Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

The Comparative Analysis of the Effectiveness of Inj. Methotrexate and Tab Mifepristone vs Inj. Methotrexate alone in the Medical Management of Ectopic Pregnancy

Dr. Vinita Goel[1], Dr. Swati Kumari[2], Dr. Richa Kumari[3],

Dr.Madhuri Akhilesh Agnihotri[4]

1. Dr. Vinita Goel, Associate Professor, Department of Obs and Gynae, NCMCH, Israna, Panipat, Haryana, drgoelvinit@gmail.com
2. Dr. Swati Kumari, Senior Resident , Department of Obs and Gynae, NCMCH, Israna, Panipat, Haryana, swati.pmch1623@gmail.com
3. Dr. Richa Kumari, Senior Resident , Department of Obs and Gynae, Patna, Bihar, richa2108j@gmail.com
4. Dr.Madhuri Akhilesh Agnihotri, Professor, Department of Biochemistry, SSIMS, Bhilai

Corresponding Author:

Dr.Madhuri Akhilesh Agnihotri, Professor, Department of Biochemistry, SSIMS, Bhilai, agnihotrim19@gmail.com

Abstract

Background: Recent trends in ectopic pregnancy morbidity and the percentage of young, childless patients make it critical to identify EP early to save patients' lives and preserve their fertility to the fullest extent possible. The most commonly used conservative therapies are methotrexate and mifepristone, but it is impossible to determine which treatment is superior. **Aim and Objective:** The Comparative Analysis of the Effectiveness of Inj. Methotrexate and Tab Mifepristone vs Inj. Methotrexate alone in the Medical Management of Ectopic Pregnancy. **Material and Method:** This was a randomized control trial. Patients with a progressing ectopic pregnancy meeting criteria for medical management were included in the study. Patients were assigned to two groups based on random selection. Group 1 was given a combination of 200 mg of Tab mifepristone and inj. Methotrexate IM (50 mg/m2). Group 2 received only injections of methotrexate. The dose of methotrexate was repeated depending on the individual patient's response. **Results and Conclusion:** In terms of success rate and the requirement for a second dosage of methotrexate, there was no statistically significant difference between the two groups. However, employing a combination therapy instead of just methotrexate for medical care resulted in a quicker resolution of the ectopic pregnancy and a shorter hospital stay. p=0.002275.

Introduction

Ectopic pregnancy, which primarily involves fallopian tube pregnancy, occurs when a blastocyst is implanted outside the uterus. Ectopic pregnancy is one of the main causes of maternal death and a common acute clinical abdominal condition in

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

obstetrics and gynecology. The frequency of ectopic pregnancy has been rising steadily over the past few years, with a younger patient trend.

Ectopic pregnancy affects 1–2% of women worldwide (1). In India, it ranges from 0.3 to 0.7%. Ectopic pregnancies are on the rise right now. The number of infertility patients using assisted reproductive techniques has increased, and tubal reanastomosis and sterilization treatments have also increased. The development of transvaginal ultrasonography and beta-hCG testing has made it possible to detect ectopic pregnancy early. Serum beta-hCG and USG are used to diagnose ectopic pregnancy.

With documented intrauterine pregnancy, the risk of coexisting ectopic (heterotopic) pregnancy is approximated at 1 case in 10,000 patients to 1 case in 30,000 [2, 3]. The risk increases to approximately 9 case in 10000 patients if the woman is being treated for infertility [4].

When serum beta HCG levels are between 1500 and 1800 mIU/ml, a transvaginal ultrasound can detect the gestational sac. It can diagnose multiple pregnancies at a level of roughly 2300 mIU/ml. Ectopic pregnancy does not show the same doubling of serum beta-Hcg titre in 48–72 hours as intrauterine pregnancy. [5] Risk factors for ectopic pregnancy are strongly associated with conditions that cause alterations to the normal mechanism of Fallopian tube transport. It is postulated that the more damage that occurs to the Fallopian tube, the higher the risk of developing an ectopic pregnancy. This damage may result from a number of factors, such as infection, surgery, congenital anomalies, or tumors. Many potential risk factors have been reported in the literature, some with good evidence and others with less convincing data. There is good evidence to support the following as risk factors for developing an ectopic pregnancy: history of previous ectopic pregnancy, previous tubal surgery, tubal ligation, tubal pathology, in utero diethylstilbestrol exposure, and current use of an intrauterine device (IUD) [6].

