Single Dose Methotrexate as a Primary Treatment of Ectopic Pregnancy

Hanan Dh. Al-Jeboury
CABOG

Abstract:

Objectives: To determine the efficacy of single-dose intramuscular methotrexate as the primary treatment of ectopic pregnancy.

Study design: A hospital based- cohort clinical study.

Setting: The study was carried out in the Department of Obstetrics and Gynecology in Al-Yarmouk teaching hospital.

Methods: A hospital based- cohort study was done from October 2004 to November 2005 in AL-Yarmook teaching hospital to a total of 82 women referred because of clinical suspicion of ectopic pregnancy. 35 women were excluded because they needed surgical interference, the remaining 47 patients with clinical suspicion of ectopic pregnancy, made using a combination of β-hCG titers with ultrasound.

50 mg intramuscular methotexate regimen was given, β-hCG levels were measured on days 1,4,7 and then weekly . If β-hCG levels were not dropping enough after 1 week, a second dose of methotrexate given. Successful treatment was defined as the resolution of ectopic pregnancy with a single dose without surgical interference.

Results: Our over all success rate was 78.7 %(37/47 women). The median pretreatment serum β-human chorionic gonadotropin level was lower in those women in whom treatment was successful compared with those women with treatment failure (974 vs. 3804 mIU/mL, $P<0.05$). In our study 37 of 47 patients with ectopic pregnancy the level of β-hCG dropped.

Six of 47 patients the dose needed to be repeated for another one week and the level of β-hCG monitored after another one week and was droping; the remaining 4 patients need surgical interference.

Conclusion: Single dose of IM methotrexate was associated with a high success rate in selected cases of ectopic pregnancy especially after exclusion of factors which causes treatment failure.

Key words: Ectopic pregnancy, Methotrexate

Introduction:

Ectopic pregnancy (fertilized ovum becomes implanted in a site other than the uterine cavity [1,2] is accounted for approximately 2% of reported pregnancies and 9% of all pregnancy related deaths in U.S.A. [3] It remains the second leading cause of maternal mortality in united states, and is the leading cause of maternal mortality in the first trimester .[4]

Until recently, the only treatment for ectopic pregnancy was an open operation. This meant a long stay in hospital and recovery time afterwards. Now we are able to offer another option-medical treatment. Methotrexate (MTX) has become popular in selected cases of ectopic pregnancy and it has found that it is at least as good as following surgery and usually better. [5].

Peak serum concentrations of methotrexate occur 2 hours after an IM dose, and have life of about 2-4 hour. Methotrexate does not seem to be appreciably metabolized with 90% of an intravenous dose excreted via the kidneys within 24 hours. The single IM injection of 50 mg/m^2 body surface area for the treatment of ectopic pregnancy is associated with (uncommon) transient side effects but persistent complications are virtually absent.

The Analysis of the criteria of inclusion and exclusion for the treatment by MTX in the various international publications does not make it possible to reach a univocal consensus**,** however the indications include, stable hemodynamic state, hematosalpinx (<3 or 4 cm in its largest diameter), and agreement of the patient and compliance in the follow up[6]**.**

Major complications of MTX includes, bone marrow suppression (very rare with single dose MTX used in ectopic pregnancy), acute and chronic hepatotoxicity with occasional transient elevation of serum liver transaminases, rapidly progressive pulmonary toxicity (pneumonitis and pulmonary fibrosis), and dermatologic effect (rashes, itches, hives, follicullitis, photosensitivity, pigment changes and rarely alopecia) [6].

Side effect of MTX includes common side effects (abdominal pain, cramping pain, vaginal bleeding or spotting, nausea, vomiting, indigestion, fatigue, light headedness, and dizziness) and other rare side effects (skin sensitivity to sunlight, inflammation of the membrane covering the eye, sore mouth and throat, temporary hair loss, severe low blood count due to bone marrow suppression, and inflammation of the lung (pneumonitis) for this reason MTX treatment requires close medical supervision.[7].

