ISSN (Print): 2663-9491 ISSN (Online): 2789-6897

Original Article

Comparison of Side Effects — Vaginal Versus Oral Misoprostol in Management of First Trimester Missed Abortion

DOI: dx.doi.org

Taslima Abid[1*], Farhana Yesmin Rumpa[2], Surovi Sultana[3], Umme Kulsum[4], Nofisa Khatun[5]

Received: 19 November 2024
Accepted: 28 November 2024
Published: 15 December 2024

Published by:
Gopalganj Medical College,
Gopalganj, Bangladesh

*Corresponding Author

ABSTRACT

Introduction: *The therapeutic potential of misoprostol as an abortifacient has clearly been demonstrated in a randomized study. Misoprostol is active and safe both by oral and vaginal routes but the latter has been found to be better in many trials. The aim of the objective is to compare the efficacy and safety of vaginal misoprostol to oral misoprostol for the treatment of first trimester missed abortion.* ***Methods & Materials:*** *The study was conducted in the Gynaecology and Obstetrics Department of Shaheed Ziaur Rahman Medical College Hospital (SZMCH) in Bogra over a period of six months, from May 2015 to October 2015. The participants included women diagnosed with miscarriage, based on both their medical history and physical examinations, and referred from the outpatient department for admission.* ***Result:*** *Most respondents in both groups were aged 20-25. Among 118 respondents, 9.3% had a previous miscarriage, while 89.8% of Group A and 91.5% of Group B had no history of abortion. Around 42.4% of Group A and 37.3% of Group B were primigravidae. Group B had twice as many second gravidae as Group A. The mean gravidity was 1.81 (SD 1.004) for Group A and 1.78 (SD 1.018) for Group B, with an average gestation period of 10.9 weeks for both. Group B had 76.3% complete expulsion, while Group A had 37.3%. Incomplete and no expulsion rates were higher in Group A.* ***Conclusion:*** *This study concludes that, per vaginal administration of Misoprostol in*

(The Insight 2024; 7(1): 111-121)

1. *Junior Consultant (CC), Sariakandi Upazila Health Complex, Bogura, Bangladesh*
2. *Junior Consultant (CC), Upazila Health Complex, Adamdighi, Bogura, Bangladesh*
3. *Junior Consultant (CC), Department of Obstetrics & Gynaecology, Upazila Health Complex, Sunderganj, Gaibandha, Bangladesh*
4. *Junior Consultant (CC), Ullapara Upazila Health Complex, Sirajganj, Bangladesh*
5. *Junior Consultant, Dhupchanchia Upazilla Health Complex, Bogura, Bangladesh*

posterior fornix is more effective than Oral Misoprostol. The former has faster onset of action and better efficacy. Per vaginal Misoprostol have fewer side effects.

Keywords: *Missed Abortion, Misoprostol, Sonography*

INTRODUCTION

One of the most frequent pregnancy problems, first trimester miscarriages occur in 10–15% of clinically recognised pregnancies[1]. Nearly one-third (30%) of maternal deaths worldwide occur in South Asia (Bangladesh, Nepal, India, Pakistan, and Sri Lanka), a heavily populated, resource-constrained, and undeveloped region. Of these, roughly 13% are related to abortions and its procedures[2]. The abortion rate in Pakistan is 29 per 1000 women aged 15-49 years, whereas 890,000 women present with missed or incomplete abortions each year. Over the past 50 years, dilatation and uterine evacuation have been the standard, well recognised treatment for early pregnancy failure, with a success rate of over 95%[3,4]. The focus has shifted to expectant and medical management with major cost advantage due to the difficulties (sepsis and haemorrhage) connected with the surgery when performed by unskilled personnel, which is prevalent in low-resource countries[5]. Although expectant management is an option for incomplete spontaneous abortion, patients may find it less appealing due to its suboptimal success rate (25-76%), unpredictable interval to spontaneous expulsion, uncertainty and anxiety, and emotional trauma associated with carrying a non-viable pregnancy[6,7]. For women who are unfit for general anaesthesia or do not want to be admitted to the hospital, medical care of early pregnancy failure provides a safe, effective, and affordable alternative to surgery[8]. A safe alternative that is becoming more and more well-liked due to its uterotonic and cervical priming effects is misoprostol, an analogue of prostaglandin E1. It is stable at room temperature and reasonably priced. The oral, vaginal, sublingual, and rectal routes of misoprostol delivery were examined in pharmacokinetic research[9]. Due to the buccal mucosa's strong vascularity, the sublingual route has the highest bioavailability when compared to other routes, avoids the first pass effect through the liver, and has the shortest time to peak concentration 30 minutes as opposed to 75 minutes for the vaginal route. Additionally, it avoids uncomfortable vaginal administration and is more convenient for women to consume[10-12]. Shivering, overheating, and gastrointestinal side effects are the main disadvantages[12]. Misoprostol's effectiveness in treating early pregnancy failure has been assessed in over 20 different trials; the success rate ranges from 13 to 100% and is impacted by a number of variables, including diagnosis, sac size, and dosage frequency. In comparison to a manual hoover aspirator, two recent trials reported effectiveness rates over 90%[13,14]. For first-trimester failures, there are several dose regimens published in the literature that are administered via various ways; however, very few use the sublingual route. When the embryo dies

