Misoprostol for Obstetric and Gynecologic Uses: A Literature Review

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Overview

Misoprostol is a prostaglandin E\textsubscript{1} analog indicated for the prevention and treatment of gastric and duodenal ulcers resulting from long-term nonsteroidal anti-inflammatory drug use. Produced by Searle Pharmaceuticals under the product name Cytotec\textsuperscript{®}, misoprostol is available in more than 80 countries around the world (Searle, 1999). In the United States, the wholesale cost per 200-\textmu g tablet is approximately US$0.37 (1999 Physicians General Prescription).

Misoprostol is closely related to other prostaglandins such as dinoprostone, carboprost, gemeprost, and sulprofoste. While misoprostol’s effectiveness as an adjunct to mifepristone and methotrexate for medical abortion has been well established, the use of misoprostol alone for gynecological purposes has received comparatively little attention. Awareness of various misoprostol-only regimens—and their potential to decrease the incidence of septic abortions—appears to be increasing, however. In addition to the articles included in this report, several recent meeting reports—such as the Population Council’s Critical Issues in Reproductive Health (1998) and Towards Safe and Effective Use of Medical Abortion (1998), and the Center for Reproductive Health Research and Policy’s Manual Vacuum Aspiration in the Prevention and Treatment of Unsafe Abortion (1998)—have acknowledged that the use of misoprostol alone for early pregnancy termination merits additional evaluation.

Obstetric and gynecological applications for which misoprostol-only regimens are being evaluated include induction of first- and second-trimester abortion, treatment of miscarriage, cervical priming, induction of labor, and prevention and management of postpartum hemorrhage. Among the key advantages of misoprostol for these indications are its effectiveness, low cost, stability (tablets have a shelf life of several years at room temperature), accessibility, and potential to lead to safer reproductive health outcomes than currently used therapies. Investigators from Asia, Africa, Europe, Latin America, the Middle East, and North America have shown a strong interest in increasing the awareness and understanding of the appropriate use of this drug, and women themselves have reported highly positive experiences with misoprostol-only medical abortion regimens (Carbonell et al., 1999).

Despite the enthusiasm for misoprostol use for these indications, the off-label use of misoprostol, particularly for induced abortion, has been marked by controversy in countries in which abortion is restricted or illegal. In 1985, when the drug came before the Advisory Committee of the USFDA for approval, one reviewer noted that misoprostol’s gastrointestinal effects were overshadowed by its abortifacient effects, and he cautioned the medical community about the potential for misuse by
pregnant women. Soon after, the use of the drug as an abortifacient was reported in Brazil, where the absence of legal abortion and the availability of Cytotec without restrictions in drugstores and pharmacies resulted in widespread use for self-induced abortion. In 1991, Brazilian authorities issued extensive restrictions on misoprostol sales and use.

Interest in misoprostol and its potential to reduce the complications of unsafe abortion and other gynecological and obstetric conditions remains strong around the world, especially for developing countries. However, appropriate administration guidelines—including information about individual and total doses, dosing intervals, administration routes, and duration of treatment—are lacking for each potential indication. Physicians, women, and pharmacists need clear and uniform guidelines; in many cases, pharmacists may be the primary information source for women attempting to induce abortion with misoprostol. Such guidelines should include information about potential adverse effects. In particular, women and clinicians should be aware that use of misoprostol may be associated with significant pain, excessive bleeding, and, if unsuccessful, teratogenic effects. Determination of appropriate guidelines and increased information dissemination will help ensure the successful use of misoprostol during abortion, postabortion, and perinatal care.

This document reviews 100 articles that investigate the efficacy and safety of misoprostol used for first- and second-trimester abortion, cervical priming, induction of labor, and postpartum hemorrhage, as well as absorption kinetics, safety and teratogenicity, and experiences with misoprostol use in developing countries. These articles were identified through MEDLINE, PubMed, Ovid, Cochrane, and Internet searches for misoprostol-only regimens for obstetric and gynecological indications; articles that addressed the mifepristone-misoprostol regimen were excluded from this review (except in relation to some misoprostol-specific issues). The first edition of this review, which reflected the majority of the literature review and analysis, was completed in March 2000. In April 2001, the document was updated to include key documents that had been published in the intervening year.

Because misoprostol has a range of obstetric and gynecological uses, this review has been divided into 12 sections. Each section includes an overview of the section’s topic, brief descriptions of relevant articles, and supporting tables as appropriate. An alphabetical index of articles is provided at the end of the document.
Review/General Articles

These nine articles provide useful information about misoprostol and medical abortion. Most of the articles provide general overviews of the wide range of misoprostol’s uses, and highlight its usefulness for low-resource settings. The articles by Pollack and Pine (2000), Winikoff et al. (1996), and the consensus statement published by the Population Council provide an important context for these and other medical abortion studies.

This commentary reviews the documented obstetric/gynecological benefits of misoprostol as well as the difficulties inherent to deciphering the available data. The authors note that regimens used in clinical trials are difficult to compare and often cumbersome for women. They also cite a lack of data on pharmacokinetics as well as observed differences in the success rates of various regimens. These issues prompt the authors to ask, “How good is good enough?” They call for more thorough assessments of misoprostol’s benefits (e.g., success rates, easy access, and increased privacy) and risks (including treatment failure, side effects, and the possibility of incomplete abortions or ongoing pregnancies). They suggest that acceptability may increase by improving misoprostol’s benefits, reducing its risks, or both. The authors conclude that simplified misoprostol regimens, including self-administration, should be evaluated. They also recommend that researchers identify reasons for the differences in reported success rates and develop a coherent research strategy for the future.

This document provides a comprehensive review of the use of misoprostol for obstetric and gynecological purposes over the last 15 years. The author reviews misoprostol’s effectiveness as an agent for cervical priming before a surgical abortion, and as a cervical primer before hysteroscopy and endometrial biopsy. The article discusses misoprostol’s use as an effective agent alone or as an adjunct to mifepristone or methotrexate for medical first- and second-trimester pregnancy termination. It also describes misoprostol’s potential effectiveness for
treatment of incomplete or inevitable abortion, prevention and treatment of postpartum hemorrhage, induction of fetal death in all trimesters, and cervical ripening and labor induction after viability. The author notes that use of misoprostol is associated with tachysystole/hypertension and uterine rupture, especially for patients with a previous uterine scar. Because misoprostol is stable, inexpensive, and easily stored, the author describes it as an inexpensive lifesaving alternative to other prostaglandins and oxytocics in low-resource settings. On the other hand, he notes, its medically unsupervised and unregulated use as an abortifacient has created obstacles to its acceptance worldwide. The author concludes that, as the only inexpensive oral prostaglandin alternative, misoprostol has found widespread use in the clinical practice of obstetrics and gynecology in the developed and developing world.

This article provides a thorough review of studies evaluating the use of misoprostol in pregnancy. Using U.S. Preventive Service Task Force guidelines to grade the strength of their recommendations, the authors review the pharmacokinetics, mechanism of action, dosage, efficacy, and safety of misoprostol in pregnant women. The authors first review misoprostol’s use during the first trimester. Given the inconsistency of complete-abortion rates when vaginal misoprostol is used alone, particularly in light of safe alternative regimens, they conclude that misoprostol cannot be recommended for medical abortions in the first trimester. In the case of early failed pregnancy or embryonic death, the authors conclude that 800 μg of misoprostol administered vaginally once or twice (with the second dose given 24 hours after the first) is effective in evacuating the uterus. The authors conclude that misoprostol is not recommended for the treatment of inevitable or incomplete abortion, due to low success rates and decreases in hemoglobin concentrations. For cervical ripening in the first trimester, the authors state that 400 μg of vaginal misoprostol given three to four hours before suction curettage is the best regimen. Comparing data for abortion during the second trimester is more difficult. The authors conclude that the optimal regimen has not been determined, but they state that 200 to 600 μg of misoprostol given vaginally every 12 hours, or 400 μg given vaginally every 3 hours, successfully induces labor in the second trimester. During the third trimester, available data suggest that the best dose for inducing of labor with misoprostol is 25 μg given vaginally every
four to six hours. In cases of induction of labor with fetal death at term, a dose as low as 50 µg
given every 2 hours may be adequate. The authors note that misoprostol should not be used to
induce labor in women with uterine scars due to several reports of uterine rupture. In their
discussion of misoprostol use for treatment of postpartum hemorrhage, the authors state that there
currently is insufficient evidence to support the routine use of misoprostol when oxytocin or
methylergonovine is available, but misoprostol may lower the incidence of postpartum
hemorrhage if these drugs are not readily available. In their conclusion, the authors state that
misoprostol is one of the most important medications in obstetrical practice, and that more than
200 studies involving a total of more than 16,000 pregnant women support its continued use.

Contemporary Ob/Gyn September 1997;42(9)157-164.
This review article summarizes results of clinical studies in which misoprostol has been used
alone or as an adjunct to another drug or surgical procedure for induction of abortion. It reviews
the mechanism of action (cervical effacement and uterine contractions by an as-yet
underdetermined mechanism), use alone during the first trimester (concluding that the maximum
effectiveness of vaginal administration is about 66%), and use alone during the second trimester
(during which time it is much more effective; effectiveness rates approach 100%). The article
also reviews misoprostol use in conjunction with other drugs for medical abortion (the
mifepristone-misoprostol combination is very effective for terminating pregnancies at less than 9
weeks’ gestation, and the methotrexate-misoprostol combination also offers an effective
alternative to surgical abortion or medical abortion with mifepristone for pregnancies of less than
9 weeks’ gestation) and as an adjunct to surgical abortion in the first trimester (both oral and
vaginal misoprostol are effective for surgical dilation prior to first-trimester surgical abortion,
with the vaginal administration of 600 µg of misoprostol as effective as vaginal administration of
1 mg of gemeprost). Results of an evaluation of misoprostol use after spontaneous abortion also
are discussed; in one study, the need for curettage was avoided in 60% of women. The author
also reviews congenital malformations associated with misoprostol failures, noting that instances
of unusual skull malformation and limb deficiencies with or without Mobius sequence
(congenital facial paralysis) have been associated with misoprostol use during the first trimester.

This commentary re-positions the safety and efficacy of medical abortifacients such as misoprostol within an international context. The authors argue that rather than comparing the safety of misoprostol to the medically supervised use of abortifacients in legal settings, misoprostol use should be compared to unsafe abortion methods performed in illegal settings. In this respect, medical abortifacients such as misoprostol can be seen to reduce maternal morbidity and mortality, both because their cervical ripening effects can reduce the complications of subsequent surgical interventions, and because the complications associated with misoprostol use are significantly lower than the rates of infection, blood transfusions, and physical injuries (such as tears and perforations) associated with other methods. The authors also revisit assumptions pertaining to efficacy, as they argue that many incomplete or “failed” medical abortions ultimately are successes because they enables women to gain access to legal medical services of reasonable quality, which enable them to terminate unwanted pregnancies without serious harm to themselves. The authors conclude that the public health community must work to enhance the quality of services that can be legally and legitimately provided through mainstream service-delivery systems in order to strengthen the medical safety net available to unsupervised users of medical abortifacients. The combination of broader knowledge and use of medical abortifacients with accessible postabortion services will save lives and enable women to terminate their pregnancies without serious harm.


This consensus statement of researchers, health care providers, women’s health advocates, donors, and representatives of Ministries of Health affirms that medical abortion (mifepristone-prostaglandin) can be delivered in a manner that is safe, effective, and acceptable for women in developing countries. Introduction by governments is urged in order to respond to women’s desire for this method and to avoid emergence of a black market for medical abortifacients. The statement indicates that medical abortion services can be used safely even in the most basic settings, as long as back-up care is available in case of complications or method failure. The
article states that medical abortion techniques are well suited to provision by nonphysician health workers who are appropriately trained. While ultrasonography can facilitate clinical assessments, it is not essential for the provision of safe medical abortion. The authors note that the mifepristone-misoprostol regimen is consistently safest, most effective, and easiest to use during the earliest durations of pregnancy. It also is safe and effective at gestations of 57 to 63 days since last menstrual period (LMP), although less so. An alternative, the mifepristone-gemeprost regimen, has no decline in efficacy at 57 to 63 day LMP. In their conclusion, the authors state that medical abortion methods may offer a critical improvement in women’s health even if optimal conditions are not present. Additional research is needed to establish appropriate service delivery strategies.

7. Scheepers HCJ, van Erp EJM, van den Bergh, AS. Use of misoprostol in first and second trimester abortions: a review. Obstetrical and Gynecological Review 1999; 54:592-600. This review examines 76 articles that refer to misoprostol, whether used alone or with mifepristone and methotrexate. A review of nine studies on cervical priming before surgical abortion finds that the different dosages and routes of administration used make comparisons difficult, but concludes that 400 to 600 μg of vaginal misoprostol administered four hours before surgery seems to be the preferred method. The authors review three studies of misoprostol used alone for first trimester pregnancy termination (Bugalho et al., 1996; Creinin and Vittinghoff, 1994; and Carbonell et al., 1997) and conclude that results are not very promising. They review ten studies of misoprostol used alone for second-trimester termination, and state that the usual dose of 100 to 200 μg of misoprostol to terminate second-trimester pregnancy seems inadequate; they suggest that either a higher dose or combination with methotrexate and mifepristone might be preferable. The authors also review the literature on side effects, safety, and teratogenicity.

8. Templeton A. Misoprostol for all [commentary]. British Journal of Obstetrics and Gynaecology 1998; 105:937-939. After stating that few drugs have been as enthusiastically received by obstetricians and gynecologists as misoprostol, this commentary (which accompanies the Zalanyi and Slade articles in this issue) briefly chronicles misoprostol’s history—from FDA review in 1985 to demonstration of its abortifacient potential in 1987 to present uses of the drug. The author
acknowledges that misoprostol has several therapeutic uses, including induction of labor, first- and second-trimester induced abortion, evacuation of the uterus following miscarriage, postpartum hemorrhage, and cervical dilation. The article notes that misoprostol has a shelf life of several years at room temperature, is easily stored and transported, and has an extremely low cost. It also states that the uterus becomes progressively more sensitive to the drug with advancing gestation, noting that single doses of 400 µg to 800 µg are therapeutic in the first trimester following mifepristone, while doses of 50 µg or even 25 µg can be used for the induction of labor. The author notes that, in the UK, gemeprost has been the main prostaglandin used for cervical preparation prior to surgical abortion, but that there is increasing interest in the use of misoprostol, which has been shown in several randomized studies to have comparable efficacy to gemeprost. Acknowledging that issues such as the optimum route, dose, and time of administration remain undetermined, the author states that a vaginal dose of 400 µg is better than 200 µg at gestations of 7 to 11 weeks, and that the added benefit or risk of higher doses (such as the 600 µg to 800 µg doses recommended by 1997 RCOG guidelines) are unclear. When given orally, the therapeutic effect of misoprostol occurs in <12 hours due to rapid absorption and swift onset of action. Where surgical abortions are being performed, misoprostol has established itself as one of a range of effective dilation options, and its place for other reproductive indications will become clearer in the near future.


Although this article does not focus on misoprostol-only regimens, it provides an important context for evaluating medical abortion failures. Stating that the differences between medical and surgical abortion preclude analogous definitions and comparisons of failure rates, the authors propose that failures in medical abortion be defined as surgical interventions performed for any reason. Additionally, the authors recommend that failures be classified into three types: those attributable to user choice, provider choice or error, and true drug failures. There are several reasons why the definition of failure rate is important in describing the probability of success. It can guide the women’s choice of methods; help the clinicians determine whether the medical methods are suitable in their settings; help clinics track performance; and help compare and refine new methods of medical abortion. The authors argue that true biological failure rates (drug
failure rates) are not yet known, but are lower than failure rates found in the literature published to date (perhaps as low as 2% for mifepristone and misoprostol). Furthermore, the proposed classification of failure contrasts with clinical protocols, which often limit waiting time or set other restrictions.
**Misoprostol Alone for First-Trimester Abortion**

This section reviews 13 articles that evaluate misoprostol-only regimens for first-trimester abortion; in nearly all of these articles, the investigators evaluate the effects of misoprostol tablets that have been administered vaginally. As Blanchard et al. note in their 1999 *Contraception* article, studies of misoprostol-only approaches to first-trimester abortion differ significantly in study design, population, and regimens. Total dosages and efficacy rates vary tremendously (see Table 1 on pages 20 through 22). The oft-cited study by Norman et al. (1991) indicated that misoprostol-only approaches to first-trimester abortion achieve effectiveness rates of only 5%; doses in this study, however, were small and administered orally. More recent studies of 800-μg doses administered vaginally and repeated several times have achieved complete abortion in 85% to 94% of cases. Side effects such as nausea, vomiting, pelvic pain, and, in some cases, severe blood loss appear to be more common with the higher doses and shorter administration intervals. The 800-μg vaginal regimen has emerged as the most successful approach to misoprostol-induced first-trimester abortion.

The majority of women who abort after misoprostol administration do so after the first dose. Some women require repeat doses, which have been administered at 24-hour intervals in several of these studies. As Carbonell et al. (1999) demonstrated, reducing dosing intervals from 24 to 12 hours does not improve efficacy. It is important to note that, with the exception of Norman et al. (1991), investigators in each of these studies relied on ultrasound to detect any unexpelled uterine contents; they then administered repeat doses if necessary. Determining the need for repeat doses, particularly in circumstances without access to ultrasound services, is an important consideration for service delivery.

Additionally, many of the studies listed in this section were of relatively short duration, and the decision to proceed with surgical abortion often was made within 12 to 24 hours of the final misoprostol dose. As a result, these studies may not reflect the complete effects (and side effects) of misoprostol treatment. Performing surgical evacuation of cases that failed to fully abort by a pre-determined deadline, for example, may have limited investigators’ opportunity to observe longer-term side effects and/or complications such as excessive bleeding.

In most of these studies, misoprostol tablets were administered by health care personnel, although four of the five studies by Carbonell et al. evaluated self-administered regimens. The studies by Ngai et al. (2000) and Harwood and Mishell (2000) discuss the beneficial effect on efficacy that water may have when placed on the misoprostol tablets just prior to administration.

