International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Palani RS et al. Int J Reprod Contracept Obstet Gynecol. 2023 Jul;12(7):2309-2315
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20231958

Review Article

Narrative review on misoprostol for first trimester termination of pregnancy

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Received: 16 January 2023
Accepted: 22 May 2023

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ABSTRACT

Misoprostol, a prostaglandin E1 analogue, is first used to prevent peptic ulcers. The first FDA-approved indication in the product labelling is for the prevention and treatment of intestinal ulcer disease caused by the use of nonsteroidal anti-inflammatory medications. The main advantages of misoprostol include it's reasonably priced, compared to other prostaglandins, it has modest effects on the smooth muscle of the heart and bronchial tree and is readily preserved (shelf life: 7 years) and it may be stored and used without refrigeration. Misoprostol has been authorised as an effective medication for termination of pregnancy at different gestations, cervical ripening, labour inducing in term pregnancy, and possibly therapy of postpartum haemorrhage in the last two decades.

Keywords: Abortion, First trimester abortion, Medical termination of pregnancy, Misoprostol

EPIDEMIOLOGY

Abortion is the spontaneous or induced termination of pregnancy before the time of viability (birth weight of 500 gm or 20-weeks' gestation).[1] In India, there were reportedly 15 million abortions (15 million-17 million) in 2015. The abortion rate was 47.0 (42–52) per 1000 women between the ages of 15 and 49. A total of 3.4 million abortions (22%) were performed in medical facilities, 11.5 million (73%) were performed outside of facilities using medication, and 0.8 million (5%) were performed outside of facilities using techniques other than medical abortion.

Overall, 2 million (14%) surgical abortions, 12.7 million (81%) medical abortions, and 0.8 million (5%) other abortions that were likely dangerous were performed. In addition, it was predicted that there were 48 million pregnancies, 144 pregnancies for every 1000 women aged 15 to 49, and 71 unwanted pregnancies for every 1000 women in this age group. Nearly half of pregnancies were unplanned, and one third of all pregnancies were abortions.[2]

According to the World Health Organization (WHO), some 42 million pregnancies are deliberately aborted each year across the world, 20 million by untrained practitioners or in unsanitary settings, and 22 million by legal means. The estimated yearly number of abortions in India varies widely, from 0.6 to 6.7 million. Because abortions are grossly underreported, it is impossible to determine the true frequency. The most often quoted estimate has the yearly number of abortions at roughly 6.7 million, of which only around one million are legally done.[3]

LEGAL STATUS OF ABORTION IN INDIA

Pre MTP era

In 1860, the British colonial administration passed the Indian Penal Code (IPC). A person who induces an abortion would be liable to imprisonment for three years or more and/or payment of a fine, according to IPC sections 312-316. The only situation in which this wasn't true was if the lady needed an abortion to save her life. Ironically, India did not modify its criminal code until

1971, while Britain did so in 1967. Because of the presence of this criminal statute, several women lost their lives as a consequence of hazardous illegal abortions. Because of this high death rate and the pressure from a growing population, the government decided to change the existing legislation in 1971 by enacting an act.[4-7]

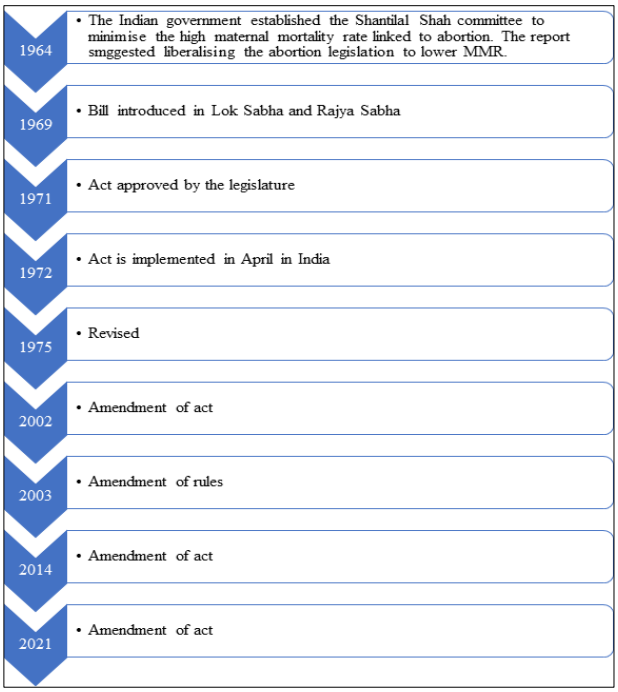

Figure 1: History MTP act in India.