Methotrexate is an anti-tumor drug, mainly anti-folate. MTX binds effectively with folate reductase pharmacologically and strongly inhibits dihydrofolate reductase in a competitive way, so that dihydrofolate cannot be transformed into tetrahydrofolate, which acts as a coenzyme in the synthesis of purine nucleotides and thymine nucleotides, thus destroying the synthesis of DNA and competitively inhibiting the effective synthesis of DNA, RNA, and other proteins. So it is a commonly used clinical anti-tumor immunosuppressant.

Mifepristone combined with methotrexate for ectopic pregnancy treatment was first reported by Perdu in 1998 [7]. This pioneering study compared the curative effect of combination therapy with that of methotrexate therapy, reaching the conclusion that combination therapy can dissolve trophoblast cells more quickly than methotrexate therapy, so combination therapy has a lower risk of rupture of the fallopian tube or peritoneal hemorrhage.

In a non-randomized phase II study (Perdu et al., 1998), patients treated with mifepristone and methotrexate had a failure rate that was much lower than patients previously treated with methotrexate alone. According to the interval until resolution of b-hCG levels in a randomized controlled trial (Gazvani et al., 1998), unruptured ectopic pregnancy appeared to resolve substantially more quickly with the

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

combination of methotrexate and mifepristone than with methotrexate alone. Therefore, the purpose of this study was to evaluate the effectiveness of combination therapy for the effective medical management of ectopic pregnancy.

Material and Methods

The study was conducted between 2022 and 2023 at the Department of Obstetrics and Gynecology at NCMCH, Panipat, Haryana. 80 women with ectopic pregnancies meeting the criteria for medical management were counseled to participate in this study.

Exclusion Criteria

- Hemodynamically unstable patient
- Gestational sac, >4 cm on TVS
- Serum beta-HCG >4000 mIU/ml
- Cardiac activity is present in the sac
- The patient is not agreeing for follow-up
- Patients with hepatic and renal or skin disease

Inclusion Criteria

- hemodynamically stable patients,
- G sac size <4cm on TVS.
- Serum beta-HCG levels <4000 mIU/ml
- Cardiac activity absent on TVS
- Patients is agreeing for follow up.
- Serum beta-HCG level , UPT, and USG were done for all the patients. A detailed history of symptoms and past medical history was recorded. Physical exam findings and vitals are recorded. A complete haemogram, RFT, and LFT were done.
- Blood grouping typing was done for all the patients, and those who were RH negative were given anti D Inj.
- All patients received an IM Injection of Methotrexate 50 mg/sqm of Body surface area, a single dose of oral mifepristone 200 mg for patients in group 1, and a inj Methotrexate for patients in group 2.
- Patients underwent close follow-up. They were reviewed on days 4 and 7.
- All women had serial serum β-hCG, hepatic and renal function tests, and full blood counts on each visit.
- If β-hCG levels dropped by >15% between days 4 and 7 of Inj. Methotrexate then women were reviewed weekly until beta-HCG falls below 5 MIU,
- Patients were instructed to refrain from alcohol and intercourse, to avoid vitamin preparations containing folic acid until complete resolution of the ectopic pregnancy, and to use barrier contraception for 3 months after treatment completion.
- Repeat transvaginal scanning was performed to rule out rupture of an ectopic pregnancy if the patient presented with increasing abdominal pain. When gestational cardiac activity was seen at treatment initiation, transvaginal scanning was performed on alternate days until cardiac activity disappeared.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

Repeated clinical pelvic examinations were not performed in any patients to avoid the potential of iatrogenic tubal rupture after treatment initiation.

- Surgical treatment was indicated if the β-HCG level had not decreased sufficiently after day 14 and if pelvic pain was not controlled by non-opiate analgesics or if signs of internal hemorrhage developed.

Outcome

The primary outcome was the success rate of the medical treatment, defined by the absence of an indication for surgical intervention before serum β-HCG levels were below 5 mIU/ml, irrespective of the number of injections of methotrexate.

The secondary outcomes were:

efficacy criteria: indications for surgical intervention, surgical modalities, need for a second dose of methotrexate, number of days in hospital, time interval from randomization to fall in β-HCG levels to 5 mIU/ml.

safety and tolerance criteria: gastritis, stomatitis, reversible alopecia, increase in serum aminotransferase concentrations, severe neutropenia, or thrombocytopenia.

