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Vaginal Misoprostol in Early Pregnancy Failure

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Abstract: Early pregnancy failure (EPF) occurs in 10-15% of clinically diagnosed pregnancies. 65% of these women are not willing for surgical evacuation. Medical evacuation is gaining acceptance as a treatment of option than surgical or expectant management. This is a prospective clinical trial of 150 pregnant women with EPF of <13weeeks gestation managed by 400µg of vaginal misoprostol 4hourly to a maximum of 3 doses. Failure to expel the products of conception in 24 hours, excessive bleeding per vagina and incomplete expulsion were managed by surgical evacuation. Complete and incomplete evacuation was confirmed by transvaginalsonography (TVS). All surgical evacuations done under I.V. sedation required no anesthesia because of the cervical priming effect of misoprostol. Tolerable prostaglandin side effects *were* seen and no women required blood transfusion. Acceptance of medical management is 89%. Successful complete medical evacuation occurred in 86%, completely failed in 7.3%, incomplete evacuation in 3.3% and 3.3% underwent emergency surgical evacuation for excessive bleeding per vagina. Misoprostol, an antiulcer drug is still not approved by FDA for EPF management. But acceptance of medical management in EPF is 89%, it is economical without the surgical complication of anesthesia, uterine perforation, infection and uterine adhesions. Thus instead of going for expectant management, medical management has definitely a role in EPF in women not willing for surgical evacuation.
Keyword: medical evacuation, vaginal misoprostol, early pregnancy failure.

Introduction

EPF affects 1 in 4 women during her lifetime, or 1 in 9 clinically recognized pregnancies [1-2]. Prompt surgical evacuation of the uterus recommended in the past because of the risk of infection and coagulation disorder [3-4]. An emotional aspect of losing a pregnancy, especially in nillipara and conception following infertility makes surgical evacuation not acceptable. Surgical management carries the risk of anesthesia, being nil by mouth, bed occupancy when waiting for a convenient O T list, uterine perforation, intrauterine adhesions, cervical trauma, infection and infertility [5]. Expectant management of waiting for spontaneous expulsion is an option, but success rate *being* suboptimal (25-75%), prolonged follow up of 4weeks required [6]. Uncertainty in its time of expulsion requiring unplanned surgical curettage which cannot be practiced when assess to the medical care is far requiring transportation. In women who do not accept surgical management medical management is the treatment of choice. Misoprostol has been studied as a solo agent in the management of miscarriage.

Following are some potential treatment regimens for misoprostol as a solo agent

- 800µg vaginally up to 2 doses, 24 hours apart. Effectiveness range (53-93%), mean 73.8% or median ~85% [4,7-9]
- 600µg vaginally or orally, 2-3 total doses 24-48 hours apart. Effectiveness range 46-96%, mean 80% and median ~86% [8,10-12]

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- 400µg vaginally or orally given every 4 hours, 24 or 48 hours, up to max of 3 doses. Effectiveness range 13-95% mean 68% and median ~70 or 78% [4, 8,13-15]

Misoprostol is a prostaglandin E1 analogue, 15-deoxy, 16-hydroxy, 16 methyl PGE1, water soluble, viscous liquid, rapidly absorbed from GIT, in vaginal route of administration it bypasses the GIT and hepatic metabolism, sustains a plasma levels up to 4 hours thus the dose is administered 4 hourly. The side effects are more in oral and sublingual than vaginal route [16-17]. This study is to determine the efficacy, acceptance, side effects of 400µg of 4 hourly vaginal misoprostol for a maximum of 3 doses in 24 hours.

Materials and Methods

This was a prospective clinical trial on women with early pregnancy failure of <13 weeks visiting ANC clinic, Al-Ameen Women and Children Hospital from April 2007 to march 2009. Women who refused surgical evacuation were motivated for medical management, with the permission of the hospital ethical committee, written consent, these women were admitted for 24 hours for medical evacuation with 400µg of vaginal misoprostol moisten in 3 drops of distilled water every 4 hourly to a maximum of 3 doses and given a period of 24 hours for complete evacuation.
Diagnostic criteria for early pregnancy failure are:

(a) Fetal demise with fetal pole of at least 5-6mm without cardiac activity,
(b) An embryonic pregnancy with the presence of gestational sac of >15-20mm without fetal pole or lack of interval growth on repeat sonogram after 10 days,
(c) Incomplete abortion with thickened heterogeneous endometrial lining of >15mm in AP diameter without gestational sac [18].
(d) Inevitable abortion where cervix has dilated products of conception has not been expelled.

Exclusion criteria were unstable hemodynamic, s/s of pelvic infection, past h/o hypersensitivity to prostaglandins, bronchial asthma, cardiac disease, epilepsy and hypertension. Prerequisites were general physical examination, pelvic examination to note the size of uterus, cervical status and fornix. Investigations – Hbg/dl, BT, CT, blood grouping & typing (anti D administration in Rh-ve), urine-routine, TVS to diagnose EPF. Outcome noted were Induction-evacuation time interval in relation to the dose of administration of misoprostol, side effects - increased bleeding per vagina i.e., soakage of 1 pad in one hour, abdominal cramps requiring analgesia, nausea, vomiting, diarrhea, fever, chills, TVS to rule out incomplete evacuation- endometrial thickness of >15mm and complete failure to evacuate in 24 hours. Surgical evacuation done if there was increased bleeding per vagina, incomplete evacuation, complete failure to evacuate. All women were advised to report back after 14 days or if there were complaints of abdominal pain, fever, increased bleeding per vagina. The amount (soakage and number of pads changed) and duration of bleeding enquired, and repeat Hbg/dl done after 14days.

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Results

In this study 282 women were diagnosed as EPF, 182(65%) refused surgical evacuation, 162 agreed for medical evacuation, acceptance of medical evacuation was 89%.

