Original Article

A prospective observational study of the follow-up of medical management of early pregnancy failure

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Abstract

Background: Medical termination for missed miscarriage with the use of 800 μg of vaginal misoprostol as a single agent is recommended as a cheap option before 14 weeks of gestation in developing countries. A few studies have looked at its efficacy. **Methods:** A prospective, observational study was done on women having medical termination with up to three doses of 800 μg vaginal misoprostol at 12 hourly intervals. The number of women who needed check curettage was collected. Ultrasound findings if done were collated. Follow-up was done telephonically at the end of first week, fourth week and sixth week. **Results:** The cohort comprised 145 women. The primary outcome was the need for curettage after expulsion of products following medical management and this was 49/145 (37.8%) of women. The induction expulsion interval was 36 hours. The mean endometrial thickness of the 113/145 women who had an ultrasound was 11 mm. The mean endometrial thickness in women who had check curettage was 18 mm. Persistent spotting was the only significant symptom at follow-up. Resumption of cycle at the end of the sixth week was seen in 105/132 (80.15%) of women who were followed up. **Conclusion:** Findings of our study showed the check curettage rate of 37.8%. However, the regime which we used, that is, 800 μg vaginal misoprostol at 12 hourly intervals had a long induction to expulsion interval of 36 hours. In all, 80% of women resumed normal cycles at the end of the sixth week. No significant complications were noted on follow-up.

Keywords: Curettage, medical termination, misoprostol, missed miscarriage

Introduction

Medical termination with misoprostol is one of the modes of management for anembryonic pregnancy or fetal demise before 14 weeks of gestation.[1,2] Even though, addition of mifepristone has shown improved efficacy,[2] it may not always be used especially in developing countries as it is expensive. Studies have shown reasonable efficacy even with the use of misoprostol as a single agent.[3,4] Surgical termination is an option for women who want a quick evacuation of the uterus but this mode of management has no other major benefit.[5] Medical termination has the advantage of avoiding complications such as uterine perforation, pelvic inflammatory disease, intrauterine adhesions and injury to the cervix causing cervical incompetence.[6,7] It also has the advantage of avoiding the need for anesthesia for surgical evacuation with a closed cervical os. Medical management would therefore make it a very convenient mode of management for practice in primary care. However, very few studies have evaluated the efficacy of this medical regime using only misoprostol in early fetal demise and lot of the evidence is from studies on termination of a live fetus.[8] Misoprostol is cheap, stable at

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room temperature[9] and easy to administer, but unlike surgical evacuation, the process can be long drawn, at times taking as long as 48 hours. In about 20%-30%[3,4] of cases, a check curettage may be required after the attempted medical termination. The effective regimes with minimal side effects seem to be with the vaginal use of 800 μg of misoprostol at 12 or 24 hourly intervals but the debate on the optimal regime is still not resolved.[10] A decision for a check curettage after medical management is made arbitrarily as ultrasound and clinical criteria for check curettage is not well defined.[11] Very few studies[11,12] have follow-up of these women after completion of treatment. Few studies have described clinical and ultrasound findings before a curettage is performed especially from a developing country.[13] Thus, the main aim of our research was to study the number of women who need a check curettage following termination using the 800 μg of misoprostol at 12 hourly intervals (total of three doses). The other objectives of the study were to describe the clinical and ultrasound findings in women who had medical termination with misoprostol that subsequently needed check curettage and to follow-up symptoms after discharge as part of evaluation of the misoprostol regime executed in our institution.

Methodology

This prospective, observational study to evaluate the misoprostol (four tablets of 200 μg – Zitotec, Sun Pharma Laboratories Ltd) regime was conducted in women with embryonic or fetal demise before 14 weeks of gestation. It was conducted in a large tertiary center between November 2015 and January 2018 after obtaining Institutional Review Board approval [IRB No. 9691 dated 20.10.2015]. Informed consent was signed by all participants.

The inclusion criteria were as follows. Women carrying an anembryonic pregnancy or a pregnancy with embryonic or fetal demise before 14 weeks of gestation required a termination. They had to be hemodynamically stable with no active bleeding and the cervical os had to be closed. Women with active bleeding with an open cervical os, women with fetal demise after 14 weeks, women with prior attempt to terminate pregnancy either medically or surgically, women with allergy to misoprostol, those with bleeding disorder or evidence of sepsis were excluded. In all, 305 women (refer Figure 1) were screened for eligibility and 93 women with incomplete abortion requiring immediate curettage were excluded. However, 212 women met the inclusion criteria but 67 were unwilling to participate in the study. The regime followed were a total of three doses of 800 μg of misoprostol at 12 hourly intervals. Thus, 145 women were included in this study and 71/145 (49%) of this cohort had three doses. After completion of regime, women who continued to have significant bleeding requiring the use of more than five pads but did not warrant an immediate curettage, had an ultrasound examination. Therefore, 113 women had an ultrasound. Complete expulsion was diagnosed if the sac expelled in toto or if there were ultrasound features such as regular endometrial cavity and the absence of echogenic foci in the cavity. Findings such as, thick endometrium, irregular lining, presence of echogenic material or presence of sac were taken as indicators of incomplete abortion and a check curettage was done or an additional dose of misoprostol was given at the physician's discretion. These women were discharged and followed-up by telephone at first, fourth and sixth weeks.