This article reviews eight English-language studies of the use of misoprostol alone for early pregnancy termination. (Descriptions of these studies follow in this section.) The authors note that the efficacy rates demonstrated by the same total dose differ among studies, perhaps due to varying definitions of success, varying time to measurement of outcome, and varying duration of pregnancy of study participants. The authors state that, despite the differences in study design, the evidence suggests that a vaginal regimen (as opposed to an oral regimen) could greatly improve access to safe medical abortion services by women in developing countries. They note, however, that two significant problems exist. First, vaginal regimens are complex (in all but one of the studies they evaluate, the drug was administered by health care personnel; the number of doses ranged from two to seven and administration intervals ranged from 4 to 48 hours; repeated vaginal ultrasounds were required; and women had to remain recumbent for a significant period of time). Second, the side effects (pelvic pain and cramping comparable to the mifepristone-misoprostol regimen) might prove intolerable for some women. The authors state that while little information about oral misoprostol-only regimens is available, the oral regimen would be easier to administer, easier to register with drug regulatory bodies (since the toxicology and safety data already on file for misoprostol’s ulcer treatment/prevention indications could be relevant), and more acceptable to women. They recommend investigating the potential of an oral regimen and making efforts to simplify promising vaginal regimens; they note that reducing the number of doses and the need for vaginal ultrasounds would be vital to use in developing countries. The authors conclude that the misoprostol-only regimen holds promise but that more research is needed.


This study compared the efficacy of two misoprostol-only regimens among women of two different pregnancy duration ranges in Maputo, Mozambique. The first regimen was 200 µg (one tablet) of misoprostol administered vaginally every 12 hours for a total of 800 µg; the second regimen was 400 µg of misoprostol administered vaginally every 12 hours for a total of 1600 µg.
Both regimens were tested in women with pregnancy duration of 5 to 7 and 8 to 11 weeks from their LMP. In all cases, women underwent a surgical abortion 48 hours after the initiation of treatment if the abortion was not complete, or if the woman experienced heavy bleeding at any time during the study period. Success rates (defined as no embryonic tissue in the uterine cavity observable by vaginal sonography) for the 200-μg regimen were 19% for the 5- to 7-week group (n=45) and 25% for the 8- to 11-week group (n=57). For the 400-μg groups, the success rates were 37% for the 5- to 7-week group (n=87) and 30% for the 8- to 11-week group (n=46). Total rates of abortion (complete and partial) were 46% for the 5- to 7-week group and 45% for the 8- to 11-week group receiving 200 μg, and 55% for the 5- to 7-week group and 67% for the 8- to 11-week group receiving 400 μg. The authors reported that 71% of the women in the 200-μg group and 75% of the women in the 400-μg group experienced lower abdominal pain. In addition, women in both dose groups (200 μg, 400 μg) reported the following side effects: nausea (19%, 20%) vomiting (6%, 11%), diarrhea (7%, 6%), and fatigue (12%, 12%) within 12 hours after misoprostol administration. (Description adapted from Blanchard’s 1999 Contraception article.)


A total of 141 women in Havana, Cuba, with pregnancies <70 days LMP each self-administered up to three "main" doses of 800 μg vaginal misoprostol at 48-hour intervals. Tablets were moistened with a few drops of water before insertion, and women were instructed to remain recumbent for 3 hours after misoprostol administration. Women also were given additional doses of misoprostol depending upon the amount of "remains" present in the uterus, as determined by ultrasound. For "large" amounts of remains (occupying >50% of the uterine cavity) women received 600 μg vaginal misoprostol every 12 hours for up to two doses; for "moderate" amounts of remains (occupying 25% to 50% of the uterine cavity) women received one additional dose of 600 μg vaginal misoprostol; and for "small" amounts of remains (occupying <25% of the uterine cavity) women received one additional dose of 400 μg misoprostol vaginally. Unfortunately, details as to which women received additional doses were not presented and, therefore, total dose administered is not available. Details of when success was determined also were not presented. The rate of success (defined as the nonsurgical evacuation of the products of conception,
including (1) complete abortion with remains and (2) incomplete abortion with different amounts of remains which were expelled with the additional misoprostol doses) reported was 94%. Side effects reported included nausea (24%), vomiting (25%), diarrhea (58%), dizziness (21%), headache (13%), fever (35%), chills (57%), and pelvic pain (93%). The authors reported that success varied by participants’ duration of pregnancy, and that success among women with pregnancies <9 weeks LMP was 96%, compared with 83% for women with pregnancies >9 weeks LMP. (Description adapted from Blanchard’s 1999 *Contraception* article.)


A total of 175 women in Havana, Cuba, with pregnancies ≤63 days LMP self-administered up to three "main" doses of 800 µg vaginal misoprostol, repeating the initial 800-µg dose at 48 and 96 hours if needed. Women in this study received "additional" doses of misoprostol based on the amount of remains present in the uterus (see previous discussion regarding treatment of remains). Participants were instructed to cleanse the vagina with boiled water the night before each misoprostol administration, and to remain recumbent for 3 hours once the misoprostol tablets had been inserted. A surgical abortion was performed within 48 hours of a failed final dose, or 6 days after the initiation of misoprostol administration. The success rate (defined as the nonsurgical evacuation of the products of conception, including (1) complete abortion with remains and (2) incomplete abortion with different amounts of remains which were expelled with the additional misoprostol doses) reported was 92%, and women experienced the following side effects: nausea (21%), vomiting (26%), diarrhea (58%), dizziness (12%), headache (15%), fever (30%), chills (54%), and pelvic pain (93%). (Description adapted from Blanchard’s 1999 *Contraception* article.)


Also in Havana, 120 women with pregnancies of 64 to 84 days LMP received up to three "main" doses of 800 µg misoprostol administered vaginally by health care personnel, and "additional" doses were administered based on the amount of remains in the uterus (see previous discussion
regarding treatment of remains). The main doses of misoprostol were administered every 24 hours, and tablets were moistened before insertion. Women were asked to remain recumbent for 3 hours after misoprostol administration. Surgical abortion was performed within 24 hours of a failed final "main" dose of misoprostol, a maximum of 4 days after the initiation of treatment, and success rates are described as "immediate." The success rate reported was 87%. Side effects reported included the following: nausea (22%), vomiting (17%), diarrhea (54%), dizziness (25%), headache (19%), fever (26%), chills (72%), and pelvic pain (99%). (Description from Blanchard’s 1999 Contraception article.)

Also in Havana, 720 women with pregnancies of 35 to 63 days were trained to self-administer, at home, up to three doses of 800 µg (four 200-µg tablets) by the vaginal route. Participants were instructed to cleanse the vagina with boiled water the night before each misoprostol administration, and to remain recumbent for 3 hours once the misoprostol tablets had been inserted. If no abortion occurred or the abortion was incomplete, patients were instructed to self-administer an additional 800-µg dose every 24 hours up to a maximum of three “main” doses. If ultrasound indicated that the gestational sac was present or the abortion was incomplete 24 hours after the third dose, the treatment was considered a failure and patients were offered surgical abortion. An additional 600-µg dose was administered to subjects who had a complete abortion; the investigators did not indicate why this final dose was administered. Complete abortion (passage of the fetus and placenta) occurred in 89% of women. Of these, 65% aborted after the first dose, 18% aborted after the second dose, and 6% aborted after the third dose. Side effects were nausea (24%), vomiting (23%), diarrhea (50%), dizziness (15%), headache (11%), fever (18%), chills (50%), rashes (0.8%), and pelvic pain (96%). Thirty-three (5%) of the 720 women had a clinically significant decrease in hemoglobin (between 1.0 and 2.0 g/dL); of these, two were medical emergencies requiring blood transfusion. Nine patients received antibiotic therapy because of septic complications.

A total of 180 women in Havana, Cuba, with pregnancies of 64 to 91 days self-administered 800 µg of vaginal misoprostol every 12 hours for a maximum of three doses. Participants were instructed to moisten the tablets with two to three drops of saline solution before each misoprostol administration, and to remain recumbent for 3 hours once the misoprostol tablets had been inserted. Women with complete abortion (as determined by ultrasound) received one additional dose of 600 µg (reason not specified). Failure was defined as the recourse to surgical abortion, which was performed on the third day of the study if needed. Successful abortion occurred in 85% of subjects; 64% aborted after the first dose, 13% aborted after the second dose, and 8% aborted after the third dose. The median dose of misoprostol administered was 1780 µg (range: 140 to 3000 µg). Side effects included nausea (16%), vomiting (17%), diarrhea (54%), dizziness (16%), headache (13%), fever (14%), chills (28%), and pelvic pain (94%). The results from a post-study patient questionnaire indicated that 90% of the women would use the method again in the future should they need it. The authors noted that reducing the dosage intervals from 24 hours to 12 hours between main doses did not improve efficacy.

Creinin MD, Vittinghoff E. **Methotrexate and misoprostol vs. misoprostol alone for early abortion: a randomized controlled trial.** *Journal of the American Medical Association* 1994;272:1190-1195.

In this study, conducted in San Francisco, participants with pregnancies ≤56 days LMP were randomized to receive either methotrexate and misoprostol, or misoprostol alone. Women who received only misoprostol (n=30) were given an initial dose of 800 µg misoprostol vaginally. The dose was repeated after 24 hours if the woman had not yet aborted (37% received a second dose). Final success rates were determined 14 days after the initiation of treatment, at which time a surgical abortion was performed if there was observable cardiac activity or if β-hCG was increasing. Of the women, 47% had complete abortions, 27% had ongoing pregnancies, and 27% had incomplete abortions. Side effects reported included diarrhea (18%) and nausea and vomiting (5%). The authors conclude that the misoprostol-only regimen was less effective than misoprostol used in conjunction with methotrexate, which achieved complete abortion in 90% of cases. (Description from Blanchard’s 1999 *Contraception* article.)

Thirty women with pregnancies ≤56 days LMP were given a maximum of two doses of 800 μg misoprostol vaginally. Women received a second dose if a gestational sac was present 24 hours after the first administration of misoprostol. Misoprostol tablets were covered with a 3-mL NaCl solution after being placed in the posterior fornix of the vagina, and women remained recumbent for 30 minutes after misoprostol administration. Of the study participants, 97% had complete abortions. The mean decrease in hemoglobin was 0.1 g/dL, and 76% experienced bleeding of <7 days' duration. (Description from Blanchard’s 1999 Contraception article.)


This study was conducted in Los Angeles, California, among women with pregnancies ≤10 weeks LMP. Four different misoprostol-only regimens were explored in 33 women: 200 μg misoprostol administered vaginally every 8 hours for a maximum total dose of 1200 μg (n=10); an initial dose of 400 μg vaginally followed by 200 μg vaginally every 8 hours for a maximum total dose of 1400 μg (n=3); an initial dose of 400 μg vaginally followed by 200 μg every 4 hours for a maximum total dose of 1200 μg (n=15); and an initial dose of 400 μg orally followed by 400 μg vaginally every 8 hours for a maximum total dose of 1600 μg (n=5). Suction curettage was performed 12 hours after the last dose if there was no passage of the products of conception, if there was incomplete expulsion, or if the woman experienced heavy bleeding. Success rates reported were 50% for the vaginal regimen based on a 200-μg initial dose, 1200-μg total dose, and 8-hour administration interval; 100% for the vaginal regimen based on a 400-μg initial dose, 1400-μg total dose, and 8-hour administration interval regimen; 60% for the vaginal regimen based on a 400-μg initial dose, 1200-μg total dose, and 4-hour administration interval regimen; and 60% for the oral/vaginal regimen based on a 400-μg initial oral dose, 1600-μg total dose, and 8-hour administration interval. The overall success rate was 61%. Side effects, reported for all four groups combined, were nausea (9%), vomiting (5%), diarrhea (5%), and fever (4%).

(Description adapted from Blanchard’s 1999 Contraception article.)

This randomized study investigated the efficacy of misoprostol and water versus misoprostol alone for first-trimester abortion in women at ≤9 weeks of gestation. In group 1 (n=40), women received 800 µg of vaginal misoprostol on days 1, 3, and 5; each misoprostol tablet was moistened with three drops of water. In group 2 (n=40), women received the same misoprostol regimen without water applied to the tablets. Transvaginal ultrasound was performed in all women on day 15. Women who did not require vacuum aspiration before the return of their first menstrual period were classified as having had a complete abortion. The complete abortion rate appeared higher in group 1 (85%, 95% CI 70-94%) than in group 2 (65%, 95% CI 48-79%), but the difference did not reach statistical significance. The authors note that 70% of women in both groups passed the tissue mass after the second misoprostol dose, and a further 10% passed the tissue mass after the third dose. Nausea and vomiting were common in both groups, but these side effects were well tolerated. In their discussion, the authors conclude that the use of misoprostol alone, with or without water, is not recommended for medical abortion up to 9 weeks of pregnancy because of the high failure rate and low acceptability by patients, and that additional studies focusing on medical abortion up to 7 weeks are warranted.


In this letter, the authors object to three conclusions made in the article by Ngai et al. First, they question the conclusion that there is no statistically significant difference in efficacy between the water-and-misoprostol group versus the misoprostol-only group. Citing results of earlier studies that demonstrated a difference in effectiveness, they state that a greater number of subjects would be needed to determine statistical significance, which would likely be demonstrated. Second, they object to Ngai et al.’s conclusion that an efficacy rate of 85% is not clinically acceptable, both because mifepristone-misoprostol regimens have demonstrated only slightly higher efficacy rates, and because this efficacy rate may be clinically acceptable in areas of the world where mifepristone and surgical abortion are not available. Third, the authors comment that Ngai et al.’s acceptability data did not report acceptability by method group, gestational age, or success rates. In their conclusion, the authors cite prior data that support the safety, efficacy, and acceptability...
of moistened vaginal misoprostol for inducing abortion of gestations of 7 or less weeks. [In their reply to this letter, Ngai et al. maintain their conclusions regarding lack of statistical significance and low efficacy, and provide additional acceptability data.]


This small study (n=40) contains information on a potential oral regimen of misoprostol for medical abortion. The researchers compared a mifepristone-misoprostol medical abortion regimen (200 mg mifepristone followed by varying doses of misoprostol 48 hours later) with a single dose of 400 µg oral misoprostol among women with pregnancies <56 days measured LMP. The study also included an examination of the physical effects (uterine pressure) of the same dose of oral misoprostol alone. Although the authors did find a significant effect of oral misoprostol on uterine contractility, the success rate they report for the single-dose misoprostol-only group was only 5%. In this group, 21 women experienced some bleeding in the 7 days after misoprostol administration, but only two had complete abortions. This 400-µg dose is small compared with the total doses used in the various vaginal regimens (see Table 1), and unfortunately this study does not include information on the efficacy of increased oral doses and varying administration schedules. (Adapted from Blanchard’s 1999 *Contraception* article.)
<table>
<thead>
<tr>
<th>Author, Date, and Location</th>
<th>Sample Size</th>
<th>Gestational Age</th>
<th>Success Rate</th>
<th>Maximum Total Dose/Each Dose</th>
<th>Details of Regimen</th>
<th>Side Effects</th>
<th>Initiation of Back-up Surgical Abortion (if needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norman, Thong, and Baird (1991); Lothian, Scotland</td>
<td>40</td>
<td>&lt;56 days</td>
<td>5% complete abortion</td>
<td>400 µg</td>
<td>ORAL: single dose</td>
<td>Abdominal pain (35%), diarrhea/vomiting (2.5%)</td>
<td>7 days</td>
</tr>
<tr>
<td>Creinin and Vittinghoff (1994), San Francisco, US</td>
<td>30</td>
<td>≤56 days</td>
<td>47% complete abortion</td>
<td>1600 µg/800 µg</td>
<td>VAGINAL: 800 µg repeated 24 h later if no abortion</td>
<td>Diarrhea (18%), nausea and vomiting (5%)</td>
<td>14 days unless no cardiac activity and no increase in βHCG, in which case women were monitored weekly.</td>
</tr>
<tr>
<td>Bugalho, Faundes, Jamisse, Usfa, Maria, and Bique (1996), Maputo, Mozambique</td>
<td>Ia: 45</td>
<td>Ia: 5-7 wk</td>
<td>Ia: 19% complete abortion</td>
<td>Ia &amp; Ib: 800 µg/200 µg IIa &amp; IIb: 1600 µg/400 µg</td>
<td>VAGINAL: 200 µg every 12 h or 400 µg every 12 h</td>
<td>Ia &amp; Ib: nausea (19%), vomiting (6%), diarrhea (7%), and fatigue (12%)</td>
<td>Surgical abortion performed 48 h after initiation of treatment, or if women experienced heavy bleeding.</td>
</tr>
<tr>
<td>Koopersmith and Mishell (1996), California, US</td>
<td>I: 10 II: 3 III: 15 IV: 5</td>
<td>≤10 wk</td>
<td>I: 50% complete abortion</td>
<td>I: 1200 µg/200 µg II: 1400 µg/1x 400 µg, 5x200 µg III: 1200 µg/1x 400 µg IV: 200 µg/400 µg IV: 1600 µg/400 µg</td>
<td>I: VAGINAL: 200 µg every 8 h II: VAGINAL: initial dose of 400 µg followed by 200 µg every 8 h VAGINAL: initial dose of 400 µg followed by 200 µg every 4 h IV: ORAL/VAGINAL: initial dose of 400 µg orally, plus 400 µg vaginally every 8 h</td>
<td>Nausea (9%), vomiting (5%), diarrhea (5%), and fever (4%)</td>
<td>Suction abortion 12 h after last dose if no passage of products of conception, incomplete expulsion, or heavy bleeding.</td>
</tr>
<tr>
<td>Carbonell, Varela, Velazco, and Fernandez (1997), Havana, Cuba</td>
<td>141</td>
<td>&lt;70 days</td>
<td>94% complete or partial abortion</td>
<td>2400 µg/800 µg (plus “additional” 600-µg doses if “remains” were detected)</td>
<td>VAGINAL: 800 µg main dose self-administered every 48 h</td>
<td>Nausea (24%), vomiting (25%), diarrhea (58%), dizziness (21%), headache (13%), fever (35%), chills (57%), and pelvic pain (93%)</td>
<td>Time not specified.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Author, Date, and Location</th>
<th>Sample Size</th>
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<th>Maximum Total Dose/Each Dose</th>
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<th>Side Effects</th>
<th>Initiation of Back-up Surgical Abortion (if needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonell, Varela, Velazco, Fernandez, and Sanchez (1997), Havana, Cuba</td>
<td>175</td>
<td>≤63 days</td>
<td>92% complete abortion</td>
<td>2400 μg/800 μg (plus “additional” 600-μg doses based on amount of “remains”)</td>
<td>VAGINAL: 800 μg self-administered, repeated at 48 and 96 h</td>
<td>Nausea (21%), vomiting (26%), diarrhea (58%), dizziness (12%), headache (15%), fever (30%), chills (54%), and pelvic pain (93%)</td>
<td>6 days (surgical abortion was performed within 48 hours of failed 3rd dose).</td>
</tr>
<tr>
<td>Carbonell, Varela, Velazco, Cabezas, Tanda, and Sanchez (1998), Havana, Cuba</td>
<td>120</td>
<td>64-84 days</td>
<td>87% complete abortion</td>
<td>2400 μg/800 μg (plus “additional” 600-μg doses based on amount of “remains”)</td>
<td>VAGINAL: 800 μg every 24 h administered by health care personnel</td>
<td>Nausea (22%), vomiting (17%), diarrhea (54%), dizziness (25%), headache (19%), fever (26%), chills (72%), and pelvic pain (99%)</td>
<td>4 days (surgical abortion was performed within 24 h of failed 3rd dose).</td>
</tr>
<tr>
<td>Jain, Mishell, Mekstroth, Lacarra (1998), Los Angeles, US</td>
<td>30</td>
<td>≤56 days</td>
<td>97% complete abortion</td>
<td>1600 μg/800 μg</td>
<td>VAGINAL: One 800-μg dose followed by second 800-μg dose at 24 h if needed</td>
<td>Not specified</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Carbonell Esteve, Varela, Velazco, Tanda, Cabezas, Sanchez (1999), Havana, Cuba</td>
<td>720</td>
<td>35-63 days</td>
<td>89% complete abortion</td>
<td>2400 μg/800 μg (women who aborted also received an “additional” 600-μg dose)</td>
<td>VAGINAL: 800 μg self-administered, repeated at 48 and 96 h; an additional 600-μg dose was administered to subjects who had a complete abortion.</td>
<td>Nausea (24%), vomiting (23%), diarrhea (50%), dizziness (15%), headache (11%), fever (18%), chills (50%), rashes (0.8%), and pelvic pain (96%).</td>
<td>4 days (surgical abortion was performed 24 h of failed 3 dose).</td>
</tr>
<tr>
<td>Carbonell, Varela, Velazco, Tanda, Sanchez (1999), Havana, Cuba</td>
<td>180</td>
<td>64-91 days</td>
<td>85% complete or partial abortion</td>
<td>2400 μg/800 μg (women who aborted also received an “additional” 600-μg dose)</td>
<td>VAGINAL: 800 μg self-administered, repeated at 12 and 24 h; an additional 600-μg dose was administered to subjects who had a complete abortion.</td>
<td>Nausea (16%), vomiting (17%), diarrhea (54%), dizziness (16%), headache (13%), fever (14%), chills (28%), and pelvic pain (94%)</td>
<td>Cases that failed to abort had surgical abortion performed on the 3rd day of the study.</td>
</tr>
</tbody>
</table>

