Medical treatment for early fetal death (less than 24 weeks)

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Vaginal misoprostol is an effective treatment for the termination of non-viable pregnancies before 24 weeks. It is likely to be more beneficial in under-resourced settings because miscarriages due to maternal infection are likely to respond better to medical therapy than miscarriages resulting from genetic fetal abnormalities.

RHL Commentary by Weeks A

1. EVIDENCE SUMMARY

In this review (1), the authors analyse all randomized controlled trials conducted up to November 2005, and make recommendations about the efficacy of medical treatment for early fetal death. The review methods are appropriate and the review is of a very high standard.

Although 24 studies (involving 1888 women) are included in the review, each study compared different elements of management of early fetal death. Most of the analyses and conclusions of the review come from only one or two studies. The largest study on this topic, which compares surgical, expectant and medical management (mifepristone and misoprostol) in over 900 women with early fetal demise (2), was published too late for it to be included in this review. Its conclusions however, are broadly similar to those of this review.

When compared with placebo, vaginal misoprostol speeds up the miscarriage process (complete or incomplete) and reduces the need for uterine curettage. There were no side-effects from the use of misoprostol. A single dose of 800 µg appeared to be more effective than lower doses. One trial that had evaluated whether wetting misoprostol tablets (with acetic acid or saline) was beneficial, found no added benefit from doing so. There was also no benefit from adding methotrexate to misoprostol (in the first trimester) or laminaria tents (after 14 weeks).

In the first trimester, vaginal misoprostol is more effective than dinoprostone (prostaglandin E2), but is of similar efficacy to sublingual misoprostol (600 µg, three hourly). Vaginal misoprostol (800 µg) is more effective than oral misoprostol (400 µg), but is of similar efficacy to oral misoprostol 800 µg. In the second trimester, vaginal misoprostol (200 µg, three hourly) is of similar efficacy to vaginal gemeprost. There were two trials of mifepristone treatment, with one showing benefit and the other showing no benefit.

This review brings together evidence from multiple small studies. Overall, the studies show that vaginal misoprostol is an effective treatment for termination of non-viable pregnancies before 24 weeks. Although the optimal dose for the first trimester is not yet clearly established, 800 µg vaginally, repeated after three days was effective in 79% of women by seven days (or 87% by day 30) in the study by Gilles (3). In the
second trimester (from 10–24 weeks) a lower dose, such as 200 µg vaginally repeated every 12 hours as used by Jain (4), is recommended.

2. RELEVANCE TO UNDER-RESOURCED SETTINGS

2.1. Magnitude of the problem

The term 'early fetal death' refers to situations in which the fetus is no longer alive, but the uterus has not yet started to expel its contents. A variety of terms were previously used to describe this condition, including 'blighted ovum', 'missed abortion' and 'silent miscarriage'. In practical terms in such situations the fetus is dead, but the cervical os remains closed. The diagnosis is made by ultrasound scan following the clinical findings of vaginal bleeding, absent fetal heart sounds on electronic auscultation (from 12 weeks), a failure to feel fetal movements (from 16 weeks) or a uterus that is significantly smaller than the expected size.

Early fetal death is very common in all settings, occurring in 15% or pregnancies in the developed world. This figure is likely to be similar in under-resourced setting, for while the younger age of pregnant women will reduce the number of miscarriages for genetic abnormality, the figure is likely to be raised by higher frequency of infection (malaria and syphilis).

The lack of ultrasound and pregnancy testing facilities means that few women are diagnosed with early fetal death. Instead, women with this condition are likely to delay their presentation until they have an inevitable or incomplete miscarriage. At this stage clinical diagnosis will be possible with the finding of an open cervical os. Treatments for these women are the subject of different reviews.

Traditionally, early fetal death has been treated by surgical uterine evacuation up to 14 weeks, and labour induction after that, using a variety of agents including oxytocin and prostaglandins. It has recently become clear that medical agents, especially the orally active prostanaglandin misoprostol, are effective in emptying the uterus at all gestational ages and is an effective alternative to surgical evacuation.

The option of expectant management of early fetal death at less than 24 weeks is the subject of another Cochrane review (5). Two forthcoming reviews will also consider the best management options of women with incomplete miscarriages (incomplete and inevitable abortions or retained products of conceptions; Cochrane review awaited), intrauterine fetal death at over 24 weeks (Cochrane review in progress), and termination of unwanted pregnancies in the first and second trimesters.

2.2. Applicability of the results
The results of the review are applicable to women in low-resourced settings. Indeed, misoprostol is likely to be more beneficial for women in low-resourced settings. There are two reasons for this. First, miscarriages that occur due to maternal infection are likely to respond better to medical therapy than those that result from genetic fetal abnormality. Thus, misoprostol may be most effective in younger populations with high infective morbidity (as is the case in many low-resourced settings).

Second, the highest risk of infection with miscarriage seems to occur as a result of uterine instrumentation rather than failure to evacuate rapidly the products of conception (2, 5). Thus, in settings where there are high rates of HIV, pelvic inflammatory disease and cervical infection, one should try to avoid surgical instrumentation of the uterus with either manual vacuum aspiration or sharp curettage. The small risks of allowing the products of conception to remain within the uterus can be reduced by the use of misoprostol to empty the uterus. This may not be true if the woman has undergone an unsafe ‘backstreet’ abortion – but these women generally present with incomplete abortions rather than early fetal death.

### 2.3. Implementation of the intervention

Misoprostol is already available in many low-resourced settings and should be made available to women for the treatment of miscarriage. However, there are two issues to consider with regard to misoprostol use for the treatment of early fetal death. First, the commonly available misoprostol preparation is for the treatment of gastric ulcers and the packet labelling reflects this. The lack of a specific product for early pregnancy can lead to confusion with regard to correct dosages. Dosage guidelines are available on the Internet [www.misoprostol.org](http://www.misoprostol.org) and a WHO misoprostol dosage guideline will be available in 2007.

Second, health-care providers will need to be trained in the correct administration of misoprostol in the right dosages for the relevant indication. Misoprostol is a very powerful drug in late pregnancy and its use in a high dose (i.e. over 50 µg vaginally) with a live fetus can easily result in fetal death and uterine rupture. The wide variation in dosages used at different stages of gestations means that it is important to have an accurate diagnosis before commencing treatment. For this reason, many health-care services will make misoprostol available only at a level where both trained staff and facilities for diagnosis are available.

### 3. RESEARCH

As early fetal death is rarely diagnosed in low-resource settings, research in this area is not a high priority. Instead, research should be focused on the use of misoprostol for the treatment of incomplete miscarriage.

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### References

medical or surgical? Results of a randomised controlled trial (the MIST trial). *BMJ* 2006;332:1235-1238.


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