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ORIGINAL ARTICLE

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Efficacy and safety of intravaginal followed by sublingual misoprostol for second trimester pregnancy termination

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OBJECTIVE(S) : To assess the safety and efficacy, complete abortion rate, induction abortion interval (IAI), and side effects of misoprostol for voluntary termination of second trimester pregnancy.

METHOD(S) : Fifty selected women admitted for second trimester (13-22 weeks) abortion from January 2005 to November 2005 were administered 800 µg misoprostol intravaginally followed by 300 µg sublingually every 3 hours upto a maximum of 3 doses or till abortion if it occured earlier. They were observed for 24 hours. Main outcome measures were IAI, success rate, complete abortion rate, mean blood loss and side effects.

RESULTS : Of the 50 women, 49 aborted within 24 hours of administration of vaginal misoprostol giving a success rate of 98%. The complete abortion rate was 88%. Mean IAI was 9.36 ± 3.50 hours and mean dose of misoprostol required was 1485.63 ± 219.25 µg. The mean blood loss was 60.2 ± 2.01 mL. The main side effects were vomiting, diarrhea and fever in 12% each.

CONCLUSION(S) : Intravaginal misoprostol (800 µg) followed by sublingual (300 µg x 3 hourly) misoprostol is a safe, effective, cheap and acceptable method for the second trimester pregnancy termination.

Keywords : misoprostol, second trimester pregnancy termination, sublingual misoprostol

Introduction

Every year throughout the world approximately 210 million women become pregnant [1]. Some of these are carried to term, while others end in spontaneous or induced abortion. Estimates indicate that 46 million pregnancies are voluntarily terminated each year, 26 million legally and 20 million outside the legal system [1]. Second trimester termination of pregnancy is 12 times more risky than first trimester abortion mortality being 322 per lakh in second trimester, compared to 26 per lakh in first trimester [2].

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Various medical and surgical methods are used for termination of second trimester pregnancy. Surgical methods need hospitalization and are associated with risk of complications of surgery and anesthesia. Intraamniotic and extraamniotic instillation of ethacridine lactate, urea and saline, and use of $PGF_2\alpha$ by various routes are associated with variable success rate of 70-90% and a long induction-abortion interval (IAI) (11.05 - 40.04 hours). Misoprostol a synthetic anologue of PGE_1 developed for treating prevention of peptic ulcer is also found to have uterotonic and cervical ripening effects as well [3]. Safety and efficacy of misoprostol in early first trimester abortion is already established. It has also been used with high success for terminating second trimester pregnancy with administration by various routes and regimens, either alone or with mifepristone. Misoprostol is cheap, stable at room temperature, and associated with few side effects.

The present study was undertaken to assess the safety and

efficacy of high dose of intravaginal misoprostol followed by sublingual doses for second trimester termination of pregnancy.

Methods

All the cases coming to the department of Obstetric and Gynecology for 2nd trimester termination of pregnancy (13-22 wks) were screened for inclusion in the study. A detailed history regarding duration of amenorrhea, gravidity, parity, and previous spontaneous or induced abortion and medical diseases was recorded. General and systemic examination was done. Vaginal examination was done to assess the duration of the pregnancy and to rule out any pelvic pathology. The gestational age was determined by menstrual history and vaginal examination. Sonography was done if required. Routine investigations like hematogram, blood sugar, urine examination, platelet count, bleeding time and clotting time were done.

Those with organic heart disorder, respiratory disorder, diabetes mellitus, renal disorder, uterine scar, large myoma, pelvic tumor, uterine anomalies, hemorrhagic disorder, contraceptive device, jaundice, severe anemia and allergy to postaglandin were excluded from the study.

All women were given 800μg misoprostol vaginally in the posterior fornix followed by 300 μg sublingually at 3 hourly interval for 3 doses unless abortion occurred earlier. Bleeding, pain, cervical dilatation and expulsion of fetus were looked for. If active bleeding was present either acceleration of process with syntocinon drip or surgical evacuation was done. They were kept under observations for 2 hours after abortion.

All vital parameters were closely monitored and side effects if any were symptomatically managed.

Success was defined as complete abortion within 24 hours of vaginal instillation of misorostol. If abortion did not occur within 24 hours other methods for termination of pregnancy were adopted.

Abortion was considered complete if fetus, placenta, and membranes were expelled spontaneously.

Results

Table 1 gives the characteristics of the women in the study. Fortynine (98%) women aborted within 24 hours of vaginal insertion of misoprostol. One who did not abort within 24 hours had 14 weeks pregnancy and underwent surgical evacuation. The complete abortion rate was 88% and in the remaining cases surgical evacuation was done. In majority of the women pain started within 2 hours (mean 3.8 ± 2.33 hours) and vaginal bleeding started within 4-6 hours (mean 6.25 ± 2.20 hours) after vaginal insertion of misoprostol tablet. The mean induction abortion interval was 9.36 ± 3.50 hours and it decreased with increasing gravidity. It was inversely proportionate to the gravidity (Table 2).

The mean blood loss was 60.2 ± 2.01 mL and none of the women required blood transfusion. The mean dose of misoprostol required was 1485.63 ± 219.25 μg (Table 2). Misoprostol requirement was not much different in different gestational age and the mean IAI were independent of gestational age (Table 3). Side effects observed were vomiting, diarrhea, and fever, each in 12%.

Table 1. Epidemiological parameters.

Parameters	
Age in years (mean ± SD)	28.38 ± 6.56
Minimum age	18 years
maximum age	37 years
Married	88%
Unmarried	12%
Gravidity (Mean ± SD)	3.4 ± 1.31
Gestational age in weeks (Mean ± SD)	17.8 ± 2.5

Table 2. Gravidity, mean induction abortion interval and mean dose of misoprostol required.

