# Medical termination of pregnancy with mifepristone and misoprostol combined therapy: Evaluation of its safety and efficacy in clinical practice in India

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**ABSTRACT :**

**Background and Objective:**

Most current clinical protocols for medical termination of pregnancy require the use of prostaglandins in combination with an antiprogesterone. The present prospective observational study was undertaken to assess the safety and efficacy of mifepristone and misoprostol combined therapy in Indian women.

**Settings and Design:**

An observational study involving six doctors across the various states of India, who prescribed mifepristone and misoprostol combined therapy to adult women (≥ 18 years) requiring medical termination of intrauterine pregnancy (MTP) upto 63 days' gestation.

**Methods and Material:**

Mifepristone was administered under the supervision of the qualified service providers as specified under MTP Act 2002 & MTP Rules 2003 in a total of 270 pregnant women who had opted for the medical termination of their pregnancy. Adverse events which were observed during the therapy were recorded. Efficacy rates were determined as complete abortion rate, incomplete abortion rate or no response rate observed at Day 14.

**Results:**

On clinical assessment, 96.3% cases aborted successfully. Ultrasonography assessment for confirmation of termination of pregnancy was carried out in 190 subjects (70.4% of 270) at the end of 14 days therapy with mifepristone and misoprostol combined therapy and 94.7% women amongst them had shown a complete termination of pregnancy. Side-effects were observed in 11.1% of the women – the commonest being nausea & vomiting (6.7%) and abdominal pain (3.7%).

**Conclusions:**

The present observational study demonstrates that mifepristone and misoprostol combined therapy is an effective and well tolerated medication in Indian adult women (≥ 18 years) requiring medical termination of intrauterine pregnancy (MTP) up to 63 days' gestation.

## INTRODUCTION:

Unsafe abortion is the cause of serious complications and disability for millions of women each year and is a prominent cause of maternal death. Despite efforts to achieve Millennium Development Goal 5 Target 5A – reduce by three quarters the maternal mortality ratio between 1990 and 2015 – the percentage of maternal deaths due to unsafe abortion remains unchanged at 13%. Over the years, surgical abortion using vacuum aspiration of dilatation and curettage has been the method of choice for termination of pregnancy up to 63 days' gestation [1]. However, surgical evacuation has certain complications like perforation, hemorrhage, sepsis, cervical incompetence, incomplete abortion etc. [2].

Over the last three decades, many studies have explored the use of medical methods for inducing abortion up to 63 days' gestation. Earlier regimens included intrauterine injection of prostaglandins

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followed in the 1980s by the introduction of the antiprogesterone, mifepristone. The current clinical protocols for medical termination of pregnancy require the use of prostaglandins in combination with an antiprogesterone [3].

Mifepristone (a synthetic steroid) is an anti-progestin which blocks the action of progesterone, a hormone necessary to maintain pregnancy and thus inhibiting the action of progesterone. Mifepristone alters the endometrium, softens the cervix, initiates uterine contractions and induces menstrual bleeding, which eventually causes the uterine lining to shed. Mifepristone is used in conjunction with misoprostol, an analog of prostaglandin E1 which causes myometrial contractions by interacting with the specific receptors on the myometrial cells. The misoprostol interactions with specific receptors results in a cascade of events, including a change in the calcium concentration, thereby initiating muscle contraction. Misoprostol also softens the cervix which leads to uterus contraction, resulting in the expulsion of the uterine contents.

The US FDA approved mifepristone in September 2000 for use in combination with misoprostol for medical abortion ≤ 49 days of gestation. FDA-approved regimen is mifepristone 600 mg followed by 400 μg of oral misoprostol two days after the mifepristone [4]. The World Health Organization began advocating the use of a lower dose of mifepristone as early as 1991[5]. Extensive clinical research with lower dose (200 mg) of mifepristone followed by 800 μg vaginal misoprostol have shown similar efficacy to 600 mg mifepristone followed by 400 μg misoprostol with additional benefits of better tolerability and cost effectiveness [6].

## METHODS AND PROCEDURES

This prospective observational study was undertaken to evaluate the clinical efficacy and safety of mifepristone and misoprostol combined therapy in adult women (≥ 18 years) requiring medical termination of intrauterine pregnancy (MTP) of up to 63 days gestation based on the first day of the last menstrual period. None amongst the observed women had known hypersensitivity to mifepristone / misoprostol / prostaglandins and none had confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass, intrauterine device in place, chronic adrenal failure, renal or hepatic failure, porphyria and hemorrhagic disorders, with concurrent anticoagulant therapy or long-term corticosteroid therapy.

