

# Misoprostol for the Treatment of Early Pregnancy Failure

Sheila A. Doggrell\*

*School of Science, Charles Darwin University, Casuarina, NT 0811, Australia*

**Abstract:** Nearly 20% of all pregnancies end in early pregnancy failure, and surgical evacuation of retained products of conception is often used to manage this failure. Misoprostol is an inexpensive, stable analog of prostaglandin E<sub>1</sub>, and is powerful at contracting the uterus. With intravaginal misoprostol, the peak plasma levels are lower, but the levels after 4 hours are higher, than after oral or sublingual administration. With oral misoprostol, the evacuation rates in early pregnancy varied from about 50% up to 96%. Similar variation in evacuation rates were obtained from small trials with intravaginal misoprostol. To date, only small studies have used sublingual misoprostol, and there has been no direct comparison to oral or intravaginal misoprostol. A recent large clinical trial has shown, that with intravaginal misoprostol 800 µg, an expulsion rate of 84% can be achieved by 8 days. This large trial also established that women prefer misoprostol to surgical evacuation. Two economic evaluations have shown that misoprostol treatment is less costly than surgical intervention. On the basis of recent findings, it seems likely that misoprostol treatment will become a standard or preferred treatment for early pregnancy failure.

**Key Words:** Early pregnancy failure, intravaginal, misoprostol, missed abortion, oral, surgical evacuation.

## INTRODUCTION

Nearly 20% of all confirmed pregnancies end in spontaneous abortion [1]. About one in four women will have an early pregnancy failure during their lifetime, with the most common causes being spontaneous abortion, anembryonic gestation, and embryonic or fetal death [2].

The standard management of spontaneous abortion up to the 1990s was the universal evacuation of the retained products of conception, and this management had been undertaken for the preceding 60-70 years. This method dates from the time of many illegal abortions, which commonly resulted in hemorrhage and sepsis. By the 1990s, people were beginning to question whether such an invasive method was really necessary to evacuate the uterus in missed abortions.

In the US, it was estimated in 1998 that 100,000 uterine curettages were performed annually for early pregnancy failure at a yearly cost of over \$100 million [3]. The overall complication rates with surgical evacuation are between 4 and 10%, and consists of cervical injury, uterine perforation, pelvic infection and excessive bleeding [4,5].

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% [6,7]. With this method, the time to spontaneous expulsion is unpredictable and can be up to a month [6,7]. 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.

Recently, two developments have led to further consideration being given to how to manage early pregnancy failure. The first was technological advancements allowing a

detailed examination of the uterine cavity with high-resolution transvaginal sonography for any retained products of conception. This technique can be used to identify the one in three women with a spontaneous abortion who do not retain significant amounts of tissue in the uterus, and consequently do not require any potentially damaging treatment.

The second advancement was the development of misoprostol. Misoprostol is often used alone or in combination with the progesterone receptor antagonist mifepristone to induce abortion. However, in early pregnancy failure anti-gestagens (mifepristone) are not really necessary for medical termination of missed abortion as progesterone levels are usually low.

In addition to use in early pregnancy failure, misoprostol is also used for pregnancy termination [reviewed in 8], induction of labour [reviewed in 9] and the prevention or treatment of postpartum hemorrhage [reviewed in 10]. These uterine uses of misoprostol are "off-label" with the pharmaceutical industry having largely avoided involvement in the development and product registration for these uses [11]. Presumably, this was to avoid any role in or association with the abortion debate.

This review is of the use of misoprostol for the treatment of early pregnancy failure only. The first part of the review discusses the pharmacology of misoprostol. This is followed by a detailed discussion of the use in early pregnancy failure of oral, intravaginal and sublingual misoprostol, considered in sequence. The economics of using medical management of early pregnancy failure with misoprostol is discussed, prior to some concluding comments.

## PHARMACOLOGY OF MISOPROSTOL

### Pharmacodynamics

The naturally occurring prostaglandins (PGs) PGE<sub>1</sub>, PGE<sub>2</sub> and PGF<sub>2α</sub> are potent stimulants of human uterine contractility at any stage of pregnancy, and also cause cervical ripening and dilatation. However, the naturally occurring

\*Address correspondence to this author at the School of Science, Charles Darwin University, Casuarina, NT 0811, Australia; Tel: + 61 8 8946 6993; Fax: + 61 8 8946 6847; E-mail: sheila.doggrell@cdu.edu.au

PGs are rapidly metabolised. Misoprostol is a synthetic 15-deoxy-16-hydroxy-16-methyl analog of prostaglandin E<sub>1</sub> that is active after oral administration [12]. The initial clinical development of misoprostol was for use in the prevention and treatment of peptic ulcer associated with the use of non-steroidal anti-inflammatory drugs [12]. When misoprostol is used in the treatment of peptic ulcers, it is given as 800 µg daily in two or four divided doses, and it has a comparable efficacy to the histamine H<sub>2</sub> receptor antagonists [12]. The main adverse effect with this oral dosing of misoprostol is diarrhea (due to stimulation of the gastrointestinal tract), and this occurs in about 10% of patients, but is usually mild and self-limiting [12].