The current study was conducted aiming to determine the efficacy of single-dose intramuscular methotrexate as the primary treatment of ectopic pregnancy.

Patients & methods:

In a hospital-based randomized clinical trial from October 2004 to November 2005, a total of 82 patients referred to Al-Yarmouk Teaching Hospital for a clinical suspicion of ectopic pregnancy, 35 patients were excluded from the study either because of profuse hemorrhage, acute abdomen requiring emergency surgical interference. Finally, 47 patients were included in this study. These patients were in the reproductive age group and had some or all of the following clinical presentation. The patient may or may not have symptoms pointing to pregnancy, with or without a period of amenorrhea, lower abdominal pain or pelvic pain and irregular vaginal bleeding, in addition to one or more of risk factors for ectopic pregnancy.

Each patient was informed about the method of examination and a verbal consent was obtained under the study protocol.

Complete history (Obstetrical and Gynecological), was taken from them and data collected included the following; age of patients, gravidity, parity, obstetrical and menstrual history, history of contraception, infertility and ovulation induction. Also any history of sexually transmitted disease, pelvic inflammatory disease (PlD), history of previous ectopic pregnancy and history of smoking and their complaint were registered.

Examination was performed looking for any vaginal bleeding, adnexial or pelvic mass, its size, consistency, mobility and tenderness, also the presence of an enlarged soft uterus, was looked for.

β-hCG samples were assayed in the same laboratory by Minividas technique. The sensitivity of assay was 20m IU / ml.

The assay principle combines an enzyme immunoassay sandwich method with a final fluorescent detection (ELFA). The solid phase Receptacle (SPR), serves as the solid phase as well as the pipetting device for the assay. Reagents for the assay were ready to use and predispensed in the sealed reagent strips. All of the assay steps are performed automatically by the instrument. The reaction medium is cycled in and out of the SPR several times.

Firstly, 5 ml of blood samples were centrifuged, sera was taken and transferred into the well containing alkaline-phosphatase labeled anti-hCG antibody. The sample/ conjugate mixture are cycled in and out of the SPR several times to increase the reaction speed. The antigen binds to antibodies coated on the SPR and to the conjugate forming a "sandwich". Then, the remaining free hCG sites are saturated by cycling the conjugate in the fifth well of the strip in and out of the SPR. Unbound components arc eliminated during the washing steps.

During the final detection step, the substrate (4-methyl-umbellifery l phosphates) is cycled in and out of the SPR. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4-methyl-umbelliferone). The fluorescence of which is measured at 450 nm. The intensity of fluorescence is proportional to the concentration of antigen present in the sample. At the end of the assay, result is automatically calculated by VIDAS in relation to the calibration curve stored in memory, and then printed out.

After evaluation in the inpatient department, the patients with stable clinical course were referred to the ultrasound unit where by they were examined by trans-vaginal ultrasonography. Sonographic examination was performed on a Kretz-Voluson 350 D apparatus using a 5-8MHz/ Vaginal probe.

Our criteria in selecting appropriate candidates for MTX treatment of ectopic pregnancy:

1-A highly compliant and reliable patient, since close follow up is required.
2-healthy women, unruptured tubal ectopic pregnancy and hemodynamically stable.
3-ultrasound examination without evidence of intrauterine pregnancy.
4-Ectopic size <4 cm in greatest diameter.
5-Absence of fetal heart tones.
6-hCG titer of less than 10,000 mIu /ml.

Once a candidate is selected, the following protocol was applied:

1-Pretreatment hCG titre, blood group and Rh, complete blood picture and chemistry profile (LFT, RFT).
2-Informed consent and discuss the risk and benefits as well as alternatives.
3-Review the medications that may interact and disallow their use.

