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Vaginal Misoprostol for Second Trimester Pregnancy Termination in Women with Prior One Caesarean Delivery

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Abstract

Background Misoprostol, a synthetic prostaglandin analogue, has become the leading mean for terminating the pregnancy. It is not clear, however, whether misoprostol is a safe abortifacient after thirteen weeks gestation in women who have a uterine scar from a previous lower segment caesarean delivery.

Objective To evaluate the efficacy and maternal side effects of misoprostol used vaginally for second trimester termination in women with a single previous lower segment caesarean delivery.

Method Sixty participants with a history of previous one lower segment caesarean delivery underwent pregnancy termination for missed abortion or lethal fetal anomaly between 14-28 weeks gestation using intra vaginal misoprostol. The dose of which was 400 microgram up to 20 weeks gestation and 200 microgram thereafter, repeated every 4 hours with a 12 hours nightly rest from misoprostol application up to a maximum of 72 hours. Women having termination for similar reasons but lacking a history of cesarean section served as a control group.

Results Abortion rate was 96.66% in the study group and 95% in the control group. The mean induction to abortion interval was 21.81±9.51 for the study group and 22.21±8.52 for the control group with no significant difference between the two groups. No cases of uterine rupture occurred in either groups.

Conclusion Inducing abortion with lower misoprostol doses appear to be safe and effective throughout the second trimester in women with a single previous lower segment cesarean delivery.

Keywords Second trimester, Misoprostol, Termination of pregnancy

Introduction

Second-trimester termination of pregnancy in women with a previous caesarean delivery is becoming increasingly common [(1)]. Although various methods for second-trimester terminationare effective, there are many risks to the patients for example: intraamniotic hypertonic saline infusion may precipitate heart failure, septic shock, water intoxication and consumptive coagulopathy [(2)].

Evacuation and curettage are associated with infection, uterine perforation and cervical trauma [(2)]. Various methods for second trimesterterminationof pregnancy have been investigated tofind the more effective methods with fewer complications to the patients.

The medical method recommended by the World Health Organization [(3)] and the Royal College of Obstetricians and Gynecologists [(4)] for termination of pregnancy between 13 and 26 weeks gestation, is the regimen of mifepristone followed by a prostaglandin analogue. When this combined regimen is used, the induction to abortion interval is significantly shorter than when prostaglandins are used alone [(3,4)].

Due to the limited access of mifepristone and greater costs of the combined method, medical abortions in the second trimester are most commonly performed by the administration of

prostaglandin analogues, using a variety of doses by various routes [5].

Induction of labor with misoprostol, a synthetic prostaglandin E1 analogue, is common practice worldwide and its use in the second trimester has shown good results [6,7,8]. The cervical ripening and uterotonic properties of misoprostol make the drug very useful [9]. Although various doses and routes of administration have been studied, the optimal dosage and route has not been defined.

Unfortunately, most of the studies have generally excluded patients with previous caesarean section. For these women, induction of labor with prostaglandins during the mid or third trimester, is considered dangerous due to the risk of uterine rupture [10,11] because of the increasing rate of caesarean deliveries which has been observed during the last two decades, the number of women with such an obstetric history who are offered pregnancy termination is also increased. The objective of our study is to assess the efficacy and safety of misoprostol used vaginally for second trimester termination in women with a single previous lower segment caesarean delivery.

Method

This prospective study was conducted between Jan. 2009 and Oct. 2010 at the Department of Obstetrics and Gynecology in Al-Kadhimyia Teaching Hospital, Baghdad, Iraq. Sixty pregnant women at 14 up to 28 weeks of gestation were enrolled. All of them had one previous lower segment cesarean delivery, and all underwent a second trimester termination for missed abortion, or lethal fetal anomaly that was confirmed by an ultrasound examination. Gestational age was calculated by the first day of a reliable last menstrual period or by a first trimester ultrasound scan if there was a discrepancy of more than 7 days.

The control group consisted of sixty women without a history of cesarean section matched for the maternal age, gestational age and gravidity to those of the study group. All patients had received authorization by the Abortion Committee of Al-Kadhimyia Teaching Hospital and all were counseled about the method for termination, side effects and possible complications. Following the counseling, a consent form was signed by all patients. Medical and obstetric history was taken and physical examination was performed. Exclusion criteria included cardiovascular or cerebrovascular disease, or a known allergy or contraindication to prostaglandins.