At the initial visit, the women's demographic data, obstetrical history with details regarding any MTP(s) in the past, concomitant diseases and concomitant therapy, any other abortifacients if used presently and date of last menstrual period (LMP) were recorded. Mifepristone was administered under the supervision of the qualified service providers as specified under MTP Act 2002 & MTP Rules 2003 who were able to assess the gestational age of pregnancy and diagnose ectopic pregnancy. All the women had timely access to emergency medical facilities for the surgical abortion in the event of failure of the medical abortion.

The standard mifepristone-misoprostol regimen typically involved three visits. Counseling and administration of the mifepristone was done on the same day (Day 1). Patients returned 36-48 hours after ingestion of mifepristone and were assessed for the possibility of pregnancy expulsion clinically or by ultrasonography (USG), since between 2% and 5% [4, 7, 8] of women could have aborted with mifepristone alone. If abortion had not occurred, 800 μg misoprostol (four 200-μg tablets) was administered intravaginally by or under the supervision of the qualified service providers and the patient was observed for at least six hours. For women with 49-63 days of gestation, if abortion had not occurred 4 hours after administration of misoprostol, a second dose of misoprostol 400 mcg (two tablets of 200 mcg) vaginally or orally (depending upon the preference and the amount of bleeding) was also permitted. Finally, the patient returned for a follow-up visit approximately 14 days after the administration of mifepristone for final confirmation by clinical examination or ultrasonographic scan that a complete termination of pregnancy had occurred.

Efficacy findings were recorded as complete termination of pregnancy, incomplete termination of pregnancy or no evidence of termination of pregnancy. Efficacy rates were determined as complete abortion rate, incomplete abortion rate or no response rate observed at Day 14. Based on the outcome of the treatment for each patient, the investigators rated the therapy as excellent, good, fair or poor. The patient's feedback in terms of their own assessment to the therapy was also recorded. Each investigator also recorded the adverse events (if any) which were observed during the therapy.

The data which was collected during the study was analyzed descriptively and it was described as the percentage and the total number of observations alongwith the mean and standard deviation. The safety was estimated by measuring the proportion of women who reported any adverse event.

## RESULTS

The study was conducted during the period Apr'14 to Apr'15, wherein six qualified service providers as specified under MTP Act 2002 & MTP Rules 2003 across three states of India provided the data of the 270 women who were prescribed mifepristone + misoprostol combined therapy for the medical termination of intrauterine pregnancy (MTP) upto 63

days' gestation.

**Patient Characteristics**

The mean age of all the 270 subjects enrolled into the study was 30.9 ± 5.7 years with a range of 18-51 years (Figure 1). Majority of the women i.e. 220 (81.5%), enrolled in to the study were in the age group of 18-35 years. A total of three pregnant women (1.1%) enrolled in to the study were more than 46 years of age. The mean duration of pregnancy / period of amenorrhoea in the subjects enrolled in to the study was 52.5 ± 10.8 days (7.1 ± 1.6 weeks) with a range of 23 to 80 days (3 to 11 weeks). Interestingly, the duration of amenorrhoea of 19 women (7.0%) enrolled in to the study was more than nine weeks (63 days) (Table 1).

Of the 270 pregnant women in the study, 97 women (35.9%) had a past history of abortions. A total of 4 subjects (1.2%) had received other abortifacients before participating in the study. Of the 270 subjects – 25.5% of the subjects enrolled into the study were prescribed additional dose of misoprostol tablets during the course of the study for the termination of their pregnancy.

| Sr. No. | Period of amenorrhoea (Weeks) | No of subjects | % of subjects |
|---|---|---|---|
| 1 | 3 weeks | 2 | 0.7 |
| 2 | 4 weeks | 8 | 3.0 |
| 3 | 5 weeks | 42 | 15.6 |
| 4 | 6 weeks | 60 | 22.2 |
| 5 | 7 weeks | 34 | 12.6 |
| 6 | 8 weeks | 96 | 35.6 |
| 7 | 9 weeks | 9 | 3.3 |
| 8 | 10 weeks | 17 | 6.3 |
| 9 | 11 weeks | 2 | 0.7 |
| **Total** | | **270** | **100.0** |

