

Efficacy of Combination Therapy with Methotrexate and Misoprostol in Termination of Pregnancy in the First Trimester

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Abstract

Background: Induced abortion is the medical or surgical termination of pregnancy before fetal viability. It has maternal or fetal indications. The aim of the present study was to evaluate the efficacy of the combination of methotrexate and misoprostol for termination of the pregnancy in the first trimester.

Methods: This analytic study was performed on 100 women at the first trimester of pregnancy (<14th week), during 2004-2006. Each woman received intramuscular methotrexate (50 mg/m²) and intravaginal misoprostol (800 µg) 72 hours after methotrexate administration. The second dose of misoprostol was administered if abortion did not occur after 24 hours. Abdominal ultrasonography was performed 7 days after abortion.

Results: Of the 100 women, 76 had gestational age >9 weeks and 24 has gestational age <9 weeks. Eighty one women (81%) had successful medical abortion and 19% women required curettage. Fifty nine patients with gestational age >9 weeks and 22 patients with gestational age <9 weeks had complete abortion. Failure rate was higher in missed abortion. Required dose of misoprostol and duration of conceptus expulsion were higher in pregnancies with missed abortion.

Conclusion: Combination therapy with methotrexate and misoprostol represents a safe and effective alternative to invasive methods for termination of the pregnancy in the first trimester.

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Keywords • Medical abortion • misoprostol • methotrexate • first trimester of pregnancy • induced abortion • missed abortion

Introduction

Surgical termination of pregnancy (dilatation and curettage) has been the standard management of early pregnancy failure. Medical management of early pregnancy termination using prostaglandin analogues has been proposed as an alternative to surgery. Prostaglandin analogues combined with mifepristone (RU486) for elective abortion at the first trimester of pregnancy result in success rate of about 95% (complete uterine evacuation without surgery).¹ Published studies using various prostaglandins for early abortion report success rates ranging from 13% to 95%.²⁻⁵ The widely varying success rates may reflect the inclusion of

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different types of pregnancy failure (missed abortion, blighted ovum, or incomplete abortion). The efficacy diminishes with missed abortion because of placental fibrotic tissues, firm residual adhesion, duration of pregnancy (efficacy to be decreased after 49 days of gestation), and different treatment protocols (vaginal v oral; vaginal route has more efficacy, presumably because of greater tissue bioavailability).¹

Three medications have been used for early medical abortion, including the antiprogesterin mifepristone, the antimetabolite methotrexate, and the prostaglandin misoprostol. These agents cause abortion by increasing uterine contractility, either by direct stimulation of the myometrium (misoprostol) or by reversing the progesterone-induced inhibition of uterine contraction (mifepristone and methotrexate).⁶

Recently, medical termination of pregnancy has been the suitable replacement for surgical methods in China and Europe. Methotrexate is a cytotoxic drug for the placental tissue and therefore it is prescribed for the treatment of malignant trophoblastic tumors. Also it is applied as a safe and effective drug in unruptured ectopic pregnancy. Methotrexate has been used for a long time in the treatment of benign diseases such as rheumatoid arthritis and psoriasis.⁷

Iamakov and his colleagues reported a success rate of 96% in terminating the pregnancy until 9th week of gestation by the combination of methotrexate and misoprostol. They concluded that medical abortion with these two drugs was safe and effective and this protocol could be recommended to the gynecologists.⁸

Burgata co-workers studied the women aged 15-21 years for induced abortion, and compared them with women older than 21 years. They reached the better results in the younger women (89.4% v 83%); however satisfaction rate with this method was similar in both groups.⁹

In different studies, the success rate of the medical abortion in the first 7 to 9 weeks of pregnancy with methotrexate (50 mg/m², intramuscular) and misoprostol (800 µg vaginally, repeated as needed), has been reported 89.5%, 84.1%, 96%, and 90%.⁹⁻¹²

The aim of the present study was to evaluate the efficacy of the combination of methotrexate and misoprostol for termination of the pregnancy in the first trimester.

Patients and Methods

The present study was an interventional analytic study. A total of 100 women with gestational age of 14 weeks or less who needed termination of pregnancy and referred to teaching hospitals affiliated to Mashhad University of

Medical Sciences from October 2004 to March 2006 were enrolled into the study.

The inclusion criteria were:

1- Gestational age of 12 weeks or less, with intrauterine pregnancy on the basis of abdominal ultrasonography.

2- Specific reasons for pregnancy termination (legal abortion, missed abortion, blighted ovum).

