

2

Original article

Doi: 10.5281/zenodo.13198207

A COMPARISON OF SINGLE-DOSE AND TWO-DOSE METHOTREXATE PROTOCOLS FOR THE TREATMENT OF UN-RUPTURED ECTOPIC PREGNANCY- A RETROSPECTIVE STUDY

Bushra Shakil¹

Humaira Tabassum²

Azmat Jahan³

Syed Nawaz Ahmad⁴

1= Senior Resident Obstetrics and Gynaecology Government Medical College Anantnag

2= Senior Resident Obstetrics and Gynaecology SKIMS Medical College, Bemina

3= Senior Resident Obstetrics and Gynaecology SKIMS Soura

4= Associate Professor and In charge Head Department of Obstetrics and Gynaecology Government Medical College Anantnag

Abstract

Introduction: Ectopic pregnancy (EP) is a significant cause of maternal morbidity and mortality, particularly in developing regions like India. Methotrexate, administered either as a single-dose or multiple-dose regimen, is commonly used for medical management of EP. This study aims to compare the efficacy and safety of these two regimens in women from Jammu and Kashmir, India.

Materials and Methods: This observational analytical study was conducted retrospectively over six months at Government Medical College Anantnag. A total of 90 women with EP were admitted, of which 32 were managed medically with methotrexate. Fourteen patients received the multiple-dose regimen, while the remaining 18 were treated with the single-dose regimen. Data on sociodemographic characteristics, clinical presentations, treatment outcomes, and adverse events were collected and analyzed.

Results: The majority of participants were aged between 25-29 years. Nulliparity was observed in 47.1% of the single-dose group (group S) and 71.4% of the multiple-dose group (group M). Common symptoms included abdominal pain (88.2% in group S, 92.9% in group M), amenorrhea, and vaginal bleeding. Ampullary pregnancy was the most common type of EP (82.4% in group S, 50% in group M). The success rate was significantly higher in the multiple-dose group (85.7%) compared to the single-dose group (58.8%) ($p=0.013$). Adverse events such as nausea and vomiting were reported by 10 participants in group M and 6 in group S. Both groups had similar ICU admission rates (four each), and no fatalities were recorded.

Conclusions: The multiple-dose methotrexate regimen demonstrated a significantly higher success rate in the management of EP compared to the single-dose regimen. Although the multiple-dose group experienced more adverse events, these differences were not significantly different. These findings support the preferential use of the multiple-dose regimen for better efficacy.

Keywords: Ectopic pregnancy, methotrexate, single-dose regimen, multiple-dose regimen, treatment outcomes, adverse events,

Introduction

Ectopic pregnancy is a serious and potentially life-threatening condition that occurs when a fertilized egg implants outside of the uterus, typically along the reproductive tract, most commonly in the fallopian tube.¹ Ectopic pregnancies account for about 2% of all pregnancies and are a leading cause of maternal mortality.² Ectopic pregnancies have also been reported to occur concurrently with an intra-uterine pregnancy, a condition known as a heterotopic pregnancy.³ Ectopic pregnancy is a global problem, occurring in pregnancies throughout the developed as well as the developing world, such as in India. Alarmingly still, the incidence of ectopic pregnancy has been increasing in recent years due to a variety of factors, including an increase in the number of women delaying pregnancy until later in life, the use of assisted reproductive technology, and an increase in the prevalence of pelvic inflammatory disease.⁴

India still has a high burden of maternal morbidity and mortality, with a significant proportion of these deaths being attributed to ruptured ectopic pregnancies.⁵ The risk factors for an ectopic pregnancy include previous ectopic pregnancies, pelvic inflammatory disease, tubal surgery, and use of assisted reproductive technology. However, not all patients with these risk factors will experience a rupture, and some patients without any known risk factors may still experience a rupture.⁶ Medical management of ectopic pregnancy with methotrexate, a folic acid antagonist, involves either a single-dose or a multi-dose regimen. The single-dose protocol typically involves administering 50 mg/m² of methotrexate intramuscularly, followed by monitoring hCG levels to ensure a decline. In contrast, the multi-dose regimen alternates methotrexate (1 mg/kg) with leucovorin (0.1 mg/kg) over several days. Both regimens aim to terminate the ectopic pregnancy by inhibiting rapidly dividing cells, with success rates ranging from 70-95% depending on the initial hCG levels and the absence of embryonic cardiac activity. Medical management of EP with MTX has been demonstrated to be more cost-effective than surgical

management while maintaining similar treatment success and future fertility.^{7, 8} However, research comparing the two modalities between each other is scarce.

