Title: Misoprostol for Incomplete Abortion or Inevitable Miscarriage

Date: 05 November 2007

Context and policy issues:

Early pregnancy failure (EPF) is a common event.\textsuperscript{1,2} It occurs in 15 to 25 percent of clinically recognized pregnancies.\textsuperscript{1,2} EPF is a general term used to define the following events: spontaneous abortion or inevitable miscarriage and embryonic or fetal death. Treatments for EPF include surgical (D&C, aspiration or vacuum), medical (pharmaceutical therapy) and expectant management (natural course).\textsuperscript{2}

Medications used for evacuation of product of conception (POC) are prostaglandins, mifepristone, mifepristone with prostaglandins and methotrexate with prostaglandins.\textsuperscript{3} Mifepristone is not available in Canada.\textsuperscript{4} Provincial guidelines from British Columbia\textsuperscript{5} and guidelines from the US\textsuperscript{6} were identified for termination of non-viable POC. Misoprostol, methotrexate and prostaglandins are used in Canada. Misoprostol (Cytotec\textsuperscript{®}) a prostaglandin E1 analogue is currently approved in Canada for the prevention of gastric ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs).\textsuperscript{7} Prostaglandins cause contractions of smooth muscles such as the uterus or intestines; causes dilatation of the blood vessels and mediate the inflammatory response. Misoprostol is an effective abortifacient when used alone or in conjunction with other drugs, because of its ability to contract the uterus and ripen the cervix.\textsuperscript{8} Misoprostol is inexpensive, easy to store and widely available. Its administration is easy to do, it can even be self-administered.\textsuperscript{8} Misoprostol only exist as an oral tablet which is inserted into the vagina.\textsuperscript{6}

In the US, misoprostol is commonly prescribed off-label to cause uterine contractions and the ripening of the cervix as a part of the FDA approved mifepristone regimen for the early termination of pregnancy.\textsuperscript{8} Mifepristone has not received notice of compliance in Canada.\textsuperscript{4} In addition, misoprostol (Cytotec) as a therapy alone is not approved for early termination of pregnancy in Canada nor the US.\textsuperscript{8}
Research questions:

1. What is the clinical effectiveness of administering misoprostol to pregnant women who would otherwise require dilation and curettage?
2. What are the guidelines for use of misoprostol for this off-label indication?

Methods:

A literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 3, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI's HTAIS, EuroScan, international HTA agencies, and a focused Internet search. Results include English language publications from 2002 to date. Another literature search in CINAHL was conducted (October 25th, 2007) on misoprostol and nursing interventions. Results include English language publications from 2000 to date.

Summary of findings:

A Cochrane review conducted by Neilson et al in 2006 was identified. An analysis was performed on the medical management, including the use of misoprostol, for early fetal death less than 24 weeks. Misoprostol was compared to surgical management, expectant management and placebo in some cases. Twenty-one of 24 randomized clinical trials (RCTs) addressed the use of vaginally administered misoprostol. Treatment with vaginal misoprostol hastened miscarriages when compared to placebo: miscarriages less than 24 hours (two trials, 138 women, relative risk (RR) of 4.73, 95% confidence interval (CI) 2.70 to 8.28); miscarriages less than 48 hours (two other trials, 84 women, RR 5.74, 95% CI 2.70 to 12.19); complete miscarriages without need for surgical intervention at seven days (one trial, 83 women, RR 2.99, 95% CI 1.80 to 4.99). There was a decreased need for surgical curettage (two trials, 88 women, RR 0.40, 95% CI 0.26 to 0.60). Consistent with these observations, treatment with vaginal misoprostol decreased the need for surgical evacuation of the uterus when compared with a policy of immediate surgical evacuation (three trials, 154 women, RR 0.42, 95% CI 0.34 to 0.52) at a cost of more nausea (one trial, 154 women, RR 21.85, 95% CI 1.31 to 364.37) and diarrhea (one trial, 154 women, RR 40.85, 95% CI 2.52 to 662.57). Overall, the available evidence from these RCTs confirms that vaginal misoprostol is effective as a medical treatment when compared to expectant management or placebo to terminate non-viable pregnancies before 24 weeks.