When used in the treatment of peptic ulcers, misoprostol was contraindicated in pregnant women as it is powerful at contracting the uterus and could induce miscarriage. Subsequently, misoprostol has been developed as an agent to induce abortion (often with mifepristone) and in the treatment of pregnancy failure. The use of misoprostol to induce abortion is not discussed in this review, whereas the use of oral, vaginal and subcutaneous misoprostol in early pregnancy failure is discussed extensively later in this review.

### Pharmacokinetics

Misoprostol was developed in an oral formulation for the prevention of gastric ulcers. Misoprostol is rapidly absorbed after oral administration, and rapidly and extensively de-esterified to the active metabolite misoprostol acid. The free acid is excreted mainly in urine, with an elimination half-life of 20-40 minutes.

After the oral administration of misoprostol, diarrhea (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 gastrointestinal side effects, when misoprostol is being used as a uterine stimulant, these tablets have been administered by other routes, including vaginally. Oral formulations are generally designed to be soluble in an aqueous environment, and for drugs that can cross the gastrointestinal cell membranes. 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 thickness of vaginal epithelium, fluid volume and composition [13]. Thus, when the tablets designed for oral administration were used by another route, it was important to study the pharmacokinetics.

In the first study comparing the pharmacokinetics of oral and vaginally administered misoprostol, subjects either ingested two 200 µg tablets with a glass of water or had them placed in the posterior fornix of the vagina with a vaginal speculum [14]. There was no obvious difference in pharmacokinetics of oral and intravaginal misoprostol between 10 women who were pregnant and undergoing an abortion and 10 women who were not pregnant, although the extent of absorption was highly variable among subjects in each group [14]. Thus, the data from pregnant and non-pregnant women were combined, and it was shown that after a 400 µg dose of misoprostol, peak blood levels of the main metabolite misoprostol acid were significantly higher after oral administration (277 pg/ml) than intravaginal administration (165 pg/ml) [14]. After this dose, the time to peak was longer with the

intravaginal administration (84 minutes) than oral administration of misoprostol (34 minutes) [14]. The area under the concentration curve was much higher with intravaginal than oral misoprostol measured between 0 and 4 or 6 hours (0-4 hours: oral, 273; vaginal, 503; 0-6 hours: oral, 300; vaginal, 958 pg/hr/ml) [14]. This suggests that quicker and more pronounced effects will occur with oral than vaginal misoprostol. However, from the area under the concentration curve data, it is likely that vaginal misoprostol will be active for longer than oral misoprostol.

There is some evidence that the moistening of misoprostol before vaginal administration improves its efficacy in inducing abortion [15], possibly by improving the rate and extent of absorption. The pharmacokinetics of moistening misoprostol have been determined and compared with the oral and sublingual administration of misoprostol. Sublingual administration is another route to avoid high gastrointestinal levels of misoprostol. The study determined the pharmacokinetics of oral and sublingual misoprostol 400 µg, and intravaginal misoprostol 400 µg that was either dry or had been moistened with 3 drops of water in 40 subjects who were having a termination of pregnancy [16]. There was no statistical difference between the serum levels of misoprostol acid with dry and moistened intravaginal misoprostol, although the moistened misoprostol gave a higher mean level throughout the study (Fig. 1) [16]. Peak levels of misoprostol acid were higher with sublingual (574 pg/ml) than oral (288 pg/ml) or dry intravaginal (125 pg/ml) or moistened intravaginal misoprostol (163 pg/ml) [16]. Time to peak was similar with sublingual (26 min) and oral (28 min) misoprostol, and shorter than with dry (72 min) or moistened intravaginal misoprostol (75 min) [16]. The area under the misoprostol concentration curves had a lot of variation in it, but was higher with sublingual (702 pg/hr/ml) than oral (369 pg/hr/ml), dry intravaginally (330 pg/hr/ml) or moistened intravaginally (477 pg/hr/ml) at 4 hours, and a similar pattern was observed after 6 hours [16]. The results for the oral versus vaginal part of this study are similar to the previous study, except for the area under the concentration response curve results where the area was similar in this study [16], when the area was larger after vaginal than oral administration in the previous study [14]. The large variation between individuals, especially in peak levels, and the small numbers of subjects may be responsible for this discrepancy. One thing that is consistent between the two studies is that 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.

