International Journal of Obstetrics and Gynaecology Research (IJOGR)
Vol. 3 (2016) No.5, pp. 326-337
http://www.ijogr.com/

Saline Infusion Sonohysterography for Assessment of Tubal Patency after Methotrexate Therapy versus Linear Salpingostomy

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Abstract

To evaluate the tubal patency after methotrexate therapy compared to linear salpingostomy using saline infusion sonohysterography. It was a case-series study that was done at Ain Shams University Maternity Hospital (ASMUH) and included women who were admitted for having tubal pregnancy and treated by a single modality either methotrexate (MTX) or linear salpingostomy, over a 5-year period, between January 2010 and December 2014. 300 patients were recruited and divided into two equal arms 150 women in each. Group I were treated by methotrexate either single dose or multiple doses, while group II included women who underwent conservative surgical management (linear salpingostomy) either through laparoscopy or laparotomy. Saline infusion sonohysterography was performed for all participants and tubal patency was assessed in all women. Data was gathered from patient records present at "Patient Records Department" at ASUMH. There was no statistically significant difference between the two groups as regards to the tubal patency either on affected side or contralateral side. However, patients had multiple doses of methotrexate had less tubal patency rates than those who treated by a single dose therapy. The approach of linear salpingo(s)tomy did not show a significant difference in tubal patency.

Keywords

Tubal pregnancy; Methotrexate; Salpingostomy; Saline infusion sonohysterography

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I. Introduction

Ectopic pregnancy (EP) is the abnormal blastocyst implantation outside the uterine cavity. The incidence of ectopic pregnancy is 2% of all gestations and is linked with significant maternal morbidity and mortality. It is the main cause of maternal mortality during early gestation [1]. The fallopian tube is the most common site of implantation (especially the ampullary section) but can also be ovarian, abdominal, cervical, or on the scar of a previous cesarean section [2]. Women with abnormal fallopian tubes are at high risk of ectopic pregnancy [3]. So, the risks for EP comprise pelvic inflammatory disease (PID), previous ectopic, history of infertility, history of previous abdominal or pelvic or tubal surgeries, endometriosis, smoking which decreases cilial motility, increased maternal age, and in-utero exposure to diethylstilbestrol. Some of these situations end in scarring of the fallopian tubes and thus may hinder the fertilized egg to reach the cavity of the uterus. In fact, the management is classically surgical, but early diagnosis allows the utilization of a medical therapy [4], thus avoiding the surgery-linked complications and keeping the pelvic anatomy. Different medical therapies had been described such as methotrexate (MTX), prostaglandins (PG), actinomycin-d, etoposide, hyperosmolar glucose, anti-hCG antibodies, potassium chloride (KCL), or mifepristone (RU486). Methotrexate (MTX) had shown better results and now it is considered the first choice for medical treatment [5]. MTX is chemotherapeutic antimetabolite agent which combines the enzyme tetrahydro-folate reductase and antagonizes folic acid. It prevents the formation of puric and pyrimidic bases, needed for the synthesis of DNA and RNA. It affects cells with fast division, including the trophoblast [6]. Methotrexate may be used systemically (intramuscular injection) or by local injection in the gestational sac, guided by ultrasound or through a laparoscopic technique. It damages rapidly dividing cells (as the trophoblast). But, this process may end in residual damage to the fallopian tube. After conservative management of ectopic pregnancy, fertility can be attested indirectly through a hysterosalpingography or directly by diagnosing a new pregnancy [7]. Saline-infused sonohysterography (SIS) is a technique that may help improve visualization of the uterine cavity and evaluate tubal patency. It consists of instillation of fluid into the endometrial cavity with simultaneous pelvic ultrasonography (US) [8].

Sonohysterography can be provided in an outpatient setting, and it is linked with minimal patient discomfort and a low infection risk. This method is noninvasive and easy to perform in almost any medical setting because it does not need sedation or anesthesia, nor does it have any major side effects or severe related morbidities [9].