and fails to develop, the gestational sac is retained in the uterus for several weeks and even months, the condition is known as "Missed Abortion". Mild symptoms like those of threatened abortion are followed by absence of usual signs of progress of pregnancy. 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 ultrasonographic scan will reveal the true state of affairs[15]. The standard treatment for missed abortions for the last 50 years has been dilatation and curettage which is typically done in an operating room, thus significantly increasing the costs[16]. Surgical method of abortion carry several risks like haemorrhage, uterine perforation, incomplete abortion and cervical injury and intrauterine adhesions[17]. In recent years use of oral or vaginal misoprostol has grown in popularity. Infection, haemorrhage, acute haematometra and retained tissue are among the most common complications. Induced abortion does not harm women's reproductive capacity. Premature birth, infertility, ectopic pragnancy spontaneous abortion and adverse pregnancy outcome are not increased in frequency in abortion[18]. Aim of the objective is to compare the efficacy and safety of vaginal misoprostol to oral misoprostol for the treatment of first trimester missed abortion.

METHODS & MATERIALS

The study was conducted in the Gynaecology and Obstetrics Department of Shaheed Ziaur Rahman Medical College Hospital (SZMCH) in Bogra over a period of six months, from May 2015 to October 2015. The participants included women diagnosed with miscarriage, based on both their medical history and physical examinations, and referred from the outpatient department for admission. The diagnosis of missed miscarriage was confirmed by sonography. Only women who met the specified inclusion and exclusion criteria were enrolled, leading to a total sample size of 118 participants, divided into two groups of 59 each. The sampling technique employed was purposive and convenient. The inclusion criteria required participants to have a gestational period of less than 13 weeks, as confirmed by ultrasound, to be haemodynamically stable with a haemoglobin level of more than 10g/dL, to have a closed cervical os, an axillary temperature of less than 37.5°C, no history of inflammatory bowel disease, and no allergy to misoprostol. The exclusion criteria ruled out women with incomplete miscarriage, gestational age over 13 weeks, gravidity of five or more, retained products of conception, a history of caesarean section, cardiorespiratory disorders, haemoglobin levels below 8g/dL, or those unwilling to give consent.The women selected were then sequentially allocated into one of two groups. Group A received oral misoprostol, and Group B received vaginal misoprostol. In Group A, 400 micrograms of misoprostol were administered orally and repeated every four hours, up to a maximum of three doses if necessary. In Group B, 400 micrograms of misoprostol were inserted into the posterior vaginal fornix,

with a second dose administered after four hours if required. The outcome was assessed over the next 10 to 12 hours using transabdominal sonography (TAS) to document complete, incomplete, or no expulsion. Data analysis was conducted using the SPSS statistical software package (version 26 for Windows). This study received approval from the Ethical Committee of the Bangladesh College of Physicians and Surgeons (BCPS).

RESULTS

A total of 118 cases were included in this study and they were divided into two groups. (Group A – 59 and Group B – 59) Cases (**Table I**). In both the groups most of the respondents were in the '20 to 25 years' age group; out of the 59 respondents each in groups, 33.9% of group A and 42.4% of group B were in the age group. Mean ± SD of age was calculated to be, (24.60 ± 3.049) for group A and for Group B (23.98 ± 2.387). The p-value was 0.7597 for t-test and 0.7819 for chi-square, which means there was no statistically deference in age distribution between the groups.