**Table 1: Duration of amenorrhoea in the subjects (*n=270*)**

| Sr. No. | Nature of adverse event | No of events | % of subjects |
|---|---|---|---|
| 1 | Nausea & Vomiting | 18 | 6.7 |
| 2 | Abdominal pain | 10 | 3.7 |
| 3 | Headache | 7 | 2.6 |
| 4 | Bleeding | 2 | 0.7 |
| 5 | Dizziness | 2 | 0.7 |
| **Total** | | **39** | |

**Table 2: Adverse events reported in the study**

**Clinical and USG assessment**

On clinical assessment after the administration of mifepristone + misoprostol combined therapy, 260 (96.3%) women had a complete abortion, six (2.2%) women had incomplete abortion while four (1.5%) women had no evidence of termination of pregnancy on Day 14 (Figure 2).

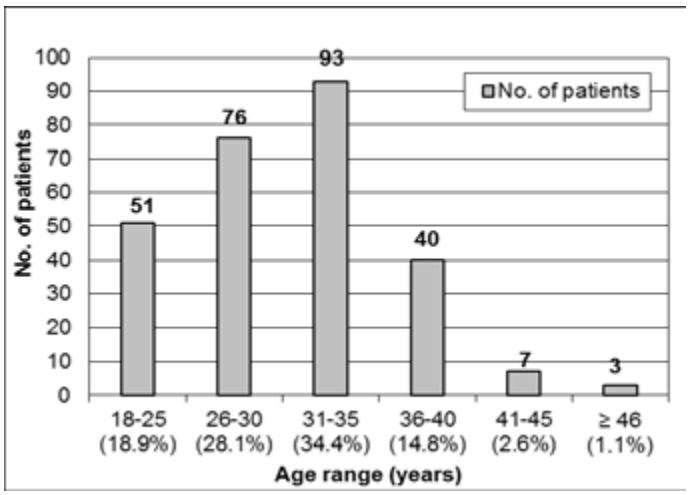


**Figure 1: Age-wise distribution of subjects (n=270)**

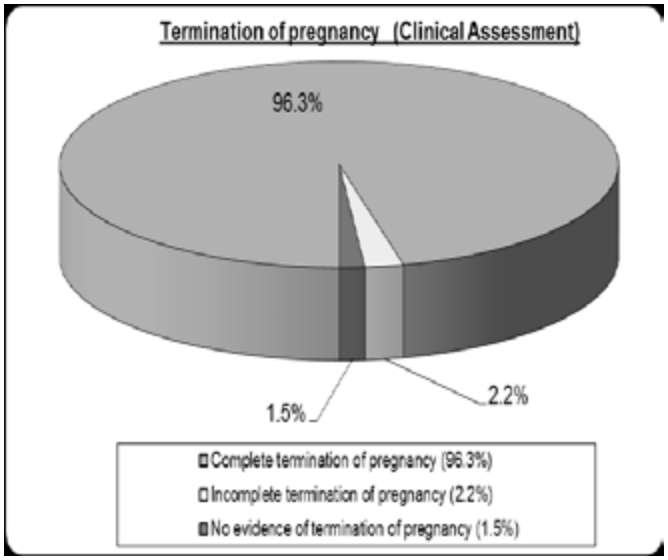


**Figure 2: Efficacy of mifepristone and misoprostol combined therapy: Clinical Assessment (n=270)**

Of the 270 enrolled women in to the study, USG assessment for confirmation of termination of pregnancy was carried out in 190 subjects (70.4%) at the end of 14 days therapy with mifepristone + misoprostol combined therapy. Of these 190 women, 180 women (94.7%) had shown a complete termination of the pregnancy, six women (3.2%) had incomplete termination of pregnancy, while four women (2.1%) had no evidence of termination of pregnancy (Figure 3).

Among the 19 women with duration of amenorrhoea >63 days, while on clinical assessment all the 19 women had a complete termination of pregnancy, 17 women (89.5%) had undergone an USG scan on Day 14 after administration of mifepristone +

misoprostol combined therapy and all the 17 women had shown complete termination of pregnancy on USG assessment.