Additionally, women with multiple gestations, polyhydramnios or a history of myomectomy or surgery for uterine malformations were also excluded. The dose of misoprostol was 400 µg up to 20 weeks gestation and 200 µg thereafter applied vaginally every 4 hours daily, with a 12 hour nightly rest from misoprostol application, until contractions appeared but not more than 72 hours. The misoprostol tablets were placed in the posterior vaginal fornix by an obstetric resident. No additional co interventions were used.

The protocol was approved by the hospital ethics committee. Cervical progression was evaluated by vaginal examination before insertion of the next dose of misoprostol. Vital signs were monitored and the participants were checked regularly for adverse effects from misoprostol (such as fever, chills, and diarrhea) as well as signs of uterine rupture.

The occurrence of scar dehiscence or uterine rupture was assessed either clinically by observing for the signs and symptoms of dehiscence or rupture that includes: loss of uterine contractility, lower abdominal pain and tenderness at the site of the previous cesarean section scar, severe vaginal bleeding and maternal shock, or by transvaginal ultrasound examination of the site of the uterine scar.

The need for an infusion of oxytocin that was given at a dose of 10 units in 500 ml normal saline infused at a rate of 30 drops per minutes, i.e., 40 milliunit per minute, which was started at least 6 hours after the last application of misoprostol when the products of conception were retained after expulsion of the fetus; and the need for surgical evacuation which was

established after one hour of oxytocin infusion. Treatment success was defined as expulsion of the fetus within 72 hours after the initial dosage of misoprostol. Induction to abortion interval was defined as the time from the initial dosage of misoprostol to the expulsion of the fetus.

As documented at our institution, a misoprostol treatment longer than 72 hours places many women with a previous cesarean delivery at risk of scar dehiscence. This is why, on the recommendation of the institutional ethics committee, the upper limit of the interval was set at 72 hours for purposes of analysis. If expulsion had not occurred within 72 hours of the first dose of misoprostol, the participant could either receive higher doses of misoprostol or undergo pregnancy termination by hysterotomy; depending on her own wishes and the attending consultantsjudgments. Uterine curettage was performed if the placenta was not expelled within 1 hour.

Statistical analysis: performed using the x^2 test for categorical variables and the 2-tailed t test for continuous variables. Results are presented as mean, standard deviation, or as number and percentage. $P < 0.05$ was considered statistically significant.

Results

There were no significant differences in the demographic criteria of the two groups (the study and the control groups) (Table 1).

Table 1. Demographic data of the patients and the control groups

Demographic data	Study group N = 60	Control group N = 60	*P* value
Maternal age (yr)	24.8 ± 5.8	24.6 ± 6.0	0.81
Gestational age (weeks)	20.9 ± 0.72	21.5 ± 0.8	0.983
Gravidity	1.4 ± 1.28	1.43 ± 1.03	0.927

According to the dosage and time allowed by the study protocol, abortion was achieved in 58 of the 60 participants in the study group (96.66%), and in 57 of the 60 participants in the control group (95%) with no significant difference between the two groups ($P > 0.05$). There were 7 live fetuses in each group but none showed signs of life at delivery. All participants had a pretreatment Bishop score less than 4 indicating an unfavorable cervix. The mean gestational age in both groups was 21.2.

Table 2. Induction to abortion interval and total dose of misoprostol in the studied subjects

Variables		Study group N = 60	Control group N = 60	T test	*P* value
Induction to abortion interval (hours)		21.81±9.51	22.21±8.52	0.238	0.8124
TMD for gestations (µg)	< 20 weeks	720±354.6	724.13±371.9	0.061	0.9653
	≥ 20-28 weeks	592.85±224.7	614.28±204.0	0.5356	0.7584

TMD = total misoprostol dose

The mean induction to abortion interval was 21.81±9.51 hours for study group and 22.21±8.52 hours for the control group, with no significant difference between the two groups. The mean of the total misoprostol dose for those with gestations less than 20 weeks was 720±354.6 µg in the study group and 724.13±371.9 µg in the control group with no significant difference between the two groups and for gestations =or> 20 weeks up to 28 weeks, the mean dose of misoprostol was 592.85±224.7 µg in the study group and

614.28±204 µg in the control group and again with no significant difference between the two groups (Table 2).

