J. of Obst. & Gyn. of India Vol. 52, No. 6 : November/December 2002 Pg 50-55

Single Dose Methotrexate Followed by Vaginal Misoprostol for Early Abortion – A Non-Surgical Method

Muralidhar V Pai, Rupinder Kaur

Department of Obstetrics & Gynecology, Kasturba Medical College, Manipal 576 119

Summary

This prospective phase II clinical trial was conducted at Department of Obstetrics & Gynecology, Kasturba Medical College, Manipal, to evaluate the efficacy of single intramuscular dose of methotrexate followed by vaginal misoprostol, as an alternative to surgical method, for early first trimester medical termination of pregnancy.

43 pregnant women at gestational age of < 63 days' seeking an elective abortion fulfilling the selection criteria entered the study. Intramuscular administration of Methotrexate 50-mg/ sq.m of body surface area, followed 1 week later by vaginal administration of 800μg of Misoprostol. Misoprostrol dose was repeated 24 hrs later if abortion didn't occur. Outcome measure was successful complete abortion without surgical intervention.

Out of 43, one woman dropped out due to noncompliance with the visit schedule. Out of 42 women that completed the study, 39 (93%) had successful abortion, in that 38 had immediate success. Three women had failure of which 2 had continuing pregnancies and one had an incomplete abortion. All were terminated eventually by surgical method. All 3 failures fell in the same gestational age group : 50 – 56 days. The results with this regime to induce an effective abortion were seen best in the gestational age group < 49 days. Most (74%) of the patients did not report any side effects following methotrexate administration. The most common side effects were nausea (12%) and fatigability (9.5%). No complication was observed.

In women who received the misoprostol, bleeding occurred after a mean time of 7.83 ± 15.32 hours. The mean duration of bleeding was 6.71 ± 2.67 days. Most (95%) expressed that they were very satisfied with the method. 76% women said that they would opt for this method again in future if they were to have another abortion.

It was concluded that the induction of early first trimester abortion using this regime seems to be an effective and acceptable alternative to surgical abortion.

Introduction

Over the year we have been using surgical evacuation as means to terminate early pregnancy which has been known to be associated with certain complications like incomplete abortion, perforation, hemorrhage, sepsis, cervical incompetence, etc.

Recent trends have shown us the way to a medical method – a more safe, noninvasive approach with decreased morbidity which can be performed on an out patient basis, even in very early gestations. Also, the relatively increased incidence of failure of surgical abortion in early pregnancy owing to reasons such as cervical stenosis, extreme vaginismus, uterine anomalies, secondary to fibroid, very uncooperative patients highlights the benefits of medical abortion. Medical abortion has been described as a safer, more private and natural method by patients that have had an experience with this method.

The present study was undertaken to evaluate

the efficacy of single dose Methotrexate followed by vaginal Misoprostol in achieving early first trimester (<63 days' gestation) abortion.

Materials and Methods

This prospective, phase II clinical trial was done at the Department of Obstetrics and Gynecology, Kasturba Medical College and Hospital, Manipal.

43 women with early pregnancy at < 63 days' gestation (pregnancy confirmed by ultrasound) seeking elective abortion were recruited for termination of pregnancy by medical (chemical) method using methotrexate and misoprostol. Women with hematocrit < 30%, total WBC < 3000 / cmm, platelet Count < 100,000/ cmm, AST 2 times the normal (11-47 IU/L) / active liver disease, serum creatinine > 1.5 mg/dl / active renal disease, inflammatory bowl disease, known intolerance / allergy to either Methotrexate or Misoprostol were excluded from the study.

Study protocol, risks, benefits, visit schedule and consent were reviewed with each woman. Written informed consent was taken for use of study drugs as well as for suction evacuation, should the pregnancy still be viable. Vaginal ultrasound was done to confirm a normal intrauterine pregnancy and the gestational age. Gestational age was based on LMP, but corrected if ultrasound estimate differed by > 4 days.

Complete Blood Count, Blood Group and Rh Type, AST, serum creatinine were done prior to the onset of study and repeated a week later.

