Drug Therapy

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MEDICAL TERMINATION OF PREGNANCY

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TERMINATION of pregnancy has been practiced since antiquity. Although many societies accept this practice, some reject it, and it is sometimes even considered a crime. The most widely used methods for terminating pregnancy early in the first trimester are surgical, primarily vacuum aspiration, which is safer and less painful than dilation and curettage. An estimated 26 million pregnancies are terminated legally each year throughout the world, and 20 million are terminated illegally, with more than 78,000 deaths.[1] A safe medical method would save many lives.

In the United States, where abortion is legal and is performed by trained personnel, the rate of death from surgical termination of pregnancy is 0.6 per 100,000 women, with serious morbidity in less than 1 percent of women.[2] Women often resort to abortion because they lack information on contraception or fear the side effects of contraceptive methods. Abortion is often considered when contraception fails and in countries where contraceptive methods are not widely available. However, termination of pregnancy should not be used as a method of family planning.

Even in some developed countries, abortion services are not always readily available. The United States has one of the highest abortion rates among developed countries, yet in 1995, approximately 86 percent of U.S. counties had no abortion providers or facilities.[2] Indeed, access to abortion is becoming increasingly difficult in the United States because of the harassment of both patients and health care personnel outside abortion facilities by opponents of abortion. As a consequence, the number of physicians who perform abortions has decreased, and not all residency programs in obstetrics and gynecology in the United States offer training in abortion procedures.[3] The availability of acceptable, safe drugs for the termination of pregnancy would be of immeasurable value for women and the medical profession.

In this review, we focus on advances in the medical termination of pregnancy during the early part of the first trimester, when most abortions are performed.[1] Late first-trimester and second-trimester medical abortions are beyond the scope of this review, and postcoital contraception, as well as menstrual regulation, has been reviewed elsewhere.[4,5]

PHYSIOLOGIC ACTIONS OF DRUGS INDUCING ABORTION

Implantation of a fertilized ovum (embryo) involves complex interactions with the endometrium. The embryo becomes attached to the endometrial epithelium and invades the endometrial stroma on day 6 to 10 after ovulation. These events depend on progesterone, which modifies the transcription of many genes involved in the implantation process (Fig. 1). Progesterone also inhibits myometrial contractions.[8] The drugs used to terminate pregnancy (Fig. 2) act by inhibiting the synthesis of progesterone, inducing myometrial contractions, antagonizing the action of progesterone, or inhibiting the development of the trophoblast.

Inhibition of Progesterone Synthesis

Modified steroidal molecules, such as (2α,4α,5α,17β)-4,5-epoxy-17-hydroxy-4,17-dimethyl-3-oxoandrostane-2-carbonitrile (epostane), and other competitive inhibitors of ovarian and placental 3β-hydroxysteroid dehydrogenase, such as trilostane, inhibit the synthesis of progesterone from its precursor, pregnenolone.[11] The action of epostane in reducing progesterone synthesis and terminating pregnancy is prevented by the administration of progesterone.[11]

Induction of Myometrial Contractions

Prostaglandins and oxytocin stimulate uterine contraction by binding to specific receptors on the myometrial-cell surface.[9] This action results in increased calcium production by the endoplasmic reticulum and, consequently, in uterine contraction (Fig. 1).[9]

Antagonism of the Action of Progesterone

The first progesterone antagonist (antiprogestin) to be developed was mifepristone (Fig. 2), also known as RU 486 or RU 38486, which binds to the progesterone receptor with an affinity five times as great as that of progesterone.[12] Unlike progesterone, this complex inhibits transcription,[6,13,14] resulting in the down-regulation of progesterone-dependent genes, with decidual necrosis and detachment of the products of conception.[6] Antiprogestins also act on endometrial blood vessels, causing damage that further compromises the embryo.[15] These agents directly promote uterine contractions by increasing myometrial-cell excitability,[16] and they also cause cervical dilation.