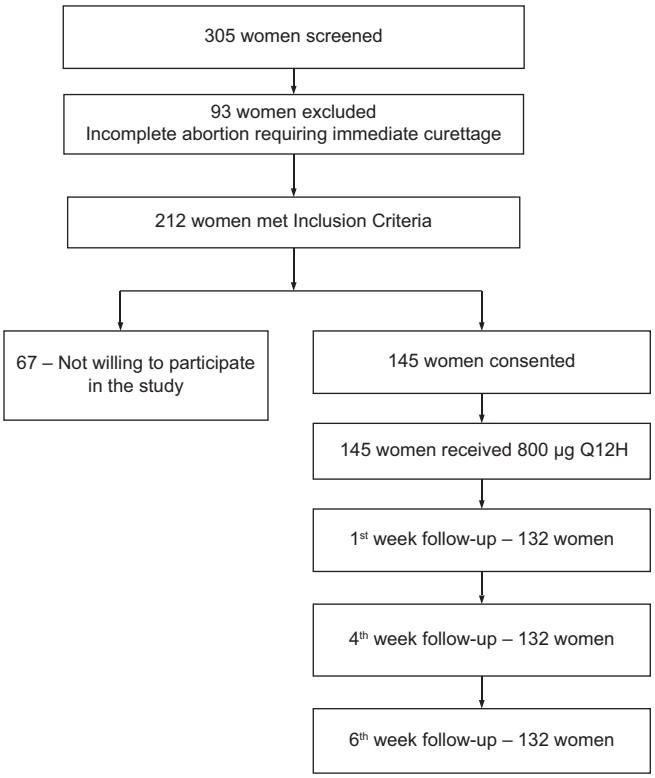

Figure 1: Flow diagram

The primary outcome was the number of women that needed check curettage. The secondary outcomes were (1) Induction to expulsion interval, (2) Ultrasound findings when there was persistent bleeding after expulsion of uterine contents, (3) Clinical and sonological findings that contributed to the decision for need of a check curettage, (4) Minor or major side effects or complications, (5) Total duration of hospital stay, (6) The presence of symptoms such as bleeding or spotting per vaginum, significant foul smelling discharge, pelvic pain or fever requiring medical attention at follow-up, (7) Unscheduled visits to the hospital and (8) Resumption of menstrual cycles. Demographic details such as age, parity, history of previous medical termination of pregnancy (MTP), previous history of pelvic inflammatory disease (PID) or abnormal uterine bleeding (AUB), gestational age, presence of symptoms were collected. Primary and secondary outcomes were documented. Telephonic follow-up at first, fourth and sixth week was also collated.

Statistical analysis

Statistical analysis was performed using STATA IC 15.1. Categorical variables were summarized using counts and percentages. Quantitative variables were summarized using the

mean and standard deviation or median and inter quartile range. The sample size of 150 was calculated for a 26%[12,4] probability of incomplete evacuation with a 7% margin of error.

Results

The cohort comprised 145 women who underwent medical management with misoprostol prior to 14 weeks of gestation. The baseline demography of the cohort is detailed in Table 1. About 50.3% of the cohort was primis; 28.3% of women had previous MTP. Gestational age was less than 12 weeks in 83% of women and 58% of the cohort were asymptomatic.

Outcomes of the above cohort are listed in Table 2. The primary outcome which was the need for uterine curettage after expulsion of products following medical management was 38% (49/145). The induction to expulsion interval was 36 hours. Among the cohort, only 113 women suspected to have incomplete expulsion not warranting an immediate curettage had ultrasound. The mean endometrial diameter in this group that had ultrasound was 11.08 mm (6.7) (SD). Echogenicity or irregularity was seen in 23 women (20.3%) of the 113 women who had ultrasound and all of these women had curettage. Among the 49 women who had the curettage, the main reason for curettage were ultrasound findings in 28/49 (60%) women and persistent bleeding in 21/49 (40%) women. In the 28 women who had the curettage and the ultrasound, the mean endometrial diameter on ultrasound was 18.3 mm (SD 9.3).

There were no major side effects like excessive vomiting, diarrhea or fever with chills. Only one woman had blood transfusion just before treatment for a pre-existing hemoglobin of 6 gm/% and not for excessive bleeding. Mean duration of hospital stay was 48 hours (28, 72 IQR). Only three women had a fourth dose.

The number of women who were followed up telephonically was 132/145. Persistent spotting was seen in 25/132 (18.9%) in first week, 49/132 (37%) in fourth week and 1/132 (0.75%) in sixth week. None of the women had significant foul smelling discharge or pelvic pain requiring medical attention. Cycles resumed by sixth weeks in 105/132 (80%) of women. There were no unscheduled visits.

