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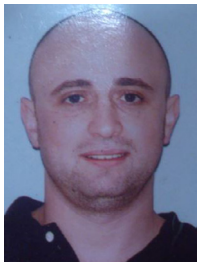
ARTICLE

Tubal patency assessment using sequential transvaginal ultrasound and hysterosalpingo-foam sonography after methotrexate treatment for tubal pregnancy



BIOGRAPHY

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KEY MESSAGE

In this study, 40% of women who were treated with methotrexate for tubal pregnancy and who desired a further pregnancy were diagnosed with a tubal pathology. Sequential transvaginal ultrasound and hysterosalpingo-foam sonography are recommended as routine follow-up for these women, to offer timely referral to the appropriate specialist.

ABSTRACT

Research question: What is the efficacy of sequential two-dimensional transvaginal ultrasound (2D-US) and hysterosalpingo-foam sonography (HyFoSy) after methotrexate (MTX) treatment for tubal pregnancy among patients who desire a future pregnancy?

Design: A prospective trial conducted between May 2019 and November 2020. Patients who had a suspected tubal ectopic pregnancy diagnosed by ultrasound and treated by MTX were included. These patients underwent sequential transvaginal 2D-US assessment of the pelvic organs and a complementary HyFoSy for tubal patency. The primary outcome was tubal obstruction in the affected side.

Results: A total of 360 women underwent sequential transvaginal 2D-US assessment of the pelvic organs and a complementary HyFoSy for tubal patency. Of these, 40 (11.1%) women fulfilling the inclusion criteria were enrolled. In six out of 40 (15%), hydrosalpinx of the affected tube was found during the initial transvaginal ultrasound examination and were excluded from further investigation. In the remaining 34 (85%) patients, HyFoSy was carried out. Tubal block was found in 10 out of 34 (29.4%) patients. Of these, eight out of 34 (23.5%) and two out of 34 (5.9%) had a proximal block of the affected tube and bilateral proximal obstruction, respectively. Hysterosalpingography confirmed the tubal obstruction in all the affected cases. No procedure-related complications were documented.

Conclusions: Forty per cent of women who were treated by MTX for tubal pregnancy were diagnosed with tubal obstruction. We recommend that sequential transvaginal ultrasound and HyFoSy become part of routine follow-up for these women, thus offering them timely referral to the appropriate specialist.

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KEYWORDS

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Hysterosalpingo-foam sonography
Methotrexate
Ultrasound

INTRODUCTION

Ectopic pregnancy occurs when the fertilized egg is implanted outside the uterine cavity. Most extrauterine pregnancies are located in the fallopian tube (*Bouyer et al., 2002*). Studies have indicated that 2% of all reported pregnancies are ectopic (*CDC, 1995*; *Barnhart et al., 2006*).

Routine use of transvaginal sonography and serial beta-HCG assays in early pregnancy has increased the detection of unruptured tubal ectopic pregnancies (*Condous et al., 2005*). Consequently, in recent years, a dramatic shift from surgery to medical treatment for this condition has taken place (*Maymon and Shulman, 1996*; *Guvendag et al., 2007*), with systemic methotrexate (MTX) as the drug of choice (*Maymon and Shulman, 1996*; *Guvendag et al., 2007*).

Hysterosalpingography (HSG) is often used for assessing future reproductive outcomes subsequent to MTX treatment of tubal ectopic pregnancy (*Maymon and Shulman, 1996*; *Elito et al., 2005*; *Guvendag et al., 2007*). It is thought that patency ranges from 75–85% (*Maymon and Shulman, 1996*; *Elito et al., 2005*; *Garcia Grau et al., 2011*). The pregnancy rate is reported to be around 60–80%, of which 10–13% are repeat tubal pregnancies (*Maymon and Shulman, 1996*; *Bouyer et al., 2000*; *2003*; *Canis et al., 2003*; *Fernandez et al., 2013*). These figures suggest that some tubal ectopics may be caused by previous tubal damage, rather than being a consequence of an intrinsic pregnancy abnormality. This makes it particularly difficult to counsel infertile patients who have been treated for an ectopic pregnancy, as many of these women will continue to have poor reproductive outcomes.

