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Vaginal Versus Oral Misoprostol for Second-Trimester Pregnancy Termination: A Randomized Trial

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Abstract: The purpose of this study was to compare the efficacy and side effects of two different misoprostol regimens for second-trimester pregnancy termination. Sixty women in second trimester of gestation with indications for pregnancy termination were randomly assigned in two equal groups to receive either vaginal or oral misoprostol. The dosing regimen was 400 µg as the initial dose followed by 400 µg up to 3 doses (1200 µg) if needed in each group. Efficacy and side effects were compared. The percentage of women who delivered was significantly higher in vaginal group than the oral group (86.7 vs. 43.3 p = 0.0006). No significant differences in complication rates and induction to delivery interval were noted between the two groups. Vaginal administration of misoprostol resulted in a higher success rate for second trimester pregnancy termination, whereas, no significant differences in induction to delivery time and complication rates were noted between vaginal and oral groups.

Key words: Pregnancy termination, misoprostol, prostaglandin E₁

INTRODUCTION

Various management protocols have been used for second trimester pregnancy termination. These include surgical technique (dilation and evacuation) and medical approaches such as intra-amniotic prostaglandin F_{2α} instillation, prostaglandin E₂ vaginal suppositories, prostaglandin E₁ and high dose oxytocin (Ramsey *et al.*, 2004). Although dilation and evacuation is an effective approach for the second trimester pregnancy termination, it is an invasive method and may lead to the possible complications such as cervical trauma, cervical or uterine perforation, cervicovaginal fistula, sepsis and bleeding. Surgical method also needs the availability of adequately trained individuals and equipments (Ramsey *et al.*, 2004; Cunningham, 2005). Among the medical regimens misoprostol, a PGE₁ analogue has been used to reduce complications and costs generated by surgery and also to improve patient satisfaction (Beucher *et al.*, 2003).

In series of studies success rate of vaginal and oral misoprostol for terminating of second trimester pregnancy were compared. Some studies reported higher success rate for vaginal route than the oral (Gilbert and Reid, 2001) and some reported lower success rate for vaginal than the oral plus vaginal method (Saha *et al.*, 2006). On the other hand, some reports have shown the same results for either routes (Feldman *et al.*, 2003). There are also different

reports about the rate of side effects for these two methods of administration (Cunningham, 2005; Bebbington *et al.*, 2002; Elsheikh *et al.*, 2001). One case report have reported a uterine rupture during misoprostol use in the second trimester in a woman with a uterine previous section scar (Nayki *et al.*, 2005). However, we found some studies which had shown, in the second trimester abortion, the use of misoprostol in women with prior cesarean delivery was not associated with an excess of complications compared with women with unscarred uteri (Daskalakis *et al.*, 2005; Dickson, 2005).

Because of controversial reports about efficacy and complications of oral and vaginal misoprostol administration for second trimester pregnancy termination and to determine the success rate of this drug for this reason, present study was designed.

MATERIALS AND METHODS

This randomized trial was conducted in Kashan Shabih Khani hospital (Iran) in 2006 to compare the relative efficacies of two regimens for second-trimester pregnancy termination: oral or vaginal misoprostol. After obtaining approval from our local IRB and written consent 60 women who were at 14 to 28 weeks of gestation and candidate for pregnancy termination due to different reasons such as missed abortion, fetal death, fetal

abnormality (confirmed by 2 ultrasonography) and premature rupture of amniotic sac were randomly assigned to receive either oral or vaginal misoprostol. All women were excluded if any of the following criteria were encountered: (1) contraindications to prostaglandin therapy (e.g., unstable cardiopulmonary status, hypersensitivity to prostaglandins), (2) placenta previa (partial or complete), (3) cervical changes (dilated internal os), (4) uncontrolled convulsion, (5) glaucoma and (6) inflammatory bowel disease.

Women randomized to each group received an initial 400 µg (two 200 µg tablets) dose of misoprostol (Cytotec®) vaginally or orally. This regimen followed by 400 µg up to 3 doses (1200 µg) if needed.