A third study comparing the oral and vaginal pharmacokinetics of misoprostol 400 µg has confirmed that time to peak is slower after vaginal than oral administration in pregnant women [17]. This study also showed that the area under the curve was greater after vaginal than oral misoprostol, and the levels after 4 hours were much higher with vaginal than oral misoprostol [17]. This study had a 3<sup>rd</sup> group, where the misoprostol was administered rectally. After rectal administration, the time to peak was similar as with vaginal administration [17]. The area under the curve with misoprostol administered rectally 0-4 h (190 pg/h/ml) was slightly higher

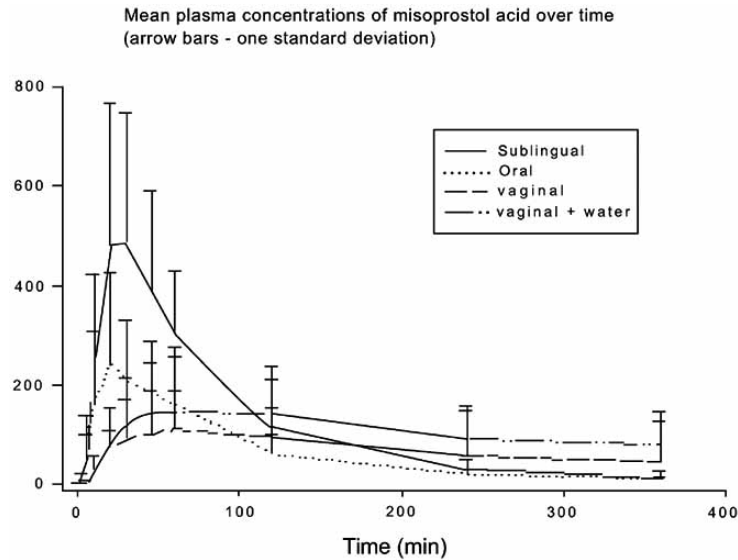


Fig. (1). Mean plasma concentrations of misoprostol acid over time [16].

than after oral administration (152 pg/h/ml) but much lower than with vaginal administration (446 pg/h/ml) [17]. This suggests that the effects of vaginal misoprostol will persist for longer than either oral or rectal misoprostol.

Another study has found similar comparative pharmacokinetic data for oral and rectal misoprostol with a higher dose of misoprostol. This study compared oral misoprostol 600 µg with the tablets formulated for oral use given rectally in the third stage of labour [18]. After rectal administration, the peak levels of misoprostol acid were 23 minute later than after oral administration, but the area under the curve for misoprostol concentration was higher after rectal than oral administration of misoprostol [18].

There has also been a study comparing the pharmacokinetics of buccal (inside of the cheek) and sublingual (under the tongue) misoprostol 800 µg in healthy women [19]. The peak concentration and the area under the concentration curve were greater with sublingual than buccal misoprostol, as were the side effects [19]. The peak concentrations were 1140 pg/ml and 229 pg/ml and the area under the curve 0-4 were 1600 pg/ml and 380 pg/ml with sublingual and buccal misoprostol, respectively [19]. This study shows that 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 early pregnancy failure 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.

#### ORAL MISOPROSTOL IN EARLY PREGNANCY FAILURE

The initial reports of the use of misoprostol for the termination of early pregnancy failure were of oral use, and were

associated with variable success rates. The first report, of the use of oral misoprostol 400 µg in early pregnancy failure, appeared in 1993 and suggested there was a 96% success rate [20]. The 44 women in this study were all shown to have retained products of conception by transvaginal ultrasound, and the first 20 were treated with sulprostone im [20]. When sulprostone was withdrawn by its manufacturer, the study was continued with misoprostol, and as similar results were obtained with both agents, the results were combined [20]. Treatment failed in only 2 of the women, and of the 44 women only 11 women required oral analgesia, and only 2 required narcotic analgesia [20]. Hemoglobin levels fell by a median of 2g/l [20]. Twenty-three of the women were able to return to normal daily activities immediately, and the remainder had a mean duration of inactivity of 3 days [20].

However, in the next study comparing oral misoprostol and surgical curettage for incomplete miscarriage, only 3 of 25 women receiving misoprostol 400 µg had a successful evacuation [21]. Haemoglobin levels fell in those subjects treated with misoprostol, but not in those treated surgical [21]. One suggestion for the lower rates of success with misoprostol in this study was that the mean duration of amenorrhea was longer, 80 days, than in the previous study, 66 days [21]. A large proportion of women had required blood transfusions before randomisation and this might also have some role in the high failure rate and/or haemoglobin results [21].

