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REVIEW ARTICLE

Misoprostol for induction of labor with a live fetus

A. Weeks^{a,*}, Z. Alfircvic^a, A. Faúndes^b, G.J. Hofmeyr^c, P. Safar^d, D. Wing^e

^a School of Reproductive and Developmental Medicine, University of Liverpool, Liverpool Women's Hospital, Liverpool, UK

^b Department of Gynecology and Obstetrics, State University of Campinas (UNICAMP), Campinas, SP, Brazil

^c Effective Care Research Unit, East London Hospital Complex and University of the Witwatersrand/University of Fort Hare, South Africa

^d Department of Obstetrics and Gynaecology, General Public Hospital, Korneuburg, Austria

^e Division of Maternal–Fetal Medicine, Department of Obstetrics and Gynecology, University of California, Irvine, USA

Recommended Dosages

25 µg p.v. 4 hrly (max. ×6)
p.o. Oral misoprostol 50 µg
p.o. 4 hrly (max. ×6). Oral
Misoprostol solution 20 µg
p.o. 2 hrly (max. ×12)

KEYWORDS

Misoprostol;
Induction of labor;
Prostaglandins;
Pregnancy

Abstract

Induction of labor is common in clinical practice. Many different medical and mechanical methods have been used, but the current gold standard is vaginal dinoprostone. Misoprostol has been used for the induction of labor since 1987. In early studies with large misoprostol doses (e.g. 200 µg) there were high rates of uterine hyperstimulation. Cochrane meta-analysis, however, shows that when used in low doses it is as effective as vaginal dinoprostone and with no excess of hyperstimulation. 25 µg vaginal misoprostol 4-hourly, 50 µg oral misoprostol 4-hourly or 20 µg oral misoprostol solution 2-hourly are all safe and effective regimens. Reports of uterine rupture in women with previous cesarean sections mean that it remains contraindicated in this group.

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1. Background

Induction of labor is commonly performed in clinical practice. Compared to spontaneous labor the main risks of induction are ineffective labor and excessive uterine activity, which may cause fetal hypoxia. In women with previous cesarean sections or uterine scars there also appears to be a higher incidence of uterine rupture.

Labor may be induced using medical methods (oxytocin or prostaglandins) or mechanical methods (e.g.

extra-amniotic balloon catheters or artificial rupture of the membranes [ARM]). The most common methods in hospital practice worldwide are oxytocin (combined with ARM where possible) and vaginal prostaglandins. Prostaglandins have been shown to be of benefit to reduce the need for cesarean section when the cervix is unfavorable [1]. Prostaglandin E₂ (dinoprostone) has now become the drug of choice in well-resourced settings for cervical ripening and induction of labor, but it is expensive, unstable and requires refrigerated storage.

Misoprostol was first used for the induction of labor with a dead fetus in 1987 [2], and since then there have been over 100 randomized trials that have evaluated the effectiveness of misoprostol for labor induction with a viable fetus. These have been reviewed for *The Cochrane Library* by Hofmeyr and Gumezoglú [3], Alfircvic and Weeks [4] and Muzonzini

* Corresponding author. School of Reproductive and Developmental Medicine, University of Liverpool, Liverpool Women's Hospital, Crown Street. Tel.: +44 151 702 4240; fax: +44 151 702 4024.

E-mail address: aweeks@liv.ac.uk (A. Weeks).

and Hofmeyr [5]. The data below are derived from those reviews.

In using misoprostol for induction, there is a balance to be reached between high doses (which cause rapid delivery but frequent hyperstimulation), and low doses that have the reverse effect. Much of the research conducted over the last 20 years has been an attempt to find a safe but effective induction dose.

When vaginal misoprostol is compared to vaginal dinoprostone, the need for oxytocin augmentation was reduced with misoprostol (25 trials, RR 0.65, 95% CI 0.57 to 0.73), as was failure to achieve vaginal delivery within 24 h (13 trials, RR 0.80, 95% CI 0.73 to 0.87). Uterine hyperstimulation with fetal heart rate changes was variable between trials, but overall more common with misoprostol (19 trials, RR 2.04, 95% CI 1.49 to 2.80). Cesarean section rates were variable between trials, with no significant differences overall (21 trials). Many of the above trials used relatively high doses of vaginal misoprostol. A meta-analysis of trials comparing misoprostol with prostaglandin E2 by Crane [6] found no difference in outcomes when 25 µg of vaginal misoprostol was compared with prostaglandin E2. Vaginal misoprostol doses of over 25 µg were associated, as in the Cochrane review above, with a shorter labor needing less oxytocin, but with higher rates of hyperstimulation.

In the comparisons of vaginal misoprostol and intracervical dinoprostone, 'failure to achieve vaginal delivery within 24 h, and oxytocin use was consistently reduced with misoprostol (RR 0.68, 95% CI 0.59 to 0.78, and RR 0.56, 95% CI 0.51 to 0.61 respectively). Uterine hyperstimulation both with and without fetal heart rate changes was more common with misoprostol. There was no significant difference in cesarean section rates.

The appropriate dosage of vaginal misoprostol appears to be 25 µg rather than 50 µg as, although both are effective, the 25 µg dose reduces the risk of hyperstimulation [7].

