Misoprostol for induction of labour to terminate pregnancy in the second or third trimester for women with a fetal anomaly or after intrauterine fetal death

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For the termination of second- or third-trimester pregnancy involving fetal anomaly or intrauterine fetal death, vaginal misoprostol is more effective than oral misoprostol. It is also as effective as the traditionally-used and more expensive prostaglandins such as PGF2α and gemeprost, which are more difficult to store than misoprostol and are associated with more side-effects.

RHL Commentary by Mathews JE

1. INTRODUCTION

Termination of a pregnancy involving a dead fetus or one with a lethal anomaly is a challenge for health-care professionals in any setting. In addition to the theoretical concern of the dead fetus in-utero causing disseminated intravascular coagulation (1), continuation of such a pregnancy may not be psychologically and socially acceptable to many women, and both the woman and the caregiver are keen to see the end of pregnancy, preferably without an incision on the uterus.

Misoprostol (PGE1) is an anti-gastric ulcer medication, which is not registered for use in pregnancy termination in many countries of the world. Ironically, it has revolutionized the termination of pregnancy as a result of its wide availability and ease of administration. Its property of being stable at room temperature makes it valuable for use in under-resourced settings. However, one of the concerns with its use in pregnancy is hyperstimulation of the uterus and, in extreme cases, uterine rupture. Even though hyperstimulation, leading to utero–placental insufficiency, is not a major concern during the induction of labour for pregnancy termination in the second or third trimester in women with a fetal anomaly or intrauterine fetal death, the possibility of uterine rupture remains a major worry with its use. Hence, importantly, this review (2) aimed to compare the benefits and adverse effects of using misoprostol, as compared with other methods, for the induction of labour to terminate pregnancy in the second and third trimester in women carrying a fetus with an anomaly or after intrauterine fetal death.

2. METHODS OF THE REVIEW

The review authors performed a comprehensive search of all relevant randomized controlled trials and a complete assessment of risk of bias in included studies. The primary outcomes of interest in these studies were vaginal birth not achieved within 24 hours and the induction-to-delivery interval. The secondary
outcomes included blood loss, analgesia, serious maternal morbidity (including uterine rupture) and side-effects such as nausea, vomiting, diarrhoea and pyrexia.

The overall quality of the included trials varied from 'good' to 'fair'. The authors of the review used fixed-effect inverse variance meta-analysis for combining data where trial participants and methods were judged to be sufficiently similar. When the review authors suspected heterogeneity between studies, the authors used random-effects meta-analysis. They did not conduct a sensitivity analysis. Even though a subgroup analysis was planned in the protocol, the authors were unable to execute it as most studies did not have the indication for induction of labour or gestational age. Moreover, most studies did not report outcomes according to the trimester in which the termination was performed. The effects of parity and presence of a scar on the uterus could not be assessed as these patients were often excluded from the trials.

3. RESULTS OF THE REVIEW

Even though the review included 38 studies involving 3490 women, the sample size in each intervention was small, ranging from 855 women in the vaginal misoprostol versus oral misoprostol trial and 18 women in the intervention comparing combined oral misoprostol and loading dose vaginal misoprostol versus dilatation and curettage.

The main interventions and salient results of the comparisons were as follows:

1. Vaginal misoprostol versus oral misoprostol

Women administered vaginal misoprostol were more likely to achieve vaginal birth within 24 hours [relative risk (RR) 0.37; confidence interval (CI) 0.15–0.87] and had shorter mean induction-to-birth interval [mean difference (MD); ?5.54 hours; 95% CI (?8.92 to ?2.16) compared to women administered oral misoprostol. There were no differences for other outcomes such as need for analgesia and side-effects including nausea, vomiting, diarrhoea and pyrexia.

2. Vaginal misoprostol versus other prostaglandins (PGE2, PGF2? and gemeprost)

There were similarities between the groups with regards to vaginal birth not achieved within 24 hours and induction-to-delivery interval. However, women who were administered vaginal misoprostol were less likely to have nausea [RR 0.59 (0.35–0.99)] and diarrhoea [RR 0.2(0.06–0.67)] when compared to those who received PGE2 and less likely to require surgical evacuation of uterus compared with those that received PGF2? [RR 0.63 (0.41–0.98)].

