

## Research Article

# Methotrexate and Misoprostol against Misoprostol Alone for Early Medical Abortion: Comparative Study

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## ABSTRACT

**Background:** Vaginal mifepristone oral misoprostol have proven to be highly effective medical abortion methods and are used widely in modern countries.

**Objectives:** The objective of this study is to compare the efficacy for two medical abortion regimens used in one clinic setting misoprostol alone, intramuscular methotrexate and vaginal misoprostol.

**Methods:** An intervention study was conducted on a total of 100 randomly selected women with gestations of first-trimester pregnancy, who sought a missed abortion. Study population was assigned as two groups, the first was subjected to vaginal administration of Misoprostol and the second was subjected to IM injection of methotrexate and self-administration of vaginal misoprostol After 72h. All patients were followed up for recording any side effects of the drugs, progress of abortion & if there was any need for surgical interference [manual vacuum aspiration (MVA) or dilatation and curettage

**Results:** Success rate of the methotrexate regimen was 80% and did not differ significantly from the misoprostol regimen that had success rate of 84%.

**Conclusions:** In this real-use setting, the use of misoprostol in combination with methotrexate or alone for the missed abortion termination are both safe and effective methods without serious side effects.

**Key words:** Methotrexate, Misoprostol, Pregnancy, Abortion

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## INTRODUCTION

Regimens of 200 mg mifepristone followed by 400 micrograms oral misoprostol or 800 micrograms vaginal 48 hours later have proven to be highly effective medical abortion methods and are used widely in the USA and elsewhere.<sup>(1)</sup> In many settings; however, women do not have access to mifepristone. These are often settings with highly restrictive abortion laws. Latin America and the Caribbean provide some of the most dramatic examples: abortion is illegal in all but extreme circumstances in many countries or is entirely prohibited, as is the case in Colombia, Chile, and El Salvador. Except for Guyana and Puerto Rico, mifepristone is not registered anywhere in the region. Consequently, mortality due to unsafe abortion remains high, with an estimated 6000–7000 deaths annually.<sup>(2,3)</sup> Given these obstacles; safe abortion services must often be provided through reserved means and, with respect to medical abortion, using alternative regimens of misoprostol alone and/or methotrexate with

misoprostol. In the published literature, trials tend to show slightly lower success rates for misoprostol-alone regimens compared with methotrexate–misoprostol regimen for early abortion. Several studies have documented success rates of 83–97% using variants of a misoprostol-alone regimen.<sup>(4–9)</sup> A small number of trials have tested oral misoprostol, although a recent review of seven misoprostol-alone regimens for early medical abortion found that vaginal administration was significantly more effective.<sup>(10)</sup> While further research would help determine the optimal protocol, 800 micrograms vaginal misoprostol, repeated after 24 hours, has been recommended for pregnancies up to 63 days last menstrual period (LMP).<sup>11</sup> For methotrexate–misoprostol regimens, success rates in past trials generally range from 91 to 98%.<sup>(12–15)</sup> For pregnancies up to 49 days of gestation, a widely used current regimen is 50 mg/m<sup>2</sup> intramuscular (IM) methotrexate followed 5–7 days later by 800 micrograms vaginal misoprostol, repeated in 24 hours if necessary. Comparable efficacy rates have also been found using 50 mg oral methotrexate.<sup>(12,16–18)</sup>

As with any pharmacological agent, both misoprostol and methotrexate are associated with risks and adverse effects. Methotrexate is a known teratogen and as such requires careful follow up for women with failed methotrexate–misoprostol abortions. Several cases of anomalies associated with in utero exposure to misoprostol have also been documented; however, the absolute risk of teratogenicity appears to be low, at roughly 10 per 1000 exposed fetuses.<sup>(11)</sup> Adverse effects of the two medical abortion regimens are generally similar and include bleeding, cramping, fever, nausea, vomiting, and diarrhea.

Since both regimens include similar doses of misoprostol, this similarity in adverse effect profile is perhaps not surprising. In the large majority of trials, these conditions are short-term and easily managed.