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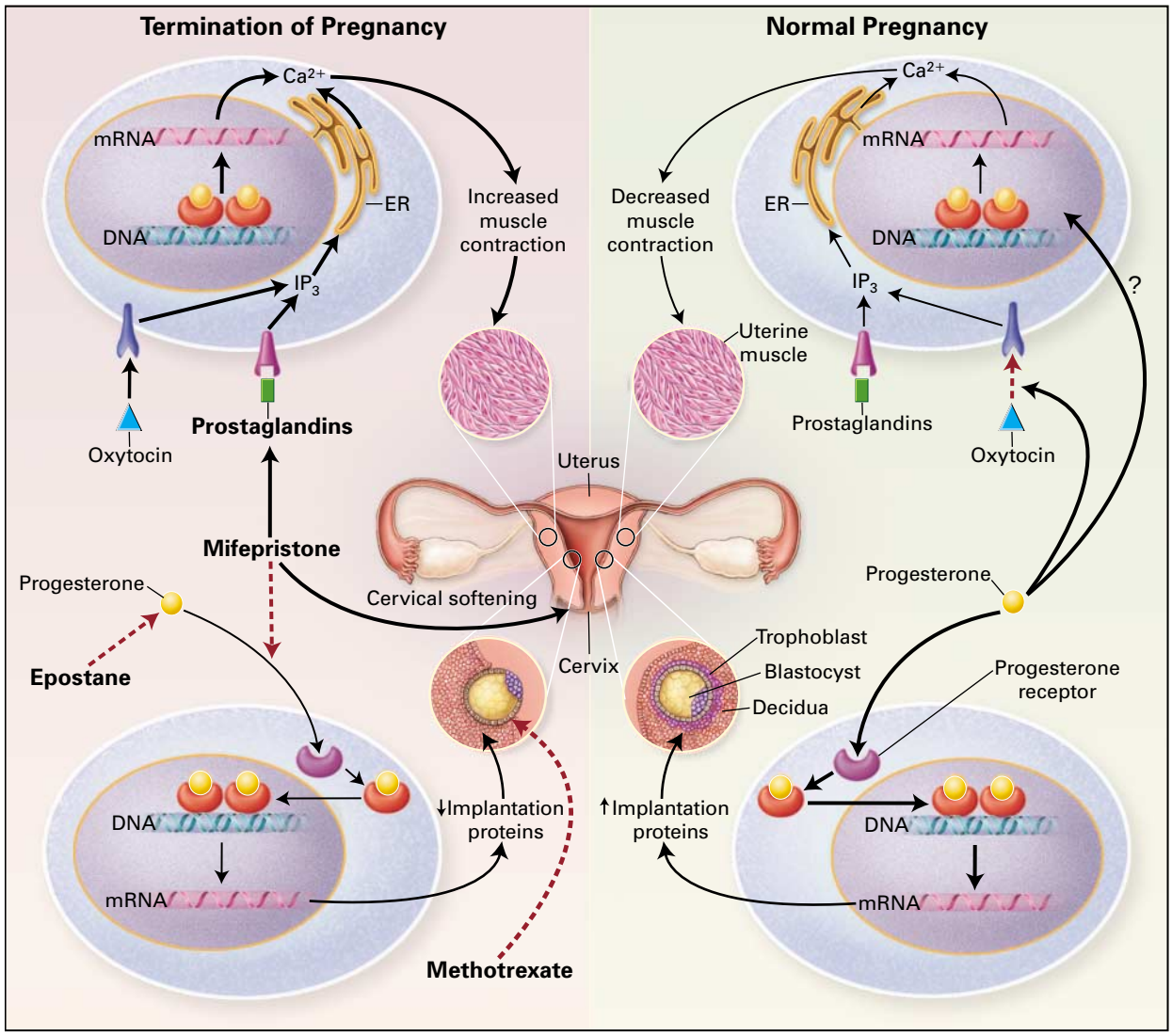

Figure 1. Physiology of Pregnancy and Site of Action of Drugs Used to Terminate Pregnancy.

After progesterone binds to its receptor, the complex forms a dimer and binds to a segment of the promoter region of different target genes.[6] This genomic effect leads to changes in the structure of epithelial-cell membranes and in the synthesis of implantation proteins.[7]

Progesterone decreases uterine contraction, probably by a genomic effect.[8] In contrast, during labor, oxytocin and prostaglandins induce uterine contraction. They bind to their respective receptors, resulting in increased phospholipase C activity and increased intracellular concentrations of inositol triphosphate (IP_3) and calcium. The released calcium interacts with myosin light-chain kinase on the contractile filaments to cause uterine contraction.[9] In addition, progesterone may have a nongenomic action by binding to the oxytocin receptor and inhibiting the action of oxytocin[10] or by other mechanisms, including the nitrous oxide system.[8]

During a normal pregnancy (right-hand panel), the blastocyst attaches to the receptive endometrium, or decidua, on day 6 or 7 after ovulation. The trophoblast then traverses adjacent cells and invades the endometrial stroma. The agents used to terminate pregnancy (left-hand panel) are methotrexate, which inhibits trophoblast division; prostaglandins, which increase muscle contraction; and epostane, which decreases progesterone synthesis. Mifepristone, a progesterone antagonist, blocks the binding of progesterone to its receptor, amplifies the action of prostaglandins on the myometrium, and induces cervical softening. ER denotes endoplasmic reticulum, and mRNA messenger RNA. The broken arrows indicate inhibitory or blocking actions.