3. Vaginal misoprostol versus sublingual misoprostol

Two studies involving 202 women were available for this comparison. Women who were administered sublingual misoprostol were more likely to achieve vaginal birth within 24 hours (vaginal birth not achieved within 24h, RR 0.24; 95% CI 0.08 – 0.74) and had a shorter mean induction-to-birth interval (MD ?4.81 hours; 95% CI ?8.26 to ?1.37) when compared with the vaginal misoprostol group. There were no differences in other outcomes such as the need for analgesia and side-effects.

4. Vaginal misoprostol 6-hourly versus vaginal misoprostol 12-hourly

Three studies (416 women)showed there were no significant differences in the primary outcomes between these two groups. However, the 6-hourly dose interval was associated with an increased risk of vomiting and pyrexia.
5. **Low-dose vaginal misoprostol (<800 µg in 24 hours) versus moderate-dose (800 µg–2400 µg in 24 hours)**

This comparison was assessed in a single study with 150 women. Low cumulative dose of misoprostol was associated with an increased chance of women not achieving vaginal birth within 24 hours (RR 1.85; 95% CI 1.13–3.03) but a reduced risk of need for surgical evacuation of the uterus (RR 0.57; CI 0.33–0.98). Both dosage regimens were similar in their side-effect profile.

6. **Combined oral and loading dose vaginal misoprostol versus vaginal misoprostol alone**

One small study (43 women) showed that women who were administered vaginal misoprostol alone had a longer mean induction-to-birth interval (MD 5.20; 95% CI 3.42–6.98) compared with those who received combined oral and loading vaginal dose of misoprostol. There were no statistically significant differences between the groups with regard to other outcomes and side-effects (nausea, vomiting, diarrhoea).

4. **DISCUSSION**

This review shows that, for the termination of second- or third-trimester pregnancy involving a dead or abnormal fetus, vaginal misoprostol is more effective than oral misoprostol and it is as effective as the traditionally used and more expensive prostaglandins like PGE2, PGF2α and gemeprost, all of which are more difficult to store than misoprostol and are associated with more side-effects.

4.1 **Applicability of the results**

Although this systematic review included all relevant randomized controlled trials of reasonable quality, it was unable to address the most important concern with regard to misoprostol, namely rupture of the uterus during induction of labour in the second and third trimester. This was either because the sample sizes in all included studies were small or because of poor reporting of such outcomes in the included trials. Besides sample size issues, only few studies (4–6 out of 38) included in the review had women in their third trimester of pregnancy, a period when the risk of uterine rupture is perceived to be higher. Hence, caution should be exercised in applying the findings of this review to the third trimester. As mentioned before, since subgroup analyses was not possible, again due to small sample sizes, the results may not be similar in women with scarred uterus regardless of the gestation at which termination is performed.

4.2 **Implementation of the intervention**

In most developing countries, misoprostol is easily available and is inexpensive. Findings of this review would support its use in a grieving patient who would be expected to appreciate a short induction-to-delivery interval. However, since there is very little information on the most important outcome which is severe maternal morbidity due to rupture of the uterus, misoprostol should be used only in centres capable of managing severe maternal complications such as uterine rupture. It is not uncommon for stillbirths or lethal anomalies with a live fetus to be diagnosed only at term. Users of this commentary should also refer to the systematic review entitled ‘Misoprostol for induction of labour: a systematic review’ (3).

4.3 **Implications for research**

There is a need for a large multicentre study to address the safety issues associated with the use of misoprostol for second- and third-trimester pregnancy termination in both women with scarred and unscarred uteri. Such a study should ensure recruitment of adequate numbers of women in their third trimester of pregnancy in order to improve applicability of its results for women in this category. For vaginal misoprostol, the optimal dosage, dosing intervals and relationship to gestational age at induction need to be
researched. Larger studies are also needed to compare vaginal misoprostol with sublingual misoprostol in order to assess their comparative effectiveness and to determine the optimal dose and dosing intervals. Further information about the benefits of combining oral and vaginal misoprostol is also needed.

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