With regards to efficacy, useful comparisons between misoprostol-alone and methotrexate–misoprostol regimens based on published trials are hampered by the wide variability of samples, regimens used, gestational age limits, and points of follow up. In a study by Creinin et al.,<sup>(7)</sup> women with pregnancies  $\leq 56$  days LMP (Last Menstrual Cycle) were randomized to a regimen of either IM methotrexate plus misoprostol or 800 micrograms vaginal misoprostol alone, repeated after 24 hours if the abortion had not occurred. Success rates, defined as complete abortion at the 2-week follow up, were 90% for the methotrexate–misoprostol group and 47% for the misoprostol-alone group.<sup>7</sup> The study is designed to compare between administration of Misoprostol and combined Misoprostol & methotrexate in treatment of missed abortion.

## METHODS

### Study Setting & Design

An intervention study was conducted at antenatal clinic of El-Shatby Maternity University hospital.

### Sample Size and Method of Selection

A power of 80% was used to detect the significance of the difference of the induction to abortion time between groups of pregnant women with missed abortion receiving combined methotrexate with misoprostol & others receiving misoprostol alone = 1.2hrs, SD=2hrs for each group,  $\alpha = 0.05$ ,<sup>(20)</sup> The minimal required sample size was found to be 50 women per group. The sample women were randomly selected and allocated after fulfilling the inclusion criteria. The sample size was calculated using STATA11 software (P is significant at  $\leq 0.05$ ). The patients were randomly allocated and divided into two groups designated Group (A), the first group that included fifty patients, and all were subjected to vaginal administration of Misoprostol (800µg). If conceptus residual remained, the same dose of misoprostol was

repeated and Group (B), the second group that included fifty patients, who were subjected to injection of 50 mg of methotrexate intramuscularly. After 72h, patient administered herself 800 µg of misoprostol vaginally. If conceptus residual remained, the same dose of misoprostol was repeated after 24h.

All patients were followed up for recording any side effects of the drugs, progress of abortion & if there was any need for surgical interference [manual vacuum aspiration (MVA) or dilatation and curettage (D&C)]. Furthermore, ultrasound was done following the last dose of drugs taken by 24 hours to diagnose if abortion is complete or not and managed accordingly.

All recruited cases were interviewed for thorough history taking with special emphasis on gestational age, amount and duration of bleeding, presence or absence of pain. All cases were subjected to clinical examination with careful recording of pulse and blood pressure. Per vaginal examination or bimanual examination was done to detect uterine size, degree of cervical dilatation and amount of bleeding. Ultrasound examination was done to certify the mean gestational age, to ascertain the absence of pulsation in an embryo of crown-rump length (CRL) more than 6 mm or absence of yolk sac or embryo in a gestation sac of mean diameter more than 20 mm, the absence of other obstetrical causes of bleeding in the first trimester; ectopic pregnancy and vesicular mole (VM), and the absence of other gynecological causes of bleeding e.g. fibroid uterus.

### Statistical Analysis

Chi-square test was performed to compare patient characteristics by abortion outcome (success/failure). The impact of selected variables on method success was explored through logistic regression. The main outcome measure was the abortion outcome (success/failure) at 2-week follow up.

### Ethical statement

The study was approved by the institutional review board and the medical ethics committee at the faculty of medicine Alexandria university, Egypt. The research complied with the international ethical research guidelines of declaration of Helsinki. All participants were invited to sign a written consent after explaining the aim and concerns of the study. Data sheets were coded to ensure anonymity and confidentiality of patient's data.

## RESULTS

### Period of gestation

The mean gestational age of group 1 (misoprostol only) and of group 2 (misoprostol and methotrexate) were  $9.5 \pm 2.6$  and  $10.3 \pm 2.3$  weeks respectively, and it is statistically insignificant as  $p = 0.091$  ( $p$  is significant at  $\leq 0.05$ ). (Table 1)

### Induction to abortion interval

The mean time interval between the first dose and start of uterine colics in group 1 (misoprostol only) and in group 2 (misoprostol and methotrexate) were  $16 \pm 10$  and  $18 \pm 9$  hours respectively (Table 2). This variable showed statistically non-significant difference between the two groups ( $p > 0.05$ ).