The aim of this study is to assess the tubal patency following medical treatment of EP compared with linear salpingostomy in order to counsel patients willing to have future pregnancies about the most appropriate method of conception.

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II. Patients and Methods

This was a case-series study that was done at Ain Shams University Maternity Hospital and included 300 women who were admitted to Ain Shams University Maternity Hospital, for having tubal pregnancy and treated successfully by methotrexate therapy or linear salpingostomy, over a 5-year period, between January 2010 and December 2014.

Inclusion criteria:

1. Patients diagnosed as tubal pregnancy and treated by single modality either by methotrexate or salpingostomy
2. No other laparotomies
3. No history of pelvic infections in the period after treatment
4. No recurrence of ectopic either in the same tube or the other side

Exclusion criteria:

1) Patients who underwent Laparotomy for other reasons.
2) Patients with history of pelvic infections after initiating the treatment for ectopic pregnancy.
3) Patients with history of recurrent ectopic pregnancy in either the same fallopian tube or the other fallopian tube.

Data was gathered from patient records present at "Patient Records Department" at ASUMH. Informed consent was taken from every participant, after they were fully informed about the nature and scope as well as the potential risks of the study. All included women were subjected to revising history and examination sheets with particular emphasis on personal history: age, residence, education level and socioeconomic status, history of infertility, obstetric history including parity and gravidity and mode of delivery. SIS was done for all patients to evaluate the tubal patency on both sides. Bimanual examination was performed to the patient in the dorsal lithotomy position. Initially TVUS was performed by the same gynecologic sonographer using a 7.5 MHz endovaginal 2D transducer (Medison x6) to exclude the presence of fluid in the douglas pouch, also the morphology and the size of the uterus, features and thickness of endometrium, and the ovaries and tubes were assessed by obtaining sagittal and transverse scans. Then saline infusion sonohysterography was performed. After disinfecting the vagina with povidone-iodine solution, speculum was inserted vaginally and up to 25 ml of saline solution was injected into the uterine cavity through pediatric foley's catheter with its guide to distend the endometrial cavity. A transvaginal transducer of ultrasound machine was used to scan the uterine cavity. The findings at SIS were recorded in a standardized manner on the case records. The procedure was done between the 7th and 11th day of the cycle.

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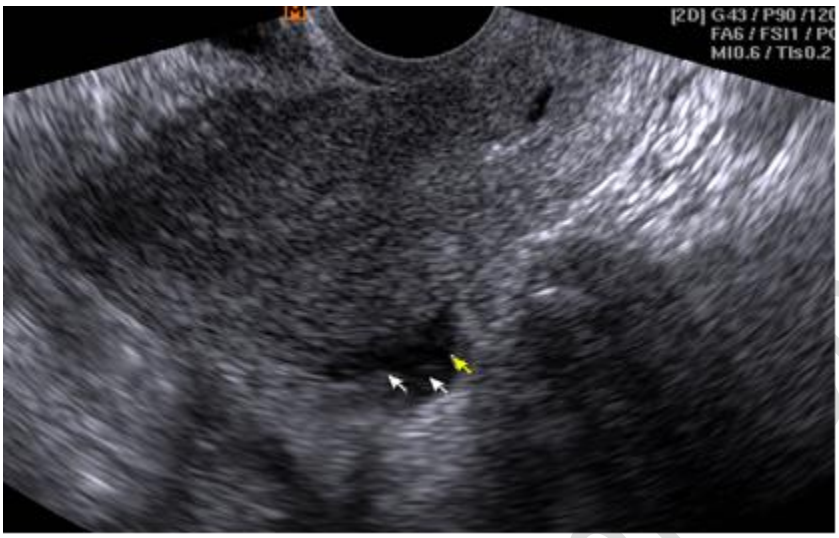

Figure (1): Positive fluid in Douglas pouch after saline infusion sonohysterography indicating at least one patent fallopian tube.