50 mg per meters squared surface area MTX was given intramuscularly (this considered Day 1) and the patient is monitored clinically and biologically. Clinical monitoring include, observe the patient in hospital, informed the patient of the inherent side effect of MTX (stomatitis, nausea, and diarrhea), and pelvic pains which are frequent in the week follow MTX injection, while biological monitoring includes;

Day 1→ Serum hCG, blood group, hemoglobin, platelet count.

Day 4→ Serum hCG.

Day 7→ Serum hCG.

If the rate of hCG drops of more than 15% between Day 1 and Day 7, weekly hCG measurement along with woman's clinical status until it is determined that the ectopic pregnancy has been resolved when the rate of hCG is <20 mUI/ml. If the rate of hCG with Day 7 > Day 1 or if the rate drops by less than 15% (from the maximal hCG concentration) between Day 1 and Day 7 or if the Day 7 hCG concentration did not drop from the maximal hCG concentration (at Day 4) by 15%, or titer begin to rise, a second same

dose of IM injection of MTX is made, and we repeat blood assessment 7 days later.

Serum β-hCG levels are measured weekly until < 20mIU/ml. Patient in whom the β-hCG is falling following treatment they are clinically stable have been discharged from hospital and monitored as an out patient.

Data were collected and described by using; number, percentage, mean, and standard deviation, accuracy, association between variables were measured by using t-test when appropriate. The association was considered to be statistically significant when $P \leq 0.05$.

Results:

Forty-seven patients were finally included in this study. The mean± S.D age of the patients was 26.7 ± 5.1 years with an age range of 18 - 41 years. The parity of the patients ranged from (0-8). Gestational ages, calculated from the last menstrual period ranged between 30 - 76 days, with a mean ± S.D of 51.9 ± 10.2 (table 1)fig.1.

Lower abdominal pain with vaginal bleeding were the common presenting symptom for our patients with ectopic pregnancy (46.8 %), while vaginal bleeding only (31.9 %), lower abdominal pain and pelvic pain (21.2 %) as shown in table (1) fig 2.

Table 1: The socio-demographic characteristics of patients with ectopic gestation.

Characteristics	**Range**	**Mean ± SD**
Age	18-41	26.7±5.1
Parity	0-8	-
Duration of gestation (days)	30-76	51.9±10.2
Clinical symptoms	**No**	**%**
Vaginal bleeding ±abdominal pain	22	46.8
Vaginal bleeding	15	31.9
Abdominal pain or pelvic pain	10	21.2

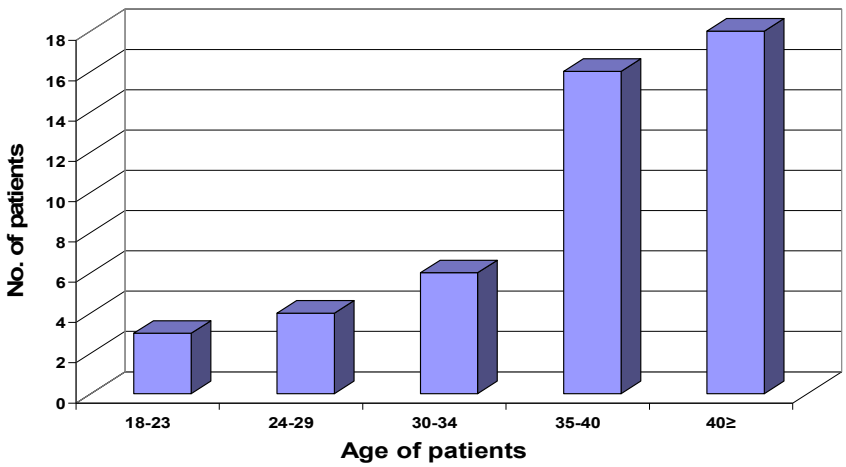

Figure 1: The frequency of age distribution of cases

The commonest risk factor for ectopic pregnancy was, more than one risk factors (62.5 %), while the age (more than 35 years old, 34.0%), (PID) pelvic inflammatory disease (31.2%), previous surgery 28.1%, previous ectopic pregnancy (15.6%), intrauterine contraceptive device 6.2%, induction of ovulation (15.6 %), cigarette smoking (6.2 %), as shown in table (2).