Medical termination of pregnancy act

The MTP legislation in India was enacted by the parliament in 1971 and went into effect on 01 April 1972.

The MTP act, 1971: benefits and challenges

A pregnancy may be terminated "on the recommendation of one registered medical practitioner if the duration of the pregnancy does not surpass twelve weeks; or on the advice of two registered medical practitioners if the length of the pregnancy surpasses twelve weeks but does not exceed twenty weeks," according to the MTP Act of 1971.[8] This Act expanded the grounds for terminating a pregnancy and defined the procedure's location as well as the credentials of the person carrying out the procedure. In order to encourage better and more widespread implementation and expanded access for women, particularly in rural areas, the MTP Act, 1971 was changed in 2002 to allow pregnancy termination up to 20 weeks of gestation. The Act, however, lagged behind technological developments in terms of foetus health assessment and seeking an abortion for an undesirable or malformed foetus. According to Singh et al, around 15.6 million abortions were carried out in India in 2015, with 73% of those procedures taking place outside of medical institutions.[2,9]

Technology advancements in genetics and ultrasonography throughout time have made it possible to diagnose a variety of foetal diseases during pregnancy. The necessity for expanding the maximum gestational limit for terminating pregnancies is highlighted by the fact that a diagnosis of a congenital defect is often established beyond 20 weeks of gestation for a variety of scientific and biological reasons. The concerned medical experts have been advocating to the Ministry of Health and Family Welfare to revise the MTP Act and bring it in line with worldwide thinking due to the continuous rise in writ petitions requesting abortion in situations of serious foetal abnormalities.[9,10] As a result, the MTP Act of 1971 has been significantly modified by the MTP Act of 2021, which is now a law. These changes will provide expectant parents freedom from constraints on late-term pregnancy termination and give obstetrics, reproductive medicine, and foetal medicine professionals the time to detect foetal defects accurately.[11,12]

The MTP (amendment) Act, 2021

The MTP Act of 1971 is no longer sufficient to protect the rights of women due to the passage of time and developments in medical technology, such as genomics and ultrasonography. Raising the maximum gestational age for pregnancy termination stresses the necessity for prenatal diagnosis of a significant number of foetal abnormalities. The Ministry of Health and Family Welfare has been represented by the relevant medical experts to revise the MTP Act and bring it in line with the worldwide thinking in light of the continuous rise in writ petitions requesting termination of pregnancy in situations of serious foetal abnormalities. The MTP Act of 1971 has undergone substantial changes as a result of the MTP Act of 2021, which were published in the Indian Gazette on 25 March 2021.[13]

The proposed law would require that a single RMP's opinion be obtained (rather than two or more) before a pregnancy up to 20 weeks of gestation may be terminated (fetal development period from the time of conception until birth).

It has increased the gestational age limit for "special categories" of women, which includes sexual assault survivors, incest victims, and other vulnerable women like differently-abled and minors.

It brings the necessity of perception of two RMP for pregnancy termination between 20 and 24 weeks of gestation.

It also specifies that, "save to a person permitted in any legislation already in effect," "the name and other specifics of a woman whose pregnancy has been terminated must not be divulged." Anyone who violates these rules faces a possible year in jail, a fine, or both as punishment.

In the event of any significant foetal abnormality, the maximum gestational age restriction for termination must not apply to the pregnancy termination where such termination is required by a Medical Board's diagnosis of any significant foetal defect as defined by the Act.

One gynaecologist, one paediatrician, one radiologist or sonologist, and as many more members may be announced in the Official Gazette by the State Government or Union territory, as the situation may be, shall make up the Medical Board.

