Effect of Previous Live Birth and Prior Route of Delivery on the Outcome of Early Medical Abortion

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OBJECTIVE: To determine the association between type of previous delivery (vaginal compared with cesarean) on the success of medical abortion with mifepristone–misoprostol in early pregnancy.

METHODS: The records of 879 women with intrauterine pregnancies at or before 56 days of gestation who underwent medical abortions were reviewed. Medical treatment consisted of 600 mg mifepristone orally followed 48 hours later with oral misoprostol. An ultrasound examination was performed 14–21 days after treatment, and a successful medical abortion was defined as an empty uterus without surgical intervention. Univariable and multivariable logistic regressions were used to determine risk factors for failure of medical abortion.

RESULTS: A total of 797 (90.7%) women had successful medical abortions; 82 (9.3%) had failed medical abortions. Multivariable logistic regression indicated that women with gestational ages greater than 42 days (odds ratio [OR] 2.53, 95% confidence interval [CI] 1.55–4.05) had higher odds of failed abortion compared with a gestational age less than 43 days. Parous women (OR≥3.94, 95% CI 1.83–8.53) and those with prior cesarean delivery (OR 9.59, 95% CI 4.30–21.39) were more likely to have failed abortions compared with nulliparous women. Among 523 parous women (68 had failed abortion), those with gestational ages greater than 42 days (OR 2.07, 95% CI 1.22–3.50) and prior cesarean delivery (OR 3.33, 95% CI 1.95–5.69) were more likely to have failed abortions compared with those with gestational ages less than 43 days or with prior vaginal delivery.

CONCLUSION: Parous women are at increased risk for failed medical abortion in comparison with nulliparous women. Prior cesarean delivery is significantly associated with failed medical abortion.
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LEVEL OF EVIDENCE: II

A medical abortion regimen containing mifepristone–misoprostol has been highly effective in more than 90% of cases.[1–3] Approximately 80–90% of women who choose medical abortion to avoid surgical procedures were satisfied.[4,5] Satisfaction with the medical procedure correlated with its success but was inversely correlated with the gestational age of the fetus and the intensity of pain, nausea, vomiting, and dizziness.[4] Nulliparous women generally experience more pain and a longer duration of bleeding compared with multiparous women.[5,6] However, previous studies have shown that parous women are more likely to have failed medical abortions than their nulliparous counterparts.[1,3,7,8]

In a retrospective study of 3,161 consecutive cases of early medical abortion treated with mifepristone and vaginal gemeprost, Bartley and his colleagues[1] reported that parity is a major determinant of successful medical abortion, with parous women being twofold more likely to have incomplete abortion or ongoing pregnancy. Likewise, Ashok et al[3] studied 4,132 women undergoing early medical abortion and found that women with a previous live birth but without a prior termination were more likely to have a failed medical abortion (odds ratio [OR] 2.03). In a smaller study of 316 Europeans with a gestational of less than 63 days, women who previously had three or more live births were more than fourfold less likely to terminate the pregnancy using the medical procedure than were nulliparous women.[7] Creinin[8] also demonstrated that successful medical treatment of early

pregnancy failure with misoprostol is significantly more likely in women who are nulliparous. For medical abortion using methotrexate–misoprostol, Aldrich and Winikoff[9] also showed that parous women were less likely to have successful abortions than their nulliparous counterparts. These data indicate that parous women have an increased risk of failed medical abortion, yet no explicit reasons have been postulated or influence of prior route of delivery examined.

Few studies have examined the influence of previous cesarean delivery on the outcome of medical abortion in early pregnancy. Xu et al[10] found that the complete abortion rate was comparable between women with prior cesarean delivery and those without for medical termination in early pregnancy. Only 35 cases with prior cesarean delivery were included, and parity was not documented clearly. Two other studies reported the effectiveness and safety of using intravaginal misoprostol for early medical termination in women with prior cesarean delivery.[11,12] However, no control group of women with previous vaginal delivery was presented.

The effect of the type of prior delivery on the outcome of medical abortion remains unclear. The purpose of this study was to investigate the effect of previous live birth and the prior route of delivery on the success of medical abortion with mifepristone–misoprostol in early pregnancy.

