

Intravaginal misoprostol for medical management of missed abortions up to twenty weeks of gestation

Neelima Agarwal^{1,*}, Manisha Gupta², Alpana Agrawal³, Rashmi Saxena⁴, Divya Shubham⁵, Anuradha Tyagi⁶

¹⁻³Professor, Professor and HOD, ^{4,5}Assistant Professor, ⁶Senior Resident, ¹⁻⁶Dept. of Obstetrics & Gynaecology, Santosh Medical College and Hospital, Ghaziabad, Uttar Pradesh, India

***Corresponding Author:**

Email: agarwalneelima2@gmail.com

Abstract

Introduction: Missed abortion is a type of abortion in which the dead fetus is retained within the uterus. The objective of the study was to find out whether the use of one or two doses of 800 µg misoprostol alone, administered intra-vaginally, is effective and safe in termination of missed abortion up to 20 weeks of pregnancy.

Materials and Methods: This Interventional study was conducted in a tertiary care hospital, for a period of 12 months. Sample size consisted of 67 cases of missed abortion up to 20 weeks of pregnancy which was confirmed by ultrasound. These patients were given 800µg misoprostol and were followed up for successful termination of pregnancy and side effects, viz., pain, excessive bleeding, need for surgical evacuation, rupture uterus and infection. If complete abortion had not been attained by a single dose, a repeat dose of 800µg vaginal misoprostol was inserted.

Results: In the present study, 88.06% patients aborted completely after giving misoprostol alone; where as 72.9% patients requiring only single dose of misoprostol. The success rate decreased with increasing parity and number of previous abortions in patients and results were found statistically significant ($p = 0.008$ and 0.035 respectively). Side effects were tolerable and required only proper counseling.

Conclusion: Misoprostol alone is a safe and effective method of termination of missed abortion up to 20 weeks of gestation; and will prove to be a good alternative to surgical management.

Keywords: Missed abortion, Misoprostol, Intra-vaginally, Termination of pregnancy, 20 weeks gestation, Surgical evacuation.

Introduction

Missed abortion is defined as unrecognized intrauterine death of the embryo or fetus without expulsion of the products of conception. It constitutes approximately 15% of clinically diagnosed pregnancies.¹ Intrauterine demise in pregnancies up to 20 weeks of gestation can be managed by expectant management, surgical evacuation (in pregnancies less than 14 weeks) and medical methods.

The problems with expectant management are its low success rate (24-47%)^{2,3} and uncertainty of time of spontaneous expulsion, during which women may suffer anxiety. Surgical evacuation has been the main method for termination of missed abortion of less than 14 weeks gestation. However, the costs of surgery and hospitalization, as well as the complications associated with surgery and anesthesia are a major unresolved concern. Hence, the search for a non-invasive method with high success rate and patient acceptability has led to the use of medical methods of management as an alternative to expectant management or surgery.

Medical methods are easy to administer and overcome the disadvantages of surgical methods. The drug currently used most commonly for medical management of missed abortion is prostaglandin analogue Misoprostol. It has added benefits of being inexpensive, convenient and acceptable to patients.⁴

Misoprostol can be given by various routes (vaginal, oral, sublingual and rectal). Vaginal route has

been found to have better systemic bioavailability, more sustained levels and fewer side effect^{5,6} for termination of viable early pregnancies, medical treatment consists of giving either progesterone antagonist mifepristone orally followed by misoprostol vaginally or orally, or intramuscular methotrexate injection prior to the vaginal or oral misoprostol. In cases of missed abortion, administration of mifepristone may be superfluous, as progesterone levels are usually already low. Apart from this, mifepristone is more expensive which will add to unnecessary expenses. Therefore misoprostol alone is effective in these cases.⁷

Various doses schedules of vaginal misoprostol have been tried for termination of non-viable pregnancies. A single dose of 800 micrograms of misoprostol by vaginal or oral for missed abortion was recommended by National Institute for Health and Care Excellence (NICE).⁸ There are only few studies including non-viable pregnancies up to 20 weeks gestation, as diagnosed by ultrasound. The present study was designed to assess the success rate and side effects of one or two doses of 800 µg misoprostol, administered vaginally, for medical management of non-viable pregnancies up to 20 weeks gestation.

Materials and Methods

An interventional study was designed at department of obstetrics and gynaecology, Santosh Medical College and Hospital, Ghaziabad, India.