During the treatment period, from the administration of the first dose to 6 h after the last dose, patients' vital signs (blood pressure, pulse rate, temperature) were being controlled and recorded every 1 h. Any complication such as fever, abdominal pain, diarrhea and vomiting (if occurred) in both groups were managed and recorded. Operating room was ready to manage the rare complications of therapy such as uterine rupture and severe uncontrollable bleeding.

After expulsion of pregnancy products, placenta was checked exactly. After delivery all women received 30 unit oxytocin (in 1000 mL ringer's solution) to avoiding uterine atony and also their vital signs and uterine status were checked every 15 min up to 1 h. In cases with stable clinical status, patients were discharged and ultrasonography was carried out 2 weeks later to consider for any remained products of conception. If the placenta remained undelivered after 2 h, an attempt was made at manual extraction under general anesthesia and sterile condition in operating theater.

Women in either groups who were remained undelivered by 48 h after last dose (totally received 1200 µg) subsequently received concentrated oxytocin infusion until delivery. Finally, women who remained undelivered in spite of mentioned interventions underwent to surgical management (uterine curettage).

RESULTS AND DISCUSSION

Sixty women were assigned randomly in two equal groups, vaginal and oral groups. No significant differences were noted between the study groups with

respect to maternal age, nulliparity and cesarean delivery history (Table 1).

The percentage of women, who delivered was significantly higher in vaginal group than the oral group. The average induction to delivery interval was shorter for the vaginal group but this difference was not significant. No significant differences in complication rates or side effects were noted between the two groups. There was no significant difference between two groups regarding to manual extraction of the placenta (Table 2).

In vaginal misoprostol group fever was the most complication (20%) and in oral group shivering (33%) and fever (20%) were the most complaint. Neither of the women in both groups had abdominal pain, vomiting or diarrhea as a side effect of therapy. Severe complications such as uterine perforation and heavy bleeding have not seen in both groups of study. In 26 women (86.7%) in vaginal group and 13 cases (43.3%) in oral group, complete expulsion of pregnancy products occurred during 48 h after treatment. Four cases in vaginal group and 17 cases in oral group did not respond to treatment. In vaginal group 2 cases needed manual removal of the placenta and 2 cases required surgical intervention. In oral group 11 cases needed concentrated oxytocin to expulsion, in 3 cases manual removal of the placenta were done and 3 cases underwent hysterotomy.

Present study showed that second trimester pregnancy termination success rate in the vaginal misoprostol administration was significantly higher than oral route, whereas, no significant differences in complication rates or side effects were noted between two groups. We did not find any severe complication such as heavy bleeding or uterine rupture even in women with previous cesarean delivery history.

Several clinical trials have compared vaginal and oral usage of misoprostol for termination of second trimester pregnancy (Gilbert and Reid, 2001; Saha *et al.*, 2006; Feldman *et al.*, 2003; Bebbington *et al.*, 2002; Elsheikh *et al.*, 2001).

Table 1: Patient demographics data

| Parameters | Vaginal misoprostol (n = 30) | Oral misoprostol (n = 30) |
|---------------------------|------------------------------|---------------------------|
| Age (year) | 28.23±7.69 | 26.73±5.43 |
| Nullipar | 14 | 16 |
| Cesarean delivery history | 2 | 4 |

Table 2: Labor induction results in two groups of study

| Parameters | Vaginal misoprostol (n = 30) | Oral misoprostol (n = 30) | p-value |
|--|------------------------------|---------------------------|---------|
| Complete expulsion (%) | 86.7 | 43.3 | 0.0006 |
| Induction delivery interval (h) | 9.7±4.2 | 12.7±7.3 | 0.0830 |
| Side effects (%) | 23.3 | 46.7 | 0.0580 |
| Pharmacologic management of side effects (%) | 20.0 | 20.0 | 1.0000 |
| Manual extraction of placenta (%) | 6.6 | 10.0 | 0.3300 |

