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Incidence of uterine rupture in second-trimester abortion with gemeprost alone compared to mifepristone and gemeprost☆,☆☆

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ABSTRACT

Objectives: To compare uterine rupture rates in women having a medical abortion receiving gemeprost alone to those receiving mifepristone plus gemeprost.
Study design: We reviewed the records of women undergoing medical abortion at 13 0/7–23 6/7 weeks from January 2007 to December 2014 at a single center in Italy. Prior to January 2011, we used gemeprost 1 mg vaginally every 3 h up to a maximum of five doses. After January 2011, we added mifepristone 200 mg orally 24 h prior to the same gemeprost protocol. The primary outcome of the study was the incidence of uterine rupture. We compared the outcome between women receiving gemeprost alone with the combination of gemeprost and mifepristone.
Results: One thousand and sixty-one (58.5%) and 753 (41.5%) women underwent medical abortion in the gemeprost-alone and the gemeprost/mifepristone groups, respectively. Five (0.47%) uterine ruptures occurred in the gemeprost and four uterine ruptures occurred in the gemeprost/mifepristone groups, respectively (0.53%) (p=.89). All uterine ruptures occurred in women with prior cesarean delivery.
Conclusions: We rep orted no difference in the incidence of uterine rupture between the gemeprost-alone and gemeprost and mifepristone groups.
Implications: Uterine rupture is a rare complication of second-trimester medical abortion with gemeprost. Use of mifepristone prior to gemeprost does not affect this risk.

1. Introduction

Women can choose to have second-trimester abortion by medical induction or standard dilation and evacuation (D&E). Providers perform D&E more commonly in the United States, while in Europe, providers use mifepristone and a prostaglandin analogue to induce abortion medically [1–3].

Second-trimester abortion is extremely safe, and complications are uncommon [4]. While the incidence of complications is very low, bleeding and cervical trauma are most common, with uterine rupture and perforation being rare [5,6]. The presence of a uterine scar from one or more prior cesarean deliveries is an important risk factor for uterine rupture [7–13]. Two systematic reviews on second-trimester abortion with misoprostol support the finding that previous cesarean section is a risk factor for uterine rupture during abortion, with an absolute risk of 0.4%, 10 times higher than in women with an intact uterus [13,14]. Previous studies suggest that gemeprost use for second-trimester medical abortion results in a higher risk of uterine rupture than misoprostol [15].

The commonly used second-trimester abortion regimen is mifepristone combined with a prostaglandin analogue. This regimen reduces the induction–abortion interval by 50%; however, few data exist on this regimen's impact on risk of uterine rupture [4,16–19].

We aim to compare uterine rupture rates between women having a medical abortion with gemeprost alone and mifepristone plus gemeprost.

2. Materials and methods

We reviewed charts of pregnant women at 13 0/7 to 23 6/7 weeks of gestation undergoing medical abortion from January 2007 to December 2014 at University of Naples Federico II, Naples, Italy, and prospectively entered the data into a deidentified database.

We included women with a viable singleton pregnancy between 13 and 24 weeks with an indication for second-trimester abortion allowed

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by the Italian law. In Italy, law allows termination after 13 0/7 weeks when the life of women would be at risk if the pregnancy is carried to term or if the fetus carries genetic or other serious malformations which would put the mother at risk of serious psychological or physical consequences. We only included women who had an abortion performed according to our standard protocol to make accurate between-group comparisons.

From 2007 to 2010, we used gemeprost 1 mg vaginally (Cervidil®, Merck Serono, Italy), the only drug licensed for this indication in Italy, every 3 h up to a maximum of five doses or until fetal expulsion. In women with prior cesarean delivery, we interrupted gemeprost administration as soon as labor started. If abortion had not occurred within the first 24 h, we offered a washout period of 1 day, and we administered gemeprost 1 mg vaginally again every 3 h up to a maximum of five doses. We defined a failed induction abortion as absence of fetal expulsion after three induction cycles. We performed D&E in case of failed induction. After 2011, we offered a single dose of mifepristone 200 mg orally (Mifegyne®, Exelgyn, France) 24–72 h before prostaglandin administration [2,18].