In another study of oral misoprostol in early pregnancy failure, after diagnosis by transvaginal ultrasound examination, only women with a closed cervical os and minimal vaginal bleeding were enrolled [23]. Twelve subjects received 400 µg misoprostol orally and 8 subjects 800 µg misoprostol orally and, if the gestation sac was still present when the subject returned 24 hours later, the dose of misoprostol was repeated [23]. Complete uterine evacuation only occurred in 3 of the 12 subjects with the lower dose, but a higher success rate (7 of 8 subjects, 88%) was achieved with

misoprostol 800 µg [23]. With these doses of misoprostol 400 and 800 µg, there were quite high rates of adverse effects with vomiting occurring in 13 and 30%, and diarrhea occurring in 38 and 50% of subjects, respectively [23].

A larger, prospective, observational study of women admitted to hospital with spontaneous abortion gave support to the use of misoprostol to remove the retained products of conception, but showed low success rates [24]. Transvaginal scan was used to identify the women who did not have retained products of conception, who were then excluded [24]. Of the remainder, 225 were treated with misoprostol, and at 48 hours, 148 (66%) had had evacuation of the uterus [24].

Subsequently, the same group of researchers performed a randomized, controlled trial comparing surgical evacuation with misoprostol [25]. This trial investigated 653 consecutive women admitted to a gynaecological unit with a spontaneous abortion, and transvaginal sonographic evidence of retained products of conception [25]. Patients were excluded if they had severe blood loss or sepsis [25]. Eventually, 604 subjects with a mean length of gestation of nearly 11 weeks, were enrolled to either surgical evacuation or 400 µg misoprostol orally every 4 hours up to a total of 1,200 µg [25]. About half of the subjects treated with misoprostol eventually had an evacuation [25]. More of the misoprostol group needed analgesic treatment than in the evacuation group; evacuation, 19 subjects; misoprostol, 89 subjects [25].

A higher rate of successful removal of retained products of conception was reported with three sequential doses of oral misoprostol in a later study [26]. Thus, retrospective analysis of 112 women showed that a complete miscarriage had been achieved in 85% of them after misoprostol treatment with the remaining 15% requiring surgical intervention [26]. Other studies have shown a 78% success rate with 400 µg oral misoprostol in 131 women [27] and of 96% with oral misoprostol 600 µg in 185 women with incomplete miscarriages [28]. Recently, similar high rates of success have been achieved with a single or repeated dose of oral misoprostol 400 µg for incomplete abortions [29]. The success rate was 82% and 92% with the single and repeat dose, respectively [29]. Diarrhea occurred more often with the repeat dose (40%) than with the single dose (18%) [29].

#### **VAGINAL MISOPROSTOL IN EARLY PREGNANCY FAILURE**

Indications that vaginal misoprostol may be more effective than oral misoprostol at causing an emptying of the uterus were initially obtained from studies using misoprostol for abortion. For instance, in 270 subjects that had been treated with mifepristone to terminate pregnancy within 63 days of onset of amenorrhoea, expulsion of the conceptus was achieved with misoprostol 800 µg in 87% of subjects who received the misoprostol orally and in 95% who received it vaginally [30]. However, studies of misoprostol in early pregnancy failure have failed to establish any superiority of intravaginal over oral misoprostol.

The first reports of vaginal misoprostol for early pregnancy failure appeared in 1998. Seven women with transvaginal ultrasound confirmation of first trimester missed abortion and a gestation age of 9 weeks were treated with 4 x

200 µg misoprostol tablets intravaginally, and this was repeated if products of conception were not expelled in 12 hours [31]. Five of the women (71%) had evacuation with a mean time of 10 hours [31]. All women experienced cramping, which was moderate in 6 and mild in one patient, and one patient had mild nausea and one episode of diarrhea [31]. Average blood loss with misoprostol treatment was 434 ml [31].

In the same year, 25 women who had retained products of conception, and a mean gestation length of 11.2 weeks had moisten misoprostol 200 µg tablets inserted into the posterior fornix of the vagina every 4 hours to a maximum dose of 800 µg [32]. Twenty-two of the 25 women (88%) had an expulsion within 10 hours (mean 6.1 hours), while the others required dilatation and curettage [32]. Five of the women had expulsion after the first dose, 13 after the second dose, 3 after the third dose, but none after the fourth dose of misoprostol [32]. A retrospective study of women with early pregnancy failure who were treated with intravaginal misoprostol 800 µg, and a second course of misoprostol if evacuation did not occur in 24 hours, showed a 78% success rate [33].