METHODS OF FIRST TRIMESTER ABORTION

Medical methods of first trimester abortion

Abortion by medical means has been shown to be both safe and successful.[14]

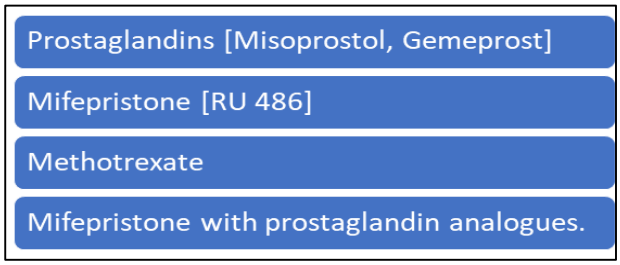

Figure 2: Drugs used for medical termination of pregnancy.

Misoprostol

Misoprostol is a prostaglandin E1 analogue made synthetically. It is a 11 alpha 16 dehydroxy 16 methyl 19 isoprost-13E-en-coate. It is a synthesized prostaglandin that resembles mcgE structurally. 100 mcg and 200 mcg tablets are available.[15]

Mechanism of action

Misoprostol improves mucosal blood flow, reduces stomach acid release, and encourages bicarbonate secretion. It is utilised in drug-induced peptic ulcer because it is mucoprotective. Natural fatty acids generated by a variety of bodily tissues are prostaglandins. Prostaglandin E1 interacts with certain receptors on myometrial cells to generate myometrial contractility. Through a series of connected events, including a shift in calcium concentration, this interaction causes muscular contraction.

By interacting with prostaglandin receptors, the mcgE1 analogue misoprostol softens the cervix and induces the uterus to contract, causing the ejection of the uterine contents. Misoprostol has a prolonged effect because it is metabolically resistant. Misoprostol is a superior substitute for mifepristone for the induction of abortion and is just as effective as gemeprost.[16]

Pharmacokinetics

When misoprostol is administered orally, vaginally, or rectally, it is quickly absorbed. De-esterification converts it to misoprostol acid, which is subsequently converted to prostaglandin F mimics.

The half-life of oral administration is shorter than 30 minutes, and the peak level is reached within 15 minutes. Following vaginal administration, there is a slow increase to a peak level at 60–120 minutes, but by 240 minutes, the level is still at 60% of peak level.[17]

For MTP, vaginal application is preferable than oral administration.

PAST LITERATURE ON THE MEDICAL REGIMENS USING MISOPROSTOL

Van Bogaert and Sedibe studied a single misoprostol dose for first and second trimester TOP.[18] No matter the gestational age, 400 mcg misoprostol orally and 800 mcg vaginally daily were used; buccal and vaginal self-administration were simultaneous. The day after misoprostol, all patients had trans abdominal ultrasound (TAUS). Clinical (minimal blood, few or no contractions) and sonographic criteria were employed to determine abortion success. 189 patients (69.2%) responded to misoprostol after one dosage, while 84 (30.8%) required more than one dose (2.4+0.8; median 2.0; 95% CI 2.2-2.6). First-trimester GA was 10.7 and second-trimester GA was 15.4. Nine (32.1%) of 28 first-trimester abortions required three or more misoprostol treatments, compared to 13 (23.2%) second-trimester abortions. 39 single administrations and 71 recurrent administrations were nulliparous. This shows that parity doesn't affect misoprostol treatment needs. 10.2% of first medical abortions and 8.6% of second required a D&C. Four patients (1%) returned owing to abortion complications. One was released without sonography; she hadn't undergone an abortion. Three exhibited metrorrhagia but no sonographic evidence of an incomplete abortion.

