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# PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN—GYNECOLOGISTS

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## Medical Management of First-Trimester Abortion

*Over the past three decades, medical methods of abortion have been developed throughout the world and are now a standard method of providing abortion care in the United States. Medical abortion, which involves the use of medications rather than a surgical procedure to induce an abortion, is an option for women who wish to terminate a first-trimester pregnancy. Although the method is most commonly used up to 63 days of gestation (calculated from the first day of the last menstrual period), the treatment also is effective after 63 days of gestation. The Centers for Disease Control and Prevention estimates that 64% of abortions are performed before 63 days of gestation (1). Medical abortions currently comprise 16.5% of all abortions in the United States and 25.2% of all abortions at or before 9 weeks of gestation (1). Mifepristone, combined with misoprostol, is the most commonly used medical abortion regimen in the United States and Western Europe; however, in parts of the world, mifepristone remains unavailable. This document presents evidence of the effectiveness, benefits, and risks of first-trimester medical abortion and provides a framework for counseling women who are considering medical abortion.*

### Background

#### **Medications Currently Used for Medical Abortion**

##### **Mifepristone**

Mifepristone, a derivative of norethindrone, binds to the progesterone receptor with an affinity greater than progesterone itself but does not activate the receptor, thereby acting as an antiprogesterin (2). Its known actions on a uterus in pregnant women include decidual necrosis, cervical softening, and increased uterine contractility and prostaglandin sensitivity (3, 4). Human studies have suggested that uterine contractility does not increase until 24–36 hours after mifepristone administration (3). At this

point, the sensitivity of the myometrium to the stimulatory effects of exogenous prostaglandins increases five-fold (3). However, more recent studies have shown high efficacy when vaginal misoprostol is administered less than 15 minutes after mifepristone (5). The effectiveness of such a regimen cannot be attributed to the actions of the misoprostol because misoprostol alone has a much lower efficacy than mifepristone. Accordingly, these studies suggest that some or all of these actions occur sooner than previously believed or that the effects of mifepristone that are important and necessary for its abortifacient activity remain incompletely understood.

As a progesterone receptor antagonist, mifepristone also has several other potential medical applications, including emergency contraception; cervical ripening and

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labor induction; and treatment of symptomatic uterine leiomyomas, endometriosis, Cushing syndrome, breast cancer, early pregnancy loss, and glaucoma (6, 7).

## Misoprostol

Misoprostol is an inexpensive prostaglandin  $E_1$  analogue in a tablet form that is stable at room temperature. It is approved by the U.S. Food and Drug Administration (FDA) for oral administration to prevent gastric ulcers in individuals who take antiinflammatory drugs on a long-term basis, and it is included in the FDA-approved labeling of mifepristone for use in abortion. It is used off-label in other regimens for abortion, labor induction, treatment of early pregnancy loss, prevention and treatment of postpartum hemorrhage, and cervical priming before uterine procedures, such as hysteroscopy (8). Pharmacokinetic evaluations of misoprostol absorption when administered by various routes have been performed (9–13). Routes that result in a longer duration of action (ie, buccal and vaginal) also appear to result in greater efficacy compared with oral administration. Similarly, those routes with rapid and significant absorption (ie, sublingual) also have high efficacy, but the greater maximum concentration results in more adverse effects. Misoprostol-only medical abortion regimens are significantly less effective than those that use a combination of mifepristone and misoprostol (14, 15).

## Other Agents

Methotrexate in combination with misoprostol was adopted in the United States and Canada as an alternative to mifepristone regimens before mifepristone was available (16, 17). However, methotrexate rarely is used anymore in the United States for medical abortion because of the greater availability and efficacy of mifepristone regimens. Methotrexate blocks dihydrofolate reductase, an enzyme involved in producing thymidine during DNA synthesis. Methotrexate exerts its action primarily on the cytotrophoblast rather than the developing embryo, which inhibits syncytialization of the cytotrophoblast (18). Thus, methotrexate stops the process of implantation rather than weakening the implantation site directly. In contrast, the antiprogesterin mifepristone has no direct effect on the trophoblast.

Tamoxifen has been used in some studies of early abortion in combination with misoprostol. However, randomized trials have demonstrated no benefit of using tamoxifen–misoprostol over methotrexate–misoprostol or misoprostol alone regimens (19, 20).

Two small studies from China suggest that multiple daily administrations of letrozole followed by misoprostol, 800 micrograms vaginally, may be another effective

option for medical abortion, but more research is needed regarding this regimen (21, 22).

## Mifepristone Regimens

### Regimen approved by the U.S. Food and Drug Administration

The FDA-approved regimen, as detailed in the mifepristone package labeling, is based on the original regimen registered in France 25 years ago. This regimen includes mifepristone, 600 mg orally, followed approximately 48 hours later by a prostaglandin analogue, usually misoprostol 400 micrograms orally. The FDA-approved regimen includes this treatment with a follow-up visit approximately 14 days after mifepristone administration (23). If clinical history indicates that the woman had a confirmed abortion, a pelvic examination is performed to confirm uterine involution. If clinical history and physical examination do not confirm expulsion, ultrasonography is performed. Suction aspiration at the follow-up evaluation is not specified as necessary unless the pregnancy is ongoing (23).

The efficacy of the FDA-approved regimen is approximately 92% in women with gestations up to 49 days (24, 25). Complete abortion rates are higher with earlier gestations; approximately 96–98% in gestations of up to 42 days, 91–95% in gestations from 43 days to 49 days, and less than 85% in gestations beyond 49 days (24, 26, 27). When abortion does not occur within 3–4 hours after oral misoprostol administration, use of an additional dose does not improve efficacy (26, 28).