Gravidity	Number	Induction abortion interval (Mean ± SD hours)	Dose of misoprostol (Mean ± SD μg)
1	6	10 ± 2.58	1450 ± 164.31
2	5	11 ± 7.75	1490 ± 164.31
3	10	8.3 ± 4.33	1454.545 ± 294.4
4	21	7.8 ± 2.36	1440.909 ± 213.9
5	6	7.4 ± 1.68	1464 ± 17.20
6	1	13	1700
7	1	8	1400
Mean ± SD	3.4±1.31	9.36 ± 3.50	1485.63 ± 219.25

Table 3. Gestational age, induction abortion interval and misoprostol required

Gestational age (weeks)	Induction abortion interval (Mean ± SD;hours)	Mean Dose of misoprostol (Mean ± SD; μg)
14-16	7.4846 ± 2.53	1380 ± 239.64
17-18	10.167 ± 2.60	1550 ± 154.34
19-20	8.68±2.19	1512.5 ± 223.20
21-22	11.083 ± 6.68	1500 ± 259.80

Table 4. Comparision with different studies.

Author	Year	Dose schedule	Success rate (%)	Induction abortion interval(hours)	Total dose (μg)	Side effects (%)
Wong et al [4]	2001	400μg vaginal 3 hourly x 5 times	90.5	15.2	-	
Pongsatha et al [5] and Tongsons	2001	800μg vaginal 2 hourly		21.38 ± 13.68	-	40% diarrhea
Dikinson and Evans [6]	2003	600μg vaginal + 200 μg orally 3 hourly	74	16.4	-	
Tang et al [7]	2004	400μg 3 hourly x 5 times sublingnal vs vaginal	91 sublingual 95 vaginal (24 hours)	13.8 sublingnal 12 vaginal		
Langer et al [8]	2004	800μg vaginal + 400μg 3 hourly orally x 3 times	98	12.7 ± 8	1800	12.2% vomiting 20% fever
Edwards and Sims [9]	2005	400μg vaginally 6 hourly	81	13.25	-	-
Herabutya et al [10]	2005	600μg vaginal 6 hourly vs 12 hourly		16 for both regimen	1800 in 6 hourly schedule 1200 in 12 hourly schedule	
Present study	2005	800μg vaginal + 400μg sublingual 3 hourly x 3 times	98	9.36 ±3.50	1485.63 ±219.25	12% vomiting 12% fever 12% diarrhea

Discussion

Second trimester pregnancy termination deserves special attention. There is a need for a method which is efficacious convenient, simple, has shorter induction abortion interval, is free of side effects and complications, and is cost effective.

Misoprostol has uterotonic and cervical ripening properties. It is safe, well tolerated, stable at room temperature, and inexpensive. It can be given by oral, vaginal, sublingual and rectal routes. Oral misoprostol reaches a high peak concentration in blood very quickly before a rapid fall in plasma level. After vaginal administration, there is gradual rise up to peak level and then a slow fall of level.

We gave a high loading dose (800 μg) intravaginally to be followed by a maximum of three sublingual doses (300 μg) at 3 hourly interval.

Mean IAI was 9.36 hrs ± 3.50 hours, the shortest being only 3.28 hours in a 3rd gravida with 22 weeks pregnancy, and the longest was 15 hours, also in a 3rd gravida with 18 weeks pregnancy. The IAI observed was shorter than that observed in other studies using misoprostol by various routes or by combination of routes for 2nd trimester termination of pregnancy[4-10] (Table 4).

Pongsatha and Tongsong in 2001[5], administered 800 μg of misoprostol intravaginally every 12 hourly and found that the IAI was three times that observed in the present study (21.38 ± 13.68 hours vs 9.36 ± 3.50 hours) (Table 4).

Similarly a large IAI of 13.8 hours was observed by Tang et al[7] who used misoprostol only sublingually for 2nd trimester termination of pregnancy (Table 4). On receiving oral misoprostol, plasma concentration rises quickly, peaks between 7.5 and 30 minutes (mean 14 minutes) and thereafter falls steeply by 60 minutes while after vaginal dose it rises gradually, reaches a maximum level between 45 and 120 minutes and declines slowly. In our study a high loading vaginal dose gave initial high blood level of misoprostol which was then maintained by frequent small doses of sublingual misoprostol. Thus the overall exposure to high concentration of misoprostol was increased. This combination is advantageous as it results in longer persistence and higher bioavailability of the drug and hence the shorter IAI and higher success rate.

Tang et al[7], Edwards and Sims [9], and Dickinson and Evans [6] used a low dose schedule without loading dose while Herbutya et al[10] used a high dose of 600 μg every 6 hourly or 12 hourly. All these studies had longer IAI. Thus a high initial dose

followed by frequent smaller doses results in shorter IAI. Wong et al [4] report that 3 hourly dosage is more effective than 6 hourly dosage. Misoprostol gives effective uterine contraction and reduces the blood loss. Mean blood loss in our study was only 60.2±2.01 mL. Our success rate of 98% within 24 hours was higher than that observed in other studies[4,5,7-9]. In 88% complete abortion was achieved and this is comparable to previous studies.

Misoprostol is a safe drug with very few side-effects. Only side effects we observed were vomiting, diarrhea and fever each in 12% each. These required symptomatic management only. In Langer et al's[8] study, fever was observed in 20%.

Conclusion

A high dose of intravaginal misoprostol followed by frequent small sublingual doses is a highly effective, safe, and cost effective method of second trimester pregnancy termination. However, our study is small and larger studies are needed.

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