Statistical analysis: Retrieved data were recorded on an investigative report form. The data were analyzed with SPSS® for Windows®, version 15.0 (SPSS, Inc, USA). Description of quantitative (numerical) variables was performed in form of mean, standard deviation (SD) and range. Description of qualitative (categorical) data was performed in the form of numbers and percent. Analysis of numerical variables was performed by using student's unpaired t-test (for two groups) or ANOVA (for more than two groups). Analysis of categorical data was performed by using Fischer's exact test and Chi-squared test. Logistic regression analysis was performed to calculate association between variables and their odds ratios. Association between variables was estimated using Pearson's correlation coefficient (for parametric variables) and Spearman's correlation coefficient (for non-parametric variables). Significance level was set at 0.05.

III. Results

The current study was conducted on 300 women admitted at Ain Shams University Maternity Hospital during the period between January 2010 and December 2014. The study included 2 groups of women: group I [n=150]; women who were treated by methotrexate for tubal pregnancy, and group II [n=150]; women who were managed by linear salpingostomy for the ectopic pregnancy. There was no significant difference between the two groups concerning age [31.4 ± 4.2 vs 32.3 ± 4.5]. Also, The BMI, mean gravidity and parity, duration of marriage, mode of delivery,

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educational level and occupation showed no significant difference in women who had methotrexate therapy when compared to women of the other group. As regards to previous history of pelvic infections in the two groups, there was no significant difference between both goups P >0.05 (table 1).

Table (2) shows a comparison between the two studied groups as regards to the tubal patency (ipsilateral and contralateral tubes) after treatment (outcome). In group (methotrexate) I the patency was 78% (n=117) in the previously affected tube and 84.7% (n=127) in the other tube while in group II (linear salpingostomy), the patency was 76% (n=114) in the affected tube and 84% (n=126) in the contralateral one with no significant difference between both groups.

Among the women in Group I (n=150), 110 women received single dose of methotrexate therapy whereas 40 women were administered multiple doses of the drug. Tubal patency in the previously affected tube and contralateral one was compared which showed a statistically significant difference between the two groups (table 3).

In Group II (n=150), 102 women had undergone laparoscopic linear salpingostomy while 48 women underwent linear salpingostomy through a laparotomy. Tubal patency in the affected and contralateral tubes was compared and showed no statistically significant difference between the two routes (table 4).

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Table (1): The clinic-demographic differences between group I (methotrexate) and Group II (linear salpinostomy).

	Group I (150)	Group II (150)	P- value
Age	31.3 ± 4.2	32.3 ± 4.5	> 0.05 (NS)
Body mass index (kg/m^2)	26.2 ± 5.4	26.1 ± 2.9	> 0.05 (NS)
Previous gravidity	2 ± 0.8	1.8 ± 0.6	> 0.05 (NS)
Previous parity	1.1 ± 0.5	1.3 ± 0.1	> 0.05 (NS)
Duration of marriage	6.6 ± 1.1	7.1 ± 1.5	> 0.05 (NS)
Mode of delivery			
Vaginal	112	120	> 0.05 (NS)
Cesarean	38	30	
Education			
≤High school	124	122	> 0.05 (NS)
>High school	26	28	
Occupation			
House wife	103	107	> 0.05 (NS)
Employed/business Woman	47	43	
Previous history of pelvic infection	37 (24.7%)	41 (27.3%)	> 0.05 (NS)

*** Analysis using independent student's t-test. NS = non-significant**

Table (2) shows a comparison between the two studied groups as regard to thetubal patency (ipsilateral and contralateral tubes) after treatment (outcome).