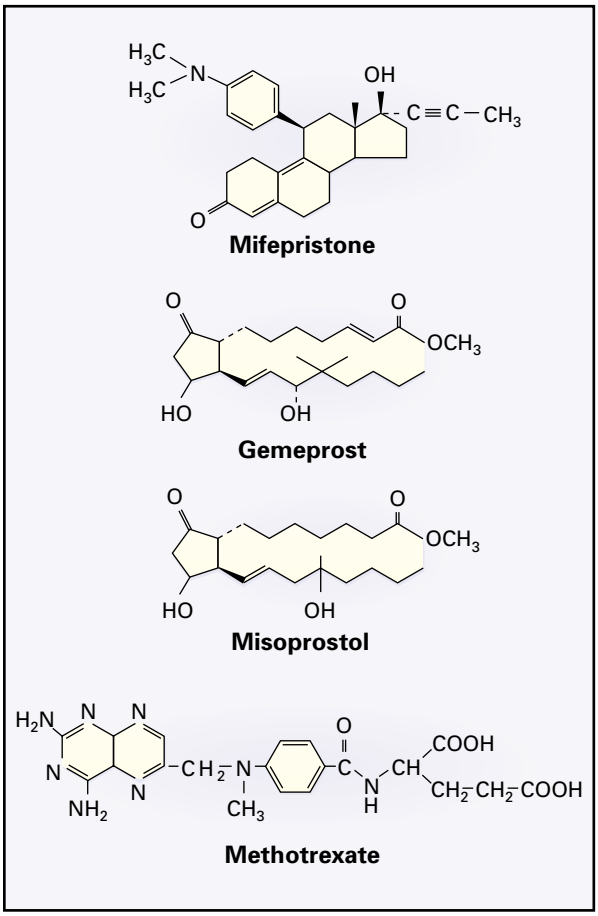

Figure 2. Compounds Used Most Frequently to Terminate Pregnancy.

Mifepristone is (11β,17β)-11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one; misoprostol is (11α,13E)-11,16-dihydroxy-16-methyl-9-oxoprost-13-en-1-oic acid methyl ester; gemeprost is 16, 16-dimethyl-*trans*-Δ2-prostaglandin E_1 methyl ester; and methotrexate is *N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid.

Inhibition of Trophoblast Development

Methotrexate (Fig. 2), a folic acid antagonist, interferes with DNA synthesis.[17] Actively proliferating cells, including those from malignant tumors, bone marrow, and trophoblast, are sensitive to methotrexate, which is used to treat choriocarcinoma and ectopic pregnancy.[18,19]

USE OF DRUGS TO TERMINATE PREGNANCY

Medical termination of pregnancy is considered successful if complete expulsion of the conceptus occurs without the need for surgical intervention. Medical termination can be performed as soon as the pregnancy has been confirmed.[20] However, it is not recommended after nine weeks of gestation because of the high incidence of failure and uterine bleeding.[21,22] Since success depends on the duration of gestation, it must be accurately determined, which is best done by vaginal ultrasonography.

Medical abortion requires more clinic visits than surgical abortion. After providing written informed consent, the woman ingests a drug (methotrexate, mifepristone, or a prostaglandin) at the clinic and is sent home. If a combined regimen is used, the woman receives methotrexate or mifepristone at the clinic, goes home, and then usually returns to the clinic to take the prostaglandin. She may or may not remain under observation at the clinic for three to six hours. A final visit is required one to four weeks later to ensure that the pregnancy has been terminated.

If medical termination fails or results in incomplete abortion or excessive bleeding, surgical termination is performed. On occasion, vacuum extraction is required for other medical reasons (e.g., severe pain or vomiting).[22]

Epostane

Epostane given alone or in combination with prostaglandin E_2 pessaries has been used to terminate pregnancies of less than 56 days' duration.[23-25] A dose of 200 mg must be given every six or eight hours for seven days. In one study, epostane caused nausea in 86 percent of women and had a success rate of only 84 percent.[24] For these reasons and because the manufacturer has not applied for approval from the Food and Drug Administration (FDA) for use of epostane to terminate pregnancy, it is not used for this purpose.

Prostaglandins

Natural prostaglandins, the first agents of this class used for medical abortion, are unstable, lack specificity, and are poorly tolerated.[26] Use of the parenteral prostaglandin analogue sulprostone has been discontinued because it was associated with cardiovascular complications, such as acute myocardial infarction and severe hypotension.[27]

The synthetic prostaglandin E_1 compounds currently used are misoprostol and gemeprost (Fig. 2). Misoprostol is inexpensive, can be stored at room temperature, and is available in many countries for the treatment and prevention of peptic ulcer caused by nonsteroidal antiinflammatory drugs. In contrast, gemeprost, which is available only as a vaginal pessary, is expensive, is thermolabile, requires refrigeration, and is not approved for use in the United States.

Efficacy

Oral doses of misoprostol ranging from 400 to 3200 μg induce abortion in only 4 to 11 percent of women with pregnancies of 56 days' duration or less.[28-30] The bioavailability is greater when the drug is administered vaginally,[31] and higher success rates have been reported with vaginal administration.[32-36] Nonetheless, the results with doses ranging from 800

to 2400 μg vary considerably; rates of complete abortion of 22, 47, 61, and 94 percent have been reported. The results of four studies, each involving more than 100 women, are shown in Table 1. The reason for the differences in success rates is unknown,[51] but it is not related to the dose of misoprostol or the duration of gestation. Misoprostol tablets were not formulated for vaginal use; however, even when the tablets are moistened for vaginal insertion, the success rate is not improved.[36]

The response to vaginal gemeprost is more predictable. In one study, a dose of 1 mg of gemeprost (with additional doses given, if necessary, every three hours for up to five doses) terminated pregnancy in 97 percent of women who had been pregnant for less than 56 days.[52] The same dose administered every six hours for up to three doses was less effective (an 87 percent success rate) (Table 1).[37]

