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REVIEW ARTICLE

Misoprostol for the termination of pregnancy up to 12 completed weeks of pregnancy

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Recommended Dosage
Vaginal misoprostol 800μg 6 hourly x3

KEYWORDS
Misoprostol alone;
Medical abortion;
Effectiveness

Abstract

The aim was to review the current knowledge about the use of misoprostol alone for abortion induction during the first 12 weeks of pregnancy. Publications reporting experiences with misoprostol alone for pregnancy termination within the first 12 weeks of pregnancy were included in the analysis. Vaginal administration of 800 μg repeated up to three times at 6, 12 or 24 h intervals has an 85% to 90% effectiveness, defined as complete abortion, in most studies. Oral administration is less effective, but sublingual administration at 3-hour interval has the same effectiveness, with more frequent side effects. The oral and sublingual routes appear to be better accepted than vaginal administration. Most studies are limited to the first 9 weeks of pregnancy. The experience on pregnancy termination between 10 and 12 weeks is not yet sufficient for a recommendation.

1. Introduction

It is estimated that 46 million pregnancies are terminated voluntarily each year, 27 million carried out under safe conditions and 19 million falling into the category of "unsafe abortions" [1]. Until the second half of the twentieth century, dilatation and curettage (D & C) was the most common and virtually only method used for safe termination of early pregnancy. Abortion by vacuum aspiration gained greater acceptance in the 1960s and has become the standard of care. First trimester pregnancy can also be terminated safely pharmacologically (medical abortion).

The regimen of mifepristone followed by a suitable prostaglandin analogue (usually misoprostol) has become increasingly available and is now the gold standard for this indication.

Mifepristone is an antiprogestin that blocks most progesterone receptors. When a prostaglandin is administered 24 to 48 h after mifepristone, uterine contractions expel the products of conception and the effectiveness of the combination is greatly enhanced. This medical abortion regimen is highly effective and well accepted [2–4] and women who wish to avoid invasive procedures regard medical abortion as a more natural and preferable option [5]. The combination of metrotrexate and misoprostol has also been used, but this combination has not proven advantages over misoprostol alone.

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Where mifepristone is not accessible, various misoprostol-only regimens are being used, and dozens of reports have been published on the outcomes of various treatments. The comparison of the results of the published data on the use of misoprostol is not possible due to a lack of uniformity in many variables: intervals between doses vary from 3 to 48 h, the time point for assessing this outcome varies from a few days to several weeks (Table 1), and the gestational age of women differs between reports. These factors make it difficult to conclude what regimen might be the most effective.

Most publications report vaginal administration of multiple doses of 800 μg of misoprostol (4 tablets of 200 μg) [4,6–13] up to three doses. The available information suggests that effectiveness is dose related with doses up to 800 μg if administered by the vaginal route [14].

When misoprostol is used alone, the oral route is less effective than vaginal [15–18]. Vaginal administration should therefore be chosen unless there are reasons to avoid it. The sublingual route is a reasonable alternative and may be used as second choice.

Alternative routes may be sought as some acceptability studies, have shown that women prefer a non-vaginal route [19,20]. Moreover, when given vaginally, fragments of the tablets may remain visible for many hours.

The sublingual route is a reasonable alternative [19,21,22]. Although the sublingual route is significantly less effective than the vaginal route if misoprostol is administered every 12 h, the effectiveness is similar if administered with a 3-h interval between doses [22]. The main drawback of the sublingual route is that it may cause more frequent gastrointestinal side-effects (such as nausea, vomiting, shivering and hyperthermia) than vaginal administration [22]. These side effects are dose dependent and last only for a short time.

Recently, the buccal route of administration has also been investigated, but not yet for this indication [23].

Intervals between doses vary from 3 [22] to 48 h [8,23]. According to pharmacokinetics and clinical experience, the interval between vaginal doses may not need to be shorter than 5–6 h [24,25] and probably no longer than 24 h.

There is experience on the use of these regimens up to 63 days (9 weeks) pregnancy [23,26,27], but too few reports on the use of misoprostol between 9–13 weeks [7,28] to affirm that these regimens are equally effective during that period.