	Group I		Group II		X2	P
	No.	(%)	No.	(%)		
Ipsilateral tubal patency	117	(78)	114	(76)	0.68	> 0.05
Contralateral tubal patency	127	(84.7)	126	(84)	0.87	(NS)

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Table (3): comparison between rates of occlusion among cases in group I as regard to the number of doses of methotrexate

	Single dose (N=110) No. (%)	multiple doses (N=40) No. (%)	X2	P
Ipsilateral tubal patency	91 (82.7)	26 (65)	5.37	<0.05 (sig)
Contralateral tubal patency	98 (89)	29 (72.5)	6.21	

Table (4) comparison between rate of patency in the ipsilateral and contralteral tubes in group II as regard to the method of salpingiostomy

	Laparoscopy N=102 No. (%)	Laparotomy N=48 No. (%)	P
Ipsilateral tubal Patency	82 (80.4)	32 (80)	>0.05 (NS)
Contralateral tubal patency	86 (84.3)	40 (83.3)	

IV. Discussion

The most common cause of tubal pregnancy is damage to the fallopian tube as in conditions such as pelvic inflammatory disease (PID) and endometriosis. Nowadays, proper diagnosis is aided by absent intrauterine gestational sac and an associated increase in β-HCG levels. The diagnosis is established by the presence of a fetal sac outside the uterus. Laparoscopy is needed for establishing the diagnosis in query cases, especially if the gestational sac is implanted in an unusual site (e.g. abdominal cavity). Methotrexate (MTX) is an antimetabolite utilized in the management of certain neoplastic diseases, psoriasis, and rheumatoid arthritis. Since its use in the therapy of ectopic pregnancies, systemic administration has been proven to be a successful mode of management in stable cases of ectopic pregnancies [10].

The aim of the current study was to explore the effect of methotrexate compared to linear salpingo(s)tomy on tubal patency at a tertiary

hospital, Ain Shams University Maternity Hospital, during the period between January 2010 and December 2014. This study included women who had admitted with tubal pregnancy and were treated by a single modality either medical treatment in the form of methotrexate (single or multiple doses) or linear salpingostomy (by laparoscopy or laparotomy). 300 women were recruited and were divided into two groups, first group (150 women) who received methotrexate and another matched group (150 women) who underwent linear salpingostomy. In the current study there was no statistically significant difference in tubal patency in both groups either in the previously affected tube or the other one.

Advances in endoscopic techniques had enabled a laparoscopic route in many cases with tubal ectopic pregnancy [11]. Salpingo(s)tomy has become the procedure of choice in patients seeking for future fertility. A well-recognized risk of a salpingo(s)tomy is partial removal of trophoblastic tissue, leading to increasing or plateauing postoperative serum HCG levels (persistent trophoblasts) [12]. Medical and expectant managementa, have become a focus of many researches as laparoscopy is no longer required for the confirmation of tubal pregnancy.

Reproductive capacity was evaluated by Sowter MC et al. 2011 in 74 women seeking for fertility 18 months after treatment completion. No statistically significant difference was observed for spontaneous intrauterine gestation (OR 0.82, 95% CI 0.32 to 2.1) and recurrent tubal pregnancies [13]. Women managed by MTX had a better physical functioning than after surgery (significant differences in physical functioning was observed in favor of MTX on day 4 of follow up but not in the depression and anxiety scores, $P < 0.01$). No differences were observed in psychological functioning [14].

In another study, hysterosalpingogram (HSG) was performed in 11 patients of linear salpin(g)ostomy and 11 patients of tubal gestations treated by methotrexate. Ipsilateral patency was documented in 8 of 11 (72%) cases managed by linear salpingostomy and 9 of 11 (81%) methotrexate-treated tubes. One methotrexate case had a prior ipsilateral ectopic treated by salpingostomy, and two additional patients had a previous contralateral ectopic treated by salpingectomy. Each one of these 3 cases had ipsilateral tubal patency after methotrexate for the most recent ectopic gestation [15].Medically managed women reported more hindrance of physical, role and social functioning, meanwhile, surgically managed women showed more health perceptions, more energy, less pain, less physical symptoms, a better overall quality of life, and were less depressed than medically treated women ($P < 0.05$). In agreement with the current study, in a randomized clinical trial, there was no statistically significant difference in the ipsilateral tubal patency rate after both modalities in patients with unruptured tubal pregnancy [16].

