

Comparison the Results of Hysterosalpingography in Patients with Ectopic Pregnancy Treated by Laparoscopic Salpingostomy, Laparotomy, and Treated with Methotrexate

Abstract

Background: Ectopic pregnancy (EP) occurs in 1% of pregnancies, and may seriously effects on women's health and future fertility so this study aimed to compare the results of hysterosalpingography (HSG) after treatment of EP by laparoscopy, laparotomy, and methotrexate (MTX) therapy. **Materials and Methods:** This was a clinical trial study was done on 112 EP women with treatment indication referred to Isfahan Al-Zahran and Shahid Beheshti Hospitals from 2017 to 2018. They were divided into 33 populated groups of laparoscopic salpingostomy, laparotomy and MTX. Then patients of three groups underwent HSG 3 months after intervention. The factors such beta human chorionic gonadotropin (β -hCG) (mIU/mL), size of EP (mm), infection, hospital length of stay (LOS), and tubal patency were recorded and compared between the groups. **Results:** There were no significant differences between groups for age, body mass index, β -hCG, Size of EP, and hospital LOS ($P > 0.05$). The infection was more frequent in laparotomy group with no significant difference among three groups. The infection rates were 9%, 12%, and 6% for MTX, laparotomy, and laparoscopy arms, respectively. Between the three groups tubal patency as primary outcome had higher frequency than laparoscopy group, although, the difference was not statistically significant ($P = 0.595$). **Conclusion:** Although infection was more in laparotomy and that tubal patency was more within 3 months in laparoscopy and MTX, there were no statistically significant differences in the results of laparoscopy, laparotomy, and MTX in HSG results.

Keywords: Ectopic pregnancy, Hysterosalpingography, laparoscopy, Salpingostomy, laparotomy, Methotrexate

Introduction

Ectopic pregnancy (EP) is defined as the abnormal implantation of an embryo outside the uterine endometrium that it mostly occurs in a fallopian tube (in the ampullary section, fimbrial end or isthmus).^[1]

The number of EP cases has been increasing in recent years, due to improved earlier diagnostic techniques and continues to be a major cause of morbidity and mortality in reproductive-age women that complicates 1%–2% of all pregnancies. The risk factors of EP include pelvic inflammatory disease, cigarette smoking, assisted reproductive techniques (ARTs), and cesarian sections.^[2,3]

Further, an increased incidence of sexually transmitted infections, earlier diagnosis of pelvic inflammatory disease resulting in tubal damage but not complete blockage, and the rise in the

number of ectopic pregnancies resulting from ART may account for the overall increase.^[4] The current treatment options include medical (Methotrexate [MTX]) and surgical (salpingectomy, salpingostomy, or milking) approaches. Although the classic treatment of EP is surgical, early diagnosis allows the implementation of a medical treatment for most women with un-ruptured EP.^[5] As a medical treatment, MTX, which is an effective chemotherapeutic agent that acts as a folic acid antagonist targeting actively proliferating cells, is widely used for different types of ectopic pregnancies.^[6] Although single-dose systemic MTX treatment is accepted as a highly effective, noninvasive treatment for EP, there is an important concern of adverse effect on fertility by targeting actively dividing cells within the ovaries. In addition, surgical treatment may also have a negative effect on ovarian reserve.^[7]

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However, there are controversial results according to the effect of MTX and surgical treatment on ovarian reserve.^[8-11]

Early diagnosis of EP and better access to care has shifted concern to the issue of preserving subsequent fertility. Fertility is compromised in women whose first pregnancy is ectopic. Well-developed ARTs could improve long-term delivery rates in women with Eps.^[12]

Medical therapy of EP is appealing over surgical options for a number of reasons, including eliminating morbidity from surgery and general anesthesia, potentially less tubal damage, and less cost and need for hospitalization. Several medical treatments have been used such as prostaglandins, actinomycin, etoposide, hyperosmolar glucose, anti-human chorionic gonadotropin (hCG) antibodies, potassium chloride, or mifepristone. However, the treatment with MTX has shown better results and is presently considered the first option for medical therapy.^[13] The effect of different management strategies on subsequent fertility following tubal EP is unknown. Some small studies have shown that tubal patency and future reproductive outcomes are significantly improved in women managed expectantly compared with those who underwent surgery.^[14] The main concern following management of an EP is the risk of recurrence and future fertility outcome. Fertility outcome for these patients can be evaluated by hysterosalpingography (HSG) or future pregnancy.^[15] HSG is the radiographic evaluation of the uterine cavity and fallopian tubes after the administration of a radio-opaque medium through the cervical canal. It is a safe and inexpensive procedure, being the most cost-effective method in the study of the fallopian tubes.^[16] HSG plays a crucial role in infertility evaluation to determine the anatomic causes of female subfertility and/or infertility, especially for uterine structure and tubal status abnormalities with high reproducibility. Hence, considering the high prevalence of EP and high mortality and morbidity and lack of adequate studies in treatment of this disease and comparison the results of different therapeutic approaches, the aim of this study was to compare the results of HSG after treatment of EP by laparoscopy, laparotomy, and MTX therapy.