The misoprostol-only regimen has been approved for the termination of early pregnancy in only one country (Brazil) at the time of writing (February 2007). However, its widespread use in countries with restricted abortion laws appears to be associated with reduction in maternal morbidity and mortality [29–32].

2. Contraindications

- Known allergy to misoprostol.
- Suspected ectopic pregnancy or non-diagnosed adnexal mass.
- Unstable hemodynamics.

3. Precautions

- If molar pregnancy is diagnosed, intrauterine aspiration and curettage is preferred [33].
- If there is an intrauterine device (IUD) in place, this should be removed before administering misoprostol.
- Coagulation disorders/currently taking anticoagulants.
- Women should be advised that the treatment can fail and they should be prepared to terminate the pregnancy by

Table 1 Summary of studies with vaginal administration of misoprostol alone for first trimester abortion

Author	Gest. age	Doses	N	Interval	No. doses	Observ. time	Complete abortion	Cont. pregnancy	Nausea	Vomit	Diarrhea	Hyperthermia	Shivering
[14]	5–11	200	101	12 h	4	48 h	23%	61%	19%	6%	7%	–	–
[14]	5–11	400	113	12 h	4	48 h	46%	34%	20%	11%	6%	–	–
[7]	10–11	800	120	24 h	3–5	14 days	87%	6.7%	22%	17%	54%	26%	72%
[8]	10–13	800	180	12 h	3–5	14 days	85%	7.2%–	16%	17%	54%	14%	28%–
[8]	5–9	800	720	24 h	3(?)	48 h(?)	89.4%	6.5%	24%	23%	50%	18%	49%
[9]	≤8	800[a]	100	24 h	2	15 days	88%	–	–	14%	9%	(5	5)
[23]	≤9	800[a]	40	48 h	3	15–43 d.	85%	2.5%	15%	2.5%	2.5%	–	–
[23]	≤9	800	40	48 h	3	15–43 d.	65%	10%	7.5%	5.0%	0.0%	–	–
[10]	≤8	800[a]	75	24–7 days	3	8 days	90.7%	4.0%	–	36%	56%	(88.0%)	
[10]	≤6	800[a]	101	7 days	2	8 days	92.1%	–	21.4%	4.9%	12.6%	–	–
[51]	≤8	800[a]	125	24 h	3	15 days	88.8%	–	51.7%	21.5%	11.2%	(71.5%)	
[13]	≤8	800[a]	160	24 h	3	72 h	87.5%	–	(18.1%)[a]	14.4%	15.6%	–	
[11]	≤8	800[a]	100	24 h	3	72 h	93.0%	5%	–	29%[a]	23%[a]	(77%)	
[27]	≤9	800[a]	450	8 h	3	24 h	86.3%	5.6%	29.1%	20%	11.6%	15.3%	48%
[27]	≤9	800[a]	450	8 h	6	48 h	90.5%	3.3%	–	–	–	–	–
[26]	8–9	800[a]	162	12 h	3	72 h?–	91.0%	–	30.8%	21.6%	12.3%	15.4%	46.2%
[18]	≤8	800[a]	51	24 h–7 days	2–3	7–8 days	80.4%	5.9	43.8%	31.4%	–	(82.4%)	
[18]	≤8	800[a]	50	24 h	2	7 days	66.0%	4.0%	30.6%	16.3%	–	(52.1%)	
[22]	≤9	800[a]	498	3 h	3	14 days	87.1%	4.0%	23.6%	6.2%	23.1%	15.5%	36.5%
[22]	≤9	800[a]	487	12 h	3	14 days	85.5%	5.0%			22.8%	5.4%	32.1%

[a] Moistened.

surgical method, because there have been reports of congenital malformations in newborn infants of mothers given misoprostol during the first trimester of pregnancy [34].
- Breastfeeding: Small amounts of misoprostol or its active metabolite may appear in breast milk [35]. There is no information on the effects on nursing infants. It is recommended therefore that breast milk is not given to the infant for 4 h after oral administration or 6 h after vaginal misoprostol administration.
- Anemia detected at the time of abortion should be treated without delaying the procedure. The average blood loss during medical abortions may be more than in surgical abortions [36–38].
- Previous cesarean section: there is evidence from one study that the safety and efficacy of early abortion (up to seven weeks) is unaffected by previous cesarean section [39]. Although extremely rare, uterine rupture in early pregnancy has been described [40].