MATERIALS AND METHODS

A chart review was performed for 1,028 consecutive amenorrheic women requesting medical abortion at Taipei Medical University Hospital between 2002 and 2007. Abortion care is one of the family planning services of this hospital, which provides comprehensive medical care to the public. The study was approved by the institutional review board of Taipei Medical University Hospital.

Intrauterine pregnancy was confirmed, and gestational age was determined by measuring the crown-rump length by transvaginal ultrasonography. A crown-rump length of 10–15 mm indicated 42 to 56 days of gestation. Twin pregnancies (n=3) were included. Exclusion criteria for medical abortion included gestational age more than 56 days, menorrhagia, hemorrhagic disorders, chronic adrenal failure, impaired liver or kidney function, inherited porphyria, and concurrent anticoagulant or corticosteroid therapy. To avoid selection bias or change of status from nulliparity to parity, women undergoing repeat medical abortion were excluded.

After thorough discussion about failure rates, risks, and benefits, the women gave informed consent to undergo medical abortion. Per protocol, each woman was administered mifepristone (600 mg orally, Apano, Lotus, Nantou, Taiwan) under supervision, followed 48 hours later with the prostaglandin E1 analogue misoprostol (600 micrograms orally, Cytotec, Pfizer, Northumberland, United Kingdom). Oral acetaminophen was given as requested to relieve pain. Fourteen to 21 days after administration of mifepristone, the women were required to return to the clinic for an interview, bimanual pelvic examination, and transvaginal ultrasound examination.

At transvaginal ultrasonography follow-up, endometrial thickness and intrauterine content were evaluated. Incomplete abortion was suspected if the endometrial thickness was more than 15 mm. If an incomplete abortion or ongoing pregnancy was identified, a repeat dose of misoprostol was given. Weekly clinic visits were arranged for follow-up. Serum β-hCG was measured to confirm abortion at the discretion of the attending physician. Failed medical abortion was defined as surgical intervention (dilation and curettage) performed after a complete medical regimen for the following reasons: 1) excessive vaginal bleeding, 2) intractable lower abdominal pain, 3) suspected septic abortion, 4) persistent incomplete abortion, or 5) ongoing pregnancy in follow-up visits. Dilation-and-curettage specimens were examined microscopically by a pathologist and classified as trophoblast, chorionic villi, or fetal tissue. A successful medical abortion was defined as an empty uterus observed by transvaginal ultrasonography at follow-up and no surgical intervention.

We compared the patient characteristics of the initial population and the various subgroups with the success of the procedure. For continuous variables, such as maternal age, the results are presented as the mean±standard deviation; for categorical variables, such as parity, previous induced abortion, and type of previous delivery, the number in each category and the proportion were presented. We also divided gestational age into the following two groups: 1) 42 days or less and 2) more than 42 days. Independent t-tests and χ^2 tests were used to examine whether those characteristics were significantly different between those who had successful medical abortion and those who had failed medical abortion. For the 879 women who were included, univariable logistic regression was used to identify the risk factors for induced abortion failure and to estimate the individual effect of each variable. Factors that were significant in the univariable logistic regression were analyzed by mul-

tivariable logistic regression. For 879 women, parity and type of previous delivery (both variables were highly correlated) were put into different multivariable logistic regression models–model I and model II. Model I comprised maternal age, gestational age, and parity; model II comprised maternal age, gestational age, and type of previous delivery. Odds ratios with 95% confidence intervals were used to estimate the relative odds for failed abortion. The univariable and multivariable logistic regressions were applied to the 523 parous women as well to detect the additional effects of risk factors. SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL) was used to perform all the statistical analyses, and the significance level (α value) was set at 0.05.

RESULTS

Of 1,028 women whose charts were reviewed, 43 who failed their follow-up visit and 106 who were seen for repeat medical abortion were excluded. Of the 879 participants included in our analysis, 797 (90.7%) successfully achieved medical abortion by taking mifepristone–misoprostol; 82 (9.3%) had medical-abortion failure. As shown in Table 1, women with failed medical abortions tended to be older (33.3 compared with 31.4 years, $P=.042$), had a gestational age of more than 42 days at the time of taking mifepristone (58.5% compared with 37.0%, $P<.001$), had higher parity (82.9% compared with 57.1%, $P<.001$), and had at least one cesarean delivery (37.8% compared with 11.4%, $P<.001$). However, women with successful and failed medical abortions were similar with respect to previous induced abortions and the number of prior cesarean and vaginal deliveries (all $P>.05$).

