Alternatives to mifepristone for early medical abortion

N.L. Moreno-Ruiz a,⁎, L. Borgatta a, S. Yanow b, N. Kapp a, E.R. Wiebe c, B. Winikoff d

a Department of Obstetrics and Gynecology, Boston University School of Medicine, Boston MA, USA
b Abortion Access Project, Cambridge MA, USA
c Department of Family Practice, University of British Columbia, Vancouver, BC, Canada
d Gynuity Health Projects, New York, USA

Received 30 May 2006; received in revised form 17 August 2006; accepted 11 September 2006

Abstract

Objective: To review published reports of first-trimester medical abortion regimens that do not include mifepristone. Methods: Reports listed in Pubmed and Medline on prospective and controlled trials of the efficacy of misoprostol, alone or associated with methotrexate, for first-trimester abortion were analyzed if they included more than 100 participants and were published since 1990. Results: The efficacy of regimens using misoprostol alone ranged from 84% to 96%, and when misoprostol was used with methotrexate the efficacy ranged from 70% to 97%. Efficacy rates were influenced by follow-up interval. Treatment for infection, bleeding, and incomplete abortion were infrequent with both methods (0.3%–5%). Conclusion: Alone or in combination with methotrexate, misoprostol is an efficacious alternative to mifepristone for the medical termination of pregnancy.

© 2006 International Federation of Gynecology and Obstetrics. Published by Elsevier Ireland Ltd.

KEYWORDS
Abortion; First trimester; Methotrexate; Misoprostol

1. Introduction

Medical termination of pregnancy, also called medication or pharmacologic abortion, is an effective and acceptable alternative to surgical termination of pregnancy.

Mifepristone was the first medication to be approved specifically for medical abortion, and it has been used in combination with a prostaglandin analogue, usually misoprostol, to increase its efficacy [1,2]. Mifepristone in association with misoprostol has a high efficacy (92%–99% of complete abortions) and an excellent safety profile [1]. The most frequently reported adverse effects were nausea and vomiting [1,3,4]. Contraindications to mifepristone use include long-term corticosteroid use, chronic renal failure, anticoagulants use, inherited porphyria, allergy to the medications, suspicion of ectopic pregnancy, and intrauterine device in situ. Coagulopathies and severe anemia are contraindications for medical abortion with any agent.

⁎ Corresponding author. Department of Obstetrics and Gynecology, Boston University School of Medicine, 85 East Concord St, 6th Floor, Boston, MA 02118, USA. Tel.: +1 617 414 5112 (work), +1 617 459 5290 (home); fax: +1 617 414 7300.
E-mail address: Nilda.Moreno@bmc.org (N.L. Moreno-Ruiz).
Where available, mifepristone/misoprostol regimens are well accepted. However, mifepristone is not globally available. Even in countries where abortion is legal and mifepristone is available, political and economic factors may restrict its use. The purpose of this article was to review published reports of medical abortion regimens that do not include mifepristone.

2. Classification and follow-up of medical abortion outcomes

In studies of medical abortion, success is defined as the expulsion of all products of pregnancy, with no need for surgical intervention (uterine aspiration). A medical abortion is still considered successful if additional doses of medication are required for complete expulsion. A surgical intervention is classified as a failure of the medical technique. Uterine aspiration may be used to end a pregnancy that continues after a medical intervention, for an incomplete abortion or unspecified bleeding, or if it is the choice of the woman or her clinician [5].

Reported success rates are influenced by surgical interventions made upon patients' request or clinicians' preference, often due to the length of the abortion process. These outcomes do not represent pharmacologic failures, but decrease the overall success rate as each surgical intervention is recorded as a “failure.”

The timing of follow-up can influence overall success rates. Women using any medical technique may have delayed passage of the products of pregnancy (e.g., 14 days or more after taking the medication). If the regimen mandates a surgical termination after a fixed period, then the rate of success is determined at the cut-off date. Without the cut-off date, some of these pregnancies might abort completely without surgical intervention. An early follow-up date without routine surgical intervention might increase efficacy if it provided an opportunity for additional medication. In general, if women were willing to wait for the passage of the products of pregnancy, the wait would

