International Journal of Medical and Health Research
ISSN: 2454-9142
Impact Factor: RJIF 5.54
www.medicalsciencejournal.com
Volume 3; Issue 10; October 2017; Page No. 49-53

A review of medical treatment of ectopic pregnancy with systemic methotrexate

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Abstract
Introduction: The aim of this review is to reassess the effectiveness of systemic methotrexate for the treatment of selected cases of ectopic pregnancy.
Materials & Methods: A retrospective review of 21 cases of ectopic pregnancy from October 2015 to June 2017 who received systemic methotrexate at MGM Medical College, Jamshedpur, Jharkhand.
Results: There were total of 21 cases included in the study who received systemic methotrexate. Of these 13 (62%) cases were successfully treated with single dose of injection methotrexate. Four patients (19%) required additional dose of injection methotrexate. Total 17 case out of 21 (81%) were successfully treated with systemic methotrexate.
Four cases (19%) who received single dose of inj methotexate underwent surgery (having failed medical treatment) for tubal abortion/tubal rupture.
Conclusion: With early diagnosis and adopting proper selection criteria medical treatment of ectopic pregnancy with systemic methotrexate is on effective and safe alternative to surgical treatment.

Keywords: serum beta human chorionic gonadotrophins (serum beta HCG), methotrexate, ectopic pregnancy

Introduction

Ectopic pregnancy occurs when a fertilized egg implants somewhere other than the main cavity of the uterus. Ectopic pregnancy account for 1.4% of all pregnancies and for approximately 15% of maternal deaths. It has three district methods of clinical presentation

1. **Acute:** Nearly 1/5th of all ectopic pregnancies which require urgent intervention (Surgery)
2. **Asymptomatic high risk:** Less than one fifth of cases fall in this group, with history of impaired tubal function, previous tubal surgery, previous ectopic pregnancy and inferlility cases undergoing ovaerian hyperstimulation in assisted reproductive technology (ART), etc. As they become biochemically pregnant, they are screened, followed up and managed very early before symptoms develop.
3. **Subacute cases:** Nearly 60-70% constitates this major group. They present with or without amenorrhea, regular vaginal bleeding and abdominal pain.

Current treatment approach is to use

(Transvaginal Sonography) TVS & urine β-HCG kits for early diagnosis of ectopic pregnancy which is than followed up in a controlled way monitoring blood concerntration of β-HCG coupled with Transvaginal Sonographic Guidance.

The objective is to treat the patients with minimal invasive sugery/surery if required or without sugery using medicine (methotrexate) and to send them back to their normal day to day life at the earliest with a treatment directed to restore tubal function.

Diagnosis of Ectopic Pregnancy

A paired serum β-HCG samples taken at least 48 hours apart may indicate fall, flattening or a rising trend of hormone concentration. If increase is less than 66% over 48 hours & equivalent to doubling time of 2.7 days) EP (ectopic pregnancy) is indicated and laparoscopy is recommended (KADAR *et at.* 1988) TVS always discerns intrauterine gestational sac when β-HCG is above discriminatory level (1,000-1,500 miu/ml) whereas empty uterus always suggests extraterine gestation.

Now a days

The use of TVCOS (transvaginal colour Doppler sonography) is used routinely to display the increased vascular areas randomly dispersed in the adnexal complex mass and assess the trophoblastic activities, which correlates well with β-HCG liter (Kurjak *et al.* 1994)

This prognosticates trophoblastic invasiveness and also differentiates an active trophoblast from nonviable (IUP) intrauterine pregnancy and psuedogestational sac.

Das *et al.* 2001

Three dimensional (UG) ultrasonography 3D Doppler used for confirming the diagnosis of ectopic pregnancy. This can also diagnose cornual or interstitial ectopic pregnancy with certaininty this is used for monitoring the vascularity of ectopic pregnancy which is treated conservatively by MTX Decreasing vascularity [lessening blood flow Indicates a regressing pregnancy. Methotxate is an antimetabolite that interferes with DNA synthesis and disrupts cell proliferation.

Medical Management MTX (mthotrexate), an antifolic acid metabolite, has been successfully used in he trerment of gestational trophoblastic diseases for last four decades 1st used by tanka & colleges in 1982, MTX has been the most commonly used drug administered intravenously,

intramuscularly or orally employing different regimens with Folinic acid rescue claiming a success rate of around 60-70% [Goldenberg *et al.* 1993.

Single dose MTX IM (1mg/kg of body weight) proves to be quite useful in majority of selected cases in ambulatory patients (stovell *et al.* 1993)

Medical treatment with MTX (methatrexare) has many advantages is effective, less costly, simple and preferable to surgery and thus is more acceptable to the patient.

