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Mid-Trimester Termination of Pregnancy by Vaginal Misoprostol in Missed Abortion

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Abstract **Original Research Article**

The use of vaginal misoprostol, a prostaglandin analogue is an effective and safe management option for missed abortion. This study evaluated a low-dose (200 microgram) vaginally administered misoprostol four hourly to assess the success rate of medical management in mid-trimester missed abortion. A total of fifty patients with missed abortion, who had agreed to undergo medical treatment with vaginal misoprostol were enrolled. They were apparently healthy, between 18-40 years of age, less than 20 weeks of gestation, and had missed abortions verified by ultrasonogram report. All study women with missed abortion; misoprostol tablet (200 microgram) was applied in the posterior fornix of the vagina every four hourly. Complete abortion was confirmed by passage of products of conception and by clinical finding at the pelvic examination along with ultrasonogram report. In this study, we have demonstrated that 92% of patients were successfully treated by vaginal misoprostol. Only one patient needed oxytocin drip and three patients were managed by evacuation and curettage. This study showed that vaginal misoprostol is safe and effective method of treatment for mid-trimester missed abortion.

Keywords: Misoprostol; Missed Abortion; Mid-trimester; Pregnancy; Termination.

1. INTRODUCTION

Abortion is defined as termination of pregnancy by any means before the fetus become viable [1]. Missed abortion refers to unrecognized intrauterine death (IUD) of the embryo or fetus without expulsion of the products of conception [2] Missed abortion constitute about 15% of all clinically diagnosed pregnancies [3, 4]. Mild symptoms like those of threatened abortion are followed by absence of usual signs to progress of pregnancy [5]. Sometimes there may be no bleeding and the condition is diagnosed clinically when the doctor notices that the uterus is not increasing in size. The uterus may be found smaller than would be expected and on ultrasonogram (USG) scan will reveal the true state of affairs [6]. Spontaneous abortion is the most common complication of early pregnancy. Approximately 10-20% of clinically recognized under 20 weeks [3]. It was reported that, the total rate of pregnancy loss after implantation was 31%; 70% of this loss (22% of all pregnancies) occurred before the pregnancy detected clinically [7]. Estimated abortion ratio was about 30 per 1000 women for 15-34 years of old and 35 per 1000 women for 15-49 years old [8, 9]. In many studies, abortion related deaths were found to be nearly 20% [10-12]. Chromosomal abnormalities are causative in approximately 50% of spontaneous abortions; of which autosomal trisomy 50%, monosomy X 20%, polyploidy 22%, others account 8% [13, 14]. Multiple other factors also may play role such as anatomical abnormalities- uterine malformation, hormonal abnormalities, maternal TORCH infection, immunological disorder, environmental agent, blood group incompatibility and unknown factors [14]. In missed abortion, it is not known why the pregnancy is not expelled. It is possible that normal progesterone

production by the placenta continues while the estrogen level fall, which may reduce uterine contractility to expel the product of conception [14]. All missed abortion would probably be expelled spontaneously in the long term, but there may be a delay of weeks or months. In a few late cases there is risk of hypofibrinogenemia after death of fetus for some weeks, probably caused by thromboplastin from the chorionic tissue entering the maternal circulation [15]. Therefore, active management is often choosing [16]. Missed abortion is a cause of worry both for the patient and the gynecologist. The gynecologist's concern is deciding the method of terminating pregnancy. The problems are because of closed cervix, bulk of products and the possibility of adherence of products to the uterine wall [17]. This adherence increases the chance of incomplete evacuation and uterine perforation. A major coagulation disorder is rare if the fetus is retained for less than one month, but occurs in 25-30% of cases thereafter [15, 18]. The commonly practiced method of managing missed abortion is dilatation and evacuation of uterus. Use of medical methods is expected to bring about gradual non traumatic dilatation of cervix, separation of products and its expulsion. However, few cases might require surgical evacuation to remove the retained products. In' 1950s; synthetic oxytocin become available and increasing doses were used to terminate mid-trimester abortion [19]. But in early 1980s till now numerous studies have shown locally applied prostaglandins (principally PGE_1, PGE_2) results are very promising [19-21]. Use of prostaglandins alone in missed abortion without progesterone antagonists is suggested logical because death of the concepts brings about natural fall in progesterone level [20]. Prostaglandin and their synthetic analogues are successfully employed in medical management of missed abortion using different routes of administration [19-21].

