, and it softens and dilates the cervix (12). Misoprostol also softens the cervix, and additionally it increases uterine contractility (13). An early induced abortion with mifepristone and misoprostol without postabortion curettage may produce less trauma to the cervix and the uterus than the mechanical dilation of the cervix and curettage of the uterine wall that takes place in first-trimester vacuum aspiration or postabortion curettage, and this may allow for the expression of the effect of gravidity on the risk of preterm delivery.

The rates of preterm delivery and low birth weight among singleton livebirths were lower than expected and reduced the anticipated statistical power of the study. Low rates of low birth weight in mainland China have been reported by other observers (14, 15). Rates of preterm delivery and low birth weight similar to those of our study were recently reported from hospital-based studies carried out in Qingdao and Shanghai in China (16, 17). The age range of the women, the exclusion of women with previous spontaneous abortion and chronic diseases, and the low prevalence of smoking during pregnancy may have contributed to the low rates of preterm delivery and low birth weight in our study. Moreover, the study was undertaken in affluent cities in China; a large number of the participating women were professionals, and they had a level of education well above the Chinese average. The high rate of cesarean section in our study is similar to that of other reports from China (18, 19). In Wu’s report, 86 percent of cesarean sections were undertaken because of failure of progression, fetal distress, breech presentation, uterine scarring, and prolonged pregnancy, which indicates that the large majority of cesarean sections occur in full-term pregnancies (19).

We relied on self-reported abortion history for details on the procedures and cannot rule out misclassification of abortion exposure. In a pilot study, we attempted to verify abortion histories from case records but failed because many mifepristone abortions were performed in private clinics with poor record-keeping. Since the information on abortion history was gathered prior to the outcomes, we would not expect it to be systematically misclassified; thus, any misclassification should have biased the comparisons toward the null. Data on most of the outcome variables, including birth weight, pregnancy duration, stillbirth, preeclampsia, and birth defects, were collected from hospital or clinic records, and the recording of these data should not have been influenced by abortion history. The rates of preeclampsia and malformations were very low, and these conditions may have been underreported. The women in the abortion cohorts reported one abortion and no other pregnancy, and women without induced abortion had not previously been pregnant. Hence, the generalizability of the results from the study is restricted; in particular, they do not speak to possible effects of repeated mifepristone abortions or effects of mifepristone abortion among women with a history of spontaneous abortion.

The study had very low rates of loss to follow-up, which to a large extent can be attributed to the well-organized antenatal care in the three cities in the study. Prevalences of potential confounders that might affect pregnancy outcome were well balanced between the mifepristone abortion group and the two reference groups. We investigated a range of possible confounders and adjusted for those found significant in multivariate analyses. However, the crude and adjusted odds ratios and mean values were largely similar. This study suggests that one early abortion induced by mifepristone and misoprostol in nulliparous women has no adverse effects on the outcome of a subsequent pregnancy.

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REFERENCES