### Evidence-Based Regimens

Additional “evidence-based” regimens have been developed to improve medical abortion in terms of expense, safety, speed, and adverse effects. Regimens that use low doses of mifepristone (200 mg) have similar efficacy and lower costs compared with those that use mifepristone at 600 mg (29). Based on efficacy and the adverse effect profile, evidence-based protocols for medical abortion are superior to the FDA-approved regimen. Vaginal, buccal, and sublingual routes of misoprostol administration increase efficacy, decrease continuing pregnancy rates, and increase the gestational age range for use as compared with the FDA-approved regimen (30). By changing the route of misoprostol administration, the timing between mifepristone and misoprostol dosing can be varied to allow women more flexibility to accommodate personal situations, such as work and childcare. Regimens that use vaginal misoprostol can be provided simultaneously with mifepristone to terminate gestations of up to 63 days (5). A 6–8-hour interval between mifepristone administration and vaginal misoprostol

administration is as effective as a 24-hour interval and results in significantly fewer adverse effects (31). Buccal and sublingual misoprostol can be administered as early as 24 hours after mifepristone administration (32, 33). Women can safely and effectively self-administer misoprostol at home as part of a medical abortion regimen (32, 34, 35).

## Counseling Patients

### Medical Abortion Versus Surgical Abortion

Counseling must first emphasize early pregnancy options to ensure that a woman is certain about her decision to have an abortion. If she is uncertain, then the decision about abortion technique must be delayed until she has reached a firm decision, even if the delay means that she will be unable to choose a medical option.

Only when a woman has considered her options and decided to have an abortion does the discussion about the different methods become an issue. Most women who seek early abortion will be eligible for medical and surgical methods. The general advantages and disadvantages of each approach should be explained early in the counseling process (Box 1) (36–38). Even for women

who think they are unsure about the method, most will have some preference after counseling (37). Studies that have compared abortion method preferences have included groups of patients who choose their method and those who are randomized to their method. The applicability of these studies to current U.S. medical abortion practice is limited given that no studies included the mifepristone–misoprostol regimen, and in two studies, surgical abortion was performed only under general anesthesia. Generally, women are satisfied with the method they choose but, when randomized, prefer surgical abortion to medical abortion (36–38).

Most women choose medical abortion because of a desire to avoid surgery, a perception that medical abortion is safer than surgical abortion, and a belief that medical abortion is more natural and private than a surgical procedure (39). Compared with surgical abortion, medical abortion takes longer to complete, requires more active patient participation, and is associated with higher reported rates of bleeding and cramping. With medical abortion, expulsion of the products of conception most likely will occur at home, but a few women will still require surgical evacuation to complete the abortion. An early surgical abortion takes place most commonly in one visit and involves less waiting and less doubt about when the abortion occurs compared with medical abortion. In addition, women who undergo surgical abortion will not see any products of conception or blood clots during the procedure.

### Adverse Effects

Bleeding and cramping will be experienced by most women undergoing medical abortion and are necessary for the process to occur. Adverse effects commonly associated with mifepristone use include nausea, vomiting, diarrhea, headache, dizziness, and thermoregulatory effects (5, 31, 32, 40–42; Table 1). The incidence of each adverse effect is based on the regimen used (especially the prostaglandin analogue), the dose and route of administration of the prostaglandin analogue, and the gestational age. Gastrointestinal adverse effects are less common when misoprostol is administered vaginally as compared with regimens that use oral, buccal, or sublingual misoprostol (29, 43). Buccal and sublingual administration cause similar adverse effects, with the sublingual route associated with a higher rate of chills (44).

Counseling should emphasize that the woman is likely to have bleeding that is much heavier than menses (and potentially with severe cramping) and is best described to patients as comparable with a miscarriage. The woman should understand how much bleeding is considered too much. An easy reference for the patient

#### Box 1. Features of Medical and Surgical Abortion ↵

##### **Medical Abortion**

- Usually avoids invasive procedure
- Usually avoids anesthesia
- Days to weeks to complete
- Available during early pregnancy
- High success rate (approximately 95%)
- Bleeding commonly not perceived as light
- Requires follow-up to ensure completion of abortion
- Patient participation throughout a multiple-step process

##### **Surgical Abortion**

- Involves invasive procedure
- Allows use of sedation if desired
- Complete in a predictable period of time
- Available during early pregnancy
- High success rate (99%)
- Bleeding commonly perceived as light
- Does not require follow-up in most cases
- Patient participation in a single-step process

**Table 1.** Adverse Effects in Selected North American Trials of Medical Abortion Regimens ↵

| Trial                        | Incidence of Adverse Effects (%) |             |              |             |              |             |              |             |              |             |              |             | Thermoregulatory Effects* |             |
|------------------------------|----------------------------------|-------------|--------------|-------------|--------------|-------------|--------------|-------------|--------------|-------------|--------------|-------------|---------------------------|-------------|
|                              | Nausea                           |             | Vomiting     |             | Diarrhea     |             | Headache     |             | Dizziness    |             |              |             |                           |             |
|                              | Mifepristone                     | Misoprostol | Mifepristone | Misoprostol | Mifepristone | Misoprostol | Mifepristone | Misoprostol | Mifepristone | Misoprostol | Mifepristone | Misoprostol | Mifepristone              | Misoprostol |
| Schaff (1997) <sup>†</sup>   | 36                               | 36          | 14           | 14          | 8            | 22          | 18           | 19          | 22           | 37          | 20           | 37          | 37                        |             |
| Schaff (1999) <sup>‡</sup>   | 45                               | 43          | 13           | 26          | 11           | 23          | 14           | 13          | 15           | 28          | 14           | 32          | 32                        |             |
| Wiebe (2002) <sup>§</sup>    | 45                               | 39          | 13           | 15          | 5            | 16          | 19           | 29          | N/R          | N/R         | N/R          | 23          | 23                        |             |
| Creinin (2004) <sup>  </sup> | 20<br>39                         | 44<br>52    | 5<br>14      | 23<br>30    | 1<br>7       | 27<br>25    | 10<br>20     | 37<br>37    | 12<br>20     | 35<br>37    | 9<br>19      | 56<br>53    | 56<br>53                  |             |
| Creinin (2007) <sup>†</sup>  | N/R<br>29                        | 58<br>51    | N/R<br>9     | 31<br>31    | N/R<br>5     | 35<br>26    | N/R<br>18    | 40<br>36    | N/R<br>9     | 39<br>37    | N/R<br>15    | 69<br>56    | 69<br>56                  |             |
| Winikoff (2008) <sup>#</sup> | N/R<br>N/R                       | 64<br>66    | N/R          | 40<br>40    | N/R          | 35<br>34    | N/R<br>N/R   | 31<br>34    | N/R<br>N/R   | 30<br>32    | N/R<br>N/R   | 33<br>41    | 33<br>41                  |             |

Abbreviation: N/R, not reported.

