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A prospective trial to study the safety and effectiveness of oral RU-486 (mifepristone) and Prostaglandin analogue (misoprostol) in missed abortion

Pranabika Mahanta[1,*], Phatik Chandra Kalita[2], Anuradha Hazarika Medhi[3]

[1]Assistant Professor, [2]Professor & HOD, Dept. of Obstetrics & Gynecology, [3]Lecturer, Dept. of Community Medicine, Jorhat Medical College & Hospital

***Corresponding Author:**
Email: drpranabikamahanta@gmail.com

Abstract

Aim: To evaluate the effectiveness of oral Ru-486 (mifepristone) and Prostanglandin analogue (misoprostol) in facilating spontaneous abortions in pregnant women with missed abortion and also to study its safety and side-effects associated with these drugs.

Materials and Methods: This study was undertaken in the Department of Obstetrics & Gynaecology, Jorhat Medical College & Hospital, Jorhat Assam from August 2012 to June 2013. It was a prospective study. In this study 60 patients attending gynaecology OPD with a diagnosis of missed abortion were included. The diagnosis is confirmed with ultrasonography. Patient with diagnosis of missed abortions were first counselled for medical abortion. They were also counselled for the need of surgical intervention if this fails. Written consent is taken. Heamoglobin estimation, ABO grouping and Rh typing, platelet count Bleeding time clotting time, s.creatinine, liver function test were the minimum investigations done before prescribing the drugs. Tab mifepristone 200mg is advised to take on day 1, followed by tab Prostanglandin analogue 800microgam on day 3 after 48 hrs. Patient's data were entered in a pretested questionnaire. Patients are asked to attend OPD after one week. Again they are interviewed with the same questionnaire to find of any side effect or complications. On day 10 ultrasonography was done to confirm complete abortion of the product of conceptus. Data were analysed with statistical tests.

Results: Data were analysed using the SPSS for Windows Statistical Package.

Conclusion: The results of the present study suggest that the use of mifegest and misoprost orally is safe and effective to induce expulsion of the products of conception in cases with diagnosis of missed abortion.

Keywords: Missed abortion, l Ru-486, Mifepristone, Prostanglandin analogue, Misoprostol

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Introduction

Missed abortion is the presence of non-viable intrauterine pregnancy which, in normal circumstances would have been expelled by the intra uterine forces, but has been missed. There are no reasons to have suspected that the pregnancy is not going to continue but the embryo has died. Often the cause of such abortion remains unknown. The most common cause for abortion is a blighted ovum—a gestational sac without an embryo. Another common cause is a genetic defect.

Ultrasound screening for fetal anomaly has shown the incidence of non-viable pregnancy at 10-13 wks to be 2.8%. The traditional management of such usually consists of waiting for spontaneous expulsion or suction evacuation. The traditional suction evacuation has numerous disadvantages including infections, cervical tears, perforation of the uterus, intrauterine adhesions and anesthetic complications which could adversely affect the future pregnancy. Infections and adhesions can lead to infertility, pelvic pain and also increased risk of ectopic pregnancy.

Mifepristone, anti-progesterone; binds to the progesterone receptor to block the receptor site thus inhibiting progesterone from binding to its receptor site. It does not activate a true biological response to progesterone. It does however have both weak anti-glucocorticoid and antiadrenergic activity. Mifepristone softens and dilates the cervix, causes decidual necrosis (which lead to placental detachment), increases uterine lining prostaglandin release increases uterine contraction and enhance uterine sensitivity to administration of prostaglandin.

Although management of missed abortion had changed over the years theoretically but in practice majority (up to 88%) of women prefer surgical evacuation.[1] There has been established risks associated with surgical evacuation[2,3] and established medical treatment is potentially cost savings.[4] Age old expectant management of missed abortion could not withstand the test of time and its use is not justified in routine clinical practice.[5] With the advent prostaglandin analogue the various medical regimens with or without the anti-progesterone, mifepristone, medical management of missed abortion has been tried by various authors. The efficacy of various regimes varies widely from 25–92%, depending on the variables like dose, duration and route of administration of prostaglandins, type of miscarriage, outcome measures used etc.[6,7]

Based on various published data researches developed a regimen comprising of mifepristone 200

mg followed by vaginal or oral administration of misoprostol (800–1600 μg) after 48 hrs for first trimester medical abortion and missed abortion cases.[8,9,10]

Materials and Methods

This study was undertaken in the Department of Obstetrics & Gynaecology, Jorhat Medical College & Hospital, Jorhat Assam from August 2012 to June 2013. It was a prospective study. In this study 80 patients attending gynecology OPD with a diagnosis of missed abortion were included. Patients with diagnosis of missed abortions were first counseled for medical abortion. They were also counseled for the need of surgical intervention if this fails. Written consent is taken. Heamoglobin estimation, ABO grouping and Rh typing, platelet count, Bleeding time, clotting time, liver and renal function tests were the minimum investigations done before prescribing the drugs.

