APPLICATION FOR INCLUSION OF MIFEPRISTONE AND MISOPROSTOL IN THE 14th WHO MODEL LIST OF ESSENTIAL MEDICINES

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Application
The Geneva Foundation for Medical Education and Research (GFMER) - WHO Collaborating Center in Education and Research in Human Reproduction - is submitting the application of two individual medicines (200mg mifepristone and 200microg misoprostol) as a sequential regimen for early medical abortion in the 14th WHO EDL1.

Background
Unsafe abortion is a public health problem worldwide. One way of reducing the number of unsafe procedures is to increase safe choices for pregnancy termination. In developed countries, of the 28 million pregnancies occurring every year, 36% end in abortion. In developing countries, of the 182 million pregnancies occurring every year, 20% end in abortion. Almost 80% of all abortions are conducted in developing countries. Worldwide 3,6% of women aged 15-44 are estimated to have pregnancy terminations yearly which make a total of more than 46 million abortions per year2.

There is a great concern about the effectiveness and safety of surgical methods (vacuum aspiration or dilatation and curettage or hysterotomy) that may be less effective and may increase the risk of infection (sepsis), uterine perforation, cervical laceration, incomplete evacuation, hemorrhage, miscarriage, future sterility and death. Even though, in developing countries those unsafe methods are commonly used. According to WHO3, 19 million women have an unsafe abortion worldwide each year and 18.5 million of these occur in developing countries. Mortality due to unsafe abortion is estimated about 68000 women each year4.

In a Cochrane systematic review5 of three clinical trials, vacuum aspiration versus dilatation and curettage, and flexible versus rigid vacuum aspiration cannula were compared. There was no indication of a preference of providers for one or the other method. There were no reports of maternal deaths and cases of uterine perforation in the trials identified. There were no statistically significant differences in negative outcomes, probably because the trials included are small and lack power to present meaningful differences among groups.

Medical abortion became an alternative method of first trimester pregnancy termination. It has the potential to be easier to perform and be lower in cost compared to surgical methods. A Cochrane systematic review of five small studies6 evaluated medical methods in comparison to surgical method (vacuum aspiration) for first-trimester abortion. The efficacy rates were ranging between 76% and 97.2% for medical and between 94 and 100% for surgical abortions in the individual trials. The rate of incomplete abortions was statistically significantly higher in the prostaglandin used alone group (OR = 2.7, 95%CI: 1.1-6.8) in comparison to vacuum aspiration. There were no data on the most commonly
medical (mifepristone/misoprostol) and surgical abortion methods available to be included in the review. There were no statistically significant differences among mifepristone, mifepristone and prostaglandin, methotrexate and prostaglandin versus vacuum aspiration. Duration of bleeding was longer in the prostaglandin and methotrexate and prostaglandin groups compared to vacuum aspiration. Also, medical methods may be more painful. There was only one major complication (uterine perforation) in one trial in the surgical group. Another comparison between medical (600 mg mifepristone followed by 1 mg gemeprost) and surgical (vacuum aspiration) abortion evaluated patients’ satisfaction with each method and tried to identify potential confounders affecting satisfaction. Satisfaction with both medical and surgical abortions is high, although higher with the surgical than the medical procedure. Satisfaction with the medical procedure was inversely correlated with the intensity of pain, nausea, vomiting and dizziness, while satisfaction with the surgical procedure was unaffected by these side effects.

The most widely researched medicines for medical abortion are prostaglandins (PGs), misoprostol (a synthetic prostaglandin E1 analogue), mifepristone (an antiprogestogenic steroid) and methotrexate used alone or combinations of mifepristone with prostaglandins or misoprostol and methotrexate with prostaglandins. The concern about their widespread use as a self-medication has justified their non-approval for marketing in various countries, mainly where abortion is considered illegal. However, in about thirty countries where medical abortion has been registered, millions of women have used it. Mifepristone has been licensed in France and China since 1988, in Great Britain since 1991 and in Sweden since 1992 followed by other European countries between 1999 and 2001. In September 2000, the FDA approved mifepristone, in combination with misoprostol for the termination of early pregnancy (defined as 49 days or less). In those countries where medical abortion has been freely available for about 10 years, such as France, Scotland and Sweden, about 60–70% of eligible women elect the combination of a single dose of mifepristone followed 48 hours later with a suitable prostaglandin for early abortion. Mifepristone facilitates uterine response to the subsequent administration of misoprostol or a prostaglandin. Misoprostol has been shown to be an effective myometrial stimulant of the pregnant uterus, even at the beginning of pregnancy. Thus, it is an effective abortive agent. The use of misoprostol has become increasingly common because it is inexpensive, easily stored at room temperature (36 months validity), effective in causing uterine contractions, and has few systemic side effects.