(Das *et al.* 2001)

The first author (K.K. Das) observed how amazingly the symptoms settle down within 2-3 days offer single dose of MTX abdominal pain an day 2-3 is a common finding, but alone without hemoperitoneum is not an indication for surgical intervention.

However, very ranely one may find the POD fluid (hemoperitoneum) cantinas to increase along with the deterred rating general condition, then surgery should be performed the clinician motivates the patient, offers proper counseling so that she understood the possible risks involved clinician mast obtain her informed consent and ensure access to 24 hours emergency treatment.

Materials & Methods

Based an above discussion the selected patients of ectopic pregnancy were treated with systematic methotrexate therapy the selection criteria for medical therapy were defined as follows-

1. Hemodynomically stable patients
2. Serum beta HCG levels less than 5000 /U/L
3. Adnexal mass of less than 4 cm
4. Less than 300ml of free flaid in pouch of douglas
5. Patient in whom methotrexate is not contrain dictated.

The dose of methotexate in these patients were calculated by /mg/kg of body weight and given intramuscularly. The patients were observed for abdominal pain and any signs and symptoms of rupture.

Transvaginal sonography and serum beta HCG level were repeated on Day 4 and Day 7 of injection methotrexate. If serum beta HCG level decreased greater than 15% of initial level and if thane were no signs of rupture patients were then followed up with weekly serum beta HCG level as outpatient till the time it reached to non pregnant level.

If serum beta HCG level increased or diseased less than 15% the initial level on day 7, second dose of injection methotrexate was given.

Treatment was described as successful if no surgical intervention was needed.

Surgical intervention was done for tubal rapture or tubal abortion.

Results

A total 13 out of 21 (62 %) cases were successfully treated with single dose of Injection methotrexate & 4 out of 21 {19 %} required additional dose of Injection methotrexate. Total 17 cases out of 21(81%) were successfully treated with systemic methotrexate (Figure 2 and3).

Four cases out of 21 (19 %) who received single dose of Inj. methotrexate, underwent surgery (Failed medical treatment) for tubal abortion/tubal rupture. Average HCG resolution time was 16 days & range was 8 to 37 days.