Side Effects

Prostaglandins are associated with a high incidence of side effects, including pain, dizziness, nausea, vomiting, diarrhea, chills, and rashes. Fifty-three percent of women given 5 mg of gemeprost required opiate analgesia, as compared with 16 percent given 3 mg.[52] Because of the need for narcotic analgesia, the women receiving more than 3 mg of gemeprost frequently had to remain in the hospital overnight, with the associated inconvenience and additional expense.[37] With misoprostol, the mean duration of bleeding was 11 days,[38] as compared with 14 days with gemeprost.[37]

In cases in which misoprostol failed to terminate pregnancy, congenital abnormalities in the infants, including scalp or skull defects, cranial-nerve palsies, and limb defects such as talipes equinovarus, have been reported.[53-56] The increase in uterine pressure related to uterine contractions or vascular spasm may be the cause of these teratogenic effects.[55,56] Although prostaglandins can be used alone to terminate pregnancy, because of the high incidence of side effects they are usually used at reduced doses in combination with mifepristone or methotrexate.[30,57,58]

Methotrexate and Prostaglandins

Methotrexate and misoprostol used in combination are very effective in terminating pregnancy (Table 1).[45,47,59] The methotrexate is usually given in a dose of 50 mg per square meter of body-surface area, administered by intramuscular injection. A higher dose (60 mg per square meter) does not increase the success rate.[44] Oral administration (25 or 50 mg) is also effective.[47-49] Three to seven days after the methotrexate has been administered, misoprostol (800 μg) is administered by the vaginal route.

Efficacy

For women with a pregnancy of less than 56 days' duration, the overall success rate with the combined use of methotrexate and misoprostol ranges from 84 to 97 percent. Efficacy is often defined as either immediate success (complete abortion before the administration of misoprostol or during the 24 hours after its administration) or delayed success (complete abortion more than 24 hours after the administration of misoprostol). The rate of immediate success is much lower than the overall success rate, because abortion is often delayed; in 12 to 35 percent of women, it occurs approximately 20 to 30 days after the administration of misoprostol.[40,42,44,60] Since serum methotrexate concentrations are similar two hours after oral and parenteral administration,[61] it is not surprising that the success rates are similar with the two routes of administration.[47-49]

Side Effects

The incidence of side effects of this regimen varies markedly (Table 1). Nausea occurs in 3 to 66 percent of women, vomiting in 2 to 25 percent, and diarrhea in 3 to 52 percent; 8 to 60 percent of women have fever and chills.[41,47,48] Other side effects of methotrexate include mild stomatitis and oral ulcers, which occur in up to 5 percent of women.[40,47-49] From 40 to 90 percent of women have reported that they took medication for the relief of pain.[40,43,47-49,60] The side effects of misoprostol, such as pain and diarrhea, occur more often when methotrexate is given orally than when it is given intramuscularly.[47]

The mean duration of vaginal bleeding (estimated from the time of the last dose of misoprostol) ranges from 10 to 17 days.[40,42,44,46-49] Of the 3122 women in the studies summarized in Table 1, only 2 required blood transfusion.[44,60] In one study, 4 percent of women treated with methotrexate and misoprostol required surgical termination of their pregnancies because of excessive bleeding.[44]

The main concern with methotrexate is its cytotoxic effect on the trophoblast. Limb defects, including shortened limbs and missing digits, have been reported in aborted fetuses.[42,44,62] In one study, 6 of 13 fetuses that were at least 70 days old and had been exposed to methotrexate were abnormal.[44] Since the rate of ongoing pregnancy ranges from 1 to 10 percent (Table 1), careful follow-up by vaginal ultrasonography is mandatory.

Methotrexate has also been used alone, but the success rate is lower than with the combined regimen, and abortion usually occurs more than three weeks after the administration of the drug.[46]

Tamoxifen and Prostaglandins

In one small study, tamoxifen (20 mg once daily for four days) followed by vaginal misoprostol (800 μg) induced complete abortion in 92 percent of women (Table 1).[50]

Antiprogestins and Prostaglandins

The efficacy of mifepristone in terminating pregnancy was demonstrated in 1982.[63] When single or

TABLE 1. EFFICACY AND SIDE EFFECTS OF PROSTAGLANDINS AND METHOTREXATE USED ALONE OR IN VARIOUS COMBINATIONS TO TERMINATE PREGNANCY.*