Symptom log was maintained and reviewed at each visit to record the absence or presence of vaginal bleeding, nausea, abdominal cramping, vomiting, headache, diarrhoea, dizziness and tiredness.

Questionnaire charts were maintained to record, reason for wanting an abortion, reason for opting medical abortion, prior experience, if any, with surgical abortion, experience with medical abortion, if any and psychological response to procedure.

The data was supplemented by forms filled out by medical personnel, summarizing the information obtained during the pre-abortion visit (medical history, possible contraindications) and the post-abortion follow up visit (side effects, prescription of medication, outcome of abortion). Patients were permitted at any time to request a surgical procedure.

Intervention: Intramuscular administration of Methotrexate 50-mg / sq.m of body surface area, followed 1 week later by vaginal administration of 800 μg of Misoprostol. Misoprostol dose was repeated 24 hrs later if abortion didn't occur.

Outcome measures

(1) Successful Abortion:
Immediate Success: Abortion after methotrexate or within 24 hrs of initial / repeat dose of misoprostol. Day of heavy vaginal bleeding was considered the day of abortion. Delayed Success: Abortion that occurred > 24 hrs after the repeat dose of Misoprostol.
(2) Onset of vaginal bleeding
(3) Duration of vaginal bleeding
(4) Incidence of reported side effects

Statistical analysis was carried out using the SPSS Software. The tests carried out included 95% confidence interval, chi-square test and chi-square test for linear trend.

Results

Out of 43 women that entered the study, one did not comply with visit schedule and hence was not included in the data analysis. None of the patients had vaginal bleeding / abdominal cramping prior to entry into the study. The methotrexate dose administered ranged from 66mg to 86.5mg. with a mean of 74.32mg. Table I shows the patient profile.

Table I: Patient Characteristics (n=42)

Patient Characteristics	Mean ± S.D.	Range
Age (years)	28.4 ± 4.8	18 – 42
Gestational Age (days)	47.2 ± 8.04	32 – 63
Gravidity	2.43 ± 1.29	1 - 7
Parity	1.21 ± 1.05	0 – 5
Body Surface area (sq. m)	1.48 ± 0.12	1.24 – 1.73
Previous LSCS	28.6%	0 - 3
Previous MTP	7.1%	0 – 2
Previous Miscarriage	11.9%	0 -2

Abortion occurred without the need of a surgical procedure in 39 (92.9%) of 42 women (95% Confidence Interval : 81.5% - 100%) who received methotrexate (mtx) and misoprostol. Of the 39 (92.9%) women that had a successful abortion, 38 (90.5%) had immediate success (95% Confidence Interval : 81.6% - 99.4%).

Out of 38 that had immediate success, two (4.8%) did not require the first dose of misoprostol and had successful abortion with methotrexate alone. The other 36 (85.7%) had successful abortion following the first dose of misoprostol (95% confidence interval : 75.1% - 96.3%). A repeat dose of misoprostol was necessary only

in 1 (2.4%) of 39 women. She went on to have a successful abortion after a delay of 4 days (on day 13). Bleeding lasted for 3 days followed by spotting for 7 days. This was the only patient in the study who had a delayed abortion. Out of 3 failures 2 (4.8%) had continuing pregnancies and 1 (2.4%) had incomplete abortion. All the three underwent suction evacuation. (Table II).

Outcome by gestational age on the day of methotrexate administration is detailed in Table III. Success rate was better before 49 days' gestation. This finding was statistically significant. All the three failures fell into gestational age group 50 – 56 days.

Every woman that entered the study completed symptom log. Side effects from methotrexate / misoprostol were infrequent and occurred over the first 4 days of the study. Most (73.8%) patients did not report any side effects following methotrexate administration (p value = 0.014; 95% confidence interval : 60.5% - 87.1%) (Table IV). No patient reported dizziness, tiredness or headache following misoprostol administration. Pain from uterine cramping did not require any medication in 92.8% of patients. The other patients were relieved by oral medication with narcotic analgesics. All the symptoms were relieved after the pregnancy was expelled. Side effects were unrelated to gestational age or body surface area.