Misoprostol, a synthetic prostaglandin E1 (PGE1) analogue of the prostaglandin which was initially used in peptic ulcer treatment, is a promising agent in cervical ripening [16, 21, 22]. It is closely related to other prostaglandins such as dinoprostone, carboprost, gemiprost [23]. Both oral and vaginal form of misoprostol independent of their local effect on cervix, prostaglandin also stimulates the myometrium, resulting uterine contraction and helps to expel the pregnancy [16, 22]. Misoprostol has potent uterotonic and cervical ripening activity that also softens and opens the cervix [16, 21, 22]. It is rapidly absorbed after oral, vaginal and rectal administration [16]. Misoprostol is safe, inexpensive, easily stored, has minimal side effects in comparison with other prostaglandins [24]. Previous reports on use of vaginal misoprostol alone in abortion cases documented that it is comparatively better than oral misoprostol [16, 21]. Recent evidence suggested that there might be an improved efficacy of uterine evacuation and a reduced incidence of side effects if misoprostol administrates per vaginally [16, 21, 24]. This study assessed the efficacy, pharmacological effect, side effects and short-term complications associated with vaginal administration of low dose misoprostol as the initial management of mid-trimester missed abortion.

2. MATERIALS AND METHODS

This prospective randomized clinical trial was conducted at the Department of Obstetrics and Gynaecology, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh. The study protocol was approved by the Institutional Review Board (IRB), Dhaka Medical College (DMC), Dhaka, Bangladesh. A total of fifty (50) women with missed abortion at mid-trimester were enrolled following selection criteria. Mid-trimester pregnancy (between 12 to 20 weeks of gestation), diagnosed cases of missed abortion by ultrasonogram (USG), without any medical disorders were included. Patients with known hypersensitivity to prostaglandin, patients with clinical or laboratory evidence of severe anemia and patients with active vaginal bleeding or cramping and dilatation of internal os were excluded from this study.

Study Procedure

The patients having missed abortion within 12 to 20 weeks of gestation were selected. After selection, the objectives, procedure and risk/benefits of this study were explained to the patients. Informed written consent was taken from each study patient prior to enrollment. Then a detailed case history was taken and relevant clinical examinations were performed. The gestational age was evaluated by the last menstrual period, bimanual examination and ultrasonogram (USG). Some patients were asymptomatic, who were incidentally diagnosed by USG during antenatal check-up. But according to USG finding (gestational age) and bimanual examination (height of the uterus) their gestational age was less than the period of amenorrhea. After confirmation of diagnosis their complete blood count and coagulation profile such as- bleeding time (BT), clotting time (CT), platelet count, fibrin degradation products (FDP) were done following standard procedure. In each case, 1 bag of cross-matched with screened blood was kept ready for blood transfusion, whenever needed.

Insertion Procedure

With all aseptic precautions, 1 misoprostol tablet (200 microgram) was introduced per vaginally and applied in the posterior fornix. This dose was repeated for every 4 hours for a total of maximum 6 doses or until expulsion of the product of conception. Follow up was done at 4 hours interval or whenever the patient complained of any problem. If the patient did not respond (even after 6 doses of misoprostol therapy) then oxytocin drip was started approximately 4-6 hours after the last dose of misoprostol. In spite of misoprostol and oxytocin, if the patient still failed to respond, surgical evacuation was done. The spontaneous expulsion time was defined as the time taken from insertion of the drug to the time after complete expulsion of conception.

Ultrasonogram was done after 12-24 hours of misoprostol insertion to confirm complete abortion. Complete abortion was confirmed by passage of products of conception and by clinical findings at the pelvic examination. The side effects such as nausea, vomiting, diarrhea, headache, fever, and severe cramping, shivering was evaluated based on nursing observation and individual study women's complaints. All women were then observed for vital sign/symptoms and for excessive vaginal bleeding. An antibiotic [tablet ciprofloxacin (500 mg) 12 hourly] was prescribed to all study patients. Non-steroidal anti-inflammatory drugs (NSAIDs) was used for pain relief. Some patients needed antiemetic drug for nausea and vomiting. The patients were discharged after few hours of spontaneous expulsion. They were requested to return for follow-up visit two weeks later or earlier if bleeding didn't cease within ten (10) days or any other complaints.