Aims and Objectives

The aim of the present study was to compare the outcomes of ectopic pregnancies managed with either single dose methotrexate or multiple dose methotrexate regimes presenting to a referral hospital of Jammu and Kashmir, India.

The specific objectives of the present study were:

- To study the management outcome in terms of success rate between the two regimens
- To compare the outcome in terms of morbidity and mortality following ectopic pregnancy

Materials and methods

Study type and design: The present study was an observational analytical study with a retrospective design.

Study area: The present study was conducted in the Department of Obstetrics and Gynaecology, Government Medical College Anantnag, India.

Study period: The study was conducted over a period of 6 months (December 2021 to June 2022).

Study population: The study population for the present study consisted of all patients who presented to the study institution and were diagnosed as ectopic pregnancy.

Inclusion criteria:

- All cases diagnosed with ectopic pregnancy.
- Certainty that there is no intrauterine pregnancy.
- Willingness for follow-up

Exclusion criteria:

- Any intrauterine pregnancy

- Any history of blood dyscrasia, deranged liver function tests, or deranged renal function tests, and sensitivity to methotrexate in cases where medical management was planned.

Ethical clearance:

Proper ethical clearance was obtained from the Institutional Ethics Committee of the study institution.

Study sample:

A thorough records review was done in order to recruit all patients presenting to the study institution with a diagnosis of ectopic pregnancy between Dec 2021 and June 2022. All patients who were managed by means of medical management with either single dose or multiple doses of methotrexate were recruited into the present study.

Study technique

A comprehensive record-review was conducted to access the medical records of all patients presenting to the study institution with a diagnosis of ectopic pregnancy between Dec 2021 and June 2022 to the department of Obstetrics and Gynecology of the study institution. From the records, a list of patients managed with medical regimens (single-dose or multiple-dose methotrexate) were identified and recruited as the sample for the present study. A predesigned pretested proforma was used to collect the data regarding the sociodemographic and clinical characteristics of the patients, and the recruited sample of patients were divided into single dose methotrexate group (Group S) and multiple-dose methotrexate group (Group M). Those in group S were treated with 50 mg/m² IM methotrexate for a single dose and those in group M were managed with 1 mg/kg IM methotrexate, alternating with 0.1 mg/kg leucovorin IM (with up to four daily doses of each drug).The records of the individual patients of either of the two groups were assessed to obtain data regarding their treatment and obstetric outcomes.

Statistical analysis:

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD and categorical variables were summarized as frequencies

and percentages. In cases where analytical statistics were done, a p-value of <0.05 was considered statistically significant.

Results

Over the period of study, 90 ectopic pregnancy cases were admitted to the study institution. Of them, 32 (35.6%) were managed medically. Of these patients 14 were managed with multiple dose methotrexate, and the rest were managed with single dose methotrexate regimen. Most of the women were aged between 25-29 years, with the mean age of the group S participants being 31.2 ± 3.1 years and that of the group M participants being 30.6 ± 5.8 years. It was seen that majority of the participants in both the group S (8/18, 47.1%) as well as group M (10/14, 71.4%) were nulliparous. The women in either of the two groups were not significantly different from each other with respect to their age and parity. (Table 1)

Majority of the women in either of the two groups presented with abdominal pain (88.2% in group S and 92.9% in group M, p-value 0.665). This was followed by amenorrhea (76.5% in group S, 85.7% in group M, p-value 0.517), and vaginal bleeding (64.7% in group S, 78.6% in group M, p-value 0.397) respectively. Regarding signs, abdominal tenderness was present in 76.5% of the group S patients and 71.4% of the group M patients (p-value 0.750), while adnexal tenderness was present in 52.9% of the group S and 50% of the group M patients (p-value 0.970). Ampullary EP was the commonest type of EP in the participants (82.4% in group S, 50% in group M), followed by fimbrial (5.9% in group S and 21.4% in group M) and isthmic (11.8% in group S and 28.6% in group M) respectively. (Table 2)