In the comparisons of oral misoprostol and vaginal dinoprostone, there was no significant difference in the risk of cesarean section for all women (RR 0.88, 95% CI 0.76 to 1.01), but a significant decrease in cesarean section for those with intact membranes (RR 0.78, 95% CI 0.66 to 0.94). There were no statistically significant differences between the groups in any of the other outcomes including hyperstimulation rates and frequency of meconium-stained liquor [4,6]. In the 2 trials that compared oral misoprostol with intracervical dinoprostone there were no significant differences in any of the major outcomes.

Hofmeyr et al. [8] pioneered the use of titrated oral misoprostol solution in 2001. A single misoprostol tablet is dissolved in tap water (so that 1 mL contains 1 µg) and small doses of misoprostol solution (20–25 µg) are then given every 2 h, with increasing doses if there is no response. Since the initial report by Hofmeyr it has been compared to vaginal dinoprostone in at least 6 further randomized trials. Oral regimens of this type now dominate the 2006 Cochrane review [4] and the subgroups analyses are in line with the overall conclusions.

Many previous studies have used relatively high doses of misoprostol (e.g. ≥50 µg vaginally or ≥100 µg orally).

These have given strong contractions resulting in short labors, but high rates of fetal heart rate abnormalities. The latest studies using 25 µg tablets vaginally or 20–50 µg orally show very similar outcomes to vaginal prostaglandin E2.

Oral and vaginal misoprostol have been compared in multiple studies, the majority of which compare oral doses of 50 µg with what is now considered to be a comparatively high vaginal dose (50 µg). In these studies overall [4], labors induced with oral misoprostol require a more frequent use of oxytocin (RR 1.28, 95% CI 1.11 to 1.48), but had significantly lower rates of uterine hyperstimulation without fetal heart rate changes with oral regimens (RR 0.37, 95% CI 0.23 to 0.59). There was no difference in the rate of hyperstimulation with FHR changes. In many of these results there was heterogeneity with higher oral doses causing hyperstimulation and rapid delivery. Overall there was no difference in cesarean section rate between the oral and vaginal regimens.

2. Standard induction method

The use of vaginal or intracervical prostaglandins followed by intravenous oxytocin is generally accepted to be the standard induction method for women with an unfavorable cervix [9,10]. Studies using low dose misoprostol in the regimens described below show this to be as effective as dinoprostone, and with potential benefits (see above). However, misoprostol is available as a licensed low dose product for the induction of labor only in very few countries (Prostokos in Brazil and Vagiprost in Egypt). Logistical problems resulting from this (difficulty in cutting the tablets accurately, legal liability and potential dosage mistakes resulting from the lack of dosage instructions on the packet) means that dinoprostone remains the gold standard in countries where there is no low-dose misoprostol product licensed for labor induction.

3. Contraindications

There are many contraindications to the induction of labor in general. The only specific contraindication to misoprostol is sensitivity to misoprostol, although please see comments on previous cesarean section below.

4. Precautions

1. Previous caesarean section(s) or other uterine scarring. The risks of uterine rupture in this situation are high (reported rates up to 12% – see below). The use is therefore contraindicated except in circumstances in which the benefits are considered to outweigh the risks.
2. Trained staff and tocolytic agents should be on hand to manage uterine hyperstimulation where possible. Women with hyperstimulation syndrome should be given tocolytic agents (e.g. subcutaneous terbutaline 250 µg as a single dose). Women with tachysystole or hypertonia should have electronic fetal monitoring commenced. If this is not available or the fetal heart rate is abnormal, then tocolytics should be administered.

- Where possible, an operating theatre should be available to perform an emergency cesarean section should the woman develop complications and fail to respond to medical treatment.

5. Regimens

There are many possible misoprostol regimens for induction of labor. Each of the three below has been widely used. There is no evidence that any one regimen is better than the other.

- Vaginal misoprostol**
Misoprostol tablet cut to 25 µg size administered vaginally every 4 h with a maximum of 6 doses [25 µcg vaginal pessaries are currently only manufactured in Egypt and Brazil, but others may soon be available].
- Oral misoprostol solution**
A single misoprostol tablet is dissolved in drinking water so that 1 mL contains 1 µg (e.g. 200 µcg tablet in 200 mL water, or a 100 µg tablet in 100 mL water), and 20–25 mL of misoprostol solution (20–25 µg) is then given every 2 h. If there is no response after 2 doses in nulliparous women then the dose can be doubled. The solution is stable for up to 24 h at room temperature, but should then be discarded [11]. [Misoprostol tablets can also be cut so as to obtain a 25 µg segment and then administered 2-hourly as above.]
- Oral misoprostol tablets**
Misoprostol tablets cut to 50 µg size and administered orally every 4 h to a maximum of 6 doses.

These regimens can be used irrespective of the state of the membranes (ruptured or intact), parity, cervical state and gestation. Care is needed in women with favorable cervixes and ruptured membranes as they often progress rapidly in labor once induced. The dose needed for induction of labor after intrauterine fetal death is lower. Specific dosage advice is given by Gomez et al. [12].