Table 2: Frequency distribution of risk factors of ectopic pregnancy

Risk factor	Ectopic pregnancy	
	No.	%
Age >35 years	16	34.0
Prior ectopic pregnancy	5	15.6
Pelvic inflammatory disease (PID)	10	31.2
Intra-uterine contraceptive devises (IUCD)	2	6.2
Induction of ovulation	5	15.6
Smoking ≥20 cigarettes/day	2	6.2
Previous surgery	9	28.1
More than one risk factor	20	62.5
None	3	9.4

Among the 47 patients, ultrasound findings included an adnexial mass seen in (19/47 women, 40.2%), and free fluid in (28/47 women, 59.8%) table (3).

The mean and median pretreatment β-hCG levels respectively were 2215 and 974 mIU/ml. table (4) , and for post treatment table (5) fig 2.

Table 3: Ultrasound finding of cases

Finding	No.	%
Adnexial mass	19	40.2
Free fluid	28	59.8
Total	47	100

Table 4: Laboratory parameters (pretreatment)

Pretreatment β-hCG	No. of patients	Percentage
649-790	18	38.3%
791-970	9	19.2%
971-2897	7	14.9%
2898-4367	5	10.6%
4368-7890	8	17%
Total	47	100%

Table 5: Laboratory parameters for **β-hCG(post treatment)**

post treatment β-hCG	No. of patients	Percentage
974-118.5	9	24.3%
119.5-145.5	6	16.2%
146.5-434.55	7	18.9%
435.55-581.85	8	21.6%
582.82-1183.5	7	18.9%
Total	37	100%

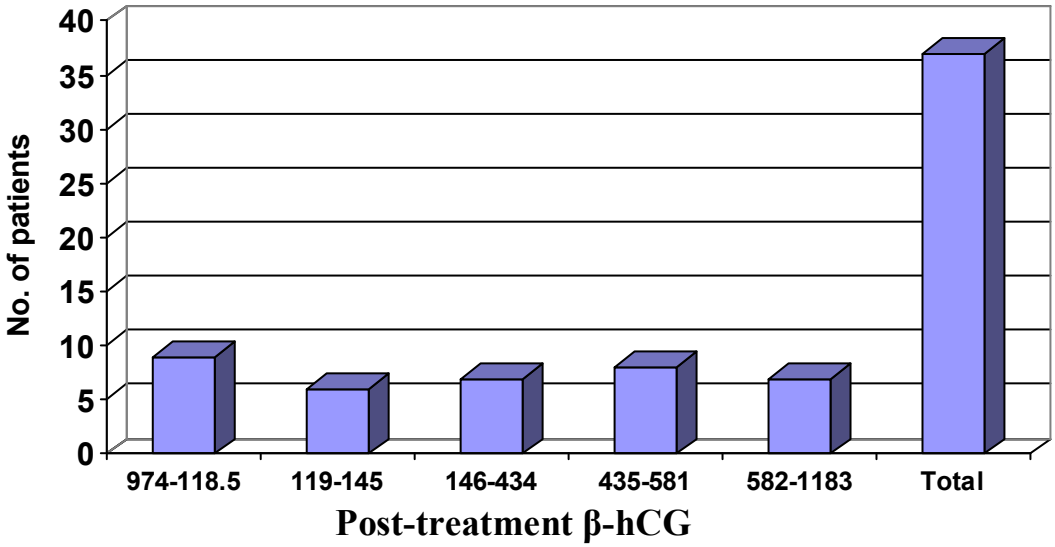

Figure 2: The post-treatment β-hCG of the examined sample.