It was seen that those patients treated with multiple doses of methotrexate had a statistically significantly higher success rate (85.7%) as compared to those treated with single dose of methotrexate (58.8%, p-value 0.013). Of the two groups of women, 4 each were admitted to the intensive care unit (ICU), and none of the women died. (Table 3)

Discussion

This study was conducted in order to compare between single and multiple dose regimens of methotrexate in the management of ectopic pregnancies among women in Jammu and Kashmir. In the assessment of 26 women presenting with the condition, it was seen that a substantial proportion of ectopic pregnancies among women in their late twenties. Most of the women were

in the age group of 25-29 years, with the mean age being 31.2 ± 3.1 years for group S and 30.6 ± 5.8 years for group M. This finding is consistent with global trends where ectopic pregnancies are most common in women aged 25-35, a period characterized by high reproductive activity.⁹ Similar reports regarding age distribution of women presenting with ectopic pregnancy have been made by Alleyasin et al. and Ranji et al. in their studies.¹⁰ ¹¹Regarding parity, the study found that 47.1% of the women in group S and 71.4% in group M were nulliparous. This aligns with literature suggesting that nulliparous women might have a higher risk due to undiagnosed tubal abnormalities or infections. In their studies on the topic, Din et al. and Negewo et al. also reported that the highest proportion of participants with ectopic pregnancies were nulliparous women.^{12, 13}

The clinical presentation of ectopic pregnancies in this study closely mirrors the symptomatology reported in broader medical literature. In the present study, most of the patients in either of the two study groups, came with abdominal pain, followed by amenorrhea, and vaginal bleeding. Regarding signs, abdominal tenderness and adnexal tenderness were found to be the common findings. Classical triad of pain abdomen, amenorrhea and vaginal bleeding was present in 6 (42.8%) of group S patients and 8 (44.4%) of group M patients. Shah et al. in their study observed abdominal pain as the most common clinical symptom in 37 (97.3%) cases followed by amenorrhea in 28 (73.6%) cases and vaginal bleeding in 22 (57.8%) patients. **Error! Bookmark not defined.** The classical triad of amenorrhea, pain abdomen and vaginal bleeding was present in 71.25% of cases in a study done by Mehta et al.⁹ Wakankar et al. and Rose et al. had also reported classic triad in 53.84% and 66% cases respectively.^{14, 15}

It was seen that the most common type of ectopic pregnancy in the present study was ampullary pregnancy, observed in 82.4% in group S and 50% in group M. This finding is consistent with existing literature as the ampullary region of the fallopian tube is the most frequent site for ectopic implantation due to its relatively larger diameter and slower transit time for the fertilized ovum.³ ¹⁶Isthmic pregnancies were the second most common, accounting for 20% of the cases. Isthmic ectopic pregnancies can be particularly dangerous because the narrower diameter of the isthmus makes it more prone to rupture early, often leading to significant internal bleeding.¹⁷ Fimbrial pregnancies occurred in 11.8% in group S and 28.6% in group M participants. These pregnancies occur at the distal end of the fallopian tube be managed

conservatively if diagnosed early, although the risk of tubal abortion remains high. The prevalence of isthmic and fimbrial ectopic pregnancies observed in the present study are similar to what has been reported by authors like Barnhart et al. and Din et al.^{13, 18}

The primary objective of this study was to compare the efficacy of single-dose versus multiple-dose methotrexate regimens in the management of ectopic pregnancies (EP). The findings of this study point to a statistically and clinically superior success rate with the multiple-dose regimen (85.7%) compared to the single-dose regimen (58.8%, p-value 0.013). This significant difference in success rates is consistent with findings from several other studies. For instance, a meta-analysis by Barnhart et al. reported that the multiple-dose regimen of methotrexate was more effective than the single-dose regimen in achieving complete resolution of ectopic pregnancies.¹⁸