The success rate with misoprostol for terminating early pregnancy may be lower when a lower dose of misoprostol was used. Thus, in a group of 74 women with first-trimester missed abortions (9.8 weeks since last menses), misoprostol 600 µg was administered intravaginally, and repeated 4 hours later if necessary [34]. With this regimen, only 42 women (57%) had complete evacuations [34], whereas higher rates of evacuation have been achieved with misoprostol 800 µg (see previously). There was also a high incidence of side effects in this study with nearly all the women having abdominal pain [34].

#### **Placebo-Controlled Studies**

The first placebo-controlled study with vaginal misoprostol used 200 µg or placebo tablets in missed abortion, the day before the planned dilatation and aspiration [35]. The mean gestation age was about 13 weeks, and 35 of 42 (83%) women in the misoprostol group had an evacuation before the scheduled operation, compared to 6 (17%) in the placebo group [35]. Two of the 40 women treated with misoprostol needed intramuscular pethidine as analgesia [35].

In a series of 44 women with blighted ovum, intravaginal misoprostol 400 µg caused evacuation in 63%, compared to 19% who received placebo tablets [36]. In 50 women with missed abortion, intravaginal misoprostol up to 800 µg caused complete abortion in 20 of 25 (80%) compared to 4 in the placebo group [37]. The mean reduction in haemoglobin from day 1 to 7 was 3.2 g/l in the misoprostol group, compared to 4.3 g/l in the placebo group [37]. Nineteen of the women treated with misoprostol reported that they would try medical management if they experienced another missed abortion [37].

In a larger study of 126 women with non-viable, first trimester miscarriage at gestation age of about 75 days, 81% of those treated with misoprostol 400 µg intravaginally had had an evacuation by day 7, compared to 52% of those treated with placebo tablets [38]. Patients in the misoprostol

group had more pain on a visual analog scale (60 vs 44 mm) and required analgesics more often [38]. However, there was no difference between the groups for gastrointestinal side effects, reduction in haemoglobin or sick leave [38].

A recent small study suggests that a rapid evacuation can be obtained in patients with early pregnancy, closed cervix, and minimal vaginally bleeding. Thus, after treatment with misoprostol 800 µg, there was expulsion of uterine contents in 15 of 18 (83%) within one day, and this compared favourably with the 2 of 16 (13%) in the placebo group [39].

### Intravaginal and Oral Misoprostol

Oral and vaginal misoprostol were compared directly in 201 women with incomplete miscarriage supported by a positive urinary pregnancy test and confirmed by transvaginal ultrasonography [40]. Women, with a mean gestation of 10 weeks, were administered oral or vaginal misoprostol 800 µg, and the dose was repeated 4 hours later if the women had not passed products of conception [40]. In this study, transvaginal ultrasonography was performed the following day to detect empty uteri, and the success rate was similar with both routes of administration with 58 of 95 (61%) in the vaginal misoprostol group and 67 of 103 (64%) of the oral misoprostol group not requiring surgical evacuation [40]. The remainder of the women went to theatre the day after misoprostol treatment, and most of these misoprostol-treated patients had an open cervical os at surgical evacuation [40]. The incidence of nausea and vomiting was low and not different between the groups. However, more patients in the oral misoprostol group than the vaginal misoprostol group suffered diarrhea (oral, 65%; vaginal, 14%) [40].

A higher success rate was achieved if the misoprostol was given longer to be effective. Thus, in a comparison of misoprostol 800 µg orally or intravaginally, two days after treatment, expulsion had occurred in 42% of the women given oral misoprostol and 53% of those given vaginal misoprostol [41]. A week after treatment expulsion had occurred in 89 of 100 women (89%) in the oral and 91 of 98 women (93%) in the vaginal misoprostol group [41]. Bleeding was similar in nature between the two groups, as was the incidence of side effects [41]. In this study, 25% of the patients given oral misoprostol reported diarrhea, compared to 24% given vaginal misoprostol [41].

One study has used a combination of intravaginal misoprostol 200 µg for 5 days followed by misoprostol 200 µg four times a day, and shown a 95% success rate [42]. Nearly all the women in this group of 40 were satisfied with this treatment, and the haemoglobin levels in this group were not different from that of the 40 subjects treated by curettage [42].