4. Regimen

4.1. Dose/route of administration

The first choice is 800 μg administered by the vaginal route every 6, 12 or 24 h for a maximum of three doses. Three doses of 800 μg at 3-hourly intervals can also be used sublingually [22]. Moistening the tablets appears to slightly increase plasma levels [41], but no improvement in the clinical effects has been demonstrated [42]. Doses higher than 800 μg are not recommended due to increased side effects [43,44].

4.2. Course of treatment

Several studies carried out in developed and developing countries have shown that home administration of misoprostol is effective and safe up to 9 weeks since the last menstrual period. Most of those studies have been done using the combination of mifepristone and misoprostol [20,45–48] and only a few with misoprostol alone [8,27].

Prerequisites:
- Voluntary termination of the pregnancy and informed consent of the woman about her choices and the nature of the procedure.
- Backup arrangements for surgical abortion.
- Dating of gestational age and ruling out ectopic pregnancy according to local standards.
- If required by national guidelines, blood group and Rhesus factor should be determined and in cases where women are Rhesus negative, a dose of anti-D serum should be administered prior to treatment. However, there is currently little evidence to support that Rhesus factor isoimmunization occurs for pregnancies up to 63 days gestation [49,50].

Where resources are available, and depending on the clinical situation, the following tests may be useful:

- Hemoglobin, hematocrit and screening for STDs may also be provided depending on local prevalence and guidelines. In addition, serological tests to diagnose for syphilis, HIV and hepatitis B and C surface antigen may also be used.

5. Effectiveness

Despite the wide range of results from different studies and different regimens, the success rate, defined as a complete abortion, is around 90% during the first trimester of pregnancy (Table 1). Success depends on the length of the time interval between treatment and the assessment of the outcome.

Depending on the regimen used, pregnancy continues in 4% to 8% of women with gestational age of up to 63 days when vaginal misoprostol is used alone (Table 1).

5.1. Time to achieve effect

In the majority of cases, expulsion of the products of conception occurs hours after administration: close to 70% within the first 12 h [14,26,28], around 80% during the first 24 h, 95% within 48 h and further increases until at least 72 h after the initial dose [4,6,13,28,51]. However there may be a large variability depending on route, dose and time interval between misoprostol doses.

6. Effects and side effects

Prolonged or serious side effects are rare.

6.1. Bleeding

Vaginal bleeding during abortion induced with misoprostol is generally more intense than regular menstrual bleeding and is usually no different from that which occurs with a spontaneous abortion [45]. Although there may be great variations, there is typically menstrual-like or heavier bleeding for the first week and then spotting for an additional week. The mean pre- to post-abortion fall in hemoglobin varies between 0.2 and 1.0 g/dL (Table 2). Prolonged and intensive bleeding affects between 1% and 10% of women and may necessitate emergency surgical uterine evacuation, preferably with manual vacuum aspiration. The need for transfusion has been rarely reported (Table 2).

6.2. Cramping

Cramping usually starts within the first few hours and may begin as early as 30 min after misoprostol administration. The pain may be stronger than that experienced during a regular period and can be present in 80%–90% of women [22]. Non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesia can be used for pain relief without affecting the success of the method [11,52].