### Surgical evacuation

The percentage of cases needed surgical evacuation in group 1 (misoprostol only) and that in group 2 (misoprostol and methotrexate) were 16% and 20% respectively (Table 3), and it is statistically non-significant as ( $p > 0.05$ ).

**Table 1:** Comparison between the two studied groups regarding gestational age. (GA)

		Group		t (P)
		Misoprostol	Methotrexate & misoprostol	
GA (weeks)	. Range	5.0-13.0	5.0-13.0	1.7 (0.091)
	. Mean	9.5	10.3	
	. SD	2.6	2.3	

P is significant at  $\leq 0.0$

**Table 2:** Comparison between the two studied groups regarding the interval between the first dose and the start of uterine colics

Parameter	Group		Z	P
	Misoprostol	Methotrexate & misoprostol		
Induction to abortion interval(hours)				
Minimum	4	5	1.3	0.209
Maximum	36	36		
Mean	16	18		
SD	10	9		
Median	11	15		

**Table 3:** Comparison between the two studied groups regarding surgical evacuation

Parameter	Group				X <sup>2</sup> (P)
	Misoprostol		Methotrexate & misoprostol		
	No	%	No	%	
Surgical evacuation					
Yes	8	16.0%	10	20.0%	0.27 (0.603)
No	42	84.0%	40	80.0%	

P < 0.05 (significant)

## DISCUSSION

In the present study, group 1 showed non-significantly higher percentage of complete abortion group 2. The vaginal bleeding lasted a mean of 11 days in group 1 and 13 days in group 2, which was statically significant but it is clinically not significant. On contrary to our study, Moran T, *et al.*,<sup>(4)</sup> reported that the surgical evacuation rate was lower in methotrexate/ misoprostol group. In agreement with our study, Vahid Roudsary, et al.<sup>(5)</sup> stated a total of 200 pregnant women at first trimester were randomized and divided into two groups for termination of pregnancy. The first group received 800 µg vaginal misoprostol. If conceptus residual remained, the same dose of misoprostol was repeated. The second group received 50 mg/m<sup>2</sup> intramuscular

methotrexate, and then 800 µg vaginal misoprostol was administered after 72 hours. If conceptus residual remained the same dose of misoprostol was repeated after 24 hours. Abdominal ultrasonography was performed at seventh day for both groups. If conceptus residual remained or if pregnancy continued, curettage was performed. The results were analyzed statistically in terms of chi-square, and student's t-test, using the SPSS software. Eighty-three percent of the first group (misoprostol alone) and 81% of the second group (misoprostol & methotrexate) had successful abortion, which was statistically not significant. Misoprostol alone or in combination with methotrexate could be an acceptable method for the first-trimester abortion. Since the rate of success is similar in both methods, it is possible to eliminate the administration of methotrexate, which is a cytotoxic

drug with many potential side-effects. Of course, it should be mentioned that side-effects of methotrexate appear in large doses for chemotherapy and for our patients that have received low doses (50 mg/m<sup>2</sup>), no serious side-effects was observed. For administration of methotrexate, it is necessary to perform liver and renal tests and CBC, which would all bear extra costs. However, with the use of misoprostol alone, the cost of medical abortion and the number of visits are effectively decreased and there is no need for intramuscular injection.

### CONCLUSION AND RECOMMENDATIONS

The use of misoprostol in combination with methotrexate or alone for the missed abortion termination are both safe and effective methods without serious side-effects. These two methods can be used alternatively, but the results of the present study suggest misoprostol alone is easier. This is due to the fact that the number of visits is decreased, there is no need for intramuscular injection and possible side-effects of methotrexate that is a cytotoxic drug are eliminated. Most of the patients expressed their consent of this method and suggested it to other patients.

### CONFLICT OF INTEREST

All authors declare no conflict of interest

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