The first crucial step regardless of future decisions is an evaluation of tubal patency. Familiarity with diagnostic tools assessing tubal damage may enable the clinician to apply the most suitable procedure for the patient's needs. Laparoscopy with chromopertubation has been considered the gold standard (*Saunders et al., 2011*; *NICE, 2013*) despite the high cost, its invasive nature and intraoperative complications (*Saunders et al., 2011*). Practically, laparoscopy is usually reserved for women who are likely to benefit from the assessment or treatment of another pelvic pathology (*NICE, 2013*), such as endometriosis. This explains why HSG, which is broadly accepted, is considered to be an effective alternative modality for the assessment of tubal patency (*Tur-Kaspa, 2012*; *Groszmann and Benacerraf, 2016*). It should be noted that the procedure exposes patients to ionizing radiation and contrast media, which may be allergenic (*Groszmann and Benacerraf, 2016*). Another key drawback of HSG is that it is associated with pain (*Saunders et al., 2011*; *Tur-Kaspa, 2012*). This may help explain the reluctance among various professional societies, including the American College of Obstetricians and Gynecologists (number 193), the Royal College of Obstetricians and Gynaecologists (2016) and the American Society for Reproductive Medicine (2013) to recommend routine tubal assessment consecutive to MTX treatment of tubal ectopic pregnancy.

Hysterosalpingo-foam sonography (HyFoSy) has recently been promoted as a new technique to evaluate fallopian tube patency. During the procedure, the passage of a hyper-echogenic foam made up of a mixture of gel and purified water can be visualized as it travels from the uterine cavity through the fallopian tubes into the peritoneal cavity (*Emanuel et al., 2012*). Therefore, HyFoSy constitutes a promising alternative to laparoscopy and HSG (*Ludwin et al., 2017*; *Exalto and Emanuel, 2019*).

Other investigators have used air–saline HyCoSy for ultrasound-based examination of tubal patency (*Ludwin et al., 2017*). Accordingly, they found this test to be highly accurate, the least expensive and most globally accessible positive contrast agent used for ultrasound-based examination of tubal patency (*Ludwin et al., 2017*).

The aim of the present study was to evaluate the efficacy of sequential two-dimensional transvaginal ultrasound and HyFoSy after MTX treatment of suspected tubal pregnancy in women aiming for a future pregnancy.

MATERIALS AND METHODS

This prospective trial was conducted at the Department of Obstetrics and Gynecology, Shamir Medical Center, Israel, between May 2019 and November 2020. It was approved by the Institutional Ethics Committee on 25 March 2019 (number 085-19), and written informed consent was obtained from all participants. The sample was composed of women who had undergone HyFoSy after treatment with MTX for an unruptured ectopic pregnancy.

Patients: previous tubal pregnancy diagnosis and methotrexate treatment

Before MTX, ectopic tubal pregnancy was sonographically suspected based on the identification of an adnexal mass at the location of the adnexa, without coexistent intrauterine gestation.

Treatment was administered solely to patients who were asymptomatic and haemodynamically stable, who were willing to undergo conservative treatment with the required follow-up and had no contraindications for MTX treatment (*Mukul and Teal, 2007*). Patients with anticipated low compliance for follow-up were excluded.

A pretreatment laboratory examination included a blood count and kidney and liver function tests. The patients received intramuscular MTX at a dose of 50 mg/m^2 based on individual body weight (*Guvendag et al., 2007*). The day on which MTX was administered was regarded as day 0. For outpatient surveillance, serum beta-HCG measurements were evaluated weekly until the concentration was below 5 mIU/ml. If the difference between the beta-HCG levels on days 0 and 7 was greater than 15%, the treatment was considered successful. If the difference was less than 15%, the treatment was considered a failure. A second dose of MTX was administrated for treatment failure (*Guvendag et al., 2007*). Surgical intervention was carried out for patients who refused MTX treatment again, and when tubal rupture was suspected from unstable haemodynamics, a falling haemoglobin level, or severe abdominal pain was experienced during follow-up.

