Valley International Journals
Open Access Journal
International Journal Of Medical Science And Clinical Inventions
Volume 2 issue 03 2015 page no. 788-793 ISSN: 2348-991X
Available Online At: http://valleyinternational.net/index.php/our-jou/ijmsci

Management Of Unruptured Ectopic Pregnancy By Single Dose Methotrexate.

Dr.K.S.Raja Kumari

Associate professor, Raichur Institute of Medical Sciences, Raichur. RGUHS, Bangalore.

Abstract: Background: Tubal pregnancy if diagnosed early, and unruptured, can be managed by a number of therapeutic modalities, like conservative surgery by operative laparoscopy, by medical management, by laparotomy, and occasionally by observation alone. Management must be tailored to the clinical condition and future fertility requirements of the woman.

Aim of study: To show in properly selected cases, medical management of ectopic pregnancy is appealing for several advantages like less tubal damage, less cost, avoiding surgical risk, and enhanced potential for future fertility.

Material and methods: Retrospective study was conducted on all cases of ectopic pregnancies admitted and managed in OBG department, in an undergraduate teaching hospital in North Karnataka. This study was conducted to review four cases, treated with single dose methotrexate as medical management for unruptured ectopic pregnancy during the period from 2011 to 2014. *Successful completion of medical therapy is defined as a documented serum β-human chorionic gonadotropin of less than 5 miu/ml or a negative urine pregnancy test.*

Results. Out of all 26 cases of ectopic pregnancies treated in RIMS hospital, between 2011 to 2014 majority of cases i.e 22 cases were managed by surgical treatment, and four cases were selected for medical management, as per the medical management guidelines. Out of 4 cases two were successfully managed by a single dose metrotrexate, and one case was submitted for laparotomy, as HCG levels are not falling satisfactorily with single dose and patient also insists surgical management with concurrent tubectomy and for the other one second dose of methotrexate was given on 4th day. All four had uneventful recovery, and discharged on 7th day. Two of them had bilateral patent tubes, as shown by HSG, taken six months later. Two of them conceived six to ten months after HSG.

Conclusion: There are multiple options available for management ectopic pregnancy depends on the hemodynamic stability of the patient. In properly selected patients medical management still holds good. Medical treatment should be preferred if the patient has undergone surgery many times previously, has extensive pelvic adhesions, a contraindication for general anesthesia, a cornual pregnancy, and after failure of a conservative laparoscopic treatment. Medical treatment is possible: if serum beta is-HCG is below10,000 mUI/mL, if the ectopic pregnancy size is less than 4 cm in diameter, or if the score is adequate. Medical treatment should be the preferred treatment if serum beta-hCG<1000 mUI/mL, if the patient has no pain and if the ectopic pregnancy cannot be visualized at ultrasound.

Key words: Unruptured ectopic pregnancy, beta HCG, medical management, methotrexate.

Introduction:

Ectopic pregnancy is the implantation of blastocyst outside the uterine cavity in an area, which is not lined by endometrium, and uterine musculature. It not only leads to pregnancy loss, but also increases the incidence of maternal mortality and morbidity, and negatively affects future conception.[1]

A).METHODS AND PATIENTS:

A retrospective case sheet review was conducted of all cases of ectopic pregnancies managed in between 2008 to 2014 in undergraduate teaching

hospital in north Karnataka. India. Total ectopic pregnancies managed during that period were 26 cases, out which four cases were selected for medical management, as per the medical management guidelines**.** Successful completion of medical therapy is defined as a documented serum β-human chorionic gonadotropin of less than 5 miu/ml or a negative urine pregnancy test. Two cases were successfully managed by single dose metrotrexate, in one case, dose was repeated on the 4th day, another case was submitted for laparotomy and salpingectomy and concurrent tubectomy.