Table No-1: reason for refusing surgical evacuation;

no-162	Reasons to refuse surgical evacuation
42	Wanted medical evacuation, name of the drug, dose not known
40	Anxious about the procedure
48	Thought might cause infertility in future
32	Not confident about the procedure

12 women in whom medical management was contraindicated were excluded from the study group. Mean age was 25±5.5 years, 58(38.6%) were nullipara, mean gestational age according to LMP was 9.36±1.62 weeks, mean size of uterus by pelvic examination was 8.68±2.54 weeks, mean gestational sac size was 18±2mm. Medical evacuation was successful in 129(86%) and failed in 21(14%).

Table No-2: the type of EPF and its failure rate in each type.

Type of EPF	n-150	Failure rate in each type
Missed abortion	65(43.3%)	6(9.2%)
An embryonic	55(36.6%)	5(9%)
Incomplete abortion	20(13.3%)	9(45%)
Inevitable abortion	10(6.6%)	1(10%)

Mean induction evacuation interval was 11.4±5.24 hours, if the women expelled with 1st dose the second dose was not repeated, 79(61.2%) women expelled after the 3rd dose. No women required oxytocics.

Table No-3: The induction-evacuation interval and the dose required

No of dose of 400µg of vaginal misoprostol used	Induction-evacuation interval in hours	n-129
1st dose	1-4hours	13(10%)
2nd dose	4-8hours	37(28%)
3rd dose	8-12hours	64(49.6%)
	12-24hours	15(11.6%)

Table No-4: The type of failure

Failure as	n-21
Complete failure	11(7.3%)
Emergency evacuation	5(3.3%)
Incomplete abortion	5(3.3%)

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Adverse effects were nausea in 7(4.6%), vomiting in 4(2.6%), diarrhea in 3(2%), fever in 5(3.3%) which subsided with paracetamol, chills in 4(2.6%), abdominal cramps requiring analgesia (mefenemic acid and dicyclomine) in 6(6.6%), emergency evacuation in 5(3.3%). No oxytocics or anesthesia used during evacuation. Only surgical evacuated women were given antibiotics. During follow up after 14days 136 reported back and 14 were lost for follow up. Bleeding per vagina was mild to moderate with mean duration of bleeding 9.37±2.67 days, post evacuation decrease in Hbg/dl was -0.67±0.29g/dl, and only two women had less of 1.2g/dl. No complaint of fever, pain abdomen and emergency unplanned evacuation. 130(86.6%) women were satisfied with the medical evacuation and wanted to opt for the same and recommend the same to others.

Discussion

El Refeay. H et al was the first to report medical management in EPF with *mefipristone* 600mg and oral misoprostol 600 µg after 48 hours with 90%(90% CI) success. But the nonviable and unstable decidual lining in abnormal pregnancy donot requires an antiprogestational, mifepristone. In this study 400µg vaginal misoprostol 4hourly to a maximum of 3 doses used to reduce the gastrointestinal side effect and to get the efficacy with minimum dose, time and adverse effects. TVS being the gold standard in confirmation of complete and incomplete evacuation, 90-100% sensitivity and 80-92% specificity [19] helps to decide about the surgical evacuation, thus decreasing the incidence of emergency unplanned admission due to bleeding per vagina and infection. No women visited with these complaints in 14 days of follow up. The failure rate after medical management in various trials ranges from 10-50% and surgical management 0-4% [5,7, 9,20-22]. Our study showed 14% failure. In our study success rate of 61.2% was after the 3rd dose and many large trials have also shown the requirement of 2nd dose administration but the dose used in these trials were 600 or 800µg [7,20,22-23]. Studies show higher failure rate of 47-50% [9, 22] when assessed in 24-48 hours than after one week with failure rate of 10-29% [7,20-21] but in our study assessment after 24 hours with TVS and admission of 24 hours helped us in the direct supervision of expulsion and prevented emergency admission and blood transfusion. No women required anesthesia during evacuation because of priming of cervix by misoprostol. Safety of medical management is comparable to surgical management as shown in two meta-analysis pooled data [6, 24]. The largest MIST trial by Trinder et al [25] also showed no difference in risk of infection, blood transfusion of 1% in medical group, median duration of bleeding was 11-12 days. Our study also showed no follow up complaint of fever, pain abdomen, unplanned emergency admission, no blood transfusion mean duration of bleeding was 9.37days. The mean decrease in Hb level was -0.6g/dl in our study. Trinder et al [25] showed no difference in Hb level from baseline. Davis et al [28] reported mean decrease of -0.7g/dl comparable to our study. Studies comparing routes of administration and side effects are inconsistent. Studies comparing medical and surgical or expectant management reported higher incidence of side effect in medical management [7,9,22] Bagratee J S et al and Blohm F et al compared misoprostol with placebo and showed

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no difference of side effects. EPF itself and the process of expulsion are associated with some degree of side effects [26-27]. Our study showed tolerable prostaglandin side effects. Acceptance of medical management was 86.6% in our study. Acceptability of medical management is high, 83 to 92 % want to recommend it to a friend, 70 to 93 % want to choose the same again [7,21,26,28-30].

Conclusion

Even though the success rate of medical management is 86% the acceptance of medical management is high. Admission of 24 hrs, expulsion under direct supervision combined with TVS minimizes unplanned emergency evacuation and hemorrhage in rural set up. Women opting medical management are counseled to anticipate tolerable prostaglandin side effects and expect bleeding for 14 days or longer. Risk of serious complication is low. Medical evacuation is economical compared to surgical evacuation. In women who refuse surgical evacuation, medical evacuation is the treatment of choice and slowly may become standard treatment for EPF in future.

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