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Spontaneous pregnancy rates in infertile women after sequential hydrosonography and hysterosalpingo-foam sonography

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A R T I C L E I N F O

Keywords:
Hydrosonography
Hysterosalpingo-foam sonography
Infertility
Spontaneous pregnancy
Tubal patency

A B S T R A C T

Objective: To determine the clinical pregnancy rate following sequential hydrosonography and hysterosalpingo-foam sonography (HyFoSy) in tubal patency assessment among women undergoing infertility work-up.
Study design: Prospective follow-up of women referred to our department between July 2019 and October 2020. Sequential hydrosonography and HyFoSy were carried out.
Results: Out of 250 having the procedure, 100 women were excluded from study due to limited infertility, semen abnormal or not examined, evaluation for social egg freezing or they were single. Of the remaining 150 women, 48 (32%) conceived during a 10–24 months follow-up period: 17 (11%) conceived naturally and 7 (4.7%) by IUI. The mean time to conception was 5.5 ± 5.4 months and the pregnancy rate was 52% within 6 months. Among the spontaneous pregnancies 47% occurred within a month and 76% within 3 months.
Conclusion: Sequential hydrosonography and HyFoSy is a promising method for assessing the uterine cavity and tubal patency in women undergoing infertility workup. The findings suggest that the procedure may increase the chance of a spontaneous pregnancy following the procedure. Given the other known advantages of sequential hydrosonography and HyFoSy, this test is worth including in the initial workup for infertile patients.

Introduction

Routine infertility workups typically include an accurate assessment of fallopian tube patency, since an incorrect diagnosis can result in unnecessary tubal surgery or an unwarranted decision to engage in costly in-vitro fertilization (IVF) treatment [1]. Hysterosalpingo-Foam Sonography (HyFoSy) is a relatively new procedure to verify fallopian tube patency. It involves injecting a hyper-echogenic foam, which can be visualized as it goes from the uterine cavity through the fallopian tubes into the peritoneal cavity [2,3]. Recent studies have been reported showing that the procedure can be administered easily in an outpatient setting, with low levels of pain, and good diagnostic accuracy [4]. However, hyper-echogenic contrasts are not appropriate for evaluating the uterine cavity, because they impede the identification of hyperechoic intracavitary lesions. The solution has been to use two different contrasts for ultrasound evaluation in infertility: first the uterine cavity is evaluated with an anechoic contrast (saline) or lidocaine [5] until satisfactory distension and visualization of the uterine cavity achieved and then the patency of the uterine tubes is evaluated with a hyperchogenic contrast (HyFoSy).

The controversy as to whether a patency test itself can promote a spontaneous pregnancy dates back more than 70 years [6,7]. It has been argued that a patency test can flush out debris or mucus plugs in the fallopian tubes mechanically [8], enhance ciliary activity [9] and have an immunobiological effect on the endometrium or peritoneum [10–14].

However, there is scant data on post-procedure pregnancy rates comparing sequential hydrosonography and HyFoSy compared with other interventions or none at all [4]. The current study took advantage of a large hospital database to evaluate the likelihood of spontaneous clinical pregnancy in women undergoing sequential hydrosonography and HyFoSy in an infertility workup.

Methods

We investigated prospectively a consecutive cohort of women

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referred to our department for an assessment of tubal patency as part of their fertility workup between July 2019 and October 2020. Approval for this observational study was obtained from the Institutional Research Board (# 0189-19; approval 11-07-2019) and written informed consent was obtained from all participants.

Data on demographic characteristics and fallopian tube patency after sequential hydrosonography and HyFoSy were retrieved from the medical records. The fertility of the participants was assessed by a review of their medical records and by conducting telephone interviews. Details on fertility, infertility treatment (including ovulation induction and IVF), and infertility workups were acquired telephonically.

The sample was composed of women who had undergone sequential hydrosonography and HyFoSy. All procedures were performed by a single sonographer (Y.M.). All women were scheduled before the 14th day 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, infections of the genital tract (e.g., pelvic inflammatory disease (PID)), suspected sexually transmitted diseases (purulent vaginal discharge upon speculum insertion), salpingitis or tubo-ovarian abscess. After signing a written informed consent form, an initial transvaginal scan to detect pelvic pathologies was conducted.

