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REVIEW ARTICLE

Misoprostol: Pharmacokinetic profiles, effects on the uterus and side-effects

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Key facts

Route	Onset of action	Duration of action
Oral	8 min	~2 h*
Sublingual	11 min	~3 h
Vaginal	20 min	~4 h
Rectal	100 min	~4 h

*After oral administration, uterine tonus develops, which is not followed by uterine contractions, unless repeated doses are given.

KEYWORDS
Pharmacokinetics;
Misoprostol;
Uterus;
Side effects

Abstract

Misoprostol, a synthetic prostaglandin E1 analogue, is commonly used for medical abortion, cervical priming, the management of miscarriage, induction of labor and the management of postpartum hemorrhage. It can be given orally, vaginally, sublingually, buccally or rectally. Studies of misoprostol's pharmacokinetics and effects on uterine activity have demonstrated the properties of the drug after various routes of administration. These studies can help to discover the optimal dose and route of administration of misoprostol for individual clinical applications. Misoprostol is a safe drug but serious complications and teratogenicity can occur with unsupervised use.

1. Pharmacology of misoprostol

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a synthetic prostaglandin E1 analogue. It was developed for the prevention and treatment of peptic ulcers because of its gastric acid anti-secretory properties and its various mucosal protective properties [1]. It has become an important drug in obstetric and gynecological practice because of its uterotonic and cervical priming action. In comparison to other prostaglandin analogues, misoprostol has the advantages of being cheap, widely available, stable at room temperature and having few side effects. Its clinical applications include medical abortion, medical evacuation for miscarriages, cervical priming before surgical procedure, induction of labor and management of postpartum hemorrhage.

2. Structure and chemistry of misoprostol

Fig. 1 shows the structures of misoprostol and the naturally occurring prostaglandin E1. The naturally occurring prostaglandin E series was discovered to inhibit gastric acid secretion

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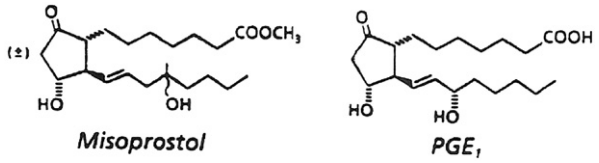

Figure 1 The structure of misoprostol and naturally occurring prostaglandin (PGE1).

in 1967 by Robert et al. [2]. However, naturally occurring prostaglandins have three drawbacks that hindered their clinical application. These problems were: (1) rapid metabolism resulting in a lack of oral activity and a short duration of action when given parenterally, (2) numerous side effects, and (3) chemical instability leading to a short shelf life. Misoprostol differs structurally from prostaglandin E by the presence of a methyl ester at C-1, a methyl group at C-16 and a hydroxyl group at C-16 rather than at C-15. The methyl ester at C-1 increases the anti-secretory potency and duration of action of misoprostol, whilst the movement of the hydroxyl group from C-15 to C-16 and the addition of a methyl group at C-16 improves oral activity, increases the duration of action, and improves the safety profile of the drug.

3. Pharmacokinetic properties of the various routes of administration of misoprostol

Misoprostol tablets were developed to be used orally. Other routes of administration, however, including vaginal, sublingual, buccal and rectal, have also been used extensively in obstetric and gynecological applications. Over the past decade there have been a number of studies looking at the pharmacokinetic profile of various routes of administration of misoprostol. Three pharmacokinetic properties, the peak concentration, time to peak concentration and the area under the serum concentration versus time curve were studied [3–6]. The time to peak concentration (Tmax) represents how rapidly the drug can be absorbed; the peak concentration (Cmax) reflects how well the drug is being absorbed while the area under the serum concentration versus time curve (AUC, equivalent to bioavailability) denotes the total exposure to the drug.

3.1. Oral route

Early studies concentrated on the pharmacokinetic properties after oral administration. After oral administration, misoprostol is rapidly and almost completely absorbed from the gastrointestinal tract. However, the drug undergoes extensive and rapid first-pass metabolism (de-esterification) to form misoprostol acid. Following a single dose of 400 μg oral misoprostol, the plasma misoprostol level increases rapidly and peaks at about 30 minutes (Fig. 2) declines rapidly by 120 minutes and remains low thereafter [3–6].