Bleeding and/or cramping occurred in women

Table II: Outcome of Abortion with MTX and Misoprostol (n = 42)

Outcome	Number	%	95% CI
Treatment Success			
Total	39	92.9	85.1% - 100%
Immediate success	38	90.5	81.6% - 99.4%
Before Misoprostol	2	4.8	
After Misoprostol	36	85.7	75.1% - 96.3%
Delayed Success	1	2.4	
Treatment Failure			
Total	3	7.1	
Continuing Pregnancy	2	4.8	
Incomplete Abortion	1	2.4	

CI– 95% Confidence Interval

Table III: Details of Outcome of Abortion with MTX & Misoprostol By Gestational Age (n = 42)

Outcome		< 42 Days N = 13	43 – 49 Days N = 14	50 – 56 Days N = 9	57 – 63 Days N = 6	P
			Treatment Success			
Abortion before	N	1	1			
Misoprostol	%	7.7	7.1			
Abortion after I dose of	N	12	12	6	6	NS*
Misoprostol	%	92.3	85.7	66.7	100	
Abortion after II dose of	N		1			
Misoprostol	%		7.1			
Immediate success	N	13	13	6	6	
	%	100	92.9	66.7	100	
					NS*	
Delayed success	N		1			
	%		7.1			
			Treatment Failure			
Continuing pregnancy	N			2		
	%			22.2		
Incomplete abortion	N			1		
	%			11.1		
Statistical Significance			p=0.0079			

* NS – Not Significant

Table IV: Side Effects Reported After MTX Administration (n = 42)

Side Effects	Overall		First 24 Hours		P
	N	%	N	%	
None	19	45.2	31	73.8	0.014
Cramping	8	19.1	3	7.1	
Nausea	8	19.1	5	11.9	
Vomiting	5	11.9	2	4.8	
Dizziness	4	9.5	4	9.5	
Tiredness	4	9.5	4	9.5	
Headache	1	2.4	1	2.4	
Diarrhoea	1	2.4			

who received the misoprostol administration within a mean time of 7.51± 14.76 hours (Table V). Mean time was 5.38 hours in patients with immediate success.

Table V: Length of Time Between Intravaginal Insertion Of Misoprostol and Onset of Vaginal Bleeding (n=40)

Time	Number	%
< 2 Hours	4	10
2 – 6 Hours	21	52.5
6- 12 Hours	12	30
12 – 24 Hours	2	5
24 – 48 Hours		
2 – 4 Days	1	2.5
Mean ± S. D.	7.52 ± 14.76 hours	
Range	1.5 ± 96 hours	

SD – Standard Deviation

The mean duration of overall (n=42) vaginal bleeding was 6.71 ± 2.67 days. However the mean duration of bleeding in successful women (n=39) was 6.64 ± 2.3 days (Table VI). The bleeding was no greater than spotting by the 10th day (following the onset of vaginal bleeding), except in 2 patients: one who went on to have an incomplete abortion and the other who had a successful abortion with bleeding for 12 days and spotting for 2 days. No patient described any bleeding after day 6 of onset of bleeding to be heavier than a "light period".

Table VI: Duration of Bleeding After Abortion

Duration (days)	Number	
	Overall (42)	Successful (39)
> 1	1 (2.4%)	0
2 – 4	6 (14.3%)	5 (12.8%)
4 – 7	20 (47.6%)	20 (51.3%)
7 – 10	11 (26.2%)	11 (28.2%)
10 – 14	4 (9.5%)	3 (7.7%)
> 14		
Mean ± S. D.	6.71 ± 2.67	6.64 ± 2.3

SD – Standard Deviation

Changes in hemoglobin values after abortion are reported in Table VII. Overall, the hemoglobin decreased by 0.1 – 9.9% in 78.6% patients and in 81.6% of the patients with immediate success. Platelet counts, white cell counts an AST remained stable in all patients and showed no appreciable change from baseline when evaluated on day 7 or day 14.