(continues)
<table>
<thead>
<tr>
<th>Author, Date, and Location</th>
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<th>Initiation of Back-up Surgical Abortion (if needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ngai, Tang, Chan, Ho (2000), Hong Kong</td>
<td>I: 40 II: 40</td>
<td>≤63 days</td>
<td>I. 85% complete abortion II. 65% complete abortion</td>
<td>2400 µg/800 µg</td>
<td>VAGINAL: I. 800 µg on days 1, 3, 5; three drops of water placed on each tablet. II. 800 µg on days 1, 3, 5; no water.</td>
<td>Nausea and vomiting common. Uterine cramps (66%), fatigue (50%), breast tenderness (20%).</td>
<td>If ultrasound showed pregnancy on day 15, vacuum aspiration was performed.</td>
</tr>
</tbody>
</table>

* “Complete abortion” refers to abortions that were completed with misoprostol alone; “partial abortion” refers to abortions that were induced by misoprostol and completed with another procedure determined by the investigator.
Misoprostol Alone for Second-Trimester Abortion

The uterus is increasingly sensitive to misoprostol as gestation advances. Therefore, success rates for second-trimester abortion presented in the following nine articles generally are higher than those observed during the first trimester, even with lower misoprostol dosages (see Table 2 on pages 29 and 30). In Jain and Mishell’s 1999 study, vaginal misoprostol regimens based on initial doses of 200 µg and total doses of 600 µg have been associated with “success” rates approaching 90% (43% were complete abortions and 46% were partial abortions). Bugalho et al. (1993) recommend using dosages no greater than 400 µg in pregnancies greater than 15 weeks’ gestation, as the severity of side effects and risk of uterine hypercontractility (i.e., frequent and painful uterine contractions) have increased with higher doses. After evaluating three different dosages, Herabutya and O-Prasertsawat (1998) concluded that a 600-µg regimen (in which 600-µg doses are administered vaginally every 12 hours) is most effective for second-trimester abortion, but associated with more side effects than 200-µg or 400-µg regimens. Misoprostol-only regimens have been demonstrated to be as effective as PGE₂ (Jain, 1994) and at least as effective as gemeprost (Wong, 1998; Wong 1996). The two articles by Jain et al. (1999) and Jain and Mishell (1994) also demonstrate that misoprostol is more effective for terminating pregnancies involving dead rather than live fetuses. As is the case with misoprostol use during the first-trimester, both vaginal and oral misoprostol regimens used during the second trimester are associated with side effects such as nausea, vomiting, and pelvic pain. The occurrence and intensity of these side effects rise with increasing dosages and decreasing time between doses.

It is important to note that these studies varied in their definitions of “success.” Many include complete abortions as well as partial abortions in the overall success rate; wherever possible, success rates for both outcomes have been provided. In addition, the interval between misoprostol administration and determination of success varied considerably among trials.

This study evaluated oral doses of 200 µg oral misoprostol in 42 patients with intrauterine complicated pregnancies (intrauterine exitus, fetal abnormality, anembryonic pregnancy, anhydramnios, other) of 14 to 28 weeks (mean: 19 weeks). All patients received an initial dose of 200 µg misoprostol. If no contractions or bleeding were observed, supplementary doses of 200 µg
misoprostol were given once an hour, with an average total dose of 1000 µg administered (range: 200 to 1200 µg). Successful abortion was defined as the complete termination of pregnancy within 2 days after the first or second misoprostol dose. Abortion was induced in 92.9% of women; 59.6% had complete abortion and 33.3% had partial abortion within 48 hours. The mean time to expulsion was 9 hours. After expulsion of the fetus and fetal membranes, curettage was performed in all cases. Side effects included diarrhea (28.6%), abdominal pain (16.7%), and nausea and vomiting (14.3%).


In Maputo, Mozambique, 132 women with pregnancies of 11 to 22 weeks (mean: 14 weeks) received a dose of 800 µg of misoprostol vaginally. If there was no cervical maturation or softening at 18 hours, a supplementary dose of 400 µg was administered. If the cervix remained unaffected at 24 hours, another supplementary dose of 400 µg was given. Women who did not respond at 56 hours after the first application were considered nonresponders (8.3%) and received curettage. A total of 106 (80.3%) women received only the initial dose (800 µg) of misoprostol before abortion occurred. Four of these women were subsequently excluded from the trial due to family or social problems; all of the remaining 102 women aborted upon treatment with the single dose. Twenty-six (19.6%) women received 1200 to 1600 µg of misoprostol. Of these, 11 (8.3%) did not respond and were considered failures. The mean time to expulsion was 15 hours. With all dosages combined, 88.6% of women achieved expulsion of the fetus without curettage. After expulsion, all women received curettage. The major side effect reported was pain requiring paracetemol in 20%.


In Mozambique, 169 women with pregnancies between 12 and 23 weeks (mean: 14 weeks) were treated with vaginal misoprostol. The initial dose was 800 µg for 121 women, but subsequently was reduced to 600 µg for 10 women, 400 µg for 28 women, and 200 µg for 10 women. The dose was repeated 24 hours later if abortion had not occurred or was not in progress. Medical abortion
(defined as evacuation of the fetus and placenta) was obtained in 91.1% of women. Of these, 101 (66%) aborted after the initial dose. The study did not assess the proportion of abortions that were complete. The mean time from initial dose to expulsion was 14.3 hours. Side effects other than abdominal pain (5%) were not observed. Follow-up vacuum aspiration of the uterine cavity was carried out in all subjects. Although the authors did not provide information about the success rates for the different initial doses, they recommend that doses greater than 400 µg should not be used in pregnancies greater than 15 weeks’ duration due to the risk of uterine hypercontractility (i.e., frequent and painful uterine contractions).


In Havana, 151 women with pregnancies from 85 to 105 days (mean: 14 weeks) received 800 µg of vaginal misoprostol every 24 hours for a maximum of three doses. Misoprostol tablets were moistened prior to insertion. Patients were instructed to remain fully recumbent for 3 hours after administration. Women with complete or incomplete abortion received one additional dose of 600 µg every 12 hours for up to two complete doses (reason not specified). Abortion was induced in 121 (80%) of subjects; 101 (67%) women aborted after the first dose, 18 (12%) women aborted after the second dose, and two (1%) women aborted after the third dose. Of the 121 cases classified as successes, 103 (85%) were complete abortions (defined as simultaneous passage of the fetus and placenta) and 18 (15%) were classified as incomplete abortions (defined as having remains which were expelled after another dose of misoprostol). The mean time to expulsion was 9 hours. Thirty women (20%) needed surgical evacuation. Side effects included nausea (23%), vomiting (22%), diarrhea (32%), dizziness (11%), headache (20%), fever (32%), chills (59%), rashes (1%), and pelvic pain (95%), which was treated with paracetemol. In a post-treatment patient questionnaire, 89% of participants indicated that they would use the method again if needed.


Three misoprostol dosing regimens were evaluated in 151 women in Bangkok, Thailand. Three
dosages (200 μg, 400 μg, and 600 μg) were administered and followed by repeat doses of the same size every 12 hours for up to 48 hours. Fifty-one women were placed on the 200-μg regimen (mean gestation: 19 weeks), 50 women were placed on the 400-μg regimen (mean gestation: 19 weeks), and 50 women were placed on the 600-μg regimen (mean gestation: 18.7 weeks). The treatment was considered a failure if abortion had not been induced within 48 hours. At 48 hours, the induced abortion rate was 70.6% for the 200-μg group, with a mean expulsion time of 45 hours; 82% for the 400-μg group, with a mean expulsion time of 33 hours; and 96% for the 600-μg group, with a mean expulsion time of 22 hours. The mean total dose required to induce abortion was 416.7 μg in the 200-μg group, 772.8 μg in the 400-μg group, and 1296 μg in the 600-μg group, with a mean expulsion time of 33 hours. The incidence of side effects (nausea/vomiting, diarrhea, fever) increased as the dosage increased, while the incomplete abortion rate declined from 35.3% to 22%. The investigators concluded that the 600-μg regimen is a more effective abortifacient for second-trimester abortion in terms of the 48-hour success rate and the rate of incomplete abortion, but was associated with more side effects.

28. Jain J, Kuo J, Mishell D. A comparison of two dosing regimens of intravaginal misoprostol for second-trimester pregnancy termination. Obstetrics and Gynecology 1999;93:571-575. This study compared the efficacy of vaginal administration of 200 μg of misoprostol either every 6 or every 12 hours for up to 48 hours. One hundred women at 12 to 22 weeks’ gestation were evaluated. Treatment failure was defined as failure of abortion (complete or partial) to occur within 48 hours after administration of the initial misoprostol dose or severe side effects that were unrelieved by medications. Within 6 hours of expulsion, the uterine cavity of each patient was curetted. The incidence of abortion induction within 48 hours of first administration was 87.2% in the 6-hour group and 89.2% in the 12-hour group; the rates of complete abortion (defined as simultaneous passage of the fetus and placenta) were 43.9% and 33.3% for the 6-hour and 12-hour groups, respectively. The mean abortion intervals were 13.8 hours and 14.0 hours from initiation of treatment, respectively. The incidence of side effects (fever, vomiting, diarrhea, severe pain) was higher but not statistically significant (P>.05) in the 6-hour group than in the 12-hour group. The authors concluded that shortening the dosing interval from 12 hours to 6 hours produced no significant benefit. In their discussion, the authors also consolidated the result of this trial with two earlier trials conducted at their institution to draw statistically valid conclusions.
They found that misoprostol is less effective for terminating pregnancies involving live fetuses than those involving dead fetuses.


This randomized study compared the safety and efficacy of 200 μg of misoprostol, administered vaginally every 12 hours, and 20 mg of PGE₂ (dinoprostone), administered vaginally every 3 hours, in 55 women with pregnancies of 12 to 22 weeks (mean: 17 weeks). Treatment failure was defined as failure of abortion to take place within 24 hours after the initial medication or the occurrence of systemic adverse events that could not be relieved with medications. Within 24 hours, the rate of successful abortion induction was 89% in the misoprostol group (n=28) and 81% in the PGE₂ group (n=27). The rate of complete abortion (defined as simultaneous passage of the fetus and placenta) was 43% in the misoprostol group and 32% in the PGE₂ group. Within 38 hours, 100% of women receiving misoprostol had aborted; the mean time to expulsion was 12 hours. The mean number of PGE₂ doses was 3.7 and the mean number of misoprostol doses was 1.4. In both groups, women who had an intrauterine fetal death aborted earlier than those with a live fetus. Certain side effects (pyrexia, uterine pain, vomiting, and diarrhea) were more frequent in group receiving PGE₂.


The authors report on two cases in which vaginal administration of misoprostol was used to terminate one 18-week and one 26-week pregnancy. In the first case, a total of three 200-μg tablets were inserted over a 6-hour period. In the second case, two 200-μg tablets were inserted in a 3-hour period. In both cases, misoprostol successfully terminated the pregnancy.


One hundred forty women with pregnancies of 14 to 20 weeks received either 400 μg vaginal
misoprostol or 1 mg vaginal gemeprost every 3 hours for a maximum of five doses in the first 24 hours. Women who failed to abort 24 hours after initiation of treatment were given a second course of misoprostol or gemeprost at the same dosage schedule. Within 24 hours, 80% of the misoprostol group (n=70) and 58.6% of the gemeprost group (n=70) had aborted. The abortion was complete (defined as the fetus and placenta being expelled without operative assistance) in 60% of the misoprostol cases and 58.6% of the gemeprost cases. An additional 11.4% of women in the misoprostol group and 12.9% of women in the gemeprost group aborted after another course. The median induction-abortion time was 14.1 hours for the misoprostol group and 19.5 hours for the gemeprost group. When the patients were divided into primigravidas and multigravidas, the rate of successful abortion within 24 hours was significantly higher in the primigravidas using misoprostol when compared with gemeprost (83.3% vs. 55.3%). The median total amount of misoprostol used was 1600 μg, and the median total amount of gemeprost used was 5 mg. The incidence of side effects was approximately equal among the two groups except for diarrhea, which was more common in the gemeprost group, and fever, which was more common in the misoprostol group.
Table 2. Studies of Misoprostol-Only Regimens for Second-Trimester Abortion*

<table>
<thead>
<tr>
<th>Author, Date, and Location</th>
<th>Sample Size</th>
<th>Gestational Age</th>
<th>Success Rate</th>
<th>Maximum Total Dose/Each Dose</th>
<th>Details of Regimen</th>
<th>Side Effects</th>
<th>Management of Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bugalho, Bique, Almeida, Bergstrom (1993), Maputo, Mozambique</td>
<td>132</td>
<td>11-22 weeks (mean: 14 weeks)</td>
<td>88.6% complete abortion</td>
<td>1600 µg/800 µg</td>
<td>VAGINAL: Initial dose of 800 µg followed by additional dose of 400 µg at 18 hours and 400 µg at 24 hours if needed</td>
<td>Pain requiring analgesia (20%)</td>
<td>Women who did not respond (8.3%) at 56 hours received curettage. All women received curette after expulsion.</td>
</tr>
<tr>
<td>Bugalho, Bique, Almeida, Faundes (1993), Maputo, Mozambique</td>
<td>169</td>
<td>12-23 weeks (mean: 14 weeks)</td>
<td>91.1% complete abortion</td>
<td>1600 µg/800 µg or 1200 µg/600 µg or 800 µg/400 µg or 400 µg/200 µg</td>
<td>VAGINAL: Initial dose of 800 µg, 600 µg, 400 µg, or 200 µg followed by repeat dose 24 hours later if needed</td>
<td>Abdominal pain (5%)</td>
<td>Vacuum aspiration was performed in 10 treatment failures after 48 hours. All women received preventive vacuum aspiration of the uterus after treatment.</td>
</tr>
<tr>
<td>Jain, Mishell (1994), Los Angeles</td>
<td>28</td>
<td>12-22 weeks (mean: 17 weeks)</td>
<td>43% complete; 46% partial at 24 hours; 100% success at 38 hours</td>
<td>600 µg/200 µg</td>
<td>VAGINAL: 200 µg every 12 hours for 24 hours</td>
<td>Fever (11%), uterine pain (57%), severe pain (4%), vomiting (4%), diarrhea (4%)</td>
<td>Failure defined at 24 hours. All 3 failures got additional 200 µg dose and delivered within 38 hours. All women received curettage within 6 hours after expulsion. Women with partial or incomplete abortions were given oxytocin, manual removal, then curettage as needed.</td>
</tr>
<tr>
<td>Batioglu, Tonguc, Haberal, Celikkcanat, Bagis (1997), Turkey</td>
<td>42</td>
<td>14-28 weeks (mean: 19 weeks)</td>
<td>59.6% complete; 33.3% partial at 48 hours</td>
<td>1200 µg/200 µg</td>
<td>ORAL: Initial dose of 200 µg followed by 200 µg once each hour if no contraction or bleeding occurred. Maximum dose of 1200 µg.</td>
<td>Diarrhea (28.6%), abdominal pain (16.7%), nausea and vomiting (14.3%)</td>
<td>Surgical abortion carried out in women who did not abort despite a second day’s administration.</td>
</tr>
<tr>
<td>Carbonell, Valera, Velazco, Tanda, Sanchez (1998), Havana, Cuba</td>
<td>151</td>
<td>85-105 days</td>
<td>68% complete; 12% partial</td>
<td>2400 µg/800 µg (plus “additional” 600-µg doses if “remains” were detected)</td>
<td>VAGINAL: 800 µg every 24 h</td>
<td>Nausea (23%), vomiting (22%), diarrhea (32%), dizziness (11%), headache (20%), fever (32%), chills (59%), rashes (1%), and pelvic pain (95%)</td>
<td>Surgical abortion was performed if patient did not respond to 3rd dose, which was administered 2 days after the first dose.</td>
</tr>
</tbody>
</table>