The steps of the procedure were illustrated in our recent publication [5]. 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 according to the local protocol, a balloonless GIS catheter (GynaecologIQ) (http://www.exemfoamkit.co.uk/faq.php) with a soft tapered tip was inserted into the endocervical canal [5]. A tenaculum or a cervical dilator was not used. A *trans*-vaginal ultrasound probe was introduced after removing the speculum to avoid moving the catheter. A solution of 2% lidocaine (Rafa Laboratories, Israel) was slowly introduced into the uterine cavity via the catheter until satisfactory distension and visualization of the uterine cavity were achieved [5]. Foam was produced according to the manufacturer's instructions for the ExEm® Foam-kit [3]. Under direct ultrasound guidance, the foam was injected slowly through the GIS catheter to assess its passage through the fallopian tubes [5]. Tubal patency assessment can be sub-divided into four phases (Fig. 1A-1D): (1) latent, characterized by 2% lidocaine solution filling of the pelvic cavity and intraluminal accumulation of the hyperechogenic contrast (*); (2) double jet strain, in association with the maximal intensity of foam passage through the tube (*) and spillage into the abdominal cavity ("dragon sign"; see Fig. 1B); (3) single jet strain, in which there is a decrease in intensity of the passage of the foam through the tube (*) and spillage; and (4) the refractory phase. Azithromycin (1 g) was administered orally as a prophylactic antibiotic in all cases.

In the data reported below, the descriptive variables are expressed as the mean ± SD. Frequencies are given as percentages. SPSS software (SPSS Inc., version 26 Chicago, IL, USA) was used to perform the calculations and to plot the Kaplan-Meier curve. Pregnancy rate was calculated after the procedure (including HyFoSy menstrual cycle).

Results

During the study period, 250 women referred for an assessment of tubal patency as part of their fertility workup were evaluated by sequential hydrosonography and HyFoSy (Fig. 2). Of these, 100 (40%) were excluded from the study because: the duration of infertility was less than 12 months (n = 44); their partner had a serious semen abnormality or no semen examination had been conducted (n = 23); they were being evaluated for purposes of social egg freezing (n = 5); or were