Materials and Methods

This was a clinical trial study that investigated HSG results following treatment of patients with EP by laparoscopic salpingostomy, laparotomy, and MTX treatment in Isfahan Al-Zahran Hospital in 2017. It has been registered in the Iranian Registry of Clinical Trials (IRCT) with the code of IRCT20201111049352N1. The patients with a history of EP and treatment indication were entered the study. The sample size was calculated as 112 using formula of comparing ratios considering the respective parameters of $Z_{1-\alpha/2} = 1.96$, $Z_{1-\beta} = 0.84$, $(P_1 - P_2) = 0.05$.

Before the research onset, patients were asked to sign the informed consent form in case of tendency to take part in

the study. Prior to entry of patients to study, demographic information including age, history of underlying diseases such as blood disorders, liver disease, renal disease, radiographic contrast sensitivity were recorded from patients' files.

Inclusion criteria were the Mass diameter <3.5 cm, Stable hemodynamics, beta hCG (β -hCG) <5000, No EP reoccurrence in one side pipe, lack of embryonic heart activity in the EP, lack of history of blood disorder, renal-liver disease, lack of lung disease, or active peptic ulcer and No breast-feeding. Subjects were excluded from the study in the case of Sensitivity to MTX, radiology contrast sensitivity, reluctance to continue participation in research and incidence of pelvic infection. Qualified individuals were randomly assigned to one of the research groups using Random Allocation software.

Laparoscopic surgery method was so that 11 mm trocar enters the abdomen from umbilical region after development of pneumoperitone by electronic pneumoperitone. Then, the laparoscope, attached to the Xenon cold light, enters the respective trocar and attaches to the camera at the outer end. Following the abdominal and pelvic area examination under direct vision, two 5.5 mm trocars were inserted into the lower abdomen (the outer edge of the left and right iliac region) for passage of the surgical instruments. First, the tube was identified and released by a microelectrode laser or a 1–2 cm cut was done by scissors in the antimesenteric part of the tube just in the thinnest part containing tube pregnancy. Pregnancy product often spontaneously emerged from the incision and calmly exited the tube, or it was removed using hydro dissection and laparoscopic forceps. Washing with pressure of the tube opening separates pregnancy products from its implantation site. Pregnancy products were removed by the of 5 or 10 mm trocar.

In Laparotomy surgery, a 10–15 mm incision was created at the antimesenteric margin on the EP after opening abdominal layers and ovarian expose. Pregnancy product often is removed from the incision site. Pregnancy products can be removed precisely or they can be removed using high pressure washing system, which causes more complete removal of trophoblastic tissue. Small bleeding sites were controlled by electro-coagulation of needle and incision site was left without stitching so that it recovered through secondary healing. In order to keep homeostasis in both laparoscopic and laparotomy methods, in some cases, an electrocautery was used and after the surgery, the abdomen was washed with an average of 1 L of warm normal saline.

In the other group of patients, MTX was intramuscularly injected as mg/m² 50 single dosage, and the medicine effect would be evaluated by serum series measurement at 1st, 4th, and 7th day. If serum level of β -hCG was not reduced by 15% from 4th to 7th day, or if the reduction level was <15% within the weekly supervision, additional dosage would be needed.

Then, patients of three groups underwent HSG. It was done 3 months after intervention, 2–5 days after onset of the menstrual period, but before the ovulation period, so that it was ensured about the subject was not pregnant. If women suffer from pelvic inflammatory disease, the HSG was not performed. The last night laxative was used to empty the intestine. Before taking the procedure, the patient was given an analgesic and was prescribed appropriate antibiotics before and after the procedure. Patients were asked about the history of drug allergy. They were examined laying on the examination bed and their feet were placed on the pedal. A speculum was placed in the vagina, the cervix was cleaned, and a catheter was passed through the cervix. Then, speculum was removed. The specific solution was injected through the catheter so that it entered the uterus - uterine tube and pelvic cavity, and imaging was done in various steps. In abnormality cases, a delayed image was taken after 30 min. Then, occurrence of abnormality, opening of tubes, and adhesion was studied and compared.