According to WHO, the risk of death due to unsafe abortion complications in developing countries is one hundred times higher compared to when performed under safe conditions. Medical methods offer a safe treatment alternative in those settings, because their administration requires little training and a simpler infrastructure compared to surgical procedures. Although abortion is a worldwide reality, provision of ongoing contraception and encouragement of emergency contraception can reduce unintended pregnancies and the need for abortion.

Aims of the search: To assess the effectiveness and safety of mifepristone followed by misoprostol for first trimester (until 9 weeks) medical abortion, in order to decide on its inclusion as 200mg and 200microg tablets, respectively, in the 14th
edition of WHO Model List of Essential Medicines. Additionally, choose the appropriate dosage regimen and route of administration of the combined medicines.

Methods: A Medline search for systematic reviews and randomised controlled trials (RCTs), from 2000 to 2005, yielded three Cochrane systematic reviews, three meta-analyses and 30 RCTs (15 if the search uses “mifepristone misoprostol early abortion”). The systematic reviews have compared different surgical methods, medical methods versus surgical method (vacuum aspiration) and different medical methods for first trimester abortion. The first meta-analysis estimated rates of primary clinical outcomes of medical abortion (successful abortion, incomplete abortion, and viable pregnancy) and compared them by regimen and gestational age; the second evaluated safety of mifepristone in combination with misoprostol; the third identified conditions that intervene in outcomes. The RCTs mainly compared different drug regimens in respect with efficacy and side effects. Additionally WHO documents were reviewed.

Comments

EFFECTIVENESS

Comparisons among different medical methods
A Cochrane systematic review of 39 randomised controlled trials compared the effectiveness of different medical methods for first trimester abortion. The main outcome measure was failure to achieve complete abortion. Combined regimens were more effective than single agents. The most common combined regimen, oral mifepristone (200mg) followed by misoprostol vaginally (400microg) evidenced to be an effective and safe method for pregnancy termination in the first trimester. Some of the results were only based on small studies and therefore carry some uncertainty. Almost all trials were conducted in hospital settings with good access to support and emergency services. It is therefore not clear if the results are readily applicable to under-resourced settings where such services are lacking even if the agents used are available.

A meta-analysis of 54 studies estimated rates of primary clinical outcomes of medical abortion (successful abortion, incomplete abortion, and viable pregnancy) and compared them by regimen and gestational age. The efficacy decreases with increasing gestational age ($P<0.001$), and differences by regimen are not statistically significant except at gestational age $\geq 57$ days. For gestations $\leq 49$ days, mean rates of complete abortion were 94–96%, incomplete abortion 2–4%, and ongoing (viable) pregnancy 1–3%. For gestations of 50–56 days, the mean rate of complete abortion was 91% (same for all regimens), incomplete abortion 5–8%, and ongoing pregnancy 3–5%. For $\geq 57$ days, success was lower for mifepristone/misoprostol (85%; 95%CI: 78–91%) than for mifepristone/other prostaglandin analogues (95%; 95%CI: 91–98%; $P = 0.006$).

Comparisons among agents used alone or in combination
A randomised, double-blinded and placebo-controlled trial compared vaginal 800microg misoprostol alone or 48 hours later 200mg mifepristone orally for termination of early pregnancy. Successful abortions occurred in 95.7% and 88.0%
of women receiving combined regimen and misoprostol alone, respectively \( (P < 0.05) \).