The multiple-dose regimen involves administering methotrexate in conjunction with leucovorin rescue, typically over a period of several days. This approach ensures sustained therapeutic levels of methotrexate, which may enhance its cytotoxic effects on the trophoblastic tissue, thereby improving treatment efficacy.¹⁹ The single-dose regimen typically involves a single intramuscular injection of methotrexate, and its effectiveness relies heavily on the initial response of the ectopic tissue to the drug. In cases where the initial dose is insufficient, additional doses may be required, leading to a de facto multiple-dose treatment, which could complicate management and patient compliance. Lipscomb et al. noted that while the single-dose regimen is less invasive and requires fewer healthcare resources, it may necessitate closer follow-up and potential additional dosing, which can mitigate its convenience.²⁰

The difference in efficacy between the two regimens may also be influenced by the initial levels of β -hCG (human chorionic gonadotropin). Higher β -hCG levels have been associated with a lower success rate of the single-dose regimen, as the ectopic tissue is less likely to respond to a single dose of methotrexate. This study did not specifically stratify patients based on β -hCG levels, but the higher success rate of the multiple-dose regimen suggests that it may be more effective across a broader range of β -hCG levels.²¹

Another factor to consider is the location of the ectopic pregnancy. The multiple-dose regimen may be particularly advantageous in cases where the ectopic pregnancy is located in less accessible areas or is larger in size, requiring more aggressive treatment to achieve resolution.²²

The safety profile of both single-dose and multiple-dose methotrexate regimens was also evaluated in this study, with one of the objectives being the incidence of adverse outcomes and the need for intensive care. Both treatment groups had similar rates of ICU admissions, with four patients from each group requiring intensive care. Notably, there were no fatalities in either group, indicating that both regimens are relatively safe when managed appropriately. Methotrexate, being a cytotoxic drug, can have side effects such as nausea, vomiting, stomatitis, transient liver dysfunction, and bone marrow suppression.²³ In the multiple-dose group (group M), 6 participants experienced such adverse events such as nausea and vomiting, while in the single-dose group (group S), 8 participants reported similar symptoms (p-value 0.622). In their study, Alur-Gupta et al. also reported similar findings, noting that while multiple dose regimen was associated with higher incidence of adverse events, the difference was not statistically significant.²³ The comparable ICU admission rates between the single-dose and multiple-dose groups suggest that the increased dosing frequency in the multiple-dose regimen does not substantially elevate the risk of severe adverse outcomes.

Limitations

While the findings of the present study provide insights to the characteristics and outcomes of ectopic pregnancies in the region, it is limited by its sample size and single-hospital focus. Future research including larger, multi-center studies is therefore indicated to validate these findings and explore additional factors influencing ectopic pregnancy outcomes.

Conclusion

The findings of the present study showed that multiple dose methotrexate regimen was significantly better than single dose regimen in the management of ectopic pregnancies. While the multiple dose regimen was associated with a higher incidence of adverse effects, it was not significant, and the rates of intensive care were comparable between the two modalities.

Table 1. Sociodemographic and clinical profile of the study participants (n=90)

Parameters	Group S	Group M	p-value
Mean Age (years)	31.2±3.1	30.6±5.8	0.717
Parity			0.565
Nulliparous	8 (47.1)	10 (71.4)	
1	3 (17.7)	2 (14.3)	
2	1 (7.1)	4 (23.5)	
3	1 (7.1)	2 (11.8)	

Table 2. Ectopic pregnancy related characteristics of the study participants (n=90)

Parameters	Group S (%)	Group M (%)	p-value
Symptoms			
Abdominal pain	15 (88.2)	13 (92.9)	0.665
Amenorrhea	13 (76.5)	12 (85.7)	0.517
Vaginal bleeding	11 (64.7)	11 (78.6)	0.397
Signs			
Abdominal tenderness	13 (76.5)	10 (71.4)	0.750
Adnexal tenderness	9 (52.9)	7 (50.0)	0.970
Type			
Ampullary	14 (82.4)	7 (50)	0.154
Fimbrial	1 (5.9)	3 (21.4)	
Isthmic	2 (11.8)	4 (28.6)	