Table I: Distribution of the Participants by their Age (*n*=59)

Age	Group A	Group B	t-test	*p*-value
<20 years	15	12	0.3202	0.7597
20-25 years	20	25		
25-30 years	19	17		
>30 years	6	5		
Total	59	59		
Mean ± SD	24.6 ± 3.049	23.98 ± 2.387		

X^2=1.08, df = 3; *p*-value = 0.7819

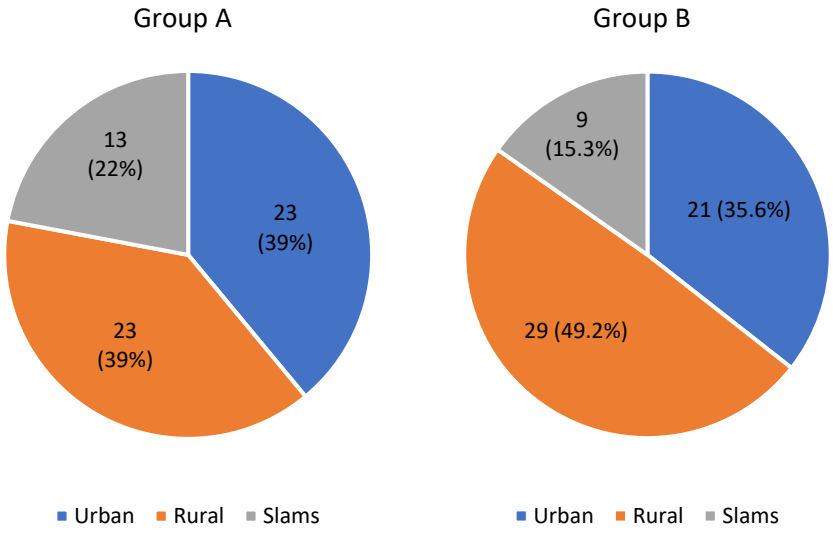

Figure – 1: Distribution of the Respondent by their Area of Residence

Figure 1 shows that, about two-fourth of the participants in group A [23 (39.0%)]. and half of the participants in Group B [29 (49.2%)] were Rural dwellers. Urban dwellers were counted as [23 (39.0%)] among Group A and [21 (35.6%)] among Group B. There was no statistically significant difference in the distribution

as chi square calculated p value to be 0.470011.

Table II explains that, in both groups respondents were basically from middle and low socio-economic classes. Chi-square calculates, p-value = 0.6; which explains that there was no significant statistical difference in the groups.

Table – II: Distribution of the Patients by their Socioeconomic Status (*n*=59)

Socio-economic	Group A	Group B	X^2	p-value
High	7	6	0.6	0.74082
Middle	33	30		
Low	19	23		
Total	59	59		

About two-fifth of the respondents in both group (42.4% Group A and 37.3% Group B) were primigravidae. Mean ± SD was calculated for Group A (1.81 ± 1.004) and for Group (1.78 ± 1.018). There was no statistical significant difference in gravidity among the groups, *p*-value = 0.8722 for t-test and 0.571608 for chi-square (**Table III**).

Table – III: Distribution of the Respondents by their Gravidity (*n*=59)

Gravidity	Group A	Group B	T-test	p-value
Primi	25	22	0.1612	0.8722
Multi	34	37		
Total	59	59		
Mean ± SD	1.81 ±1.004	1.78 ± 1.018		