### Compared to Surgical Management

Eighty women with incomplete miscarriage diagnosed by ultrasound, and a mean gestation age of about 10 weeks, were randomized to surgical curettage or vaginal misoprostol 800 µg [43]. In the misoprostol group, 33 of 40 patients (82.5%) had successful removal of the retained products [43]. Subsequently, it was shown that of the 7 patients in whom misoprostol was unsuccessful, 2 had an anembryonic sac, 4 had missed miscarriages and only one had an incom-

plete miscarriage [43]. Thus, the authors suggested that the true failure rate for misoprostol was only 7% [43]. There was a higher incidence of nausea with misoprostol treatment than with the surgery (surgical, 45%; misoprostol, 85%) [43]. Abdominal pain and the associated use of analgesics occurred less often in the misoprostol than surgery group [43]. There was no difference in the incidence of vaginal bleeding, which occurred in most patients, or in the duration or severity of bleeding between the groups [43]. Most of the bleeding was mild, and haemoglobin values were similar between the groups [43].

These high rates of success were not duplicated in all studies of intravaginal misoprostol in early intrauterine pregnancy failure. One trial compared 800 µg misoprostol placed within the posterior vaginal fornix with surgical evacuation at a mean estimated gestation age of 8.2 weeks [44]. Intravaginal misoprostol was re-administered after 24 and 48 hours if ultrasound showed that the women had retained products of conception [44]. With this protocol, 15 of 25 (60%) of misoprostol treated subjects had an evacuation without curettage [44]. Twelve of 25 misoprostol patients reported nausea, and one vomited [44]. There were no differences between the misoprostol group and the surgical group in post-treatment hematocrit levels or the time needed to achieve negative human chorionic gonadotropin test results [44].

Another study with vaginal misoprostol showed low rates of success in early pregnancy failure, when misoprostol treatment was undertaken after initial expectant management for one week [45]. This suggests that one week of expectant management prior to misoprostol treatment is not the ideal approach in early pregnancy failure. In the study only 53% of 79 patients had had an evacuation after vaginal misoprostol 800 µg, which had been repeated 24 hours later, if it was unsuccessful [45]. The other 75 patients in the study had an immediate curettage, and the severity of pain and bleeding was lower in this group than the misoprostol group [45]. In this study, 58% of the patients in both groups would choose the same treatment in the future [46]. In the misoprostol group, there was a higher satisfaction in the women who had a successful evacuation with misoprostol (78%) compared to only 38% of women who needed curettage after unsuccessful treatment with misoprostol [46].

A recent large clinical trial compared intravaginal misoprostol and surgical management for early pregnancy failure in 652 women with a first-trimester pregnancy failure (anembryonic gestation, embryonic or fetal death, or incomplete or inevitable spontaneous abortion) and average gestation age of 7.6 weeks [47]. Of the women, about a quarter underwent surgical management (manual vacuum aspiration) and the other 491 were assigned to misoprostol 800 µg administered as 4 x 200 µg tablets inserted into the posterior fornix through a speculum [47]. The women were given 30 tablets of ibuprofen 200 mg and 20 codeine tablets 30 mg and were instructed to take ibuprofen primarily for pain relief and the codeine as needed [47]. On day 3, if expulsion of the products of conception was not complete, a second dose of misoprostol 800 µg was administered intravaginally, and on day 8, if the expulsion was still not complete, vacuum aspiration was offered [47]. In the misoprostol group, 71% had a com-

plete expulsion by day 3 and 84% by day 8 [47]. The 16% failure rate with misoprostol was greater than the 3% observed with surgical management [47]. Hemorrhage and endometritis requiring hospitalization occurred in 1% or less of patients [47]. Vomiting occurred in 20% of women treated with misoprostol compared to 7% with aspiration, and pain scores were also higher in those treated with misoprostol than with aspiration [47]. Nevertheless, in the misoprostol group, 78% of the women stated they would use misoprostol again, if needed [47]. Among the 190 women who had undergone vacuum aspiration in previous failed pregnancies, but who received misoprostol in the trial, 80% stated that they would recommend misoprostol treatment [47].

Similar results were obtained when a lower dose of misoprostol (600 µg) was compared with surgical evacuation in 94 subjects with incomplete first-trimester abortion [48]. Thus, there was a 100% success rate with the surgical method compared to 91.5% with misoprostol [48]. Patients in the misoprostol group had a longer duration of bleeding and a greater need for analgesia [48]. More women who received medical treatment (97.9%) would recommend the same treatment that those who received surgical treatment (85.1%) [48].

The long term conception rate and pregnancy outcome are not different following misoprostol treatment and surgical management of early pregnancy failure. Of 261 women who had attempted to become pregnant since miscarriage, the conception rate of 98% was the same in the 130 with surgical and 131 with misoprostol treated groups [49]. The median time-to-pregnancy was 8 months in both groups, and the subsequent live birth rates were 85% in the misoprostol and 88% in the surgical group [49].