\*Fever, warmth, hot flushes, or chills.

<sup>†</sup>Mifepristone, 600 mg, followed by misoprostol, 800 micrograms vaginally, 36–48 hours later. (Schaff EA, Stadalius LS, Eisinger SH, Franks P. Vaginal misoprostol administered at home after mifepristone (RU486) for abortion. *J Fam Pract* 1997;44:353–60.)

<sup>‡</sup>Mifepristone, 200 mg, followed by misoprostol, 800 micrograms vaginally, 48 hours later. (Schaff EA, Eisinger SH, Stadalius LS, Franks P, Gore BZ, Poppema S. Low-dose mifepristone 200 mg and vaginal misoprostol for abortion. *Contraception* 1999;59:1–6.)

<sup>§</sup>Mifepristone, 600 mg, followed by misoprostol, 400 micrograms orally, 36–48 hours later. (Wiebe E, Dunn S, Guilbert E, Jacot F, Lugtig L. Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol. *Obstet Gynecol* 2002;99:813–9.)

<sup>||</sup>Mifepristone, 200 mg, followed by misoprostol, 800 micrograms vaginally, 6–8 hours later (first row) or 24 hours later (second row). (Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion. *Obstet Gynecol* 2004;103:851–9.)

<sup>¶</sup>Mifepristone, 200 mg, followed by misoprostol, 800 micrograms vaginally, 0–15 minutes later (first row) or 24 hours later (second row). (Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn L. Mifepristone and misoprostol administered simultaneously compared with 24 hours apart for abortion: a randomized controlled trial. *Obstet Gynecol* 2007;109:885–94.)

<sup>#</sup>Mifepristone, 200 mg, followed by misoprostol, 800 micrograms orally (first row) or buccally (second row), 24–36 hours later. (Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg A, Gonzales J, et al. Two distinct oral routes of misoprostol in mifepristone medical abortion. A randomized controlled trial. *Obstet Gynecol* 2008;112:1303–10.)

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to use is the soaking of two maxi pads per hour for 2 consecutive hours (45). Patients should be advised to call their health care providers if they experience this level of bleeding. The need for emergency care is based on how the patient is feeling, her baseline hemoglobin (Hb) or hematocrit level, whether the bleeding seems to be slowing, and her distance from an emergency facility. Overall, large series demonstrate that less than 1% of women will need emergency curettage because of excessive bleeding (26, 46–48). Moreover, the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days (24); this risk will vary based on the regimen used.

Pain management is an important consideration. The woman should be sent home with appropriate instructions for analgesia with over-the-counter medications and can be provided with prescriptions for oral narcotics to use when needed. Nonsteroidal antiinflammatory drugs, such as ibuprofen, are not contraindicated in women who undergo a medical abortion and are appropriate first-line agents for pain management. One randomized trial found that ibuprofen taken when needed was more effective than acetaminophen to reduce pain associated with medical abortion (49). Nonsteroidal antiinflammatory drugs inhibit the synthesis of new prostaglandins, but they do not block the action of prostaglandin receptors and should not inhibit the action of a prostaglandin used for medical abortion. In a retrospective analysis of nonsteroidal antiinflammatory drugs and complete abortion, in 416 women who received misoprostol after methotrexate for medical abortion of gestations up to 56 days, the use of ibuprofen did not interfere with the action of misoprostol to induce uterine contractions and expulsion of the products of conception (50). One randomized trial found that multiple doses of ibuprofen given prophylactically at the time of misoprostol administration did not significantly reduce pain associated with medical abortion compared with ibuprofen taken when needed (51).

### ***Need for Surgical Evacuation***

The overall rate of surgical evacuation with medical abortion varies greatly based on the regimen used, the gestational age of the pregnancy, and many other factors. In most studies of medical abortion of gestations up to 63 days with mifepristone 200 mg followed by misoprostol, less than 5% of patients undergo surgical evacuation (52).

To determine whether a surgical evacuation is needed, it is important to distinguish incomplete abor-

tion from the normal course of medical abortion. When an ultrasound examination is performed at the follow-up visit, the sole purpose is to determine whether the gestational sac is present. After surgical or spontaneous expulsion, the uterus will normally contain sonographically hyperechoic tissue that consists of blood, blood clots, and decidua. Rarely does this finding in women who have undergone medical abortion indicate a need for intervention. In the absence of excessive bleeding, health care providers can monitor such patients based on symptoms.

Guidelines for intervention vary for women who have a persistent gestational sac on ultrasonography without evidence of embryonic cardiac activity or continuing development. Patients with a persistent gestational sac 1 week after treatment can safely receive another dose of misoprostol or continue with expectant management (32, 53). Studies indicate that even with a retained sac 2 weeks after mifepristone, intervention is unnecessary and that expulsion will typically occur in the ensuing weeks (45). Women who prefer not to wait longer may choose to have a surgical evacuation at any time. Most commonly, women who are awaiting delayed expulsion will no longer feel pregnant or have medication-induced symptoms; patients will be waiting for the onset of bleeding or cramping similar to anticipating the start of menses (54). Health care providers must differentiate these women from those who have incomplete expulsion of the pregnancy tissue with symptoms, such as prolonged and irregular bleeding episodes.

Continuing pregnancies are typically reported in less than 1% of women who begin medical abortion at or before 63 days of gestation with evidence-based regimens (55). Ongoing pregnancy may be treated with uterine aspiration or a repeat dose of vaginal misoprostol. In an analysis of data from two randomized trials with 14 cases of ongoing pregnancy with gestational cardiac activity, treatment with a repeat dose of misoprostol, 800 micrograms administered vaginally, resulted in expulsion of the products of conception in five cases (36%); in an additional four cases (29%), gestational cardiac activity was no longer present at the next follow-up visit (53). If gestational cardiac activity persists at follow-up after a second dose of misoprostol, uterine aspiration should be performed. Repeat doses of buccal misoprostol to treat ongoing pregnancy have not been studied.

Women who undergo medical abortion may need to access emergency surgical intervention, and it is medically appropriate to provide referral to another health care provider. However, state or local laws may have additional requirements. In women who receive mifepristone and vaginal misoprostol, emergency curettage within the



first 24 hours of treatment is rare, occurring in 0.2% of patients (56). Clinicians who wish to provide medical abortion services either should be trained in surgical abortion or should be able to refer to a clinician trained in surgical abortion.