3.2. Vaginal route

It was found in clinical studies that vaginal administration was more effective than oral administration in medical abortion [7,8]. Zieman et al performed the first pharmacokinetic study comparing oral and vaginal routes of administration [3]. In contrast to the oral route, the plasma concentration increases gradually after vaginal administration, reaching its maximum level after 70-80 minutes before slowly declining with detectable drug levels still present after 6 hours.

Although the peak concentration after oral administration is higher than for vaginal administration, the 'area under the curve' is higher when given vaginally. The greater bioavailability of vaginal misoprostol may help to explain why it is more effective in medical abortion.

It has been shown that the coefficient of variation of the AUC after vaginal administration is greater than that after oral

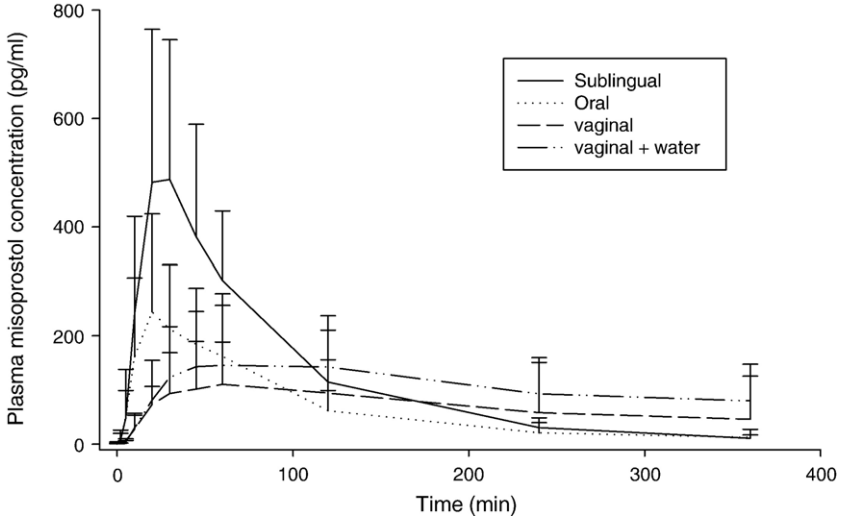

Figure 2 Mean plasma concentrations of misoprostol acid over time (arrowbars = 1 SD). [Tang. Pharmacokinetics of different routes of administration of misoprostol. Hum Reprod 2002. Reproduced by permission of Oxford University Press].

administration [3]. This means that the vaginal absorption of misoprostol is inconsistent. In clinical practice, remnants of tablets are sometimes seen many hours after vaginal administration, indicating that the absorption is variable and incomplete. This may be due to the variation between women in the amount and pH of the vaginal discharge. Variation in the amount of bleeding during medical abortion may also affect the absorption of misoprostol through the vaginal mucosa. Numerous attempts have been made to improve the absorption of vaginal misoprostol.

The addition of water to the misoprostol tablets is a common practice. However, this has been shown not to improve the bioavailability of vaginal misoprostol. [4]

3.3. Sublingual route

Recently, sublingual administration of misoprostol has been studied for medical abortion and cervical priming. The misoprostol tablet is very soluble and can be dissolved in 20 minutes when it is put under the tongue.

A pharmacokinetic study compared the absorption kinetics of oral, vaginal and sublingual routes of administration of misoprostol [4]. It found that sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration and the greatest bioavailability when compared to other routes. (Fig. 2)

The peak concentration is achieved about 30 minutes after sublingual and oral administration, whereas following vaginal administration, it takes 75 minutes [4]. Therefore, it appears that the sublingual and oral routes have the quickest onset of action. After 400 μg of misoprostol, a sublingual dose achieves a higher peak concentration than that of oral and vaginal administration. This is due to rapid absorption through the sublingual mucosa as well as the avoidance of the first-pass metabolism via the liver. The abundant blood supply under the tongue and the relatively neutral pH in the buccal cavity may be contributing factors. The rapid onset and high peak concentration means that of all the possible routes the systemic bioavailability, as measured by the AUC in the first 6 hours, is greatest for sublingual administration. In contrast to the previous study by Zieman et al. [3], the AUC360 after oral and vaginal administration are similar but only 54% and 58% respectively of that after sublingual administration [4]. The difference in the findings on the bioavailability of these two studies may be due to the wide variation in the absorption of misoprostol through the vaginal mucosa among different women. On the other hand, although vaginal absorption has been shown to be slower and the peak concentration lower than that for the other routes, the serum level of misoprostol is sustained at that low level for a longer period of time. In fact, at the end of 6 hours the serum level of misoprostol acid after vaginal administration is higher than those of the sublingual and oral routes. Therefore, the effect of misoprostol may linger for more than 6 hours after a single dose, though the threshold serum level for clinical action is unknown. Recently, a direct vagina-to-uterus transport was described for progesterone absorption [9]. A similar mechanism may exist for misoprostol absorption and may explain the improved clinical performance of vaginal administration.

