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Clinical Guidelines

Medical management of first-trimester abortion☆,☆☆,☆☆☆,☆☆☆☆,★,★★,★★★

Society of Family Planning Clinical Guideline

#2014-1

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.

1. Background

1.1. Medications currently used for medical abortion

1.1.1. 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 antiprogestin [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 h after mifepristone administration [3]. At this point, the sensitivity of the myometrium to the stimulatory effects of exogenous

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★ The American College of Obstetricians and Gynecologists, 409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920

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prostaglandins increases fivefold [3]. However, more recent studies have shown high efficacy when vaginal misoprostol is administered less than 15 min 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 labor induction; and treatment of symptomatic uterine leiomyomas, endometriosis, Cushing syndrome, breast cancer, early pregnancy loss, and glaucoma [6,7].

1.1.2. Misoprostol

Misoprostol is an inexpensive prostaglandin E1 analogue in a tablet form that is stable at room temperature. It is approved by the US 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 (i.e., buccal and vaginal) also appear to result in greater efficacy compared with oral administration. Similarly, those routes with rapid and significant absorption (i.e., 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].

1.1.3. 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 antiprogestin 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 mcg vaginally, may be another effective option for medical abortion, but more research is needed regarding this regimen [21,22].

2. Mifepristone regimens

2.1. Regimen approved by the US 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 h later by a prostaglandin analogue, usually misoprostol 400 mcg 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 h after oral misoprostol administration, use of an additional dose does not improve efficacy [26,28].

3. 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