Duration of study was from December 2017 to November 2018. Ethical clearance was obtained from the Institutional Ethical Committee. A total of 67 patients as per the inclusion criteria included in study. All patients having pregnancies of less than 20 weeks gestation with either an embryonic gestational sacs or fetal demise (Empty intrauterine gestational sac with mean sac diameter > 16 mm or CRL > 5 mm with no cardiac activity), as diagnosed by ultrasound, with os closed, no contraindication to prostaglandin E1, had blood haemoglobin level more than 9 gm% and Willing for alternative modalities of termination in case of failure of this method. Those cases had blood haemoglobin level less than 9 gm%, any evidence of incomplete abortion, pregnancy with multiple gestations, Contraindication to prostaglandin treatment (drug allergy, cardiovascular disease, glaucoma, coagulopathies, severe hypertension, asthma, or renal disease), Uterine scar (e.g. in cases of previous caesarian section or previous hysterotomy), systemic or local infection, associated pelvic mass (fibroid, ovarian tumor, etc.) and history of intake of any abortifacient were excluded from the study. Informed written consent was taken from all the participants.

After taking detailed history taking and examination, baseline investigations (Hb, TLC, DLC, BT, CT, CRT, blood grouping and Rh typing and urine (albumin and sugar) were done for all patients. Ultrasonography was performed on all the cases to confirm intrauterine pregnancy, assess the period of gestation, confirm absent cardiac activity and to rule out other pelvic pathology.

All patients were admitted to the ward. On day 1, 800µg misoprostol (4 tablets of 200µg each) moistened with a few drops of saline was inserted in the posterior vaginal fornix. Patients were advised to lie down for half an hour after which they could move about. Each

patient was observed for 24 hours after administration of the first dose for the effects of the drug. They were given sterile vulval pads which were weighed previously, and were told to save all pads and any expelled products. The time when bleeding started was noted for all the women. An ultrasound scan was done at the completion of abortion process or after 24 hrs.

On day 2, if complete abortion had not been attained by a single dose, a repeat dose of 800µg vaginal misoprostol was inserted. A repeat ultrasound scan was done at the completion of abortion process (if that occurred on day 2) or 24 hours after insertion of the second dose.

If products of conception were retained 24 hours after the second dose, surgical evacuation was done. Blood loss was estimated by knowing the weight of dry and blood soaked pads.

All the women were instructed to come for follow up after 2 weeks (or earlier in case of heavy bleeding), noted for amount of bleeding or any side effects and complete hemogram sent.

Success rate, incidence of incomplete evacuation, induction abortion interval and side effects were the outcome parameters studied.

Statistical analysis was done using student's t-test, chi square test, Wilcoxon-non parametric rank test and Mann-Whitney U test, wherever required.

Results

Sixty-seven women who had pregnancies of less than 20 weeks of gestation with absent cardiac activity and were willing for medical method of management were included in study.

For the purpose of analysis, the women were divided into two groups based on gestational age according to ultrasound measurements.

Table 1: Distribution according to period of gestation (Weeks)

S. No.	Period of Gestation	No. of Patients	Percentage
1	<12 weeks	51	76.1
2	12-20 weeks	16	23.9
Total		67	100.0

Minimum period of gestation = 6 weeks

Maximum period of gestation = 19 weeks

Mean period of gestation = 12.39 weeks

Table 2: Success Rate

Outcome	Period of Gestation < 12 weeks		Period of Gestation 12 -20 weeks		Total	
	No. of Cases (n=51)	% age	No. of Cases (n=16)	% age	No. of Cases (n=67)	% Age
Success	45	88.2	14	87.5	59	88.06
Failure	6	11.8	2	12.5	8	11.94
				p-value	0.206	

Table 2 shows the rate of successful abortion with misoprostol (without requiring any surgical intervention). Overall success rate was 88.06% and

failure rate was 11.94%. The difference in the success and failure rate in the two groups was found statistically insignificant (p= 0.206).

Table 3: Number of doses of Misoprostol Required

No. of doses of Misoprostol Required	Period of Gestation ≤ 12 weeks		Period of Gestation 12 -20 weeks		Total	
	No. of Cases (n=45)	% Age	No. of Cases (n=14)	% Age	No. of Cases (n=59)	% Age
1	30	66.7	13	92.9	43	72.9
2	15	33.3	1	7.1	16	27.1
				p value	0.05	

Table 3 shows the number of doses of misoprostol required for achieving complete abortion in those who achieved a successful abortion.

Overall 72.9% of patients required a single dose and another 27.1% required two doses of misoprostol for attaining a complete abortion by medical methods.