Pregnant women with liver or kidney diseases, asthma or hematologic disorders were excluded from the study, with the exception of the cases that the dosage of misoprostol and methotrexate was safe for them. If medical termination failed or resulted in incomplete abortion, or severe hemorrhage, surgical termination was performed.

The study protocol was approved by the Human Investigation Unit of Ethical Committee of the University, and all the women provided with informed consent.

A data sheet was completed for each patient including the gestational age, the dose of misoprostol, the time of spontaneous expulsion, need for curettage, reason for abortion, presence or absence of fetal heart activity, uterine cramp, and bleeding patterns after abortion.

Data collection was performed according to the patients' responses and observing the outcomes during a few steps.

Three clinic visits were scheduled. At the first visit (day 1), each patient received an intramuscular injection of methotrexate (50mg/m²). Gestational age was measured from the first day of the last menstrual period, and by using abdominal ultrasonography and pelvic examination. Blood group, Rh, complete blood count (CBC), blood urea nitrogen, hematocrit (Hct), creatinine, and liver function tests were requested before initiating the study. At the second visit (day 4), the patients received 800 microgram (as 200-microgram tablets) misoprostol intravaginally. After taking misoprostol, the women were monitored for 4 hours for potential adverse events such as nausea, vomiting, diarrhea, and abdominal pain. At the third visit (day 5), the same dose of misoprostol was prescribed unless the complete abortion had already occurred.

The patients were classified into three groups: blighted ovum, missed abortion and fetus with heart activity. The relations between the type of pregnancy and curettage, dose of misoprostol and time needed for expulsion of conceptus were studied.

Vaginal bleeding, uterine cramp, and expulsion of conceptus were recorded on a diary card from day 1 through 7 of the study.

Follow-up was extended to the fourth visit (day 12) if bleeding continued or if there was

uncertainty about the completeness of abortion by abdominal ultrasonography.

Efficacy was defined as the termination of pregnancy with complete expulsion of conceptus without the need for surgical procedure. The need for surgical methods (dilatation and curettage) was considered as failure. Surgical procedure was performed as needed if the investigators believed there was a threat for women's life (severe hemorrhage), or at the end of the study for an ongoing pregnancy or incomplete abortion. Endometrial thickness <10 mm was considered as complete abortion. Statistical analysis was performed by descriptive statistics and frequency distribution in SPSS software version 11. The study's findings were analysed by χ^2 test. $P < 0.05$ was considered as statistically significant.

Results

In the present study, 100 pregnant women were evaluated for termination of pregnancy at the first trimester. Mean age of the patients was 27.3 ± 2.6 years, mean gravidity was 2.8 ± 1.6 and mean gestational age was 9 ± 1.9 weeks (6-12 weeks). Among the patients, 14 had therapeutic abortion with live fetuses. From a total of 100 patients, 81 women had successful abortion by methotrexate and first or second administration of misoprostol and 19 patients required surgical intervention. Among the 81 patients, 60 (74.7%) had successful abortion following the first dose

of misoprostol, and 21 patients (25.9%) had complete abortion by receiving the second dose. There was a significant correlation between the prescribed dose of misoprostol and successful abortion ($P=0.000$).

There were 76 women in > 9 weeks and 24 women in < 9 weeks of gestational age groups.

There was no significant correlation between gestational age and curettage rate, dose of misoprostol, and the time needed for expulsion ($P=0.476$; table 1).

There was no significant correlation between the presence or absence of fetal heart activity and curettage ($P=0.223$), dose of misoprostol ($P=0.347$), and the time needed for conceptus expulsion ($P=0.678$).

In the present study, the duration between misoprostol administration, onset of uterine cramps and the time needed for conceptus expulsion, was divided into < 12 hours and > 12 hours.

There was significant correlation between abortion and duration of uterine cramp ($P=0.000$).

Spotting duration after abortion was divided into < 10 days and > 10 days. There was a significant correlation between the time needed for conceptus expulsion and duration of spotting after abortion ($P=0.001$). There was a significant relationship between the type of pregnancy and curettage ($P=0.010$), dose of misoprostol ($P<0.001$), and the time needed for conceptus expulsion ($P=0.018$; table 2).