After the study was completed the women were asked to evaluate their medical abortion experience compared to prior surgical abortion, if any. They were also asked about their feeling towards referring other

Table VII: Change in Hemoglobin Values From Study Days 1 -14

	Overall (n = 42)		Immediate Success (n = 38)	
	N	%	N	%
> 20 %	1	2.4		
10 – 19.9%	6	14.3	5	13.2
0.1 – 9.9%	33	78.6	31	81.6
or No Change	2	4.8	2	5.2
Mean ± S.D	7.08 ± 5.69	6.42 ± 4.16		
Range	0 – 30.7%	0 – 18.2%		

SD – Standard Deviation

Table VIII: The Main Reason that the Patients felt a Medical Abortion with Methotrexate and Misoprostol was a Good Experience (n = 39)

	Reason	Number	%
1.	Did not need a surgical abortion	27	69.2
2.	Emotionally easier than surgical abortion	27	69.2
3.	More private / at home	26	66.7
4.	Safe than surgical /less risk	25	64.1
5.	Abortion was more natural / like periods	22	56.4
6.	Easy to tolerate / few side effects	21	53.8
7.	Effective	18	46.2
8.	Gave a choice in method of abortion	13	33.3
9.	Easy to fit into schedule	10	25.6
10.	Could be done earlier in gestation than surgical abortion	3	7.7

women for this method of pregnancy termination. All patients completed these questionnaires. Although this was a self-selected group of women, they overwhelmingly preferred the medical termination of pregnancy to the surgical method. The reasons that women stated it was a good experience are listed in Table VIII.

2 women that remained unsatisfied states the following reasons: the bleeding was emotionally difficult to see, the anxiety involved with the waiting between the injection and the misoprostol, waiting for pregnancy to pass, severe cramping and treatment failure. Their abortion did not appear so easy and quick as they had expected.

Patients that were fairly satisfied stated that they faced some emotional difficulty with their decision to have an abortion but said they would choose a medical abortion again. Other reasons included medication side effects and multiple hospital visits. There was a concern for the distance between the hospital from their residence, they probably wished to avoid the extra hospital visit that may be necessary with medical abortion.

Discussion

Methotrexate (mtx) is believed to destabilize the trophoblastic attachment to the decidua. Effects of Mtx induced trophoblast cytotoxicity has been evidenced by abnormal rate of β-hCG increased by 7th day after the injection in studies done earlier (Creinin and Darney (1993) Stovall and Ling (1993). β-hCG estimations were not done in this study due to cost factor and multiple visits required which was not a part of the protocol. In a trial using Mtx alone for inducing abortion, all pregnancies eventually aborted but after a delay of 24 ± 10 days (range is 7 – 46 days).

Misoprostol alone has been evaluated for 1st trimester abortion (Koopsmith and Mishell (1996). The success rate is still unacceptably low compared with the use of misoprostol following mifepristone or methotrexate for early abortion. However a recent study using multiple dose misoprostol at a set interval showed equivalent results (Carbonell et al 1997).

Table IX shows a comparison of the success rates obtained in similar studies done by various authors in the past. The success rate obtained in this study was comparable to those achieved by the other authors.

Table IX: Comparison of success rates

Author	Year	Success Rate (%)
Present Study	1997 – 99	93
Crenin MD et al	1994	90
Klaise et al	1995	98
Hausknecht R et al	1995	96
Darney P et al	1996	93
Wiebe ER et al	1996	92
Krohn et al	1997	94

In this trial, 39 of 42 patients passed pregnancy after an initial or repeat dose of misoprostol. In the remaining 3 patients that failed to abort, the cytotoxic effect of mtx on the early trophoblast caused descent of early embryonic development. In this study, the misoprostol was repeated after 24 hours in one case to achieve success. Probably she would have aborted if more time was given. It would be worth evaluating whether repeat dose is required at all.