6. Course of treatment

- The woman should be admitted to hospital from the beginning of the labor induction process.
- Prior to starting the induction process, the woman should be carefully assessed for evidence of fetal compromise. This should include electronic fetal heart rate monitoring for 30 minutes if available.
- If electronic fetal heart rate monitoring is not available, the baby's condition should be assessed by clinical assessment of growth and amniotic fluid volume, the mother's report of fetal movements, and if necessary clinical fetal arousal tests.
- Once a misoprostol regimen has been started, the woman must be monitored closely. The fetal heart rate and uterine activity, as well as the mother's vital signs must be constantly monitored for 30 min after each dose of misoprostol has been administered, and every 30 min from the onset of uterine contractions. Where available, electronic fetal monitoring should be used from the time at which regular contractions of every 3 min or more commence.

- At the time of each planned misoprostol dose, the woman should be clinically reassessed. If there are 0–1 contractions every 10 minutes, then a further dose of misoprostol can be given. If there are 2 or more clinically adequate uterine contractions in 10 minutes, then clinical judgment should be used to assess the best way of continuing the induction to achieve optimal contractions (3 strong contractions in 10 minutes). An intravenous oxytocin infusion for labor induction should not be commenced less than 4 hours after the last dose of vaginal misoprostol or 2 hours after the last dose of oral misoprostol.
- If the cervix remains unfavorable after the course of misoprostol is completed, a senior member of staff should review the situation. The alternatives include switching to an alternative method, a repeat course of misoprostol, or a cesarean section.

7. Risks and side effects

7.1. Uterine hyperstimulation

Serious side effects may occur as a result of over-stimulation of the uterus. Although these are primarily seen with too high doses (or where the wrong route or dosage frequency has been used), they may also occur at recommended dosages. Serious maternal and fetal complications may result, principally uterine rupture (especially in women with previous uterine scars) and fetal hypoxia.

The majority of studies comparing labor induction with misoprostol and dinoprostone or oxytocin show a greater incidence of uterine hypercontractility with misoprostol. However, most of those studies were conducted using relatively high doses of vaginal or oral misoprostol. In studies using 25 µg vaginal misoprostol 4-hourly, 50 µg oral misoprostol 4-hourly or 20–40 µg oral misoprostol solution 2-hourly, hyperstimulation rates are similar to those in women induced with dinoprostone (4%–12%) [3,4].

7.2. Uterine rupture

There have been several reports of uterine rupture following misoprostol labor induction with and without previous cesarean section. One published trial of misoprostol for labor induction in women with prior cesarean section (using vaginal misoprostol 25 µg 6-hourly to a maximum of four doses) was terminated prematurely because of disruption of the uterine incision in two of the first 17 misoprostol-treated women [13]. There is also evidence of an increased uterine rupture risk from observational studies: in a retrospective review, uterine rupture occurred in 5/89 (5.6%) of women with previous cesarean delivery who had labor induced with vaginal misoprostol, compared with 1/423 (0.2%) of those induced with dinoprostone [14]. In contrast, other sources have found low rates of uterine rupture. In a retrospective review, no uterine ruptures were detected among 48 women with previous cesarean section whose labor was induced with misoprostol 50 µg vaginally four hourly [15]. In another study from the USA, there were 2 ruptures of 142 women (1.4%) with previous cesarean section induced with misoprostol [16]. In this study, various dosages of misoprostol were used and the

study included women with more than one cesarian section and classical uterine incisions. The uterine rupture rate with misoprostol was not statistically significantly different to that seen when oxytocin alone was used (5/430, 1.2%).

There is less evidence for oral misoprostol, but there was a rupture rate of 10% (4 of 41) in a study using oral misoprostol for induction [17]. Whilst the lack of ruptures in the women in the Cochrane reviews' randomized trials who underwent induction with oral misoprostol is encouraging, it would take a trial of over 60,000 women to evaluate whether there was a significant increase in the 0.5% background scar rupture rate in women undergoing a trial of vaginal delivery. An increase in uterine rupture rate also appears to occur with dinoprostone, albeit not to the same degree. In a large retrospective study of 8904 women undergoing induction following a previous cesarean section the uterine rupture rate was 0.87% for those induced with prostaglandins compared to 0.3% for those induced without prostaglandins [18].

7.3. Meconium staining of the liquor

The finding of significantly more meconium-stained liquor with misoprostol versus vaginal or intracervical prostaglandins is of interest. It has been suggested that meconium passage occurs in response to uterine hyperstimulation or as a direct effect of absorbed misoprostol metabolites on the fetal gastrointestinal tract. An increased rate of meconium-stained liquor in women who have ingested castor oil was previously observed, though causality was not proven, and a possible direct effect of the castor oil metabolites on fetal bowel suggested [19]. It is unlikely that the small amount of hydrogenated castor oil found in misoprostol tablets [20] would have any pharmacological effect, but the possibility that misoprostol metabolites may directly stimulate fetal bowel is of interest. An *in vitro* effect of misoprostol on isolated rat ileum (as well as myometrium) has been shown [21].

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Conflict of interest

The authors do not have any conflict of interest.

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