The results of univariable analysis revealed that maternal age, gestational age, parity, and types of previous deliveries were significantly associated with failed medical abortion (Table 2). When compared with women with younger age or gestational age less than 43 days, the odds of failed abortion increased as maternal age increased (OR 1.05, $P=.007$) and increased for women with gestational age of more than 42 days (OR 2.40, $P<.001$). The odds of failed abortion increased more than threefold from nulliparity to the first birth (OR 3.42, $P=.001$); the higher odds accompanied by the higher parity ($P<.001$). Women who have had cesarean delivery had the highest risk of failed abortion (OR 8.32, $P<.001$) relative to women who have not had children; women with prior vaginal delivery only also had significantly higher odds of failed abortion than did nulliparous women (OR 2.48, $P=.005$, Table 2).

Table 1. Characteristics of Women Who Had Successful or Failed Medical Abortion

Variables	Successful (n=797)	Failed (n=82)	P*
Maternal age (y, mean±SD)	31.4±6.4	33.3±5.5	.042†
Gestational age (d)			<.001†
42 or less	502 (63.0)	34 (41.5)	
More than 42	295 (37.0)	48 (58.5)	
Parity			<.001†
Nulliparous	342 (42.9)	14 (17.1)	
1	157 (19.7)	22 (26.8)	
2	250 (31.3)	36 (43.9)	
3 or more	48 (6.1)	10 (12.2)	
Previous induced abortion			.058
No	369 (46.3)	29 (35.4)	
Yes	428 (53.7)	53 (64.6)	
Type of previous delivery			<.001†
Nulliparous	342 (42.9)	14 (17.1)	
Vaginal only	364 (45.7)	37 (45.1)	
Ever cesarean	91 (11.4)	31 (37.8)	
Number of cesarean deliveries‡			.869
1	46 (50.5)	14 (45.2)	
2 or more	45 (49.5)	17 (54.8)	
Number of vaginal deliveries§			.221
1	132 (35.2)	12 (30.0)	
2	202 (53.7)	20 (50.0)	
3 or more	42 (11.1)	8 (20.0)	

Data are n (%) unless otherwise specified.
* Independent *t*-tests and χ^2 tests were performed for continuous and categorical variables.
† Significantly different between successful and failed groups, $P<.05$.
‡ Only among those with prior cesarean delivery.
§ Only among those with prior vaginal delivery.

The results of multivariable analysis were very similar to the results of univariable analysis. Gestational age of more than 42 days (OR 2.53, $P<.001$), parity (OR≥3.94, $P≤.001$), prior cesarean delivery (OR 9.59, $P<.001$), and prior vaginal delivery only (OR 2.88, $P=.007$) all were associated significantly with failed medical abortion. Overall, parity (relative to nulliparity) and cesarean delivery (relative to vaginal delivery) exhibited higher risks of failed medical abortion (Table 2).

In the subset analysis of only parous women, gestational age and type of previous delivery were related to failed abortion as well, whereas the association between parity and failed abortion was not significant (all $P>.05$, Table 3). Multivariable logistic regression analysis showed that participants with gestational ages more than 42 days had 2.07 times higher odds of abortion failure than those with gestational ages less than 43 days (OR 2.07, $P=.007$). Women with prior cesarean delivery were more likely to have

Table 2. Logistic Regression Analyses of Obstetric Factors in Failed Medical Abortion in 879 Women