(continues)
<table>
<thead>
<tr>
<th>Author, Date, and Location</th>
<th>Sample Size</th>
<th>Gestational Age</th>
<th>Success Rate</th>
<th>Maximum Total Dose/Each Dose</th>
<th>Details of Regimen</th>
<th>Side Effects</th>
<th>Management of Treatment Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herabutya, O-Prasertsawat (1998), Bangkok, Thailand</td>
<td>I: 51 II: 50 III: 50</td>
<td>2nd trimester mean I: 19 wk II: 19 wk III: 18.7 wk</td>
<td>I: 35.3% complete; 35.3% partial II: 54.0% complete; 28.0% partial III: 74.0% complete; 22.0% partial</td>
<td>I: 800 μg/200 μg II: 1600 μg /400 μg III: 2400 μg/600 μg</td>
<td>VAGINAL: I: Either 200 μg, II: 400 μg, or III: 600 μg in 12-hour intervals up to 48 hours</td>
<td>Nausea/vomiting (3.9%), nausea/vomiting (12%), diarrhea (6%), Fever (2%) Nausea/vomiting (20%), diarrhea (22%), Fever (28%)</td>
<td>If abortion had not occurred in 48 h, women were continued with misoprostol unless cervical dilation was at least 2 cm, in which case IV oxytocin at incremental dosages was started. If the abortion failed to occur at 96 h, prostaglandin E2 gel or sulprostone were used at the discretion of the investigators. If the placenta was not completely out 1 hour after fetus, the procedure was classified as incomplete and curettage performed.</td>
</tr>
<tr>
<td>Wong, Ngai, Wong, Tang, Ho (1998), Hong Kong</td>
<td>70</td>
<td>14-20 weeks</td>
<td>60% complete; 20% partial</td>
<td>2000 μg/400 μg e</td>
<td>VAGINAL: 400 μg every 3 h for a maximum of 5 doses in the first 24 h Compared with Gemeprost</td>
<td>Nausea (24.3%), vomiting (20.0%), dizziness (21.4%), fatigue (14.3%), breast tenderness (4.3%), diarrhea (24.3%), headache (20.0), fever (50.0)</td>
<td>Women were given a second course if they failed to abort in 24 h; evacuation of the uterus was performed if placenta was found to be incomplete.</td>
</tr>
<tr>
<td>Jain, Kuo, Mishell (1999), Los Angeles, USA</td>
<td>100</td>
<td>12-22 weeks</td>
<td>I: 43.9% complete; 43.3% partial II: 33.3% complete; 55.9%</td>
<td>I: 1800 μg /200 μg II: 1000 μg/200 μg</td>
<td>VAGINAL: I: 200 μg every 6 hours for up to 48 hours II: 200 μg every 12 hours for up to 48 hours</td>
<td>Fever (26%), vomiting (9%), diarrhea (2%), moderate uterine pain (49%), severe pain (17%) II. fever (8%), moderate uterine pain (49%), severe pain (8%)</td>
<td>Women who did not abort within 48 hours received one or more IM injections of Hemabate (carboprost) every 2 hours or had D&amp;E. All women were curetted within 6 hours regardless.</td>
</tr>
</tbody>
</table>

* “Complete abortion” refers to abortions that were completed with misoprostol alone; “partial abortion” refers to abortions that were induced by misoprostol and completed with another procedure determined by the investigator.
Misoprostol for Spontaneous Abortion or Complicated Pregnancy

The studies described in this section evaluate the potential for low-dose misoprostol regimens to induce—and in some cases complete—the evacuation of retained products of conception in women with spontaneous abortion. Three studies (Chung et al., 1995; Chung et al., 1997; and Chung et al., 1999) showed that use of misoprostol for management of spontaneous abortion averted over 50% of surgical interventions even when used for only 24 hours. In addition, a randomized trial of 354 women conducted by Chung et al. (1997) demonstrated that extending oral misoprostol treatment from 24 to 48 hours enables an additional 30% of women to complete an abortion. In their 1997 study, Creinin et al. showed that a 800-μg regimen (in which 800-μg doses were administered vaginally and repeated in 24 hours) is far more effective during the first trimester than an oral regimen based on 400-μg doses. De Jonge et al. (1995) found that an oral 400-μg dose resulted in successful evacuations in only 13% of women. Table 3 (page 37) provides additional information about regimens, success rates, and side effects. Side effects included nausea, vomiting, diarrhea, and pain.

A large, randomized trial demonstrated that the successful use of misoprostol for these applications enables women and clinicians to reduce the short- and long-term risks inherent to curettage (Chung et al., 1999). Although the risks associated with surgery and anesthesia are infrequent, they can be serious. Potential complications include hemorrhage, infection, uterine adhesions, and cervical trauma. Infections resulting from curettage also have been implicated in elevated rates of secondary infertility and other long-term effects (Ballagh, 1998). In addition to the health benefits of noninvasive approaches, misoprostol-only regimens offer significant cost-savings over traditional surgical methods. Misoprostol also appears to be at least as effective as gemeprost (Chung et al., 1995).

There are no studies comparing misoprostol with expectant management, in which women would be able to go home and wait—in some cases for up to a week—for her abortion to resolve. It is possible that if studies were performed in which the waiting time after misoprostol administration was longer (the studies listed below extend only to 48 hours) and women were able to go home before completing their abortion, the success rate may be higher.

This article provides a history of the management of spontaneous abortion. Since the late 1800s, the practice of immediate curettage has been the standard approach to miscarriage. The authors argue, however, that the risks associated with curettage are no longer justified for all women with uncomplicated, incomplete spontaneous abortion. They discuss two recent randomized trials that suggest that, in settings where abortion is legal, expectant management is as good—perhaps better—an option compared to immediate surgery in incomplete spontaneous abortion. Instead, conservative management—either expectant (observational) or medical management with misoprostol, sulprostone, gemeprost, and mifepristone—should be considered a viable alternative that may reduce the incidence of perforations and infections. The authors believe that medical management will prove to be the most appropriate treatment for uncomplicated spontaneous incomplete abortion in the future.

33. Chung THK, Cheung LP, Leung TY, Haines CJ, Chang AMZ. Misoprostol in the management of spontaneous abortion. *British Journal of Obstetrics and Gynecology* 1995;102:832-835. Conducted in Hong Kong, this study evaluated 252 women with a mean gestation of 9 weeks (range: 6 to 18 weeks) who presented with spontaneous abortion. Of the 141 women who had evidence of retained products of conception and were treated with misoprostol (400 μg orally every 4 hours for a total of three doses), 62% did not require surgical evacuation of the uterus. There was no significant difference in infection rates between the women who were treated with misoprostol alone (infection rate: 3%) compared with women who required curettage after treatment with misoprostol (infection rate: 4%) or those who were discharged without needing any treatment (infection rate: 3%). Three women treated with misoprostol had prolonged bleeding and 11 had irregular bleeding for 3 or more months. There was one case of molar pregnancy. Side effects other than bleeding were minor. The authors conclude that the avoidance of curettage in more than 60% of women represents a large cost savings and worthwhile benefit. They note that results with misoprostol appear to be superior to those obtained with gemeprost.

34. Chung TKH, Lee DTS, Cheung LP, Haines JC, Chang AMZ. Spontaneous abortion: a randomized, controlled trial comparing surgical evacuation with conservative management using misoprostol. *Fertility and Sterility* 1999;71(6):1054-1059. Also conducted in Hong Kong, the effectiveness of routine surgical evacuation and the
effectiveness of medical evacuation using misoprostol were compared in 635 women who spontaneously aborted. Women randomized to misoprostol (n=321; mean gestational age of 10.7 weeks) were given 400 µg of misoprostol every 4 hours up to a total dose of 1200 µg. Evacuation was performed if the uterus was not empty (based on transvaginal ultrasound) by 24 hours. Approximately 50% of the misoprostol group subsequently required surgical evacuation. Women treated with misoprostol had significantly more blood loss and required significantly more analgesia than women in the surgical group. The evacuation group had a significantly shorter hospital stay. The incidence of immediate/short-term complications and major complications in 6 months after treatment were significantly lower in the misoprostol group than in the surgical evacuation group. Side effects, particularly gastrointestinal, were common in the misoprostol group, but seldom severe.


This study evaluated the effect of extending misoprostol treatment of spontaneous abortion to a maximum of 48 hours. In Hong Kong, 354 women presented with spontaneous abortion; 225 had retained products of conception and were treated with misoprostol (up to three 400-µg doses per day administered orally) for up to 48 hours. Of the 214 women who completed treatment, 107 (50%) had complete evacuation of their uterus within 24 hours and 149 (69.6%) had complete evacuation within 48 hours of misoprostol treatment. Six women (2.8%) experienced complications (including one ectopic pregnancy, three cases of continued bleeding requiring curettage, and two pelvic infections). In contrast, 6.6% of women managed with surgical evacuation experienced short-term complications. The authors note that 27% of women treated with misoprostol required some form of analgesia, including 12% who required intramuscular narcotics. In their conclusion, the authors state that the 48-hour oral regimen can easily be adapted to the vaginal route of administration, which some studies have associated with a lower incidence of side effects.

This small, randomized, non-blinded prospective U.S. study compared 400 µg oral with 800 µg vaginal misoprostol in 20 women with early pregnancy failure for gestations of 8 weeks or less. All women presented with a closed cervix. Women in the oral regimen (n=12) received an initial dose of 400 µg misoprostol and women in the vaginal regimen (n=8) received an initial dose of 800 µg. The dose was repeated on the second day if ultrasound determined that the gestational sac was still present. Suction curettage was offered to women after 3 days if complete uterine evacuation had not occurred. Misoprostol was successful in three (25%) of the 12 women in the oral group and seven (88%) of the eight women in the vaginal group. None of these women had incomplete abortion requiring curettage, although one had tissue removed from the cervix. Side effects (nausea, vomiting, diarrhea) occurred in eight (67%) of women in the oral group and seven (88%) of women in the vaginal group. The authors conclude that vaginal administration of 800 µg misoprostol is the more effective regimen, and may be an effective alternative to D&C.


This South African study was conducted to compare the efficacy and morbidity of medical and surgical management of incomplete miscarriage. Fifty women with gestations of less than 14 weeks were randomized to receive either 400 µg of misoprostol orally (n=23) or surgical evacuation (n=27). A pelvic examination and, if needed, pelvic ultrasound were performed 12 hours after misoprostol administration. Only 3 (13%) of the women who received misoprostol had successful evacuations, compared with 26 (97%) of women in the surgical group. Women in the misoprostol group experienced a significant drop in hemoglobin concentration. The authors conclude that while medical management of incomplete miscarriage can help meet the needs of women in developing countries, the results of this study did not confirm the efficacy of a single 400-µg dose of oral misoprostol in completing the expulsion of retained products of conception.

A total of 84 women with first-trimester complicated pregnancy (intrauterine death, blighted ovum pregnancy, missed abortion, or other; 9.4 ± 2.1 weeks of gestation) were treated with an initial oral dose of 200 µg misoprostol. If no contractions or bleeding were observed, supplementary doses of 200 µg were given once an hour. The average total dose was 1000 µg (range: 200 µg to 1000 µg). Within 48 hours of initial treatment, 11.9% of women had complete abortions, 83.3% had partial abortions, and four (4.8%) did not abort. Residual uterine contents in the 83.3% of patients with incomplete abortion were surgically evacuated; the authors state that morbidity was decreased in these women due to the cervical priming effect of the misoprostol. There were no major complications, and side effects (nausea, vomiting, diarrhea) were minor. All women received curettage.


The authors compared the effects of 200 µg vaginal misoprostol against a placebo administered the day before a scheduled D&C in 84 women with missed abortions of 8 to 19 weeks’ gestation (mean: 12 to 14 weeks). In the misoprostol group (n=42), 83.3% began to spontaneously abort prior to the scheduled procedure, which was completed in all cases. In the placebo group, 17.1% began to spontaneously abort. Two women in the misoprostol group required intramuscular pethidine for pain; no other side effects were reported.


Women with missed abortion up to 13 weeks LMP were treated with moistened tablets of 200 µg vaginal misoprostol every 4 hours to a total dose of 800 µg or expulsion of the gestational sac. Treatment was successful (defined as complete emptying of the uterus checked by ultrasound) in 22 (88%) of the 25 women within 10 hours. Five (20%) aborted after one dose, 13 (52%) aborted after the second dose, and four (16%) aborted after the third dose. The mean induction-abortion time was 6.1 hours. The remaining three women did not abort even after the fourth dose and were treated with surgical evacuation. Additionally, one woman required curettage for heavy bleeding after the gestational sac was expelled. The authors recommend a maximum dose of 600 µg, as
there were no complete abortions after the application of higher doses or after 10 hours of observation.
<table>
<thead>
<tr>
<th>Author, Date, and Location</th>
<th>Sample Size</th>
<th>Gestational Age</th>
<th>Success Rate</th>
<th>Maximum Total Dose/Each Dose</th>
<th>Details of Regimen</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung, Cheung, Leung, Haines, Chang (1995), Hong Kong</td>
<td>141</td>
<td>Mean: 9 weeks (range: 6-18)</td>
<td>62% complete abortion</td>
<td>1200 µg/400 µg</td>
<td>ORAL: 400 µg every 4 hours for a total of 3 doses</td>
<td>Nausea/vomiting (1.4%), diarrhea (2.1%), dizziness (0.7%), fever (9.2%), transient hypotension (0.7%)</td>
</tr>
<tr>
<td>De Jonge, Makin, Manefeldt, De Wet, Pattinson (1995), South Africa</td>
<td>23</td>
<td>&lt;14 weeks</td>
<td>13% complete abortion</td>
<td>400 µg</td>
<td>ORAL: single dose of 400 µg</td>
<td>Significant drop in hemoglobin concentration</td>
</tr>
<tr>
<td>Haberal, Celikkanat, Batioglu (1996), Ankara, Turkey</td>
<td>84</td>
<td>Mean: 9.4 ± 2.1 weeks</td>
<td>11.9% complete abortion; 83.3% partial abortion</td>
<td>1200 µg/200 µg</td>
<td>ORAL: initial dose of 200 µg followed by supplementary doses of 200 µg per hour</td>
<td>Most common: nausea and vomiting (28.6%), diarrhea (19%), moderate vaginal bleeding (3.8%) Less common: abdominal flatus, hypotension, fever, headache, abdominal pain</td>
</tr>
<tr>
<td>Chung, Leung, Cheung, Haines, Chang (1997), Hong Kong</td>
<td>225</td>
<td>Not stated</td>
<td>Within 24 h: 50% complete; Within 48 h: 69.9% complete abortion</td>
<td>2400 µg/400 µg</td>
<td>ORAL: 400 µg up to three times per day for up to 48 hours</td>
<td>Pain requiring analgesia (27%); other side effects not listed.</td>
</tr>
<tr>
<td>Creinin, Moyer, Guido (1997), Pittsburgh, USA</td>
<td>20 (12 oral and 8 vaginal)</td>
<td>≤8 weeks</td>
<td>Oral group: 25% complete; Vag. group: 88% complete abortion</td>
<td>Oral: 800 µg/400 µg Vaginal: 1600 µg/800 µg</td>
<td>ORAL: 400 µg per day for up to 2 days; VAGINAL: 800 µg per day for up to 2 days</td>
<td>Oral: nausea (50%), vomiting (25%), diarrhea (42%) Vaginal: nausea (63%), vomiting (13%), diarrhea (38%)</td>
</tr>
<tr>
<td>Herabutya, O-Prasertsawat (1997), Bangkok, Thailand</td>
<td>42</td>
<td>8-19 weeks (mean: 12.6 weeks)</td>
<td>83.3% aborted before curettage; 45.7% had less than 10 µg of POC obtained by curettage</td>
<td>200 µg</td>
<td>VAGINAL: 200 µg the day before a scheduled D&amp;C</td>
<td>Pain requiring analgesia (5%)</td>
</tr>
<tr>
<td>Zalanyi (1998), Keszthely, Hungary</td>
<td>25</td>
<td>Mean: 11.2 ± 4.34 LMP</td>
<td>88% complete abortion</td>
<td>800 µg/200 µg</td>
<td>VAGINAL: 200 µg repeated every 4 h to a total dose of 800 µg or expulsion of gestational sac</td>
<td>Heavy bleeding requiring curettage (4%)</td>
</tr>
<tr>
<td>Chung, Lee, Cheung, Haines, Chang (1999)</td>
<td>321</td>
<td>Mean: 10.7 ± 2.5 weeks</td>
<td>50% complete abortion</td>
<td>1200 µg/400 µg</td>
<td>ORAL: 400 µg every 4 hours for up to a total of 3 doses</td>
<td>Diarrhea (8%), nausea (22%)</td>
</tr>
</tbody>
</table>
**Misoprostol for Pre-abortion Cervical Priming**

Mechanical cervical dilation is a leading cause of complications related to uterine evacuation, including uterine perforation, cervical laceration, incomplete evacuation, and excessive bleeding. Citing these risks, the authors of these studies evaluated the effects of misoprostol for pre-abortion cervical priming. Singh et al. (1997, 1999, 1999), Fong et al. (1998), and MacIsaac et al. (1999) demonstrate that 400 µg of misoprostol administered vaginally 3 hours prior to evacuation is the optimal regimen, resulting in dilation in nearly all first-trimester abortion cases included in their studies. Positive results also were obtained with 600-µg regimens (El-Refaey et al., 1994) and, to a lesser degree, 200-µg regimens (Henry and Haukkamaa, 1999). These results imply that the need for provider skill in mechanical dilation could be reduced by the use of misoprostol for pre-evacuation priming. It is important to note that all of these studies evaluated the effects of misoprostol on first-trimester pre-abortion priming; dosages and intervals would likely vary for other gestation periods.


This study evaluated misoprostol and gemeprost as cervical priming agents prior to surgical abortion in women with pregnancies of 9 to 13 weeks. Women were randomized to receive either 600 µg of vaginal misoprostol (n=30), 1 mg of vaginal gemeprost (n=30), or no treatment (n=30). The baseline dilation, the cumulative force required to dilate the cervix up to 9 mm, and blood loss were significantly different between the control and treatment groups, but not between the two treatment groups. Misoprostol administration led to an increase in the baseline cervical dilation, reduction of the mechanical force required to dilate the cervix, and reduction of blood loss (mean of 148 mL, compared with a mean of 233 mL in the control group). These results were comparable to those obtained with gemeprost, a widely used prostaglandin. Histochemical evaluation also demonstrated that the cervical changes induced by both drugs were similar in nature and degree. The authors conclude that vaginal administration of misoprostol and gemeprost offers clear therapeutic benefit and negligible side effects.
42. Fong YF, Singh K, Prasad RN. A comparative study using two dose regimens (200 µg or 400 µg) of vaginal misoprostol for pre-operative cervical dilatation in first trimester nulliparae. *British Journal of Obstetrics and Gynaecology* 1998;105:413-417. Conducted in Singapore, this prospective, double-blind, randomized study evaluated the effects of 200-µg and 400-µg doses of misoprostol administered vaginally for pre-operative cervical dilation. This study, and those of Singh et al. that follow, define a “successful” cervical dilation as at least 8 mm. Seven (23.3%) of 30 women in the 200-µg group achieved a dilation of ≥8 mm, compared with 29 (96.7) of women in the 400-µg group. The mean cervical dilation was 6.4 mm for the 200-µg group and 8.2 mm for the 400-µg group. The investigators also compared 3-hour and 4-hour administration intervals among women in the 400-µg group. High success rates (93.3% and 100%, respectively) were observed in both groups, but more women in the 4-hour group experienced side effects (such as vaginal bleeding and abdominal pain) and had passage of products of conception at the os; only the incidence of women experiencing abdominal pain was statistically significant. The authors conclude that vaginal administration of 400 µg of misoprostol and an administration interval of 3 hours is the optimal regimen for pre-operative cervical dilation of 8 mm before vacuum aspiration in first-trimester nulliparae.

