

Single dose Methotrexate injection, could be a safe and effective treatment for early cases of tubal ectopic pregnancy, with minimal maternal health hazards

Original
Article

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ABSTRACT

Objective: The current study aims to evaluate two methods of management of early cases of tubal ectopic pregnancy. The first method is described as a conservative medical method in which we use a chemotherapeutic agent (Methotrexate) to eradicate the ectopic tubal conception, whereas the second method implies a conservative laparoscopic surgery in which overwhelming efforts are done in order to maintain a tube affected by ectopic pregnancy as healthy as possible following removal of the ectopic pregnancy mass. The fallopian tubes are assessed for patency and tubal lumen contour and pattern 3 months following successful treatment, in order to detect which method would lead to a high cure rate with the least tubal detrimental effect.

Patients and Methods: In the current study, 58 patients diagnosed with tubal ectopic pregnancy were given Methotrexate as a first choice chemotherapeutic agent aiming to resolve the ectopic pregnancy, whereas 58 patients with the same condition gone directly through laparoscopic salpingostomy, with the aim of maintaining patent healthy tube finally after successful treatment.

Results: The study revealed no significant difference for either treatment modalities in affecting the rate of bilateral tubal obstruction, or tubal patency with a recognized tubal defect with a $p > 0.05$. On the other hand, cases with unilateral tubal obstruction involving the affected tube were remarkably increased in the methotrexate group (13 cases) out of 52 cases with successful treatment compared to 6 cases successfully treated by salpingostomy (6 cases) out of 52 cases successfully treated, with a $p < 0.05$.

Conclusion: In conclusion, single dose methotrexate has proven to be a safe, effective and reasonably convenient treatment for most patients, shown during counseling to be so worry about surgery and its potential detrimental consequences on their future fertility. Yet, it should be obviously highlighted that such concepts and perspectives for keeping fertility can't be taken as for granted and a guarantee for a healthy patent tube as it is quite obvious that even with successful elimination of the chorionic tissue in the tube, the affected tube might still be blocked and with a significant rate further exceeding the expected rate with laparoscopic salpingostomy.

Key Words: Tubal ectopic pregnancy, methotrexate, laparoscopic salpingostomy, hysterosalpingography, tubal patency

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INTRODUCTION

Ectopic pregnancy is defined as the abnormal implantation of the blastocyst outside the uterine cavity. The estimated prevalence rate of such condition thought to be about 2% of all human conceptus^[1]. The fallopian tube is known as the most common site for implantation^[2] with the ampullary, isthmus and initial end of the tube all being recognized as possible sites of implantation. In addition to the possibility of interstitial tubal portion, ovarian, abdominal and cervical implantation, even the site of previous cesarean section scar^[2] could be an implantation site. Since the fallopian tube is the usual site of fertilization, more than 95 % of ectopic pregnancies occur in the fallopian tube followed by 2.5% in the cornu of the uterus and the others occur in much less common sites such as the ovary, cervix and the abdominal cavity^[3]. It is clear that all

the mentioned sites for ectopic pregnancy are ultimately confined spaces not permitting any considerable expansion to accommodate a growing embryo with consequent rupture and hemorrhage. Ruptured ectopic pregnancy is a leading cause of maternal mortality in the first trimester accounting for 10-15% of all maternal deaths, thus representing a true medical emergency^[4,5].

There are different risk factors contributing to the increased incidence of ectopic pregnancy in the past decades, those are partially due to the advancement in the diagnostic methods and tools leading to more precise diagnostic capability. Yet from other perspective, sexually transmitted disease, pelvic inflammatory disease, increased rate of pelviabdominal surgeries and the utilization of artificial reproductive technology on wide scale could also greatly account to the overall suspected increased rate^[1].

Some of these conditions result in scar tissue at the fallopian tubes, hindering the usual motion of the fertilized ovum on its way to the intrauterine implantation site with substitutive implantation in the fallopian tube^[6]. Endometriosis is also considered of the major risk factors^[7,8].