Exclusion criteria

- Patient not willing for medical management
- Sign & Symptoms of infection (raised temperature, tachycardia)
- Hemoglobin level less than 10 gm%
- Maternal co-agulopathy
- Unstable vitals(tachycardia, hypotension)
- Uncontrolled BP
- Active renal or hepatic disease
- No access to telephone or transportation
- Scarred uterus
- Known allergy to either mifepristone or misoprostol
- Patient on anti-thyroid or steroid medication

After USG confirmation of missed abortion consent was taken for medical abortion as well as for participation in the research work. Women were admitted to the gyaenaecology ward /send home according to the choice of the lady. Tab mifepristone 200mg was advised to take on day 1, followed by tab misoprost 800microgam on day 3 after 48 hrs. Patient's data were entered in a pretested questionnaire.

Immediately after complete investigations, Tab mifepristone 200mg given followed by four tablets of misoprostol 200 μg after 48 hrs. If the process of abortion starts the women were observed for 4 h before being allowed home. Vitals of the lady is monitored hourly. Combination of analgesic and antispasmodic was used for pain management.

Patients are discharged and asked to attend OPD after one week .Again they are interviewed with the same questionnaire to find of any side effect or complications. On day 10 ultrasonography was done to confirm complete abortion of the product of conceptus. If ultrasound shows RPOC then the case is taken as failure .Case with excessive or prolong vaginal bleeding were asked to go for an ultrasonography even before day 10 and if that shows RPOC then she is considered to be a case of failure.

Those cases who refused admission were counseled thoroughly about possible side effects of drugs like feeling of chill and rigor, pain abdomen, passage of fleshy mass etc. She is also being explained that in case she does not start bleeding after 48hrs then she will probably need further treatment/Surgical evacuation. If spontaneous abortion does not take place after 48 hours of tablet misoprost intake she is considered to be a case of failure. They were also given principal investigator's contact number for any emergency.

Those cases who failed to come for review were confirmed for the completeness of abortion over phone and also were enquired about any complications and need for analgesic in particular.

If the lady failed to abort within 72 hrs of tab misoprostol she was taken as failure of medical abortion. She is counseled for second dose of misoprostol or surgical evacuation.

Results

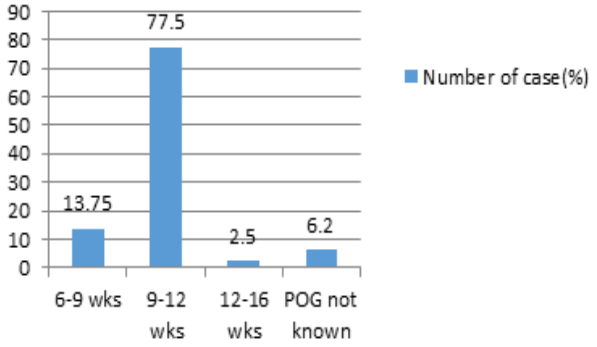
In this study 80 patients (N=80) attending gynecology OPD with a diagnosis of missed abortion were included. The maximum number of case who reported with diagnosis of missed abortion were in the age group between 31-34 yrs of age and constituted about 35% of total cases. The range of age is 18-38 years. 77.5% of cases has been diagnosed and treated between 9-12 wks. 13.75% of the cases were between 6-9 wks.2.5% cases were between 12- 16 weeks of gestation. In 6.2% of cases Gestational age at the time of diagnosis was not known. In 83.73% cases induction to spontaneous expulsion time (after misoprostol 800 microgram) was less than 5hrs. In 12.5% cases induction to spontaneous expulsion time was 5-12 hrs 2.5% cases induction to spontaneous expulsion time was 10-15 hrs. In 1.25% cases induction to spontaneous expulsion time was 15-20 hrs. 56.25% Patient had no side effects at all.43.75% had minor side effects. Shivering (8.75%), fever(2.5%), vomiting(1.25%), flushing(1.25%) Abdominal pain (0.3). Outcome of the study have proved that the combination of mifegest 200 mg and misoprost 800 microgram orally is 90% effective (P- value< 0.0001, highly significant). 10% of the cases has failed induction of spontaneous abortion or incomplete abortion who have undergone surgical evacuation.

Table 1: Maternal age at the time of diagnosis of missed abortion

Age group	Number of case	Percentage
15-18 yrs	5	6.25%
19-22yrs	10	12.5%
23-26yrs	9	11.25%
27-30 yrs	12	15%
31-34 yrs	28	35%
35 -38 yrs	12	15%

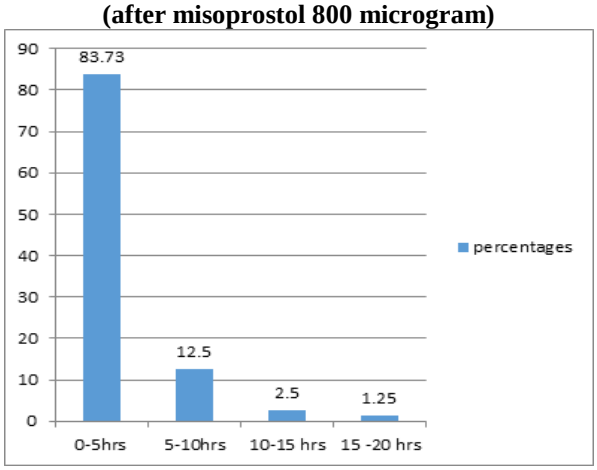
38-42 yrs	4	.05%

Table 2: Gestational age at the time of diagnosis (N=80)