Bebbington *et al.* (2002) used of misoprostol orally and vaginally for mid trimester of pregnancy. They randomly assigned 140 women to receive either misoprostol orally (n = 65) in dose of 200 µg every 4 h for 3 h followed by 400 µg every 4 h, or vaginally (n = 39) in dose of 400 µg every 4 h. The protocol was followed for 24 h. According to their results, significantly more patients in vaginal group were delivered within 24 h (85.5 vs. 39.5%). Pregnancy termination success rate in our study was higher also in vaginal group within 24 h (83.3 vs. 40%). The mean induction to delivery interval was significantly shorter for vaginal than oral group (19.6±17.5 h vs. 34.5±28.2 h) in Bebbington's study. Gilbert and Reid (2001) reported higher success rate for vaginal administration of misoprostol than oral route (93 vs. 19%) in mid trimester pregnancy termination. This rate increased within 48 h for vaginal and oral groups (100 vs. 70%, respectively). The dosing regimen in their study was 400 µg as the initial dose followed by a second dose of 200 µg 2 h later and then 4 h 200 µg doses until delivery or 32 h from commencement of treatment. Overall, the average induction to delivery interval in vaginal and oral route was more than present results.

Two mentioned studies had comparable success rate for vaginal and oral misoprostol when compared to our study. On the other hand in both of them average induction to delivery interval was significantly shorter for vaginal than the oral misoprostol. In this study the mean induction to delivery interval was also shorter for vaginal group (9.7±4.2 vs. 12.7±7.3), but this difference was not significant. As vaginal absorption of misoprostol is more effective than oral (Muffley *et al.*, 2002), it may be the reason for higher success rate and shorter induction to delivery interval in vaginal administration route of this drug.

Saha *et al.* (2006) conducted a randomized control trial orally evaluating the relative efficacies of two regimens: misoprostol given only vaginally or orally followed by vaginal administration of the same drug for second trimester abortion. Women allocated into two groups. Patients in the only vaginal misoprostol group were given 400 µg 6 h only through vaginal route up to a maximum of 4 such doses. Women in the other group the oral plus vaginal misoprostol group, received 400 µg of the drug at intervals of 12 h for 2 doses, followed by 400 µg 6 h per vaginum up to maximum of 4 such. They demonstrated that in the second group oral plus vaginal resulted in a significantly greater percentage of complete expulsion rate (87.5%) and shorter median induction to delivery interval (8.93±0.01 h) compare with only vaginal group (83.3% and 13.28 h, respectively). Compare with our study and two mentioned above studies, Saha *et al.*

(2008) have not used pure orally misoprostol, therefore it is difficult to conclude orally administration of misoprostol was more efficacious than vaginal route.

Feldman *et al.* (2003) compared vaginal and oral misoprostol for second trimester pregnancy termination with different protocol. In a randomized clinical trial all of their patients received 800 µg of vaginal misoprostol and were assigned randomly to receive 400 µg of vaginal misoprostol or 400 µg oral misoprostol every 8 h. According to their findings, induction time and hospital stay were slightly shorter for oral group, however, the differences were not significant.

In present study we also compared complication rates and side effects of oral and vaginal route of misoprostol administration. According to our results, we did not find any significant differences between two groups of study regarding side effects and complications.

Several studies confirmed no significant difference about complication rates and side effects in oral and vaginal misoprostol administration (Saha *et al.*, 2006; Feldman *et al.*, 2003; Dickson, 2005). In mentioned studies investigators have been reported acceptable side effects for misoprostol which provide it a convenient alternative for mid trimester pregnancy termination (Elsheikh *et al.*, 2001; Nayki *et al.*, 2005). Because of we found a case report which confirmed uterine rupture after misoprostol use in a woman with previous uterine scar (Nayki *et al.*, 2005), in the present study we considered serious complications such as heavy bleeding and uterine rupture. Fortunately we did not find any uterine rupture or severe bleeding during our study even in women with previous cesarean delivery. Daskalakis *et al.* (2005) and Dickinson (2005) during two different study used misoprostol in second trimester abortion in women with previous cesarean delivery and neither of them found any evidence that a previous uterine scar affect the incidence of complications when patient with such a history undergo a mid- trimester pregnancy termination with misoprostol.

Finally, we concluded that vaginal administration of misoprostol resulted in a higher success rate for second trimester pregnancy termination, whereas, no significant differences in induction to delivery and complication rates were noted between vaginal and oral groups.

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