The collected data were analyzed using SPSS 20 software (SPSS. Inc., Chicago, Ill., USA). Quantitative data reported as mean ± standard deviation and qualitative data reported as the numbers and percent. Statistical tests used for data analysis include Chi-square test and one-way variance analysis. $P < 0.05$ was considered as significant in all analyses.

Results

One hundred and twelve patients were reviewed to selected eligible patients, 13 patients did not enter (nine subjects were not eligible and four refused informed consent). Ninety-nine eligible patients randomly allocated into three intervention groups. Finally, 33 patients in each group completed the study and analyzed [Figure 1].

The mean of age in studied participants was 28.6 ± 6.9 years (16–41 year). Other demographics and clinical characteristics according to treatment groups are shown in Table 1. As it shown in Table 1, there were no significant differences between groups for age, body mass index (BMI), β -hCG, size of EP and hospital length of

stay ($P > 0.05$). The infection more frequent in laparotomy group. However, it was not significantly different among three groups. The infection rates were 9%, 12% and 6% for MTX, laparotomy and laparoscopy arms, respectively).

Tubal patency as primary outcome was in higher frequency than laparoscopy group, although, the difference between groups was not statistically significant ($P = 0.595$).

Discussion

Despite the increasing incidence of EP since the mid-twentieth century due to numerous factors, advancements in early diagnosis and treatment have decreased maternal morbidity and mortality.^[1,2] As the current treatment options are focused on decreasing the mortality and morbidity related to EP there are controversial study results in the literature.

This study was performed on three groups of 33 EP women treated with laparoscopy, laparotomy, and MTX and salpingectomy to evaluate the results of HSG. The age range of the patients was between 20 and 35 years and the patients were mostly overweight; however, the three groups were similar in terms of age and BMI. In addition, the three groups were homogeneous in terms of β -hCG and EP and there were no significant differences between them.

The outcomes of these three therapies showed that infections in patients under laparotomy was more than that in both laparoscopic and MTX methods; however, this difference was not significant. In addition, the duration of hospitalization in all three groups was between 2 and 4 days, and no significant differences were found between the three groups in this regard. Finally, tubal patency was reported as a primary outcome of more than 80% in all three groups. In the two groups treated with laparoscopy and MTX, it was reported to be more than 90%, but these differences were not significant among the three groups.

Vermesh *et al.*, in a prospective study on the patients with unruptured EP in two groups of laparoscopy and laparotomy reviewed the postoperative complications, duration of hospitalization, recovery period, hospital costs, the openness of the fallopian tubes in the hysterosalpingography and the gestational age in the two groups. Both the methods were similarly reliable and useful; however, the laparoscopic procedure was very cost-effective and required a shorter recovery time. Pregnancy rate was higher in laparoscopy because of postoperative adhesion.^[17]

A systematic study of randomized controlled trials revealed that open salpingostomy reduced the closure of the tube compared with laparoscopic salpingostomy (4.2 vs. 12.5), which is probably due to an increase in the incidence of sustained trophoblast after laparoscopic surgery. However, there was no difference in the later openness of the fallopian tubes, or the incidence of intrauterine pregnancy or recurrence of EP. Only the amount of bleeding during

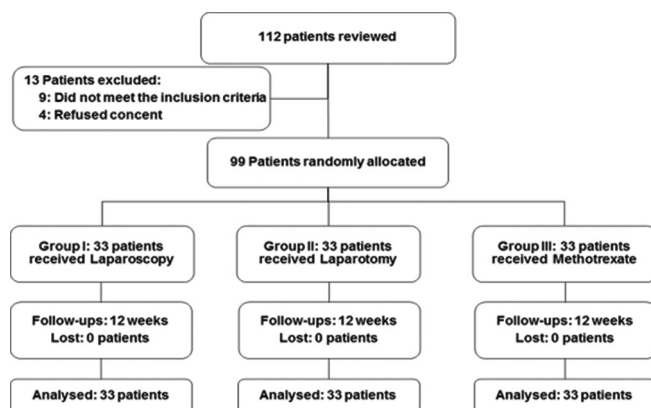


Figure 1: Trial profile

Table 1: Comparison the results of hysterosalpingography in patients with ectopic pregnancy by group

Characteristics	Group			P
	Laparoscopy	Laparotomy	Methotrexate	
Age (year)	28.9±6.8	27.7±6.5	29.1±7.6	0.698*
BMI (kg/m ²)	26.9±4.9	26.6±4.2	27.5±4.6	0.718*
β-hCG (mIU/mL)	1513.7±875.6	1871.0±1353.8	1837.2±1165.1	0.381*
Size of ectopic pregnancy (mm)	23.8±6.1	24.4±6.7	22.2±6.6	0.358*
Infection	3 (9.1)	4 (12.1)	2 (6.1)	0.906†
Hospital LOS	2.2±0.4	2.1±0.3	2.1±0.3	0.758*
Tubal patency	31 (93.9)	28 (84.8)	30 (90.9)	0.595†