Data Analysis

All data were collected in a separate data collection sheet for each patient. The highest levels of confidentiality and ethical standards were maintained during the analysis of the data. The collected data were cleaned, cross-checked and verified accordingly to reduce inconsistency. Then statistical analysis was done using the statistical package for social science (SPSS) version- 26. Quantitative data were expressed as mean with standard deviation (±SD) and qualitative data were expressed as frequency (n) with percentage (%).

3. RESULTS AND OBSERVATION

This study was intended to evaluate effectiveness and safety of vaginal misoprostol in mid-trimester termination of pregnancy among the cases of missed abortion. A total of fifty (50) women with missed abortion at mid-trimester (between 12 to 20 weeks) of gestation were included as study population. Mean±SD age of the study patients was 26±4.27 years and the age ranged from 18-35 years. Maximum (60%) study patients were in 21-30 years age group (Table-1). Majority (56%) of them were 12 to 16 weeks of gestational age and 44% were in 17 to 20 weeks of gestational age (Table-2). Most of the study patients (82%) were multiparous and only 18% was nulliparous (Figure-1).

Table-1: Age distribution of the study patients (N= 50)

Age (years)	Number (n)	Percentage (%)
Age groups		
18-20 years	10	20
21-30 years	30	60
>30 years	10	20
Mean±SD	26±3.27 years	
Range	18-35 years	

Table-2: Distribution of the study population according to the gestational age (N= 50)

Gestation age (weeks)	Number (n)	Percentage (%)
12-1 6weeks	28	56
17-20 weeks	22	44

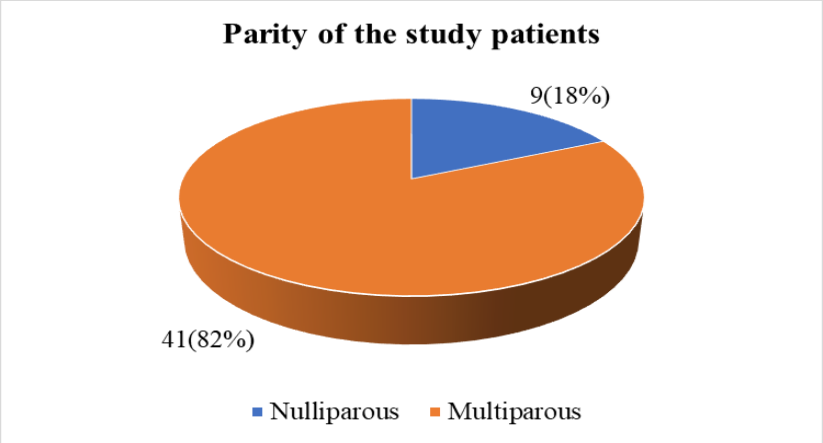

Figure-1: Distribution of the study patients on parity (N= 50)

Among the study cases, there was no previous history of abortion in 54% cases. On the other hand; previous history of one (1) abortion in 30% cases, previous history of 2 abortions in 14% cases and only 1 (2%) patient had 3 previous abortions (Table-3).

Table-3: Previous history of abortion among the study patients (N= 50)

Previous history of abortion	Number (n)	Percentage (%)
No previous abortion	27	54
1 previous abortion	15	30
2 previous abortions	7	14
3 previous abortions	1	2

Regarding the clinical presentation; out of total 50 study patients, 12 (24%) patients was asymptomatic, 30 (60%) patients had active per vaginal bleeding, while pregnancy symptoms were disappeared in 8 (16%) patients (Table-4).