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of studies of medical abortion using misoprostol alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td>Year of publication</td>
</tr>
<tr>
<td>Carbonell [12]</td>
<td>2003</td>
</tr>
<tr>
<td>Singh [30]</td>
<td>2003</td>
</tr>
<tr>
<td>Zikopoulos [31]</td>
<td>2002</td>
</tr>
<tr>
<td>Jain [32]</td>
<td>2002</td>
</tr>
<tr>
<td>Jain [33]</td>
<td>2001</td>
</tr>
<tr>
<td>Carbonell [34]</td>
<td>2001</td>
</tr>
<tr>
<td>Bugalho [35]</td>
<td>2000</td>
</tr>
<tr>
<td>Velazco [36]</td>
<td>2000</td>
</tr>
<tr>
<td>Carbonell [37]</td>
<td>1999</td>
</tr>
<tr>
<td>Carbonell [38]</td>
<td>1997</td>
</tr>
<tr>
<td>Carbonell [39]</td>
<td>1997</td>
</tr>
</tbody>
</table>

a. Number of days after first misoprostol dose; interim evaluations may have taken place.
b. Additional medication given if abortion was incomplete at follow-up.
c. Misoprostol, 400 or 600 mcg, 1–3 doses given after abortion depending on ultrasonographic assessment of the uterus.
d. Women with pregnancies less than 63 days had a completion rate of 96%; between 63 and 70 days the completion rate was 83%.
* The first dose was administered by the clinician, second dose self-administered.
** All doses were self-administered; first dose vaginally; other doses orally or vaginally.
*** All doses were administered by the clinician.
**Table 2** Summary of studies of medical abortion using methotrexate and misoprostol

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>No. of participants</th>
<th>No. of days since last menstruation</th>
<th>Dose and route of administration</th>
<th>Interval between methotrexate and misoprostol, days</th>
<th>Follow-up period (No. of days after methotrexate)</th>
<th>Overall success, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiebe [20]</td>
<td>2004</td>
<td>300</td>
<td>≤ 49</td>
<td>50 mg/m² IM, IM</td>
<td>600 mcg oral Twice, 24 h apart 600 mcg vaginal twice, 24 h apart</td>
<td>3, 4 or 5</td>
<td>7</td>
</tr>
<tr>
<td>Borgatta [27]</td>
<td>2001</td>
<td>1987</td>
<td>≤ 49</td>
<td>50 mg/m² IM, IM</td>
<td>800 mcg vaginal Twice, 24 h apart 800 mcg vaginal</td>
<td>4 to 6</td>
<td>7</td>
</tr>
<tr>
<td>Wiebe [42]</td>
<td>2002</td>
<td>518</td>
<td>≤ 49</td>
<td>50 mg/m² IM, IM</td>
<td>800 mcg vaginal Twice, 24 h apart 800 mcg vaginal</td>
<td>3 to 6</td>
<td>42</td>
</tr>
<tr>
<td>Borgatta [27]</td>
<td>2001</td>
<td>1987</td>
<td>≤ 49</td>
<td>50 mg/m² IM, IM</td>
<td>800 mcg vaginal Twice, 24 h apart 800 mcg vaginal</td>
<td>4 to 6</td>
<td>7</td>
</tr>
<tr>
<td>Wiebe [43]</td>
<td>1999</td>
<td>148</td>
<td>≤ 49</td>
<td>50 mg/m² IM, IM</td>
<td>800 mcg vaginal Twice, 24 h apart 800 mcg vaginal</td>
<td>5 to 7</td>
<td>14</td>
</tr>
<tr>
<td>Creinin [23]</td>
<td>1999</td>
<td>240</td>
<td>≤ 49</td>
<td>50 mg/m² IM, IM</td>
<td>800 mcg vaginal Twice, 24 h apart 800 mcg vaginal</td>
<td>5 to 6</td>
<td>7</td>
</tr>
<tr>
<td>Carbonell [29]</td>
<td>1999</td>
<td>148</td>
<td>≤ 56</td>
<td>25 mg oral</td>
<td>800 mcg vaginal (e), up to 3 doses q 48 h if no abortion</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Dose</td>
<td>Route</td>
<td>Dose</td>
<td>Frequency</td>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
<td>------</td>
<td>-------</td>
<td>------</td>
<td>-----------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Carbonell [25]</td>
<td>1998</td>
<td>154</td>
<td>mg oral</td>
<td>50</td>
<td>800 mcg vaginal (e), up to 3 doses q 48 h if no abortion</td>
<td>90.0</td>
<td></td>
</tr>
<tr>
<td>Creinin [45]</td>
<td>1997</td>
<td>100</td>
<td>mg IM</td>
<td>75</td>
<td>800 mcg vaginal (e)</td>
<td>77.8</td>
<td></td>
</tr>
<tr>
<td>Creinin [26]</td>
<td>1997</td>
<td>299</td>
<td>mg oral</td>
<td>50</td>
<td>800 mcg vaginal (e)</td>
<td>70.2</td>
<td></td>
</tr>
<tr>
<td>Carbonell [46]</td>
<td>1997</td>
<td>287</td>
<td>mg/m² IM</td>
<td>50</td>
<td>800 mcg vaginal, repeated in 48 and 96 h if needed (f)</td>
<td>92.0</td>
<td></td>
</tr>
<tr>
<td>Creinin [47]</td>
<td>1996</td>
<td>300</td>
<td>mg/m² IM</td>
<td>50</td>
<td>800 mcg vaginal (e,f)</td>
<td>69.7</td>
<td></td>
</tr>
<tr>
<td>Wiebe [48]</td>
<td>1996</td>
<td>100</td>
<td>mg/m² IM</td>
<td>50</td>
<td>800 mcg vaginal (e)</td>
<td>69.0</td>
<td></td>
</tr>
</tbody>
</table>