Statistical Analysis

The collected data were coded, then entered and analyzed using SPSS version 16. The following tests were used: Descriptive analysis of the results in the form of percentage distribution for qualitative data and minimum, maximum, mean, and standard deviation calculations for quantitative data

Obsession and Results

Group 1

Out of the 40 cases treated with mifepristone and methotrexate, 34 cases resolved completely. The success rate was 85%. Three patients required surgical intervention due to a failure of medical management. (15%). Six patients required a second dose of methotrexate. The average time taken for a complete resolution was 21 days. The average duration of a hospital stay was 7 days.

Group 2

Out of the 40 cases in group 2, 28 were successfully managed with methotrexate, with a success rate of 70%. 12 cases needed surgical intervention. Failure rate of 30%. 10 out of the 28 cases required a second dose of methotrexate. The average time taken for a complete resolution was 28 days. The average duration of a hospital stay was 12 days.

Statistical Analysis

The collected data were coded then entered and analyzed using the SPSS version16. The following tests were used: Descriptive analysis of the results in the form of

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

percentage distribution for qualitative data and (minimum, maximum, mean and standard deviation) calculation for quantitative data.

Observation and Results

Group 1

Out the 40 cases treated with mifepristone and methotrexate 34 cases resolved completely. The success rate was 85%. Three patients required surgical intervention due to failure of medical management.(15%). 6 patients required a second dose of methotrexate. The average time taken for a complete resolution was 21 days. The average duration of hospital stay was 7 days.

Group 2

Out of the 40 cases in group 2, 28 cases were successfully managed with methotrexate with a success rate of 70 %. 12 cases needed surgical intervention . Failure rate of 30%. 10 out of the 28 cases required a second dose of methotrexate. The average time taken for complete resolution was 28 days. Average duration of hospital stay was 12 days.

Analysis of Study

Table 1-Success Rate

	Success	**Failed medical management**
Group1	34 (85%)	6 (15%)
Group2	28 (70%)	12 (30%)

Chi square value-1.2903 and P-value of 0.255989 which was not significant statistically at $p \geq 0.005$. Thus the combination of mifepristone and methotrexate in medical management was not statistically significant .

Table 2 Need for Second Dose of Methotrexate

	2nd Dose of Methotrexate	**1st Dose of Methotrexate**
Group1	6	28
Group2	10	18

chi quare- 1.3089 p value-0.252595 not statistically significant at $p \geq 0.005$. The combination of drugs did not alter the requirement of a 2nd dose methotexrate.

Table 3-Time taken for Resolution

	<3weeks of Resolution	**>3weeks of Resolution**
Group1	26	8
Group2	3	22

The chi square test -9.3136 P=0.002275. Highly significant.65% of patients in group 1 showed complete resolution in less than 3 weeks as compared to 15% in group 2

Table 4-Duration of Hospital Stay

	Duration of the Days
Group1	7
Group2	12

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

The average duration of hospital stay in group 1 was 7 days whereas in group 2 it was 12 days.The difference was statistically significant.

Discussion

In this study, combination therapy for the medical management of ectopic pregnancy did not show a significant success rate when compared to methotrexate, which is supported by another study published by Patrick et al. [8]. USG is the most important tool for the diagnosis of ectopic pregnancy. Color flow doppler USG helps in the better detection of ectopics by increasing the sensitivity or specificity. Ectopic pregnancy can be treated medically or surgically. [9]

Patients with ectopic pregnancy who are young and childless should accept conservative treatment for the reasons that the function of the oviduct can be protected from damage and an optimal treatment effect can be achieved. Methotrexate is a folic acid antimetabolite as well as a preferred medicine to treat ectopic pregnancy. And mifepristone is a progestin antagonist, which can also destroy the embryo. However, there are limitations if only mifepristone is used. On the contrary, mifepristone combined with methotrexate to treat ectopic pregnancy can achieve mutual advantages and interaction, which brings advantages and potential in clinical application.

Medical Management

Only methotrexate has been extensively studied as an alternative to surgical therapy [10]. De novo purine and pyrimidine synthesis is halted, which leads to arrested DNA, RNA, and protein synthesis. Thus methotrexate is highly effective against rapidly proliferating tissue such as trophoblasts, and overall ectopic tubal pregnancy resolution rates approximate 90% with its use.

For ease and efficacy, IM The injection of methotrexate is used most frequently for ectopic pregnancy resolution. Single-dose and multi-dose protocols are available. Single-dose therapy offers simplicity, less expense, and less intensive post-therapy monitoring and does not require leucovorin rescue. However, some but not all studies report a higher success rate for the multidose regime.