Traditionally surgery has been the classical treatment of ectopic pregnancy, with laparoscopic salpingostomy highly utilized as an option, yet an increasing trend towards medical chemotherapeutic treatment in early diagnosed cases in order to avoid the surgery associated distortion of the tubal anatomy and at the same time avoiding the possible risk of residual trophoblastic tissue being left behind with conservative laparoscopic surgery^[9]. There is a growing consensus that women with visible ectopic pregnancy and low plateauing serum HCG concentration could be offered the option of medical treatment with methotrexate^[10] as it proved to yield superb curative results compared to diverse medication that might cure such condition, as prostaglandins, dactinomycin, etoposide, hyperosmolar glucose, anti HCG antibodies, potassium chloride and mifepristone^[11]. Methotrexate acting as folic acid antagonist; it combines with tetrahydrofolate reductase inhibiting the formation of Purim and pyrimidin bases essential for the formation of DNA and RNA, its action is exerted on cells of fast replication including trophoblastic cells^[12].

Hysterosalpingography (HSG) is the radiographic evaluation of the uterine cavity and fallopian tubes using a radio-opaque medium injected intrauterine through the cervical canal, such substance make it possible to outline the whole uterine cavity delineating its contour in addition to outlining the pattern of the fallopian tubes along the full length and revealing the degree of spillage; diagnosing any tubal obstruction on either or both sides. Accordingly and due to its safety and relatively cheap availability, it had much acceptance as suitable graphing method for assessment of tubal latency following treatment of ectopic pregnancy^[13].

AIM OF THE STUDY

The main aim of the study was to compare methotrexate single intramuscular (IM) injection vs laparoscopic salpingostomy as 2 conservative modalities for treating ectopic pregnancy. As well as to investigate how successful either method in resolving the ectopic pregnancy and to investigate the long term residual effects of both treatment methods on the fallopian tube regarding patency and tubal defects.

PATIENT AND METHODS

In the duration between September 2012 and March 2016, the number of 156 patients were inspected and examined in the emergency room (ER) and outpatient clinic of Obstetrics and Gynecology Department at Saudi German Hospital Jeddah and Al Galaa Maternity Teaching Hospital, all patients were presented with B-HCG level ranging between 3000 and 8000 mIU/ml without any

gestational sac visualized intrauterine using 7.5 MHz vaginal probe of a Phillips HD 15 system ultrasound machine, in addition to an associated adnexal mass detected in either side of the adnexa, during sonographic pelvic scanning, with an adnexal size mass ranging between 2 and 4 cm. In small number of those adnexal masses, heart pulsation was seen (11 cases) due to the small number of pulsating hearts seen in the ectopic masses. Patients with pulsation were not considered in the 156 patients of our study. Patients had their B-HCG checked for its value every 48 hours and those with B-HCG increase with a value less than 40% in 48 hours duration were considered suitable candidates to be included in the study; such cases with suggested ectopic pregnancy were evenly distributed into 2 groups, group (A) included 58 patients and group (B) included the same number of patients. The patients were counselled about sharing in the study and were given the option to choose between conservative surgical salpingostomy via laparoscopy versus medical treatment attempt using methotrexate as a chemotherapeutic agent to treat and resolve the condition. Both groups were informed the probability of failure of either therapeutic modes with laparoscopic salpingectomy versus open surgical salpingectomy are to be considered as salvage procedure to resolve the condition and stop any morbid bleeding that might threaten and put the pregnant lady in further risk.

Both groups had to fulfil some inclusion criteria, also some exclusion criteria had to be considered during group selection. All patients were in an age range between 19 and 39 having a B-HCG level between 3000 and 8000. Parity was not considered exclusion criteria, so primigravidas as well as multigravidas were included in the study only those with previous history of ectopic pregnancy as well as those with definite history of infertility were excluded from that study.

The exclusion criteria included morbid obesity with a BMI above 45, any appreciable amount of fluid detected intraperitoneal (a set off 75 ml level) was predetermined, marked pelvic pain existing without provocative pelvic examination. Also, history of previous ectopic pregnancy, definite history of infertility or the use of assisted reproductive technology to conceive were all considered exclusion criteria. Patients with autoimmune disease, abnormal liver, kidney functions, blood picture or coagulation profile as well as history suggestive of pelvic inflammatory disease, or endometriosis were excluded. IUD with ectopic pregnancy was also considered as exclusion criteria. Patient with malignant tumor, vaginal bleeding or diabetes mellitus were not included in the study.

The patients who received methotrexate as the first treatment option were informed about the possible side effects of methotrexate which included bone marrow depression with associated agranulocytosis, stomatitis, temporary oropharyngeal ulcers, temporary appearance of facial dark patches, and possible occurrence of vaginal bleeding and marked drop of platelet count with bleeding tendency. Consents indicating the possibility of

persistently blocked tube on side after the end of treatment or persistently calcified pelvic mass or hematocele that might require drainage were explained and signed.