3.4. Buccal route

Buccal administration is another way of giving misoprostol. The drug is placed between the teeth and the cheek and allowed to be absorbed through the buccal mucosa. Clinical studies, although limited compared to other routes, have shown that the buccal route is also effective for medical abortion, cervical priming and labor induction [10–12].

The shape of the buccal route absorption curve is very similar to that for vaginal absorption but the serum drug levels attained are lower throughout the 6 hours study period.(Fig. 3) [6]

After buccal administration the Tmax is 75 minutes which is similar to that after vaginal administration, but the AUC of buccal administration is just half that of the vaginal administration. Another study comparing buccal to sublingual administration has also shown that the AUC of sublingual

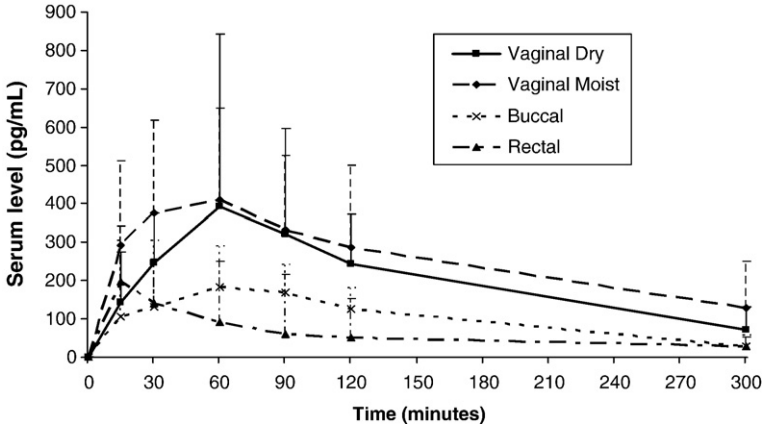

Figure 3 Mean serum levels of misoprostol acid in pg/mL for four epithelial routes of misoprostol administration over 5 hours. Error bars represent standard deviation. [Meckstroth. Misoprostol Absorption and Uterine Response. Obstet Gynecol 2006. Reproduced by permission of Lippincott Williams & Wilkins].

misoprostol is 4 times that of buccal administration [13]. The buccal route is a promising way of administering misoprostol and more studies are required to compare it with other routes of administration.

3.5. Rectal route

The rectal route of administration has been studied recently for the management of postpartum hemorrhage. This route of administration is less commonly used for other applications.

The shape of the absorption curve after rectal administration is similar to that of vaginal administration but its AUC is only 1/3 that of vaginal administration. (Fig. 3)

The mean Tmax after rectal administration is 40-65 minutes [6,14], although a recent study reported a much shorter Tmax of 20 minutes.

An understanding of the pharmacokinetic properties of different routes of administration can help to design the best regimens for the various clinical applications. However, it may not be able to predict clinical outcomes for various clinical indications. Sublingual misoprostol, which has the shortest Tmax, is perhaps useful for clinical applications that require a fast onset of clinical action, such as postpartum hemorrhage or cervical priming. Vaginal misoprostol on the other hand, which has a high bioavailability and sustained serum level, is useful for indications that require a longer time for the manifestation of its clinical effects, like medical abortion. The absorption kinetics can also explain why some routes of administration are associated with a higher incidence of side effects. Sublingual administration, which gives the highest Cmax, is associated with highest incidence of side effects when compared to other routes.

4. Pharmacokinetics in human breast milk

Breastfeeding mothers may be given misoprostol for postpartum hemorrhage prevention and treatment. It is important therefore to consider its potential effects on the fetus. However, there are very few studies on the pharmacokinetics of oral misoprostol in breast milk.

Misoprostol was detected in breast milk within 30 minutes of oral administration. The peak concentration was attained in 1 hour, which is slightly slower than the plasma level (30 minutes). The level in breast milk rapidly drops afterwards and is undetectable by 4-5 hours after ingestion.