Hysterosalpingo-foam sonography procedure

Hysterosalpingo-foam sonography was carried out 3–6 months after MTX treatment as ectopic pregnancy mass is usually not detected on transvaginal ultrasound examination before this time, and levels of beta-HCG tend to be below 5 mIU/ml (*Elito et al., 2005*). The primary outcome in the present cohort

was tubal obstruction in the affected side. The only inclusion criteria for HyFoSy procedure were women who had undergone successful MTX treatment for ectopic pregnancy (single dose) and hoped to initiate a future pregnancy. Women with an ultrasound-diagnosed ectopic pregnancy were excluded from the sample if the ectopic pregnancy at inclusion occurred while they were using contraception because these women were considered less likely to plan another pregnancy. Women with an ectopic pregnancy not detected by ultrasound who were managed expectantly, or women managed surgically, were excluded.

All HyFoSy procedures were carried out by a single sonographer (YM). All women were scheduled before the day 14 of their ovulatory cycle and after the cessation of menstrual bleeding from their previous period. Women were excluded from the sample if they had engaged in unprotected intercourse, experienced profuse vaginal bleeding or reported inflammation or infections of the genital tract, e.g. pelvic inflammatory disease or suspected sexually transmitted diseases (purulent vaginal discharge upon speculum insertion), salpingitis or tubo-ovarian abscess. After providing written informed consent, an initial transvaginal scan was conducted to detect pelvic pathologies.

After placing the woman in the supine position, a vaginal speculum was introduced to visualize the cervix. After the cervix and vagina were flushed with iodine solution, a balloon-less GIS catheter (GynaecologIQ) (http://www.exemfoamkit.co.uk/faq.php) with a soft tapered tip was inserted into the endocervical canal. Neither a tenaculum or a cervical dilatator were used. A trans-vaginal ultrasound was introduced after removing the speculum to avoid moving the catheter. Normal saline was slowly introduced into the uterine cavity through the catheter until achieving satisfactory distension and visualization of the uterine cavity. Foam was produced according to the manufacturer's instructions for the ExEm® Foam kit (*Emanuel et al., 2012*). Under direct ultrasound guidance, the foam was injected slowly through the GIS catheter to assess its passage through the fallopian tubes. All examinations were conducted on a Samsung WS80A ultrasound system fitted with a V5–9 MHz endovaginal probe. Azithromycin (1 g) was administered orally as a prophylactic antibiotic in all cases. Confirmatory HSG was only carried out in cases in which the fallopian tube on one or both sides were occluded during HyFoSy.

Statistical analysis

The primary outcome was fallopian pathology in the affected side. SPSS software (SPSS Inc., version 25 Chicago, IL, USA) was used for statistical analyses. The descriptive variables are presented as the mean ± SD. Frequencies are presented as percentages.

RESULTS

During a study period, a total of 360 women underwent sequential transvaginal two-dimensional ultrasound assessment of the pelvic organs and a complementary HyFoSy for tubal patency. Of these, 40 (11.1%) women with an ultrasound diagnosis of tubal pregnancy who were treated with MTX were enrolled. The pregnancy characteristics and ultrasound findings of the women with tubal pregnancies treated with MTX are presented in TABLE 1. The mean age was 33.4 ± 5.5 years, with a mean body mass index of 24.4 ± 5.2, a mean gravidity of 3.5 ± 2.6 and a mean parity was 1.5 ± 1.3. Of the 40 women evaluated by HyFoSy, two (5.0%) had a history of pelvic infection and endometriosis, five (12.5%) had undergone previous abdominal surgery and four (10%) had a history of assisted reproductive technology (ART). In addition, 11 (27.5%) had previous caesarean deliveries and four (10.0%) had experienced a previous ectopic pregnancy.

The mean gestational age at the time of diagnosis was 6.3 ± 0.7 weeks. Two of the women (5.0%) had conceived by assisted reproductive technology. Upon admission, the mean diameter of the ectopic pregnancy mass was 19.5 ± 8.7 mm as identified by transvaginal ultrasound, and the mean serum HCG level before MTX treatment was 671.4 ± 490.0 mIU/ml.

