

Medical Management of Ectopic Pregnancy: An Observational Study

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Abstract:

Objectives: The aim of this study was to explore the safety and efficacy of medical management of ectopic pregnancy.

Materials and methods: This prospective observational study was conducted between February 2011 to August 2013 in Chittagong Medical College Hospital (CMCH) and in different private clinics of Chittagong city. Twenty-seven patients of ectopic pregnancy conceived by fertility treatment were recruited for medical treatment after proper evaluation. Ectopic pregnancy was diagnosed by serum β -hCG and progesterone level but missing intrauterine pregnancy by transabdominal sonography (TAS). Serum β -hCG was repeated after 48 hours to observe doubling of the level. If level was not doubled or increment was not at least 66% and serum progesterone level was less than 15ng/ml then it was considered as ectopic pregnancy. Patients were treated with Injection methotrexate 50 mg intramuscularly either by single dose or two doses. After 4 days of 1st injection β -hCG was repeated and if level decreased > 15% then patients were assessed weekly till β -hCG fell to <5IU/L. If drop was <15% after 4 days a second dose of methotrexate was given.

Results: Overall success rate was 66.66% . Surgical intervention was needed in 22.22% patients. All patients were treated after hospitalization in CMCH and different private clinics of Chittagong. They got injection methotrexate, antibiotic, antispasmodic and analgesics for abdominal pain. Single dose cured 55.55% patients and 11.11% patients needed second dose, another 11.11% patients were misdiagnosed –later on they were diagnosed as intrauterine pregnancy and medical termination was done. Within one year of treatment 33.33% patients conceived again. There was no side effect or complications of the treatment.

Conclusion: This small trial gave a good impression about medical treatment in selective cases. The efficacy should be assessed in a randomized clinical trial with a different set of population.

Keyword: Ectopic pregnancy, medical management, methotrexate.

Introduction:

A pregnancy located outside the uterine cavity is defined as an ectopic pregnancy. About 99% of ectopic pregnancy occur in the fallopian tube and it accounts for 1-2% of all pregnancies.¹ Ectopic pregnancy are potentially life threatening and incidence of it continues to increase day by day due to the occurrence of sexually transmitted disease, prior salpingitis, IUCD users, pelvic adhesions and after infertility treatment. Until recently, ectopic pregnancy was considered an exclusively surgical condition. In 1989 stoal showed that outpatient medical management of women with

an ectopic pregnancy who were clinically stable, using methotrexate was safe and available, and by 1991 had developed single –dose outpatient regimen which is commonly used today². The death rate for ectopic pregnancy is about 0.3%.³ The most sensitive initial indicator of an early pregnancy is serum β -hCG and early indicators of a potential ectopic pregnancy are a slower rise of serum β -hCG level in early pregnancy⁴. But any amount of serum β -hCG in blood with empty uterine cavity in ultrasonography is suggestive for ectopic pregnancy. Exception may occur, where presence of both an intrauterine and ectopic pregnancy

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exist⁵. If undiagnosed and left untreated the majority of ectopic pregnancies will eventually rupture causing internal bleeding and in some cases death may occur⁶. Typical diagnostic features of ectopic pregnancy is short period of amenorrhoea and severe lower abdominal pain followed by fainting attack, where it ends with tubal abortion or tubal rupture. The traditional treatment for ectopic pregnancy has been surgical either with an open incision or by minimally invasive laparoscopic surgery⁷. Non-surgical or medical treatment for unruptured ectopic pregnancy has been evolved with good success.

The most widely used protocol is a single dose of injection methotrexate intramuscularly with subsequent doses if needed^{4,8}. Methotrexate inhibits the synthesis of purines and pyrimidines. Thus, it interferes with DNA synthesis and cell multiplication. Rapidly dividing cells are most vulnerable to methotrexate. This accounts for the drug's effect on trophoblastic tissue⁹.