A double-blind randomized clinical trial\(^{15}\) compared 0.5 mg gemeprost vaginally (group I, \( n = 499 \)) with 800 microg misoprostol vaginally (group II, \( n = 500 \)) administered approximately 48 hours after 200 mg mifepristone as a single oral dose in women undergoing an abortion at gestational age \(< \) or \(= 63 \) days. The rate of complete abortion was very high in both groups but significantly higher after treatment with misoprostol than with gemeprost (98.7\% versus 96.2\%; \( P = 0.019 \), difference 2.5\%, 95\%CI: 0.4- 4.7\%). Both incomplete abortion and ongoing pregnancies were more frequent in the women who received gemeprost than in those who received misoprostol. Side effects were similar in women who received misoprostol or gemeprost.

**Protocol Comparisons**

On the basis of a French clinical trial\(^{16}\), a single oral dose of mifepristone (600mg) became to be commonly used as a pre-treatment, followed by oral misoprostol (400microg) 36 to 48 hours after, as a single dose too. Two studies\(^{17, 18}\) tested this regimen in women at \(\leq 49 \) days’ gestation. The rate of complete abortion was 97\% and 92\% in French and US studies, respectively. The efficacy and safety of this regimen were comparable to vacuum aspiration at the same gestation\(^8\).

The application for inclusion proposed a sequential regimen with mifepristone (200mg) orally as a single dose followed 36-48 hours after by misoprostol (800microg) vaginally as a single dose too. The pharmaceutical formulation is oral tablets (mifepristone 200mg and misoprostol 200microg).

**Pharmaceutical formulation**

In many countries oral misoprostol tablets are used vaginally, although they are not formulated for the vaginal route. Oral tablets may be different from vaginal tablets. In Brazil misoprostol is registered as vaginal tablets (25, 100 and 200 micrograms). Oral tablets put inside the vagina may be poorly dissolved, then suffering expulsion (Personal communication). Extensive clinical experience has demonstrated that vaginal administration is more effective and is associated with fewer side effects, as nausea and diarrhoea.

**Dosage**

In a Cochrane systematic review\(^{12}\), when the combined regimen mifepristone/prostaglandin was used (4 trials), mifepristone 200 mg versus 600 mg showed similar effectiveness in achieving complete abortion (RR: 1.07; 95\%CI = 0.87-1.32). In the same combined regimen, misoprostol used vaginally at a higher dose (800 mcg) seemed to be more effective than gemeprost 0.5 mg according to data from a single trial (RR = 2.86; 95\%CI: 1.14-7.18).

A WHO study\(^{19}\) compared the efficacy of a single oral dose of mifepristone (200mg or 600mg) followed by a single oral dose of misoprostol (40microg) 48 hours later for medical abortion in 1589 women with menstrual delay of \(< \) or \(= 35 \) days. The complete abortion rate with the lower dose of mifepristone was similar to that with the higher dose (89.3\% vs. 88.1\%) The crude relative risk of failure to achieve complete abortion with the 200 mg dose compared with the 600 mg dose was 0.9 (95\% CI: 0.7-1.2).
Another study\textsuperscript{20} proposed 100mg mifepristone orally as an effective dose for early abortion when followed 2 days later by misoprostol 400microg orally (group 1) or 800microg vaginally (group 2) in women at up to 49 days' gestation. Twenty-four hours after receiving misoprostol, 85% versus 95% of the women in group 1 and group 2, respectively, had complete abortions (\(P = 0.03\)). Side effects occurred with similar frequency in both treatment groups. Misoprostol oral dose of 400 microg is restricted to very early pregnancy (\(\leq 49\) days) because beyond this gestation the incidence of failures is too high to be clinically acceptable. Although the most frequently used dose of vaginally administered misoprostol (800microg) is slightly higher than that used orally (400 microg), the improved efficacy at later gestations and shortened expulsion time are likely also due to differing pharmacokinetics of vaginally and orally administered misoprostol\textsuperscript{21}.

