

Review Article

Role of Misoprostol in Missed Abortion

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Abstract

Spontaneous abortion or miscarriage is the spontaneous end of a pregnancy at a stage where the embryo or fetus is incapable of surviving independently, generally defined in humans at prior to 20 weeks of gestation, but in our country before 28 weeks of gestation. Nearly 20% of all confirmed pregnancies end in abortion. The incidence of this type of abortion is very high during first trimester and decreases with increasing gestational age. Of many types of abortion, missed abortion occurs when the embryo or foetus has died, but a miscarriage has not yet occurred. The retention of a fetus known to be dead for ≥ 4 weeks. The cervix is closed and there is no or only slight bleeding. Ultrasound examination shows an empty gestational sac or an embryo/fetus without cardiac activity. Surgical evacuation is the most common method of treatment of missed abortion. It is considered to be safe but carries some risk of complications related to anaesthesia and of surgical complications such as uterine perforation, cervical trauma, intrauterine adhesions and infections. Expectant management and medical treatment are the two other ways of treatment of missed abortion. Based on a review of the published literature, a single dose of 800 μ g vaginal misoprostol may be offered as an effective, safe and acceptable alternative to the traditional surgical treatment for this indication in the first trimester. Alternatively, 800 μ g misoprostol can be administered sublingually. Treatment may be repeated twice with a 3-4 hour interval for maximum three doses can be given orally or sublingually. Where as, vaginally, dose can be repeated 6-8 hourly for three doses. For the rest, 12-28 weeks of missed abortion, 400 μ g of misoprostol every 4 hours until expulsion. Majority of cases have the expulsion within 48 hours. After administration of misoprostol, hospitalization is not necessary and the time of expulsion varies considerably. Bleeding may last for more than 14 days with additional days of light bleeding or spotting. The woman should be advised to contact a provider in case of heavy bleeding or signs of infection. A follow up is recommended after 1 to 2 weeks.

Introduction:

Abortion is one of the most common complications of pregnancy occurring in clinically recognized pregnancies¹. South Asia (Bangladesh, Nepal, India, Pakistan and Srilanka) being highly populated, resource constrained and underdeveloped region, holds almost one third (30%) of world's maternal deaths and approximately 13% of them are related to abortions and its procedures². There is no exact data

of missed abortion in Bangladesh annually. But the annual induced abortion rate in Bangladesh is estimated to be 28 abortions per 1,000 women aged 15-49. Dilatation and evacuation of uterus has been the standard, acceptable approach to early pregnancy failure of a period of 50 years with more than 95% success rate³. The overall complication rates with surgical evacuation are between 4 and 10% and consists of cervical injury, uterine perforation, pelvic

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infection and excessive bleeding^{4,5}. The complications (hemorrhage and sepsis) associated with the procedure when done by unskilled personal commonly in low resource countries has changed the focus towards expectant and medical management with significant economic advantage as well.⁶ An alternative approach to surgical management is expectant management i.e. waiting for the process of pregnancy loss to end spontaneously. The success rate with this approach for early pregnancy failure ranges from 25-75%^(7,8). With this method, the time to spontaneous expulsion is unpredictable and can be upto a month^(7,8). For patients, this method creates uncertainty and anxiety and sadness resulting from pregnancy loss, and is often not appealing. Nevertheless, many women are willing to accept these inconveniences to avoid an invasive procedure. About medical management: is the development of misoprostol. It is often used alone or in combination with the progesterone receptor antagonist Mifepristone to induce abortion. However, in early pregnancy failure, antiprogesterones (Mifepristone) are not really necessary for medical termination of missed abortion as progesterone levels are usually low. This review is of the use of misoprostol for the treatment of missed abortion. The first part of the review discusses the pharmacology of misoprostol. This is followed by a detailed discussion of the use of oral, intravaginal, sublingual, misoprostol in missed abortion.