## Clinical Considerations and Recommendations

### ► *Who are candidates for medical abortion with mifepristone and misoprostol?*

Women are candidates for medical abortion with mifepristone and misoprostol if they meet the gestational age criteria for the regimen and have no contraindications to the medical abortion process. Women with twin gestations can be treated with the same regimens as those with singleton gestations (57). Medical contraindications are infrequent.

Most studies exclude women with anemia who have Hb levels of less than 9.5 g/dL or less than 10 g/dL; accordingly, the safety of medical abortion in women with anemia is unknown. Although the transfusion rates associated with medical abortion are low (0.05%), they exceed those reported for surgical abortion in early pregnancy (0.01%) (55, 58).

Other medical contraindications to abortion with mifepristone regimens include confirmed or suspected ectopic pregnancy, intrauterine device (IUD) in place, current long-term systemic corticosteroid therapy, chronic adrenal failure, known coagulopathy or anticoagulant therapy, and intolerance or allergy to mifepristone. Most clinical trials also have excluded women with severe liver, renal, or respiratory disease or uncontrolled hypertension or cardiovascular disease (angina, valvular disease, arrhythmia, or cardiac failure).

Misoprostol should not be used in women who have an allergy or intolerance to misoprostol or other prostaglandins. Asthma is not a contraindication because misoprostol is a weak bronchodilator.

Women are not good candidates for medical abortion if they are unable or unwilling to adhere to care instructions, desire quick completion of the abortion process, are not available for follow-up contact or evaluation or cannot understand the instructions because of language or comprehension barriers.

### ► *Which pretreatment laboratory tests are needed?*

Confirmation of pregnancy is necessary before attempting abortion, regardless of method. Preoperative assessment of Hb or hematocrit is indicated when anemia is

suspected. Rh testing is standard of care in the United States, and RhD immunoglobulin should be administered if indicated. Other laboratory evaluations are not indicated but may be required by local and state legislation.

### ► *What is the upper gestational age limit for use of medical abortion?*

The upper gestational age limit at which a medical abortion regimen is still an option varies based on the types, dosages, and routes of administration of the medications. Complete abortion rates with all regimens are highest for women with earlier gestations and are clinically similar in women with pregnancies up to 42 days of gestation. After 49 days of gestation, evidence-based regimens have advantages over the FDA-approved regimen and are medically preferable (Table 2). After 49 days of gestation, the efficacy of the FDA-approved regimen decreases significantly, and the likelihood of continuing pregnancy increases (27). However, regimens using vaginal, sublingual, and buccal misoprostol provide efficacy rates when used up to 63 days of gestation that exceed the approximately 92% efficacy of the FDA-approved regimen when used up to 49 days of gestation (24, 29). Moreover, the continuing pregnancy rates with these alternative methods of administering misoprostol remain low, at approximately 1% or less for vaginal, buccal, and sublingual regimens up to 63 days of gestation (32, 59–61). The amount of published data on sublingual regimens is relatively small compared with vaginal regimens.

The use of the mifepristone–misoprostol regimen has been evaluated for medical abortion in women with pregnancies beyond 9 weeks of gestation, most commonly with regimens that involve the use of vaginal misoprostol and in an in-patient setting (62, 63). In a published review of more than 1,000 women who were observed as inpatients after misoprostol treatment, primarily by the vaginal route, the efficacy rate exceeded 92% for women with pregnancies through 13 weeks of gestation (with a rate of 97% at 9–10 weeks of gestation), steadily decreasing to 92% for those with gestations at 12–13 weeks (64). Continuing pregnancy rates were less than 1% for women with gestations through 11 weeks. The published experience with sublingual misoprostol in this gestational age range is relatively small (62, 64).

A more recent U.S. multicenter trial evaluated 629 women with pregnancies from 57 days of gestation to 70 days of gestation who received mifepristone with buccal misoprostol in an outpatient setting (65). Success rates were 94% for women with gestations from 57 days

**Table 2. Comparison of Common Medical Abortion Regimens** ↵

| Common Regimens  | Overall Success Rate (%) | Advantages and Disadvantages   | Gestational Age |
|--|--------------------------|--|-----------------|
| Mifepristone 600 mg orally, followed by misoprostol 400 micrograms orally 48 hours later (regimen approved by the U.S. Food and Drug Administration)   | 92 <sup>1</sup>          | Must return to office or clinic for misoprostol administration; can be used only up to 49 days of gestation  | Up to 49 days   |
| Mifepristone 200 mg orally, followed by misoprostol 800 micrograms vaginally, buccally, or sublingually 24–48 hours later (alternative evidence-based regimens; with vaginal administration, misoprostol may be administered 6 hours or less after mifepristone) | 95–99 <sup>2–7</sup>     | Compared with the regimen approved by the Food and Drug Administration: <ul style="list-style-type: none"> <li>• More effective</li> <li>• Less time to expulsion</li> <li>• Fewer adverse effects</li> <li>• Lower cost</li> <li>• More convenient because allows home administration of misoprostol</li> </ul> | Up to 63 days   |
| Methotrexate, 50 mg/m <sup>2</sup> intramuscularly or 50 mg vaginally plus misoprostol, 800 micrograms vaginally 3–7 days later  | 92–96 <sup>8–10</sup>    | Compared with mifepristone–misoprostol regimen: <ul style="list-style-type: none"> <li>• Takes longer for expulsion in 20–30% of women</li> <li>• Readily available medications</li> <li>• Low drug cost</li> </ul>  | Up to 49 days   |
| Misoprostol only, 800 micrograms vaginally or sublingually administered every 3 hours for three doses (with vaginal administration, dosing interval may be as long as 12 hours)  | 84–85 <sup>11</sup>      | <ul style="list-style-type: none"> <li>• Significantly higher incidence of adverse effects than other regimens</li> <li>• Readily available medication</li> <li>• Low drug cost</li> </ul>   | Up to 63 days   |

<sup>1</sup>Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. *N Engl J Med* 1998;338:1241–7.