The post-MTX treatment ultrasound findings of the fallopian tubes are presented in FIGURE 1. In six out of 40 (15%), hydrosalpinx of the affected tube was found during the initial transvaginal scan before the HyFoSy procedure, and these women were excluded from further investigation. In the remaining 34 out of 40 (85%) patients, HyFoSy was carried out (FIGURE 2). A tubal obstruction was

TABLE 1 CHARACTERISTICS OF THE COHORT OF WOMEN WITH ECTOPIC PREGNANCY TREATED WITH METHOTREXATE

Parameter	Results (*n* = 40)
General characteristics	
Age, years	33.4 ± 5.5
BMI, kg/m^2	24.4 ± 5.2
History of pelvic infection and endometriosis	2 (5.0)
History of abdominal surgery[a]	5 (12.5)
History of ART	4 (10.0)
Obstetric history	
Gravidity	3.5 ± 2.6
Parity	1.5 ± 1.3
Previous caesarean delivery	11 (27.5)
Previous ectopic pregnancy	4 (10)
Pregnancy characteristics and ultrasound findings	
Gestational age at presentation (weeks)	6.3 ± 0.7
Conception by ART	2 (5.0)
Beta-HCG level upon admission before MTX, mIU/ml	671.4 ± 490.0
Diameter of the ectopic pregnancy mass, mm	19.5 ± 8.7

Data are presented as the number (%) or as the mean ± SD.

ART, assisted reproductive technology; BMI, body mass index; MTX, methotrexate.

[a] Abdominal surgery included laparoscopic salpingectomy for ectopic pregnancy, ovarian cystectomy, appendectomy and surgical treatment of endometriosis.

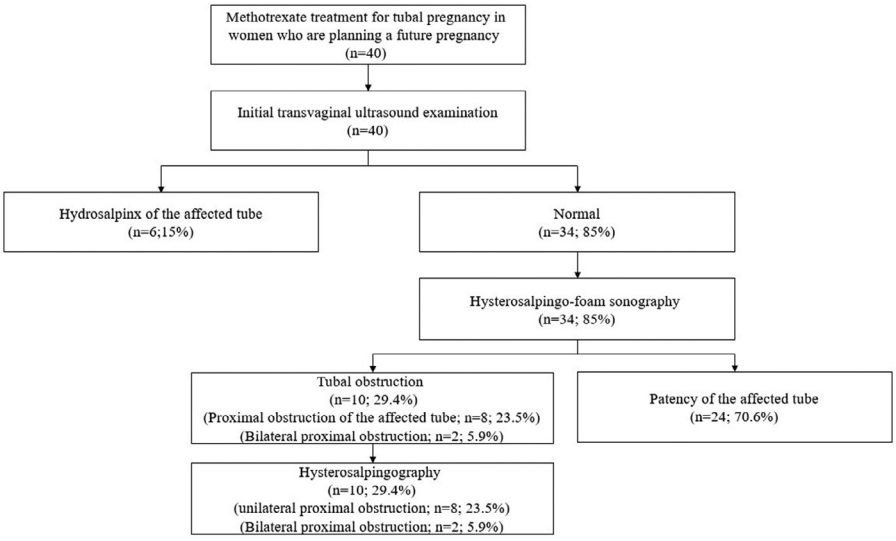

FIGURE 1 Ultrasound findings of recruited patients after methotrexate treatment.

found in 10 out of 34 (29.4%) patients. Of these, eight out of 34 (23.5%) had a proximal block of the affected tube (FIGURE 2C) and two out of 34 (5.9%) had bilateral proximal obstruction. The HSG confirmed the tubal obstruction in all the affected cases (FIGURE 2D). No procedure-related complications, i.e. infections, severe abdominal pain or vaginal bleeding, were documented.

DISCUSSION

This prospective study focused on patients who were treated by MTX for tubal pregnancy, with an overall tubal pathology diagnosis of 40%. The advantages of HyFoSy is that it is an office procedure in which patients are not exposed to radiation, and the procedure itself involves less patient discomfort (*Exalto and Emanuel, 2019*). The office setting is likely to be more comfortable than a radiology department in which HSG is carried out on a hard flat X-ray table (*Exalto and Emanuel, 2019*). In addition to tubal patency, data on pelvic anatomy, including the uterus and the ovaries, as well as pelvic pathologies, i.e. endometriosis, adenomyosis, uterine abnormalities and ovarian findings, could be identified. Most women tolerate HyFoSy well and it has few adverse effects (*Exalto and Emanuel, 2019*). Reports indicate that it is less painful for women than HSG (*Dreyer et al., 2014*; *Van Schoubroeck et al., 2015*). These factors can all enhance patient compliance.