Table 4: Induction-Abortion Interval

Gestation Period (weeks)	No. of Cases	Minimum (Hrs)	Maximum (Hrs)	Mean
< 12 weeks	51	3.5	48.0	18.872
12 - 20 weeks	16	4.0	29.0	10.882

Table 4 shows the induction-abortion interval in patients. Mean induction-abortion interval in patients with gestational age less than 12 weeks was 18.872

hours, while it was 10.882 hours in patients with gestational age 12-20 weeks.

Table 5: Effect of sociodemographic factors on success

Sociodemographic Factors		No. of Cases (n =67)	Success		Failure		p-value
			No. of Cases (n=59)	% Age	No. of Cases (n=8)	% Age	
Age (Years)	< 20	5	5	100.0%	0	0	0.083
	21 – 25	32	28	87.5	4	12.5	
	26 – 30	24	22	91.7	2	8.3	
	> 30	6	2	66.7	2	33.3	
Parity	0	20	19	95.0	1	5	0.008
	1	29	27	93.3	2	6.8	
	2	9	7	77.8	2	22.2	
	3	9	6	66.6	3	33.3	
Previous Abortions	0	44	43	97.7	1	2.2	0.035
	1	14	12	85.7	2	14.3	
	2	7	4	57.1	3	42.9	
	3	2	0	0	2	100	

Table 5 shows the correlation between sociodemographic factors of the patients and success rate.

Age: The general trend observed was that as the age of patients increased, the success rate declined (100% in women < 20 years and 66.7% in > 30 years of age). However, this observation was not found to be statistically significant (p=0.083).

Parity: An inverse relationship was observed between the two variables i.e. success rate of medical abortion was higher in nulliparous women (95.9%) and declined

as parity increased (66.6% in para 3). Failure rate of medical management increased as parity increased. This observation was found to be highly statistically significant (p=0.008).

Previous Abortions: The success rate of medical abortion was 97.7% in patients with no previous abortions and decreased with increase in the number of previous abortions to 57.14% in patients with 3 previous abortions. Thus, an inverse relation was observed (i.e. the success rate decreased with increase

in number of previous abortions). This observation was found to be statistically significant ($p=0.035$).

Table 6: Side effects

Sl. No.	Side effect	No. of Patients (n = 67)	Percentage (%)
1	Pain	17	25.4
2	Fever	5	7.69
3	Vomiting	5	7.69
4	Bleeding requiring evacuation	1	1.5
5	Retained POCs	7	10.5
6	Infection	0	0
7	Rupture Uterus	0	0

Table 6 shows the side effects in the patients included in the study.

Pain was the most common side effect, which settled with oral analgesic in the form of one or two tablets of Ibuprofen 400mg.

Discussion

Overall success rate was found 88.06% and failure rate was 11.94%. In patients presenting with a missed abortion of less than 12 weeks gestation, success rate of medical abortion was 88.2 % as compared to 87.5% in patients with gestational age of 12-20 weeks. Failure rates in the two groups were 11.8% and 12.5%, respectively. This difference in the success and failure rate in the two groups was found statistically insignificant ($P = 0.206$). However, the difference could be attributed to the fact that usually the uterus becomes more sensitive to uterotonic agents with increasing gestational age. This may explain the reason for a higher success rate in patients between 12-20 weeks of gestation, than in earlier gestational period. The results of present study were comparable to Wood et al¹ (80%), Demetroulis et al⁹ (82.5%), Ngoc et al¹⁰ (92.7%) who used similar dose schedules. Vaginal misoprostol of 800ug was recommend for missed abortion by National Institute for Health and Care Excellence (NICE) and some clinical guidelines.^{8,11} The results of a network meta-analysis support to this regimen for medical treatment of missed abortion.¹² Complete abortion without the need for surgical was observed in 84% in a study done by Prasad et al.¹³

Out of the total cases who aborted completely, 72.9% of patients required a single dose and another 27.1% required two doses of misoprostol for attaining a complete abortion by medical methods. These results were comparable to study done by Wood et al¹ in which 60% of the patients aborted with the first dose and additional 20% aborted after the second dose. The reason why some women required a second dose of misoprostol may be because of the differences in their serum levels of the active metabolites and their levels of chemical modulators of prostaglandin E¹ activity (such as progesterone and cytokines).

Mean induction-abortion interval in our patients less than 12 weeks was 18.8 hours, while 10.8 hours

in 12-20 weeks. Herabutya et al¹⁴ (11.63 + 6.14 hours) and Ngoc et al¹¹ (13.4 hours) had similar results.