**Route of administration**

There are significant differences in the pharmacokinetics of misoprostol administered by vaginal and oral routes that may explain the difference observed in clinical efficacy. One study\textsuperscript{22} compared the pharmacokinetics after administration through each route. Misoprostol is absorbed faster orally than vaginally, with higher peak serum level. Misoprostol vaginally absorbed produces peak concentrations about two hours and more prolonged serum levels (50% peak concentrations about 4-6 hours), suggesting that vaginally administration could be used at longer intervals than oral. Another study\textsuperscript{23} compared the degree of absorption and the effect on uterine contractility of misoprostol after vaginal and oral administration in thirty women with a normal intrauterine pregnancy between 8 and 11 weeks' gestation. In all patients, the first effect of 400microg misoprostol was an increase in uterine tonus, started in 7.8 ± 3.0 minutes after oral and 20.9 ± 5.3 minutes after vaginal administration. Serum concentration reached its maximum after 25.5 ± 5.0 minutes and 46.3 ± 20.7 minutes, respectively, after oral and vaginal administration. The long-lasting and continuously increasing uterine contractility after vaginal administration can be explained only in part by a direct effect of misoprostol. The longer period of elevated plasma levels of misoprostol may also have initiated the prolonged events leading to increased uterine contractility.

In the Cochrane systematic review previously mentioned\textsuperscript{12}, misoprostol administered orally was less effective (more failures) than the vaginal route (two trials; RR= 3.00; 95%CI: 1.44-6.24) and might be associated with more frequent side effects such as nausea and diarrhoea.

Vaginal and oral route of 800microg misoprostol one day after 200mg mifepristone orally were compared in 1,144 healthy adult women up to 63 days pregnant and wanting a medical abortion. Vaginal misoprostol was more effective at inducing an early medical abortion at one day after low-dose mifepristone (97% vs. 90%), with minimal differences in side effects\textsuperscript{24}. A prospective, randomized, placebo-controlled trial\textsuperscript{25} compared 800microg misoprostol by sublingual and vaginal routes in combination with oral mifepristone (200mg) for termination of early pregnancies up to 63 days. Complete abortion occurred in 98.2% (95% CI: 93–99) of women in the sublingual group and 93.8% (95% CI: 88–97) in the vaginal group. Misoprostol is very soluble in water, usually dissolving within 15–20 minutes. Absorption of misoprostol tablets may be easier to ascertain as its dissolution can be easily observed during sublingual administration compared with vaginal administration.
Moreover, sublingual misoprostol can avoid the first-pass effect through the liver, as in the oral route, and therefore may result in a higher complete abortion rate. A pharmacokinetic study\textsuperscript{26} comparing sublingual, oral and vaginal route of administration of misoprostol has shown that sublingual administration can achieve the highest peak concentration in the shortest time. The systemic bioavailability of sublingual misoprostol was also greater than among all other routes of administration. The side-effect profile, however, has shown that 800 microg sublingual misoprostol was associated with a higher incidence of gastrointestinal side effects, chills and fever. This may be due to the higher peak concentration after sublingual administration. The side effects may be improved by decreasing the dosage of misoprostol to 600 micrograms. However, the efficacy of a lower dosage of misoprostol needs to be assessed by further randomized trials. Sublingual administration has the advantage of avoiding the uncomfortable vaginal examination that is necessary for vaginal administration of misoprostol.

**Time intervals**

Regimens with shorter intervals may be more acceptable. A multinational double blind, randomised controlled trial\textsuperscript{27} compared the efficacy of oral and vaginal administration of misoprostol (800 microg) at day 3 after a single oral dose of mifepristone (200mg) in 2,219 women with ≤63 days of amenorrhoea. Vaginal misoprostol was more effective than oral when continued with 0.4 mg oral misoprostol twice daily for seven days. Misoprostol continuation improved the efficacy in this amenorrhoea group compared with a single dose of vaginal misoprostol on day three, but it did not shorten the duration of bleeding. No differences in efficacy were observed when amenorrhoea length was <57 days. In the combined regimen mifepristone/prostaglandin\textsuperscript{12}, misoprostol administered on day 3 seems to be less effective in achieving complete abortion when compared to day 1. The difference in delay of the administration of prostaglandin may play a role in the acceptability.