Bugalho et al studied two groups given vaginal misoprostol 200 or 400 mcg.[19] Two-thirds of women given 400 mcg every 12 hours had an abortion after 48 hours, compared to 46% of those given 200 mcg. The abortion was successful for 35% of the first group and 22% of the second. Women given 400 mcg were more likely to have an abortion at 12, 24, 36, and 48 hours than those given the lesser dose. In the group that received the greater dose, a higher percentage of women had a completed abortion during that time frame, although the differences were not statistically significant. The percentage of women who had an abortion likewise increased with observation or care duration. The percentage of women who had an abortion at any gestational age did not differ between the two groups. The percentage of pregnancies ending in a complete abortion seems to vary with gestational age, but the changes are not statistically significant. Only dosage

was substantially linked with the percentage of women achieving an abortion in a multiple regression study that included age, number of previous abortions and deliveries, body weight, gestational age, and dosage. Other factors analysed: Lower belly discomfort was the most prevalent adverse event 12 hours after 200 and 400 mcg dosages. Other side effects included nausea, fatigue, vomiting, and diarrhoea. The average haemoglobin level reduced from 11.9 (SD: 1.2) g/L to 11.5 (SD: 1.3) g/l in the 200-mcg group and from 12.1 (SD: 1.2) g/l to 11.5 (SD: 1.6) g/l in the 400-mcg group. Increasing the dosage, the frequency of administration, or the length of therapy can enhance outcomes.

Bugalho et al studied the effectiveness of a single dose of vaginal misoprostol followed by extended observation.[20] Ultrasounds detected foetuses in 103 women with at least 42 days of amenorrhea. All women got transabdominal ultrasounds to confirm pregnancy and measure gestational sacs. Four 200 mcg misoprostol pills enclosed in inactive hydro soluble gel were placed into the applicant's posterior fornix while reclining. The gel was used to maintain vaginal humidity, lubricate, and hold pills in place when people stood up. Young, low-parity people dominated the study. 21.4% were 20 and 10.7% were 35. 51.5% were nulliparous and 3.9% had given birth more than four times. Over half have undergone abortions. 74 of 103 people who took 800 mcg misoprostol bled and expelled the gestational sac within 24 hours. 13 women bled but did not have an abortion, whereas 16 did not. 14 more patients quit using the drug within 24 hours or a week.

88 of 101 women (87.1%) had abortions one week after taking misoprostol, 11 (10.9%) experienced bleeding while the gestational sac was present, and 2 (2%) had no bleeding. All women who miscarried less than a week after taking misoprostol expelled tissue 24 to 72 hours later. On day 8, five of the 13 remaining women had an abortion, seven bled but did not have an abortion, and one did not bleed. Misoprostol-using women who miscarried did not need intrauterine tissue removal. No one had substantial bleeding or anaemia, and the bleeding continued 4 to 10 days. Most respondents (95/103) reported abdominal pain, although only 19 (18.4%) used medications. Twenty-two (21.4%) people felt nauseated, five (4.9%) vomited, 18 (17.5%) experienced headaches, 13 (12.6%) had diarrhoea, and 12 (11.6%) were dizzy.

Wiebe studied the effects and side effects of using misoprostol after methotrexate in a medical abortion.[21] In this cohort study, 800 microgram dry pills, 600 microgram wet tablets, and 800 microgram wet tablets were compared. By day 8, the "dry" group had fewer abortions (55.2% versus 69.7% versus 71.1%) but identical surgery rates. Vomiting (8.2% versus 16.2% versus 20.3%, p=0.01) and fever and chills (4.5% versus 25.3% versus 40.6%, p=0.0001) were less common in the dry group. 600 mcg of wet misoprostol is the most effective and has the fewest side effects, according to the study.

Carbonell et al confirmed misoprostol's effectiveness and safety for abortions before 63 days.[22] All of the women were given instructions on how to self-administer 800 mcg misoprostol intravaginally. After 48 hours without an abortion, she self-administered 800 mcg. If the second dose didn't cause an abortion, the third and final dose of 800 mcg was administered 48 hours later. These were primary dosages. 161/175 (92.0%; 95% CI 8746%) had a complete abortion, while 14/175 (8.0%; 95% CI 413%) failed. First dose: 77.7%, second: 13.7%, third: 0.6%. Before therapy, haemoglobin was 11.94 mcg/dl (SD 1.60); after therapy, it was 11.64 mcg/dl (p=0.009) (SD 1.08). Age, gravidity, parity, prior abortions, race, gestational age, or side effects did not affect success or failure rates. Third-dose misoprostol showed little impact. Vaginal bleeding lasted 5.5 (2.8) days and spotting 5.7 (3.1) days.