<sup>2</sup>Schaff EA, Eisinger SH, Stadalius LS, Franks P, Gore BZ, Poppema S. Low-dose mifepristone 200 mg and vaginal misoprostol for abortion. *Contraception* 1999;59:1–6.

<sup>3</sup>Schaff EA, Fielding SL, Westhoff C. Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion. *Contraception* 2001;64:81–5.

<sup>4</sup>el-Refaey H, Rajasekar D, Abdalla M, Calder L, Templeton A. Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. *N Engl J Med* 1995;332:983–7.

<sup>5</sup>von Hertzen H, Honkanen H, Piaggio G, Bartfai G, Erdenetungalag R, Gemzell-Danielsson K, et al. WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. I: Efficacy. WHO Research Group on Post-Ovulatory Methods for Fertility Regulation. *BJOG* 2003;110:808–18.

<sup>6</sup>Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion. MOD Study Trial Group. *Obstet Gynecol* 2004;103:851–9.

<sup>7</sup>von Hertzen H, Huong NT, Piaggio G, Bayalag M, Cabezas E, Fang AH, et al. Misoprostol dose and route after mifepristone for early medical abortion: a randomised controlled noninferiority trial. WHO Research Group on Postovulatory Methods of Fertility Regulation. *BJOG* 2010;117:1186–96.

<sup>8</sup>Creinin MD, Vittinghoff E, Schaff E, Klaisle C, Darney PD, Dean C. Medical abortion with oral methotrexate and vaginal misoprostol. *Obstet Gynecol* 1997;90:611–6.

<sup>9</sup>Creinin MD, Carbonell JL, Schwartz JL, Varela L, Tanda R. A randomized trial of the effect of moistening misoprostol before vaginal administration when used with methotrexate for abortion. *Contraception* 1999;59:11–6.

<sup>10</sup>Wiebe E, Dunn S, Guilbert E, Jacot F, Lugtig L. Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol. *Obstet Gynecol* 2002;99:813–9.

<sup>11</sup>von Hertzen H, Piaggio G, Huong NT, Arustamyan K, Cabezas E, Gomez M, et al. Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomised controlled equivalence trial. WHO Research Group on Postovulatory Methods of Fertility Regulation. *Lancet* 2007;369:1938–46.

to 63 days and 93% for those with gestations from 64 days to 70 days, and acceptability was high and similar for both gestational age groups. However, the continuing pregnancy rate was 3% for both groups.

► ***Should prophylactic antibiotics be used in medical abortion?***

Uterine infection with medical abortion is uncommon, and limited data exist to support the prophylactic use of antibiotics in medical abortion. In a systematic review of 65 studies of heterogeneous design (prospective, retrospective, and randomized), the overall frequency of diagnosed or treated infection after medical abortion in more than 46,000 patients was 0.9% (66). In these studies, as in most surgical abortion studies, the diagnostic criteria for infection were variable, which possibly led to an overestimation of infection.

Although concern regarding serious, rare, and deadly infection with clostridial bacteria in women who undergo medical abortion has been raised, it has since become evident that no specific connection exists between clostridial organisms and medical abortion. Investigations have found these organisms also are associated with other obstetric and gynecologic processes and procedures, including spontaneous abortion, term delivery, surgical abortion, and cervical cone or laser treatment for cervical dysplasia (67, 68). In addition, it is now recognized that clostridial species are a more common cause of pelvic infection than previously believed (68).

Large retrospective analyses of medical abortion safety conducted by Planned Parenthood Federation of America, Inc, since 2001 showed a decrease over time in the *serious infection* rate (defined as receipt of intravenous antibiotics, hospitalization, sepsis, or death) with a change from vaginal to buccal misoprostol (from 0.093% to 0.020%) and a further decrease (to 0.006%) when routine provision of a 1-week treatment course of doxycycline was started on the day of mifepristone administration (69). Because the study used continuous prior time periods as the comparator, the addition of a treatment course of antibiotics cannot be separated from the effect of the switch in the route of misoprostol administration. In a subsequent report, the risk of serious infection in Planned Parenthood clinics increased to 0.013% in 2009 and 0.019% in 2010 (55), a rate equal to the rate noted before routine doxycycline provision. These data indicate that the overall risk of serious infection with medical abortion is very low and that buccal administration of misoprostol may result in a lower risk of serious infection compared with vaginal administration. The benefit suggested by the addition of doxycycline may truly have been a period effect. In addition, adherence

to a doxycycline regimen of 14 tablets over 1 week is likely poor such that routine treatment is not beneficial. Accordingly, no strong data exist to support the universal use of prophylactic antibiotics for medical abortion.

Although serious infections occur rarely in patients after medical abortion, health care providers need to be aware of the signs and symptoms. Sustained fever, tachycardia, or severe abdominal pain or general malaise with or without fever that occur more than 24 hours after misoprostol administration should increase suspicion of a serious infection. Clostridial toxic shock often resembles a flu-like illness, so health care providers should have a high level of suspicion for infection when symptoms consistent with flu are present. Women with such infections typically have hemoconcentration and significant leukocytosis without fever and can rapidly progress to refractory hypotension and death.

► ***Is ultrasonography useful in the medical management of abortion before treatment?***

Before medical abortion is performed, gestational age should be confirmed by clinical evaluation or ultrasound examination. A U.S. study found that women's reported last menstrual period combined with clinical estimation of gestational age was accurate and would have resulted in medical abortion erroneously offered to only 1.6% of women after 63 days of gestation (70). Because efficacy of some regimens decreases significantly with increasing gestational age, the clinical relevance of erroneous gestational age assignment will vary based on the regimen used.

A potential concern when providing early abortion services is the possibility of an undiagnosed extrauterine gestation. The ectopic pregnancy rate in the general population is approximately 19–21 per 1,000 pregnancies and may be slightly higher (21–24 per 1,000 pregnancies) among patients who receive Medicaid (71–73). However, ectopic pregnancy rates in studies of women who seek abortion are consistently lower. A study of surgical abortion in U.S. women with pregnancies less than 6 weeks of gestation found the ectopic pregnancy rate to be 5.9 per 1,000 pregnancies (74). Similarly, the largest study of medical abortion patients published involved 16,369 women with pregnancies of 49 days of gestation or less, 21 of whom were excluded from the analysis because of an ectopic pregnancy, yielding an ectopic pregnancy rate of 1.3 per 1,000 pregnancies (75). Although ectopic pregnancy in a population of women who seek early abortion is rare, women with significant medical risk factors or history (ie, unilateral pain and vaginal bleeding) should have a pretreatment ultrasonography.