Table no1: **Gravida status of all ectopic pregnancy in our study**	
Primigravida	17
second	3
>2	6

Table no2: **Gravid status of the cases of ectopic pregnancy medically managed**.	
Primigravida	3
>2	1

Criteria for patient selection: for medical management.[2]

1. Patient should be haemodynamically stable. And does not have pelvic pain.
2. Desire for future fertility.
3. Reliable and compliant patient who will return for post treatment follow up.
4. Agree to use reliable contraception for 3-4 months post treatment.
5. USG shows no intrauterine pregnancy.
6. Gestational sac of ectopic pregnancy should measure 4cms or less in its greatest diameter.
7. There should be no evidence of rupture of ectopic pregnancy.
8. Serum beta HCG should be less than 10000 miu/ ml.

Absolute Contraindications to Methotrexate Therapy[3]

- Breastfeeding
- Overt or laboratory evidence of immunodeficiency.
- Alcoholism, alcoholic liver disease, or other chronic liver disease
- Preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia
- Known sensitivity to methotrexate
- Active pulmonary disease
- Peptic ulcer disease
- Hepatic, renal, or hematologic dysfunction

Relative Contraindications to Methotrexate Therapy

- Gestational sac larger than 3.5 cm
- Embryonic cardiac motion

After selection, Patient counseling was done concerning side effects of methotrexate, occasional possibility of surgical intervention, and need for follow up investigations. Informed, she may experience some pain in abdomen as the pregnancy resolves. Mild abdomen pain could be due to tubal abortion, tubal distension because of haematoma formation. [4]

Treatment protocol: [5]

A common treatment protocol was followed for all selected patients. i,e Single-dose regimen protocol.

Day1: Baseline HB%, TLC,DLC, platelet count, LFT, and RFT, and Quantitative serum beta HCG, and injection methotrexate 50mgs/IM/M^2 of BSA. All were monitored as inpatients. (BSA= square root [(Height in cms X wt in KG)/ 3600]

Day4: HCG titer.

Day7: HCG titer, has dropped by 15% or more, since day 4, weekly HCG levels till readings become non pregnant. Second dose of may be

Table no3: **Size of gestational ring and outcome in medically treated patients**			
Size of gestational sac	No.of patients	Successful medical treatment	Surgical intervention.
Equal or <2.5cms	3	2	Responding to medical treatment, but discontinued, and submitted for salpingectomy and concurrent tubectomy
>2.5cms	1	Repeated 2nd dose .	

required if decline in BHCG level is less than 25% on day 7, and if no drop by day 14, surgical therapy. CBC, RFT, LFT USG. Patient is discharged and advised weekly follow ups.

Follow up: [5]

Weekly HCG titer was done for two weeks, and if falling satisfactorily, repeated after two weeks, till it becomes to non pregnant levels. (15 iu/l). If USG shows blood in abdomen, patient complains of severe pain abdomen, proceed with laparotomy.

Side effects of methotrexate: Only mild nausea in two of them, one had 2-3 vomiting on second day. No side effects in the fourth patient.

Results: Out of total 26 patients of ectopic pregnancies only four patients could be recruited for medical management, as per the guiding criteria and all were started management by single-dose regimen protocol. In one patient dose was repeated on, due to poor fall in beta HCG titer on the 4th day, and she responded to 2nd dose treatment without complications. In all the patients, there was serial fall of HCG titer, and reached to non pregnant levels on 6-7weeks. In that patient, to whom 2nd dose was repeated, there are no signs of ruptured ectopic, but gestational sac was >3.5cms. One patient was subjected to laparotomy, as patient wants to discontinue monitoring and wants surgical management with concurrent tubal ligation.

Fertility following treatment: All three patients were subjected for tubal patency tests after four to six months; bilateral tubal patency is positive in one patient, single patent tube in one patient, unilateral hydrosalpinx and one side normal tube in one patient. Two of them conceived within one year of HSG, and one uneventful term delivery, at 36- 37 weeks. Peritubal adhesions were found at the time LSCS on ipsilateral tube, and other tube was found normal. The third patient was advised to undergo diagnostic laparoscope with chromotubation.

