The Use of Vaginal Misoprostol in the Management of Early Pregnancy Failure Up to Eight Weeks Gestation on an Outpatient Basis

Fadia Jassim Al-izzi
CABOG, DOG

Abstract:

Background: the medical management is an effective alternative in the management of early pregnancy failure and this may be undertaken successfully on an outpatient basis. This study is a single arm prospective study designed to use one of regimen of medical termination of early pregnancy failure up to 8 weeks gestation on outpatient basis.

Patients & Methods: In Al-Yermouk Teaching Hospital-Outpatient Clinic, a total of 100 women with an early pregnancy failure were enrolled in this study, all of them were below 8 weeks gestation, they had Hb more than 10 gm /l, haemodynamically stable, no history of clotting disorder or were using anticoagulant (aspirin not included), no previous scar, Rh positive group and they had no previous attempt to terminate the current pregnancy with other obstetricians. Four 200 microgram tablets (800 micro.) of misoprostol (cytotec) were inserted into posterior fornix through a speculum. A second dose was given after 24 hours if expulsion of the products of conception was not complete. On day 8(range, 6-10), if the expulsion of products of conception was still not complete, surgical evacuation was offered. The women were returned on day 15 for assessment including hemoglobin level and ultrasound.

Results: A total of 100 women were enrolled. The mean age was 29.5±7.3 years. The mean gestational age was 40.96±3.20days; 86% were successfully treated and aborted by day 8. Two patients refused surgical evacuation by day 8 after they failed to response to medical management, with follow up they showed a response by day 15. The other (12%) needed surgical evacuation. Two women had been hospitalized as emergency cases, one with bleeding; the second one was admitted because of endometritis. 5% of women recorded fever after misoprostol, 26% had nausea, 11% had vomiting, and 10% had diarrhea. Almost all the patients had abdominal pain but 34% of them used tramadol. 93% were satisfied with medical management, 80% would recommend this treatment for their relatives or they would use it in the future.

Conclusion: Two doses of 800 micrograms of misoprostol administered vaginally is an option for the medical management of early pregnancy failure up to 8 weeks gestation on an outpatient basis, with success rate of 88% and tolerable side effects. 93% were satisfied with medical management, 80% of the enrolled women would recommend this treatment for their relatives or they would use it in the future.

Key word: Vaginal misoprostol, early pregnancy failure.

Introduction

Early pregnancy loss, is defined as a loss within 12 completed weeks of pregnancy[1], occurs in 10-20% of clinical pregnancies and it is responsible for about 50 000 inpatient admission in UK annually[1].The most common types of early pregnancy failure include spontaneous miscarriage (complete incomplete),anembryonic gestation, and embryonic or fetal death[2]. Till the last 6-8 years 88%of women who miscarried were offered surgical evacuation in the UK. In the last 7 years, the standard management has changed, with more treatment as an outpatient basis and medical community began to question whether immediate evacuation by curettage was necessary for uncomplicated cases of early pregnancy failure [1].

Expectant management is clearly an option for incomplete spontaneous miscarriage, but the success rate with the use of this approach for embryonic or spontaneous expulsion is unpredictable, and it may take a month. The uncertainty and anxiety, along with the sadness resulting from pregnancy loss, often make expectant management less appealing to patients. Nonetheless, many women are willing to accept these inconveniences to avoid an invasive procedure. [3]

In the past decade, the prostaglandin E1 analogue misoprostol- an available, safe, and relatively inexpensive drug originally approved in the USA by the Food and Drug Administration for the prevention of gastric ulcers during long –term use of nonsteriodal anti-inflammatory drugs-has been suggested as an alternative approach to managing early pregnancy failure. Indeed, misoprostol has been proposed for a variety of other obstetrical or gynaecological indication: induction of labour, preparation of the cervix for surgery, prevention and treatment of

postpartum hemorrhage, and pregnancy termination. [4]

Zhang et al. reported the results among 652 women with early pregnancy failure who were randomly assigned either to receive misoprostol (one or two 800 microgram vaginally) or to undergo vacuum aspiration, 80 percent of women given medical treatment needed no surgical intervention. Overall, the medically and surgically treated groups had similar and highly favorable ratings of their treatment [5]. The results of Zhang et al study and other reports are considered sufficient to provide the clinician with information they need to use misoprostol responsibly for the management of early pregnancy failure. [6]

Royal College of Obstetric and Gynecology (RCOG) Guideline no. 25, published in 2006, considered the medical management an effective alternative in the management of early pregnancy failure (grade A recommendation) and this may be undertaken successfully on an outpatient basis. Medical evacuation has potential economic benefits for the health system in UK. [1]

The effectiveness of misoprostol in different types of early pregnancy failure, lowest effective dose, and the route of administration (oral, buccal, rectal, versus vaginal) all these questions remain without clear answers [6].