REGIMEN	STUDY	NO. OF WOMEN	DURATION OF GESTATION	COMPLETE ABORTION	INCOMPLETE ABORTION	ONGOING PREGNANCY	EXCESSIVE BLEEDING	MEAN DURATION OF BLEEDING	INTERVAL BETWEEN LAST DOSE AND EXPULSION	NAUSEA	VOMITING	DIARRHEA
			days	percent of women				days	hr (% of women)	percent of women		
Prostaglandin alone												
Gemeprost, 1 mg every 6 hr, up to 3 doses	Norman et al.[37]	151	≤56	87	7	6	0	14		37		21
Misoprostol, 200 μg every 12 hr, up to 4 doses	Bugalho et al.[33]	101	35–77	22	20					19	6	7
Misoprostol, 400 μg every 12 hr, up to 4 doses		133	35–77	35	27					20	11	6
Misoprostol, 800 μg every 48 hr, up to 3 doses	Carbonell et al.[36]	141	<70	94	6				8†	24	25	58
Misoprostol, 800 μg every 48 hr, up to 4 doses	Carbonell et al.[38]	175	≤63	92			<1	11±3		21	26	58
Intramuscular MTX with misoprostol												
MTX, 50 mg/m², and misoprostol, 800 μg, 5–7 days later	Hausknecht[39]	178	≤63	96	4	1	0		<24 (88)	3		5
MTX, 50 mg/m², and misoprostol, 800 μg, 7 days later	Creinin et al.[40]	300	≤56	88	4	4	1	14±7	<24 (65)		9	7
MTX, 50 mg/m², and misoprostol, 800 μg, 3 or 4 or 3–6 days later (oral or vaginal)	Schaff et al.[41]	282	≤56	97		1	2	12±5	<24 (57)	66	24	41
MTX, 50 mg/m², and misoprostol, 800 μg, 3 days later	Wiebe[42]	100	<49	89	1	7		12	<24 (48)	11	2	9
MTX, 75 mg/m², and misoprostol, 800 μg, 5 or 6 days later	Creinin[43]	100	<49	95	2	2	0	17±8	<24 (67)	47	12	22
MTX, 50 mg/m², and misoprostol, 750 μg, 4 days later	Wiebe[44]	129	≤49	90		8‡	4‡	13‡	<24 (50)‡			4
MTX, 50 mg/m², and misoprostol, 500 μg, 5 days later		160	≤49	92								
MTX, 60 mg/m², and misoprostol, 500 or 750 μg, 4 or 5 days later		226	≤49	84								
MTX, 50 mg/m², and misoprostol, 600 μg, 3 doses given 8 hr apart starting on day 5		241	≤49	92								
MTX, 50 mg/m², and misoprostol, 800 μg, 5 or 6 days later (moistened)	Creinin et al.[45]	126	≤49	95	5	2	<1	16±7	<24 (73)	30	20	36
MTX, 50 mg/m², and misoprostol, 800 μg, 5 or 6 days later (dry)		122	≤49	92	3	6		16±6	<24 (71)	30	21	21
MTX, 50 mg/m², and misoprostol, 800 μg, 4 days later	Wiebe[46]	257	<49	89	7	4		10	<24 (40)	39	16	16
Oral MTX with misoprostol												
MTX, 50 mg, and misoprostol, 800 μg, 5 or 6 days later	Creinin et al.[47]	299	≤49	91		2	0	15±8	<24 (80)	37	18	18
MTX, 50 mg, and misoprostol, 800 μg, 3 days later, up to 3 doses	Carbonell et al.[48]	100	≤63	89	1‡	1‡	<1‡	11±4‡	<24 (72)	23‡	25‡	52‡
MTX, 50 mg, and misoprostol, 800 μg, 4 days later, up to 3 doses		102	≤63	90					<24 (74)			
MTX, 50 mg, and misoprostol, 800 μg, 5 days later, up to 3 doses		98	≤63	94					<24 (69)			
MTX, 25 mg, and misoprostol, 800 μg, 7 days later	Carbonell et al.[49]	148	≤56	91		9	0	11±4	6±2	18	7	4
MTX, 50 mg, and misoprostol, 800 μg, 7 days later		154	≤56	90		10	0	12±4	7±3	17	9	3
Intramuscular MTX alone												
MTX, 50 mg/m²	Wiebe[46]	101	<49	83	1	16		9	<144 (4)	50	17	14
Tamoxifen with misoprostol												
Tamoxifen, 20 mg/day for 4 days, and misoprostol, 800 μg, 4 days later	Mishell et al.[50]	100	≤56	92	2	6	1	8	<24 (88)	46	27	8

*Only studies involving 100 or more women are included. Plus–minus values are means ±SD. MTX denotes methotrexate. †The mean value is shown. ‡The mean value for all groups is shown.

multiple doses of 200 to 600 mg of mifepristone are administered alone to women who are 49 or fewer days' pregnant, the rate of successful termination of pregnancy ranges from 64 to 85 percent.[6,14,64] The results are similar with lilopristone, a structurally similar compound.[65] These efficacy rates are inadequate for general clinical use.

The addition of a prostaglandin, given 36 to 60 hours after the administration of mifepristone, markedly improves the results.[66] Numerous studies of this combination have been reported,[21,37,52,67-75] with the prostaglandin usually given 48 hours after mifepristone (Table 2).[22,27,57,58,76-85] In one study, the results were similar with mifepristone given in a dose of 200, 400, or 600 mg, followed by 1 mg of gemeprost,[57] although a single 50-mg dose of mifepristone was ineffective.[86] There are no differences in serum mifepristone concentrations in women given doses ranging from 100 to 800 mg; protein binding of mifepristone is saturated with doses of 100 mg or higher.[14] The success rate with a single dose of 600 mg of mifepristone is similar to that with multiple doses given over a period of three to four days.[70,78]

With one exception,[78] the prostaglandin given after mifepristone has been sulprostone, gemeprost, or misoprostol (Table 2). The oral dose of misoprostol ranges from 400 to 600 μg, given as a single dose or in a dose of 400 μg followed three or four hours later by 200 μg, if abortion has not occurred after the first dose. The vaginal dose is 800 μg. The usual dose of gemeprost is 1 mg given vaginally, although 0.5 mg is also effective.[21] In the one study that compared oral misoprostol with vaginal gemeprost, there were no differences in the rate of complete abortion, but the number of ongoing pregnancies was higher with oral misoprostol.[80]