Pharmacology of misoprostol

Pharmacodynamics :

The naturally occurring prostaglandins (PGs), PGE₁, PGE₂, PGF_{2α} are potent stimulants of human uterine contractility at any stage of pregnancy, also cause cervical ripening and dilatation. However, the naturally occurring PGs are rapidly metabolized. Misoprostol is a synthetic 15-deoxy – 16 hydroxy – 16 methyl analog of prostaglandin E₁, that is active after oral administration⁹.

Pharmacokinetics:

Misoprostol was developed in an oral formulation for the prevention of gastric ulcers. Misoprostol is rapidly absorbed after oral administration, rapidly and extensively de-esterified to the active metabolite misoprostol acid. The free acid is excreted mainly in the urine, with the elimination half-life of 20-40 minutes. After the oral administration of misoprostol, diarrhoea (with or without abdominal pain and cramps), is

common due to the stimulation of gastro-intestinal motility. In an attempt to lessen the incidence of gastro-intestinal side effects, when misoprostol is being used as a uterine stimulant, these tablets have been administered by other routes, including vaginally. Successful delivery of drugs through the vagina remains a challenge, primarily due to poor absorption across the vaginal epithelium, but also because of cyclic changes in the thickness of vaginal epithelium, fluid, volume and composition¹⁰.

Studies suggest that quicker and more pronounced effects will occur with oral than vaginal misoprostol but vaginal misoprostol will be active for longer than oral misoprostol.

Sunlingual administration is another route to avoid high gastrointestinal levels of misoprostol, peak levels of misoprostol acids were higher with sublingual than oral or intravaginal.

Time to peak was similar with sublingual (26 min) and oral (28 min) misoprostol, and shorter than dry (72 min) or moistened intravaginal misoprostol (75 min)¹¹. After about 2 hours, the levels of misoprostol are higher with vaginal than oral administration, suggesting that the effects of misoprostol will persist for longer after vaginal than oral administration.

After rectal administration, the time to peak was similar as with vaginal administration¹². But the effects of vaginal misoprostol will persist for longer than either oral or rectal misoprostol. There has also been a study comparing the pharmacokinetics of buccal (inside the cheek) sublingual (under the tongue) misoprostol 800 µg in healthy women¹³. The peak concentration and the area under the concentration curve were greater with sublingual than buccal misoprostol. Higher levels of misoprostol are obtained after sublingual than buccal administration but that buccal was better tolerated. This study suggests that sublingual but not buccal may be an appropriate route of administration for a long lasting effect with misoprostol. In the treatment of pregnancy failure (abortion), three routes of administration shown to give substantial levels of misoprostol for an extended period have been used. These are the oral, vaginal and sublingual routes of administration.

Epidemiology of miscarriage

Determining the prevalence of miscarriage is difficult. Many miscarriages happen very early in the pregnancy, before a women may know she is pregnant.

Treatment of women with miscarriage at home means medical statistics on miscarriage miss many cases.¹⁴ Prospective studies using very sensitive early pregnancy tests have found that 25% of pregnancies are miscarried by the sixth week LMP.¹⁵

However, other sources reports suggest higher rates. One fact sheet from the University of Ottawa states, the incidence of spontaneous abortion is estimated to be 50% of all pregnancies, based on the assumption that many pregnancies abort spontaneously with no clinical recognition. The NIH reports, "It is estimated that up to half of all fertilized eggs die and aborted spontaneously, usually before the women knows she is pregnant. Among those women who know they are pregnant, the miscarriage is about 15-20%."¹⁶

Rational for regimen

1. Dosage and route:

A Cochrane review including 19 randomized controlled trials on pregnancies less than 14 weeks concluded that vaginal misoprostol shortens the time to expulsion when compared with placebo.¹⁷ In two RCTs, misoprostol reduced the need for uterine curettage with no significant increase in side effects like nausea or diarrhoea^{18,19}.