Chi square value 119.7 for 3 d.f, P- value <0.0001, which is Statistically significant

Table 3: Induction to spontaneous expulsion time (after misoprostol 800 microgram)



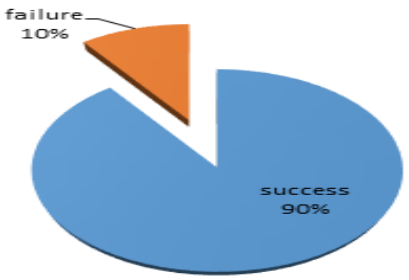
Chi square value 37.725 with 3d.f, P-value < 0.0001 Significant

Table 4: Side effects

Side effects	No of cases	Percentage
No side effects	45	56.25
Side effects	35	43.75
Abdominal pain	24	0.3
Fever	2	2.5
Shivering	7	8.75
Nausea	0	0
Vomiting	1	1.25
Headache	0	0
Flushing	1	1.25
Diarrhea	0	0
Rash	0	0
Itching	0	0
Total	80	100

t test 2.0887 with 11 d.f, P- value =0.0608, Not significant.

Data on analgesic use were recorded in 23 women in the study. Of these, 57(71.2%) required no analgesia, 20 (86, 95%) required oral analgesia only, three received diclofenac injection (13.04%).



Chi squre 52.1 with 1 d.f. P- value< 0.0001, highly significant

Discussion

P.T. Wagaarachchil et all conducted a study which till date is the largest series of the medical regimen for missed abortion. In his study Out of 220 women of early fetal demise, 139 (63.1%) had a missed miscarriage and 81 (36.8%) had an anaembryonic pregnancy. Various variables like patient characteristics, presentation, treatment outcome, induction–miscarriage interval and complications between the two groups were studied in details.[11] He has also concluded that incomplete miscarriage can be managed with misoprostol alone.[12,13] In case of unripe cervix, priming with the anti-progesterone mifepristone makes the regimen more effective.[6,15]

In the current study the total number of case studied were 80 (n=80) the range of maternal age is 18-38 years at the time of diagnosis of missed abortion. 83.73% of the cases had started the process of abortion within 5hrs of tab misoprostol 800 microgram(P-value <0.0001) Significant. Minor side effects are reported which are not statistically significant.

As stated by Nielsen *et al.* they had used combination of 400 mg of mifepristone and 400 µg of misoprostol, both taken orally and reported a success rate of 52% using a with 13% of women requiring emergency curettage.[13] In only 3.6% surgical evacuation was required. Vaginal misoprostol administration has been shown to be more effective in comparison with the oral route for first trimester termination of pregnancy.[7,9] A better plasma concentrations and bio-availability of misoprostol is promised with vaginal route as compared to the oral route.[14] One study concluded that medical regimen was more effective in women who were asymptomatic at presentation (93.5%) as compared to patient presented with pain and/or bleeding (78.8%). Nielsen *et al.* only included women who were asymptomatic at presentation and had an efficacy rate of only 52%.[16]

In the current study success rate of 90% using the combination of mifegest 200 mg and misoprost 800

microgram orally. (P- value< 0.0001, highly significant).

In P.T. Wagaarachchil et all study they had not used ultrasonography to label success or failure. If the patient shows signs of complete abortion clinically they labeled it as successful outcome. However the failure cases had been subjected to sonographic confirmation before labeling it as failure.[16] In this series only five of the women required subsequent surgical evacuation following for prolonged bleeding. P.T. Wagaarachchil et al study concluded that there is no real advantage in scanning of all women following medical abortion.

In some studies spontaneous expulsion of products of conception with tablet mifepristone 200 alone had occurred in 18.1% of women, Lelaidier *et al*. done a study using tablet mifepristone 600 mg alone and reported 82% success rate.[17] It has been established that for medical abortion in first trimester single dose mifepristone 200 mg is as effective as 600 mg, when used in combination with a prostaglandin analogue.[18] Mifepristone is a very good priming agent but is relatively expensive. Misoprostol is cheap, effective and thermostable. It is a very effective uterotonic drug for the developing world. More than eighty percent success rate has been reported by using a combination of 200 mg mifepristone with misoprostol. It has been seen that many researchers claims a success rate of 13–83% using misoprostol alone for medical management of delayed miscarriage.[19,20]

Conclusion

Missed abortion has been so far been treated surgically with or without priming of cervix. If dilatation of cervix is done forcefully that results in cervical trauma leading to infertility, cervical incompetence perforation of uterus and also synechia formation following vigorous curettage. The result of this study has shown that medical abortion with mifegest and misoprost upto 12 wks of gestational age is safe and effective to induce expulsion of diagnosed missed abortion. Medical treatment with a combination of oral mifepristone 200 mg and oral misoprostol 800 µg at 48 hrs intervals is a very effective and safe alternative in the management of missed abortion.

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