This study is a single arm study designed to use misoprostol administered vaginally on an out patient basis in Al-Yermouk Teaching Hospital/outpatient clinic and in Baghdad, as medical management of early pregnancy failure specifically in gestational age less than 8 weeks.

Patients & Methods:

After the approval of the use of misoprostol in the management of early pregnancy failure in the department of gynecology and obstetric in Al-Yarmuk Hospital, this study was conducted from Aug.2008 to Jan.2010. Patients who sought medical care for possible early pregnancy failure at the outpatient clinic were screened. Women who had anembryonic gestation, embryonic or fetal death were eligible for inclusion if they had an ultrasound examination demonstrating an embryonic pole or crown-rump length went with gestational age less than 8 weeks without cardiac activity confirmed by at least 2 ultrasound.

Women who had an incomplete or inevitable miscarriage were also included. Incomplete spontaneous miscarriage was defined as the passage of some products of conception, with residual anterioposterior endometrial thickness exceeding 30 mm on ultrasound and a uterine size less than 8 weeks of gestation. This cut–off is based on evidence from prior studies of women treated with misoprostol for medical abortion or early pregnancy failure [7]. Inevitable miscarriage was defined as an intrauterine gestational sac and internal cervical os that was open to digital examination with active vaginal bleeding [7]. Women were exclude if they had anemia (Hb less than 10 gm /l) ,haemodynamically unstable , history of clotting disorder or were using anticoagulant (aspirin not included),previous scar , Rh negative group, or they had a previous attempt to terminate the current pregnancy with other obstetricians. After that the addresses of the patients in regard to Al-Yermouk Hosp. were ascertained and whether they could get an emergency access to the hospital in the morning and night and on other side the facilities for emergency surgical evacuation also were ascertained. The last step was an informative interview with the patients and (usually) their husbands about the options available to them, the risk, benefit of medical management, when to call the obstetrician, and when to attend the hospital urgently. Then all subject provided with a written informed consent. Telephone contact also established with all patients.

At enrollment, medical history, hemoglobin level was assessed and physical examination was performed. Although trials have not identified the optimal dose of misoprostol, 800 microgram given vaginally was the most widely tested regimen. Thus, four 200 microgram tablets (800 micro.) of misoprostol (cytotec) were inserted into posterior fornix through a speculum.

A second dose was given after 24 to 48 hours if expulsion of the products of conception was not complete (that is, gestational sac was still visualized or the endometrial lining was greater than 30 mm on ultrasound).

On day 8(range, 6-10), if the expulsion of products of conception was still not complete, surgical evacuation was offered. The women were returned on day 15 for assessment including hemoglobin level and ultrasound.

The women were instructed to take ponstan capsule with or without tramadol tablets as needed for pain. They were instructed to record any side effects and to measure their temperature daily by thermometer (in those who can use thermometer).

At day 15, hemoglobin was measured and each woman completed a questionnaire assessing the acceptability of the treatment.

All women were instructed to take with them to the hospital or private lab any tissue passed so that histological examination can be arranged

Results

A total of 100 patients were enrolled. The mean age of the women was 29.5±7.3 years and the range was wide (15-42years). The mean gestational age in days was 40.96±3.20. More than 50% of the patients were multiparous, 33% Para one, 17% were nuliparous. The distribution of patients according to the type of pregnancy failure was as the following: 41% missed abortion, 36% incomplete abortion 19% inevitable abortion and 4% blighted ovum. About 50% of our patients had only primary school graduation. Abdominal pain was recorded in 44% of the patient while 70% of the women had vaginal bleeding prior to treatment **table 1.** The success rates of the treatment are presented in **table 2.** Fortunately, all the enrolled patients were not lost to follow-up. All women received 2 doses 24 hours apart of misoprostol inserted vaginally. 86% were successfully treated and aborted by day 8. Two patients refused surgical evacuation by day 8 after they failed to response to medical management, with follow up they showed a response by day 15. The other (12%) needed surgical evacuation, 9% by day 8, but 3% after 48 hours from the last dose where they requested surgical management.