Figure1. Signs and symptoms in the study participants (n=90)

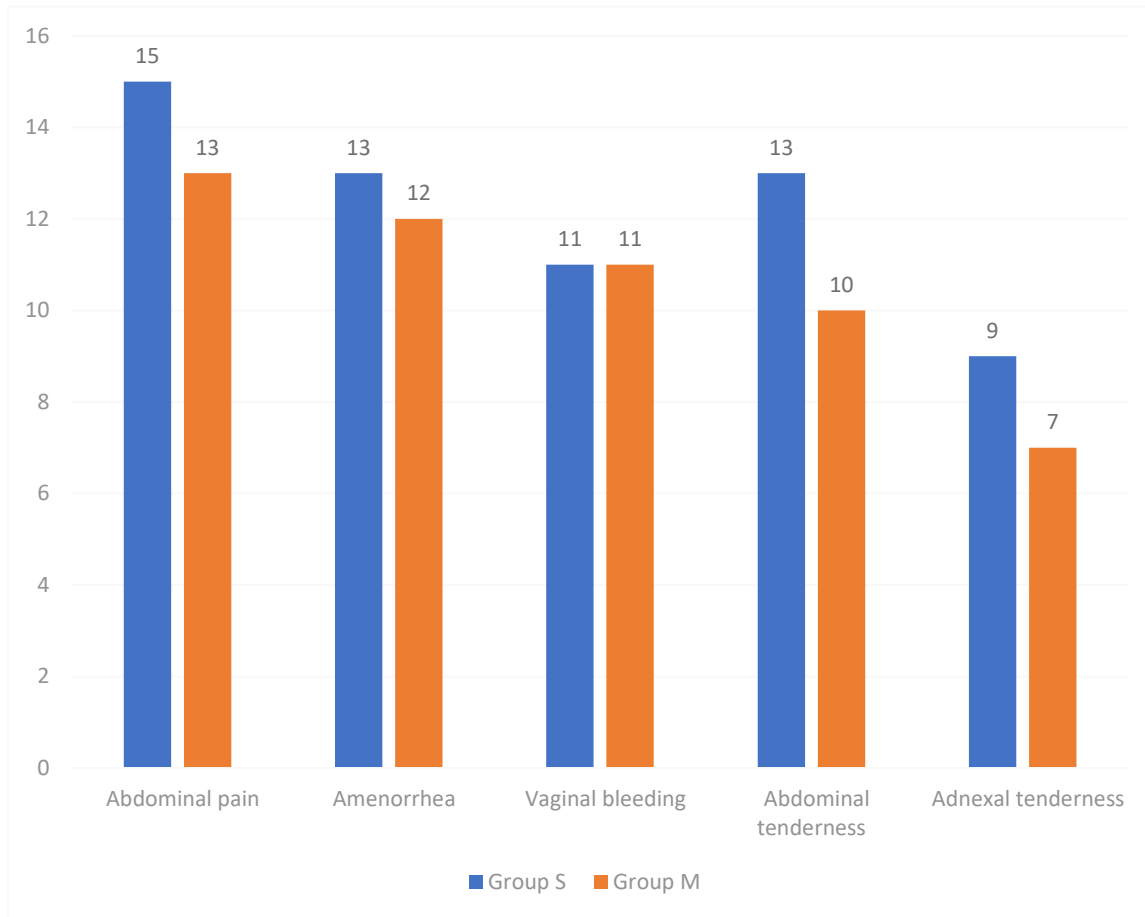
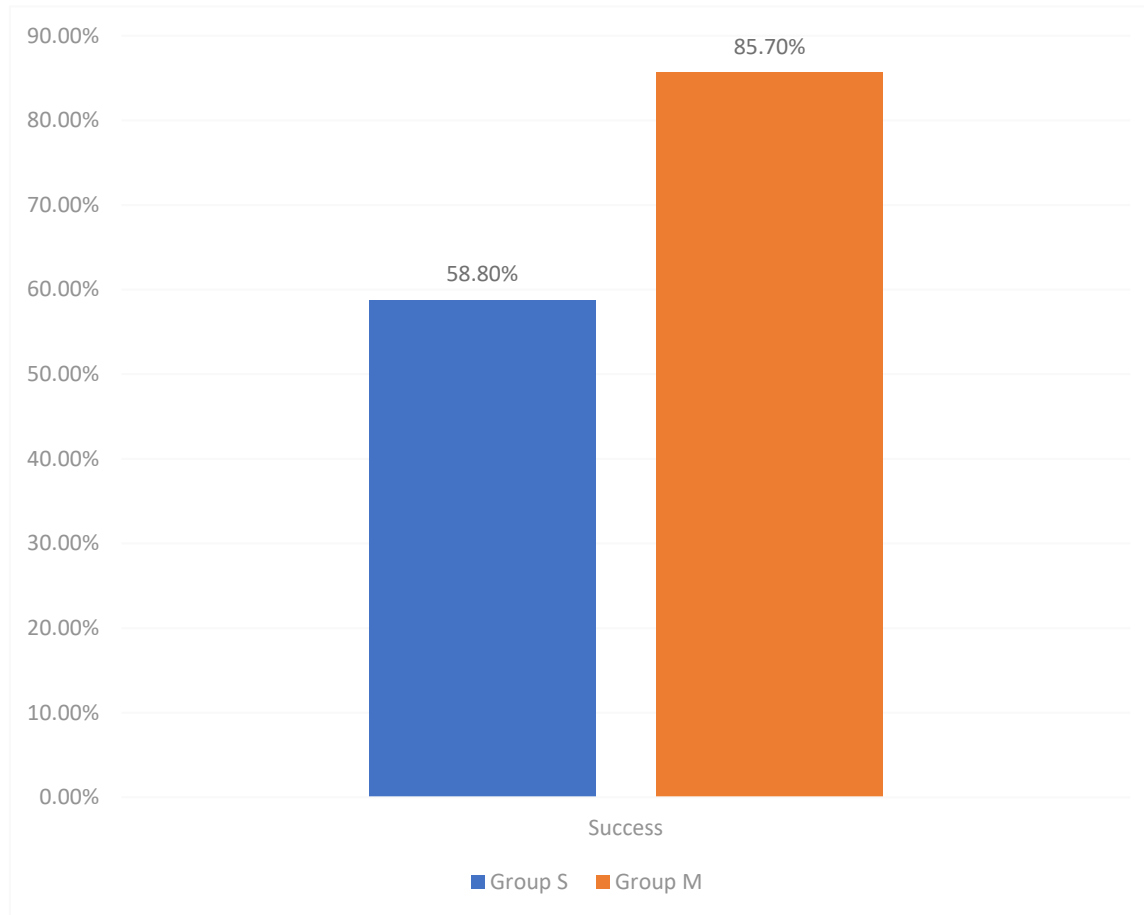