If ultrasonography is performed, abdominal ultrasonography is sensitive for diagnosing the presence or absence of a gestational sac in nonobese women (76). Thus, most women can be initially screened with transabdominal ultrasonography, reserving transvaginal ultrasonography for situations in which further clarification is required.

► ***What methods can be used to confirm complete medical abortion?***

Follow-up evaluation after medical abortion is performed to diagnose and treat complications, including ongoing pregnancy. The introduction of medical abortion into widespread clinical practice has required continued emphasis on follow-up because failure rates for medical abortion are higher than those for surgical techniques, and misoprostol is potentially teratogenic. Initial reports showed that mifepristone and misoprostol can be integrated into clinical practice with low rates of patients lost to follow-up (77, 78). However, further reports reported loss-to-follow-up rates as high as 45% in clinical settings (79).

When the clinician and the patient think that expulsion has occurred based on symptomatology, they are correct 96–99% of the time (80, 81). However, a systematic review found that women's self-assessment alone or combined with clinical assessment had low sensitivity (33–85%) and low positive predictive value (6–66%) to detect ongoing pregnancy (82). Follow-up after receiving mifepristone and misoprostol for medical abortion is important, although an in-clinic evaluation is not always necessary.

The FDA-approved regimen includes an evaluation at 2 weeks after mifepristone administration to assess for history of bleeding and evidence of uterine involution on pelvic examination. However, other options that allow evaluation sooner with a high degree of accuracy to detect ongoing pregnancy include in-clinic transvaginal ultrasound examination 1 week after treatment (83); serum human chorionic gonadotropin (hCG) level measurement before and 1 week after treatment (84); and telephone follow-up at 1 week, with subsequent urine pregnancy testing at 2 weeks or 4 weeks after treatment (81, 85). Although urine pregnancy testing alone with standard high- or low-sensitivity tests has not been shown to be a viable alternative, newer semiquantitative urine hCG tests have shown promise in accurately identifying ongoing pregnancies after medical abortion (86, 87).

Transvaginal ultrasonography is commonly used for follow-up examination after medical abortion, primarily because it provides a definitive assessment of whether

or not the products of conception have been expelled. Incorrect interpretation of ultrasound examination results may lead to unnecessary intervention. When an ultrasound examination is performed at follow-up, the sole purpose is to determine whether the gestational sac is present. For patients who are below the threshold for visualization of a gestational sac, follow-up with serum hCG testing is needed. The measurement of endometrial thickness or other findings cannot predict the need for future surgical intervention (83). In research trials, when a transvaginal ultrasound examination shows no evidence of a gestational sac 1 week after mifepristone use, only 1.6% of women will need a subsequent surgical evacuation.

Serum hCG testing is another option for follow-up examination after medical abortion, and it does not require that the patient return to the same facility; she can obtain the test at a location near her home or work. However, a phone call to the patient to discuss the result is still necessary, so the potential for failed follow-up exists in two ways: 1) the patient must present to get a test, and 2) the patient must be reached by phone. A serum hCG level decrease of at least 80% over 6–7 days after initiating treatment with mifepristone and misoprostol indicates a successful abortion (84). In a trial that randomized women to follow-up in the form of in-clinic transvaginal ultrasound examination or serum hCG testing, 24.5% of patients were lost to follow-up, with no significant differences reported in unplanned visits and interventions by 2 weeks (6.6% versus 8.2%, respectively) or in dilation and curettage rates by 4 weeks (4.4% and 1.4%, respectively) (88).

Another study examined follow-up rates for women that chose ultrasound examination or hCG testing (89). The loss-to-follow-up rate was somewhat higher among women who chose hCG testing (33.7% versus 22.9%), but in multivariable analysis, follow-up method was not associated with loss to follow-up. Instead, loss to follow-up was found to be based on patient factors, such as living at least 10 miles from the clinic, prior pregnancy, unemployment, and a history of induced abortion.

When patients are required to go to a facility for assessment of medical abortion outcome, approximately 25% are lost to follow-up, which indicates the need for development of other follow-up methods. Telephone follow-up with subsequent urine pregnancy testing avoids the need for the woman to go to a facility for her initial assessment. A feasibility study of 139 U.S. women had a 100% initial follow-up rate and an overall follow-up of 97% when need for in-person assessment, as determined by telephone contact, was included; a key part of this trial was that the ability to successfully contact the patient by phone was assessed before

medication distribution (81). Another promising method in development is an at-home semiquantitative urine hCG test; in a feasibility study of 394 women who used the product, 1-week posttreatment sensitivity and specificity were 100% and 97%, respectively (90). The study required the participants to return to the clinic on the day they performed the at-home test to review the results, and 20% were lost to follow-up. Thus, combining the semiquantitative urine hCG test with telephone follow-up may hold the most promise.

► ***Do women have a preference for route of misoprostol administration?***

Many health care providers may offer women only one option for misoprostol administration, even though all routes are not the same. Vaginal routes of administration enable the patients to complete the medical abortion process sooner because of the ability to use the misoprostol 6 hours or less from the time of mifepristone administration (5, 31). Early studies with mifepristone regimens demonstrated that women preferred a shorter interval between medications (91). Other research indicates women prefer oral routes of administration to vaginal administration (11, 92).

A U.S. study with 139 participants allowed the women to choose between buccal and vaginal misoprostol administration (81). The women were fully informed of the efficacy rates, the timing interval allowed for the two routes, and adverse effect rates based on available literature. Almost all women (94%) chose vaginal misoprostol and 74% of these women used the misoprostol at 6 hours or less after the mifepristone, which indicates that timing was a significant factor in their choice.