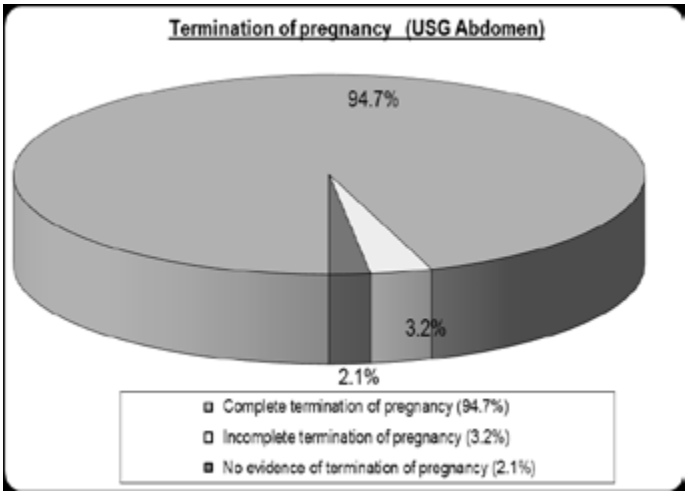


**Figure 3: Efficacy of mifepristone and misoprostol combined therapy: USG assessment (n=190)**

The six women who had incomplete termination of pregnancy and the four women who had no evidence of termination of pregnancy on clinical and USG assessment on Day 14 of the study, required surgical intervention for completion of the termination of their pregnancy at the end of the study.

**The physician's & patient's opinions about the therapy**

Participated women gave an overall assessment to the study medication at the end of treatment on a four-point scale. A total of 97.8% of the enrolled women rated the study medication as "excellent" or "good" while 1.6% and 0.6% rated the study medication as "fair" and "poor" respectively at the end of the study. On the other hand, 260 women (96.3%) were rated to have an "excellent" or "good" efficacy to mifepristone + misoprostol combined therapy by the investigators at the end of the study. A total of six women (2.2%) and four women (1.5%) were rated to have a "fair" and "poor" efficacy to mifepristone + misoprostol combined therapy respectively at the end of the study by the investigators (Figure 4).

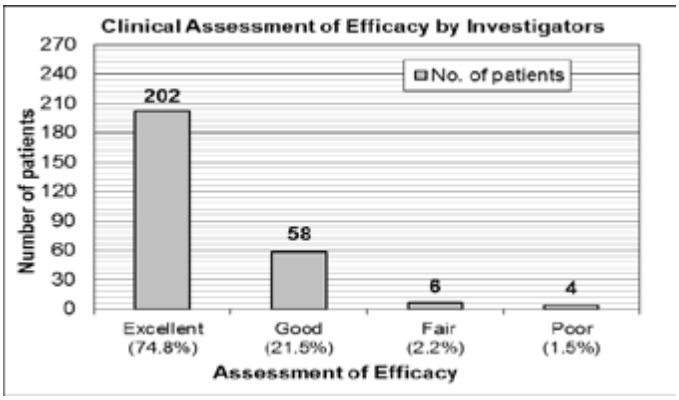


**Figure 4: Overall assessment of efficacy of mifepristone and misoprostol combined therapy by Investigators (n=270)**

**Safety Assessment**

A total of 39 adverse events (AEs) were reported by 30 subjects during the entire course of the study giving an overall patient adverse event rate of 11.1% in the study. The most common AEs reported in the study included; nausea & vomiting in 18 subjects (6.7%) followed by abdominal pain in 10 subjects (3.7%) (Table 2). Of the total 39 AEs reported in the study, 37 events (94.8 %) were reported to be of "mild" intensity and the remaining two events (5.2%) were of "moderate" intensity. All the adverse events reported in the study resolved completely with or without treatment. No "severe" or "serious" adverse event of whatsoever nature was reported by any of the subjects during the entire course of the study. Only two women required blood transfusion during the course of the study. Further no significant alteration in any of the laboratory investigations was reported in any of the subjects in our study, which could be attributed to mifepristone + misoprostol combined therapy.

On the assessment of tolerability given to mifepristone + misoprostol combined therapy by the investigators at the end of the study, 88.9% women were assessed to have tolerated the drug as "excellent". The remaining 10.4% and 0.7% women were rated to have tolerated the drug as "good" and "fair" respectively, on the assessment of tolerability. None of the subjects enrolled in to the study was rated to have tolerated the drug "poorly" (Figure 5).