Table-4: Clinical presentation of the study cases (N= 50)

Clinical presentation	Number (n)	Percentage (%)
Asymptomatic	12	24
Active per vaginal bleeding	30	60
Disappearance of pregnancy symptom	8	16

For spontaneous expulsion after misoprostol administration, total doses of misoprostol were estimated in each case; single dose was sufficient for 3 (6%) patients, 22 (44%) cases needed 2nd dose, 16 (32%) cases needed 3rd dose, 6 (12%) cases needed 4th dose and another 3 (6%) cases required 5th dose of misoprostol (Figure-2).

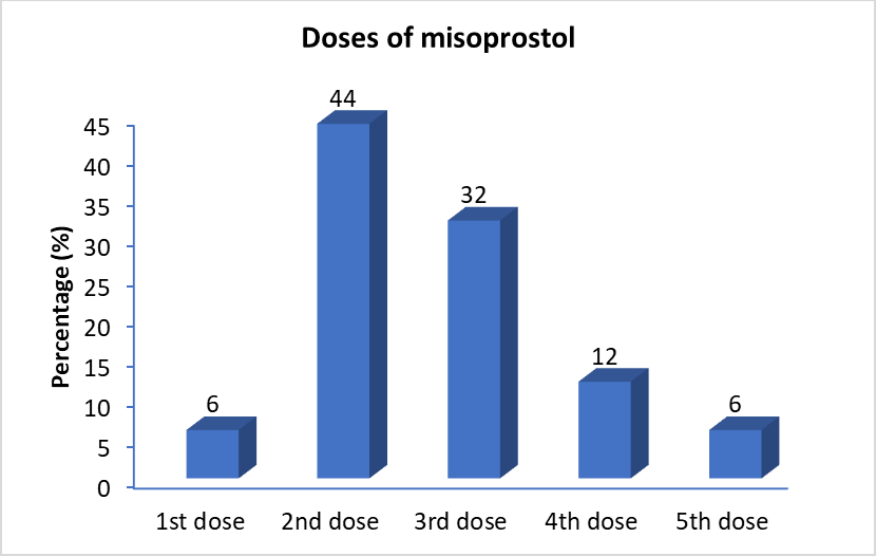

Figure-2: Doses of misoprostol required among the study cases (N= 50)

In this study, induction expulsion interval time was between 4-8 hours in 6% study cases, 9-12 hours among 42% study cases, 13-16 hours required in 32% cases and 20% cases induction expulsion interval time was more than 16 hours (Table-5).

Table-5: Induction expulsion interval time (Hours) among the study population (N= 50)

Induction abortion interval time (hours)	Number (n)	Percentage (%)
Within 4-8 hours	3	6
Within 9-12 hours	21	42
Within 13-16 hours	16	32
>16 hours	10	20

Analyzing the outcomes in this study revealed that; spontaneous expulsion after misoprostol administration was in 92% cases, spontaneous expulsion after oxytocin drip was in 1 (2%) case, but evacuation and curettage was needed in 3 (6%) cases. Analgesia was needed in 14 (28%) study cases and only 2 (4%) cases required blood transfusion (Table-6).

Table-6: Outcomes among the study patients (N= 50)

Outcomes	Number (n)	Percentage (%)
Expulsion of products of conception		
Spontaneous expulsion after misoprostol administration	46	92
Spontaneous expulsion after oxytocin drip	1	2
Oxytocin drip + evacuation curettage	3	6
Need of analgesia		
Yes	14	28
No	36	72
Blood transfusion		
Need of blood transfusion	2	4
No need of blood transfusion	48	96

Among the study patients a few side-effects of misoprostol administration were observed; such as nausea in 24% cases, vomiting in 28% cases, shivering in 22% cases, cramps/pain in 42% cases, chills/fever in 4% cases and diarrhea in 2% cases. Notable, total percentage was exceeded 100% as there was multiple responses (Figure-3).