Table 1: Demography of 145 women undergoing medical management (800 μg Q12H) for early pregnancy loss

Variable	*n* (145)
Mean age in years (SD)	26.6 (5.1)
Primi	75 (50.3%)
BMI	24.75 (5.9%)
Previous MTP	41 (28.3%)
Previous PID	2 (1.37%)
Previous AUB	7 (4.82%)
GA <12 weeks	121 (83.4%)
Asymptomatic before admission	84 (57.9%)

SD=Standard Deviation, BMI=Body Mass Index, MTP=Medical Termination of Pregnancy, PID=Pelvic inflammatory disease, AUB=Abnormal Uterine Bleeding, GA=Gestational Age

Table 2: Outcome of the cohorts

Primary Outcome	*n* (%)
No. of women required surgical treatment *n* (%)	49 (37.8%)
Secondary Outcome	
1. Induction to expulsion interval (hours) (IQR)	36 (15,48)
2. USG finding prior to curettage following expulsion (*n*=113)	
*Mean endometrial thickness mm (SD)	11.08 (6.7)
*Echogenicity or Irregularity in the endometrial echo *n* (%)	23/113 (20.3%)
3. Main reasons for curettage	
*Significant persistent bleeding	21 (40%)
*Ultrasound	28 (60%)
4. Duration of hospital stay (hours) (IQR)	48 (28,72)
5. Persistent spotting at follow-up (*n*=132)	
*First week	25 (18.9%)
*Fourth week	49 (37%)
*Sixth week	1 (0.75%)
6. Resumption of cycle at the end of sixth week	105 (80.15%)
7. Unscheduled visit to the hospital	Nil

IQR=Inter Quartile Range, USG=Ultrasonography, SD=Standard Deviation

Discussion

Our small prospective study cohort showed that 38% of women needed the check curettage and this is probably a little more than most studies[2,3,14] as the threshold to offer check curettage was very low. Moreover, about 49% of our cohort received all the three doses. This may however explain why there were no unscheduled visits in our cohort on follow-up unlike the 30% in another cohort that used only one or two doses.[3] The mean endometrial thickness in women who had ultrasound for suspected incomplete evacuation was 11.08 mm and the mean endometrial diameter in women who had curettage was 18 mm. Very few studies have this information.[11]

Most of our women remained asymptomatic. Persistent spotting that did not need any further management was the only symptom on follow-up at all three intervals. Our study showed that 80% of them resumed normal cycles in sixth weeks and this finding has not been assessed in most studies. Thus persistent spotting may be an unavoidable symptom that just needs reassurance. Though we used high dose misoprostol vaginally, our study unlike other studies[13] showed a very long intervention to expulsion interval which could be related to the interval between doses. Repeat doses as early as after 3 hours have been used without major side effects[15] and this could be a possible research question in subsequent studies.

Our study was done as an inpatient study as the departmental policy was to admit such women due to concerns of access to hospital admission in an event of a complication such as excessive bleeding. However, studies[3] have documented safety of misoprostol even when administered in outpatient setting. Admission enabled us to document the exact time of expulsion and side effects. Since no woman had any major complications, outpatient treatment with misoprostol could be considered for early pregnancy failure before 14 weeks.

Thus, the strength of our study was that, we had follow-up of our women up to 6 weeks post expulsion. Also, since women were admitted we could assess the safety and side effects. The absence of any major complications and the fact that none of the women required blood transfusion makes the use of misoprostol to medically manage missed abortion very attractive for primary care. The check curettage that may be required to prevent persistent bleeding can be done with minimal safe analgesia with no discomfort to the woman and therefore, the ideal mode of therapy for a primary care setting. Misoprostol is reasonably priced and repeat doses to prevent persistent bleeding can be used without increasing the overall cost of care in these settings. As home-based treatment is getting to be popular,[16-18] information about this regime is important. Some of the drawbacks of our study was that since we had only a single cohort without a comparison arm, we could not assess the cost-effectiveness of our regime as assessed by other studies.[19,20] We also did not document the need for pain relief. The information about pain relief would have been useful to look at acceptability of outpatient use with the same dose of misoprostol by the vaginal route when optimal pain relief is not possible. Research has shown that use of buccal misoprostol is as good as vaginal misoprostol[21-23] and this route will be more acceptable to the woman.

In conclusion, this study has shown that up to three doses of 800 μg of vaginal misoprostol at 12 hourly intervals seems to be a reasonable mode of treatment for cases of missed miscarriage at gestational age less than 14 weeks. Endometrial thickness more than 15 mm in the presence of excessive bleeding could be a general guide for predicting the need for curettage. Studies on an ideal interval between doses could help in identifying the interval that shortens the intervention expulsion duration.

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Conflicts of interest

There are no conflicts of interest.

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