### **Versus Expectant Management**

Vaginal misoprostol has been compared to expectant management and shown to have some advantages in 59 women with an ultrasound confirmed diagnosis of missed miscarriage, and a mean menstrual delay of about 45 days [50]. If the first dose of vaginal misoprostol 400 µg did not produce evacuation, this process was repeated on day 3 and, if necessary day 5 [50]. Expectant was discharge on day 1 if there was no excessive vaginal bleeding and follow-up on days 3 and 5 [50]. By day 15, 83.3% of misoprostol treated patients had had an evacuation, whereas only 48.3% of those on expectant management had [50]. Nausea occurred in more patients treated with misoprostol than expectant management (misoprostol, 47%; expectant, 24%) [50]. One woman in the misoprostol group and 3 in the expectant group underwent emergency suction evacuation because of excessive bleeding, but the mean duration of vaginal bleeding was similar in both groups [50].

A further study comparing vaginal misoprostol to expectant management also showed some benefits with the vaginal misoprostol. This study enrolled 104 women with a mean gestation age of 73 days to either 600 µg misoprostol or placebo intravaginally, with the dose being repeated the following day if treatment was not successful [51]. By day 7, the success rate was 89% in the misoprostol group (46/52) compared with 44% in the expectant group (23/52) [51]. The complete miscarriage rate was achieved quicker in the miso-

prostaglandin group than expectant group (day 2: 73% vs 14%) [51]. There were no differences between the groups at day 14 in haemoglobin levels, duration of bleeding, number of analgesics and days of analgesia, nausea, vomiting and diarrhea [51]. For instance, nausea occurred in 18 of the women treated with misoprostol (35%) and 16 of the 52 women with expectant management (31%) [51]. When asked, more women in the misoprostol group than the expectant management group, said that they would elect to have the same treatment rather than surgical evacuation (90% vs 73%) [51].

### **Moistened Versus Dry Vaginal Misoprostol**

One explanation of the variable success rate of vaginal misoprostol in early pregnancy failure may be related to differences in absorption from the vagina [52]. However, when the effectiveness of 800 µg misoprostol inserted into the posterior fornix through a speculum with and without adding 2 ml saline solution was compared there was no difference [52]. Thus, by day 3, 30 of 41 (73%) in the saline moistened group had expelled the sac, compared to 25 of 39 (64%) in the dry misoprostol group [52].

### **Dose Studies**

The intravaginal misoprostol regimens used have varied in the studies detailed above. A recent study compared intravaginal misoprostol 600 and 800 µg, and showed the higher dose to be more effective [53]. Thus, with misoprostol 800 µg, 39 of 57 women (68%) had expulsions within 24 hours, compared to 27 of 57 women (46%) of women using misoprostol 600 µg [53]. Although the levels of fever, abdominal pain, and nausea were higher with the 800 µg dose, this did not reach statistical significance [53], possibly because of the relatively small size of the study.

The continuing administration of intravaginal misoprostol 400 µg every 4 h for a maximum period of 3 days has recently been shown to be effective in first trimester spontaneous abortion [54]. Thus, with this approach 74 of 108 women (69%) had expulsions within 24 hours, and 98 (91%) within 3 days [54]. The mean dose of misoprostol administered was 1113 µg [54].

A retrospective study at one facility comparing 400 and 800 µg intravaginally has shown that the higher dose is more effective in first trimester spontaneous abortion [55]. Thus, a single dose of misoprostol 800 µg was successful in 2-4 days in 59% of cases of missed abortions (misoprostol 400 µg, 43%) and in 47% of cases of anembryonic gestation (400 µg, 36%) [55].

### **SUBLINGUAL MISOPROSTOL IN EARLY PREGNANCY FAILURE**

There have been fewer studies with sublingual than with oral or intravaginal misoprostol for early pregnancy failure. Sublingual misoprostol has been combined with mifepristone in a trial as medical management of early fetal demise [56]. The trial enrolled 56 consecutive women with a mean gestation at diagnosis of 9.6 weeks [56]. Four of the women had evacuation with mifepristone alone, and overall 84% of the women had a complete miscarriage with a median induction-miscarriage interval of 8.2 hours [56].

One relatively small study has compared sublingual with vaginal misoprostol, and shown them to be similarly effective. The 80 women with silent first trimester miscarriages were randomized to receive 600 µg of misoprostol every 3 hours for a maximum of three doses either sublingually or vaginally [57]. In both groups, 35 of 40 women (88%) had passage of products of conception [57]. Although the mean interval between misoprostol and passage was shorter in the sublingual group (9.5 hours) than the vaginal group (13.5 h), there was a large variation, and this difference was not statistically significantly [57]. The incidence of diarrhea was higher with sublingual than vaginal misoprostol (70% vs 28%), but other side effects were similar in both groups [57].