Brouns et al studied the effectiveness of misoprostol administered vaginally with mifepristone for terminating viable and non-viable pregnancies.[23] 176 pregnant women between 14 and 24 weeks had intrauterine foetal deaths, congenital or genetic foetal abnormalities, or desired pregnancy termination for psychiatric reasons. Randomly selected from two groups. Both groups took 200 mcg mifepristone. Depending on the randomization group, 200 or 400 mcg misoprostol was supplied vaginally 36–48 h later at 4-h intervals until the foetus was delivered. Complete foetal and placenta evacuation occurred in 66% (57/86) of 200-mg misoprostol patients versus 73% (66/90) of 400-mg individuals (p=NS). The misoprostol 200-mg group took significantly longer to deliver the foetus than the misoprostol 400-mg group (p=0.042). Nausea, retching, vomiting, fever, headaches, and diarrhoea were common across groups. Both 200-mcg and 400-mcg misoprostol groups experienced equivalent blood loss (p=NS). According to the study, both regimens ended viable and non-viable pregnancies equally well.

Dalenda et al compared the efficacy, side effects, complications, and acceptability of the mifepristone-misoprostol regimen, the gold standard of early medical abortion, to a single vaginal dosage of misoprostol for late first-trimester pregnancy termination.[24] Participants were randomly assigned one of two medical abortion regimens based on appointment day. Women recruited on Monday, Wednesday, or Friday (group 1) got 800-mg misoprostol by digital vaginal insertion in the clinic. Women recruited on Tuesday and Thursday (group 2) received 200 mcg oral mifepristone via vaginal insertion, followed by 400 mcg oral misoprostol two days later. 122 women participated. 73 individuals received mifepristone-misoprostol (group 1), while 49 received misoprostol-only (group 2). Randomization places more women in group 1 than group 2, resulting in a difference in group size. Gestational age, marital status, education level, parity, and uterine scars did not differ across groups. 19 women (15.5%) had prior uterus surgery, including 11 with one caesarean and 8 with two or more. 38/49 (77.5%) in group 2 and 59/73 (80.8%) in group 1 had similar success rates (p=0.54). In group 1, 40/73 (54.7%) women had a complete abortion without

further misoprostol doses, but in group 2, 28/49 (57.1%) did. Group 1 patients received surgical evacuation due to prolonged pregnancy, imperfect abortion, excessive bleeding, and patient request. In group 2, two (4%) cases of severe bleeding and nine (18.3%) cases of continued pregnancy required curettage. Misoprostol-only women had higher stomach pain (71.4% versus 43.8%, p≤0.0001). Both groups had equal rates of fever, diarrhoea, chills, nausea, vomiting, and bleeding. A single 800-mg vaginal dose of misoprostol seems as effective as mifepristone+misoprostol with equal success rates for late first-trimester termination.

Hamoda et al compared sublingual vs vaginal delivery of misoprostol and mifepristone for medical abortions up to 13 weeks of gestation.[25] Under nursing supervision, women were given 200mg mifepristone orally. They were discharged and readmitted 36–48 hours later for misoprostol. Up to nine-week-pregnant women were administered 600 mcg sublingually or 800 mcg vaginally, then 400 mcg three hours later. If the ladies did not pass conception products, a transvaginal pelvic ultrasound was planned one week later. If the products of conception were not passed 3 hours after the second dose, women 9 to 13 weeks pregnant received a third dose of 400 mcg misoprostol sublingually or vaginally. In the vaginal group, 40/144 (28%) women had no opinion, while 6/144 (4%) were dissatisfied with misoprostol administration (p=0.02). Sublingual women had a median (range) total vaginal bleeding score of 14 (1-36), while vaginal women had a score of 13 (0-34) (p=0.59). Women in the sublingual group reported median (range) pain levels of 60 (0–100) for overall discomfort and 76 (0–100) for their worst pain. The vaginal group's scores were 55 and 73 (p=0.15 and 0.07, respectively). In all groups, analgesic use reduced pain by 49 (IQR) (0-100).