43. Henry A-M and Haukkamaa M. Comparison of vaginal misoprostol and gemeprost as pre-treatment in first trimester pregnancy interruption. *British Journal of Obstetrics and Gynaecology* 1999;106:540-543. This randomized, prospective trial compared the effectiveness of 200 µg of vaginal misoprostol with 1 mg vaginal gemeprost in the pre-treatment of women undergoing first-trimester abortion. Ninety-five women received misoprostol and 93 received gemeprost. The tablets were placed in the fornix; misoprostol tablets also were moistened with citric acid before insertion. The primary outcome measure of the study was cervical dilation, as measured with Hegar dilators. The average cervical dilation was 7.1 in the misoprostol group and 6.7 mm in the gemeprost group (not a statistically significant difference). The average pre-treatment time was 4 hours 47 minutes in the misoprostol group and 3 hours and 40 minutes in the gemeprost group. The decision to pre-treat women with misoprostol for a longer period was based on reports in the literature about the length of time needed for
cervical priming with this drug. The misoprostol group was found to have a lower incidence of nausea and diarrhea; statistically significant differences were not found for the other side effects measured (pain, vomiting, blood in the vagina, and bleeding more than usual during the termination). The authors conclude that misoprostol is as effective and safe as gemeprost for pre-treatment for first-trimester abortion, but results in fewer side effects.

This blinded trial compared pre-abortion cervical dilation in three arms: 400 µg of oral misoprostol (45 women), 400 µg of vaginal misoprostol (47 women) and laminaria (14 women). Double-blinding was achieved for the two misoprostol arms, but only researchers were blinded in the laminaria group, as clients were informed about the insertion of the laminaria. The primary outcome was cervical dilation measured by Pratt dilators after 4 hours of exposure to the dilating agent. Vaginal misoprostol produced the highest mean dilation at 28 mm, a statistically significant difference from oral misoprostol (24.2 mm) but not laminaria (25.9 mm). There were no statistically significant differences in other clinical measures, including need for extra dilation, difficulty of dilation, and blood loss, although non-statistically significant trends were observed: women in the vaginal misoprostol group required less additional dilation, and extra dilation was easier. Women in the misoprostol groups were less likely to report pain at placement than women in the laminaria group, but there was no significant difference in pain reports during the waiting time or requests for pain medication. The authors conclude that vaginal misoprostol achieved the greatest cervical dilation, resulted in few side-effects, was easy to use, and is inexpensive.

This Hong Kong study compared the effectiveness of oral misoprostol and vaginal gemeprost for cervical dilation prior to vacuum aspiration in 64 nulliparous women with
pregnancies of 6 to 12 weeks. Women were randomized to receive either 400 µg of oral misoprostol 12 hours prior to the procedure (n=32) or 1 mg of vaginal gemeprost 3 hours prior to the procedure (n=32). The median cervical dilation was significantly greater in the misoprostol group (8.0 mm) than in the gemeprost group (7.0 mm). There were no significant treatment complications. Nausea, abdominal pain, and mild vaginal spotting were more common in the gemeprost group, although these differences did not reach statistical significance. Overall, the number of asymptomatic women was significantly greater in the misoprostol group. In addition, the ease of dilation assessed subjectively by the operating surgeons was improved significantly in the misoprostol group. The duration of the operation and blood loss were similar in both groups. The authors note that the difference in efficacy between the two treatment regimens may have been a result of the difference in treatment intervals. Based on its lower price, the authors conclude that oral misoprostol is better than vaginal gemeprost for cervical dilation prior to vacuum aspiration of first-trimester pregnancies.


This meta-analysis identified published trials assessing the safety and efficacy of misoprostol for cervical ripening and labor induction. Eight of 16 studies identified met the criteria for inclusion in the meta-analysis. The analysis included 966 women, of whom 488 were randomized to receive misoprostol. The 478 controls either received a placebo, oxytocin, or other prostaglandins. Taken together, this sample showed that misoprostol use was associated with a significantly lower cesarean section rate and higher rate of vaginal delivery, but also a higher rate of tachysystole. There was no noted difference in fetal effect, as measured by Apgar scores and admissions to neonatal intensive care. The authors conclude that misoprostol use for induction of labor is effective and associated with lower rates of cesarean section, shorter duration of labor, and reduced need for augmentation with oxytocin.

In Singapore, this double-blind study evaluated the effects of 200-µg, 400-µg, 600-µg, and 800-µg misoprostol doses in 120 nulliparous women with first-trimester pregnancies. Vacuum aspiration was performed 3 to 4 hours after vaginal insertion of the tablets. Successful dilation rates (defined as achieving a cervical dilation of at least 8 mm, measured with a Hegar dilator) were 23.3% for the 200-µg group, 96.7% for the 400-µg group, 100% in the 600-µg group, and 100% in the 800-µg group. The 800-µg dose was associated with significantly higher blood loss and more side effects (including abdominal pain); when the 400-µg and 600-µg doses were compared, the 600-µg dose was associated with significantly higher blood loss and more side effects. The authors conclude that vaginal application of 400 µg of misoprostol is the optimal dose for pre-abortion priming prior to vacuum aspiration for nulliparous women in their first trimester.


Also in Singapore, this prospective double-blind randomized study compared vaginal administration of 400 µg and 600 µg of misoprostol in 60 nulliparous women with pregnancies of 6 to 11 weeks. Vacuum aspiration was performed after 3 hours in the 400-µg group and after 2 hours in the 600-µg group. Twenty-eight (93.3%) of the 30 women who received 400 µg of misoprostol achieved a cervical dilation of ≥8 mm after 3 hours. Only 5 (16.7%) of the 30 women who received 600 µg achieved this dilation after 2 hours. The 600-µg dose was associated with an increase of side effects such as vaginal bleeding, abdominal pain, and fever, although only the difference in abdominal pain was statistically significant. The authors conclude that the evacuation time interval is as important as the dosage used. They also state that this study confirms that 400 µg of misoprostol with a minimal evacuation time interval of 3 hours is the optimal dosage and administration interval for nulliparous women requiring cervical priming prior to first-trimester abortion.

This double-blind study evaluated 400-µg, 600-µg, and 800-µg doses of misoprostol in 180 nulliparous women seeking abortion at 6 to 11 weeks’ gestation. Vacuum aspiration was performed after 3 hours in the 400-µg group and after 2 hours in both the 600-µg and 800-µg groups. Successful dilation (defined as dilation greater than 8 mm) occurred in 55 (91.7%) of 60 women in the 400-µg group, 11 (18.3%) of 60 women in the 600-µg group, and 15 (25.0%) of 60 women in the 800-µg group. The mean cervical dilations were 8.1 for the 400-µg/3-hour group, 6.7 mm for the 600-µg/2-hour group, and 6.8 mm for the 800-µg/2-hour group. There also were significantly more side effects (abdominal pain and fever) in the 600-µg and 800-µg groups than in the 400-µg group. In addition to noting the greater effectiveness of the 400-µg dose, the authors state that the minimal administration interval for cervical priming should be at least 3 hours before evacuation.
Misoprostol for Induction of Labor

This section reviews 13 articles that evaluate misoprostol’s effectiveness for cervical ripening and induction of labor at term. Many of the prostaglandin preparations that have been registered for these indications are expensive and unstable. Vaginal misoprostol has been shown to be more effective than oxytocin or dinoprostone (Hofmeyr et al., 1999; Danielian et al., 1999; Nunes et al., 1999). However, abnormal uterine contractile activity has been observed after misoprostol administration. No statistically significant effects on perinatal outcomes have been shown, but the possibility of uncommon serious adverse effects cannot be excluded (Hofmeyr et al., 1999; Kolderup et al., 1999). Low doses (e.g., 25 µg) and close clinical observation therefore are recommended. Additional evaluations of misoprostol use for induction of labor are warranted (Alfirevic, 2001; Hofmeyr and Gulmezoglu, 2001).


Labor induction with misoprostol has been shown to be effective, inexpensive, and associated with minimal side effects. Conducted at Louisiana State University, this randomized, double-blind study evaluated oral and vaginal misoprostol administration for labor induction in women having a singleton gestation with a live fetus of at least 24 weeks’ gestation, Bishop score of no more than 6, and medical or obstetrical indication for induction. Eligible women had absence of uterine contractions and intact membranes. In the oral group (n=93), 50.5% of women were nulliparous and the gestational age was 37.8 ± 3.4 weeks. In the vaginal group (n=85), 57.6% of women were nulliparous and the gestational age was 38.3 ± 2.5 weeks. One hundred seventy-eight women received either oral misoprostol (200 µg) or vaginal misoprostol (50 µg). Doses were repeated every 6 hours for a maximum of three doses until labor was established. After three doses had been reached or the Bishop score exceeded 6, labor was augmented with oxytocin, as necessary. Twenty-eight percent of women in the oral group and 33% of women in the vaginal group required oxytocin (not significant). In both groups, the majority of women received one dose only. Fourteen women (15%) in the oral group and 10 women (12%) in the vaginal
group received three doses. The percentage requiring two doses was higher in the vaginal group than in the oral group (39% vs. 29%). The onset of uterine contractility was shorter in the oral group than in the vaginal group; the intervals were 133 ± 78 minutes and 168 ± 93 minutes, respectively. Women in the oral group experienced a higher incidence of abnormal uterine contractile activity (tachysystole, which was defined as the presence of at least six uterine contractions in 10 minutes for at least two 10-minute windows, and hyperstimulation syndrome, which was defined as tachysystole with the presence of an abnormal fetal heart rate tracing requiring terbutaline administration). However, there was no significant difference in the number of cesarean deliveries, and neonatal outcome measures did not differ between the two groups. Vaginal delivery occurred in 24 hours or less in 72% of the oral group and 73% of the vaginal group. Eighteen percent of the oral group and 15% of the vaginal group underwent cesarean section. Maternal side effects occurred in less than 2% of both groups and included nausea, vomiting, and diarrhea. The authors conclude that the efficacy of oral administration of 200 µg misoprostol is similar to that of vaginal administration of 50 µg misoprostol, but that the oral regimen is associated with more frequent abnormal uterine contractility. The authors also state that while both routes demonstrated excellent efficacy, minimal side effects, and satisfactory neonatal outcomes, the high rate of hyperstimulation indicates that the 200-µg oral doses should be reserved for nonviable pregnancies. They note that the optimal oral dose that maintains efficacy for labor, yet minimizes hyperstimulation, remains to be determined.


The objective of this May 2000 review was to determine the effectiveness and safety of oral misoprostol used for third-trimester induction of labor, as evidenced by randomized trials. The review determined that oral misoprostol, when compared with placebo, reduces the need for oxytocin infusion and shortens delivery time in women with ruptured membranes at term. The review describes several trials that have compared oral misoprostol with vaginal prostaglandins and with vaginal misoprostol, but notes that the number of women that took part in these studies is too small for meaningful conclusions and recommendations. Acknowledging that misoprostol may be the only affordable
prostaglandin in low-resource settings, the author states that more research is needed into safety, as an overdose could be life-threatening for both the mother and the baby. He calls for methodologically sound clinical trials that are placebo-controlled and evaluate different regimens of both oral and vaginal misoprostol administration.


This study in Mozambique compared 57 women with previous cesarean section and indications for induction of labor with 57 women with previous section, indicated for trial of labor but not induction of labor. The misoprostol dose used was 50 μg vaginally, repeated one time in five women, after 18 hours. There were no statistically significant differences in the outcomes (vacuum extraction, cesarean section, fetal distress, uterine rupture) between the two groups, although a nonsignificant trend was noted toward fewer cesarean sections in the misoprostol group (47.4% versus 59.6%). The authors conclude that induction of labor using misoprostol is safe among certain women with previous cesarean section in this low-resource setting, and may reduce repeat elective cesarean sections.


This single-blind, randomized, British study compared the efficacy of vaginal misoprostol and dinoprostone vaginal gel for induction of labor at term. Subjects were 211 women at term (between 37 and 42 completed weeks of pregnancy), with singleton gestation, vertex presentation, intact membranes, with obstetrical indication for labor, and Bishop score <8. There were comparable numbers of primigravidae. Women received either vaginal administration of 50 μg misoprostol every 4 hours to a maximum of four doses (n=105) or 1 mg dinoprostone gel every 6 hours to a maximum of three doses (n=106). At Bishop score ≥8, artificial rupture of the membranes was performed. Oxytocin augmentation was used as indicated. The median induction-delivery interval in the misoprostol group (14.4
hours) was significantly lower than that of the dinoprostone group (22.9 hours). In addition, 77% of women using misoprostol delivered after only one dose and 80% delivered within 24 hours, compared to 49% and 51%, respectively, for dinoprostone. Twenty-one percent of the misoprostol group required oxytocin, compared to 47% of the dinoprostone group. Cesarean section was performed in 11% of the misoprostol group and 13% of the dinoprostone group. There were more cases of uterine tachysystole (six contractions in any 10-minute time period) in the misoprostol group (though not statistically significant). In the dinoprostone group, there was one case of hyperstimulation (defined as fetal heart rate abnormality associated with tachysystole), which required tocolytics. There was no difference in neonatal outcome with respect to Apgar scores, umbilical venous pH, base deficit, presence of meconium, and neonatal unit admission. Based on visual analogue scales completed by 42 participants postnatally, a non-statistically significant trend was noted for more pain experienced by the women in the misoprostol group in the interval between induction and receiving analgesia in labor. Analgesia requirements in labor were comparable. The authors conclude that vaginal misoprostol is a highly effective agent, and they suggest that it may be possible to retain its efficacy with doses of 25 µg.


This double-blind study in Jamaica evaluated the effects of 100 µg of misoprostol administered vaginally versus placebo in 45 women with indications for induction of labor. Each study participant received only one dose of the designated drug. Women in the misoprostol group (n=24) received half of one 200-µg misoprostol tablet, which was crushed into a powder, mixed with K-Y Jelly, and “squirted” into the posterior fornix via a sterile 5 cc syringe without a needle. Women in the placebo group (n=21) received 0.05 mg tablet of ethinyl estradiol in a white powder prepared and packaged like the misoprostol. (The authors cite the results of a study by Peedicayil et. al. as justification that the ethinyl estradiol has no effect on ripening of the cervix.) Demographic profiles, including parity and reason for induction were similar in the two groups. Results demonstrate that misoprostol was very effective for ripening the cervix. Time from insertion to delivery was
shorter in the misoprostol group (15.6 hours) than in the placebo group (43.2 hours); the mean change in Bishop (cervical) score was greater in the misoprostol group (5.3) than in the placebo group (1.5); fewer patients had no change in Bishop score in the misoprostol group (8%) compared to the placebo group (62%); and the need for oxytocin was less in the misoprostol group (29%) than in the placebo group (62%). Of those women in the misoprostol group who went into labor and delivered vaginally, none received oxytocin augmentation and all delivered within 18 hours. Few women in either group had complications (there was one case of postpartum hemorrhage among women receiving misoprostol) and there were no significant changes in maternal vital signs or mode of delivery. Fetal distress was similar in both groups; in the misoprostol group, polysystole (more than five contractions in 10 minutes) occurred in one woman.


The objective of this October 2000 review was to determine the effects of vaginal misoprostol for third-trimester cervical ripening or induction of labor. The review found that vaginal misoprostol appears to be more effective in inducing labor than conventional methods of cervical ripening and labor induction. Compared to placebo, misoprostol was associated with increased cervical ripening and a reduced need for oxytocin. Vaginal misoprostol doses ranging from 25 μg every two to three hours, to 50 μg every four hours (most common), to 100 μg every six to twelve hours, appear to be more effective than oxytocin or dinoprostone in the usual recommended doses for labor induction, but with increased rates of uterine hyperstimulation both with and without associated fetal heart changes. The authors note that the studies were not large enough to exclude the possibility of rare but serious adverse perinatal and maternal complications, particularly uterine rupture, which has been reported following misoprostol use in women with and without previous cesarean section. They also point out that a significant increase in meconium-stained liquor with misoprostol versus intracervical prostaglandins is cause for concern, and they note that information on women’s views is conspicuously lacking. In their conclusion, the authors state that misoprostol shows promise as a highly effective,
inexpensive, and convenient agent for labor induction, but cannot be recommended for routine use at this stage.

56. Hofmeyr GH, Gulmezoglu AM, Alfirevic Z. Misoprostol for induction of labour: a systemic review. *British Journal of Obstetrics and Gynaecology* 1999;106:798-803. This article reviews the scientific robustness of 31 studies that evaluate the effectiveness and safety of misoprostol administered vaginally or orally for third-trimester cervical ripening or induction of labor. The purpose of the review was to determine whether the data justify routine clinical use of misoprostol. Indicators included tachysystole, defined as >5 contractions per 10 minutes for at least 20 minutes; hypersystole/hypertonus, defined as a contraction lasting at least 2 minutes; uterine hyperstimulation without fetal heart rate changes, defined as tachysystole and uterine hypersystole/hypertonus; and hyperstimulation syndrome, defined as uterine hyperstimulation with fetal heart rate changes. Only four trials were double-blinded and placebo-controlled. The data show that, compared to oxytocin or dinoprostone used in the recommended doses, vaginal misoprostol regimens with doses ranging from 25 µg/3 hours to 50 µg/4 hours to 100 µg/6 to 12 hours are more effective methods of cervical ripening, labor induction, and achievement of vaginal delivery within 24 hours. Oxytocin augmentation was used less often with misoprostol doses of at least 25 µg every 3 hours (RR 0.64; CI 0.58-0.71). Lower doses of misoprostol (25 µg every 6 hours were less effective in achieving delivery within 24 hours and required more use of oxytocin, but were associated with less hyperstimulation than the higher dose. However, the authors found the increased rates of uterine hyperstimulation with or without fetal heart rate changes to be worrisome, and they state that the populations studied were not large enough to exclude the possibility of uncommon adverse events such as uterine rupture, asphyxial fetal death, or maternal death. Serious maternal complications were reported in only one study (maternal death from amniotic fluid embolus, shortly after amniinfusion and epidural analgesia). The authors recommend that vaginal doses of 25 µg every 3 to 6 hours be used only if women can be kept under constant supervision. The authors conclude that while misoprostol shows promise as an effective agent for labor induction, it cannot be recommended for routine use at this stage, and that lower-dose regimens should be explored.