Efficacy

Among women with pregnancies of 49 days' duration or less, the success rate associated with the use of mifepristone and a prostaglandin ranges from 92 to 98 percent, and the results are similar whether misoprostol or gemeprost is used (Table 2). The 92 percent success rate reported in one multicenter U.S. trial may have been related to a lack of experience with medical abortion as well as to a stringent definition of success (abortion within 15 days after the administration of mifepristone).[22] Among women with pregnancies of 50 to 63 days' duration, the success rate tends to be lower when mifepristone is used with oral misoprostol (77 to 95 percent)[22,80,82] than when mifepristone is used with gemeprost or vaginal misoprostol (94 to 97 percent).[58,68,80,81,83]

Complete expulsion occurs before the administration of a prostaglandin in less than 1 to 6 percent of women; the higher rates within this range are associated with earlier gestation.[22] In 44 to 70 percent of women, abortion occurs within four hours after the administration of misoprostol. The success rate is higher after vaginal administration of misoprostol than after oral administration (93 percent vs. 78 percent in one study[68]). In one study, the success rate associated with the use of mifepristone and vaginal misoprostol was 94 percent during the first six hours of observation (Table 2).[58] In two studies in which mifepristone was combined with oral misoprostol, the incidence of ongoing pregnancy increased progressively with the duration of gestation (Fig. 3)[22,82]; this association was not reported with the use of mifepristone and gemeprost.[80]

Side Effects

The most severe side effect of a regimen of mifepristone combined with a prostaglandin is excessive vaginal bleeding. Nevertheless, blood transfusions are rarely needed. Only 38 of the 25,907 women (0.1 percent) in the studies summarized in Table 2 received transfusions. In one study, the mean fall in the hemoglobin concentration was 0.7 g per deciliter, and less than 8 percent of women had a reduction in the hemoglobin concentration that exceeded 2 g per deciliter.[75] The volume of blood loss ranged from 84 to 101 ml, as compared with a mean loss of 53 ml in women undergoing surgical abortion.[87] Blood loss increases with the duration of the pregnancy.[21] The mean duration of bleeding ranges from 8 to 17 days (Table 2). In one study, mild bleeding persisted for more than 30 days in 9 percent of women and for more than 60 days in 1 percent.[22] Because of prolonged bleeding, the perception among women is that the bleeding is more pronounced after medical abortion than after surgical abortion.[88] Prolonged bleeding is troubling to many women,[89] and attempts have been made to shorten the period of bleeding by administering methotrexate or an oral contraceptive, but neither approach has been effective.[90,91]

Commonly reported side effects are abdominal pain and uterine cramps. Nearly all the women in the studies summarized in Table 2 reported abdominal pain, and 9 to 73 percent received one or more medications for the relief of pain. The need for narcotic medications is increased when high doses of prostaglandins alone are used to terminate pregnancy.[30,57,58] Among other gastrointestinal symptoms, 34 to 72 percent of women reported nausea, 12 to 41 percent reported vomiting, and 3 to 26 percent reported diarrhea (Table 2). These side effects are a consequence of the prostaglandin component of the regimen. In one study, the incidence of nausea and vomiting was higher after oral misoprostol than after gemeprost, but misoprostol caused less pain.[80] One study reported fewer side effects with vaginal misoprostol than with oral misoprostol.[68]

Rare adverse events include headache, dizziness, back pain, and fatigue. The incidence of endometritis is lower after medical abortion than after surgical abor-