a. Self-administered unless noted.
b. \( P=0.012. \)
c. The second dose was administered 24 h later if the bleeding was less than menses.
d. Differences were not significant \( (P>0.05). \)
e. Repeated if gestational sac was still present at first follow-up visit.
f. Misoprostol, 400 or 600 mcg, 1 to 3 doses given after abortion depending on ultrasonographic assessment of the uterus.
increase the success rate by decreasing the number of uterine aspirations.

In addition, a longer follow-up interval gives more information about success rates since late failures (in patients requiring surgical intervention for prolonged bleeding or infection after a diagnosis of complete abortion) are also included in the final analysis. A study protocol that evaluated patients 2 weeks and 3 months following administration of mifepristone found that the success rate decreased from 99% to 96% owing to surgical interventions may be more common after buccal administration, except that diarrhea may be more common after buccal administration, however.

Compared with vaginal administration, oral administration of misoprostol is associated with increased nausea, vomiting, abdominal pain, and diarrhea [17]. There are no differences between the reported incidence of adverse effects following buccal and vaginal administration, except that diarrhea may be more common after buccal administration [18,19].

Misoprostol may be administered buccally or intravaginally with no decrease in clinical effectiveness. When used in combination with mifepristone for termination of pregnancies up to 63 menstrual days’ duration, vaginal misoprostol is more effective [20]. Another study reported similar effectiveness with buccal and vaginal administration of misoprostol after mifepristone use (95% vs. 93%, \( P=0.51 \)) [19]. The use of buccal or sublingual misoprostol has been reported for both methods, but there is currently limited documentation.

Moistening misoprostol tablets prior to vaginal administration has been used extensively and is believed by some to improve efficacy. Although cumulative serum levels are higher after administration of moistened misoprostol, there were no differences in success rates between moistened and dry misoprostol in randomized clinical trials [21–23].

### 3. Alternative medical abortion agents to mifepristone

#### 3.1. Misoprostol

Misoprostol is a synthetic prostaglandin E1 analogue approved worldwide for the prevention of gastric ulcers. Misoprostol tablets are inexpensive and stable at room temperature, and this medication has no known adverse interactions with other drugs.

Misoprostol is effective in labor induction, the treatment of postpartum hemorrhage and early pregnancy failure, and induction of second-trimester abortion [7–10]. It is also used for cervical priming prior to hysteroscopy and surgical abortion in during the first and second trimesters [11]. However, its use for gynecologic and obstetric indications is “off-label” in most countries.

The most commonly reported adverse effects of misoprostol administration are chills, nausea, vomiting, dizziness, fever, and diarrhea [12].

Misoprostol has few medical contraindications. It is contraindicated in patients allergic to prostaglandins or when the possible adverse gastro-intestinal effects are contraindicated, such as in severe inflammatory bowel disease. Misoprostol has been associated with teratogenicity in high doses [13], and a maximum safe dose has not been established.

Although misoprostol is administered in a variety of routes, it is almost always labeled for oral use. The pharmacokinetics of the alternative routes of administration show different absorption characteristics. One hour following administration, the vaginal route produces higher serum levels of misoprostol acid, the main metabolite, than the oral route [14], and sublingual administration results in higher peak serum concentration levels as well as a higher cumulative dose (“area under the curve”) than oral administration [15]. Serum concentrations are not significantly different following sublingual or buccal administration, however [16].

4. Clinical outcomes of alternative methods

#### 4.1. Misoprostol-only methods

PubMed and Medline were used to search for articles published since 1990 that described results of misoprostol-only protocols for pharmacologic first-trimester abortion. The keywords used were “medical abortion” and “misoprostol.” Only prospective series and controlled trials with more than 100 participants were selected for analysis.

Table 1 summarizes the 13 studies identified. Publication dates range from 1997 to 2003. In most of these studies, a dose of 800 mcg of misoprostol was administered vaginally and the administration was repeated every 24 h for up to 3 doses. The median time for the completion of a misoprostol-induced abortion ranged from 6 to 9 h after the first dose (Table 1). The overall success ranged from 84% to 96%.