This randomized study compared misoprostol, a prostaglandin E₁ analogue, with dinoprostone, a prostaglandin E₂ analogue, when used for labor induction. Women eligible for labor induction received either 50 μg of vaginal misoprostol every 4 hours (81 women) or 0.5 mg of dinoprostone inserted into the endocervical canal every 6 hours (78 women). Dosing was repeated for a maximum of 6 misoprostol doses and 4 dinoprostone doses if labor was not active and the Bishop score was less than 6. The misoprostol group had an average of 19.8 ± 11.5 hours from induction to delivery, significantly less than the dinoprostone group with 28.9 ± 14.8 hours. The misoprostol group also had 58% oxytocin use compared to 88% in the dinoprostone group; oxytocin was used to augment induction in non-responsive cases. There was no difference in the cesarean or hyperstimulation rates between the two groups, but tachysystole (defined as more than six contractions in 10 minutes, for two consecutive 10-minute periods) was greater in the misoprostol group. There were more deliveries for fetal distress in the misoprostol group, although the difference did not quite reach statistical significance, and significantly more babies from the misoprostol group were admitted to intensive care. The authors conclude that misoprostol is more efficacious for labor induction than dinoprostone, but they suggest that the increase in negative fetal effects is worrying (but, due to confounding, difficult to ascribe to directly to misoprostol). They note that three out of six similar studies in the literature found an increase in fetal/neonatal morbidity with misoprostol use, and suggest it may be safer to evaluate a lower dose or longer dosing interval.


Conducted in Taiwan, this descriptive, uncontrolled study evaluated the effects of 50 μg of intracervical misoprostol in 89 women at term who required induction of labor at term. One quarter of a 200-μg tablet was administered to the cervical canal with long forceps. If labor
was not initiated in 4 hours, the same dose was repeated every 4 hours to a maximum of 200 μg. If cervical dilation did not progress for 2 hours or more during the active phase of labor, intravenous oxytocin augmentation was used. Labor induction was considered successful if delivery was achieved within 24 hours. In this study, tachysystole was defined as at least six or more contractions in 10 minutes for two consecutive 10-minute periods; hypertonus was defined as a single contraction lasting at least 2 minutes; hyperstimulation was defined as tachysystole or hypertonus associated with abnormal fetal heart rate pattern; and regular contractions were defined as at least three contractions in 10 minutes. For analysis, patients were divided into those with the Bishop score ≤4 (n=58) and those with the Bishop score >4 (n=31). The two groups were comparable with respect to demographic profile, parity, gestational age, and indications for induction. Eighty-three women (93.3%) required only one dose of intracervical misoprostol before contractions began; the other six (6.7%) required two doses. Seventy-two patients (81%) proceeded to spontaneous vaginal delivery, 61 (85% of vaginal deliveries; 69% of all deliveries) of deliveries were achieved with 12 hours. Among both groups, 22 patients (24.8%) required oxytocin augmentation. Seventeen cesarean deliveries were performed; reasons included fetopelvic disproportion (six cases), failure of induction (seven cases), and acute fetal distress (four cases). There was one case of abruptio placenta at 4-cm dilation (emergent cesarean section was performed) and three cases of postpartum hemorrhage. There was a higher prevalence of excessive uterine contractions in the group with Bishop scores ≤4. Hyperstimulation occurred in 17% of cases among the group with Bishop scores ≤4 and in 6.5% of cases among women with the group with Bishop scores ≥4. There was no significant difference of outcomes among the newborns, as judged by 1- or 5-minute Apgar scores. No infants required intubation, resuscitation, or intensive care unit admission. The authors conclude that intracervical application of 50 μg misoprostol appears to be effective for induction of labor at term, but that caution should be taken with women with unfavorable cervices. Note: 31 of 89 patients had premature rupture of the membranes (PROM) as an indication for induction. There is no indication as to whether PROM was more or less associated with excessive uterine contractions.

Vaginal misoprostol and dinoprostone were evaluated in 189 women in Almada, Portugal, with singleton term pregnancies and unfavorable cervices, defined as Bishop score of ≤ 0 or > 5. Women with premature rupture of the membranes were included. Women in the two groups were similar with regard to demographic characteristics, parity, gestational age, indication for induction, and amniotic fluid index. Women in the misoprostol group (n=95) received an initial vaginal dose of 100 μg, followed by a second dose of either 50 μg or 100 μg at 6 hours (based on the Bishop score), and, if necessary, a third dose of 50 μg at 12 hours. The total dose of misoprostol did not exceed 250 μg. In the dinoprostone group (n=94), women received an initial dose of 2 mg of vaginal gel, followed by a second dose of 0.5 mg, 1 mg, or 2 mg (as determined by the Bishop score), and, if necessary, a third dose of 1 mg. The total dose of dinoprostone did not exceed 4 mg. Cervical ripening was assessed by change in Bishop score 6 hours after initial application. Once the active phase of labor had been achieved, oxytocin augmentation was used as indicated. Artificial rupture of the membranes was performed at the discretion of the attending physician. The interval from induction to the beginning of the active phase of labor was shorter in the misoprostol group (9.8 ± 5.8 vs. 14.2 ± 10.2 hours), and the interval from induction to delivery also was shorter in the misoprostol group (15.3 ± 9.8 vs. 19.1 ± 13.2 hours). There was no difference between the two groups with respect to number in each group who delivered in less than 12 hours and number who delivered within 24 hours after initial dose. In the misoprostol group, 71 (74.7%) patients required only one dose, 24 (25.2%) required a second dose (with one patient receiving 100 μg and the others receiving 50 μg), and one (1%) required a third dose. In the dinoprostone group, 54 (57%) patients required a second dose; 7 patients received 2 mg, 40 patients received 1 mg, and 7 patients received 0.5 mg. Eight (8.5%) patients received a third dose of dinoprostone. There were no significant differences between the two groups in Bishop score change, cesarean delivery rate, or incidence of tachysystole (five contractions in 10 minutes for two consecutive 10-minute periods), hypersystole (one uterine contraction with a duration ≥90 seconds), or hyperstimulation (tachysystole associated with an abnormal fetal heart rate pattern). There were no
differences in Apgar score and umbilical cord pH. No maternal or neonatal adverse effects were observed. There were no complaints of nausea, vomiting, diarrhea, fever or any other known medication side effects. The authors conclude that vaginal misoprostol is more effective than vaginal dinoprostone for labor induction in low-risk patients with unfavorable cervices.

60. Rodrigues R; Nunes F; Tiago D; Avillez T; Vieira A; Meirinho M. **Induction of labor with intravaginal administration of misoprostol.** *International Journal of Gynecology and Obstetrics* 1998;60(3):233-237.

In Portugal, a vaginal misoprostol regimen (an initial dose of 100 µg; a second dose of either 50 µg or 100 µg at 6 hours if needed; and a third dose of 50 µg at 12 hours if needed) was evaluated in 110 women with singleton pregnancies at term. Women were included in the study if they had Bishop scores ≤6, with or without ruptured membranes, and obstetrical or medical indications for induction. In this uncontrolled, descriptive study, an initial dose of 100 µg was applied in the posterior fornix. The Bishop score was re-evaluated 6 hours later and 50 or 100 µg was administered depending on the status of the cervix and uterine activity. A third application of 50 µg was considered 6 hours after the second application. No total dose exceeded 250 µg. Oxytocin augmentation was used as indicated. The average dose used was 100 µg, and only 22% of women needed more than one dose. The average interval from administration to the beginning of active labor (defined as the increase of dilation speed and the descent of presentation that usually begins with dilation of 3 to 4 cm) was 9.5 ± 5.7 hours, and the average interval from administration to vaginal delivery was 13.4 ± 8.5 hours (14.8 ± 9.5 hours for all deliveries). Labor induction failed in 2% of cases, and cesarean delivery was performed in 15 (14%) cases for arrest of dilation or descent (12 cases) and presumption of fetal distress (three cases). Oxytocin augmentation was used in 48 (44%) cases. The incidence of tachysystole (defined as five or more contractions in 10 minutes for two consecutive periods) was 18% and hypersystole (defined as a uterine contraction with duration of at least 90 seconds) was 4%; only 3% of these cases, however, were associated with abnormal fetal heart rate patterns (hyperstimulation). Fetal heart rate abnormalities were recorded in 11 cases (10%), and 43 cases (39%) had diminished amniotic fluid. Although 13 (12%) neonates had 1-
minute Apgar scores of <7, none had scores <7 at five minutes. Note: Only 4 of the 13 infants with low 1-minute Apgar scores were among those who exhibited fetal heart rate abnormalities. No maternal side effects or adverse neonatal effects were noted. No infants were admitted to the neonatal intensive care unit.


The authors compare vaginal and oral misoprostol for cervical ripening and induction of labor in 40 women with unripe cervixes. After randomization, women received 100 µg of misoprostol either vaginally or orally, repeated every 3 hours until cervical dilation reached at least 5 centimeters, at which point artificial rupture of membranes and oxytocin were applied. The vaginal dose was doubled if there was no response after the first application; the oral dose was doubled if there was no response after two doses. The vaginal route of administration produced statistically significant shorter intervals between induction to onset of contractions, and induction to delivery. Labor was not induced in one vaginal and three oral cases. Uterine hypertonus occurred in six cases in the vaginal group and none in the oral group (a statistically significant difference), and only 10 in the vaginal group, compared with 19 in the oral group had normal fetal heart rates, detected by cardiotocographic monitoring. The authors conclude that vaginal misoprostol is more effective for cervical ripening, but was associated with more abnormal cardiotocographic tracing, and suggest that the use of vaginal misoprostol for cervical ripening requires careful fetal and maternal monitoring. Safety should be studied in a larger number of cases.


Conducted in the U.S., this single-blind study evaluated oral and vaginal administration of misoprostol for cervical ripening and labor induction. A total of 220 women with obstetrical or medical indication for labor induction, singleton, vertex, term pregnancy with intact membranes and undilated, uneffaced cervixes (Bishop scores of <4) were
randomized to receive either 50 μg of oral misoprostol (n=110) or 25 μg of vaginal misoprostol (n=110). In both groups, doses were given every 4 hours to a maximum of 6 doses or 24 hours. In the oral group, 34 (30.9%) women delivered vaginally within 24 hours of treatment initiation, compared with 42 (47.3%) of women in the vaginal group. Overall, 95 (86.4%) of women in the oral group and 83 (75.4%) of women in the vaginal group delivered vaginally. The average interval from start of induction to vaginal delivery was nearly 6 hours longer in the oral group. Women in the oral group also required significantly more doses than women in the vaginal group (3.3 ± 1.7 versus 2.3 ± 1.3 doses, respectively). Parity influenced the success of induction in both treatment arms, as multiparous women were significantly more likely to deliver vaginally within 24 hours than nulliparous women. There was no difference between the two groups in the incidence of uterine contractile abnormalities or neonatal outcomes. Terms used in this study included uterine hypertonus, defined as a single uterine contraction lasting ≥2 minutes; tachysystole, defined as ≥6 uterine contractions in 10 minutes for two consecutive 10-minute windows; and hyperstimulation, defined as either hypertonus or tachysystole associated with an abnormal fetal heart rate pattern. Contraction abnormalities were treated with either intravenous or subcutaneous terbutaline, 0.25 mg, or intravenous magnesium sulfate. The authors conclude that oral doses of 50 μg of misoprostol are less effective than vaginal doses of 25 μg of misoprostol for cervical ripening and labor induction because the oral preparation is associated with longer mean time to delivery and with a greater need for oxytocin. They also note that while misoprostol would not be appropriate for women with urgent medical or obstetric indications for induction, it may have promise for nonacute inductions.
Misoprostol for Prevention and Management of Postpartum Hemorrhage

Postpartum hemorrhage accounts for 17% to 40% of maternal mortality in some parts of the world (El-Refaey et al., 1997). The eight articles described below confirm the effectiveness of oral and rectal misoprostol for the prevention and management of postpartum hemorrhage. In the study by O’Brien et al. (1998), hemorrhage that was unresponsive to oxytocin and ergometrine was controlled and contractions were produced within 3 minutes of rectal administration of 1000 μg of misoprostol. The data obtained by El-Refaey et al. (1997) also demonstrate the effectiveness of 600 μg of misoprostol for the management of postpartum hemorrhage. The authors note misoprostol’s advantages over Syntometrine (ergometrine 0.5 mg, with 5 units of oxytocin), which is routinely used in the developed world. Unlike misoprostol, Syntometrine is contraindicated in women with hypertension in pregnancy, frequently causes nausea and vomiting, and must be administered by intramuscular injection. The authors found misoprostol to be a safe and effective alternative.

As the debate among Bamigboye et al. (1998), Ramsey et al. (1998), and Hofmeyr (1998) indicates, additional studies evaluating misoprostol’s effects on postpartum hemorrhage must be conducted.


This double-blind study, conducted in Belgium, compared the effects of misoprostol (600 μg orally) and methylergometrine (200 μg intravenously) in 200 women after delivery of the infant. Demographic, parity, gestational age, and labor variables were comparable between the two groups of women, and all deliveries were at term. The incidence of manual removal of the placenta was comparable at 3% to 4%. Postpartum hemorrhage occurred in 8.3% of the misoprostol group and 4.3% of the methylergometrine group (P=0.57). One woman in each group required blood transfusion. However, no differences were found between the two groups in hemoglobin or hematocrit levels 3 days after delivery. The need for additional oxytocic drugs was 12.8% (P=0.065) after misoprostol
and 4.4% after methylergometrine, and there was a tendency for increased blood loss among women who took misoprostol. There were no significant differences in mean blood pressure. Women in the misoprostol group were more likely to experience fever 1 hour after delivery (34% vs. 3%, P=0.0001) and shivering (42% vs. 8.5%, P=0.0001). The fevers spontaneously resolved within 5 to 6 hours. Shivering lasted 10 to 20 minutes. The incidence of other side effects such as nausea, vomiting, and diarrhea was equal in the two groups. The authors conclude that methylergometrine and misoprostol provide nearly equal protection against postpartum hemorrhage, but that misoprostol is associated with more side effects. The authors also note that in settings in which storage conditions are poor and sterile needles are unavailable, misoprostol may be the more appropriate therapy. Note: This article does not present detailed information on the clinical estimation of blood loss, circumstances of the two women who required blood transfusion, intrapartum temperatures, prolonged rupture of the membranes, or number of manual vaginal exams. The authors hypothesize that comparable hemoglobin levels 3 days postpartum may indicate that misoprostol causes sustained contraction of the uterus and, therefore, prevents later postpartum blood loss.


This prospective, single-blind, randomized trial conducted in South Africa compared blood loss in 271 women receiving prophylaxis of 400 µg of rectal misoprostol with 275 women receiving a non-identical placebo. The tablets were inserted 1 minute after normal delivery, and blood was collected for 1 hour, and then weighed. Postpartum hemorrhage was defined as blood loss of at least 1000 mL, and was detected in 4.8% of the misoprostol group and 7% of the placebo group (a non-statistically significant difference). The study’s effect may have been muted by the fact that conventional oxytocic treatments were administered to patients if blood loss was felt to be too rapid; 3.3% of the misoprostol group and 4.7% of the placebo group received oxytocics. There was no statistical difference in the incidence of shivering, abdominal pain, or vomiting; these side-effects were rare in both groups.

In response to Bamigboye et al.’s report on their study of rectally administered misoprostol for the treatment of postpartum hemorrhage (which failed to demonstrate a difference between prophylaxis with misoprostol versus placebo), Ramsey et al. argue that, to date, no well-designed studies have demonstrated significant efficacy of misoprostol for reduction of blood loss or postpartum hemorrhage. They acknowledge that misoprostol has been shown to have potent uterotonic properties, and is effective for cervical ripening and labor induction. They argue, however, that the absorption kinetics of rectally administered misoprostol likely are similar to those associated with vaginal administration. They state that the delay in attainment of peak levels after vaginal administration would prevent misoprostol from being effective for postpartum hemorrhage, as postpartum hemorrhage requires prompt intervention. The authors state that this failure likely represents a pharmacokinetic problem rather than a lack of clinical efficacy. [Note: Studies of the absorption characteristics and pharmacokinetics of rectal misoprostol have not been performed.]


This letter was written in response to Ramsey et al.’s letter to the editor, which argued that misoprostol is ineffective for the treatment or prevention of postpartum hemorrhage. Hofmeyr agrees that oral administration of misoprostol should be investigated, and states that a large multicenter trial of orally administered misoprostol for third-stage labor management currently is being conducted. Hofmeyr also states that the rectal route should be studied for the following three reasons: (1) Due to the structural and functional differences between rectal mucosa and vaginal epithelium, it cannot be assumed that absorption kinetics of rectal and vaginal administration are the same; (2) Oral administration is associated with side effects that may limit the usefulness of this route, including high rates of pyrexia and shivering with 400-µg and 600-µg doses, and
hyperpyrexia at 800-μg doses; (3) The study by O’Brien et al., which reported on rectal administration of 1000 μg of misoprostol in 14 women with postpartum hemorrhage, demonstrated that rectal misoprostol can effectively control postpartum hemorrhage.


Conducted in the UK, this uncontrolled, descriptive study evaluated oral administration of 600 μg of misoprostol in 237 women, immediately after cord clamp, during term, singleton, and vaginal delivery. After misoprostol administration, postpartum hemorrhage occurred in 6% of women, therapeutic oxytocics were needed for 5% of women, the placenta was retained in 2% of women, and the median length of the third stage of labor was 5 minutes. Thirteen (6%) patients had blood loss ≥500 mL; none had blood loss ≥1000 mL or secondary postpartum hemorrhage. Four women (2%) required manual removal of the placenta, and 4 (2%) had 2-day postpartum hemoglobin levels of less than 9 g/dL. (Note: Hemoglobin concentrations were obtained at 2-day postpartum solely from women who had had instrumental delivery [28%] or estimated blood loss of ≥500 mL.) Two women required blood transfusion; one for a broad ligament hematoma, and the other during manual removal of the placenta. Vomiting occurred in 8% of women in the first hour after delivery, and loose stool occurred in 3% of women during the first 24 hours postpartum. Shivering occurred in 62% of women. The shivering generally occurred approximately 20 minutes after swallowing the tablets and lasted 10 to 15 minutes. There was so significant difference in incidence of shivering among those who received epidural analgesia compared to those who did not receive epidural analgesia. A mean temperature increase of 0.5 degrees comparing temperature before and after delivery was noted (P=0.001). There were no cases of infection and no patient required postpartum surgical evacuation of the uterus. No third- or fourth-degree tears were noted. In their discussion, the authors state that typically, without the use of misoprostol or other oxytocic drugs, postpartum hemorrhage occurs in 18% of women, therapeutic oxytocics drugs are need by 30%, and the median length of the third stage is 15 minutes. Their study found that the incidence of vomiting among women receiving misoprostol (8%) was approximately half of that
observed after Syntometrine administration. The authors conclude that misoprostol’s efficacy in the prevention of postpartum hemorrhage is comparable to that of Syntometrine, but that misoprostol is more stable and is associated with fewer side effects. They recommend that additional research be conducted. Note: Information on how blood loss was estimated and the difficulty of manual removal of the placenta was not provided.