Of the 47 patients who were eligible for our study ,37 patients (78.7%) were treated successfully with MTX as IM single dose ,six patients needed second dose MTX intramuscularly and the rest four patients needed surgical interference, as shown in table(6).

The median time until the resolution of the ectopic pregnancy was 28 days, when a second dose of MTX was required, the ectopic pregnancy took 48 days to resolve compared to 20-28 days in ectopic pregnancies that did not required a second dose, as shown in table (7) and figure (3). Only 6 patients received a second dose of MTX because they did not have the appropriate β-hCG decline between day 4 and 7.

Table 6: Outcome of the cases treated with MTX.

Fate	**No.**	**%**
Success rate	37	78.7
Failure rate (surgical interference)	4	8.5
Failure rate (2^{nd} dose)	6	12.8
Total	47	100

Table 7: Days to resolution

Days	**No.**	**%**
28	10	27
27	6	16.2
26	5	13.5
25	3	8.1
24	8	21.6
23	1	2.7
21	2	5.4
Total	37	100

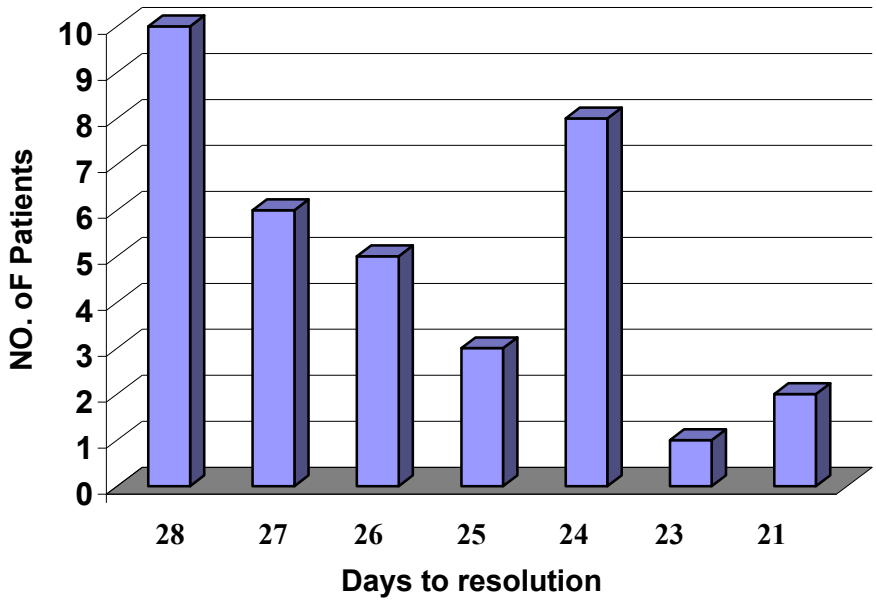

figure (3). Bar char of demonstrate No. of patients with days to resolution after treatment with MTX

The median pretreatment β-hCG level in the successfully treated patients was significantly lower than in patient with treatment failure (974 vs. 3804 mIU/ml, P<0.05). The success rate increased as the pretreatment β-hCG level decreased, as shown in table (8), only 6 patients received asecond dose of MTX because they did not have the appropriate β-hCG decline between day 4 and day 7(table 9)

All patients had a continued rise in β-hCG titer for at least 4 days after MTX injection although all levels begun to decline by day 7.

Few patients experienced minor side effects, like nausea and occasionally vomiting.