The benefits of medical treatment are- it avoids surgery in 85% cases, has the same or high cure rate as with surgery, less costly¹⁰⁻¹¹, is not skill dependent and higher future fertility rate than with surgery¹²⁻¹³. The earlier an ectopic pregnancy can be diagnosed, the higher the cure rate by using methotrexate. Lower the serum β -hCG level higher the cure rate, which is about 98% when level lies <1000 IU/L. However, there are some limitations to the use of methotrexate for successful ending like gestational sac should be less than 3.5 cm, ectopic should be unruptured, β -hCG level should be less than 5000 IU/L, there should be lack of foetal cardiac motion, and there should be no medical contraindications. Methotrexate therapy can't be used with heterotopic pregnancies as it will terminate both the pregnancies¹⁴.

The purpose of this study was to observe the efficacy and safety of medical treatment either by a single or multiple doses of methotrexate to cure ectopic pregnancy completely and to avoid surgical intervention.

Materials and methods:

This study was conducted between February 2011 to August 2013 in Chittagong Medical College Hospital and different private clinics of Chittagong city. This is

a prospective observational study. Twenty seven patients were treated medically. Patients got pregnant after fertility treatment. Women with an ectopic pregnancy meeting the criteria for medical treatment were counseled to participate in this trial. As patients got pregnant after fertility treatment they were monitored extensively and pregnancies were diagnosed at the earliest. The diagnosis of ectopic pregnancy was made by quantitative measurement of serum β -hCG and progesterone level when transabdominal ultrasonography found no intrauterine pregnancy after urinary positive pregnancy test. or any gestational sac in tubo-ovarian region at 6 weeks post ovulation. Serum β -hCG was repeated after 48 hours to see the doubling of the hormone. If β -hCG was not doubled or increment was <66% and progesterone level was <15ng/ml it was considered as ectopic pregnancy. Inclusion criteria: Patient of ectopic pregnancy with haemodynamically stable. No signs of intra-peritoneal bleeding, free from any severe abdominal pain, gestational sac of size 2.5- 4 cm without any cardiac activity, and serum β -hCG level 2000 IU/L. Exclusion criteria were acute ruptured ectopic pregnancy, chronic ectopic pregnancy, patient with hepatic and renal dysfunction. All the patients were advised for hospitalization once it was diagnosed as ectopic pregnancy. Verbal consent was taken. Protocol was a single dose of injection methotrexate 50 mg IM or 1 mg/kg body weight when body weight was less than 50 kg. All patients were reviewed after 4 days and if β -hCG level dropped by 15% then women reviewed weekly till β -hCG fell to <5 IU/L. If the drop was less than 15% after 4 days a second dose of methotrexate was given. Patients were followed up 4 days after last injection and at weekly interval if needed. Patients were instructed to refrain from intercourse until complete resolution of the ectopic pregnancy and also advised for use of contraceptives like oral contraceptive pills for 6 months after completion of treatment. Antibiotics, antispasmodic and analgesics were given to all patients and continued for 7 days for subsidence of inflammatory reactions. All patients were advised to take folic acid 4 mg daily following completion of the treatment. Patients were also instructed to notify any complains like severe abdominal pain and ultrasonogram was repeated for detection of ruptured ectopic pregnancy. Patients were informed about

laparotomy or laparoscopy may be needed due to intra-peritoneal haemorrhage, which is indicated by rapid pulse and falling blood pressure, anaemia or no subsidence of pain after using analgesics. Finally repeat ultrasonography was done to detect abnormality after cessation of β -hCG. Main outcome measure was success rate of medical treatment defined by the absence of intervention by surgery. Secondary outcome was safety of treatment in terms of complications of the drug like gastritis, stomatitis, alopecia, altered liver function, renal function and haematological profile.