Extending treatment beyond 3 sublingual doses of misoprostol has not been shown to increase effectiveness [58], possibly because the 3 doses were very effective alone. All 180 women with silent miscarriages received misoprostol 600 µg sublingually every 3 hours for a maximum of 3 doses, and half of the women received further sublingual misoprostol for a week [58]. The success rate was 92% with the 3 doses and 93% with the extended doses [58]. The incidence of diarrhea was higher in the group with the extended course of sublingual misoprostol [58]. Thus, it seems that 3 doses of sublingual misoprostol 600 µg should be the preferred option of these 2 regimens.

### ECONOMIC EVALUATION

Misoprostol is an inexpensive substance and easy to store as it is stable at room temperature. The use of misoprostol to manage early pregnancy failure is likely to reduce the cost as it avoids anaesthetic and theatre costs. A cost analysis was done in the study comparing misoprostol with curettage after initial expectant management for one week [46, discussed previously]. In this study only 53% of 79 patients had an evacuation after vaginal misoprostol 800 µg [46]. The mean direct costs per patient allocated to the misoprostol group were €433, compared to €683 for patients allocated to curettage, a saving of €250 with management using misoprostol [59]. In the 42 women in whom misoprostol resulted in complete evacuation, the mean direct cost was €137, whereas in the 37 women in whom additional curettage was needed after misoprostol, the mean direct cost was €788 [59]. Total costs were €915 for management starting with misoprostol compared to €1107 for curettage [58]. From this information, it is obvious that the cost of starting with misoprostol will become lower as the rate of successful evacuations increase. Thus, an increase of evacuation rate to 90% would make starting the management with misoprostol €550 cheaper than curettage [59].

Another cost analysis, compared expectant and surgical treatment with misoprostol treatment and showed that misoprostol was the least costly based on public health care in Hong Kong [60]. The costs were US\$1000 per patient in the misoprostol group, US\$1172 in the expectant group, and US\$2007 in the surgical group [60]. These cost varied with success rates in the misoprostol and expectant groups, but not surgical group. Thus, if the rate of complete evacuation with misoprostol was less than 59% or the rate of evacuation with expectant care was greater than 89%, expectant care would become cheaper than misoprostol treatment [60].

### COMMENTS AND CONCLUSIONS

As the oral administration of misoprostol is associated with gastrointestinal side effects, other routes of delivery have been considered. The pharmacokinetic data with misoprostol show that higher levels for longer periods are obtained with vaginal and sublingual than oral misoprostol.

After initial expectant management for one week, the rates of expulsion were low with misoprostol [45]. This may be because the population that is susceptible to misoprostol is also more likely to have a spontaneous miscarriage. Because of this, there may be little advantage to expectant treatment for one week, prior to misoprostol or surgical treatment.

The pharmacokinetics of moistened intravaginal misoprostol are highly variable and, although the plasma levels were consistently higher than after dry vaginal misoprostol, this did not reach significance [16]. In a study comparing saline moistened and dry misoprostol intravaginally, by day 3, 30 of 41 (73%) in the saline moistened group had expelled the sac, compared to 25 of 39 (64%) in the dry misoprostol group [52]. These values were not significantly different, and were taken to indicate that moistening had no benefit. However, it may be worth considering developing a consistent way of moistening the tablets, and then performing a larger study comparing the moistened to dry intravaginal misoprostol tablets. As it is known that absorption is variable from tablets intravaginally, possibly because the tablets were designed for oral use, it may be appropriate to develop a form of misoprostol that has reliable absorption from the vagina.

It is not clear whether misoprostol is more effective at causing expulsion after oral or intravaginal administration. The two small direct comparison trials have shown similar expulsion rates [40,41] with one trial showing that the rates of diarrhea were higher with oral misoprostol [40], while the other found no difference between the oral and intravaginal routes of administration [41]. A larger trial is probably indicated to compare the efficacy and safety of oral and intravaginal misoprostol for the treatment of early pregnancy failure. Alternatively, a meta-analysis of the available trial data may be appropriate.

Progress has been slow in establishing misoprostol management for early pregnancy failure, possibly because there was no pharmaceutical company backing for large clinical trials. Fortunately, a recent clinical trial has established a protocol with intravaginal misoprostol 800 µg that gives a 84% expulsion rate by day 8, and shown that women recommend misoprostol over vacuum aspiration [47]. As recent studies have shown that it is cheaper to manage early pregnancy failure with misoprostol than surgical intervention [59,60], and that women prefer this method [51], it seems likely that misoprostol treatment will become a standard or preferred treatment for early pregnancy failure.

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