► ***How should a patient be counseled about potential teratogenicity if a medical method fails to lead to abortion?***

Because teratogenicity of medical abortifacients becomes an important issue if the pregnancy continues, patients must be counseled before medical abortion treatment of the need for a surgical abortion in the event of a continuing pregnancy. No evidence exists to date of a teratogenic effect of mifepristone. Evidence suggests that misoprostol can result in congenital anomalies when used during the first trimester, possibly because of mild uterine contractions that lead to decreased blood flow during organogenesis (93). Anomalies associated with misoprostol use that have been described in the literature include defects in the frontal or temporal bones and, most commonly, limb abnormalities with or without Möbius syndrome (mask-like facies with bilateral sixth and seventh nerve palsy and frequently

coincident micrognathia) (94–98). A case–control study from Brazil compared 96 infants with Möbius syndrome matched with 96 infants with neural tube defects (97). Exposure to misoprostol during the first trimester was 49% and 3%, respectively (odds ratio [OR], 29.7; 95% confidence interval [CI], 11.6–76). Six cases of limb reduction abnormalities in fetuses examined after failed abortion with methotrexate and misoprostol also have been reported (98). Methotrexate exposure also is characterized by a variety of malformations, including growth restriction, limb defects, and craniofacial anomalies, among others (99). Because misoprostol is the common agent used with every medical abortion regimen, health care providers must counsel all women regarding potential teratogenic effects.

► ***Does medical abortion affect future fertility or pregnancy outcomes?***

Future fertility with medical abortion has been evaluated within only a 1-year period after medical abortion in a group of 93 women who received methotrexate and misoprostol for abortion (100). Although none of the women were actively attempting to achieve pregnancy, 25% became pregnant, a rate higher than the calculated rate expected for this group of women using contraception. By comparison, another report indicated a pregnancy rate of 13% within 1 year after a first surgical abortion (101).

A comparative study from China enrolled more than 14,000 nulliparous women to compare outcomes of pregnancies after medical or surgical abortion and pregnancies in women with no history of abortion (102). Women who had a prior mifepristone abortion were less likely to have preterm birth compared with those women who had never been pregnant (adjusted OR, 0.77; 95% CI, 0.61–0.98), and the frequencies of low birth weight infants and mean lengths of pregnancy were similar in both groups. No significant differences were reported in risk of preterm delivery, frequency of low birth weight infants, or mean infant birth weight in the comparisons of women with previous mifepristone abortion and women with surgical abortion. In a registry-based study from Scotland, no association was found between prior abortion and subsequent preterm birth during the period 2000–2008, when 68% of abortions were medical (103).

► ***Who is qualified to perform medical abortion?***

In addition to physicians, advanced practice clinicians, such as nurse–midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medical abortion (104). In a randomized controlled trial in Nepal, women

randomized to receive medical abortion under the care of a staff nurse had a statistically equivalent risk of complete abortion compared with those under the care of a physician, and no serious adverse events were reported (105). This evidence indicates that medical abortion also can be provided safely and effectively by nonphysician clinicians, and in some states, advance practice clinicians are allowed to provide medical abortion. However, many states require that a physician perform an abortion and prohibit provision of medical abortion by nonphysician clinicians.

Telemedicine, which involves the use of video and information technology to provide a medical service at a distance, has been used to extend the reach of physicians to provide medical abortion. In one model, patients seen at a clinic without an on-site physician have a video consultation with a physician located elsewhere. The physician is able to review electronically the patient's medical history, and ultrasonography, if requested, can be performed by a trained technician at the remote clinic. If the patient is eligible for medical abortion, the physician remotely opens a telepharmacy drawer containing the mifepristone and misoprostol and instructs the patient how to use it. This model was evaluated in a nonrandomized study and found to be equally effective when compared with an in-person visit with a physician; adverse events, including ongoing pregnancy, occurred in 1.3% of patients and were not statistically different between the two groups (106). Women who chose telemedicine medical abortion were significantly more likely to say they would recommend the service to a friend compared with women who had an in-person visit with a physician (OR 1.72; 95% CI, 1.26–2.34) (106). In an analysis of this clinic system's service-delivery statistics, after telemedicine was introduced, a significant reduction in second-trimester abortion was reported, and women in remote parts of the state were more likely to obtain an abortion than before (107). Medical abortion can be provided safely and effectively via telemedicine with a high level of patient satisfaction; moreover, the model appears to improve access to early abortion in areas that lack a physician health care provider. Despite the medical evidence, several states have passed legislation that bans the use of telemedicine to provide abortion.

► ***What is the recommended timing of contraception provision after medical abortion?***

Almost all contraceptive methods can be provided immediately after uncomplicated first-trimester medical abortion, and all are considered Category 1 for provision after first-trimester abortion according to the U.S. Medical Eligibility Criteria (meaning there is no

restriction for use) (108). Oral contraceptives, patch, ring, depot medroxyprogesterone acetate, and subdermal implants all may be started on the day of misoprostol administration (109, 110). However, this requires an additional visit to the clinic to start depot medroxyprogesterone acetate and implants, and research is exploring whether these methods can be administered on the day of mifepristone without reducing the efficacy of medical abortion.

The optimal timing of IUD insertion has been evaluated in two randomized studies. One study randomized women to insertion of a copper IUD 1 week after mifepristone versus 4–6 weeks later (111). Significantly more women in the early-insertion group received an IUD (97% versus 76%,  $P<.001$ ). Another study randomized women to insertion of either a copper or levonorgestrel-containing IUD 5–9 days after mifepristone versus 3–4 weeks later (112). Fewer women in the delayed group attended the follow-up visit to insert the IUD (1.5% versus 11%,  $P=.03$ ). In both studies, no significant difference was found in expulsion rates by group; however, the delayed-insertion groups had expulsion rates of 7–11%, which is higher than the expulsion rate noted with immediate IUD insertion after surgical abortion (113). The risk of expulsion of an IUD needs to be weighed against the risk that the patient will not return for a delayed insertion. Sterilization may be performed once abortion is confirmed.

## Summary of Recommendations and Conclusions

*The following recommendations are based primarily on good and consistent scientific evidence (Level A):*

- Based on efficacy and adverse effect profile, evidence-based protocols for medical abortion are superior to the FDA-approved regimen. Vaginal, buccal, and sublingual routes of misoprostol administration increase efficacy, decrease continuing pregnancy rates, and increase the gestational age range for use as compared with the FDA-approved regimen.
- Regimens that use low doses of mifepristone (200 mg) have similar efficacy and lower costs compared with those that use mifepristone at 600 mg.
- Women can safely and effectively self-administer misoprostol at home as part of a medical abortion regimen.