The misoprostol acid level in breast milk is only one-third of that in the plasma [15,16]. There is no data on the pharmacokinetics of misoprostol in breast milk for non-oral routes. However, it would be expected that the breast milk concentration would be lower after vaginal administration than after oral administration, but might last longer. The effect of a short exposure to low levels of misoprostol to the fetus is unknown.

5. Effects on the uterus and the cervix

The uterotonic and cervical softening effects on the female genital tract were considered as side effects rather than therapeutic effects when misoprostol was first introduced. However, it is because of these effects that misoprostol is so widely used in obstetric and gynecological practice today.

5.1. Uterus

The effect of misoprostol on uterine contractility was well studied by Gemzell-Danielsson et al. [17] and Aronsson et al. [18] (Fig. 4). After a single dose of *oral* misoprostol there is an increase in uterine tonus [18,19]. To produce regular contractions, however, a sustained plasma level of misoprostol is required and this requires repeated oral doses.

The effect of *vaginal* administration of a single dose of misoprostol on uterine contractility is initially similar to that of oral administration: an increase in uterine tonus. However, after 1-2 h, regular uterine contractions appear and they last

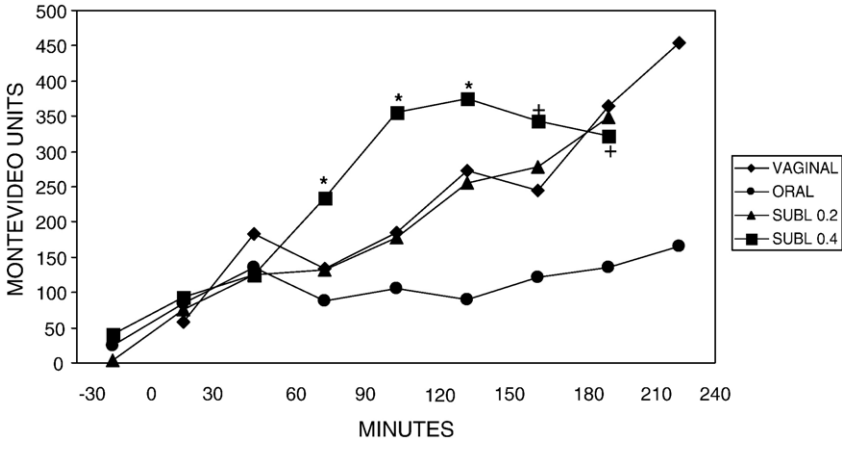

Figure 4 Uterine activity was measured in Montevideo Units (MU). The treatment groups were as follows: vaginal (0.4 mg), oral (0.4 mg) and sublingual (0.2 and 0.4 mg). Significant differences between the means of the sublingual (0.4 mg) and oral group: *$P<0.05$; †pooled sublingual groups (0.2 and 0.4 mg). [Aronsson. Effects of misoprostol on uterine contractility following different routes of administration. Hum Reprod 2004. Reproduced by permission of Oxford University Press].

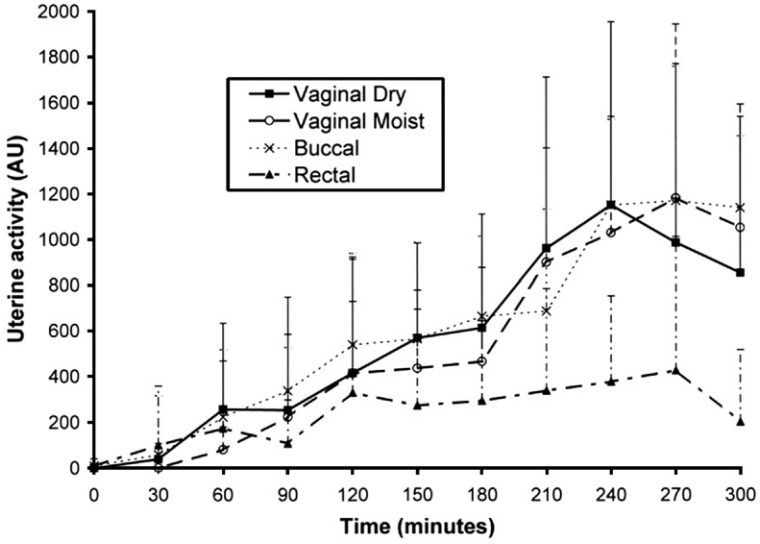

Figure 5 Mean uterine activity in Alexandria Units for four epithelial routes of misoprostol administration over five hours. Alexandria Units estimate area under the pressure-across-time curve for uterine contractions. Error bars represent standard deviation. AU, Alexandria Units. [Meckstroth. Misoprostol Absorption and Uterine Response. Obstet Gynecol 2006. Reproduced by permission of Lippincott Williams & Wilkins].