TABLE 2. EFFICACY AND SIDE EFFECTS OF MIFEPRISTONE USED WITH A PROSTAGLANDIN TO TERMINATE PREGNANCY.*

REGIMEN	STUDY	NO. OF WOMEN	DURATION OF GESTATION	COMPLETE ABORTION	INCOMPLETE ABORTION	ONGOING PREGNANCY	EXCESSIVE BLEEDING	DURATION OF BLEEDING*
			days		percent of women			days
Mifepristone, 600 mg, and gemeprost, 1 mg	Ulmann et al.[27]	1,211	≤49	97	2	<1	<1	8±4
Mifepristone, 600 mg, and sulprostone, 250 μg		11,388	≤49	95	3	1	<1	8±4
Mifepristone, 600 mg, and carboprost, 1 mg (vaginal)	Wu et al.[76]	1,572	<59	91	5	4		12±6
Mifepristone, 200 mg, and gemeprost, 1 mg	WHO[57]†	388	≤56	94	4	<1		12 (4–71)
Mifepristone, 400 mg, and gemeprost, 1 mg		391	≤56	94	4	<1		12 (4–72)
Mifepristone, 600 mg, and gemeprost, 1 mg		389	≤56	94	4	<1		12 (4–66)
Mifepristone, 600 mg, and misoprostol, 400 μg (oral)	Peyron et al.[77]	505	≤49	97	2	<1	<1	9±4
Mifepristone, 600 mg, and misoprostol, 400 μg with 200 μg after 4 hr (oral)		390	≤49	96	<1	<1	0	10±4
Mifepristone, 150 mg over 3 days, and misoprostol, 600 μg (oral)	Sang et al.[78]	301	≤49	94	3	2	0	16±9
Mifepristone, 600 mg, and sulprostone, 250 μg	Thonneau et al.[79]	369	≤49	93	4	2	0	13±5
Mifepristone, 200 mg, and gemeprost, 0.5 mg	Baird et al.[80]	391	≤63	97	2	<1	0	12 (3–51)
Mifepristone, 200 mg, and misoprostol, 600 μg (oral)		386	≤63	95	1	2	<1	12 (4–57)
Mifepristone, 200 mg and misoprostol, 800 μg (vaginal)	Penney et al.[81]	360	≤63	96	3	0		
Mifepristone, 600 mg, and misoprostol, 400 μg (oral); if no expulsion after 3 hr, misoprostol, 200 μg (oral)	Aubeny et al.[82]	487	≤49	95	3	1	<1	9±5
		380	50–56	93	4	2	<1	
		235	57–63	87	6	5	3	
Mifepristone, 600 mg, and gemeprost, 1 mg	Urquhart et al.[83]	374	≤49	95‡	4	<1	<1	
		408	50–56					
		235	57–63					
Mifepristone, 600 mg, and misoprostol, 400 μg (oral)	Winikoff et al.[84]	299 (China)	≤56	92				
		250 (Cuba)	≤56	84				
		250 (India)	≤56	95				
Mifepristone, 600 mg, and misoprostol, 400 μg (oral)	Spitz et al.[22]	859	≤49	92	5	1	3	13
		722	50–56	83	8	4	6	15
		540	57–63	77	7	9	4	15
Mifepristone, 200 mg, and misoprostol, 800 μg (vaginal)	Ashok et al.[58]	928	≤49	98	1	<1	<1	
		1072	49–63	97	2	1	<1	
Mifepristone, 200 mg, and misoprostol, 800 μg (vaginal)	Schaff et al.[85]	933	≤56	97	2	<1	<1	17±11

*Only studies involving 300 or more women are included. Plus–minus values are means ±SD. Other values are means, with ranges given in parentheses if available.

†WHO denotes the World Health Organization Task Force on Post-Ovulatory Methods of Fertility Regulation.

‡The value shown is the mean for the three groups.

tion.[22] In some studies, a longer gestation was associated with a higher incidence of adverse events.[22,77,82,83] The addition of a second dose of misoprostol three to four hours after the first dose did not improve the efficacy of the regimen and increased the incidence of side effects.[77]

Although mifepristone is not teratogenic in rats, mice, or monkeys, skull deformities attributed to uterine contractions have been noted in rabbits.[6,14,92] Misoprostol is associated with congenital abnormalities in humans.[53-56] In a review of 71 women with ongoing pregnancies after the administration of gemeprost, there were eight fetal malformations, including limb defects (talipes equinovarus) and other abnormalities as noted above.[93] In most studies, the loss to follow-up has ranged from 0.6 to 5 percent (Table 2), although in one study, it was 11 percent.[69] The frequency of loss to follow-up may increase with more widespread use of mifepristone in combination with a prostaglandin, and the need to confirm the termination of pregnancy must be emphasized.

CONTRAINDICATIONS TO MEDICAL TERMINATION OF PREGNANCY

Women with adrenal failure or severe asthma and those receiving long-term glucocorticoid therapy

TABLE 2. CONTINUED.

EXPULSION BEFORE PROSTAGLANDIN ADMINISTERED	INTERVAL BETWEEN DRUG ADMINISTRATION AND EXPULSION	NAUSEA	VOMITING	DIARRHEA	LOST TO FOLLOW-UP
% of women	hr (% of women)		percent of women		
	≤4 (44)				2
	≤4 (57)				
<1	≤6 (81)		22	3	
	≤4 (70)	53	24	4	1
	≤4 (73)	53	23		1
	≤4 (67)	53	23		2
3	≤4 (61)	43	17	14	3
6	≤6 (79)	40	15	10	3
	≤4 (69)		20	22	<1
	≤4 (42)				4
	≤4 (54)	34	12	7	3
	≤4 (56)	48	22	8	3
1	≤6 (83)				0
2	≤3 (37)	38	20	11	
1			23	11	
					<1
					<1
					0
5	≤4 (49)	61	26	20	5
2		71	38	23	
<1		72	41	26	
3					
<1	≤6 (94)				
3		45	26	23	<1

should not be given mifepristone and prostaglandins. These drugs should be used cautiously in women with complicated diabetes mellitus, severe anemia, or hemorrhagic disorders and in those receiving treatment with anticoagulants. When sulprostone was used, it was contraindicated in women over the age of 35 years who were obese, who smoked, or who had other cardiovascular risk factors, because the drug was associated with heart failure in such women.[6,14,27] These restrictions do not apply to gemeprost and misoprostol. Women given methotrexate should not take any medication containing folate, because it might interfere with the action of methotrexate.