In these trials vaginal misoprostol was administered in doses of 400µg, 600µg or 800µg. Lower dose regimens of vaginal misoprostol were tested in 2 RCTs and have shown to be less effective in inducing expulsion, but with a similar incidence of nausea.^{20,21} A study compared 800µg oral with the same dose of vaginal misoprostol with no difference in efficacy, but the mean time to expulsion was significantly longer in the oral group.²² Sublingual misoprostol had equivalent efficacy compared with vaginal misoprostol in inducing complete miscarriage, but was associated with more frequent diarrhea.²³

2. Predictors of success:

The success of the treatment seems to be higher for incomplete abortion but lower for an-embryonic pregnancy (empty gestational sac) compared to a pregnancy with an early embryonic death.^{24,25} Many studies reports on success rates are difficult to interpret or to compare efficacy rates very widely from 13% to 93%, influenced by many factors such as diagnosis, sac size, whether follow-up is clinical or involves ultrasound, be also the number or doses. Other researches have explored the efficacy of multiple misoprostol doses and timing of follow-up. Some

investigators have found that vaginal or sublingual misoprostol used every 3 hours for upto three doses is an effective treatment with acceptable side effects. Efficacy has been shown to be similar using a longer interval between doses or continued dosing for a week following the initial three doses.^{26,27} The effectiveness of treatment with misoprostol also depends on the time interval to follow-up.²⁸ To avoid unnecessary interventions to the assessment of success should be delayed for at least 7 to 10 days. There seems no clear advantages to administering a "wet" preparation of vaginal misoprostol or adding methotrexate, or of using laminaria tents.^{29,30} Two RCTs of pretreatment with Mifepristone treatment generated conflicting results^{31,32}, and further studies are needed to evaluate whether the use of mifepristone increases efficacy. Expectant management or medical treatment with misoprostol does not increase the risk of infection compared to surgery³³. Further more there is no evidence that non surgical approaches will have a negative effect on future fertility, but further larger studies are needed to confirm this.³⁴

Contraindications Known allergy to misoprostol Suspected ectopic pregnancy Unstable hemodynamics and shock Signs of pelvic infections and or sepsis. IUD in place (remove before beginning misoprostol regimen) Adrenal insufficiency Long term glucocorticoid therapy Haemoglobinopathies or anticoagulant, anemia, Hb < 10 gm/dl Porphyria, mitral stenosis, glaucoma, non steroidal drugs within the previous 48 hours. Bronchial asthma, hypertension

Regimen

A single dose of 800µg vaginal misoprostol is recommended for this indication.^{21,22} i.e medical treatment of missed abortion in the first trimester. Alternatively, 600µg misoprostol can be administered sublingually.^{23,27} Treatment may be repeated twice with a 3 hour interval but more studies are needed to evaluate the additional efficacy of repeated doses of misoprostol.^{23,26,27} Misoprostol is 90%-100% effective when used for missed abortion in women with gestational age 12-28 weeks. A majority of cases have the expulsion within 48 hours. All women should be given the choice between surgical, expectant or medical management. There is no clinical reason to withhold misoprostol for the treatment of missed abortion in women with previous caesarean section. After administration of misoprostol, hospitalization is not necessary as the time of expulsion varies

considerably – it may occur in hours or even several weeks. Bleeding may last for more than 14 days with additional days of light bleeding or spotting. Uterine contractions usually starts within a few hours following misoprostol. Routine antibiotic coverage is not necessary, but paracetamol or NSAIDs can be used for pain relief.³⁵ The women should be advised to contact a provider in case of heavy bleeding or signs of infection. The effectiveness of the treatment depends on the diagnosis and the time until follow-up evaluation. Follow-up is best performed at 1 to 2 weeks after treatment where complete evacuation of the uterus is confirmed by history, clinical examination of the uterus, and with ultrasound if necessary. A pregnancy test may also be needed. In the event of failure (or infection or heavy bleeding), surgical evacuation may be needed. However, if the woman is clinically stable and willing to continue to wait for her uterus to empty, it is acceptable to give her another dose of misoprostol, 800µg vaginally or 600µg sublingually.