at least up to 4 h after the administration of misoprostol [17]. The development of regular contractions after vaginal administration may explain the better clinical efficacy of vaginal administration when compared to oral administration [7,8].

Recently, *sublingual* misoprostol was studied in first and second trimester medical abortion [20,21]. Aronsson et al. compared the effects of misoprostol on uterine contractility following different routes of administration [18]. It was found that the increase in uterine tonus is more rapid and more pronounced following oral and sublingual treatment than after vaginal treatment.

> *The mean time to increase in tonus is 8 and 11 min for oral and sublingual administration respectively compared with 20 mins for vaginal administration.*

The mean time to maximum tonus is also significantly shorter for oral and sublingual misoprostol compared to vaginal administration. One to two hours after the administration of misoprostol, the tonus begins to decrease. In the case of oral misoprostol, this is the end of the activity. For vaginal and sublingual treatment, however, the tonus is slowly replaced by regular uterine contractions. These regular uterine contractions are sustained for a longer period after vaginal administration than after sublingual treatment, with decreased activity occurring only after 4 hours (compared to 3 hours with sublingual). (Fig. 4)

The uterine effect of *buccal* and *rectal* administration was studied by Meckstroth et al. [6] (Fig. 5). It was shown that the pattern of uterine tonus and contractility of buccal administration is very similar to vaginal administration, even though the AUC was 2 times less.

> *Rectal administration, which has got the lowest AUC, shows the lowest uterine activity in terms of tonus and contractility. Furthermore the mean onset of activity was 103 minutes, significantly longer than by other routes. [6]*

The studies on uterine contractility so far have shown that a sustained level, rather than a high serum level, is required for the development of regular uterine contractions. Studies have failed to define the threshold serum level for uterine contractility. It seems that a very low serum level of misoprostol is required for the development of regular uterine contractions. This is complicated further by the fact that the sensitivity of the uterus to prostaglandins increases with gestation. The clinical effects or actions required for different indications of use also vary. The strength of contraction that is required to achieve the clinical effects usually increases with gestation. For instance, stronger contractions are required for labor induction than medial abortion. For medical abortion, the addition of mifepristone would certainly modify the action of misoprostol and lower the serum threshold level for uterine contractility. In addition to uterine contraction, the softening effect of misoprostol on the cervix also contributes to its clinical action.

5.2. Cervix

There were many clinical studies that have demonstrated the cervical priming effect of misoprostol in the pregnant state. Misoprostol has been used extensively for its cervical softening effect before induction of labor and surgical evacuation of the uterus. Studies have demonstrated that less force was required for mechanical dilatation of the cervix if misoprostol was applied before the procedure [22,23]. While this softening effect on the cervix may be secondary to the uterine contractions induced by misoprostol, it is more likely to be due to the direct effect of misoprostol on the cervix.

The uterine cervix is essentially a connective tissue organ. Smooth muscle cells account for less that 8% of the distal part of the cervix. The exact mechanism leading to physiological cervical ripening is not known. The biochemical events that have been implicated in cervical ripening are (1) a decrease in

total collagen content, (2) an increase in collagen solubility, and (3) an increase in collagenolytic activity. The changes in extracellular matrix components during cervical ripening were described as similar to an inflammatory response [24]. Indeed, during cervical ripening there is an influx of inflammatory cells into the cervical stroma, which increases matrix metalloproteinases and thereby leads to the degradation of collagen and cervical softening [25]. It has been proposed that these cells produce cytokines and prostaglandins that have an effect on extracellular matrix metabolism. It has also been shown that various prostaglandin analogues could decrease the hydroxyproline content of pregnant cervix [26].