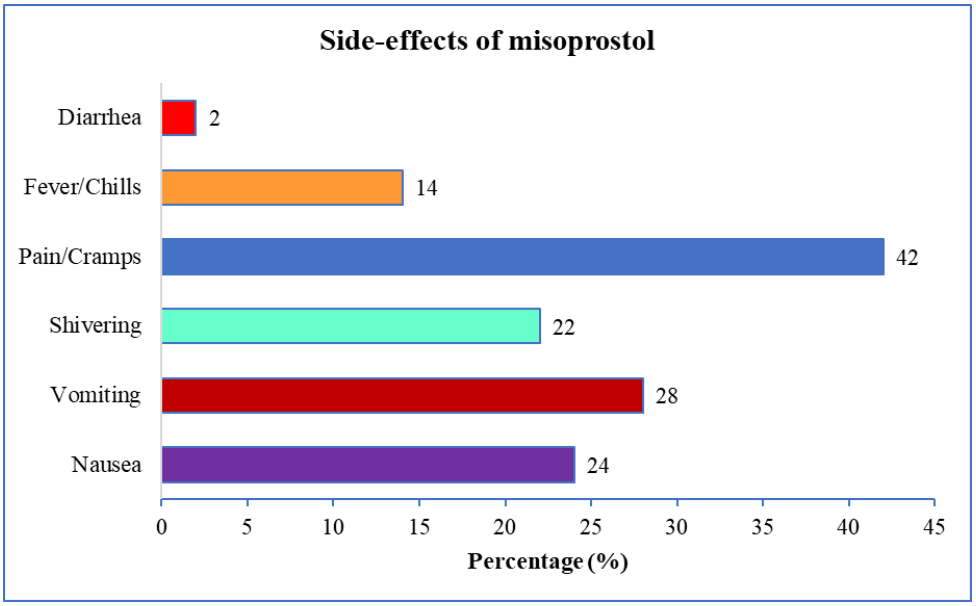

Figure-3: Side-effects of vaginal misoprostol administration among the study cases (N= 50)

It was observed that all study patients were satisfied in misoprostol induced expulsion; of them highly satisfied was 70% patients and rest 30% patients were moderately satisfied, according to their opinion (Table-7).

Table-7: Level of patient's satisfaction (N= 50)

Level of patient's satisfaction	Number (n)	Percentage (%)
Highly satisfied	35	70
Moderately satisfied	15	30
Unsatisfied	0	00

4. DISCUSSION

Abortion termed as, termination of pregnancy by any means before the viable age (at 23- 24 weeks of gestation) of the fetus [1]. Missed abortion refers to an undetected death of the fetus (or embryo) within the uterus without complete expulsion of the products of conception [2]. It constitutes about 15% of all clinically diagnosed pregnancies [3]. There are no definite symptoms of a missed abortion and experiencing women usually unaware of having this condition [1, 2]. The presence of a non-viable pregnancy is upsetting to the mother and there is a risk of coagulation defect if a dead fetus is retained for several weeks [25]. Missed abortion is a common gynaecological problem. It is best to evacuate the uterus without any delay. Surgical evacuation is the standard management for the missed

abortion that has approximately 95% success rate and widely performed around the world in last couple of decades [26]. Although the cost of surgery and complications associated with surgery are consider as major concern. Recent studies suggested that medical management is more preferable than surgical evacuation [27, 28]. Moreover, considerable savings in resources can be made if routine curettage for this condition is minimum following a medical rather than direct surgical approach [28]. The main outcome measures examined in this study were the effectiveness with safety profile of per vaginal use of low dose misoprostol (200 microgram), 4 hourly as a medical management of mid-trimester missed abortion.

In this study mean±SD age of the study patients was 26±4.27 **y**ears, that ranged from 18-35 years. Maximum (60%) study patients were in third decade of life and 56% had gestational age between 12 to 16 weeks, while majority (82%) of them were multiparous. In a similar study by Zalanyi S, showed that mean (±SD) age of the study women was 25.8±5.25 years, their mean(±SD) gravida was 2.4±1.42 and parity was 1.0±0.84; the study included only cases of amenorrhea of up to 13 weeks [21], whereas, our study includes mid-trimester (12 to 20 weeks) cases. In accordance Wood SL and Brain PH found; gestational age of the study patients was ranged 7 to 17 weeks (median 12 weeks), the mean (±SD) age of their study patients was 31±5 years and 56% were nulliparous [3]. In both previous studies, vaginal misoprostol was found to be quite effective in expulsion of product of conception in missed abortion cases, reducing the need for surgical evacuation.