Misoprostol doses of 1000 mcg in women with a pregnancy duration less than 63 days had a success rate of 93%, the midrange being reported for doses of 800 mcg [34]. For women in whom the abortion was not complete after 2 doses of misoprostol, a third dose may increase the overall success rate slightly, by 0.6% to 4% [33,39].

In the analyzed studies, the surgical intervention rates related to time constraints or patient request ranged between 5.3% and 15.3% [12,17,19,30–33,37–39]. Surgical intervention for excessive bleeding ranged between 0.3% and
3.3% and treatment for infection ranged between 0.3% and 3.3% [30,37,38].

As most women will complete the abortion within 3 days of the first dose, longer follow-up periods had a small effect on efficacy rates of misoprostol-only regimens. In a study with a follow-up period lasting up to 43 days, the final success rate was 96%, among the highest reported in medical abortion [36].

Self-medication with misoprostol to induce an abortion has been documented in both legal and illegal contexts [40,41]. At this point, complications other than incomplete abortion following self-medication have not been reported, and there are no estimations of rates of incomplete abortion.

4.2. Methotrexate methods

A similar literature search was used with the keywords “medical abortion” and “methotrexate.” The studies selected were published between 1996 and 2004, and all were prospective studies including more than 100 women (Table 2). Most of the regimens used a methotrexate dose of 50 mg/m² intramuscularly followed by 800 mcg of vaginal misoprostol 3 to 7 days later, with some exceptions (Table 2). Methotrexate doses were calculated using body surface, and for most women the final dose was between 60 and 100 mg.

Because the doses, routes, and timing of administration differ among studies for both medications, the relationship between medication regimen and outcome is complex. Inclusion criteria, such as gestational age, also vary. The overall success rate was similar at various gestational ages.

When 50 mg/m² of intramuscular methotrexate was followed by 800 mcg of vaginal misoprostol 3 to 7 days later in women with a pregnancy duration of 49 days or less, the day of misoprostol administration, was not found to have an effect on outcome [23,27,42–44].

Oral methotrexate, which avoids injection and decreases exposure risks to health care personnel, has also been used. Serum levels of methotrexate following oral administration were 85% of those after intramuscular injection, and were not affected by ingestion of food [43]. Despite the lower methotrexate serum levels with oral use, however, clinical outcomes were similar. Effectiveness and adverse effects for oral and parenteral administration were found to be similar, and women reported similar acceptability for the 2 routes.

Intramuscular and oral methotrexate followed by misoprostol administration 3 to 7 days later appear comparable in efficacy. In women with a pregnancy duration less than 49 days, the reported success rate after administration of 50/m² mg of oral methotrexate followed by 800 mcg of vaginal misoprostol was between 90% and 91% [26,43]. When 50 mg/m² of intramuscular methotrexate was followed by 800 mcg of vaginal misoprostol in women with a pregnancy duration less than 49 days, however, the observed success ranged between 75% and 95% [23,27,42,44],

Most clinicians used a second dose of misoprostol if abortion had not occurred after the first. Using a third dose did not significantly increase the success rates [25].

Surgical interventions for true method failure (continuing pregnancy) ranged from 0.4% to 8% [20,23,25–27,29,42,43,47,48]. Surgical procedures deemed medically indicated because of excessive bleeding, incomplete abortion, and infection ranged from 0.3% to 5.0% [20,23,25,42,47].

Misoprostol may be used anywhere from 3 to 7 days after treatment with methotrexate. Longer follow-up intervals are associated with higher success rates. In 2 studies conducted among 539 women with pregnancies of 49 days or less, success rates increased from 70% to 73% at 7 days, to 81% to 87% at 14 days, and to 91% to 95% at 42 to 44 days [23,26]. Follow-up up to 42 days without intervention has not been associated with adverse outcomes.

5. Summary

Ideally, medical abortion should be simple, safe, inexpensive, and accessible. There are a number of situations when mifepristone may not be used, which include lack of availability, financial concerns, or personal preference. The success rates of alternative regimens using misoprostol alone and methotrexate with misoprostol are around 90%, and these 2 drugs are inexpensive and available in many regions. Complications such as incomplete abortion, bleeding, and infection appear to be similar for these 2 regimens and for mifepristone regimens as well. Although the methods using misoprostol alone and methotrexate followed by misoprostol have lower success rates than those using mifepristone, these methods are safe and acceptable choices for women who desire an abortion early in the first trimester.

Methotrexate followed by misoprostol has been widely used worldwide and many practitioners are familiar with this method. Misoprostol alone is not as widely used by clinicians, particularly in the United States, but it has the advantage of causing a faster complete abortion without an obvious decrease in effectiveness. Although misoprostol is most often used vaginally, other routes for its administration may become more widely used. Self-induced abortion with misoprostol, because of its simplicity and quick results, is an option for women without other alternatives.

References