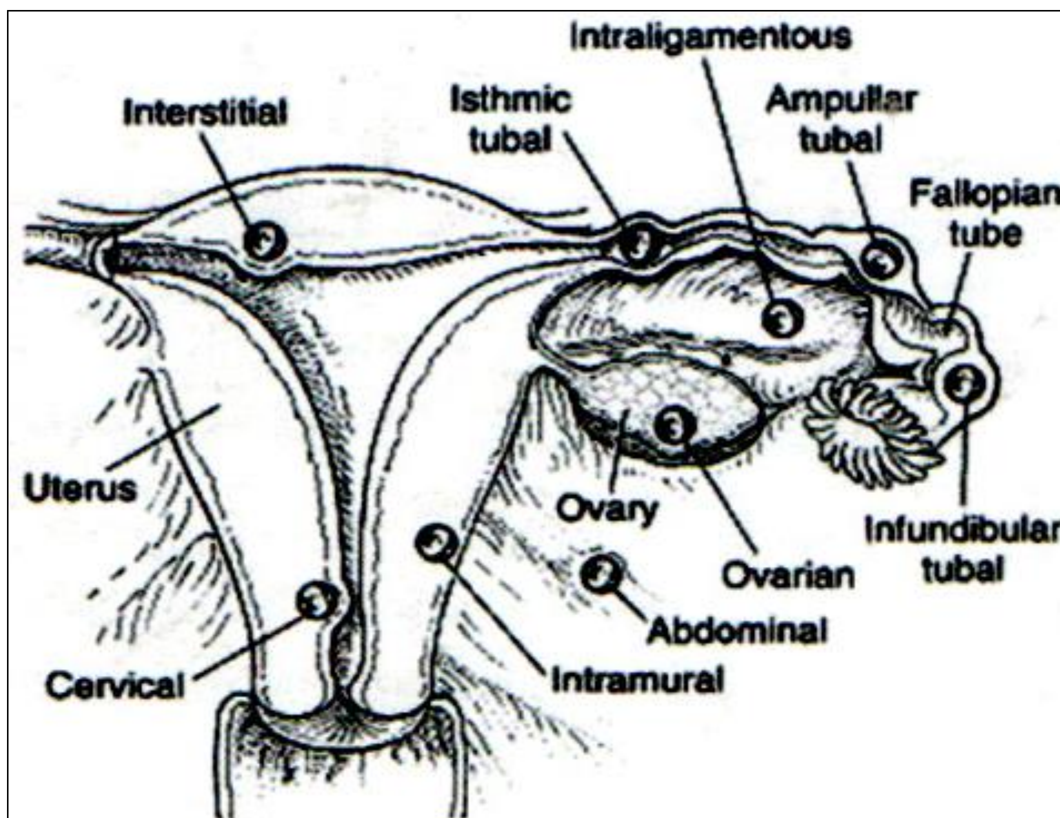

Fig 1: Types and Location of Ectopic Pregnancy

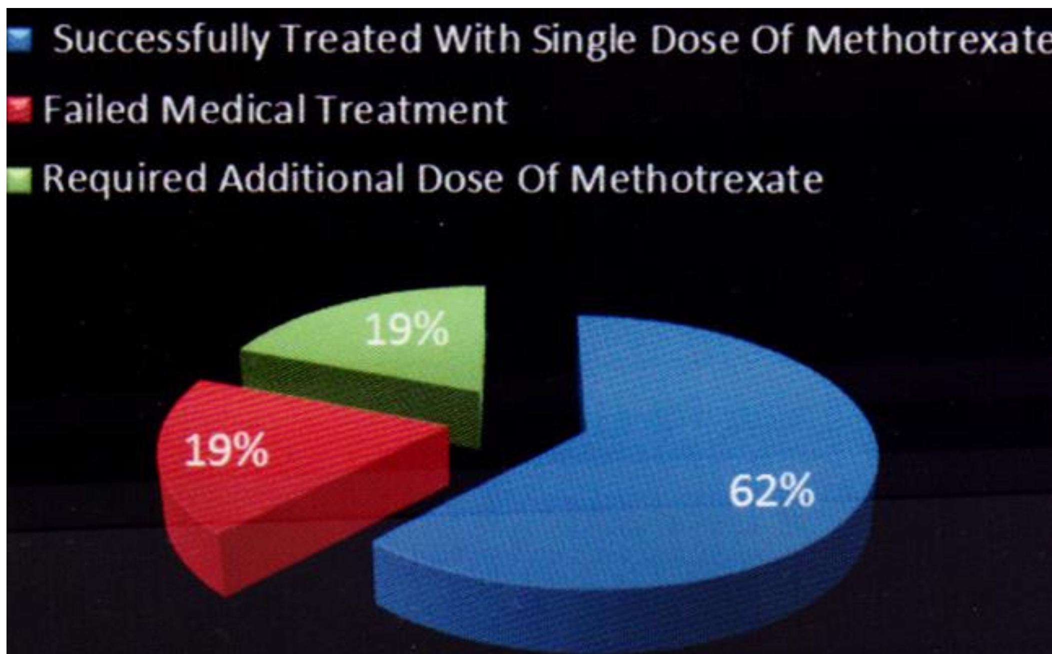

Fig 2: Overview of treatment with Methotrexate (Success and Failure)