Several studies have recommended a rigorous pelvic scan as part of the evaluation of all sub-fertile women as it provides valuable information that affects treatment decisions and prognoses (*Kelly et al., 2001*). Clearly a complete assessment of the uterus, uterine cavity, endometrium, ovaries, follicles, tubes and their patency can help identify anomalies that could necessitate prolonged, invasive or unnecessary interventions (*Kelly et al., 2001*). The present study, which focused on a specific clinical scenario, is an important example of the high yield of HyFoSy as a scanning method for evaluating infertility and also in selective clinical cases. Only 10% of the included patients had a history of assisted reproductive technology before tubal pregnancy; therefore, our results showed that 40% woman who were treated by MTX for tubal pregnancy were diagnosed as having a tubal obstruction, which obviously may impair reproduction. Specifically, when considering patients undergoing IVF, the current

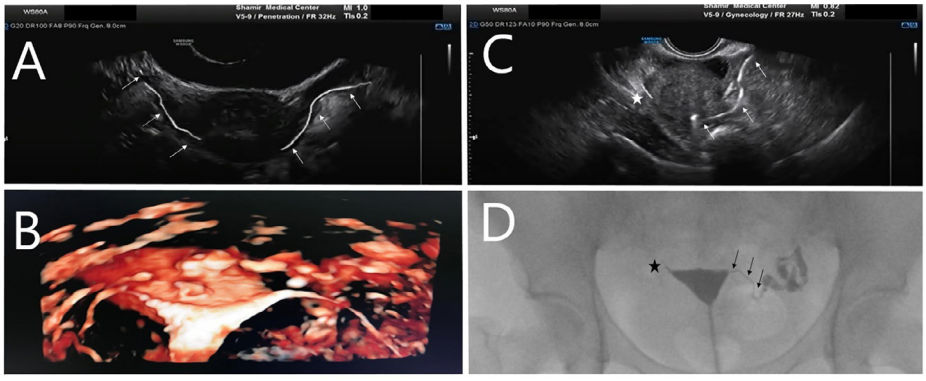

FIGURE 2 Hysterosalpingo-foam sonography and hysterosalpingography images of the uterus with fallopian tubes in two patients. (A–B) In the first patient (A) hysterosalpingo-foam sonography and (B) offline colour three-dimensional-coronal section of uterus showing patent tubes (arrows). (C–D) In the second patient, the (C) left tube was patent (arrows), the right tube was blocked (star) and (D) hysterosalpingography shows the same diagnosis as the reference standard.

results emphasize the superiority of salpingectomy over MTX. Approximately 40% of the fallopian tube pathologies after MTX are caused by other negative mechanical factors, which may reduce the IVF success rate in future cycles.

To the best of our knowledge, this is the first trial to evaluate the potential contribution and feasibility of HyFoSy after MTX treatment of tubal pregnancy in women planning future pregnancy.

In a previous study conducted by our department, tubal patency by HSG was investigated in 21 out of 37 patients with unruptured tubal pregnancy treated by local MTX injection at laparoscopy. Only women whose tubal pregnancy was less than 3 cm in diameter, had no active bleeding and intact tubal serosa with good pelvic visualization were treated with the cytotoxic drug. Accordingly, 18 out of 21 patients had bilateral tubal patency, and the only tube of a patient with a single fallopian tube was also patent (*Pansky et al., 1989*). *Seyedoshohadaei et al. (2016)* also evaluated tubal patency by HSG after treatment of ectopic pregnancy with MTX and related factors. The tubal patency rate was 75% (*Seyedoshohadaei et al., 2016*). Furthermore, HCG-β levels less than 1745 mIU/ml, ectopic pregnancy mass size smaller than 33.5 mm and those who had been treated with a single dose of MTX were significant predictors of tubal patency (*Seyedoshohadaei et al., 2016*).