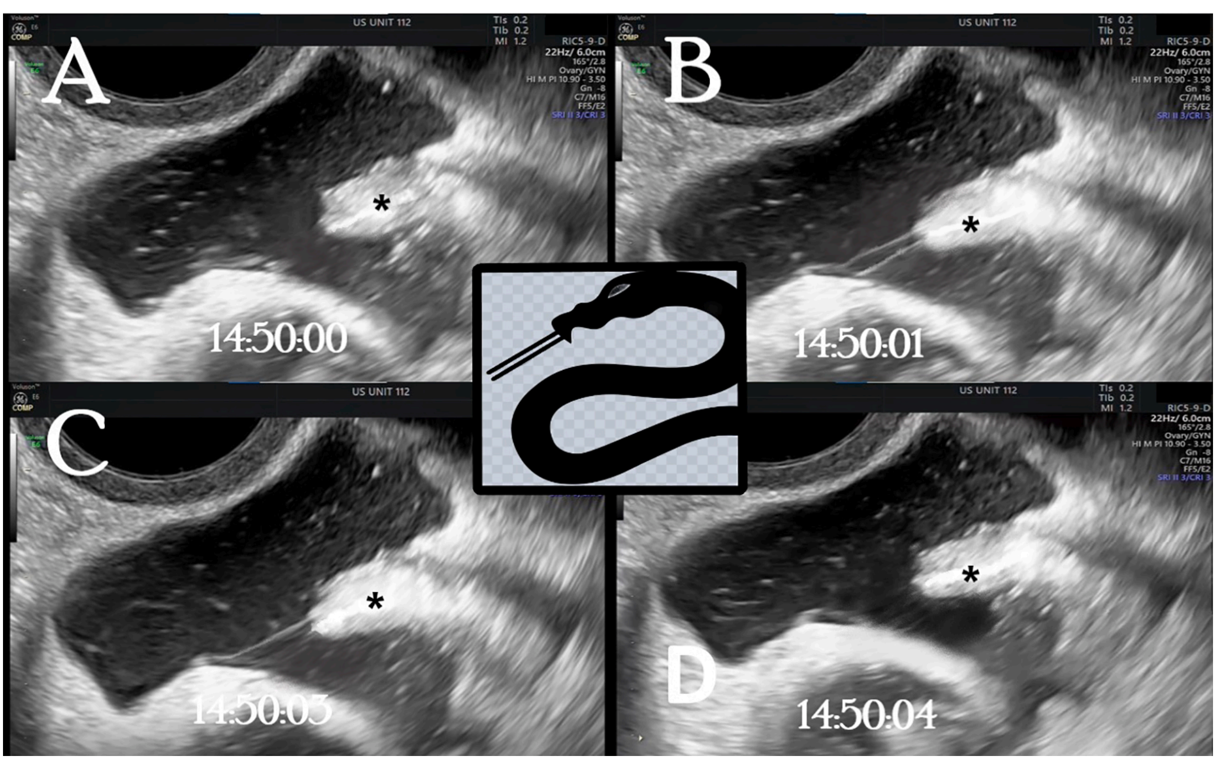

Fig. 1. Sonographic images of the passage throughout distal end of the fallopian tube and pelvic spillage during sequential approach where hypoechogenic 2% lidocaine infusion was used first to evaluate the uterus, and is then followed by hyperechogenic contrast (HyFoSy) (the asterisk indicates the intraluminal accumulation of the hyperechogenic contrast). All images necessitate the presence of lidocaine in the pelvic cavity to visualize. (A) Latent phase, characterized by lidocaine filling of the pelvic cavity and intraluminal accumulation of the hyperechogenic contrast (asterixis); (B) double jet strain, in association with maximal intensity of the passage of the foam through the tube and spillage into the abdominal cavity ("dragon sign"); (C) single jet strain, in which there is a decrease intensity of the foam passage through the tube and spillage; and (D) refractory phase.

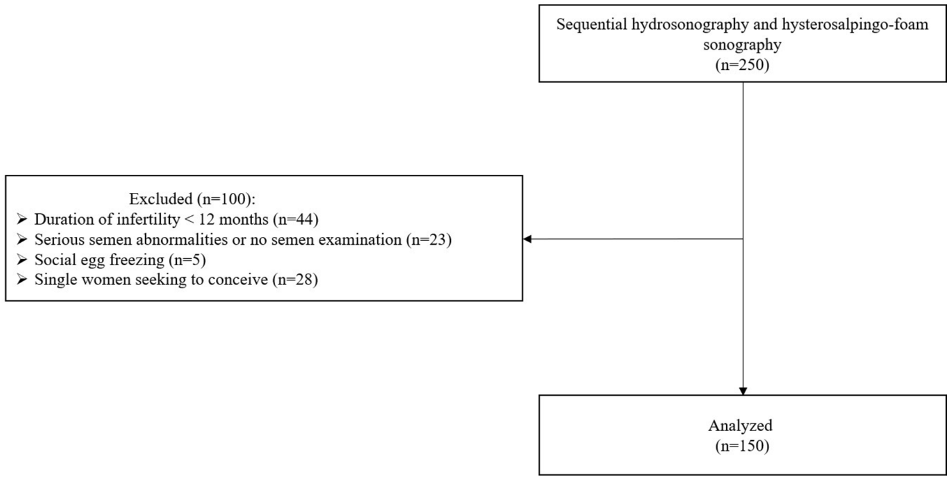

Fig. 2. Flow chart of study participants.

single women seeking to conceive (n = 28).

The study cohort comprised the remaining 150 women. The patient characteristics are presented in Table 1. Primary infertility was present in 41% and the mean duration of infertility was 21.1 ± 8.9 months. Twenty-six (17%) patients had risk factors for tubal occlusion and 23 (15%) had a history of IVF. Sequential hydrosonography and HyFoSy demonstrated tubal pathology in 30 (20%). Of these, 17 (11%) and 13 (8.7%) had a unilateral proximal block of the fallopian tube and bilateral proximal obstruction, respectively.