We administered oxytocin 10 IU intravenously (Syntocinon®, Novartis, Italy) and/or ergometrine 0.5 mg intramuscularly (Methergin®, Novartis, Italy) following expulsion of the fetus and placenta. We performed curettage of the uterus for retained placenta or suspicion of incomplete abortion documented during routine ultrasound after the abortion.

The incidence of uterine rupture is the primary outcome of the study. We defined uterine rupture as a disruption or tear of the uterine muscle and visceral peritoneum, or separation of the uterine muscle with extension to bladder or broad ligament. We confirmed clinically suspected uterine rupture at the time of laparotomy. The secondary outcome is the incidence of hysterectomy. We compared primary and secondary outcomes between women receiving gemeprost alone and those receiving gemeprost and mifepristone. We also performed a subgroup analysis of outcomes in women with prior cesarean delivery.

We performed statistical analysis was using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA). We compared univariate dichotomous data with the χ^2 or Fisher's Exact Test. We used the Mann–Whitney *U* test to make comparisons between groups.

We considered two-sided p values <.05 statistically significant.

3. Results

From 2007 to 2014, 1838 women had second-trimester medical abortion in our department (Table 1). We excluded 24 patients for lack of adherence to the standard protocol. Among the remaining 1814 cases, 1061 (58.5%) received gemeprost alone, and 753 (41.5%) received mifepristone and gemeprost.

Overall, 340 women (18.7%) had one or more prior cesarean deliveries: 160 (15.1%) in the gemeprost-alone and 180 (23.9%) in the mifepristone and gemeprost group, respectively.

In our cohort, all nine uterine ruptures (9/1814; 0.5%) occurred in women with prior cesarean delivery. The incidence of uterine rupture in the cesarean delivery group was 2.6% (9/340). We reported annual number of second-trimester medical abortions and number of patients with prior cesarean delivery, uterine rupture and hysterectomy in Table 2.

Five uterine ruptures occurred in the gemeprost-alone group (5/1061; 0.47%), and four in the mifepristone and gemeprost group (4/753; 0.53%) (p=.89).

We report details of the uterine rupture cases in Table 3. All cases in which the surgeons suspected uterine rupture did have rupture confirmed at laparotomy, two of which resulted in hysterectomy to control blood loss. We repaired the uterus in the remaining seven cases without the need for any additional procedures. No maternal deaths occurred in the study cohort.

4. Discussion

This retrospective study evaluated the incidence of uterine rupture in women undergoing second-trimester medical abortion. We reported an overall rate of uterine rupture of 0.5% (9/1814). In the subgroup analysis of women with prior cesarean delivery, the incidence of uterine rupture was 2.6% (9/340). In women with prior cesarean delivery, we reported no statistically significant difference in the incidence of uterine rupture in the gemeprost-alone or mifepristone and gemeprost groups.

The retrospective nonrandomized approach is the major shortcoming of this study. We could not assess power a priori because of the retrospective nature of the study [20]. The deidentified database created for this study did not include data on failed induction, need for surgical intervention to remove placenta or length of time from starting gemeprost to delivery. We could not power the study for the uncommon outcome of uterine rupture. More than half of the uterine ruptures (5/9) occurred in 2010–2011. The analysis had very limited power to detect differences unless such differences had been very large.

In our cohort, the uterine rupture incidence in women with prior cesarean delivery was higher than those reported by two large systematic reviews on this topic [13,14]. These studies reported uterine rupture incidence of 0.3% and 0.4% in women with prior cesarean delivery undergoing second-trimester medical abortion. Only one study reported data on uterine rupture after use of gemeprost in patients with prior cesarean delivery, with 1 rupture occurring out of 111 subjects [15]. The reasons for these discrepancies are not completely clear [21]. Misoprostol may be associated with lower rate of uterine rupture than gemeprost. If gemeprost increases risk of uterine rupture, offering misoprostol at our institution may improve patient outcomes. It may be in the best interest of patients to attempt to get misoprostol on formulary at our

Table 1
Characteristics of second-trimester medical abortion patients at University of Naples Federico II from 2007 to 2014

	Gemeprost alone, *n*=1061	Gemeprost + Mifepristone, *n*=753	p value
Maternal age	32.4±6.5	32.7±6.3	.32
Gestational age at abortion	19.7±2.9	19.8±3.2	.50
Body mass index	23.3±5.4	23.7±4.1	.07
Smoking	210 (19.8%)	161 (21.4%)	.61
Race			.63
Caucasian	980 (92.4%)	700 (93.0%)	
Other	81 (7.6%)	53 (7.0%)	
Prior cesarean delivery	160 (15.1%)	180 (23.9%)	<.01

Data are presented as mean±standard deviation or as number (percentage).