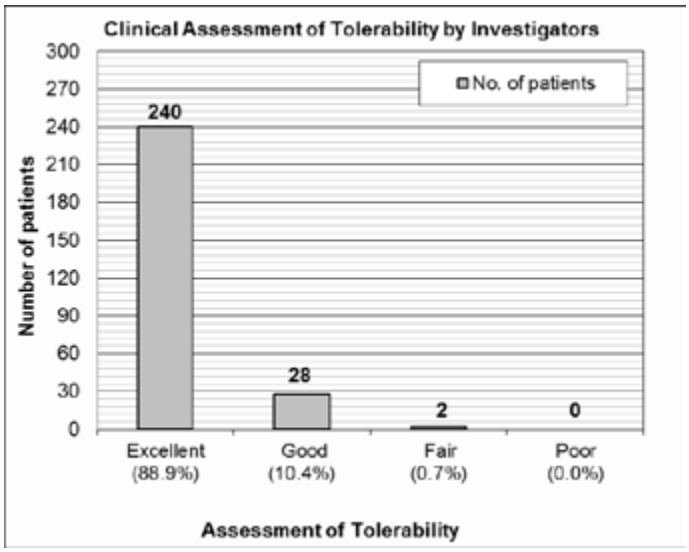


**Figure 5: Overall assessment of tolerability to mifepristone and misoprostol combined therapy by Investigators (n=270)**

## DISCUSSION

Medical abortion has been described as a safe, more private and natural method by women who have had an experience with this method. Nowadays mifepristone an antiprogesterone agent, followed by misoprostol, a prostaglandin, is the most preferred combination for MTP and has emerged as a realistic alternative to surgical abortion from the last two decades [3].

Optimization of mifepristone regimens in emergency

contraception is the main focus for the recent clinical studies on the use of mifepristone in MTP. A 200-mg dose of mifepristone, in combination with vaginally administered prostaglandin for MTP during first trimester; has been shown to be as effective as a higher dose (600 mg) of mifepristone in several clinical trials [9, 10].

The present trial administered one-third the FDA-approved mifepristone dose and twice the FDA-approved misoprostol dose for the MTP. Misoprostol was administered vaginally rather than orally and a second dose of misoprostol was permitted if needed.

The overall complete abortion rate of 94.7% achieved in our trial compares well with the two large studies carried out internationally with 200 mg mifepristone orally and 800 µg misoprostol vaginally. A retrospective analysis by Ashok et al [11] evaluated 2000 women who received single dose of 200 mg mifepristone followed 36 to 48 hours later by 800 µg misoprostol vaginally. The overall success rate in this study [11] was 97.5%, with a rate of 98.5% among the 928 women with pregnancies of ≤49 days' gestation & 96.7% among the 1072 women with pregnancies of >49 days' gestation. Schaff et al [12] similarly reported a 97% success rate with the 200-mg dose of mifepristone followed by 800 µg misoprostol vaginally at 48 hours in 933 women of ≤ 56 days' gestation. Continuing pregnancy rate of 1.5% reported in our study was higher than the 0.6% and 0.3% continuing pregnancy rate reported by Ashok et al [11] and by Schaff et al [12] respectively. Ongoing pregnancy rate with range of 0.8% to 1.5% has been reported in studies with 600 mg mifepristone followed by orally administered misoprostol (400-600 mg) [4, 7, 8]. Surgical intervention was required in 3.7% women enrolled in our study which is quite lower than the 14.6% surgical intervention rate reported by Irving M. et al [4] and slightly higher than the 2.3%, 2.5% & 2.4% surgical intervention rate reported by Peyron R. et al [7], Ashok et al [11] & Schaff et al [12] respectively.

Meta-analysis by Chen QJ et al [13] had concluded that the different medical regimens of mifepristone/prostaglandins were effective and safe for termination of pregnancy of 10-16 weeks' gestation. Although in our study, while all the 19 (7.0%) women with gestation > 63 days' (> 9 weeks) had a complete abortion on clinical assessment which was also confirmed in ultrasound assessment in 89.5% patients; no firm conclusion can be drawn regarding the efficacy & safety of mifepristone-misoprostol combined therapy in such patients due to their very small number in our study & further studies in a larger number of patients are required to determine the efficacy and safety of this regimen in such patients with higher gestational age.

Adverse reactions reported in our study with mifepristone-misoprostol combined therapy were quite lower than those reported internationally with such regimens. The most frequent adverse events reported in some studies after mifepristone administration and prior to prostaglandin administration included abdominal pain or discomfort (56%), nausea (54%), tiredness (50%) and breast pain (28%) [14]. The most common symptoms reported by Schaff et al [12] due to mifepristone were nausea (44.6%) and cramping (36.5%) and the most common symptoms due to misoprostol were cramping (91.8%), nausea (42.5%) and fever/chills (32.2%). However, the incidence of nausea & vomiting and abdominal pain was only 6.7% and 3.7% respectively in our study. Further, Henderson *et al*. [15] reviewed 3 years of experience with clinical use of mifepristone plus misoprostol in the United Sates and provided information from a database of 95,163 treated women. The Henderson et al. [15] reported an incidence of 2.2/1000 serious complications (95% CI, 1.9–2.5) the most frequent being heavy bleeding, from a database of 95,163 treated women with clinical use of mifepristone plus misoprostol in the United States. Apart from few serious medical complications occurring in routine clinical use the safety of mifepristone plus misoprostol is high concluded by the authors.