Discussion: Ectopic means “out of place”. In an ectopic pregnancy, the fertilized ovum gets implanted outside the uterine cavity. Ectopic pregnancy usually occurs as a result of delay or prevention in the passage of blastocyst to the uterine cavity resulting in premature implantation in the extrauterine tissue. 95% of ectopic pregnancies are in fallopian tube.The risk of death from ectopic pregnancy is greater than that of normally located pregnancy. Since majority of patients with ectopic pregnancy constitute sub fertile patients, tubal patency is main concern after ectopic pregnancy management. There is no role for medical management in the treatment of tubal pregnancy or suspected tubal pregnancy when a patient shows signs of hypovolaemic shock. In such patients the surgical procedure which prevents further blood loss most quickly should be used. [6]

Risk factors for ectopic pregnancy: Previous tubal surgery, previous ectopic pregnancy, prior

PID, progestin only pill, smoking, etc. Nonwhite woman had a 1.4 times increased pregnancy risk compared with white woman. [7]

Diagnosis of ectopic pregnancy: Any woman of childbearing age who has ectopic pregnancy symptoms should be considered to be pregnant until proven otherwise. She should receive an ultrasound scan (transvaginal) within 24 hours and follow up with beta hCG blood tests 48 hours apart if the scan is inconclusive. If an ectopic pregnancy is diagnosed, wherever possible, women should be given a choice of all of the treatments that are available to treat her ectopic pregnancy, taking into consideration her medical condition. This should be accompanied by relevant, understandable information so that she is able to make an informed choice.

Table no: 4 **Outcome of medical treatment**	
Regression of BHCG to normal	17- 40 days.
Anatomical regression by USG	35- 40 days.
Pregnancies after methotrexate	2 pregnancies out of 4 cases, within 18 months. No congenital anomalies.
Tubal patency after 4-6months	2 cases.
Side effects	Only minor.

HCG and pregnancy: In emergency OBG department pregnancy is diagnosed by determining the level of beta HCG in the urine or serum. While urine testing may detect levels upto 20-50 iu/l,serum testing may detect levels as low as 5iu/L. [8]

In normal pregnancy beta HCG levels double every day, until it reaches10,000-20000miu/ml. Normal intrauterine pregnancies are associated with a doubling time of 1.4-2.1days. As per ACOG recommendations an increase in serum HCG of less than 53% in 48 hours confirms an abnormal pregnancy.

Discriminatory Zone of beta HCG, is the level above which a normal IUP is reliably visualized in nearly 100% of cases.

Ectopic pregnancy is suspected, if trasabdominal USG does not show an intrauterine gestational sac, and patient's beta HCG level is >6500miu/ml. or TVS does not show an intrauterine gestational sac and the patient's beta HCG level is 1500miu/ml or greater.

Diagnosis of ectopic pregnancy is almost certain if there is absence of an intrauterine gestational sac and presence of a complex adenexal mass at HCG concentrations above the discriminatory Zone. If the HCG concentration does not double over 72 hours, the pregnancy is most likely abnormal. [9]

Signs of ectopic pregnancy on TVS:

1. Doughnut's or bagel sign: Thick, bright echogenic, ring like structure which is located outside the uterus with no intra uterine gestational sac.
2. Empty uterus or pseudogestational sac , with serum beta HCG greater than discriminatory cutoff.
3. Cystic or solid adenexal mass with probe tenderness, with serum beta HCG greater than discriminatory cutoff.

Criteria for TVS diagnosis of ectopic pregnancy (Rottem et al 1991) [10]	
STAGE	**TVS findings**
Type 1A	Well defined tubal ring displaying fetal heart
Type 1B	Well defined tubal ring displaying no fetal heart
Type 2	Ill defined tubal mass
Type 3	Free pelvic fluid, empty uterus, displaying no adenexal mass.

Other tests suggested for diagnosis of unruptured ectopic pregnancy:

1.Low serum progesterone levels – non specific
2.Doppler study: Ring of fire in the tubal mass.