Variable	Univariable	Multivariable (Model I)	Multivariable (Model II)
Maternal age (y)	1.05 (1.01–1.09)*	0.99 (0.94–1.04)	0.99 (0.94–1.04)
Gestational age (d)			
42 or less	Reference	Reference	Reference
More than 42	2.40 (1.51–3.81)*	2.53 (1.55–4.05)*	2.47 (1.53–3.98)
Parity			
Nulliparous	Reference	Reference	–
1	3.42 (1.71–6.87)*†	3.94 (1.83–8.53)*‡	–
2	3.52 (1.86–6.66)*†	4.21 (1.92–9.26)*‡	–
3 or more	5.09 (2.14–12.10)*†	7.01 (2.51–19.56)*‡	–
Type of previous delivery			
Nulliparous	Reference	–	Reference
Vaginal only	2.48 (1.32–4.67)*	–	2.88 (1.35–6.15)*
Ever cesarean	8.32 (4.25–16.30)*	–	9.59 (4.30–21.39)*

Data are odds ratio (95% confidence interval).
Dash indicates that the variables were not included in the model.
* Statistically significant, $P<.05$.
† Mental-Haenszel χ^2- test for trend, $P<.001$.
‡ Mental-Haenszel χ^2- test for trend, controlling for maternal age and gestational age, $P<.001$.

induced abortion failure than those with prior vaginal delivery only (OR 3.33, $P<.001$).

For the 82 women who experienced unsuccessful medical terminations of pregnancy and elected surgical intervention, one nulliparous (7.1%) and eight parous (11.8%) women maintained their pregnancies, ie, had no signs or symptoms of abortion; four nulliparous (28.6%) and 22 parous women (32.4%) had incomplete abortions, as defined by endometrial thickness of more than 18 mm; and nine nulliparous (64.3%) and 38 parous women (55.8%) presented with profuse vaginal bleeding, severe pelvic pain, or signs of infection. Among the pathologic tissues retrieved, most (85.7% for nulliparous patients and 97.0% for parous patients) were found to be gestational tissues

Table 3. Logistic Regression Analysis of Obstetric Factors in Failed Medical Abortion in 523 Parous Women

Variable	Univariable	Multivariable
Maternal age (y)	0.98 (0.93–1.03)	0.98 (0.92–1.03)
Gestational age (d)		
42 or less	Reference	Reference
More than 42	2.12 (1.27–3.54)*	2.07 (1.22–3.50)*
Parity		
1	Reference	–
2	1.03 (0.58–1.81)	–
3 or more	1.49 (0.66–3.36)	–
Type of previous delivery		
Vaginal only	Reference	Reference
Ever cesarean	3.35 (1.97–5.69)*	3.33 (1.95–5.69)*

Data are odds ratio (95% confidence interval).
Dash indicates that the variables were not included in the model.
* Statistically significant, $P<.05$.

regardless of parous status. The average duration between initiation of medical abortion and surgical intervention was 26.1 ± 10.8 days.

DISCUSSION

Advanced gestational age and previous live birth were shown to raise the odds of failed medical abortion, as shown in previous studies.[1,3,13] We found that the probability of failed medical abortion was increased more than three times (OR 3.94) from nulliparity to the first birth. In addition, compared with nulliparous women, those with prior cesarean delivery were nine times more likely to have a failed abortion. Similarly, women with prior vaginal delivery only exhibited twice the odds of failed medical abortion. Among parous women, women with ever cesarean delivery had a threefold increase in the failure rate of medical abortion over those with prior vaginal delivery. These findings indicate that a prior cesarean delivery affected the outcome of medical abortion using the mifepristone–misoprostol protocol described herein.

Several groups have evaluated the effect of an intrauterine scar on the outcome of medical abortion. A prior study indicated that a successful abortion rate was comparable between women with and without cesarean delivery for the termination of early pregnancy using mifepristone (25 mg×3 d) and misoprostol (600 micrograms on day 4), which is different from the protocol used in the current study.[11] In that study, only those women with gestational ages up to 49 days were recruited and parity was not documented clearly. In 66 women with prior cesarean delivery

treated with methotrexate and misoprostol, Gautam[13] reported that 96.7% (58/60) of women before 50 days of gestation had complete abortion and that only 33.3% (2/6) of women from 50–63 days of gestation had complete abortion. A different protocol using only vaginal misoprostol (400+200 micrograms/h with a maximum of 800 micrograms) was associated with a 75% complete medical abortion rate in the second trimester in women with prior multiple cesarean deliveries but only a 33% success rate during the first trimester.[12] A retrospective analysis of 252 women at 15–35 weeks of gestation who underwent induction for abortion with mifepristone and a prostaglandin analogue revealed that prior cesarean delivery was associated with a higher incidence of retained placenta than in those without a uterine scar (70% compared with 52.5%).[14] These data suggest that a cesarean scar may have an effect on the outcome of medical abortion.