X2 = 0.32; df = 3; p-value = 0.571608

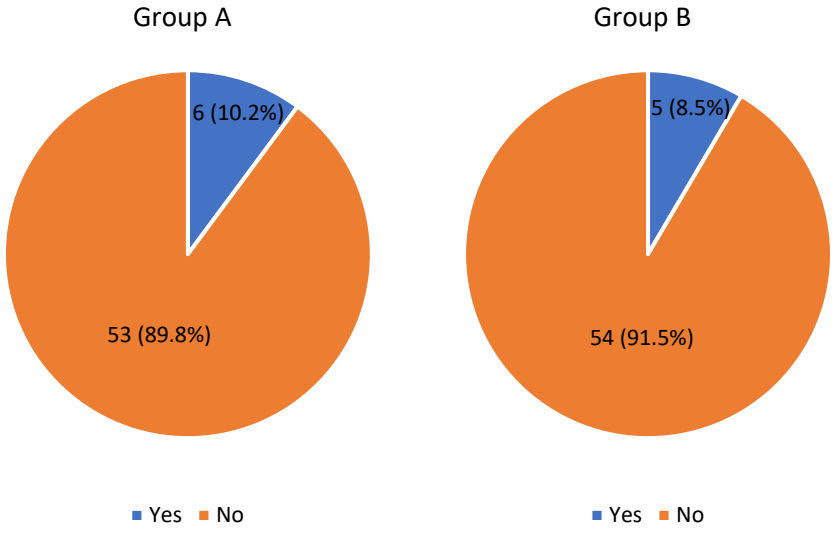

Figure 2: Distribution of the Respondents by their Previous History of Abortion

Out of the 118 respondents only 11 (9.3) had previous miscarriage. As per above Figure 89.8% of Group A and 91.5% of Group B had not experienced abortion

before. There was no statistically significant difference (p = 0.75183).

Table IV shows that, about 10.9 weeks was the average period of gestation for both groups. Both Group A and Group B had similar type of distribution and there was no statistically significant difference in gravidity among the groups (p-value = 0.9839 for t-test and 0.9324 for chi-square).

Table IV: Distribution of the Respondents by their Period of Gestation (weeks)

Gravidity	Group A	Group B	T-test	*p*-value
<10 wks	16	17	0.0202	0.9839
>10 wks	26	24		
11-12 wks	17	18		
Total	59	59		
Mean ± SD	10.89±2.732	10.88 ± 2.648		

X^2 = 0.14; df = 3; p-value = 0.9324

According **Table V** more than three-fourth ıe group B [45 (76.3%)] had successfully achieved complete expulsion of the conceptus; while in group A less than half of that [22 (37.3%)] had complete expulsion. Incomplete expulsion accounted to be $2\frac{1}{2}$ times higher in Group A and 'No expulsion' was 4 times as high as Group B. There was statistically significant difference in terms of achieving successful expulsion among the groups (X^2 = 18.54; df = 2; p-value = <0.001).

Table V: Distribution of the respondents by their successful expulsion of conceptus effects (*n*=59)

Expulsion of conceptus	Group A(n=59)	Group B(n=59)	X^2-test	*p*-value
Complete	22	45	18.54	<0.001
Incomplete	29	12		
No	8	2		
Total	59	59		

The respondents with incomplete expulsion and the non-responsive were assessed for cervical permeability during surgical management; both the group showed similar pattern of distribution. This was also proved statistically as, X^2 = 0.15; df = 1; p-value = 0.6985 (**Figure 3**).

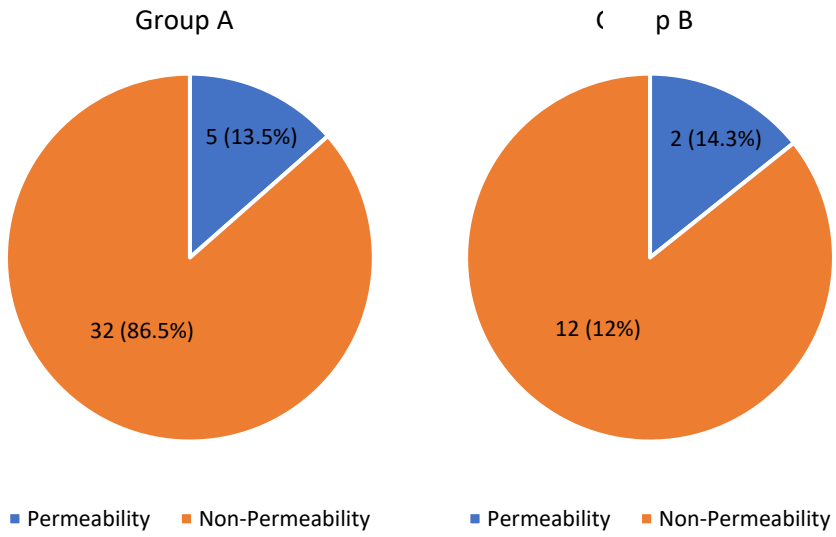

Figure – 3: Distribution of the Respondents by their Permeability of Cervix in Unsuccessful Cases