Table 8: Comparison between Pre- and post treatment with MTX

	Mean	SD
Pre-treatment	2215.0	±1801.4
Post-treatment	332.25	±270.2
Difference*	1882.75	±1531.21

* Highly significant difference (P=0.0001)

Table 9: Frequency distribution regarding women with ectopic pregnancy treated with MTX

Characteristics	**No.**	**%**
Treatment outcome		

Success rate	37	78.7
Failure rate (surgical interference)	4	8.5
Failure rate (2nd dose)	6	12.8
Days to resolution (median)	28	
Second dose MTX	6	12.8
Laboratory parameters		
Mean pretreatment β-hCG (mIU/ml)	2215	
Median pretreatment β-hCG	974	
15% fall of days 4-7 β-hCG	17	
Ultrasound finding		
Adnexial mass	19	40.4
Free fluid	28	59.6

Discussion:

Ectopic pregnancy continues to be a major cause of maternal morbidity and mortality. Accurate diagnosis rests on a combination of clinical history, serum β-hCG and sonographic appearance .[8] The incidence of ectopic pregnancy had doubled or trebled in most industrialized countries in the last 20 years[9].

This increase result, in part from an increase in pelvic inflammatory disease (P.I.D), the largest risk factors are upper genital tract infection due to sexually transmitted disease (STDs), of the long

prevalence of these factors as causative for ectopic pregnancy.

Until fairly recently, the only treatment that was widely available for ectopic pregnancy was an open operation. This meant a long stay in hospital and recovery time afterwards. A recent review [13] showed that the standard or commonest treatment for ectopic pregnancy has become laparoscopic salpingostomy .However, factors such as the length of amenorrhoea, the level of hCG and the women fertility status can lead to alternative treatments.

In an initial series of over 100 cases selected for treatment according to defined criteria with systemic MTX, the failure rate has been reported as low as 5-8 % [14, 15,16].

Localized injections into the ectopic site avoid the systemic risk of neutropenia and stomatitis which account 3% of patients [17].

A meta-analyses of 540 patients treated with single dose MTX showed that 84% did not required term complication of P.I.D are adhesion formation leading to infertility and ectopic pregnancy[10].

Two French studies [11,12] showed (50%) patients with an ectopic pregnancy had a history of salpingitis. Swedish prospective study show that the risk factors of ectopic pregnancy is six times higher following clinical salpingitis [10].

Highest risk factors for ectopic pregnancy in our study was multiple risk factors, age and PID, this was evident in (62.5%, 34,0 % and 31.2%) of cases this was in concordance with previous studies as P.I.D & STDs being the major risk factor. Preventive measures are needed to reduce the further treatment and 215 patients who attempted to conceive, 54% had subsequent intrauterine pregnancy and 8% had a recurrent ectopic pregnancy[13].

In our study our over all success rate (78.7%) is comparable with other studies that range from approximately 75% as with the three years experience in Northwestern Memorial hospital [18] and >90% as with Lipsdomb[19].

Our finding was in agreement with Megan et al who identified the successful use of IM MTX as a single dose treatment for ectopic pregnancy [20].

Patients for whom IM MTX therapy failed to resolve the ectopic pregnancy underwent an operation because of increasing pain and or inappropriate decline β-hCG levels after single treatment dose.

In conclusion, single dose of IM Methotrexate was associated with a high success rate in selected cases of ectopic pregnancy especially after

exclusion of factors which causes treatment failure, by increasing knowledge of natural history of ectopic pregnancy after methotrexate therapy has facilitated the identification of both appropriate candidates for non-surgical therapy and the potential complication of therapy, and these results are encouraging and we propose to continue this treatment depending on total adhesion of the patient to medical monitoring. The availability of newer and more sophisticated diagnostic tools allows ectopic pregnancy to be diagnosed early, before tubal rapture, without the need for surgical interference or the use of laparoscopy.

It is recommended that, Conservative treatment preserves the possibility of tubal function and may be particularly useful where there is limited access to in vitro fertilization, this conservative treatment requires early diagnoses which depend mainly on high index of suspicion (more than one transvaginal ultrasound in the large center at least one in the labour room and training of graduate student on it is needed to achieve such thing) and hence we may omit β.hCG and comensional ultrasound by color Doppler ultrasound prior to treatment.