Economic Evaluation

Misoprostol is an inexpensive substance, easy to store – as it is stable at room temperature. The use of mioprostol to manage pregnancy failure is likely to reduce the cost as it avoids anaesthetic and theater costs. The cost of starting with misoprostol will become lower as the rate of successful evacuation increase. One study of cost analysis, compared expectant and surgical treatment with misoprostol treatment was the least costly based on public health in Hong Kong.³⁶

Discussion:

The loss of wanted pregnancy is always distressing to mother. It had serious maternal consequences with appreciable risk of maternal mortality and long term morbidity. Many women suffer ill health following an abortion due to the heavy blood loss. Patient becomes severely anaemic, hence supervision is important. It is very difficult for patient to restore normal haemoglobin level. Post abortion anaemia may reduce her health and efficacy. Abortion is a common complication of all clinically recognized pregnancies. Missed abortion is one of the abortion which can occur from first trimester upto 28 weeks. With the rising use of early ultrasound, an increasing number of abortion present as missed abortion before the onset of cramping and bleeding. Many women, who already has a missed abortion is unaware of it, and they resort to unsafe, induced abortions.

Unsafe abortion is a significant contributor to worldwide maternal mortality; however, abortion law and policy liberalization could lead to drops in unsafe abortion and related deaths. In Bangladesh, abortion policy liberalization was followed by implementation of safe abortion services and other reproductive health interventions. Bangladesh also made advances in emergency obstetric care and family planning.^{46,47} One paper speaks of the unanticipated complexities when writing on reproductive rights for poor adolescent women living in the slums, where the discourses on ‘universal human rights’ are often removed from the reality of adolescent women’s everyday lives. Married adolescent women and their families remain extremely vulnerable in the unpredictable, crime-prone and insecure urban slum landscape because of their age, gender and poverty. Adolescent women’s understanding of their rights such as the decision to marry early, have children, terminate pregnancies and engage in risky sexual behaviour, are different from the widely accepted discourse on rights globally, which assumes a particular kind of individual thinking and discourse on rights and a certain autonomy women have over their bodies and their lives. This does not necessarily exist in urban slum populations. They concluded that, the experiences and decisions made pertaining to sexual and reproductive health and ‘rights’ exercised by married adolescent women, their families and slum communities, allow us to reflect on the disconnect between the international legal human rights frameworks as applied to sexual and reproductive health rights, and how these are played out on the ground. These notions are far more complex in environments where married adolescent women and their families live in conditions of poverty and socioeconomic deprivation. This was a review of the social aspects of attitude and behaviour. Surgical evacuation is the most common and standard method of treatment of all abortion and also of missed abortion. The majority of cases are currently treated by dilatation and curettage. The rationale that all spontaneous abortion should be treated with D & C to prevent infection and haemorrhage has been questioned.³⁷ Obstetricians and Gynaecologists have recently been challenged to rethink their approach to abortion, because of high success rates (more than 90%) in the medical management of abortion by misoprostol. There are varieties of methods of termination of pregnancy i.e expectant, medical and surgical methods. This review has different aspects