- ▶ Medical abortion also can be provided safely and effectively by nonphysician clinicians.
- ▶ Follow-up after receiving mifepristone and misoprostol for medical abortion is important, although an in-clinic evaluation is not always necessary.
- ▶ Misoprostol-only medical abortion regimens are significantly less effective than those that use a combination of mifepristone and misoprostol.

***The following recommendations are based primarily on limited scientific evidence (Level B):***

- ▶ Because teratogenicity of medical abortifacients becomes an important issue if the pregnancy continues, patients must be counseled before medical abortion treatment of the need for a surgical abortion in the event of a continuing pregnancy.
- ▶ Before medical abortion is performed, gestational age should be confirmed by clinical evaluation or ultrasound examination.
- ▶ Nonsteroidal antiinflammatory drugs, such as ibuprofen, are not contraindicated in women who undergo a medical abortion and are appropriate first-line agents for pain management.
- ▶ Buccal administration of misoprostol may result in a lower risk of serious infection compared with vaginal administration.
- ▶ Medical abortion can be provided safely and effectively via telemedicine with a high level of patient satisfaction; moreover, the model appears to improve access to early abortion in areas that lack a physician health care provider.

***The following recommendations are based primarily on consensus and expert opinion (Level C):***

- ▶ Women who undergo medical abortion may need to access emergency surgical intervention, and it is medically appropriate to provide referral to another health care provider. However, state or local laws may have additional requirements.
- ▶ Clinicians who wish to provide medical abortion services either should be trained in surgical abortion or should be able to refer to a clinician trained in surgical abortion.
- ▶ No strong data exist to support the universal use of prophylactic antibiotics for medical abortion.
- ▶ Rh testing is standard of care in the United States, and RhD immunoglobulin should be administered if indicated.

## Proposed Performance Measure

Percentage of patients presenting for abortion before 63 days of gestation who are offered medical management

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000–November 2013. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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**Table 1. Adverse Effects in Selected North American Trials of Medical Abortion Regimens** ↵

| Trial                        | Incidence of Adverse Effects (%) |             |              |             |              |             |              |             |              |             |                           |             |
|------------------------------|----------------------------------|-------------|--------------|-------------|--------------|-------------|--------------|-------------|--------------|-------------|---------------------------|-------------|
|                              | Nausea                           |             | Vomiting     |             | Diarrhea     |             | Headache     |             | Dizziness    |             | Thermoregulatory Effects* |             |
|                              | Mifepristone                     | Misoprostol | Mifepristone | Misoprostol | Mifepristone | Misoprostol | Mifepristone | Misoprostol | Mifepristone | Misoprostol | Mifepristone              | Misoprostol |
| Schaff (1997) <sup>†</sup>   | 36                               | 36          | 14           | 14          | 8            | 22          | 18           | 19          | 22           | 37          | 20                        | 37          |
| Schaff (1999) <sup>‡</sup>   | 45                               | 43          | 13           | 26          | 11           | 23          | 14           | 13          | 15           | 28          | 14                        | 32          |
| Wiebe (2002) <sup>§</sup>    | 45                               | 39          | 13           | 15          | 5            | 16          | 19           | 29          | N/R          | N/R         | N/R                       | 23          |
| Creinin (2004) <sup>  </sup> | 20                               | 44          | 5            | 23          | 1            | 27          | 10           | 37          | 12           | 35          | 9                         | 56          |
|                              | 39                               | 52          | 14           | 30          | 7            | 25          | 20           | 37          | 20           | 37          | 19                        | 53          |
| Creinin (2007) <sup>¶</sup>  | N/R                              | 58          | N/R          | 31          | N/R          | 35          | N/R          | 40          | N/R          | 39          | N/R                       | 69          |
|                              | 29                               | 51          | 9            | 31          | 5            | 26          | 18           | 36          | 9            | 37          | 15                        | 56          |
| Winikoff (2008) <sup>#</sup> | N/R                              | 64          | N/R          | 40          | N/R          | 35          | N/R          | 31          | N/R          | 30          | N/R                       | 33          |
|                              | N/R                              | 66          | N/R          | 40          | N/R          | 34          | N/R          | 34          | N/R          | 32          | N/R                       | 41          |

Abbreviation: N/R, not reported.

\*Fever, warmth, hot flushes, or chills.

<sup>†</sup>Mifepristone, 600 mg, followed by misoprostol, 800 micrograms vaginally, 36–48 hours later. (Schaff EA, Stadalius LS, Eisinger SH, Franks P. Vaginal misoprostol administered at home after mifepristone (RU486) for abortion. *J Fam Pract* 1997;44:353–60.)

<sup>‡</sup>Mifepristone, 200 mg, followed by misoprostol, 800 micrograms vaginally, 48 hours later. (Schaff EA, Eisinger SH, Stadalius LS, Franks P, Gore BZ, Poppema S. Low-dose mifepristone 200 mg and vaginal misoprostol for abortion. *Contraception* 1999;59:1–6.)

<sup>§</sup>Mifepristone, 600 mg, followed by misoprostol, 400 micrograms orally, 36–48 hours later. (Wiebe E, Dunn S, Guilbert E, Jacot F, Lugtig L. Comparison of abortions induced by methotrexate or mifepristone followed by misoprostol. *Obstet Gynecol* 2002;99:813–9.)

<sup>||</sup>Mifepristone, 200 mg, followed by misoprostol, 800 micrograms vaginally, 6–8 hours later (first row) or 24 hours later (second row). (Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion. *Obstet Gynecol* 2004;103:851–9.)

<sup>¶</sup>Mifepristone, 200 mg, followed by misoprostol, 800 micrograms vaginally, 0–15 minutes later (first row) or 24 hours later (second row). (Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn L. Mifepristone and misoprostol administered simultaneously compared with 24 hours apart for abortion: a randomized controlled trial. *Obstet Gynecol* 2007;109:885–94.)

<sup>#</sup>Mifepristone, 200 mg, followed by misoprostol, 800 micrograms orally (first row) or buccally (second row), 24–36 hours later. (Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg A, Gonzales J, et al. Two distinct oral routes of misoprostol in mifepristone medical abortion. A randomized controlled trial. *Obstet Gynecol* 2008;112:1303–10.)