The success rate was about 89% in those women with incomplete abortion while it was 83% in missed abortion. The response in women with primary and secondary school graduation was 86% and 85% respectively.

Table 1 Characteristics of study sample at enrollment

Characteristics	Value
Mean age of women (years)	29.5100+7.3147
Number of previous parity	Percentage
nil	17%
one	33%
Two or more	50%
Mean gestational age (Days)	40.9600+3.2001
Previous Miscarriage	Percentage
Nil	72 %
Previous 1	20 %
Previous 2	7 %
Previous 3	1 %
Type of abortion	Percentage
Incomplete abortion	36 %
Missed Abortion	41 %
Inevitable abortion	19 %
Blighted ovum	4 %
Education level	Percentage
Primary	47 %
Secondary	38 %
College	15 %
Low abdominal pain in the previous 24 hour	44%
Vaginal bleeding in the previous 24 hour	70%

Table 2 shows the outcome of vaginal misoprostol

Characteristics	Value
Women aborted at day 3	74 %
Women aborted at day 8	12 %
Women aborted at day 15	2 %
Women needed evacuation	12 %
Success in incomplete abortion	89 %
Success in missed abortion	83 %
Success in primary school women	86 %
Success in secondary school women	85 %
Women who satisfied the protocol	93 %

Two women had been hospitalized as emergency cases, one with bleeding, treated with supportive care without blood transfusion; the second one was admitted because of endometritis and surgical evacuation done to her with antibiotic cover. 5% of women recorded fever after misoprostol, 26% had nausea, 11% had vomiting, and 10% had diarrhea. Almost all the patients had abdominal pain but 34% of them used tramadol **table 3.**

93% were satisfied with medical management, 80% would recommend this treatment for their relatives or they would use it in the future.

Table 3 Adverse Events of medical treatment of early pregnancy failure

Adverse events	percentage
Hemorrhage requiring hospitalization	1%
Hospitalization due to endometeritis	1%
Decrease in Hb >2 g/dl	8%
Decrease in Hb >3 g/dl	3%
Nausea	26%
vomiting	11%
diarrhea	10%
Abdominal pain	98%

Discussion

The medical management of early pregnancy failure seems to have a special impact on the health care to women in child bearing age in the developing countries, where the high- quality surgical care is not available to all. The estimated maternal mortality due to unsafe abortion is 13% of all maternal death worldwide, almost all of which occur in developing countries [6]. The recent studies have showed the favorable outcome of medical treatment and they show that misoprostol is highly acceptable to women when used instead of surgical aspiration, not only that, but the using of misoprostol in an outpatient setting reduces the cost of services [1].

Medical management can be undertaken successfully on an outpatient basis. Clearly this approach should only be offered in situations where women can access 24-hour telephone advice and emergency admission if required [1]. And this point was a critical point in the evaluation of every patient before enrolling in this study, where the telephone contact with the patient and the feasibility of emergency admission to the hospital were secured first. The mean gestational age was around 42 days i. e. all the patients were below 8 weeks gestation in comparison with the recent studies where they use misoprostol up to 12 weeks even on an outpatient setting[5,8]. However, a study conducted in Singapore in 2002, where one day course of vaginally administered misoprostol had been shown to be effective and safe on an outpatient setting for termination of pregnancy up to 8 weeks [9].

RCOG guidelines number 25 stated that the protocols for medical management should developed locally with selection criteria, therapeutic regimens and arrangement for follow up. It has been showed that the success rates increase with the vaginal route in comparison with oral or sublingual routes without increase in the side effects, whereas the result of other studies indicate that the various routes (vaginal, oral, sublingual, rectal) are equally efficacious and have similar rates of side effects[6]. Recently, a direct vagina-uterus transport was described for progesterone absorption. A similar mechanism for misoprostol absorption may exist and can explain the more favorable clinical effects with vaginal route when compared to oral route despite similar bioavailability [4].

Studies have used a single dose, two or three consecutive doses or a single dose repeated after 24 hours if needed, the last regimen was used in a randomized retrospective study in 491 patient

conducted by Zhang et al., the success rate was 84% by day 8, and it was conducted on outpatient basis [5], therefore this study adopted this regimen.

This study indicates that treatment of early pregnancy failure up to 8 weeks gestation with 800microgram misoprostol vaginally, with the dose repeated after 24 hours, is efficacious. The success rate by day 15 was 88%. The risks of hemorrhage and pelvic infection were very low, and the side effects were tolerable. Misoprostol treatment was acceptable to most women.