It is likely that cesarean deliveries injure uterine muscle, impair integration, and reduce its physiologic stretching in early pregnancy. In addition, scar formation in the lower uterus may prevent or restrict spontaneous expulsion of the gestational tissue from an unripe cervix in the first trimester of subsequent pregnancies. In one report, lower-segment uterine scars were detected by transvaginal ultrasound examination in the nonpregnant state in more than 99% of women with previous cesarean deliveries, and the majority of scars were located close to the internal os.[15] We observed a similar rate of failed medical abortion in women with prior cesarean delivery regardless of the number. We speculate that the scar effect on the loss of integrity of the lower segment may be associated with the surgical technique and postoperative healing process rather than the number of surgeries.

The mechanisms by which parous women with prior vaginal delivery only had higher odds of failed medical abortion compared with nulliparous women remain to be elucidated. Bartley[1] has suggested that a worse outcome of induced terminations in parous women results from a more efficient establishment of pregnancy at a very early stage. Creinin[8] has suggested that stretching of the myometrium with past pregnancies may alter the receptivity of the uterus to misoprostol, subsequently decreasing the probability of successful medical abortion in parous women. Our data showed that, among women who had failed medical abortion and subsequently underwent surgical intervention, the proportion of ongoing pregnancies and incomplete abortions was comparable between nulliparous and parous women. This suggests that the process of abortion per se, rather than the drug effect, accounts for the difference in induced abortion failure between the two groups of women. Prefumo at al.[16] demonstrate that trophoblastic invasion of the decidual vessels in early pregnancy is significantly more extensive in parous than in nulliparous women. These data imply that the probability of trophoblastic adherence during trophoblast tissue expulsion is greater in parous women. The more extensive decidual vessels in parous women with only prior vaginal delivery may explain their increased odds of failed medical abortion compared with their nulliparous counterparts.

The probability of failed medical abortion was similar in women with one vaginal delivery compared with those with multiple vaginal deliveries. Similarly, women with prior cesarean delivery, regardless of the number, had a comparable likelihood of failed medical abortion. No significant increase in the odds of failed abortion was seen as the number of previous live births increased. This finding was different from the report of Niinimaki et al, who show that the risk for curettage was 4.4-fold when a patient had three previous live births or more.[7] The discrepancy between the two studies might be due to the difference in the proportion of multiparous women. The proportion of women with more than three prior births in our study and in Niinimaki's study was 6.6% (58/879) and 12.6% (40/316), respectively.

A weakness of this study was that the reporting of certain indications for curettage, such as patient request and severe symptoms, was incomplete and inconsistent with that of previous studies. Comparison of trials using misoprostol for early abortion is difficult because patient populations, dosing regimens, routes of administration, duration of follow-up, and definitions of success vary. We adopted the definition of failed medical abortion as the need for surgical intervention for any reason because initially these women opted for medical termination of pregnancy to avoid surgery. Some of the reasons were, however, subjective. For instance, the decision to have surgical intervention owing to excessive vaginal bleeding and intractable lower abdominal pain were subject to variation of individual threshold. On the other hand, there was no overdiagnosis of retained products of conception, as demonstrated by histopathological examination (95.1% were gestational tissue).

An upward trend of cesarean delivery is observed worldwide. In Taiwan, the reported primary cesarean delivery rate ranged between 27.3% and 28.7% from 1998–2000.[17] It is possible that there are more women with scarred uteri who will request medical abortion.

Matching the drug regimen to the woman's prior live birth history and gestational age or lengthening the observation period for the completion of the abortion process might be beneficial.[11,13]

In summary, these data demonstrate that the rate of failed medical abortion with mifepristone–misoprostol was higher in women with either previous live birth or a history of cesarean delivery. Clinicians may find this information useful in the management of medical abortion.

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