A clinical trial\textsuperscript{28} randomised 86 women at a gestational age up to 49 days to take 400 microg misoprostol orally six to eight hours later (Group 1) or 48 hours later (Group 2) a 600mg single dose of mifepristone. Twenty-four hours after receiving misoprostol, 50% of women in Group 1 and 91% of women in Group 2 had complete abortions.

Fox and associates\textsuperscript{29} evaluated the efficacy of mifepristone 200mg orally followed on the same day by misoprostol 800microg vaginally. Forty women from 50 to 56 days’ gestation (Group 1) and 40 women from 57 to 63 days’ gestation (Group 2) inserted misoprostol vaginally 6 to 8 hours after taking mifepristone. Twenty-four hours after receiving misoprostol, 93% (95%CI: 80-98%) and 90% (95%CI: 76-97%) of women from Groups 1 and 2, respectively, had expelled the pregnancy. By follow-up 2 weeks after taking mifepristone all 40 women in Group 1 and 98% women in Group 2 had complete abortions.

In 2004, the same group of investigators\textsuperscript{30} investigated the equivalence between mifepristone 200 mg followed 6 to 8 hours later (group 1) and 24 hours later (group 2) by misoprostol 800microg vaginally for abortion in women up to 63 days of gestation. Complete abortion rates for groups 1 and 2 were 95.8% (95% CI: 93.7-97.3%) and 98.1% (95%CI: 96.6-99.1%), respectively, which were statistically equivalent. Mifepristone 200mg followed 6 to 8 hours later by misoprostol 800
microg vaginally has significantly fewer side effects as compared with regimens using a 24-hour dosing interval.
A randomized trial\(^3\) investigated whether 800 microg of vaginal misoprostol administered at home 1, 2, or 3 days after 200 mg of oral mifepristone influences safety or effectiveness for early medical abortion in 2,225 healthy patients at gestational age of 56 or fewer. Complete medical abortion rates were 98% (95% CI: 97%-99%), 98% (95% CI: 97%-99%) and 96% (95% CI: 95%-97%) among those using misoprostol after 1, 2 and 3 days, respectively.

**Single versus split dose**
In the combined regimen mifepristone/prostaglandin\(^{12}\), there was no statistically or clinically significant difference between single versus split dose (one trial; RR = 0.70; 95% CI: 0.21 - 2.39) regarding failure rates. The side effects tended to favour the split-dose group but were not statistically significantly different in the 2 groups.

**Gestational age at the administration**
A multicentre randomized comparative clinical trial\(^3\) showed significantly differences between success rates in women with less than 49 days of amenorrhoea and more than 49 days of amenorrhoea (Mantel-Haenszel chi-square = 4.24; \(P = 0.04\)). Furthermore, no statistically significantly differences in the success rates were observed between the two treatment regimens in the women with different gravidity in the present study (\(P = 0.05\)). More recent studies\(^{27,30}\) proved the efficacy of the combination regimen for abortion in women up to 63 days of gestation.

**Setting of administration**
Some authors have defended the self-administration of misoprostol at home, highlighting privacy and reduction of cost, as well as simplification of protocol. On the other hand, medical methods can still be unsafe when performed under inappropriate circumstances such as in a non-sterile environment with lack of proper equipment and emergency drugs, or by untrained personnel. Even in countries where the procedure is legal, appropriate services are needed, because the risk of suffering severe side effects or complications exists and must be controlled. Successful abortion using medical methods requires a well-organized service, which includes referral without delay and a robust system of follow-up to identify failures.

According with WHO\(^4\), in a multinational randomized controlled trial evaluating three different misoprostol regimens, following mifepristone administration, for early medical termination of pregnancy, the majority (70%) of the study participants would prefer to have medical abortion at a health facility, compared with 23% who would prefer to have it at home.

**SAFETY**
According to GFMER application\(^1\), “The effects of medical methods for termination of pregnancy are similar to those associated with spontaneous abortion and include cramping and prolonged menstrual-like bleeding. Some side effects such as pain and nausea are due to pregnancy and can be alleviated by simple analgesics or antiemetics”.