All the patients who were given methotrexate were admitted to the inpatient ward for intimate supervision. The given dose of methotrexate was a single IM injection dose of 50mg/m² of body surface area followed by B-HCG measurement the next day following the injection and then on 48 hours intervals thereafter. Also, CBC (complete blood count) was done on daily bases and liver and kidney functions every couple of days. Also, pelvic ultrasound imaging was done on 48 hours interval to follow the adnexal mass and any appreciable increase in pelvic fluid collection. During the stay of the patients under observation, any still existing increase in B-HCG 3 days post injection, or plateauing of its level 1 week post starting treatment or occurrence of any marked pelvic abdominal pain, or sudden increase in pelvic free fluid and associated sudden drop in hemoglobin and red cell count any or either emergence of such findings was considered indication for converting from conservative management into radical surgical management (salpingectomy of the affected tube), whether through open surgery or via laparoscopy.

On the other hand, group (B) patients for whom laparoscopic salpingostomy was the chosen treatment were followed up similarly on inpatient bases utilizing the same tools and investigations to follow up and monitor. The regression vs the progression of the adnexal ectopic chorionic tissue except for the liver and kidney function tests and patient was converted to surgery on the same prerequisite as group (A). Patients of both groups were finally discharged after 1 week on detection of findings showing favorable response to treatment and vital stability of the cases and were followed up at the outpatient office every 3 days for 2 weeks utilizing (CBC), B-HCG and transvaginal pelvic ultrasonographic scanning. At the end of 3 months post implementation of treatment, HSG was done to check patency of either fallopian tubes or occurrence of noticeable defects. In cases where radical surgery was done with removal of the affected tube were spared doing the HUG investigation.

Statistical methods

IBM SPSS statistics (V.24.0 , IBM Corp, USA, 2016) was used for data analysis. Data were expressed as mean ±

SD for quantitative parametric measures in addition to both number and percentage for categorized data.

The following tests were done:

1. Comparison between two independent mean groups for parametric data using student t test.
2. Chi square test to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data.
3. Comparison between 2 proportions as regards univariate categorized data the probability of error at 0.01 and 0.001 are highly significant.

RESULTS

In the current study, patients presented to the emergency room and outpatient clinic with pregnancy of unknown location and proven to be after full investigation a tubal ectopic pregnancy, were divided into two groups. Group (A) included 58 patients for whom methotrexate injection was given as a method to treat the condition; while group (B) included 58 patients for whom laparoscopic salpingostomy was offered to resolve the condition. Six patients were excluded in each group due to failure of treatment and proceeding to salpingectomy as a salvage procedure.

Both groups showed similarity in age with a mean age of 29.62± 4.065 for group (A) compared to a mean of 29.28±3.915 for group (B) with a non-significant *P value* of 0.64.

Similarly, B-HCG level before implementing treatment showed a non-significant *P value* of 0.36 with a mean value of 6617± 1291 for group (A) compared to a value of 6399± 1263 for group (B). Adnexal mass also did not show any significant size difference (P 0.95) before starting the treatment with a mean adnexal mass size for group (A) of 3.183± 0.459 vs 3.178± 0.432 for group (B).

Regarding tubal patency, there was no significant difference in number of patients with radiographically normal looking tubes with free pelvic spill in both groups as well as in the number of patients with bilateral tubal obstruction, unilateral or bilateral tubal defect. Whereas, there was significant difference regarding the numbers who showed unilateral tubal obstruction 3 months post treatment with more cases in the methotrexate group.

Table 1: Comparison of B-HCG level between both groups showing non-significant difference with *P value* of 1.000

B-HCG level	Count &percentage	Methotrexate	Salpingostomy	Total
3000-5000	Count	12	12	24
	Percentage	20.7%	20.7%	20.7%
5000-8000	Count	46	46	92
	Percentage	79.3%	79.3%	79.3%
Total all together	Count	58	58	116
	Percentage	100%	100%	100%

Table 2: Comparison of adnexal mass size between both groups, showing non-significant difference with *P value* of 0.846

Adnexal mass size	Count &percentage	Methotrexate	Salpingostomy	Total
2-3cm	Count	21	20	41
	Percentage	36.2%	34.5%	35.3%
3-4cm	Count	37	38	75
	Percentage	63.8%	65.5%	64.7%
Total	Count	58	58	116
	Percentage	100%	100%	100%

Table 3: Comparison of parity in both groups with no significant difference with *P value* 0.980