Like mifepristone / prostaglandin abortion, the effectiveness of methotrexate / misoprostol appears to diminish with increasing gestational age. A trend for failure with increasing gestational age was also seen in a report earlier (Creinin and Vittinghoff 1994) although

it did not quite reach statistical significance. As compared to when methotrexate and misoprostol is used for abortion at < 56 days gestation, this regimen for gestational age < 63 days is less successful (90% vs. 60%).

This study demonstrates that the effectiveness is greater at < 49 days as compared to 50 – 56 days gestation. This dose may not be sufficient to reliably cause cessation of embryonic cardiac activity in gestations > 49 days. The efficacy of this regimen falls substantially with time, and by 7 weeks from LMP, the efficacy rates approach only about 83%; this may represent the better implantation into the deciduas by the trophoblast.

The mean duration of vaginal bleeding and spotting for women with complete abortion was less than 12 days. Vaginal bleeding was prolonged but not heavier than spotting after the 10th day. The length of bleeding may reflect the manner in which mtx acts to disrupt the supporting trophoblast or the ability of misoprostol to effect complete expulsion at various gestational ages. The total number of bleeding days for immediate success subjects was slightly greater than that reported in a French study that used oral administration of 400μg of misoprostol and 600 mg of mifepristone (12 vs 10 days) (Peyron et al 1993, Creinin 1994).

Earlier studies using mtx for abortion reported nausea in 10% and headache in 3%, although the incidence of side effects did not differ greatly from those women who did not receive mtx (Creinin et al 1995). In the present study side effects from mtx occurred in 11 (22.2%) patients and were short term, self-limited. The gastrointestinal side effects were minor and occurred in 7 (16.7%) of patients.

Undesired side effects from vaginal misoprostol were also infrequent. In studies done using mifepristone and misoprostol, a comparison of route of administration in terms of oral and vaginal showed that the incidence of side effects were significantly decreased with the intra-vaginal route (Creinin and Darney (1993).

In our study, 95% of women were satisfied with the treatment. However, women in this study had elected to have a medical abortion vs. a surgical abortion and hence may have been biased in favour of this method. The most common reasons stated for liking this method were avoidance of surgical procedure, ease with which the abortion occurred and it's privacy.

Congenital anomalies in continuing pregnancy are a concern. Mtx is an antimetabolite, which could damage the fetus carried to term after intrauterine exposure. Just as concerning is the use of misoprostol in first trimester, which has been associated with a specific type of anomaly: Mobius sequence with or without limb deficiency. However future fertility and congenital anomalies in subsequent pregnancies are not affected by mtx as evidenced by its use in the treatment of gestational trophoblastic disease (Creinin and Darney, 1993, Cremin 1994, O'Neill et al 1976).

The clinical experience reported here provides substantial evidence that the termination of early pregnancy (< 63 days gestation) with the combination of low dose mtx and intravaginal misoprostol is simple, safe and effective. Efficacy is more when the gestation is < 49 days. Further it is well tolerated, highly acceptable, easy to monitor with vaginal ultrasound, readily available and inexpensive.

References

1. Carbonell JLL, Varela L, Velazco A, Fernandez C: T; Contraception 55: 165, 1997.
2. Creinin MD, Darney PD; Contraception 48: 339, 1993.
3. Creinin MD, Vittinghoff E, Galbraith S, Klaise C; Am J Obstet Gynecol 173: 1578, 1995.
4. Creinin MD, Vittinghoff E.; JAMA Vol 272; no. 15: 1190, Oct. 1994.
5. Creinin MD; Contraception 50: 511, 1994.
6. Koopesmith TB, Mishell Jr DR; Contraception ; Apr 53 (4): 237, 1996.
7. O'Neill E, Pelegrina I, Hammond CB, Vicens R.; Cancer 38: 984, 1976
8. Peyron R, Aubeny E, Targosz V, Silvestre L. ; N Engl J Med 328 : 1509, 1993
9. Stovall TG, Ling FW; Am J Obstet Gynecol 168: 1759, 1993.