Incidence of nausea was higher among respondents of Group A (35.6%) than Group B (23.7%) [RR 1.5; OR = 1.7763; 95%CI = 0.7963 to 3.9626]. Incidence of vomiting was higher among respondents of Group A [RR 2.33; OR = 2.5128; 95%CI = 0.617 to 10.2329]. Higher number of respondents of Group A had experienced severe pain as the side effect of Misoprostol. [RR 1.40; OR = 1.4538; 95%CI = 0.4339 to 4.8713]. Incidence of diarrhoea had similar rate of occurrence among respondents of both Groups. [RR 0.83; OR = 0.8179; 95%CI = 0.2353 to 2.843]. Same number of respondents [3(5.1%)] of both Groups had hyperpyrexia [RR = 1; OR = 1; 95%CI = 0.1935 to 5.1688] (**Table VI**).

Table – VI: Distribution of the Respondents by their Side Effects (*n*=59)

Side effects	Group A	Group B	RR	OR	95% CI
Nausea	21	14	1.5	1.7763	0.7963 to 3.9626
Vomiting	7	3	2.33	2.5128	0.617 to 10.2329
Severe pain	7	5	1.4	1.4538	0.4339 to 4.8713
Diarrhoea	5	6	0.83	0.8179	0.2353 to 2.843
Hyperpyrexia	3	3	1	1	0.1935 to 5.1688
Total	42	31			

DISCUSSION

This study was aimed to compare the efficacy and safety of vaginal misoprostol to oral misoprostol for the treatment of missed abortion at SZMCH. Though the efficacy was the primary subject of the study, socio-economic variables and side effect have also been reported.A total of 118 respondents (59 Group A and 59 Group B) were included in this study. In both the groups most of the respondents were in the '20 to 25 years' age group;

out of the 59 respondents each in groups, 33.9% of Group A and 42.4% of Group B were in the age group. Mean ± SD of age was calculated to be, (24.60 ± 3.049) for Group A and for Group B (23.98 ± 2.387). The p-value was 0.7597 for t- test and 0.7819 for chi-square, which means there was no statistically difference in age distribution between the groups. [X^2 = 1.08; df = 3; p-value = 0.7819] in the year 2002-2003 by Rita, Gupta S and Kumar S, compared two groups in age (X^2 = 0.27, df= 2, p = 0.87). gravidity (X^2 = 3.08, df = 3, p = 0.37), residential status (X^2 = 0.37, df = 2, p = 0.53), and period of gestation (X^2 = 0.60, p = 0.89). There were no significant statistical differences[17]. Jalil S Nausheen V, Akhter AZ 2010 found the mean age of patients was 26.2 + 4.17[19]. About two-fourth of the participants in Group A [23 (39.0%)] and half of the participants in Group B [29 (49.2%)] were rural dwellers. Urban dwellers were counted as [23 (39.0%)] among Group A and [21 (35.6%)] among Group B. There was no statistically significant difference in the distribution as chi square calculated p value to be 0.470011. [X^2 = 1.51; df = 2] In both groups respondents were basically from middle and low socio-economic classes. Chi-square calculates, p-value =0.6; which explains that there was no significant statistical difference in the groups. There was statistically no difference between two groups in length of menstrual cycle (*p*-value =0.4285 for t-test and 0.8437 for chi-square). Both groups had a similar type of distribution of length of menstrual cycle. [X^2 = 0.34; df = 2; p-value = 0.8437]. Out of the 118 respondents only 11 (9.3%) had previous miscarriage. 89.8% of Group A and 91.5% of Group B had not experienced abortion before. There was no statistically significant difference. [X^2 = 0.1, df = 1; p-value = 0.75183]. About two-fifth of the respondents in both group (42.4% Group A and 37.3% Group B) were primigravidae. Among 2nd gravidae Group B (18) were double in count to Group A (9). Mean ± SD was calculated for Group A (1.81 ± 1.004) and for Group B (1.78 ± 1.018). There was no statistical significant difference in gravidity among the groups (p-value= 0.8722 for t-test and 0.228 for chi-square). [X^2 =4.33; df = 3]. Out of the 118 respondents only 11 (9.3) had previous miscarriage. As per above Figure 89.8% of Group A and 91.5% of Group B had not experienced abortion before. There was no statistically significant difference (p = 0.75183). About 10.9 weeks was the average period of gestation for both groups. Both Group A and Group B had similar type of distribution and there was no statistical significant difference of gravidity among the groups (p-value = 0.9839 for t-test and 0.9324 for chi-square). [X^2 = 0.14; df = 3] Chawla 2006 found that. The gestational age ranged from 8-22 weeks. 21 out of 30 patients were primigravidae and the rest multigravidae[20]. At Hamdard University hospital, majority of women were multiparous, median parity was 3, range (0-6). Mean gestational age 10.0 + 2.5 weeks. More than three-fourth of the group B [45 (76.3%)] had successfully achieved complete expulsion of the conceptus; while in group A less than half of that [22 (37.3%)] had complete expulsion. Incomplete expulsion accounted to be 2½ times higher in