Table 2
Annual number of second-trimester medical abortions and number of patients with prior cesarean delivery, uterine rupture and hysterectomy each year at University of Naples Federico II

	Second-trimester abortion, *n*	Prior cesarean delivery, *n* (%)	Uterine rupture, *n*	Hysterectomy, *n*
2007	274	25 (9.8)	1	1
2008	253	46 (18.1)	0	0
2009	254	45 (17.7)	1	1
2010	280	44 (15.7)	3	0
2011	244	47 (19.2)	2	0
2012	162	40 (24.6)	1	0
2013	187	54 (28.8)	1	0
2014	160	39 (24.3)	0	0
Total	1814	340 (18.7)	9	2

Table 3
Individual patient details of the nine women who experienced uterine rupture after second-trimester medical abortion at University of Naples Federico II

	Group	Year	Maternal age (years)	Gestational age at abortion (weeks)	Hysterectomy	Admission to ICU
Case 1	Gemeprost alone	2007	29	17.4	Yes	Yes
Case 2	Gemeprost alone	2009	30	19.5	Yes	Yes
Case 3	Gemeprost alone	2010	33	20.1	No	No
Case 4	Gemeprost alone	2010	34	22.1	No	No
Case 5	Gemeprost alone	2010	21	17.8	No	No
Case 6	Gemeprost+mifepristone	2011	37	19.5	No	No
Case 7	Gemeprost+mifepristone	2011	32	20.3	No	No
Case 8	Gemeprost+mifepristone	2012	30	22.7	No	Yes
Case 9	Gemeprost+mifepristone	2013	33	23.0	No	No

ICU, intensive care unit.

institution. Unfortunately, gemeprost is the only prostaglandin analogue currently available for labor induction abortion in Italy.

Variations in uterine closure at the time of cesarean may also explain these differences. In a meta-analysis of randomized trials, Di Spiezio Sardo et al. reported an increased residual myometrium thickness when double-layer suture was used at the time of uterine closure compared to the single-layer suture [7]. At our institution, we most commonly perform locked continuous single-layer closure of the hysterotomy.

Finally, should we offer D&E as the first-line option for second-trimester abortion? D&E avoids labor, and women may not need to use prostaglandins if mifepristone is used in combination with osmotic dilators [22]. Evidence suggests that D&E has fewer complications than labor induction abortion, and patients may prefer D&E [23]. However, second-trimester D&E is very uncommon in Italy. We suspect that D&E is a culturally stigmatized procedure and offering D&E as first-line treatment requires substantial education and culture change.

The discovery of the antiprogestin mifepristone in 1980 advanced nonsurgical methods for abortion and increased the availability of abortion in a variety of healthcare settings. To date, nearly 50 countries have approved mifepristone for medical abortion. However, mifepristone alone is not sufficient, and the most effective and safest regimens require the use of a prostaglandin analogue after mifepristone. Pretreatment with mifepristone increases the complete expulsion rate of prostaglandin alone from approximately 70% to more than 90% and decreases time to expulsion by up to 50% [2,24]. Furthermore, adding mifepristone to the prostaglandin-only regimen reduces prostaglandin doses, thereby reducing side effects and improving the patient experience [2,24,25].

In 2011, the International Federation of Gynecology and Obstetrics Working Group on the Prevention of Unsafe Abortion and its Consequences suggested that pretreatment with mifepristone may reduce the risk of uterine rupture. They acknowledged that this is a rare complication [21]. Our data did not support this statement, reporting similar incidence of uterine rupture in women receiving pretreatment with mifepristone compared to those who did not.

In summary, our study shows that uterine rupture is a rare complication of second-trimester medical abortion with gemeprost. Use of mifepristone prior to gemeprost does not affect this risk.

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