Chen et al examined the effectiveness and safety of medication abortion regimens for 8-16 week pregnancies.[26] Randomly divided into four groups. Groups A and B received oral mifepristone and vaginal misoprostol on day 1. If conception products were not removed, 600 mcg misoprostol was given vaginally (group A) or orally (group B) at 3-hour intervals. Group C received 200 mg of mifepristone and 600 mcg of misoprostol orally on day 1. If conception products didn't pass, 600 mcg of misoprostol was administered orally at 3-hour intervals, up to four doses.

On days one and two, group D received 100 mcg of mifepristone orally and 600 mcg of misoprostol intravaginally (i.e., within 48 h). If fertilisation was not expelled, 600 mcg of misoprostol was given vaginally at 12-hour intervals, up to three times. Mean ages, pregnancy histories, menstrual cycles, and period lengths did not differ between groups. Success rates ranged from 97.1% to 97.8% across groups (p>0.05). Complete abortion rates were comparable between groups at 2 weeks (p>0.05). Group D's induction-to-abortion intervals (5.8 h) and misoprostol dosage (0.72 mcg) were lower than the other 3 groups (p=0.05). The median time between therapy and first period and bleeding time were similar across groups. Group D had a complete abortion rate of 78.2% at 8–10 weeks, much lower than the other groups at the same gestational age, although there were no differences at higher gestational ages (11-16 weeks). The four regimens had comparable abortion rates despite differing intervals and routes.

Khazardoost conducted a randomised clinical trial to compare the effectiveness and negative effects of two misoprostol regimens for up to 16-week pregnancy termination.[27] Group I (50 women) received 200 mcg of vaginal misoprostol every six hours, while group II (50 women) received 400 mcg up to four times. Groups I and II had 74.5 and 76% complete abortions. 25.5% and 24% of group I and II abortions were incomplete. At 6, 12, 18, 24, and 48 hours, abortion rates in group I were 6%, 46%, 68%, 92%, and 94%. At 6, 12, 18, 24, and 48 hours, group II abortion rates were 12%, 46%, 82%, 100%, and 100%. Group II had more fever, diarrhoea, and stomach discomfort (p=0.022, 0.032, 0.009). There was no statistical difference between the two groups in nausea and vomiting. 200 mcg intravaginal misoprostol over four doses is more effective than 400 mcg every six hours, research shows.

Carbonell researched self-administering 1000 mcg of misoprostol vaginally for medical abortions.[28] After each misoprostol dose, ladies were followed and had an abdominal ultrasound. All abortion patients were told to return in 21 days (whether the expulsion occurred after the first, second or third dose of misoprostol). At this 21-day post-gestational sac-ejection checkup, patients got abdominal ultrasounds and clinical exams.

300 women with gestations between 42 and 63 days were given misoprostol vaginally every 24 hours for abortion. Average age was 26.5. (SD 5.8). 87 people (29%) had a temperature 2 hours after the first misoprostol dose (mean 37.6°C, SD 0.57). After the second misoprostol dose, 23.6% of patients had fever (mean 36.8°C, SD 0.55°C). Four patients (14.8%) reported a temperature two hours after the third misoprostol dose (mean 36.8°C, SD 0.44). Success rates were 92.9%, 91.4%, and 96.9% for women ages 42 to 48, 49 to 55, and 56 to 63. Failure rates were 7.1%, 8.6%, and 3.1% at 42–48, 49–55, and 56–63 weeks.

CONCLUSION

Guidelines recommend mifepristone and misoprostol for early medical abortion. Because mifepristone potentiates misoprostol's abortifacient action, the combination is very successful, resulting in complete abortion in 95% of women through 63 days and 93% between 64 and 70 days. Mifepristone is expensive and scarce. Although the medicine is licenced for commercialization in the US, the FDA has imposed distribution restrictions that limit patient and provider access. Misoprostol, which is affordable and frequently used for obstetric and gastrointestinal purposes,

can be a significant alternative for women who cannot access mifepristone.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Palani RS, Gopalan U. Narrative review on misoprostol for first trimester termination of pregnancy. Int J Reprod Contracept Obstet Gynecol 2023;12:2309-15.