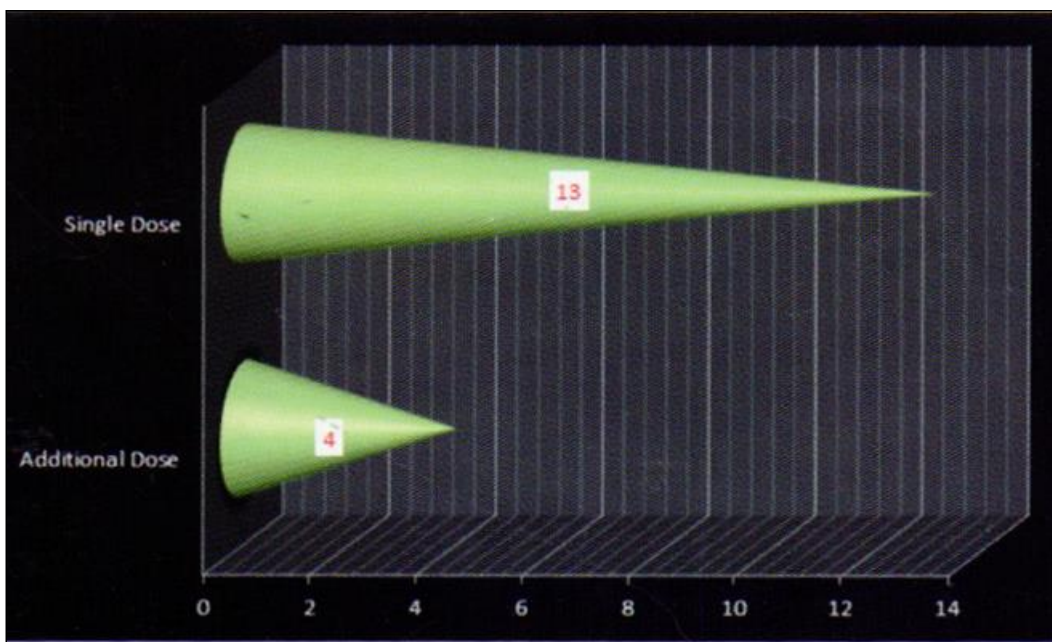

Fig 3: Patients requiring single and an additional dose of methotrexate

Discussion

An ectopic pregnancy is defined as implantation of the embryo outside the uterus (Figure 1). The most common implantation site is within the fallopian tube (95.5%), followed by ovarian (3.2%), and abdominal (1.3%) sites. The sites of tubal implantation in descending order of frequency are ampulla (73.3%), isthmus (12.5%), fimbrial (11.6%), and interstitial (2.6%).

In this retrospective study, we considered haemodynamically stable women with unruptured tubal ectopic pregnancy, diagnosed by non-invasive techniques (TVS & Serial Serum beta -HCG).

Methotrexate is a folic acid antagonist widely used for treatment of neoplasia, severe psoriasis, and rheumatoid arthritis. It inhibits DMA synthesis and cell reproduction, primarily in actively proliferating cells such as malignant cells, trophoblasts, and fetal cells. Methotrexate is rapidly cleared from the body by the kidneys.

The Medical treatment of an ectopic pregnancy with methotrexate is safe and effective in carefully selected cases. Methotrexate treatment is beneficial to avoid surgery in a patient but it requires extended follow-up of patients which can be cumbersome and difficult for some patients. The need to follow patients clinically until the Serum beta- HCG is undetectable requires multiple visits, which takes valuable time. So counseling of couple is mandatory prior to initiation

of treatment. Expectant and medical management of an ectopic pregnancy are effective options in selected cases adopting proper selection criteria as long as adequate facilities for monitoring are available. If surgery is necessary, the laparoscopic route results in shorter hospital stay, but there is no clear advantage of salpingostomy over salpingectomy. The decision should therefore be made on an individual basis. An ectopic pregnancy can be prevented by decreasing the incidence of pelvic inflammatory disease and Chlamydia trachoma is infections and improving their treatment.

During treatment with methotrexate, patients are required to avoid alcohol and folate-containing vitamins. Sexual intercourse or pelvic examinations could potentially rupture the tubal hematoma commonly noted on ultrasound after methotrexate treatment and therefore should be avoided. Patients are also requested to avoid cabbage, onions, leeks, and other potential gas producing foods to avoid the gastrointestinal distress from excess intestinal gas production that seems to be common following methotrexate treatment.

Since an ectopic pregnancy cannot be diagnosed in the community, all sexually active women with a history amenorrhea with lower abdominal pain and vaginal bleeding should be referred to hospital early for ultrasonography and if necessary, measurement of serum beta HCG. Women with a history of an ectopic pregnancy should have early access to ultrasonography to verify a viable intrauterine pregnancy in their subsequent pregnancies. Diagnostic laparoscopy is necessary if the clinical situation cannot be clarified or if the patient's condition deteriorates.

Conclusions

In conclusion, this hospital based study of medical treatment of an ectopic pregnancy with systemic methotrexate in Buraimi region of Oman, is comparable to findings from other part of the world. It is appropriate for clinicians to select suitable candidates for treatment of ectopic pregnancy with methotrexate. It is imperative to confirm diagnosis to avoid unnecessary administration of chemotherapy, such as in a completed miscarriage, or early intrauterine pregnancy, that can have severe consequences for both mother and foetus. There is usually no indication that methotrexate has to be administered at the first presentation of the patient, especially if she is clinically stable. If a woman is not stable, or is in significant pain, she is not a candidate for medical management. Follow up Serum beta-HCG or ultrasound can often avoid unnecessary administration of methotrexate. Moreover, patients should have appropriate counseling, willingness for follow-up and no absolute contraindications to methotrexate treatment. Despite high success rates, there remains a substantial rate of failure. The choice between two acceptable treatments, medicine or surgery, should be an informed & not reflective decision.

Medical therapy for an ectopic pregnancy has become an accepted option to surgical removal in many instances. With early diagnosis & adopting proper selection criteria, medical treatment of an ectopic pregnancy with systemic methotrexate is an effective & safe alternative to surgical treatment. Medical therapy can be reasonably expected to be successful in 88 to 92% of cases. These success rates are even higher if patients with relatively low serum beta HCG levels are treated.

Acknowledgement

The authors reported no conflict of interest & no funding was received for this work.

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