A WHO multinational study\(^3\) investigated side effects and women’s perceptions of three misoprostol regimens after mifepristone for early medical abortion. The
pregnancy-related symptoms decreased after misoprostol, and breast tenderness decreased already after mifepristone. Oral administration of misoprostol was associated with a higher frequency of nausea, vomiting and diarrhoea than vaginal administration. Misoprostol induced fever and lower abdominal pain appeared later with the vaginal route. A majority of women would choose medical abortion again and would prefer to have it at a health facility rather than at home. Different studies mentioned side effects of medical methods as heavy bleeding, pain, nausea, vomiting and diarrhoea, varying in severity according to the protocols and gestational age. In comparison with surgical procedures, the observed blood loss is greater in medical abortions. Failed abortion is an infrequent but important complication of medical methods. Both methotrexate and misoprostol may lead to fetal anomalies if the pregnancy persists. A Cochrane systematic review of 39 trials confirmed that major complications seem to be rare, the most common one being blood transfusion (about 0.2%). The side effects are mainly due to prostaglandins (nausea, vomiting, diarrhoea). Higher doses are associated with increased side effects such as nausea and vomiting. One Chinese meta-analysis found the relative risks (95%CI) of bleeding, abdominal pain, fever and dizziness in the medical abortion population were 3.27 (1.14 - 9.38), 1.63 (1.14 - 2.34), 1.58 (1.03 - 2.44) and 1.36 (1.06 - 1.75), respectively. These were higher in the medical abortion population than that in the surgical abortion population. In addition, the duration of bleeding caused by medical abortion was longer than that caused by surgical abortion. Its weighted mean difference was 6.49 (95% CI: 6.08 - 7.80).

An analysis of cramping and bleeding onset patterns in 2,302 subjects treated with 200mg mifepristone orally and 800microg vaginal misoprostol at 24, 48, or 72 hours after mifepristone showed in the 12 hours following misoprostol administration, cramping and bleeding patterns were similar in the three groups. The longer women waited to insert misoprostol, the more likely they were to experience early cramping and/or bleeding. Contraindications for the use of mifepristone/misoprostol are known allergies to one of the substances, suspected ectopic pregnancy, chronic or acute adrenal or hepatic failure, inherited porphyria, bleeding disorders, severe asthma uncontrolled by corticosteroid therapy and heavy smoking.

Conclusion
- Mifepristone/misoprostol combination is more effective than single agents for inducing abortion in first trimester of pregnancy.
- Misoprostol, as the second agent, has become increasingly common, even though there are no statistically significant differences in comparison with the other conventional prostaglandins, except at gestational age ≥57 days. Misoprostol is less expensive, easily stored at room temperature, effective in causing uterine contractions, and has fewer systemic side effects.
- The sequential regimen could prefer mifepristone (200 mg) orally as a single dose and misoprostol (800 mcg) vaginally, 6 to 8 hours after taking mifepristone, as a single dose too. It is also preferable to use vaginal tablets instead of oral tablets by vaginal route.
Oral mifepristone followed by misoprostol sublingual administration seems pharmacokinetically favourable, and more convenient for pregnant women. However, this route demands a lower dose (600 microg) of misoprostol, which could decrease the side effects, but has not had its abortive efficacy proven yet.

The desirable and safer administration setting would be a well-organized service, which could control severe side effects or complications and include referral without delay and a robust system of follow-up to identify failures.

Recommendation

- Mifepristone and misoprostol sequential combination shows the evidence of effectiveness for early abortion and acceptable safety and convenience, when used in adequate regimen. So, it may be recommended for inclusion in the 14th WHO EDL.
- Misoprostol should be available as vaginal tablets of 100 and 200 micrograms.
- The two items should not be listed individually to avoid the misuse of misoprostol.

References
25. Tang OS, Chan CCW, Ng EHY, Lee SWH, Ho PC. A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal


32. An ICMR Task Force Study. A multicentre randomized comparative clinical trial of 200 mg RU486 (mifepristone) single dose followed by either 5 mg 9-methylene PGE2 Gel (meteneprost) or 600 mg oral PGE1 (misoprostol) for termination of early pregnancy within 28 days of missed menstrual period. *Contraception* 2000; 62: 125-130.


14 January 2005