The objective of this July 1998 review was to assess the effects of prophylactic prostaglandin use in the third stage of labor. The review included seven randomized or quasi-randomized trials comparing a prostaglandin agent with another uterotonic (e.g., oxytocin, syntometrine, or ergometrine) or placebo as part of management of the third stage of labor. Six of these trials evaluated injectable prostaglandins (PGF2alpha or PGE2), and one evaluated rectal misoprostol; the author notes that these trials were limited by their small sample sizes (<500) and lack of blind assessment in the outcomes. The review found that injectable prostaglandins were associated with decreased blood loss and shortened duration of the third stage of labor when compared to other uterotonics. Severe postpartum hemorrhage (1000 mL or more) occurred in two of four studies and was seen in fewer women receiving prostaglandins, though the difference was not statistically significant. Adverse effects (vomiting, diarrhea, and abdominal pain) were more common with prostaglandins when compared to other uterotonic agents. The author concludes that injectable prostaglandins may be superior to currently used uterotonics in decreasing blood loss, although their high cost and inadequate safety data preclude recommending them for further research or routine use in the developing world. Misoprostol, however, is described as a promising alternative for prophylactic use because of its stability, low cost, tablet form, and demonstrated effectiveness as a uterotonic agent in other obstetric conditions.


This double-blind placebo-controlled trial was conducted in South Africa to evaluate the
efficacy of oral misoprostol for the third stage of labor. Five hundred low-risk women
expected to deliver vaginally were randomized to received either 400 µg of oral
misoprostol (n=250) or placebo (n=250) after birth. Postpartum blood loss was measured in
the first hour, and conventional oxytocics were administered immediately if blood loss was
thought to be more than usual. Measured blood loss of ≥1000 mL occurred in 15 (6%)
women who received misoprostol and 23 (9%) of women who received placebo. No
serious side effects were noted, although shivering occurred in 19% of the misoprostol
group, compared with 5% in the placebo group. The authors state that the reduction in the
rate of measured blood loss among women in the misoprostol group was not statistically
significant at the 95% level. They also note that the need for intravenous oxytocin infusion
was significantly greater in the control group, and that the potential benefit of misoprostol
may be greater in areas in which oxytocics are not available. The authors conclude that
misoprostol holds promise as a method of preventing postpartum hemorrhage, and should
be further evaluated.

misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin
This small, uncontrolled, descriptive study, conducted in London, evaluated rectally
administered misoprostol in 14 women with postpartum hemorrhage unresponsive to
oxytocin and ergometrine or, when ergometrine was contraindicated, oxytocin alone.
Women received 1000 µg misoprostol (5 tablets) rectally while awaiting carboprost. In all
14 women, hemorrhage was controlled and sustained uterine contractions were produced
within 3 minutes of administration. No woman required any further uterotonic treatment,
and all women made a full recovery. The median estimated blood loss was 1000 mL
(range: 500 to 2000 mL). Eleven (79%) of the 14 women required blood transfusion. Three
patients who lost 1700, 1500, and 2000 mL, respectively, had diagnoses of disseminated
intravascular coagulation (DIC); two of these women required admission into intensive
therapy, but all made a full recovery. Other intrapartum complications included
preeclampsia, diabetes mellitus, abruption, retained placenta, asthma, and malpresentation.
The authors suggest that, because the absorption of misoprostol is mucous-membrane–
dependent, absorption from the rectal mucosa is just as effective as from vaginal or oral administration. They also note that it is likely that the women responded to the misoprostol rather than the previously administered oxytocics, since the onset of action of intravenous oxytocics is rapid, and an appropriate therapeutic interval had passed. Additionally, because oral medication cannot be administered to women under general anesthesia and vaginal administration during heavy bleeding is unlikely to be effective, there is considerable potential for misoprostol to reduce maternal mortality from postpartum hemorrhage, particularly in developing countries. Note: No information on maternal side effects was given.
Safety and Morbidity

With misoprostol’s quick rise in popularity—particularly among women who use it without clinical guidance or observation—safety, morbidity, and teratogenicity issues must be rigorously evaluated. Side effects ranging from mild (e.g., nausea) to severe (e.g., uterine rupture) have been reported after misoprostol administration (Hofmeyr, 1998). Chen et al. (1999), for instance, report on the separation of a cesarean scar after vaginal administration of 200 µg of misoprostol. Evaluation of these risks is an important area for future research. It also is important to note, however, that misoprostol-only regimens have the potential to reduce maternal morbidity and mortality resulting from unsafe abortion practices. As Faundes et al. argue, it appears that misoprostol use has reduced the number of infections among women with incomplete abortions as well as the use of other, more invasive forms of illegal abortion. Many of the articles on misoprostol use in Brazil also support this conclusion (see “Women’s Use of Misoprostol for Self-induced Abortions” on page 76).

   This case study describes a woman admitted at 23 weeks with suspected chorioamnionitis infection of the chorion and amnion, which are two membranes surrounding the fetus. The patient, who had had two prior low-transverse cesareans, decided to terminate the pregnancy, and 200 µg of misoprostol was placed in the posterior fornix. After 3 hours, strong, regular uterine contractions had started. At 15 hours after receiving the misoprostol dose, the patient had sudden pain, vaginal blood clots, and regression of cervical dilation. By laparoscopy, it was observed that the cesarean scar had separated. The stillborn fetus was delivered and the uterus was repaired. The authors note that this case of cesarean scar separation seems to be the first in the literature associated with misoprostol used alone in second trimester abortion.

To determine whether there was an association between the use of misoprostol and the incidence of septic post-abortion complications, the authors studied 1,840 women treated for post-abortion complications in Recife, Brazil. A total of 1,417 women reported that their abortions were spontaneous, 265 reported using misoprostol, and 158 reported using other methods to induce abortion. Incidence of infection was lower in the group of women stating they had used misoprostol (4.2%) than in those stating that the abortion was not induced (7.9%), and twelve times lower than in women stating that they had used other methods (49.4%). Gestational age (more than 11 weeks) and women’s age (over age 25) also were associated with higher rates of infection. The authors state that these data confirm the widespread clinical observation among gynecologists in Brazil of a reduction in the number of infections among women with incomplete abortions since misoprostol became available. The study also suggests that the use of misoprostol to interrupt pregnancy is safer than other means of inducing abortion for women who cannot pay for safe abortions where abortion is highly restricted.


This South African editorial seeks to balance the enthusiasm for misoprostol with a discussion of some of its potential risks. The author states that teratogenic effects, particularly limb defects, have been associated with misoprostol used for first-trimester abortion, and recommends that clinicians be aware of these risks and counsel patients to complete termination of pregnancy once it is begun. The author states that misoprostol used for second-trimester abortion has been associated with uterine rupture, particularly when combined with oxytocin infusion; the author cautions clinicians to limit dosage and avoid oxytocin infusion within 6 hours. The author reviews studies reporting on misoprostol used for third-trimester induction of labor and states that the drug has been associated with uterine tachysystole (excessive uterine activity) unrelated to dosage, as well as fetal heart rate changes and increased meconium passage. The author states that the effectiveness of misoprostol used for postpartum hemorrhage has not been established. Acknowledging that misoprostol has the potential to be an extraordinarily useful drug, the author states that clear guidelines regarding its use urgently are needed.
**Teratogenicity**

Given the possibility of treatment failure when misoprostol is used as an abortifacient, *in utero* exposure to the drug may be common. Mengue et al. (1998) conclude that as many as 2.2% of infants have been exposed to misoprostol, while Costa and Vessey (1993) suggest that this figure could be as high as 10% (see page 78). Limb defects and Mobius’ syndrome (congenital facial paralysis), most likely the result of vascular disruption, have been reported, but no absolute causal relationship has been demonstrated.

The effects of prenatal exposure to misoprostol are difficult to identify and measure. In Brazil, Mobius’ syndrome is not recorded in registries of birth defects, and its incidence in the general population is unknown. Additionally, women in Brazil (and in other countries in which abortion is illegal) may be reluctant to report misoprostol use. The 1998 study by Pastuszak et al. found a strong association between misoprostol and Mobius’ syndrome; the 1999 study by Schüler et al. found no association.

In addition to evaluating these issues more closely, several of the eleven articles discussed in this section emphasize the importance of informing clinicians and women of the potential risks of misoprostol use and the possible need to provide surgical abortions to women when misoprostol use is not fully effective. Conclusive data about the teratogenicity of misoprostol are needed to provide accurate information. Presently, incomplete information, speculation, and bias—including moral judgement about abortion—cloud this literature.

74. Fonseca W, Alencar AJC, Pereira RMM, and Misago C. *Congenital malformation of the scalp and cranium after failed first trimester abortion attempt with misoprostol.*

*Clinical Dysmorphology* 1993:2;76-80.

This article reports on an unusual congenital malformation of the skull in three infants in Fortaleza, Brazil, whose mothers had taken misoprostol during the first trimester of pregnancy. In the first case, the mother reported taking 800 µg of oral misoprostol during her first month of pregnancy. The infant was born with a localized frontal-temporal defect with an asymmetric, well-circumscribed deficiency of the cranium and the overlying scalp. In the second case, the mother reported taking 600 µg of misoprostol (administration route not identified) at the time of expected menses, and an additional dose of 600 µg one month
later. The child was born with a localized frontal defect with an asymmetric, well-circumscribed absence of the cranium and overlying scalp. In the third case, the mother reported taking 600 µg of oral misoprostol and 200 µg of vaginal misoprostol at the time of expected menses, plus 1200 µg of oral misoprostol and 400 µg of vaginal misoprostol four weeks later. The child was born with a complete deficit in the cranium and scalp in a localized region of the frontal-temporal area, with exposure of the cerebrum and dura mater; he died one week after an operation to cover the exposed area was performed. In their conclusion, the authors state that two other cases of similar malformations have been reported in Fortaleza. They suggest that these teratogenic effects could be the result of anoxia following uterine contraction and constriction of the uterine vessels after misoprostol administration.


In its introduction, this article states that misoprostol is not very effective for inducing abortion, and that exposure to this drug *in utero* can result in fetal abnormalities. The authors report on 42 infants in San Paulo, Brazil, who were exposed to misoprostol during the first 3 months of pregnancy and born with congenital abnormalities. Seventeen of the infants had equinovarus (clubfoot) with cranial-nerve defects. Ten had equinovarus as part of more extensive limb defects—five cases were confined to the legs and nine cases were terminal transverse-limb defects (such as shortness or absence of one or more fingers or toes, and tapered digits) with or without Mobius’ sequence (congenital facial paralysis). The most commonly reported dose of misoprostol was 800 µg (range: 200 to 16,000 µg) and all doses were taken during the first trimester of pregnancy. Of the 39 women for whom administration data were available, 14 (36%) took the misoprostol tablets orally, 23 (59%) used a combination of oral and vaginal administration, and 2 (5%) received misoprostol intravenously. The authors conclude that uterine contractions induced by misoprostol cause vascular disruption in the fetus including brain-stem ischemia. The article also notes that further research should be done on the teratogenic effects of misoprostol.

The authors report on seven Brazilian infants whose mothers attempted to abort with misoprostol. All seven infants had limb defects, and four also had Mobius’ sequence. Seizures, slow growth, delayed psychomotor development, cranial nerve palsies, respiratory problems, and other complications also were observed in these children, who were born as of 1989. Two of the infants have since died. The mothers reported taking doses of 600 μg to 1800 μg orally or orally/vaginally during the first trimester, possibly between days 30 to 60, when embryos are most sensitive to teratogenic insults. The authors conclude that these cases do not prove the teratogenicity of misoprostol, but add evidence of its potential hazards, including vascular disruption defects that may result in Mobius sequence.


This article presents a case report of a 42-year-old woman who attempted to terminate her sixth pregnancy with misoprostol tablets (one tablet inserted vaginally on four consecutive days). One week later a minilaporotomy for sterilization, using general anesthesia, was attempted in a hospital, but during the operation it was discovered the woman was still pregnant. The woman decided to continue with the pregnancy. At approximately 30 weeks’ gestation, she underwent a cesarean section. The female infant had an extra digit on each hand (as did the mother, her husband, and three of their children), and the right lower limb was absent below the knee. The authors state that this unusual anomaly is highly suggestive of misoprostol teratogenicity, leading this to be the first reported case of a limb-reduction anomaly in a surviving infant following a failed misoprostol abortion in South Africa. The authors also state that limb reduction has been well described as a teratogenic effect of misoprostol administration in Brazil. There is no discussion of the type of anesthesia used during the attempted sterilization surgery, or any related potential teratogenic effects.

The authors present a case report of a woman from Mozambique who requested an abortion in the UK after taking five 200-μg tablets (1000 μg total) of misoprostol. After receiving counseling about the potential effects of the drug (including fetal abnormalities), the woman elected to continue with the pregnancy. She gave birth to a healthy child.


This Brazilian study sought to compare the frequency of misoprostol use during the first trimester between mothers of infants with Mobius’ syndrome and mothers of infants with neural tube defects. The authors identified 96 infants with Mobius’ syndrome and matched them with 96 infants with neural-tube defects, who served as controls. They found that 47% of the mothers of infants with Mobius’ syndrome had used misoprostol during their first trimester. The number of misoprostol capsules taken ranged from 1 to 18; 42.6% had taken misoprostol orally, 42.6% had taken it both orally and vaginally, and 6.4% had taken it vaginally. In contrast, 3% of the mothers of infants with neural-tube defects had used misoprostol. The authors conclude that use of misoprostol is associated with an increased risk of Mobius’ syndrome in infants, although the absolute teratogenic risk of misoprostol use probably is low.


The authors wrote this letter in response to the article by Pastuszak et al. (described above), which suggested that misoprostol is teratogenic. Blanchard et al. argue that the suitability of administering misoprostol during pregnancy depends entirely on the intended effect, and that concern about potential fetal malformations is misplaced if termination of unwanted pregnancy is the desired outcome. The authors briefly review misoprostol’s effectiveness for pregnancy termination, cervical priming before vacuum aspiration, and prevention of
postpartum hemorrhage, noting the advantages misoprostol has over several other drugs used for these indications. They conclude that concern about teratogenicity associated with misoprostol use should be limited to women who intend to continue their pregnancies to term.


This brief article comments on Dr. Coelho’s description of misoprostol misuse in Ceara state, Brazil. Schönhöfer reports on a project to evaluate the availability of prescription-only drugs in Brazil, during which members of a working group consulted with 102 pharmacists in the Fortaleza area. Pretending to seek help for a pregnant relative, the investigators received advice from 67% of the pharmacists, 83% of whom recommended misoprostol. The pharmacists usually recommended an 800-µg dose (400 µg orally and 400 µg vaginally) but doses of up to 46 tablets were suggested. The author also reports that in 1990 misoprostol was named as an inducing agent in 73% of emergency admissions to the maternity unit of a Fortaleza hospital, which represents a marked increase from the 1988 figure of 12%. After briefly reviewing reports of misoprostol use and adverse fetal effects, the author concludes that misoprostol is ineffective as an abortifacient in approximately half of all cases, and it exposes the fetus to the risk of severe malformation. He states that a drug such as misoprostol cannot be safely marketed in areas in which legal abortion is prohibited and drugs may be used illicitly to induce abortion.


In response to reports by Dr. Schönhöfer and Dr. Fonseca et al., representatives of Brazil’s only nationwide teratogenic information system reported on their knowledge of and experiences with misoprostol use in pregnant women. Since 1990, the Teratogenic Agents Information System in Porto Alegre, Brazil, was contacted by 29 pregnant women seeking counseling after unsuccessful use of misoprostol during the first trimester. Reported doses ranged from 1 to 56 tablets (200 to 11,200 µg), with the median dose being 20 tablets (4000 µg). Three of the pregnancies ended in second-trimester spontaneous abortion, three
women were still pregnant, and contact with six others was lost. Among the remaining 17 live births, no major malformations were found. The authors conclude that their preliminary data do not support the hypothesis that misoprostol is teratogenic in humans.


This prospective, controlled observational study in Brazil evaluated and compared the rate and type of birth defects in 86 infants exposed to misoprostol during gestation and 86 pair-matched, non-exposed controls. The total misoprostol doses taken by pregnant women ranged from one tablet (200 µg) to 98 tablets (19,600 µg) taken orally (75.3%) or orally plus vaginally (24.7%). Approximately 92% of women began their exposure to misoprostol during the first trimester, usually between 5 and 8 weeks LMP. The authors point out that the manufacturer of misoprostol claims that preclinical animal toxicology data have shown no evidence of teratogenicity of misoprostol, even at comparatively high doses. The study found no significant difference in the rates of major birth defects (2/67 vs. 2/81) or minor birth defects (7/67 vs. 3/81) between misoprostol-exposed and non-exposed infants, and no specific pattern of defects was observed. The investigators did not observe any relationship between the total dose of misoprostol and rates of birth defects. Although there were significantly more miscarriages in the exposed group, there was no statistical difference in gestational age at delivery, birth weight, sex ratio, rate of prematurity low birth weight, or rates of cesarean section between groups. The authors conclude that these data do not suggest a potent teratogenic action of misoprostol exposure during pregnancy. While misoprostol use during pregnancy may increase the incidence of congenital abnormalities, the magnitude of the increased risk is low.


The author of this letter sought to identify the possible teratogenic mechanism of misoprostol. Explaining that Mobius syndrome consists of 6th and 7th nerve palsies, the author states that these nuclei are located at a level in the embryo that could be bent or
hinged by pressure in a cephalocaudal direction, particularly during early pregnancy when there is a relative lack of tissues in this area. He suggests that if the embryo were in a position in which misoprostol-induced uterine contractions would cause flexion in the area of cranial nuclei 6 and 7, the flexed area could be subjected to decreased blood flow, and hemorrhage and/or cell death in the cranial nuclei could occur. He notes that after the 60th day of gestation, increasing amounts of amniotic fluid surround the embryo and protect it from flexion at a later stage. In the conclusion of his letter, the author states that uterine contractions caused by chorionic villus sampling and ergotamine also have been associated with Mobius syndrome.
Absorption Kinetics

These six studies indicate that, while orally administered misoprostol is rapidly absorbed, vaginal administration results in sustained plasma levels, greater bioavailability, and a local effect on the cervix that is more conducive to the physiological effects required for abortion. Many other studies of misoprostol used for abortion during the first and second trimesters also attest to the increased efficacy observed with vaginal versus oral administration. In addition to the articles in this section, the study of misoprostol use for postpartum hemorrhage by O’Brien et al. (1998) demonstrated that misoprostol also is effectively absorbed when administered rectally.