Table 3. Outcome characteristics of the study participants (n=90)

Parameters	Group S (%)	Group M (%)	p-value
Success	10 (58.8)	12 (85.7)	0.013*
Adverse event	8 (44.4)	6 (42.8)	0.622
ICU admission	4 (23.5)	4 (28.6)	0.750
Death	0	0	-

Figure 2. Success rate of the regimen in the study participants (n=90)

References

1 Te Linde's operative Gynecology. 12th ed. New Delhi: Wolters Kluwer; 2020. p. 695.

2 Lin EP, Bhatt S, Dogra VS. Diagnostic clues to ectopic pregnancy. Radiographics. 2008;28(6):1661-71.

3 Bouyer J, Coste J, Fernandez H, Pouly JL, Job-Spira N. Sites of ectopic pregnancy: a 10 year population-based study of 1800 cases. *Human Reproduction*. 2002;17:3224-30

4 Hoover KW, Tao G, Kent CK. Trends in the diagnosis and treatment of ectopic pregnancy in the United States. *Obstetrics and Gynecology*. 2010;115(3):495-502.

5 Verma ML, Singh U, Solanki V, Sachan R, Sankhwar PL. Spectrum of ectopic pregnancies at a tertiary care center of Northern India: a retrospective cross-sectional study. *Gynecology and Minimally Invasive Therapy*. 2022;11(1):36.

6 Sindos M, Togia A, Sergeantanis TN, Kabagiannis A, Malamas F, Farfaras A, et al. Ruptured ectopic pregnancy: risk factors for a life-threatening condition. *Archives of Gynecology and Obstetrics*. 2009;279:621-3.

7 Fernandez H, Pauthier S, Doumerc S, Lelaidier C, Olivennes F, Ville Y, et al. Ultrasound-guided injection of methotrexate versus laparoscopic salpingotomy in ectopic pregnancy. *Fertility and Sterility*. 1995;63:25-9

8Sadan O, Ginath S, Debby A, Rotmensch S, Golan A, Zakut H, et al. Methotrexate versus hyperosmolar glucose in the treatment of extrauterine pregnancy. *Archives of Gynecology and Obstetrics*. 2001;265:82-4..

9Mehta A, Jamal S, Goel N, Ahuja M. A retrospective study of ectopic pregnancy at a tertiary care centre. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*. 2017;6(12):5241-6.

10 Alleyassin A, Khademi A, Aghahosseini M, Safdarian L, Badenoosh B, Hamed EA. Comparison of success rates in the medical management of ectopic pregnancy with single-dose and multiple-dose administration of methotrexate: a prospective, randomized clinical trial. *Fertility and Sterility*. 2006;85(6):1661-6

11 Ranji GG, Rani GU, Varshini S. Ectopic pregnancy: risk factors, clinical presentation and management. *Journal of Obstetrics and Gynaecology of India*. 2018;68(6):487-92

12 Negewo AN, Feyissa GT, Diriba G, Gemedo DH, Kebede A. Prevalence and management outcome of ectopic pregnancy in Adama Hospital Medical College, East Shoa Zone, Oromia Region, Ethiopia. *EC Gynaecology*. 2019;8(9):844-50

13 Din M, Andleeb A, Nazir S, Basit S, Iqbal J. Role of laparoscopy in management of ectopic pregnancy. *British Journal of Pharmaceutical and Medical Research*. 2019;4(2):1794-800

14 Wakankar R, Kedar K. Ectopic pregnancy: a rising trend. *International Journal of Science and Study*. 2015;3(5):18-22

15 Rose J, Thomas A, Mhaskar A. Ectopic pregnancy: five years experience. *Journal of Obstetrics and Gynecology of India*. 2002;52:55-8

16 Sudha VS, Thangaraj DR. A retrospective study on ectopic pregnancy: a two year study. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*. 2016;5(12)

17 Job-Spira N, Collet P, Coste J, Brémond A, Laumon B. Risk factors for ectopic pregnancy. Results of a case control study in the Rhone-Alpes region. *Contraception FertilitéSexualité*. 1993;21(4):307-12.

- 18 Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. *Obstetrics and Gynecology*. 2003;101(4):778-84.
- 19 Bachman EA, Barnhart K. Medical management of ectopic pregnancy: a comparison of regimens. *Clinical Obstetrics and Gynecology*. 2012;55(2):440-7.
- 20 Lipscomb GH, Stovall TG, Ling FW. Nonsurgical treatment of ectopic pregnancy. *New England Journal of Medicine*. 2000;343(18):1325-9.
- 21 Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. *Annals of the Rheumatic Diseases*. 2009;68(7):1094-9.
- 22 Guvendag Guven ES, Dilbaz S, Dilbaz B, Aykan Yildirim B, Akdag D, Haberal A. Comparison of single and multiple dose methotrexate therapy for unruptured tubal ectopic pregnancy: a prospective randomized study. *Acta Obstetrica et Gynecologica Scandinavica*. 2010;89(7):889-95.
- 23 Alur-Gupta S, Cooney LG, Senapati S, Sammel MD, Barnhart KT. Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis. *American Journal of Obstetrics and Gynecology*. 2019;221(2):95-108

Conflict of interest Nil

Funding Nil

Acknowledge Nil