On the other hand, the blood transfusion rate in our study at 0.7% was higher than that reported with such regimens internationally. In fact, in the large US postapproval experience [15], only 0.5/1000 patients receiving mifepristone plus misoprostol therapy required transfusion. One possible reason of increased transfusion rate in our study could be the low baseline hemoglobin levels in our population (especially in pregnant women) as compared to those in the other parts of the world. Hence, at least in our setting, the women should be well informed about the risk of heavy bleeding and the instructions to be followed in case of excessive blood loss following the use of this regimen. Further, women living in areas where no medical facilities are available should preferably not be administered this regimen unless referrals and possible transportation are available for emergencies.

In conclusion, 200 mg of oral mifepristone in combination with 800 µg of vaginal misoprostol represents an effective and well tolerated regimen for the induction of abortion of gestations up to nine weeks (63 days of amenorrhoea) in our setting.

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REFERENCES:

1.Nothnagle M, Taylor JS. Medical methods for first-trimester abortion. Am Fam Physician. 2004; 70:81-3.

2.Silvestre L, Dubois C, Renault M, Rezvani Y, Baulieu EE, Ginase A. Voluntary interruption of pregnancy with mifepristone (RU 486) and a prostaglandin analogue: a large-scale French experience. N Eng J Med 1990; 645-8.

3.Hamoda H, Flett GM. Medical termination of pregnancy in the early first trimester. J Fam Plann Reprod Health Care. 2005;31:10-4.

4.Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. N Engl J Med 1998;338:1241-7.

5.World Health Organization. Pregnancy termination with mifepristone and gemeprost: a multicenter comparison between repeated doses and a single dose of mifepristone. Fertil Steril. 1991;56:32-40.

6.Newhall EP, Winikoff B. Abortion with mifepristone and misoprostol: regimens, efficacy, acceptability and future directions. Am J Obstet Gynecol. 2000;183:S44-53.

7.Peyron R, Aubény E, Targosz V, Silvestre L, Renault M, Elkik F, et al. Early termination of pregnancy with mifepristone (RU 486) and the orally active prostaglandin misoprostol. N Engl J Med 1993;328:1509-13.

8.Aubény E, Peyron R, Turpin CL, Renault M, Targosz V, Silvestre L, et al. Termination of early pregnancy (up to 63 days of amenorrhea) with mifepristone and increasing doses of misoprostol. Int J Fertil Menopausal Stud 1995;40:85-91.

9.World Health Organization. Task force on post-ovulatory methods of fertility regulation. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion a randomised trial. Br J Obstet Gynecol 2000;107:524–30.

10.World Health Organization. Task force on post-ovulatory methods of fertility regulation. Medical abortion at 57 to 63 days' gestation with a lower dose of mifepristone and gemeprost. A randomized controlled trial. Acta Obstet Gynecol Scand 2001;80:447–51.

11.Ashok PW, Penney GC, Flett GM, Templeton A. An effective regimen for early medical abortion: a report of 2000 consecutive cases. Hum Reprod 1998;13:2962-5.

12.Schaff EA, Eisinger SH, Stadalius LS, Franks P, Gore BZ, Poppema S. Low-dose mifepristone 200mg and vaginal misoprostol for abortion. Contraception 1999;59:1-6.

13.Chen QJ, Hou SP, Meads C, Huang YM, Hong QQ, Zhu HP, Cheng LN; EBM-CONNECT Collaboration. Mifepristone in combination with prostaglandins for termination of 10-16 weeks' gestation: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2011 Dec;159(2):247-54.

14.Urquhart DR, Templeton AA, Shinewi F, et al. The efficacy and tolerance of mifepristone and prostaglandin in termination of pregnancy of less than 63 days gestation; UK multicenter study — final results. Contraception 1997;55:1–5.

15.Henderson JT, Hwang AC, Harper CC, Stewart FH. Safety of mifepristone abortions in clinical use. Contraception 2005;72:175– 8.

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