Treatment Regimen.

Day 1: Give methotrexate 50mg/m2 IM. Day 4: Measure the quantitative hCG level (it is common to see a rise in serum hCG levels from Day 1).

Day 7: Measure the quantitative hCG level.

If there has been a decline of >= to 15% from the Day 4 level, follow serum hCG levels weekly until b-Hcg falls below 5 miu. A second dose of methotrexate 50mg/m2 IM should be given to the patient (new Day 1), and hCG levels should be measured again on Day 4 and Day 7 after the second dose. If values decline by > or = 15%, follow serum levels weekly until b-Hcg falls below 5 miu.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

If there is an inappropriate decline in serum hCG levels after a second dose of methotrexate, the patient should be re-evaluated, and therapy with additional methotrexate or surgical intervention is required.

Multi dose Methotrexate

Administer methotrexate (1mg/kg IM) on days 1, 3, 5, and 7. Administer leucovorin 0.1 mg/kg on days 2, 4, 6, and 8.Measure serum β-HCG levels on days 2, 4, 6, and 8 until there is a 15% decrease between two measurements. Once β-HCG levels drop by 15%, stop methotrexate and monitor β-HCG levels weekly until they reach non-pregnant levels.

Absolute Contraindications to Methotrexate Treatment

Haemodynamically unstable

Ruptured ectopic pregnancy.

Preexisting blood dyscrasias, active pulmonary disease, hepatic, renal, or hematological disorders, or immunodeficiency

Relative Contraindications

Gestational sac larger than 4 cm

Embryonic cardiac motion

Role of mifepristone in managing ectopic gestation

Mifepristone is a 19-norsteroid with potent competitive antiprogestational as well as antiandrogenic activity. It blocks progesterone support for the endometrium and stimulates uterine contractions. If implantation has occurred, it blocks decidualization, and the conceptus is dislodged.

Conclusion

The combination therapy has been found to hasten the time taken for resolution of β-HCG as well as the duration of hospital stay, as supported by our study, but failed to demonstrate a superior success rate when compared with methotrexate alone. However, larger trials are required to prove the efficacy of combination therapy versus methotrexate alone for the successful management of ectopic pregnancy.

Reference

1. Centers for Disease Control and Prevention (1995) Ectopic pregnancy, United States, 1990, 1992 MMWR Morb. Mortal. Wkly Rep., 44, 46–48.
2. Reece EA, Petrie RH, Sirmans MF, et al. Combined intrauterine and extrauterine gestations: a review Am J Obstet Gynecol 1983;146(3):323–30.
3. Condous G. Ectopic pregnancy risk factors and diagnosis. Aust Fam Physician 2006; 35(11):854–7.

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE8, 2023

4. Ludwig M., Kaisi M., Bauer O., et al. Heterotopic pregnancy in a spontaneous cycle: do not forget about it! Eur J Obstet Gynecol Reprod Biol 1999;87(1):91–3.
5. Corsan, G.H., Karacan, M., Qasim, S., et al. Transvaginal sonography and human chorionic gonadotrophin measurements in suspected ectopic pregnancy: a detailed analysis of a diagnostic approach Hum. Reprod., 8, 1307–1311.
6. Ankum WM, Mol BW, Van der Veen F, et al., Risk factors for ectopic pregnancy: a metaanalysis. Fertil Steril 1996;65(6):1093–9.
7. Marc Perdu, Erick Camus, Patrick Rozenberg, et al. Treating ectopic pregnancy with the combination of mifepristone and methotrexate: A phase II nonrandomized study 1998, 179(3):640-643.
8. Patrick Rozenberg, Sylvie Chevret, Eric Camus,et al., Olivier Garbin: Treatment of Ectopic Pregnancies: A Randomized Clinical Trial Comparing Methotrexate, Mifepristone, and Methotrexate PlaceboJournal of Human Reproduction, European Society of Human Reproduction and Embryology, 2003, 18(9), all rights reserved.
9. Alexander, J.M., Rouse,et al. (1996). Treatment of the small unruptured ectopic pregnancy: a cost analysis of methotrexate versus laparoscopy. Obstet. Gynecol., 88, 123–127.
10. ACOG Practice Bulletin (1999) Medical management of tubal pregnancy Int. J. Gynecol. Obstet., 65, 97–103