As well there were no significant differences in the response rate to misoprostol between women aged less than 20 years compared to those aged more than 20 years in both groups (the study and the control groups) p value were 0.586 and 0.876 respectively (Table 3).

Table 3. Differences in the response rate among women aged less than 20 y and those aged more than 20 y in both groups

Group	Women responded aged ≤ 20 years N = 17	Women responded aged > 20 years N = 43	*P* value
Study group	16 (94%)	42 (97%)	0.586
Control group	16 (94%)	41 (95%)	0.876

Twenty three of the 58 (39.65%) participants in the study group and 24 of the 57 (42.105%) participants in the control group needed oxytocin infusion with no significant difference between the two groups. Among the patients who achieved induction using the study protocol, 28 participants in the study group (48.27%), and 26 in the control group (45.6%) needed surgical evacuation, and again the difference was not significant between the groups. Also there was no significant difference in the occurrence of adverse effects of misoprostol between the study and the control group. One case in the control group required blood transfusion due to occurrence of placental abruption, which causes excessive vaginal bleeding (estimated blood loss was 1250 ml). No cases of scar dehiscence or uterine rupture were observed in both groups (Table 4).

Table 4. The need for surgical evacuation, oxytocin infusion, and adverse events for those who respond to the study protocol in the two groups

Variable		Study group N = 58	Control group N = 57	X^2 test	*P* value
Surgical evacuation		28 (48%)	26 (45%)	0.082a	0.775
Oxytocin use		23 (39%)	24 (42%)	0.417a	0.518
Adverse events	Fever	30 (51%)	32 (56%)	0.226a	0.635
	Chills	11 (18%)	10 (17%)	0.039a	0.844
	Diarrhea	19 (32%)	21 (36%)	0.211a	0.646
	Ruptured uterus	0 (0%)	0 (0%)		
	Severe bleeding	0 (0%)	1 (1.7%)	1.026a	0.311
	Total	35 (60%)	34 (59%)	0.006a	0.939

About the 5 participants who did not respond to the study protocol, after counseling them, they were either offered further doses of misoprostol or undergone hysterotomy, according to their wish.

Discussion

Medical abortion was started in the late eighties, becoming more widely used in the late nineties with the mifepristone–misoprostol being widely used [12]. It came as an alternative to the dilation and curettage which resulted in many more complications [12,13]. Unfortunately, mifepristone

is not available in some countries, including Iraq. This is because of the high cost of this product and its negative connotations (it is known as an emergency contraceptive and an abortifacient, with resulting ethical dilemmas in conservative Muslim societies [14,15]

Misoprostol alone for termination of pregnancy was described for the first time in 1994. It has been used widely for termination of pregnancy in the normal uterus [12,13]. Several studies have been conducted to determine the optimal dosage and route of administration of misoprostol. Comparison between vaginal and oral administration of misoprostol for the induction of labor atterm had shown that vaginal administration was more effective, because of its pharmacokinetics [16,17]. The important feature of this study is the use of misoprostol among patients with prior one lower segment caesarean delivery undergoing second trimester abortion.

Chapman et al [18] reported a higher incidence of uterine rupture and hemorrhage with this drug than with mifepristone for women with cesarean scars, whereas others have shown it to be relatively safe [19,20,21]. These conflicting reports have led to suggest that the safety of misoprostol is yet to be established for these women [22]. The current results clearly indicate that women with previous one lower segment caesarean scar can safely terminate theirpregnancy in the second trimester by inducing vaginal birth.

Misoprostol achieved an abortion rate of 96.7%in the study group and 95% in the control group with no significant difference between the two groups ($P > 0.05$), which is in accordance with a previous study [23], reporting an 86.9% vaginal birth rate at term in women with a similar history. It is well known that the uterus becomes more responsive to uterotonic agents, and thus to lower doses of misoprostol, as gestation advances [16]. This is reflected in the present study as the total mean dose for gestations less than 20 weeks was a little bit higher than for gestations more than 20 weeks. The mean induction to abortion interval did not differ significantly between the study and the control groups.