Parity	Count &percentage	Methotrexate	Salpingostomy	Total
Pg	Count	5	5	10
	Percentage	8.6%	8.6%	8.6%
P1	Count	9	11	20
	Percentage	15.5%	19%	17.2%
P2	Count	7	7	14
	Percentage	12.1%	12.1%	12.1%
P3	Count	16	18	34
	Percentage	27.6%	31%	29.3%
P4	Count	17	14	31
	Percentage	29.3%	24.1%	26.7%
P5	Count	4	3	7
	Percentage	6.9%	5.2%	6%
Total	Count	58	58	116
	Percentage	100%	100%	100%

Table 4: Comparing the normal tubal patency pattern, unilaterality, bilaterality of tubal defects, exclusion of doing HSG for tubal assessment and unilaterality/bilaterality of tubal obstruction utilizing transcervical canal injected radio opaque liquid material.

Tubal patency condition	Methotrexate	Salpingostomy	<i>P value</i>	Significance
Bilateral obstruction	3(3.4%)	1 (1.7%)	>0.05	NS
Excluded due failure of treatment	6 (10.3%)	6 (10.3%)	>0.05	NS
Normal tubes	29 (50%)	38 (65.5%)	>0.05	NS
Unilateral tubal obstruction	13 (22.4%)	6 (10.3%)	<0.05	Significant
Unilateral or bilateral tubal defect	8 (13.8%)	7 (12.1%)	>0.05	NS

DISCUSSION

The incidence of ectopic pregnancy is 1-2% in general^[14]. Such increase in incidence and early diagnosis were attributed to the advancement of technology and improved precision of the diagnostic tools such as transvaginal ultrasound, more sensitivity of pregnancy test to the minimal amount of B-HCG which lead to the early diagnosis of ectopic pregnancy^[15].

Asymptomatic women presented with suspected ectopic pregnancy with low serum B-HCG concentration can be managed expectantly utilizing both the B-HCG and transvaginal u/s counting in this sonographic management on the suggestive criteria of ectopic pregnancy (i.e. ectopic ring or mass and free fluid in the pelvic cavity.) With the elapse of time, it will eventually become clear that the ectopic nature of pregnancy vs abnormal intrauterine pregnancy^[16].

It has been well known that methotrexate injection could be offered as medical solution for cases with suspected ectopic pregnancy¹⁷. Also, laparoscopic salpingostomy, another surgical modality for ectopic pregnancy, was performed in addition to other more radical surgeries such as salpingectomy through laparoscopy and laparotomy^[17].

The current study was done over 3 years period in SGH Jeddah and included 116 patients presented with undisturbed ectopic pregnancy and B-HCG level between 3000-8000 miu/ml. The patients were divided into 2 groups depending on the treatment modality implemented to treat the ectopic gestational mass. Group A included 58 patients, who were given methotrexate injection once, with a dose of 50mg/m² body surface area and were followed by B-HCG level, complete blood picture and ultrasound 48 hours on inpatient care bases. Whereas group (B) also included 58 patients who fulfilled the same criteria as group (A) and went through laparoscopic salpingostomy

procedure to remove the ectopic mass and patients were followed up in the same manner on inpatient bases and all patients were kept under direct intimate observation for 1 week, and discharged as B-HCG started leveling down and were followed up there after for 3 months in regularly scheduled visits twice weekly for the first 1 week. Then, once weekly for 1 month and twice monthly up till the end of the predetermined 3 months duration. They were also informed to present immediately to the ER or outpatient clinic on having any sudden pelvic pain, occurrence of marked vaginal bleeding or feeling of dizziness or fainting attack.

In one aspect, B-HCG level did not show any significance in the extent of response to treatment that would favor either treatment methods on comparison with a P value >0.05 . Also, there was no significance for the ectopic mass size in determining response to either treatment modalities.

Concerning tubal patency, there were no significant differences regarding normal radiographic tubal pattern with free spill, bilaterally of tubal obstruction or unilateral and bilateral tubal defect 3 months post successful treatment with P value >0.05 . Exceptionally, a significant increase in unilateral tubal obstruction was noticed in the methotrexate group 3 months post successful treatment with a $p <0.05$, proved methotrexate treatment for management of ectopic pregnancy to be associated with larger number of blocked tube at the affected side.