Regarding the doses of misoprostol used for complete expulsion; in our study, maximum (44%) study women needed 2nd dose of misoprostol followed by 32% women needed 3rd dose of misoprostol and maximum induction expulsion interval time was 9-12 hours. The success rate of medical management was defined as a complete uterine evacuation without the need for any surgical intervention [21]. If any women needing or desiring a surgical intervention, that was considered as failure. In this current study the success rate was 92% and there were 4 failure cases; of which 1 needed oxytocin drip and 3 needed oxytocin drips with a surgical intervention. In a related previous study, 35 out of 42 women were successfully treated by misoprostol (vaginal administration) in the management of missed abortion, where induction expulsion time was 11.63±6.14 hours [29]. It was documented that the plasma level of misoprostol reached at the peak level slowly (80 minutes) after vaginal administration and the level was sustained up to 4-6 hours [30]. In a previous study by Zalanyi S [21], misoprostol 200 microgram vaginally was used in missed abortion for expulsion of products of conception and found that; 5 patients (out of 25) had a complete abortion after 1st dose of misoprostol, 13 patients after 2nd dose of misoprostol, 4 patients after 3rd dose of misoprostol, but 3 patients did not respond even after four doses of misoprostol who required surgical evacuation of the uterus. There was no febrile complication and the induction expulsion time in their study was 6.1 hours (calculated only for successful cases) [21]. In accordance Wood SL and Brain PH showed that, 80% study patients aborted completely after 2 vaginal doses of 800 microgram of misoprostol tablet [3]. In a related study, 400 microgram vaginal misoprostol was applied every 3-6 hours and found every 3 hours was more effective than every 6 hours administration [31]. It should be noted that dose of misoprostol used in this previous study was quite high than this current study. In that study, there was also an additional benefit of soft dilated cervix found during surgical treatment. There was no occurrence of life-threatening bleeding and none of the patient needed blood transfusion. The patient's satisfaction with the drug (misoprostol) was quite high [31]. It was reported that vaginal administration of misoprostol was comparatively more effective than oral route [25]. The local effect of misoprostol on the cervix was considered to be one of the reasons [25].

Regarding side effects; pain/cramps, nausea/vomiting, shivering, fever/chills and diarrhea were observed in our study. But all these side effects were well tolerated among the study patients. There was needed of some analgesia for pain relief (not all patients) and anti-emetic for nausea, vomiting. Other issues were managed accordingly. In this current study all patients were satisfied in misoprostol induced expulsion; most of them (70%) were highly satisfied and 30% was moderately satisfied (in their opinion). In this context, Lee DT *et al*., also indicates that the medical treatment of missed abortion with vaginal misoprostol is psychologically safe and higher client acceptance and satisfaction rate [32]. In this current study it was observed that, vaginally administered misoprostol in a dose of 200 microgram 4 hourly have increased the success rate of medical management of mid-trimester missed abortion. Current study demonstrated that misoprostol in vaginal administration is very safe and effective. This could be because of higher uterine levels of misoprostol due to direct absorption from the posterior fornix and local effect of misoprostol on uterine cervix. Our results were supported by a couple of previous studies [21, 33].

5. CONCLUSION

Vaginal prostaglandin is safe, effective and economic method of treating missed abortion. This medical method of evacuation avoids complications related to intra-uterine instrumentation. This study concluded that vaginal misoprostol is effective in medical management of missed abortion. In this study, three patients needed surgical evacuation but one of the important observations was that all these patients who needed surgical evacuation had soft dilated cervix. Therefore, during surgical evacuation, the risk of

perforation and cervical injury was less. Furthermore, misoprostol treatment of missed abortion can have an important role in reducing the occurrence of post-surgical infection. Proper counseling should be included specific information about the potential advantage and disadvantage of vaginal administration of misoprostol. The patients need to be involved in the management, decision making in order to improve compliance with this treatment.

Limitations of the study

The current study had several limitations. It was a single center study with a relatively small sample size. Long time follow up of the study patients after complete expulsion was not possible due to short time hospital stay. Moreover, all study patients were not returned for follow-up after two weeks.

Recommendation

A multi-center large population based study should be done to verify the findings of this current study.

Conflicts of Interest

All authors declared that there is no conflict of interest regarding this publication.

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