Failure rates in the present study increased with increasing age, parity and number of previous abortions. Ashok et al also observed this pattern of association in a study on factors affecting outcome of early medical abortion.¹⁵

Older women may have a lower success rate because they are more likely to be multiparous and have history of previous abortions, which are factors associated with decreased success rate. Similarly, previous termination of pregnancy was the strongest predictor of failed medical abortion. Women who had no previous termination were more likely to have a successful abortion. This may be due to local cervical changes such as cervicitis or due to adhesions in the uterine cavity caused by curettage done during a previous abortion, which prevent the products of conception in a subsequent pregnancy from being expelled easily.

Side effects of the regime were also assessed. The most common side effects reported were pain, nausea and low grade fever. No major complications were reported in our study. Immediate evacuation for excessive bleeding was needed in 1 case (1.5% of population).

Conclusion

A single or two high-doses of misoprostol is a safe and effective method of termination of missed abortion up to 20 weeks of gestation; and will prove to be a good alternative to surgical management.

Acknowledgements: I pay profound regards to my co-faculty and patients in the department of Obstetrics & Gynecology of Santosh Deemed to be University for their constant support and immeasurable help.

References

1. Wood SL, Brian PH. Medical management of missed abortion: a randomized clinical trial. *Obstet Gynecol.* 2002;99:563–66.
2. Jurkovic D, Ross JA, Nicolaidis KH. Expectant management of missed miscarriage. *Br J Obstet & Gynaecol.* 1998;105:670-71.
3. Waard MW, Vos J, Bonsel GJ, Bindels PJE, Ankum WM. Management of miscarriage: a randomized

- controlled trial of expectant management versus surgical evacuation. *Hum Reprod.* 2002;17(9):2445-50.
4. Darwish AM, Ahmad AM, Mohammad AM. Cervical priming prior to operative hysteroscopy: A randomized comparison of laminaria versus misoprostol. *Hum Reprod.* 2004;19(10):2391-94.
 5. Ziemann M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol.* 1997;90:88-92.
 6. Danielsson KG, Marions L, Rodriguez A, Spur BW, Wong PYK, Bygdeman M. Comparison between oral and vaginal administration of Misoprostol on uterine contractility. *Obstet Gynecol.* 1999;93:275-80.
 7. Gronlund A, Gronlund L, Clevin L, Andersen B, Palmgren N, Lidegaard J. Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation. A multi-center trial in Copenhagen county, Denmark. *Acta Obstet Gynaecol Scand.* 2002;81(11):1060-65.
 8. National Institute for Health and Care Excellence guidelines. Ectopic pregnancy and miscarriage: diagnosis and initial management. Available as www.nice.org.uk/guidance/cg154 (2012)
 9. Demetroulis C, Saridogan E, Kunde D, Naftalin AA. A prospective randomized controlled trial comparing medical and surgical treatment for early pregnancy failure. *Hum Reprod.* 2001;16(2):365-69.
 10. Ngoc NTN, Blum J, Westheimer E, Quan TIV, Winikoff B. Medical treatment of missed abortion using misoprostol. *Int J Gynecol Obstet.* 2004;87:138-42.
 11. Huchon C, Deffieux X, Beucher G, Capmas P, Carcopino X, Costedoat-Chalumeau N, et. al. Pregnancy loss: French clinical practice guidelines. *Eur J Obstet Gynec Repro Biol.* 2016;201:18-26.
 12. Hang-lin Wu, Sheeba Marwah, Pei Wang, Qiu-meng Wang, Xiao-wen Chen. Misoprostol for medical treatment of missed abortion: a systematic review and network meta-analysis: *Scientific Report.* 2017;7:1-9. Available as file:///C:/Users/HP/Downloads/s41598-017-01892-0.pdf
 13. Prasad DR, Nair NV. Medication abortion in missed abortion up to 13 weeks amenorrhoea: a prospective study. *Int J Reprod Contracept Obstet Gynecol.* 2016;5:3840-42.
 14. Herabutya Y, O-Prasertsawat P. Misoprostol in the management of missed abortion. *Int J Gynecol Obstet.* 1997;56:263-66.
 15. Ashok PW, Templeton A, Wagaarachchi PT, Flett GMM. Factors affecting the outcome of early medical abortion: a review of 4132 consecutive cases. *Br J Obstet Gynecol.* 2002;109:1281-89.