Results:

During the study period of two and half years twenty seven patients of ectopic pregnancy were recruited for medical treatment with methotrexate. Among them 21(77.77%) were in age group of 20-34 years and 6 (22.22%) patients were more than 35 years of age, 21(77.77%) patients came from middle class family and 6 (22.22%) came from affluent society. All the patients were admitted in CMCH and different private hospital in Chittagong and were treated by injection Methotrexate 50 mg intramuscularly. Patients were monitored 4 hourly for their vital signs like pulse, blood pressure and abdominal palpation for any localized tenderness. All the patients of this study series were mildly anaemic and three patients were moderately anaemic and they were treated with blood transfusion for one unit. On day 4 serum β -hCG was estimated, serum β -hCG fell >40% in 15 (55.55%) cases and managed expectantly. β -hCG fell <15% in 9 (33.33%) cases, among them 6(22.22%) patients needed intervention- 3 (11.11%) patients needed laparotomy and another 3(11.11%) needed laparoscopy. Three (11.11%) patients were misdiagnosed and follow up β -hCG level was raised. So USG was done and found intrauterine pregnancy, which was terminated by using tab misoprostol 800 mg through per vaginal route.

Overall success rate was 66.66%. In 18 cases recovery was uneventful and completed within 15 days of treatment. Six (22.22%) patients needed surgical treatment and all cases were with abdominal pain, which subsided after antibiotic and analgesics. Among successful group 15 (55.55%) patients were cured by single dose only and 3 (11.11) patients needed second dose. The patients resume their menstrual cycle within 1.5-2 months. Within one year of treatment 12 (33.33%) patients conceived. There was no side effects or complication of drug in any cases.

Table-I
Characteristics of patients

Characteristics	Number	Percentage (%)
Age in years:		
20-34	21	77.77
≥ 35	06	22.22
Socioeconomic condition		
Middle class	21	77.77
Affluent	06	22.22
Initial β -hCG level		
<1500 IU/L	18	66.66
>1500 IU/L	09	33.33
Body weight	45—55 kg	
Size of gestational sac or adnexal mass	2.5 - 4cm	

Table-II
Outcome of Treatment

Outcome	Number	Percentage(%)
Complete and uneventful recovery	18	66.66
hCG was not declining	03	11.11
Tubal rupture	06	22.22
Single dose needed	15	55.55
Second dose needed	03	11.11
Complications of drugs	00	00
Overall success rate	18	66.66

Discussion:

Ectopic pregnancy remains the great puzzle of gynaecology, no other pelvic conditions give rise to more diagnostic errors like this condition. The patient may or may not have symptoms pointing to pregnancy¹⁰. With or without a short period of amenorrhoea patient may complaints of pelvic pain and irregular vaginal bleeding. However, only half of the patients with ectopic pregnancy can be correctly diagnosed based on clinical features alone¹⁴. But diagnosis of ectopic pregnancy at the earliest without any symptoms is fully based on investigations. Estimation of serum β -hCG is the gold standard of diagnosis of pregnancy at the earliest. In a normal pregnancy, hCG present in detectable level (>2mIU/ml) in the maternal serum 8-10 days after fertilization. Level normally doubled every 48 hours for the first 5 to 8 weeks after conception, rising well above 100,000 mIU/ml then gradually decreases after 10 weeks⁶. In