We compared the effect of single dose or the impact of multiple doses of MTX on tubal patency. It was shown that in resistant cases needing more than one dose of methotrexate, the tubal damage was more apparent and this was reflected on the tubal patency rate which was significantly different between both

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patients in group I. Further research studies are needed to determine whether giving more than one dose is appropriate or better to resort to the surgical management. In an agreement with the results of the current study, a recent article reported that free passage through the ipsilateral tube was observed in 17 of 30 patients (56.7%) after multiple-dose, and 26 of 31 patients (83.9%) after single-dose MTX. Contralateral tubal patency was higher after single than multiple-doses MTX, although the value was not statistically significant. Binary logistic regression review was done to assess the parameters of age, gravida, parity, starting titers of beta human chorionic gonadotropin (HCG), size of the adnexal mass, and MTX regimen and their correlation with the hysterosalpingogram results after the clinical therapy for unruptured ectopic pregnancy. Only the type of MTX regimen was found to be utilized as a predictor of obstruction of the ipsilateral tube [17]. Large trials had shown that nearly 14% of women need more than one dose of MTX and less than 10% of cases managed with this regimen will need surgical interference [18, 19]. This had also been reported in randomised trials comparing MTX with laparoscopic salpingo(s)tomy [20, 21]. Accumulated data from many studies showed that nearly 15% of women treated medically needed more than one dose of methotrexate and 7% suffered from tubal rupture during the follow-up period [22, 23]. Less than 75% will suffer from abdominal pain following therapy. Some women will also suffer from conjunctivitis, stomatitis and gastrointestinal upset. 'Separation pain' due to a tubal abortion may be difficult to be differentiated from pain due to tubal rupture and a number of women will require hospital admission for observation and evaluation by transvaginal ultrasound following MTX treatment [24, 25]. MTX multiple dose therapy is derived from the management of gestational trophoblastic disease [26, 27]. This therapy is given with folinic acid rescue to decrease chemotherapy toxicity. In 1989, Stovall used the methotrexate dosage in management of tubal pregnancy on individual bases to increase patient compliance, to decrease adverse effects, and overall costs, which led to a single dose MTX of 50mg/m2 can be given intramuscularly without citrovorum rescue [28, 29].

The approaches of surgery either laparoscopic or through laparotomy were compared as regard to the tubal patency after the operation and there was no statistically difference between both groups. Laparoscopic techniques were linked with shorter operation times, less intraoperative bleeding, shorter hospital admission and lower analgesic needs. There was no difference in overall tubal patency rates between the two routes. In women who were seeking for future fertility, the following intrauterine pregnancy rates were the same (RR 1.2, 95% CI 0.88–1.15) and there was a trend toward less recurrence rates of tubal pregnancy if a laparoscopic approach was used. However, laparoscopic salpingo(s)tomy was less successful than an open approach in removing the tubal pregnancy, reflected a rising rates of persistent trophoblast (RR 3.6, 95% CI 0.63–21.0). Laparoscopic salpingo(s)tomy should be utilized as the primary management when treating ectopic pregnancy in the presence of

contralateral diseased tube and the desire for future fertility [30].

Four cohort trials had examined natural fertility outcomes in women with contralateral diseased tube and showed a trend toward a greater rates of intrauterine pregnancy after laparoscopic salpingotomy compared with laparoscopic salpingectomy [31] intrauterine pregnancy rate 49% versus 27%; [32] FRR 3.1, 95% CI 0.76–12; [33] OR 4.0, 95% CI 0.96–16.7); [25] risk ratio 0.463 (95% CI 0.262–0.820). However, if the subsequent requirement for assisted reproductive techniques was taken into account, an increase in intra-uterine pregnancy rate of only 3% would make salpingectomy less cost effective than salpingo(s)tomy [32].

The findings of the current study showed a similar success rate in maintaining tubal patency with either methotrexate & salpingostomy.

V. Conclusion

The findings of the current study showed a similar success rate in maintaining tubal patency with either methotrexate or salpingostomy.

VI. References

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