In stable patients various treatment modalities are available:

Table no:5 **Mode of management and hospital stay & Conception**

Total hospital stay in ectopic pregnancy		**Follow up days**	**morbidity.**	**Conception within 18 months**
Laparotomy and unilateral salpingectomy (**22 cases)**	5- 8 days	2 visits after discharge	Blood transfusion in 20 cases .	7
Medical (4 cases)	7 days	Weekly follow up to 30days, and later 2 visits for 1month .	nil	2

1. Medical management:[5]

A) Single or multi dose methotrexate: The most widely used medical treatment at present is IM/ methotrexate given as a single dose calculated from patient body surface area (50 mg/m2). For most women this will be between 75 mg and 90 mg, and about 14% of women will require more than one dose of methotrexate and less than 10% of women treated with this regimen will require surgical intervention. If BhCG<1000 mUI/mL, if the patient has no pain and if the ectopic pregnancy cannot be visualized at ultrasound, medical management is the treatment of choice. Important advantage of medical therapy is the potential for considerable savings in treatment costs.

B) Combination of methotrexate and mefepristone

2. Surgical management: via laparoscopy or laparotomy

a. salpingectomy
b. partial salpingectomy
c. salpingtomy

Summary: With availability of high resolution ultrasound, and Beta HCG estimation, ectopic pregnancies can be picked up very early, and before rupture. Medical management with single dose methotrexate is simple and effective, and cost effective, provided patient's follow up is assured. With earlier diagnosis, both maternal survival and conservation of reproductive capacity are enhanced. Intramuscular methotrexate has been found to be as effective as laparoscopic salpingostomy. Medical treatment is preferred to laparoscopy in patients with dense pelvic adhesions, in patients with surgical risk. A follow up appointment should take place with the patient two to three weeks after the ectopic pregnancy has resolved for proper counseling regarding future fertility plans. Fertility of women after ectopic pregnancy appears to be similar between those who receiver medical treatment, and those who received conservative or radical surgery.[11]

References:

1. Crochet JR, Bastian LA, Chireau MV (2013). "Does this woman have an ectopic pregnancy?: the rational clinical examination systematic review". *JAMA* 309 (16): 1722–9.doi:10.1001/jama.2013.3914. PMID 23613077..

2. [Ectopic pregnancy: criteria to decide between medical and conservative surgical treatment?].[Article in French] Canis M[1], Savary D, Pouly JL, Wattiez A, Mage G. J Gynecol Obstet Biol Reprod (Paris). 2003 Nov;32(7 Suppl):S54-63.
3. KELLY W. JONES, PHARM.D., McLeod Family Medicine Center, Florence, South Carolina, SUPEN R. PATEL, M.D., Carolina Health Care, Florence, South Carolina *Am Fam Physician.* 2000 Oct 1;62(7):1607-1612.A Family Physician's Guide to Monitoring Methotrexate, *Am Fam Physician.* 2000 Oct 1;62(7):1607-1612.
4. American College of Obstetricians and Gynecologists (ACOG). Medical management of tubal pregnancy.guidelines. Washington ..
5. .Ectopic Pregnancy Treatment & Management Author: Vicken P Sepilian, MD, MSc; Chief Editor: Michel E Rivlin, MD, medscape
6. Surgical Management of Ectopic Pregnancy Author: Allahyar Jazayeri, MD, PhD, FACOG, DACOG, FSMFM; Chief Editor: Michel E Rivlin, MD, medscape more..
7. Risk factors of ectopic pregnancy.(PMID:12930019), Bunyavejchevin S, Havanond P, Wisawasukmongchol W, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.Journal of the Medical Association of Thailand = Chotmaihet Thangphaet [2003, 86 Suppl 2:S417-21].
8. Kadar N, DeVore G, Romero R. Discriminatory hCG zone use in the sonographic evaluation for ectopic pregnancy. Obstet Gynecol 1981;58:156–61.
9. Cacciatore B, Stenman U, Ylöstolalo P. Diagnosis of ectopic pregnancy by vaginal ultrasonography in combination with a discriminatory serum hCG level of 1000 iu/l (IRP). Br J Obstet Gynaecol 1990;97:904–8
10. Criteria for transvaginal sonographic diagnosis of ectopic pregnancy. Rottem S[1], Thaler I, Levron J, Peretz BA, Itskovitz J, Brandes JM.J Clin Ultrasound. 1990 May;18(4):274-9.
11. Fernandez H, Capmas P, Lucot ,et al fertility after pregnancy the Demeter randomized trail. Hum reprod 2013.