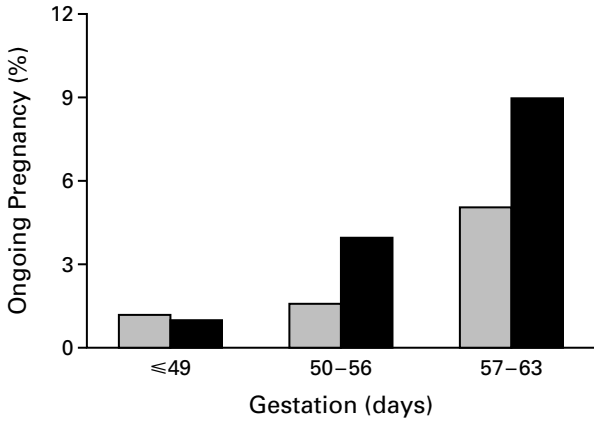

Figure 3. Incidence of Ongoing Pregnancy According to the Duration of Gestation in Two Studies of the Use of Mifepristone (600 mg) and Misoprostol (400 μg) to Terminate Pregnancy.

The study by Aubeny et al. (gray bars) involved 1102 women,[82] and the study by Spitz et al. (black bars) involved 2015 women.[22]

ACCEPTABILITY, APPROVAL, AND AVAILABILITY

Medical termination of pregnancy is acceptable to the majority of women in both developed and developing countries.[72,84,94,95] Among women who had successful abortions with methotrexate and misoprostol, 84 percent said they would choose a medical abortion over surgical abortion if facing the choice again, as did 91 percent of women in a large, multicenter U.S. study of mifepristone and misoprostol.[44,94] Since medical abortion is more painful and less effective in women who have been pregnant for more than 50 days than in those with shorter pregnancies, women with longer gestation are likely to find vacuum extraction more acceptable.[95] Women who refused the regimen of mifepristone and misoprostol usually did so because it required too much time and too many visits.[94] A major disadvantage of this approach is the need for an observation period of three to six hours after the administration of the prostaglandin. Observation may be unnecessary, however, in women who have been pregnant for 49 days or less. Indeed, vaginal administration of misoprostol at home after mifepristone has been administered in the clinic is safe and acceptable to women with pregnancies of less than 56 days' duration.[71,85] When methotrexate is given at the clinic, misoprostol is often self-administered at home.[34,41-43,45-47,49-51,60,96]

In 1988, mifepristone was approved in France for the termination of pregnancies of up to 49 days' duration; it was subsequently approved in the United Kingdom and China (in 1991) and in Sweden (in 1992) for the termination of pregnancies of up to 63 days' duration.[6,14] In April 1999, the mifepristone–

prostaglandin regimen was approved in Russia, and in July 1999, it was approved in Austria, Belgium, Denmark, Finland, Germany, Greece, Israel, the Netherlands, Spain, and Switzerland. Currently, medical abortion with misoprostol alone or with the combination of methotrexate and misoprostol is available in the United States, but the drugs have not been approved for this use by the FDA. The FDA has granted mifepristone approvable status.

In France, Sweden, and the United Kingdom, mifepristone is available only at registered centers. In France, this agent was used in 26 percent of women undergoing abortions in 1998, as compared with 21 percent in 1996 and 15 percent in 1994 (Sitruk-Ware R: personal communication). Despite the increase in the use of mifepristone, the total number of abortions performed annually has not changed. Mifepristone was introduced in Edinburgh, Scotland, in 1991, and in 1994, 57 percent of women there who were less than nine weeks pregnant and wanted to terminate the pregnancy requested medical termination.[97] In China, mifepristone has been used to terminate pregnancies in more than 6 million women.

CONCLUSIONS

Medical abortion is associated with higher rates of prolonged bleeding, nausea, vomiting, and pain than is surgical abortion, and the rate of use of analgesic drugs is greater with medical abortion.[84] Moreover, medical abortion has a lower rate of success than surgical abortion.[95,98-100] Vacuum aspiration in the first trimester of pregnancy is effective in 98 to 99 percent of women, and most failures occur at early stages of gestation.[20] For this reason, some physicians will not perform vacuum aspiration until at least seven weeks of gestation.[20] An advantage of medical termination is its high rate of efficacy in women with early pregnancies. In addition, medical abortion is safe and acceptable to women, and it does not require anesthesia. Medical abortion requires more clinic visits than surgical abortion, however, and it should be offered only by well-trained clinicians who can provide surgical treatment in the event of a failed abortion or excessive bleeding.[3] Women who choose medical abortion must have access to a specialized center where suction curettage is available, should heavy bleeding occur and blood transfusion be required.

Contrary to expectations, the legalization of abortion has not been associated with an increase in the demand for abortion. In developed countries, medical abortion offers women an alternative to surgical abortion. In underdeveloped countries, even where abortion is legal, surgical abortion may not be an option because physicians may be unwilling or inadequately trained to perform the procedure.

The views expressed in this article are those of the authors and do not necessarily reflect the views of the organizations with which they are affiliated.

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IMAGES IN CLINICAL MEDICINE

The *Journal* has a large backlog of Images in Clinical Medicine that have been accepted for publication. Therefore, we will not consider new submissions in 2000. This decision will be reevaluated in December.