The success rate in this study is comparable to that of different studies using similar regimen [5,8,10]. These studies showed variation in response according to the type of pregnancy failure, where higher success rate reported in women with incomplete or inevitable abortion, this has been seen in the current study where the success rate in incomplete abortion is 89% while it is 83% (p value <0.05) in missed abortion. Some studies used one dose of misoprostol and they waited more than 48 hours before they used the second dose in those women with incomplete abortion [5,10] while in this study there was no response after the first dose and all the women needed 2 doses including those with incomplete abortion and we found more than one study used the last regimen [11,12] .

Two women required emergency admission to hospital, one because of hemorrhage, and she had been managed in the hospital conservatively without surgical evacuation or blood transfusion where the ultrasound examination in the next morning showed empty uterus. The other women admitted at night with fever 2 days after the first dose, she had been treated with antibiotics and surgical evacuation. The other side effects like nausea, vomiting, or diarrhea were tolerable by the patients and consistent with previous studies. These findings, in accordance with that in other literature on medical abortion [5,8,10,11], suggests that hospitalizing patients for the misoprostol treatment is unnecessary. As long as clear instructions for monitoring bleeding and infection are given to women and emergency service is readily accessible. The education level was not an obstacle in providing the medical abortion to the women, where the success rate and the incidence of complication are not significantly different between women with primary school level or secondary and college graduation. This study has showed the efficacy and safety of two doses of misoprostol inserted vaginally on an outpatient basis but whether one dose is effective in certain type of abortion or not, whether other routes are more effective and the safety of this approach (outpatient) up to 12 weeks, all these questions can not be answered from this study.

Two doses of 800 micrograms of misoprostol administered vaginally is an option for the medical management of early pregnancy failure up to 8 weeks gestation on an outpatient basis, with success rate of 88% and tolerable side effects. 93% were satisfied with medical management, 80% of the enrolled women would recommend this treatment for their relatives or they would use it in the future.

References:

1-Royal College of Obstetricians and Gynaecologists. The management of early pregnancy loss. Guideline No. 25. London:RCOG;2006.

2- Alberman E. Spontaneous abortions: epidemiology. In: Stabile I, Grudzinskas G, Chard T, eds. Spontaneous abortion: diagnosis and treatment. London: Springer Verlag,1992:19-20.

3-Jurkovic D, Ross JA, Nicola ides KH. Expected management of missed miscarriage. Br J Obstet Gynaecol 1998; 105:670-1.

4-O.S. Tang, K. Gemzell-Danielsson, P. C. Ho. Misoprostol: Pharmacokinetic profiles, effect on the uterus and side effect. Inter. J of Gynae. And Obstet.2007; 99:S160-S167.

5- Jun Zhang, Jerry M. Gilles, Kurt Barnhart, et al. A comparison of medical management with misoprostol and surgical management for early pregnancy failure.N Engl J Med 2005; 353:761-9.

6-Beverly Winikoff. Pregnancy failure and misoprostol – Time for a change. N Engl J Med 2005; 353: 834-6.

7- Harwood B, Meckstroth KR, Mishell DR, Jain JK. Serum beta-human chorionic gonadotropin levels and endometrial thickness after medical abortion. Contraception 2001;63:255-6.

8- Graziosi GC, Bruinse HW, Reuwer PJ, Mol BW. Women preferences for misoprostol in case of early pregnancy failure. Eur J Obstet Gynecol Reprod Biol 2006; 124:184-6.

9- Kuldip Singh, Y. F. Fong, F. Dong. A viable alternative to surgical vacuum aspiration: repeated doses of intravaginal misoprostol over 9 hours for medical termination of pregnancies up to eight weeks. BJOG 2003; 110:175-80.

10- Wood SL, Brain PH. Medical management of missed abortion: a randomized controlled trial. Obstet Gynecol 2002; 99:563-6.

11- Davis AR, Robilotto CM, Westhoff CL, Forman S, Zhang J, NICHD Management of early pregnancy failure Trial Group. Hum Reprod 2004; 19:1655-8.

12- Zalanyi S. Vaginal misoprostol alone is effective in the treatment of missed abortion. Br J Obstet Gynaecol 1998; 105:1026-8.

AL-Mustansiriya Medical Collage Department of Obstetrics & Gynecology