Data are mean±SD or n (%). P values calculated by *One-way ANOVA and †Chi-square test. LOS: Length of stay, BMI: Body mass index, SD: Standard deviation, β-hCG: Beta human chorionic gonadotropin

the operation was greater in the open group.^[18] Therefore, more studies are needed to show if the amount of sustained trophoblast is high after laparoscopy to the same extent as previous studies. The theory that the laparoscopic method reduces the amount of new adhesion and re-formation of previous adhesions has also been proved by previous studies. The tubal restoration and the extent of pelvic adhesion in laparoscopy were re-evaluated after 15 weeks of initial primary laparoscopy,^[17-20] although the tubes were not different between the two groups, the patients treated with laparotomy had higher adhesion rates which are in accordance with the results of the present study. Shalev *et al.* found no difference in the extent of openness of the same tube within 1 year. Moreover, they found no rate of pregnancy in the two groups in which one of the groups succeeded and the other group failed in expected management.^[19] Rantala and Makimen reported 88% pregnancy rate and EP relapse rate of 4.2%. In patients treated with expected management, the fertility rate was good in the future, and improper self-efficacy of EP did not lead to an increase in tube damage and an increased risk of uterine outflow.^[20] Although EP may develop spontaneously and tubal abortion, about 90% of women with EP and serum β-hCG of higher than 2000 it will need surgical intervention due to pain or tubal rupture. Rupture of the tube occurs even when the serum level of β-hCG is lower or falling, or both. Expected management is recommended only when there is no mass in vaginal ultrasonography and the level of β-hCG and progesterone is also falling, and even in this case, due to the presence of a rupture line on the tube, the patient's precise monitoring is necessary until the β-hCG level reaches below 15, only below this level is where all of the ectopic pregnancies recover spontaneously and without rupture. The subsequent pregnancy rate was also significantly influenced by the findings on the HSG, being higher in the patients with normal HSG. Moreover, an increased proportion of spontaneous gestations was observed in these subjects. Mol *et al.* reported fecundity rate ratios of one-sided and two-sided abnormalities detected with HSG of 0.93 and 0.35, respectively.^[21]

In light of the present results, it seems reasonable to consider that performing a HSG following medical treatment of an

EP could provide prognostic information regarding future attempts to accomplish gestation. Conversely, in 97.2% of the patients the HSG findings would be unlikely to affect the initial conduct that would probably be expectant, including the group of fertile women exhibiting unilateral tubal obstruction or tubal patency with alteration.

Boots *et al.* investigated the effect of single-dose MTX administration for EP after *in vitro* fertilization (IVF) on ovarian reserve and concluded that it does not compromise ovarian reserve, responsiveness or subsequent IVF success.^[8] Similar results were reported in a large cohort study by Hill *et al.*^[9] They concluded that the number of doses of MTX treatment was not correlated with the change in values of FSH, AFC, and oocyte yield. However, Ulug and Oner proposed the opposite in their study. They stated that single or multiple doses of MTX combined with salpingectomy decreases ovarian reserve markers including AMH and follicle counts.^[10]

In a study by Sahin *et al.*, it was showed that there were no significant effects on ovarian reserve comparing single-dose MTX treatment and salpingectomy based on a highly accepted ovarian reserve test of AMH measurement. Although the early period after treatment demonstrated a significant decrease of AMH in salpingectomy only and salpingectomy following single-dose MTX treatment, in the late period of the 3rd month, this finding disappeared.^[13]

In accordance with previous studies, we also demonstrated that salpingectomy following MTX and laparotomy treatment has no significant effect on openness of the tube EP by comparison with laparoscopy. However, a relatively low number of patients who underwent salpingectomy following single-dose MTX treatment is the second limitation of this study.

On the other hand, our follow-up was at 12 weeks, and if the length of the follow-up was also more, better results might have been found. For example, such complications can be studied in the long term or short run. Meanwhile, given the dearth of studies in this regard, it is recommended that future researchers conduct this study at a wider level and in a longer follow-up (12 weeks and 24 weeks). This result can be the strength of the present study because, given the

homogeneity of the patients in terms of background and clinical conditions, the results of the treatment are more accurately reliable among the three therapeutic methods.

Conclusion

According to the results of this study, although infection was more in laparotomy and that tubal patency was more within 3 months in laparoscopy and MTX, there were no statistically significant differences in the results of laparoscopy, laparotomy and MTX in HSG results.

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Conflicts of interest

There are no conflicts of interest.

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