References

1- Neerja Bhatla, MD. Ectopic pregnancy.In international (ed). Jeffcoate's Principles of Gynecology, 5th edition, Arnold A, 2001, 208-209.

2- Stuart Campbell and Ashmona. Ectopic pregnancy. In Gynecology *by* ten Teachers, 17th edition. Arnold. 2000; p: 108.

3- NCHs. Advanced reported of final mortality statistics, 1992. hyattsville. MD, US Dept of Health and Human Services, Public Health Service, CDC, 1994. (Report No. 43, Suppl).Lange, 1997; p 607-17.

4- Westrom L. Influence of sexually transmitted diseases on fertility and ectopic pregnancy. Acta Eur Fertil, 1985; 16:21-4.

5- Lipscomp GH,et al. Nonsurgical treatment of ectopic pregnancy .New England Journal of Medicine, 2002; 343(18):1325-1.

6- American College of Obstet and Gynecologist. Medical management of tubal pregnancy. ACOG practice Bulletin, No.3. Washington, DC: American college of obstetrician and gynecologist, 1998.

7- Zilber U, Pansky M, Golan A. Local laparoscopic salpingostomy versus laparoscopic MTX injection in the management of un ruptured ectopic pregnancy. Am j Obstet Gynecol1996; 175: 600-2.

8-Stacey CM, Borton SE and Signer progress 9A, Pelvic inflammatory disease. In Studd J(ed) progress. Churchill Livingstonc, 1991, vol. 9: 228.

9- Levin AA, Schoenhaum SC, Stubblefield PG, Zimicki S; Ectopic pregnancy and prior induced abortion. Am J Public Health, 1982; 72: 253.

10- Coste J, Job-spira N, Fernandez H, Papiernik E, Spira A: Risk factors of ectopic pregnancy: A case control study in France, with special locus on infectious factors. Am J Epidemiol, 1991; 133: 839.

11- Stabile I, Gradzinskas JG. Ectopic pregnancy: A review of incidence. Etiology and diagnostic aspects- Obstet Gynecol Survey 1990; 45: 335-47.

12- Stika CS, Anderson, Fredrikson MG. Single dose MTX for ectopic pregnancy: Northwestern Memorial hospital three year experience Am J Obstet Gynecol 1996; 174: 1840-6.

13- Lappas CA, Giannakodiamos GG.Treatment of unraptured tubal pregnancy by local injection of MTX and progesterone $F_{2\alpha}$ in 52 patients .Fertility and serility, 1991; 56: 1196-97.

14- Fernandez H, Benifla JL, Lelaidier C et al. Methotrexate treatment of ectopic pregnancy: 100 cases treated by primary transvaginal injection under sonographic control. Fertility and Sterility, 1993; 59: 773-49.

15- Kooi S,Kock HC. A review of literature on non surgical treatment in tubal pregnancy, Obstetric and Gynecological Survey, 1992; 47: 739-77.

16- Slaughter JI, Grimes DA. A review of the literature on non-surgical treatment in tubal pregnancy. Obstetrics and Gynecological Survey, 1992; 47: 739-49.

17- Slaughter JI, Grimes DA (1992) a review of the literature on non-surgical treatment in tubal pregnancy. Obstetrics and Gynecological Survey 47, 739-749.

18- Verna L. Rose ACOG Issues Report on the Medical Management of Tubal Pregnancy, American Family Physician, 1999, 1-3.

19- Megan B. Potter, MD, Lisa A. Leptin, MD, and Denice J., MDMPH, Predictors of success with MTX treatment of tubal ectopic pregnancy at Grady Memorial hospital Am J Obstet Gynecol , 2003, volume 188,no.5.;1191-4.

20- Yao M, Tulandi T. Current status of surgical and non-surgical management of ectopic pregnancy. Fertility and sterility, 1997; 67: 421-33.

Senior lecturer, In Obestetrics and Gynecology, Al-Mustansiriya University, Medical College)