Group A and 'No expulsion' was 4 times as high as Group B. There was statistical significant difference in terms of achieving successful expulsion among the groups (X^2 = 18.54; df = 2; p-value < 0.001). For both the groups higher dose was required for successful expulsion. Mean of number of doses for Group A was 2.41 and for Group B was 1.69. The difference of number of doses required was statistically significant (p = 0.0201 for t-test and <0.0001 for chi-square). [X^2 =29.9; df = 2]. Respondents of Groups A required longer duration to complete successful expulsion (Mean ± SD = 9.45 ± 1.405); where as Groups B needed much less time (Mean ± SD = 7.69 ± 2.8906). The respondents with incomplete expulsion and the non-responsive were assessed for cervical permeability during surgical management; both the group showed similar pattern of distribution. This was also proved statistically as, X^2 = 0.15; df = 1; p-value = 0.6985. In Jammu nearly 90% of women in both the groups had good cervical dilatation prior to surgical evacuation (*p*=0.75, Fisher's Exact 0.65)[3]. Incidence of side effects was higher among respondents of Group A; i.e. nausea (35.6%) than Group B (23.7%) [OR = 1.7763; 95%CI = 0.7963 to 3.9626]; vomiting [RR 2.33; OR = 2.5128; 95%CI = 0.617 to 10.2329]; severe pain as the side effect of Misoprostol, [RR 1.40; OR = 1.6941; 95%CI = 0.52 to 5.5193] Same number of respondents [3 (5.1%)] of both Groups had hyperpyrexia [RR = 1; OR = 1; 95%CI = 0.1935 to 5.1688] and also diarrhoea had similar rate of occurrence. [RR 0.83; OR = 0.8179; 95%CI = 0.2353 to 2.843] Chawla 2006 expressed that, the side effects were abdominal pain(16.6%),fever (10.0%),vomiting(6.7%) and diarrhoea (3.3%). Same number of respondents [3(5.1%)] of both Groups had hyperpyrexia [RR = 1; OR = 1; 95%CI = 0.1935 to 5.1688]. Bleeding lasted for less than four days in 11, for 5-6 days in nine and for 7-8 days in eight patients. None passes clots. Two patients had irregular vaginal bleeding after two weeks with retained products on USG, of which one patient was less than eight weeks and the other less than eleven weeks of gestation[20]. ***Rita, Gupta S and Kumar S. A*** 2006 concluded, although the incidence of side effects such as nausea, vomiting, diarrhoea, severe pain, hyperpyrexia an excessive blood loss was higher in-group A but the differences were not very significant[17]. Hence vaginal misoprostol was found to be more effective and safer as compared to oral misoprostol. Regarding side effects at Hamdard University Hospital only 20% observed diarrhoea, 5% shivering, 2% nausea, 15% unpleasant taste.

Limitations of the study

This study was conducted in SZMCH in a smaller scale. So, the study findings may not reflect the exact scenario of all around the country regarding Missed abortion. In Bangladesh, study of Missed abortion in the perspective of the objective of current study is rare and for this it was tough.

Conclusion

Per vaginal administration of Misoprostol in posterior fornix is more effective than Oral Misoprostol. The

former has faster onset of action and better efficacy. Per vaginal Misoprostol have less side effects.

Funding
This research was funded by the authors themselves.

Conflict of Interest
The authors declare no conflict of interest.

Recommendation
This was a small-scale study done at a single center over a brief duration. A large scale, multi-centre study over long duration will give an elaborate picture on management of missed abortion.

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