The reported ipsilateral tube patency rate ranges from 75–85% (*Pansky et al., 1989*; *Maymon and Shulman, 1996*; *Elito et al., 2005*; *Garcia Grau et al., 2011*). This range can be ascribed to the different systemic and local inclusion or exclusion treatment protocols or may be the result of the now-discontinued technique of injection of the agent directly into the affected tube (*Pansky et al., 1989*). Therefore, HyFoSy can be considered an important diagnostic tool after treatment of tubal pregnancy. If tubal patency is detected, a natural conception may be achieved; in cases in which both tubes are blocked, it permits timely referral for IVF treatment.

In the present study, we used HyFoSy as part of our department protocol for demonstrating tubal patency. Use of other contrast media, however, have been reported (*Wang et al., 2019*), and we believe other centres may use different contrast for demonstrating tubal patency after MTX treatment. In a prospective observational study in 132 women, HyFoSy and HyFoSy with high-definition flow (HDF) Doppler technique was compared with saline HyCoSy and laparoscopy with chromopertubation as gold standard (*Ludwin et al., 2017*). Compared with laparoscopy with chromopertubation, saline HyCoSy and HyFoSy were both significantly less accurate (84.2%; $P < 0.01$, respectively, 92.1%; $P < 0.01$), whereas HyFoSy with HDF Doppler did not differ significantly from laparoscopy with chromopertubation (95.8%; $P < 0.07$). Although HyFoSy with and without HDF Doppler technique performed better, the authors concluded that saline HyCoSy may be used as a basic screening method for fallopian tube patency because of its low cost and high negative predictive value on tubal occlusion (99.6% versus 99.5%, respectively; 99% for HyFoSy without HDF Doppler technique) (*Ludwin et al., 2017*). The idea of office procedure ultrasound-guided tubal assessment after medical treatment of tubal pregnancy is the novelty of our study.

Treatment of an unruptured tubal pregnancy after IVF is particularly challenging. Debate on the most suitable options, regardless of cause, is ongoing. An approach that takes into account women's reproductive status, indications for future IVF and the severe psychological trauma of repeat tubal gestation, especially if on the same side, is needed. In this study, HyFoSy was conducted 3–6 months after MTX treatment because ectopic pregnancy mass tends not to be detected on repeated transvaginal scan and serum beta-HCG levels are not detected before this period (*Elito et al., 2005*). Nevertheless, our results revealed a hydrosalpinx of the affected tube in 15% of these patients. The presence of a distally occluded, dilated, fluid-filled fallopian tube has a deleterious effect on fertility and IVF outcomes (*Ducarme et al., 2006*; *Volodarsky-Perel et al., 2019*).

We believe that we have implemented a well-established design; however, some limitations should be mentioned. All the cases were managed by ultrasound and HyFoSy. Nevertheless, no laparoscopic surgery was carried out to confirm our findings. We believe, however, that, in contemporary practice, laparoscopy is not mandatory in cases of unruptured tubal pregnancy (*Maymon and Shulman, 1996*). Furthermore, 40 cases are a fairly small cohort, although all the participants met the rigorous inclusion criteria and the HSG concordance was 100% for all the occluded cases. Finally, HyFoSy was carried out 3– 6 months after MTX treatment because the ectopic pregnancy mass is usually not detected on transvaginal ultrasound examination at this time (*Elito et al., 2005*). A few studies, however, evaluated sonographic changes and the disappearance of hydrosalpinx over time. Therefore, it is possible that 15% of hydrosalpinx of the affected tube found during the initial transvaginal scan would not be found and the hydrosalpinx rate would be lower if the sonographic evaluation had been carried out 6 months after MTX treatment.

In conclusion, over the past few decades, treatment of ectopic pregnancy has shifted from saving lives and reducing morbidity towards preserving fertility. For these reasons, sequential transvaginal ultrasound and HyFoSy, which are simple office procedures, should be included as part of the routine follow-up after MTX treatment for tubal pregnancy, allowing these women timely referral to the appropriate specialist. This new option may be included in professional guidelines addressing the follow-up of women with a tubal pregnancy treated with MTX.

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