Although these studies show that vaginal misoprostol has greater clinical efficacy than oral misoprostol, one of the studies indicates that women prefer oral misoprostol. This important element warrants further investigation. In addition, because misoprostol tablets are meant to dissolve in the acidic pH of the stomach, solubility of vaginally administered misoprostol should be investigated. Tablets do not dissolve in all women who receive misoprostol vaginally (Bugalho, 1993); which may warrant moistening the tablets prior to insertion.


This presentation provides a general overview of misoprostol’s applications in the management of gynecological and obstetric problems. Noting that misoprostol is rapidly absorbed after oral, vaginal, and rectal administration, the speaker stated that with oral administration, the half-life is <30 minutes and peak level occurs at 15 minutes; after vaginal administration, there is a gradual rise to a maximum level at 60 to 120 minutes, with the level at 60% of peak at 240 minutes. The speaker noted that vaginal administration has demonstrated greater abortifacient efficacy than oral administration during the first trimester, and is associated with fewer side effects. The presentation provides a brief review of published data pertaining to the use of misoprostol during early pregnancy, including cervical dilation, abortion, and treatment of incomplete abortion. Despite its title, the presentation does not include detailed information about management of bleeding; it
only mentions that misoprostol’s uterotonic effects in the management of the third stage of labor and postpartum hemorrhage currently are being studied.


In this prospective, multisite trial (Pittsburgh and Havana) women seeking elective abortion using the methotrexate/misoprostol regimen were randomized to receive either dry or moistened misoprostol tablets. One hundred twenty-four women were enrolled into each arm of the study. Comparing the rates of both immediate abortion (within 24 hours) or eventual abortion showed that moistening the misoprostol tablets had no effect on efficacy of the drug. However, the group moistening the misoprostol reported greater rates of side-effects (diarrhea and fever/chills).


Nonsteroidal anti-inflammatory drugs (NSAIDs) generally are not used during medical abortion due to the belief that NSAIDs such as ibuprofen reduce prostaglandins in the body. The authors of this study point out, however, that ibuprofen prevents the body from synthesizing prostaglandins, but is not shown to reduce the effect of prostaglandins already in the body. They therefore allowed the use of NSAIDs in three medical abortion trials using the methotrexate/misoprostol regimen. By analyzing the reported analgesic use of 416 women who received methotrexate and misoprostol, the authors found that NSAIDs did not appear to interfere with pregnancy expulsion. Of women who took an NSAID after their first dose of misoprostol, 53.7% aborted within 24 hours, compared to 48.8% of those who did not take an NSAID. Of the women requiring a second dose of misoprostol, 48.2% of NSAID users aborted within 24 hours, while only 22% of non-NSAID users did.

Overall, women who had successful abortions were more likely to use narcotic pain relief and less likely to use no pain relief. The authors conclude that while NSAID use does not appear to interfere with abortion, women who have successful abortions are more likely to use pain relief.

Absorption and effects of oral and vaginal misoprostol doses (200 μg and 400 μg, respectively) were evaluated in 30 women with pregnancies between 8 and 11 weeks who requested an abortion. In all the patients, the first effect of both oral and vaginal doses was uterine tonus (uterine tension between contractions). The effects of oral administration were more rapid and the initial increase in tonus was more pronounced than after vaginal treatment; the 400-μg oral dose increased uterine tonus after 7.8 ± 3.0 minutes and reached its maximum after 25.5 ± 5.0 minutes, while the 400-μg vaginal dose increased uterine tonus after 20.9 ± 5.3 minutes and reached its maximum after 46.3 ± 20.7 minutes, sustaining uterine tonus at a higher level for a longer time than with oral administration. Plasma levels were highest 30 minutes after oral treatment and 1 to 2 hours after vaginal administration. All patients receiving misoprostol vaginally slowly developed regular uterine contractions, while only 6 (40%) of the 15 women in the oral group experienced the same effect. The authors suggest that the long-lasting and continuously increasing uterine contractility observed after vaginal administration may be due to the local effect of misoprostol on the cervix, which initiates the physiologic events leading to increased uterine contractility.


In this prospective, randomized study, 98 women with pregnancies of 14 to 20 weeks received 200 mg of mifepristone orally. Thirty-six to 42 hours after oral administration of mifepristone, women were given either oral (n=49) or vaginal (n=49) misoprostol 200 μg every 3 hours for a maximum of five doses in the first 24 hours. Those who received misoprostol orally also received a placebo (vitamin B6) vaginally, and visa versa. Patients were reassessed after 24 hours if they did not abort. If there were no signs of imminent abortion, a second course of misoprostol was given for a maximum of five doses. Those
who failed to abort after 48 hours were treated with gemeprost. Ninety percent of women in
the vaginal misoprostol group aborted and 69% of the women in the oral misoprostol group
aborted. Complete abortions (i.e., evacuation not required) occurred in 73.5% of the
vaginal group and 39.2% of the oral group. The mean total vaginal misoprostol dose was
600 µg and the mean total oral dose was 1000 µg. The median interval between misoprostol
administration and abortion in the vaginal group was 9 hours, significantly shorter than the
interval of 13 hours in the oral group. There was no significant difference in side effects
except for fatigue and breast tenderness, which were more common in the oral group. A
post-treatment patient survey indicated that 75.5% of patients preferred oral administration
because vaginal administration was painful and oral administration was more convenient
and private.

Conducted in San Francisco, this study evaluated the effects of 400-µg doses of
misoprostol administered orally or vaginally in 10 pregnant women and 10 non-pregnant
women. In the oral group, the mean time to peak plasma levels (34 ± 17 minutes) was
much shorter and the maximum mean of misoprostol serum levels (277 ± 124 pg/mL) was
significantly higher than the vaginal group. In contrast, plasma concentrations in subjects
receiving vaginal doses rose gradually, reached maximum levels (mean: 165 ± 86 pg/mL)
between 60 and 120 minutes (mean 80 ± 27 minutes), and declined slowly to an average of
61% of the peak level at 4 hours. The study finds the bioavailability of vaginal misoprostol
to be three times higher than orally administered misoprostol, which may explain why
vaginal administration is reported to be more effective for medical abortion. The authors
state that the prolonged serum concentrations observed in the vaginal group suggest that
vaginal administration could be dosed at longer intervals than with oral administration.
This study also found that mean maximum plasma concentrations were no lower among the
vaginal group even if tablets remained intact in the vagina during the study. In some cases,
two intact tablets were removed from subjects after the study, but the pharmacokinetic
findings for these women were comparable to the others.
Women’s Use of Misoprostol for Self-induced Abortions

While use of misoprostol-only methods of self-induced abortion has been reported in numerous countries (including Vietnam, Thailand, South Africa, and the United States), the majority of published reports document the use of this regimen in Brazil. Abortion is illegal in Brazil except in cases of life-threatening complications or rape. In 1993, abortion ranked fourth among major causes of maternal mortality, and there may be as many as one to four million abortions per year in this country. Cytotec (misoprostol) was approved for use as an ulcer treatment in Brazil in 1985 and quickly was surrounded by controversy. As knowledge of the widespread use for self-induced abortions grew, Cytotec sales and use were totally banned in Ceara state, and strictly restricted in other areas in July 1991. These restrictions, along with increasing anti-use campaigns in the media, led to a marked drop in Cytotec sales in 1992. Costa (1998) has noted that the attention placed on misoprostol by the media, clinicians, and women fueled awareness of misoprostol’s abortifacient potential. Information about administration and risks appears to have been exchanged informally between women and, in some cases, between women and pharmacists; formal sources of information for users do not appear to be readily available.

Barbosa and Arilha (1993) provide a thorough review of Brazilian experiences with Cytotec through 1993. During this time, studies revealed that up to 72% of abortions with complications in Brazil were induced by Cytotec. They note that the issues raised by the Cytotec debate may have created a more favorable environment for abortion discussions. The Arilha and Barbosa article is an important online follow-up to this piece. Costa’s 1998 article provides an overview of Brazilian women’s increasingly sophisticated use of the drug in more recent years. Other articles in this section also provide important information about women’s experiences with misoprostol. Despite widespread use of the drug, women have reported using a range of doses (one women reported using eighty-four 200-μg tablets) and administration routes. Though less common now, simultaneously administering misoprostol by oral and vaginal routes often has been reported.

Because of abortion’s illegal status in many countries, many women whose attempts to induce abortion with misoprostol failed may have had little choice but to carry their pregnancies
to term. As a result, these experiences also provide information about misoprostol’s potential teratogenic effects (see “Teratogenicity” section on page 65).

91. Arilha M and Barbosa RG. *Cytotec in Brazil: ‘At Least It Doesn’t Kill.’* (no publication date listed). Available online at www.hsph.harvard.edu/Organizations/healthnet/reprorights/docs/arilha.html. This is an expanded and updated version of the authors’ article, “The Brazilian experience with Cytotec,” which appeared in *Studies in Family Planning* (see next entry). Like its predecessor, this paper describes how the use of Cytotec spread in Brazil and the problems it created for the government, how it affected gynecologists’ thinking and practice, how it altered women’s experience of clandestine abortion, and the continuing problems that have resulted from the “solution” of restricting the availability of this drug. In this version, the authors note that misoprostol may be in use by women in Mexico, Venezuela, and Barbados in addition to Brazil. They also report on another drug, Dicorantil (Sarsa Laboratories), which is indicated for cardiac problems but also has been used as an abortifacient in Brazil. In their conclusion, Arilha and Barbosa argue that restriction of Cytotec has allowed abortion-related problems to continue and perhaps even worsen, and that the situation in Brazil is unlikely to change soon.


The authors provide a description of the Brazilian abortion environment, analysis of sales data for Cytotec (misoprostol), and results from focus groups with women and providers. Focus groups with women of different social and age strata revealed that women self-administer Cytotec orally or vaginally in dosages of four to sixteen 200-μg pills. Women had a distinct preference for a dosage of four pills (two taken orally and two taken vaginally), although dosages of as many as 60 pills have been reported. Women indicated that most attempts to interrupt pregnancy with Cytotec occurred during the first trimester. They cited Cytotec’s low cost, easier decision-making process, privacy, and perceived safety as key factors for choosing Cytotec. After using Cytotec, however, many women perceived their experience as negative due to significant pain and/or required hospital
assistance. Although women shared information about how to take the drug, they ignored dosage limits and lacked factual information about when to seek assistance. Focus groups conducted with male and female gynecologists confirmed the widespread use of Cytotec as an abortifacient. Gynecologists considered Cytotec a valuable therapeutic resource. They also reported that Cytotec enables them to perform abortions without becoming involved with the police, as women who have taken misoprostol can present at public health services as though they were undergoing a miscarriage and have their abortions completed in a safe environment. As result of Cytotec availability, prejudice against abortion has diminished in Brazil, and a favorable atmosphere for promoting discussion of legalized abortion has developed.


The authors reviewed the records of women admitted to the main obstetric hospital of Fortaleza, capital of Ceara state, Brazil, for uterine evacuation after incomplete abortion. The authors report that 593 (31%) of the 1,916 cases that occurred in 1991 were attributed to self-induced abortion. Although sales of Cytotec were completely suspended in Ceara state in July 1991, 444 (75%) cases were related to misoprostol use. Among these women who used misoprostol, LMP was 12 weeks or less for 90% of cases and 4 weeks or less for 44% of cases. The dose of misoprostol ranged from 200 to 9400 μg (1 to 47 200-μg tablets). Sixty-eight percent of women took an 800-μg dose, although 14 women used 10 to 20 tablets and one took 47 tablets. Sixty-eight percent of women took the tablets simultaneously by mouth and vaginally. The authors report that the number of incomplete abortions induced by misoprostol increased substantially during the first half of 1990 and declined thereafter, essentially paralleling Cytotec sales. Even with sales prohibited, misoprostol was still associated with 70% of all evacuations between August 1991 and July 1992.


The authors interviewed 1,603 women with abortion complications, 803 (50%) of whom
were classified as induced abortion cases. Of these, at least 57% induced abortion with misoprostol alone or with another (unspecified) method. Most women (84%) learned about misoprostol from friends, relatives, or colleagues, and 10% learned about it directly from their pharmacist. Seventy percent of women obtained it from a pharmacy and nearly half were given advice there on how to use it. Women said that they chose misoprostol because it was accessible, safer than other methods, and cheap. Most women (74%) self-administered misoprostol before 16 weeks’ gestation. The women reported taking doses between 200 µg and 16,800 µg. (1 to 84 tablets); the median dose was 800 µg. Routes of administration included oral (65% of cases), both oral and vaginal (29%), and vaginal only (6%). Median doses for those administration routes were 800 µg, 1000 µg, and 500 µg, respectively. The proportion of women reporting onset of bleeding within 12 hours increased with gestational age. Of the 454 women who used misoprostol, 85% needed surgical evacuation. This proportion decreased significantly with duration of gestation. Morbidity among patients who use the drug was considerable but less severe than among women who used invasive methods. Three deaths were reported among women who had reportedly used misoprostol (two cases of sepsis and one ruptured uterus). In their conclusion, the authors estimate that as many as 10% of infants carried to term may have been exposed to misoprostol in utero, possibly increasing their risk of malformation.

95. Costa SH. Commercial availability of misoprostol and induced abortion in Brazil. *International Journal of Gynecology and Obstetrics* 1998; 63 (Suppl 1):S131-S139. This article reviews a wide range of studies on misoprostol in Brazil, including the author’s 1991 study described above. Reviewing the history of misoprostol’s availability in Brazil, the author notes that pharmacies, doctors, women themselves, and the media were responsible for disseminating information about the drug. Despite government efforts to limit misoprostol use, studies have shown that a substantial proportion (40% to 78%) of women hospitalized for induced abortion attempts reported use of misoprostol. Citing the wide range of dosages (200 µg to 16,800 µg) identified in her 1991 study, the author notes that, in 1991, women and pharmacy attendants had little information about doses or routes of administration. After 1991, the population had gained experience with misoprostol, and most women limited the dose to four tablets. The author reports that although morbidity
among patients who use the drug is considerable, it is less severe than among women who use invasive methods, and has been reduced by women’s improved understanding of the method as well as health professionals’ improved management of misoprostol patients. The author states that misoprostol may have replaced some of the more dangerous abortion methods.


This report on misoprostol from Johannesburg states that “state hospitals are dishing out unlicensed abortion pills to hundreds of pregnant women, despite the manufacturer’s fears that the treatment could be dangerous.” Written 8 months after abortion on request was legalized in South Africa, the article briefly reports on Searle’s reluctance to register Cytotec for abortion use due to its side effects (e.g., heavy bleeding). It also describes the South African Health Department’s use of misoprostol for cervical priming for first-trimester abortion and abortion during the second trimester.


To assess the health implications of unsuccessful use of drugs to induce abortion in Brazil, the authors interviewed 6,102 pregnant women between 21 and 28 weeks. They asked “In order to know if you were pregnant, did you take any drugs to induce menstrual flow?” A total of 874 (14.4%) answered yes. Of these, 41% had taken herbal teas, 30% had taken estrogens and/or progestins, and 16% had taken misoprostol. Misoprostol use occurred in 2.2% of pregnancies carried to term, and was strongly associated with unplanned pregnancy, absence of partner, and previous induced abortion. In all, 14% of women used drugs of uncertain risk to their fetuses. [Note: Costa and Vessey (1993) estimated that pre-natal exposure rates may be as high as 10%.]


This article explores the epidemic of unsafe abortion in Latin America. It provides detailed
abortion-related data for each of the Latin American countries. In general, Latin America and the Caribbean have one of the highest incidences of induced abortion in the developing world. An estimated five million induced abortions occur in Latin America each year, with 65 abortions per 1,000 women of reproductive age and 30 abortions per 100 pregnancies. Nearly all of these abortions—except for those in Barbados, Belize, and Cuba, where abortions are permissible under certain circumstances (e.g., socioeconomic hardship)—are illegal and unsafe. Complications arising from unsafe, illegally induced abortion are considered the principle cause of death in women aged 15 to 39 years, resulting in an estimated 4,500 to 11,000 abortion-related deaths in Latin American each year.

Misoprostol is mentioned as one of the many abortifacients used in Brazil. The authors present three strategies for addressing this abortion problem: increasing access to and correct use of contraceptives, introducing and using safe abortion technologies, and promoting legal change.


This cross-sectional study assessed the knowledge, acceptability, and use of unprescribed misoprostol as an abortifacient among 610 women using one of three obstetrics/gynecology clinics in New York City. The women were primarily Latina (86%) and had an average age of 26. Participants answered a self-administered questionnaire about their demographic and obstetrical characteristics; patterns of contraceptive use, including emergency contraception; acceptability of and access to abortion; prevalence of misoprostol use; and knowledge, attitudes, and availability of misoprostol. Thirty-seven percent of respondents said that they were familiar with misoprostol’s use as an abortifacient, and five percent reported personal use. The authors point out that this proportion exceeds the proportion reported in Brazilian populations. The most common sources of misoprostol were doctors (67%), pharmacists (66%), “another country” (38%), and friends or family members (29%). Previous misoprostol use was highest among recent immigrants, suggesting that knowledge of misoprostol in this population may come from outside the United States. The primary reasons given for misoprostol use were ease and price. Respondents who admitted
to having taken misoprostol had a basic but incomplete understanding of its health risks. The authors conclude that these results highlight a need for increased awareness and education of pre- and post-conception family planning methods, and a decrease in barriers to these methods.
Informal Resources

As is the case with many journal articles, websites and nonclinical informal resources most often focus on misoprostol use in conjunction with mifepristone or methotrexate. Sites that do mention misoprostol-only regimens do so briefly and with minimal administration guidelines. Examples include Chapter 6 of the International Society of Abortion Doctors’ *Practical Guide for Doctors* [http://www.nedernet.nl/~ngva/prguide/p%202001%20young%20preg.htm], which states that “In any stage of the pregnancy 8 to 12 tablets taken in one dose by mouth will terminate the pregnancy,” and the Gentlebirth “Miscarriage” bulletin board [www.gentlebirth.org/archives/miscrg.html], which reads “Cytotec 800 mcg (yes you read it right) intravag and repeat in 4 hours since there is no baby no limit on the number of repetitions….WATCH FOR BLEEDING….” [sic].

Few other online or client-oriented resources that provide information about misoprostol’s abortifacient potential could be identified. One exception is the following:


In the discussion of drug-induced abortions (mifepristone or methotrexate plus misoprostol), the following warning is included: “It is important to note that misoprostol, by itself, will not cause an abortion. If you receive two doses of misoprostol at the clinic, but use only one, don’t pass the remaining dose on to desperate friends. *The use of misoprostol alone is not likely to cause an abortion and may harm a developing fetus.*” In the discussion of early drug-induced abortion in Brazil, the use of “an easily available oral prostaglandin” is mentioned, but misoprostol is not identified by name.
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Appendix A: Additional Misoprostol References