Table 1: The correlation between gestational age and curettage, dose of misoprostol, and the time needed for conceptus expulsion

Gestational age		> 9 weeks	< 9 weeks	< 9 weeks	P value
Curettage	yes	17	2	19	0.127
	no	59	22	81	
	Total	76	24	100	
Dose of misoprostol	two doses	32	8	40	0.44
	one dose	44	16	60	
	Total	76	24	100	
Time needed for conceptus expulsion	>12hours	38	10	48	0.476
	<12hours	38	14	52	
	total	76	24	100	

Table 2: The correlation between the type of pregnancy, doses of misoprostol, and the time of expulsion and curettage

		Type of pregnancy			Total	P value
		Blighted ovum	Missed abortion	Live fetus		
Curettage	Yes (%)	6 (13.6)	6 (13.6)	1 (7.1)	19 (19.0)	0.010
	No (%)	38 (86.4)	30 (71.4)	13 (92.9)	81 (81.0)	
	Total (%)	44	42	10	100	
Dose of misoprostol	First dose (%)	8 (18.2)	28 (66.7)	4 (28.6)	40 (40.0)	<0.001
	Second dose (%)	36 (81.8)	14 (31.3)	10 (71.4)	60 (60.0)	
	Total (%)	44	42	14	100	
Time of expulsion	>12 Hours (%)	15 (34.1)	27 (46.3)	6 (42.9)	48 (48.0)	0.018
	<12 Hours (%)	29 (65.9)	15 (35.7)	8 (57.1)	52 (52.7)	
	Total (%)	44	42	14	100	

Discussion

Termination of pregnancy has been practiced since antiquity. Although many societies accept this practice, some reject it and it is sometimes considered as a crime. The most widely used methods for terminating pregnancy in the first trimester are surgical, primarily vacuum aspiration, which is safer and less painful than dilation and curettage.¹³

The study performed by Hausknecht in 1995 showed the efficacy of 800 microgram vaginal misoprostol 5-7 days after intramuscular injection of methotrexate. Among 178 pregnant women with gestational age of <9 weeks, 171 cases (96%) had successful abortion and seven patients required curettage.⁷ The higher success rate in the study compared with our study may be due to lower gestational age and less study population. In the present study, all pregnant women up to 12 weeks of gestation had participated.

Borgatta and coworkers in 2001 evaluated the efficacy of methotrexate and misoprostol on 1973 women with gestational age 7 weeks or less. The rate of complete abortion was 84.1% and the need for curettage was 14.9%.⁹

Dahiya and colleagues performed a study in 1999 on 108 patients with gestational age of 9 weeks or less in three groups. For the first group, methotrexate, for the second group, misoprostol and for the third group, a combination of methotrexate and misoprostol were administered. The success rate was 69%, 57% and 89%, respectively. They concluded that the combination of methotrexate and misoprostol was a safe and suitable method for pregnancy termination at the first trimester of pregnancy.¹¹ Of course, in the most performed studies so far, this method was considered for fetus with heart activity (live fetus) and as a method for elective abortion.⁸ In the present study, however, missed abortion and blighted ovum were studied as well. And the gestational age of the pregnant women in our study was higher than other studies.⁹⁻¹⁴ Low success rate in the present study may be due to the types of pregnancy and termination at a higher gestational age.

The present study, for the first time, studied the effects of medical termination of pregnancy with methotrexate and misoprostol on missed abortion. The results showed that the failure rate was higher in pregnancies with missed abortion. The dose of misoprostol and the needed time for conceptus expulsion in missed abortion were also higher than blighted ovum and live fetus.

Moreover, we showed that there was no significant correlation between live or dead fetus in regard to curettage, dose of misoprostol and the

needed time for medical abortion. This relation has not been shown in the previous studies.

Rock and coworkers studied the efficacy of misoprostol 3, 4, or 5 days after methotrexate administration at the gestational age of 63 days or less. The success rate was 92% and there was no significant relationship with the time of misoprostol administration.¹⁵

The study performed by Carbonell and others in 1996 represented a significant relationship between the gestational age (more or less than 56 days) and success rate with medical abortion (misoprostol and methotrexate).¹⁶ But in the present study, there was no significant relationship between gestational age (more or less than 9 weeks), dose of the drugs and the needed time for conceptus expulsion. This may be due to the presence of live fetus in other studies and missed abortion in our patients.

One of the limitations of the present study was difficult access to misoprostol tablets that are not easily available in Iran drug market. The other limitation was the ambiguity about maternal outcomes after exposure with methotrexate. However, no important side effects have been reported in the present study and other studies.⁷⁻⁹

Conclusion

Pregnancy termination with low dose of methotrexate and misoprostol is safe and effective. There is no need for hospitalization and this method is accepted completely in outpatient settings. Therefore we suggest that this method is suitable alternative to surgical methods. Further studies with focus on the medical abortion with different methods will be worthwhile.

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Conflict of Interest: None declared

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