In other study by Grau EG *et al.*^[6], utilizing methotrexate as a chemotherapeutic agent for treating 144 cases with ectopic gestation with 3 different modes of the drug administration to the patients in such a way that 84(58%) patients injected with methotrexate intramuscular, while 60 (41%) of patients were injected the same medication intravascular via laparoscopy or guided by ultrasonography. Regardless of the method of drug administration, the success rate for the initial injection in resolving the ectopic pregnancy was 91% showing a failure rate of only 9%, that is only 13 cases required further management and even the majority of those cases showed a good response with full resolve of the ailment by a second IM dose of methotrexate injection (10 cases out of 13 cases), while salpingectomy was done for 3 cases as a second line of treatment.

Such results showed great compliance with the retrieved results in the current study, in which out of 58 cases who were offered methotrexate injection as a first choice of treatment, only 6 failed to respond to treatment (10.3%) out of the total number of cases in the methotrexate group and proceeded directly to salpingectomy either through laparoscopy or through open surgery to remove the affected tube with the ectopic mass in Toto. Patients for whom salpingostomy was done showed compliance of results with both the methotrexate IM injection group (A) in the present study and the Grau EG *et al.*^[6] study.

Concerning tubal patency in the current study, 50% of the patients who were given methotrexate intramuscular

injection showed bilateral tubal patency on HSG 3 months post implementing treatment, that number is not showing any significant statistical difference when compared to the number of normal HSG post salpingostomy (65.5%) with a P value of 1.689. While in the study by Grau EG *et al.*^[6], the number of patients who showed normal HSG post treatment had a figure of 72.2%. On the other hand concerning unilateral tubal obstruction, in the current study, there was a significant difference noticed in favor of cases for whom salpingostomy was done compared to those who received methotrexate (13 patients with unilateral obstruction in the methotrexate group) compared to 6 cases in the salpingostomy group with a P value <0.05 . Grau EG *et al.*^[6] in accordance with the current study showed 18.8% of the patients displaying unilateral obstruction, 2.8% showing bilateral obstruction, while 6.3% demonstrated tubal patency though with a defect.

In another study by Mostafa A. A. and Abdel-Rahman H. M.^[17] to assess the value of tubal patency test after medical treatment of ectopic pregnancy, out of 72 patients with diagnosed unruptured tubal ectopic pregnancy, 32 received a single intramuscular dose of methotrexate (50mg/m²) whereas 40 women underwent surgical salpingectomy. Treatment was successful in 28 out of the 32 cases (87.5%); resolving the condition with no need of further management whereas 4 cases were given a second dose of intramuscular methotrexate to eliminate the persisting ectopic pregnancy, yet still 2 cases of them were in need of surgical salpingectomy. Finally 83.3% (25 out of 30 cases) who received methotrexate as treatment showed ipsilateral tubal patency of the tube involved with the ectopic pregnancy, with 93.3% of the patients having their contralateral tube patent. That figure is compared to 82.5% patent contralateral tube following salpingectomy of the involved tube. Such results more or less match with the current presented study in which we realized 37 patients out of 52 following successful methotrexate treatment had patent tubes whether with or without tubal defects.

In another study by Lipscomb GH *et al.*^[18] to assess single dose methotrexate for the treatment of tubal ectopic pregnancy, out of the 350 cases with tubal ectopic pregnancy who were given intramuscular methotrexate. 320 women were successfully treated (91%) with a mean B-HCG level of 4019 ± 63 miu/ml compared to the B-HCG mean value of 13420 ± 16 miu/ml in the 30 women with failed methotrexate treatment. Out of the successfully treated women, 261 (82%) were cured by single dose methotrexate, such results showed concordance with the results in the current study in which 52 out of 58 patients were cured by a single dose of methotrexate with a failure rate of only (10.3%).

Lipscomb *et al.*, also concluded that B-HCG levels above 10000 miu/ml was a risk factor for failure of treatment with methotrexate, he reached that finding from his review of studies showing failure of methotrexate treatment of 9 cases out of 265 women with ectopic tubal pregnancy with B-HCG less than 10000 (3%) compared

to 6 out of 19 women with B-HCG concentration above 10000 mIU/ml (32%); those results are matching with the current study in which B-HCG levels were ranging between 3000-8000 mIU/ml.

CONCLUSION

In conclusion, it is quite clear that methotrexate is a safe and effective treatment in the management of cases with early detected ectopic tubal pregnancy and single precisely calculated intramuscular dose would be quite adequate in resolving the condition with no appreciable consequence on the long run other than slightly increased incidence of ipsilateral tubal block in comparison to laparoscopic salpingostomy.

CONFLICTS OF INTEREST

There are no conflicts of interest

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