an ectopic or spontaneous abortion, hCG level rise slower than normal and usually plateau at about 6 weeks below 6000mIU/ml. Lack of a 48-hour doubling or at least <66% increment indicates the presence of an abnormal pregnancy¹⁵. Plateauing β -hCG levels have the highest predictive value for ectopic pregnancy of any β -hCG pattern. Progesterone levels are usually not of much use in making the diagnosis of ectopic pregnancy but they can be another clue. A single progesterone value less than 15ng/ml is probably an abnormal pregnancy of some type and a single value over 25ng/ml is probably a normal pregnancy. Conclusive diagnosis is absence of intrauterine gestational sac in spite of positive β -hCG value. Exception is heterotopic pregnancy where both intrauterine and ectopic pregnancy may co-exist. So careful sonographic examination is very important. With a good vaginal probe by 5-6 weeks all pregnancies should be seen. Surgery either by laparoscopy or laparotomy is routine treatment for ectopic pregnancy. But now a days in selective cases medical treatment of ectopic pregnancy is prevailing with good success. Advantages of medical treatment are, it is an outpatient treatment, quick recovery and 98% success rate in properly selected cases¹³. In our study all were getting as in patient treatment. There are certain circumstances where methotrexate may be preferable to surgery. These include cervical ectopic, cornual ectopic, pelvic adhesions where surgical intervention may be associated with a high risk of severe bleeding and in cases where ectopic pregnancy co-exists with ovarian hyperstimulation syndrome where the pelvic organs are vascular and surgical intervention may be better avoided. On the other hand, in heterotopic pregnancy, methotrexate drug cannot be given because it can damage the intrauterine pregnancy. There are so many studies where pregnancy could be detected earlier as a part of routine extensive monitoring. β -hCG level was detected earlier in ART and IUI cases but in ovulation induction cases it was usually checked when there was no sac in the uterus at 6 weeks of missed period in spite of positive pregnancy test by urine. We did β -hCG in all cases when there was no gestational sac at 6 weeks of pregnancy in spite of urinary positive pregnancy test. In majority cases (66.66%) β -hCG level was within <15001U/L at 6 weeks of pregnancy. Though this range of serum β -hCG with ectopic pregnancy demands expectant management but due to some limitation we did not take the risk because

we don't have enough facilities of trans-vaginal ultrasonography which is very essential for expectant management. In our study overall success rate was 66.66% but the other study showed their overall success rate was 83.33%¹. Six patients needed surgery for ruptured ectopic. Another three (11.11%) intrauterine pregnancy was diagnosed as ectopic pregnancy. This might be due to limitation of abdominal ultrasonography. Though treatment can be done as outpatient basis, we treated all patients in the hospital. In 6 failed cases where surgery needed, no one had severe bleeding as they were diagnosed and managed immediately at rupture. Recent studies shown that cure rate is 92% when β -hCG is under 50001U/L and 98% when levels are <1000 IU/ml¹³. In our study we also observed that response was satisfactory, quick and cured by only one injection when β -hCG level was low. We found good success with single dose as most of them had β -hCG level within 2000 IU/L. Second dose were needed when hCG level did not fall >15% and required more time to fall to baseline. Corsan showed that patients did not respond to methotrexate therapy having β -hCG levels higher than 5,000 IU/L.¹⁶ We could not observe the efficacy of treatment in patients having high level of β -hCG like 10,000IU/L as our cut off level was 2000 IU/L.

Rozenberg shows that the effect of methotrexate decrease linearly when serum β -hCG level is increased¹⁷. Some investigators recommended surgical treatment when β -hCG level exceeds 40001U/ml¹⁸. Lehner and others recommended no treatment for patients where β -hCG level is below 2000 IU/L as they may regress spontaneously (expectant management)¹⁹. Others recommended multiple doses of methotrexate when β -hCG level exceeds 50001U/ml²⁰. They concluded that women treated with single dose of methotrexate were more likely to fail medical treatment of ectopic pregnancy than those treated with multiple doses.

In our series after completion of the treatment all patient were advised for oral contraceptive pill for subsequent 6 months, and then 12 (44.44%) patients got pregnant within one year.

In conclusion this small trail gave a good impression about medical treatment in selective cases. The advent of modern diagnostic and therapeutic modalities has changed the clinical scenario of ectopic pregnancy from one of possible disaster (and even death) to one of potential success. Alert women who have

awareness of the signs and symptoms of an ectopic pregnancy can help their doctors to make the diagnosis earlier, treat the problem with less invasive methods, preserve the fallopian tubes, and greatly increase the hope of achieving a healthy and fruitful outcome.