6.3. Fever and/or chills

Chills are a common side effect of misoprostol but are transient. Hyperthermia can be very severe [43] and more common with higher doses when the interval between doses is shorter or with oral or sublingual administration [3,22,52]. Fever does not necessarily indicate infection. An antipyretic can be used for relief of fever, if needed. If fever or chills persist beyond 24 h after taking misoprostol,

Table 2 Indicators of bleeding in clinical studies of misoprostol alone for first trimester abortion

Ref	(*n*)	Duration		Mean reduction in Hg	Excessive bleeding	Transfusion	Regime
		Bleeding (days)	Bleeding + spotting				
≤9 weeks							
[14]	(101)	–	–	0.4	–	0.0	200×4 °C/12 h
[14]	(133)	–	–	0.6	–	0.0	400×4 °C/ 12 h
[8]	(720)	7	14	0.3	2%	0.3	–
[9]	(100)	7		0.4	5%	0.0	800×2 °C/24 h
[10]	(75)	8.2		0.6	11% [a]	0.0	800×2 °C/24+1 day 8th
[23]	(80)	–	–	–	0%	0.0	800×3 °C/48 h
[4]	(125)	9.8	13	0.2	4.8 [b]	0.0	800×3 °C/24 h
8	(160)	–	14	–	–	1.2	800×3 °C/24 h
[27]	(452)	8.6	16	0.3	–	–	800×3 °C/8 h+600
[26]	(162)	8	16	1.0	1.2	–	800×3 °C/12 h
≥10 weeks							
[7]	(120)	–	–	0.6	0%	0.0	800×3 °C/24 h
[28]	(180)	6	13	0.4	1.1%	0.0	800×3 °C/12 h

[a] Hg<10.0 mg/dL.
[b] Decrease of ≥2 g/dl.

the woman may have an infection and should seek medical attention.

6.4. Nausea and vomiting

About 20% of women report pregnancy-related nausea and vomiting before treatment. These symptoms may increase after misoprostol administration. An anti-emetic can be used if needed, but symptoms will usually resolve within 2 to 6 h.

6.5. Diarrhea

Diarrhea may also occur following administration of misoprostol but should resolve within a day.

6.6. Fetal abnormalities

The risk of fetal abnormalities after misoprostol used early in pregnancy is probably very low [53–55], but women who do not abort after misoprostol, should have access to surgical abortion, if that is the woman's informed choice. Vacuum aspiration is the recommended option.

7. Follow-up

Women should be given simple instructions on how to recognize any complications that might require medical care.

Once administration of misoprostol has begun, women must have easy access to a health professional capable of answering their questions and providing them with assistance or hospital care. During the early first trimester, the possibility of ectopic pregnancy should be kept in mind.

Women must be informed that they will have bleeding and cramping as described above, and that they can use NSAIDs as required. The symptoms calling for clinical care include excessive bleeding, fever of more than 1 day and abdominal pain. Antibiotic treatment should be begun immediately if there is any suspicion of infection, although it is less frequent after medical than after surgical method of abortion [56,57].

Women should return for follow-up one or two weeks after the initial administration of the drug or earlier if they feel the need. A good clinical history and bi-manual exam should enable the provider to determine the absence of symptoms and that the uterus is firm and well involuted. In case of uncertainty a pregnancy test and ultrasound examination may be needed to confirm a complete expulsion. The usual urinary pregnancy tests may be positive for up to 4 weeks following the abortion as the pregnancy hormone hCG is excreted slowly from the body.

Those women who have not aborted within 72 h after the last dose should be given the option of a second course of misoprostol treatment or surgical abortion; they should be informed that their chances of success of the second course is around one in three [10,51]. If there is an urgent need to evacuate the uterus or if the woman is not prepared to accept a new attempt of treatment with misoprostol, she should be offered the alternative surgical abortion. There is clear evidence that vacuum aspiration is the preferred technique: both electric or manual vacuum aspirations are effective [58].

Women with incomplete abortion should be offered the choice of aspiration evacuation or misoprostol treatment with 600 μg of oral misoprostol if eligible [59].

7.1. Post abortion contraception

Women should be informed about immediate return to fertility, contraceptive methods, their characteristics, effectiveness and side effects, including their capacity to protect against sexually transmitted infections (STIs). After selection of the most appropriate method, that method should be provided as soon as possible [60,61].

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Conflict of interest

The authors do not have any conflict of interest.

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