of these methods and provides different options considering mass application. As so far D&C is the method of termination. In low-resource countries like Bangladesh, it is expensive and has more complications. During the last decade, medical methods for 1st and 2nd mid trimester abortion have shown a considerable development and have become safe and more considerable,^{38,39} Misoprostol can be given by all junior and senior doctors, so this can be option of termination of all missed abortion as an alternative method. Uterine evacuation by medical methods reduces the morbidity associated with surgical intervention.^{40,41} Misoprostol, a prostaglandin PGE₁ analogue has cervical ripening and uterotonic properties, thus making it a useful drug in obstetrics.^{10,11} Most of the reports shown misoprostol to be relatively safe for use in women with 1st and 2nd trimester and even in women with prior caesarean section.⁴² Misoprostol is widely available. It is of low cost and stable at room temperature. It is easy to use both for the patients and clinicians. It is thus an excellent choice of treatment for use in low- resource setting.⁴³ A Cochrane review including 19 randomized controlled trails (RCTs) on pregnancies less than 14 wks concluded that vaginal misoprostol shortens the time to expulsion when compared with placebo. In these trials vaginal misoprostol was administered in doses of 400µg, 600µg, or 800µg. Lower dose regimens of vaginal misoprostol were tested in 2 RCTs and have shown to be less effective in inducing expulsion, but with a similar incidence of nausea. A study compared 800µg oral with the same dose of vaginal misoprostol with no difference in efficacy, but the mean time to expulsion was significantly lower in the oral group. Sublingual misoprostol had equivalent efficacy compared with vaginal misoprostol in inducing complete miscarriage, but was associated with more frequent diarrhoea. Some investigations have found that vaginal or sublingual misoprostol used every 3 hours for upto three doses is an effective treatment with acceptable side effects. Efficacy has been shown to be similar using a lower interval between doses or confirmed dosing for a week following the initial three doses. The effectiveness of treatment with misoprostol also depends on the time interval to follow-up. To avoid unnecessary interventions to the assessment of success should be delayed for at least 7 to 10 days. So, to get most effective result, A single dose of 800µg vaginal misoprostol is recommended for inducing missed abortion.

Alternatively, 800µg, misoprostol can be administered sublingually. Treatment may be repeated twice with a 3 hours interval but more studies are needed to evaluate the additional efficacy of repeated doses of misoprostol. For the rest, 12-28 weeks of missed abortion, 400µg of misoprostol every 4 hours until expulsion or 200µg every 12 hours can be given. A study by Shah N, Azam SI, Khan NH., Civil Hospital Karachi & Dow Medical College, Karachi. compared the efficacy of sublingual and vaginal misoprostol in the medical management of missed miscarriage. They studied fifty women diagnosed as having missed miscarriage of gestational age less than 20 weeks were assigned randomly to receive 400 microg of either sublingual or vaginal misoprostol every three hours, up to a maximum of five doses. The primary outcome measures were, complete evacuation of products of conception, mean induction to delivery time and the occurrence of side effects. There was no significant difference in complete evacuation rates between the sublingual misoprostol and the vaginal misoprostol groups (52% vs. 48%, $p = 0.571$) mainly within the first 24 hours. Mean induction to delivery time was also similar for both groups (13.07 +/- 6.95 hours for sublingual versus 13.29 +/- 5.63 hours for vaginal group) as was the total number of doses required (4.44 +/- 1.04 for sublingual versus 4.52 +/- 0.96 for vaginal misoprostol). Side effects were seen in 18 women (72%) in the sublingual group compared to 5 women (20%) in the vaginal group ($p < 0.001$). The incidence of unpleasant taste was significantly higher in the sublingual group than in the vaginal group (60% versus 4%, $p = < 0.001$). Sublingual misoprostol is as effective as vaginal misoprostol for medical management of missed miscarriage but is associated an increased risk of side effects especially an unpleasant taste.⁴⁴ A systematic review was conducted to compare with other methods, using the best available evidence, the benefits and risks associated with the administration of misoprostol to terminate pregnancy with fetal demise in the second and third trimesters (defined as gestational age of more than 14 weeks). They assessed all published randomized controlled trials identified from the Cochrane Pregnancy and Childbirth Group Trials Register, MEDLINE, POPLINE, LILACS and CINHALL from 1987 to 2008 comparing misoprostol alone (vaginal, oral or sublingual administration) with placebo or no treatment or any other method of uterine evacuation (including cervical ripening with other prostaglandins administered vaginally or extra-

amniotically, oxytocin, as well as mechanical methods of evacuation including extra-amniotic Foley catheter or laminaria placement) in women with diagnosis of intrauterine fetal death in the second and third trimester of pregnancy vaginal misoprostol was as effective as oral administration, achieving uterine evacuation within 48 h (RR=0.96, 95% CI=0.85 to 1.09). Oral administration was associated with more side effects than vaginal administration.⁴⁵ More studies are going on and still needed for misoprostol on missed abortion to be proved it more effective and safe for application in developing and low- resource countries.

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