Another important finding in the present study was that a previous one lower segment caesarean delivery does not appear to increase the incidence of complications in women who undergo a pregnancy termination in the second trimester by induction of labor. The most common maternal side effectsfound in the present study was fever followed by diarrhea and chills. However there was no significant difference in the occurrence of these minor and transient side effects between the two groups ($P = 0.9$). Placental abruption can occur at any case of abortion regardless of the agents used however, uterine rupture is the most serious complication in cases with a previous uterine scar and may occur either in the mid-trimester [24,25] or in the third trimester [26].

The incidence of uterine rupture during second trimester termination with misoprostol is unknown [21]. However, Berghella and colleagues [27] as well as GoyalV [28] in a systematic review found that the risk of uterine rupture in these women given misoprostol was only about 0.3 to 0.4 percent.Uterine rupture with the use of misoprostol has been reported more frequently in multiparous women and in women with uterine scars. Rupture is more often observed at term than in the second trimester [19].

Studies comparing the effect of misoprostol on scarred and unscarred uteri used doses higher than those used in the current study. Herabutya et al. [29] used a median total misoprostol dose of 1200 µg. One case of uterine rupture occurred, in the unscarred uterus group. Daskalakis et al [8] used a median dose of 1600 µg (range, 1200–2400 µg in their study group and 800–2400 µg in their control group). No cases of uterine rupture occurred. Daponte et al [12] used mean total doses of 655.81±109.76 µg in one group and 990±238.2 µg in another. There, too, no cases of uterine rupture occurred.

Our total mean doses in both groups (Table 1) was lower than the mean doses used in the studies just mentioned, but it was higher than that recommended in the review articles [30,31],

however, we believe the risk of a higher dose was offset by allowing an overnight rest (from 8 pm to 8 am, with a maximum of 4 doses in any 24 hour-period commencing at 8 AM). This rest, apparently, decreased the incidence of complications without increasing the rate of failure. Absence of uterine rupture in our study can be attributed to the comparatively smaller doses of misoprostol used; to the small population size and because the lower segment is not yet markedly formed and thinned out in the second trimester. The risk of uterine rupture has been reported to be higher when oxytocin is associated with prostaglandins [32]. Therefore in our study we stopped misoprostol and initiated oxytocin treatment when regular uterine contractions begun, for better titration and a lesser risk of scar dehiscence.

Overall, 47 (40.9%) of the 115 participants needed an infusion of oxytocin and 54 (46.9%) needed surgical evacuation. This could be the result of the low misoprostol dosage. Nevertheless, the protocol achieved a 96.7% rate of vaginalevacuation in the study group with no scar rupture. It is possible that higher misoprostol doses in a 24-hour period could have reduced theuse of oxytocin and the rate of surgical evacuation, but it may have also elevated the risk of scar rupture. We chose a low misoprostol dosage for the sake of safety in this prospective observational study carried out at our institute.

Bhattacharjee et al [22] used misoprostol vaginally or sublingually every 6 hours, up to a maximum of 24 hours. The dosage was 400 µg when the gestation duration was less than 20 weeks and 200 µg when it was 20 weeks or longer. The rate of protocol failure, i.e., the necessity of administering more misoprostol or performing hysterotomy or other surgical evacuation, was 27.5% in that study. No cases of uterine rupture occurred in either group. Compared to the above study the protocol set in our study had led to a much lower overall failure rate (4.16%) without increasing the rate of complications. In order to estimate the risk of complications more precisely, a very large case series is required, probably using nationally or multicentre collected data. By using national or multicentre data, confounding variables could be explored, and an exact estimate of the relative contribution to adverse outcome could be calculated.

We can conclude from this limited observational study that the prostaglandin E1 analogue misoprostol may be safe and effective at a dose of 200 µg every 4 hours in the induction of second-trimester abortion, even after the 20th week of gestation, in women with a single previous lower segment cesarean delivery.

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Conflict of interest

There is no conflict of interest that could influence the objectivity of the research reported.

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