In addition, to the Cochrane review, 4 other RCTs were retrieved. They are summarized in the Table 1:
<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Study Design</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Conclusion / Results</th>
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<tbody>
<tr>
<td>Zhang et al. 2005²</td>
<td>RCT (non-inferiority design)</td>
<td>652 women with first-trimester pregnancy failure were recruited in a 3:1 ratio</td>
<td>Vaginal misoprostol 800 μg, day 1 and 3, if incomplete evacuation(n=491)</td>
<td>Evacuation of retained products of conception</td>
<td>Treatment of EPF with vaginal misoprostol is safe and a acceptable approach with a success rate 84 % of complete expulsion by day 8 at (95% CI 81 to 87%)</td>
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<td></td>
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<td>Baseline characteristics were similar</td>
<td>Standard of care (SoC) vacuum aspiration at day 8 if expulsion was incomplete (n=161)</td>
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<td>Patients who sought medical care for possible EPF were screened at 4 universities between March 2002 to March 2004</td>
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<td>Davis et al. 2007¹⁰</td>
<td>Data from the same RCT as above (Zhang et al. 2005²)</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Hemoglobin results at baseline and day 15 were compared</td>
<td>Participants had a greater decline of hemoglobin levels from baseline to day 15 after the misoprostol treatment than after surgery but the average decreases were small in both groups Odds ratio at 95% CI Misoprostol group versus curettage: ↓ of ≥ 2 g/dl: 3.1 (1.2 - 7.9) ↓ of ≥ g/dl: 8.3 (1.1–61.9)</td>
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<td>Moodliar et al. 2005&lt;sup&gt;11&lt;/sup&gt;</td>
<td>RCT</td>
<td>94 South African women experiencing spontaneous incomplete abortion were randomized (119 screened) Recruitment between October 2003 to April 2004.</td>
<td>Vaginal misoprostol 600 μg at day 0, if incomplete an additional identical dose on day 1 (if incomplete surgical evacuation at 1 week) (n=47) Surgical curettage for ERPC* (n=47)</td>
<td>Evacuation of retained products of conception</td>
<td>Medical treatment with 600 μg per vaginal administration in two doses is effective to treat incomplete 1&lt;sup&gt;st&lt;/sup&gt; trimester abortions Success rate 91.5% vs 100% surgical No statistical difference between 2 arms (p=0.12)</td>
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<td>Chittacharoen et al. 2003&lt;sup&gt;12&lt;/sup&gt;</td>
<td>RCT</td>
<td>80 women from Bangkok, Thailand Patients with termination of second and third trimester pregnancy with intrauterine fetal death (16-41 weeks) Recruitment between July 1999 to June 2001 Baseline Characteristics were similar in both groups</td>
<td>Vaginal Misoprostol 200 μg every 12 hours until termination of pregnancy (n=40) Oral Misoprostol 400 μg every 4 hours until termination of pregnancy (n=40)</td>
<td>Evacuation of retained products of conception</td>
<td>The number of deliveries of dead fetuses within 24 hours with oral Misoprostol (92.5%) was significantly higher than in the vaginal misoprostol group (67.5%, p&lt;0.001)</td>
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* Evacuation of retained products of conception
Three RCTs demonstrated that vaginal misoprostol is effective of ERPC when compared to expectant management of first-trimester termination of pregnancy. In second and third trimester termination of pregnancy because of fetal death, the results from one RCT, show that oral misoprostol is more effective than misoprostol per vaginal administration. More studies are needed in the second and third-trimester termination of pregnancy because of fetal death to confirm these results. In addition, the dosage regimen in the Chittacharoen et al. trial was much lower than the majority of RCTs evaluating the effectiveness of vaginal misoprostol in first-trimester EPF.

**Observational studies**

Four observational studies were identified. A prospective study compared the efficacy of vaginal misoprostol for abortion of a fetus at a gestational age less than 42 days and between 42 to 56 days. A total of 160 women were recruited to 800 µg of misoprostol per vaginal administration repeated every 24 hours, for a maximum of 3 doses. The overall complete abortion rate was 91.3%. However, vaginal misoprostol was more efficacious in women at a gestational age of less than 42 days than in women at a gestational age between 42 to 56 days (96.3% vs 86.3% p<0.025).

A large prospective observational study conducted in Latin America was identified. In this study, vaginal misoprostol 800 µg every 24 hours over 3 days was offered to women seeking early termination of pregnancy. There was no comparator group. A total of 3,225 women were recruited with gestational age up to 10 weeks, 2,900 women return for follow-up, 2,216 (76.4%) had a complete abortions within 72 hours confirmed by physicians. These results are lower than those seen in RCTs where the same dose and route of administration were employed. Lost to follow-up and self-administration may have contributed to a lower percentage of success.

A retrospective review of 355 consecutive women treated for first-trimester miscarriages with a single dose of 400 µg of vaginal misoprostol was performed. Treatment was deemed successful if a complete abortion was diagnosed at follow-up (< day 3). The overall success rate was 39.2%. The authors concluded that a single dose of vaginal misoprostol reduced the number of surgical interventions.

Finally, a second retrospective analysis was identified. This study was performed in women requiring labor induction for second and third-trimester intrauterine fetal death. A total of 82 women received misoprostol per vaginal administration 100 µg (median dose) every 4 hours, and 48 women received oral mifepristone 200 mg followed by low doses of 25 µg every 4 hours. Both regimens were deemed to be effective and safe in induction of labor after intrauterine fetal death. At 48 hours, 92.75% and 93.5% of the women had delivered the dead fetuses in the misoprostol-only group and mifepristone-misoprostol groups respectively, the difference was not clinically significant. Pre-treating with mifepristone is more effective at earlier gestational weeks.

Two meta-analyses, a Cochrane review and clinical review comparing medical management to placebo, expectant management and surgical management were identified. These included women with EPF (i.e. incomplete abortions, medical inevitable abortions, miscarriages, fetal death or embryonic death.) Although these reviews contain RCTs comparing misoprostol per vaginal administration to other treatments, they were analyzed with oral misoprostol RCTs. Conclusions on misoprostol alone could not be drawn in these reviews, but may be of interest. Furthermore, one article on the nurse’s role in misoprostol induction may provide useful information on the subject. The nursing protocol section provides guidelines for nursing administration and care as requested.
Conclusions and implications for decision or policy making:

The available evidence from the available RCTs confirms that vaginal misoprostol is an effective medical treatment when compared to expectant management or placebo for early termination of pregnancy (i.e. miscarriages, incomplete abortion, intrauterine fetal death or embryonic deaths) before 24 weeks. It is used internationally vaginally and orally for the early termination of pregnancy. Misoprostol is inexpensive, easy to store and widely available. Its administration is easy to do, it can even be self-administered.

When effective, vaginal misoprostol reduces the need for curettage or other surgical intervention for complete evacuation of products of conception. This may be translated in significant savings. In addition, the patient satisfaction should also be taken into consideration. Because misoprostol per vaginal administration is far less invasive than surgical treatment, it may provide some comfort to the patient to have this additional alternative through an already sensitive situation.

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