The histochemical changes in the pregnant cervix after misoprostol administration were studied using electron microscopy and proline uptake assay. The mean proline incorporation per μg protein and collagen density, estimated by light intensity, was significantly less than the control. This indicated that the action of misoprostol appeared to be mainly on the connective tissue stroma with evidence of disintegration and dissolution of collagen [27].

Most of the studies on uterine contractility and cervical softening after misoprostol have been conducted on pregnant women. There is, however, evidence suggesting that these changes also occur in non-pregnant uterus. Some non-pregnant women experience uterine cramps after misoprostol and misoprostol has been shown to also have a cervical priming effect in the non-pregnant state [3,28].

6. Side effects and incidence of fetal malformations

Misoprostol is a safe and well-tolerated drug. Pre-clinical toxicological studies indicate a safety margin of at least 500-1000 fold between lethal doses in animals and therapeutic doses in humans [29].

> *No clinically significant adverse hematological, endocrine, biochemical, immunological, respiratory, ophthalamic, platelet or cardiovascular effects have been found with misoprostol. Diarrhea is the major adverse reaction that has been reported consistently with misoprostol, but it is usually mild and self-limiting. Nausea and vomiting may also occur and will resolve in 2 to 6 hours.*

Some women found an unpleasant taste when it is taken sublingually or buccally. A sense of numbness over the mouth and throat has also been reported when it is taken sublingually.

The toxic dose of misoprostol is unknown, but it has been considered to be a very safe drug. However, a recent case report has identified a woman who died of multi-organ failure following an overdose of misoprostol (60 tablets over 2 days) [30].

Fever and chills have also been reported and are common following high doses in the third trimester or immediate postpartum period. The typical situation in which this is seen is when misoprostol is used for the prevention or treatment of postpartum hemorrhage.

> *In studies of misoprostol for postpartum hemorrhage prevention, chills were reported in 32% – 57% of women receiving misoprostol [31–33]. Hyperpyrexia (>40 °C) has been reported in several cases following 600 μg, and hyperpyrexia with delirium and/or ICU admission has been reported following 800 μg orally [34].*

Another concern about the use of misoprostol is the risk of uterine rupture, especially in women with a previous uterine scar. Reports of uterine rupture are rare in first trimester medical abortion [35], but the risk seems to increase with gestation. Evidence from the literature shows that most uterine ruptures that do occur take place during induction of labor in the third trimester, when it is associated with previous uterine scar and other risk factors for uterine rupture [36]. Further details are in the article by Weeks et al on induction of labor [37].

Infection is not common after medical abortion by misoprostol. The incidence has been reported to be only 0.92% [38]. Nevertheless, the recent reports on fatal infection with *Clostridium sordellii* after using vaginal misoprostol for abortion has led to concerns over the use of this method. However, after extensive investigation there is still no consensus as to the mechanism of infection in these cases [39]. It is believed that as the overall incidence of infection remains low, medical abortion should not be regarded as a method that is associated with a higher infection rate when compared to the surgical method.

Exposure to misoprostol in early pregnancy has been associated with multiple congenital defects. However, mutagenicity studies of misoprostol have been negative and misoprostol has not been shown to be embryotoxic, fetotoxic or teratogenic [40]. These malformations, therefore, may be due to a disturbed blood supply to the developing embryo during misoprostol-induced contractions.

> *It is estimated that absolute risk of malformations after exposure to misoprostol is relatively low, in the order of 1% among exposed fetuses.*

In population registers, the incidence of abnormalities does not seem high, given that exposure to misoprostol is quite common among some populations [42].

A wide range of defects is possible depending on the time of exposure to misoprostol. Central nervous system and limb defects are the most commonly reported anomalies. Mobius syndrome, which is characterized by congenital facial paralysis with or without limb defects, has been associated with misoprostol exposure [41]. Other abnormalities like transverse limb defects, ring-shaped constrictions of the extremities, arthrogryposis, hydrocephalus, holoprosencephaly and exostrophy of the bladder have also been reported [42]. Fetal malformation is more commonly associated with the use of misoprostol-only regimen for abortion as compared to sequential regimen using mifepristone and misoprostol. It may be due to the stronger uterine contraction associated with repeated high doses of misoprostol. Therefore, induced abortion by misoprostol must be performed under medical supervision. It is important to have informed consent of the woman before abortion and counsel the woman on the risk of fetal abnormality if the pregnancy is continued after exposure to misoprostol.

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Conflict of interest

The authors do not have any conflict of interest.

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