References:

- Begum MR, Dewan F, Quider E, Begum MS, Khan F. Medical management of ectopic pregnancy: Efficacy and safety. *Bangladesh Journal of obstetrics and Gynaecology* 2005; 20(2):56-60.
- Goidner TE, Lehner, Kadar Net. Surveillance for ectopic pregnancy: United States, 1970-1989. *MMWR* 1993; 42: 73-85.
- Stovall TO, Ling FW, Gray LA, Carson SA, and Buster IDE. Methotrexate treatment of unruptured ectopic pregnancy: a report of 100 cases. *Am J Obstet. Gynecol* 1991; 77: 749-753.
- Stoval TG, Ling Fw, Buster JE. Outpatient chemotherapy of unruptured ectopic pregnancy. *Fertil Steril* 1989; 51(3): 435-438.
- Glock JL, Johnson JV. and Brumsted JR. Efficacy and safety of single-dose systemic methotrexate in the treatment of ectopic pregnancy. *Fertil. Steril* 1994; 62:716-721.
- Henry M, Gentry W. Single injection of methotrexate for treatment for ectopic pregnancies. *Am J Obstet Gynecol* 1994; 171:1584-1587.
- StikaCS, Anderson L, Frederikesen MC. Single-dose methotrexate for the treatment of ectopic pregnancy. Northwestern Memorial Hospital three-year experience. *Am J Obstet Gynecol* 1966; 174:1840-1846.
- Lipscomb GH, Bran D. McCord ML, Portera JC, Ling FW. Analysis of three hundred fifteen ectopic pregnancies treated with single dose methotrexate. *Am J Obstet Gynecol* 1998; 178:1354-1358.
- Hajenius, Oloffson, Lecuru. Intervention of tubal ectopic pregnancy, *Cochrane Database Syst Rev*(issue-1), Art no :CD000324,2007.
- Tulandi, Sowteretal, Luciano, Al-Jaroudi D, Interstitial pregnancy: result from the reproductive surgeon registry, *Obstet Gynecol* 2004;103:47.
- Lecuru F, Morlock S, Robin F. Direct cost of single dose of methotrexate for unruptured ectopic pregnancy *Eur J Obstet Gynecol Reprod Biol* 2000; 88(1): 1-6.
- Golan, Lacuru, Fernandez. Management of tubal pregnancy: *BJOG* 2000;107(5): 626-30.
- Lipscomb GH, Bran D, McCord ML, Stovall TG et al, Prediction of success of methotrexate treatment in women with tubal ectopic pregnancy. *N Engl J Med* , 1999;341: 1674.
- Tuomivaara L, Kauppila A, Puolakka J. Ectopic pregnancy: an analysis of the aetiology, diagnosis and treatment in 552 cases. *Arch gynaecol* 1986; 237:135-147.
- Ankum WM, Van der Veen F, Hamerlynck JV, Lammes FB. Suspected ectopic pregnancy. What to do when human chorionic gonadotropin levels are below the discriminatory zone. *J Reprod Med.* 1995; 40: 525-528.
- Corsan GH, Karacan M, Qasim 5, Bohrer MK, Ransom MX, Kemmann E. Identification of hormonal parameters for successful systemic single-dose methotrexate therapy in ectopic pregnancy. *Hum Reprod* 1995; 10: 2719-2722.
- Rozenberg E, Agostini A, Blanc K, Ronda I, Romain F, Capelle M. Medical treatment of ectopic pregnancies: a randomized clinical trial comparing methotrexate-mifepristone and methotrexate-placebo. *Human Reproduction* 2003; 18(9): 1802-1808.
- Shalev E, Barnhut KT, Kirk E, Condous V, Haider z. Transvaginal sonography as the ultimate diagnostic tool for the management of ectopic pregnancy: experiences with 840 cases. *Fertil Steril* 1998; 69: 62-65.
- Shalev E. Oloffson, Lipscombe G. Spontaneous resolution of ectopic tubal pregnancy: natural history. *Fertil Steril* 1995; 63:15-19.
- KT Barnhart , Nguyen Q, Kaptiz M, Downes K, Silva C. The medical management of ectopic pregnancy: meta-analysis comparing single dose and multidose regimens. *Obstetrics and Gynaecology* 2003; 101:778-784.