After a 10–24 months follow-up period the reproductive and pregnancy outcomes are presented in Table 2. Seventeen women 17 (11%) conceived naturally and 7 (4.7%) by IUI. The mean time to conception was 5.5 ± 5.4 months and 52% of these conceptions occurred within 6 months. There were 30 (62%) ongoing pregnancies, 16 (33%) deliveries and 2 (4.2%) miscarriages.

Fig. 3 shows spontaneous pregnancy rate after sequential hydrosonography and HyFoSy. Of those pregnancies 47% and 76% were within one to three months after the procedure, respectively.

Discussion

The key finding emerging from this study is a spontaneous pregnancy rate of 11% following sequential hydrosonography and HyFoSy. Of those pregnancies 47% and 76% were within one to three months after the procedure, respectively.

Table 1
Demographics (n = 150).

Parameter	Mean (±SD) or %
Age (years)	32.3 ± 4.9
BMI (kg/m^2)	25.3 ± 5.7
Duration of infertility	21.1 ± 8.9
Primary infertility	61 (40.7)
Secondary infertility	89 (59.3)
History of IVF	23 (15.3)
Risk factors for tubal occlusion#	26 (17.3)
Nulliparous	61(40.7)
Previous Cesarean delivery	23 (15.3)
Tubal patency status	
Bilateral patency	120 (80.0)
Unilateral patency	17 (11.3)
Bilateral occlusion	13 (8.7)

# Risk factors for tubal occlusion include history of abdominal surgery (laparoscopic salpingectomy for ectopic pregnancy, ovarian cystectomy, appendectomy, and surgical treatment of endometriosis), previous ectopic pregnancy, previous pelvic infection and endometriosis.
BMI = body mass index; IVF = in vitro fertilization.

Table 2
Reproductive and pregnancy outcomes after sequential hydrosonography and HyFoSy (n = 150).

Parameter	Mean(±SD) or %
Desired pregnancy	150 (100)
Spontaneous pregnancy	17 (11.3)
Pregnancy after IUI procedure	7 (4.7)
Time to pregnancy (months)	5.5 ± 5.4
Pregnancy within 6 months	25 (52.1)
Ongoing pregnancy	30 (62.5)
Delivery	16 (33.3)
Miscarriage	2 (4.2)

IUI = intrauterine insemination.

To the best of our knowledge, prior to the current study, the only data on the likelihood of pregnancy after HyFoSy were reported in observational studies. A retrospective study [15] reported a 55% pregnancy rate in 359 women after HyFoSy during a follow-up period of 3 to 42 months. The authors indicated that the number of pregnancies was the highest in the cycle concurrent with the HyFoSy and the first two cycles after the procedure. In a retrospective cohort study [16] on 111 sub-fertile women, 48 (43%) conceived within 6 months of HyFoSy, of whom 24 conceived naturally. Emanuel et al. [3] reported a natural conception rate of 19% with a median of 3 months after the HyFoSy procedure. In a retrospective observational study [17] on 294 sub-fertile women who underwent HyFoSy, 157 women provided information by phone on their fertility after 12 months follow-up. There was a cumulative spontaneous pregnancy rate of 10% within 1 month after HyFoSy, 30% within 6 months, and 34% within 12 months.

More is known about the fertility enhancing effects of tubal flushing under hysterosalpingography (HSG). A recent systematic review and network *meta*-analysis was carried out [18] including 14 randomized controlled trials covering 3852 women with infertility. This showed that tubal flushing using an oil-based contrast medium was associated with higher odds of clinical pregnancy within 6 months, and more subsequent live births compared to tubal flushing using a water-based medium (odds ratio (OR), 1.67 (95% CI, 1.38–2.03) or no intervention (OR, 2.28 (95% CI, 1.50–3.47). There was insufficient evidence for a difference between tubal flushing with water-based contrast medium and no intervention (OR, 1.36 (95% CI, 0.91–2.04) for a clinical pregnancy within 6 months. However, the use of an oil-based contrast medium in HSG procedures is known to be associated with complications such as asymptomatic intravasation [18], peritoneal granulomata [19], neonatal hypothyroidism [20], and immunological effects [14].

By contrast, both hydrosonography and HyFoSy can be safely

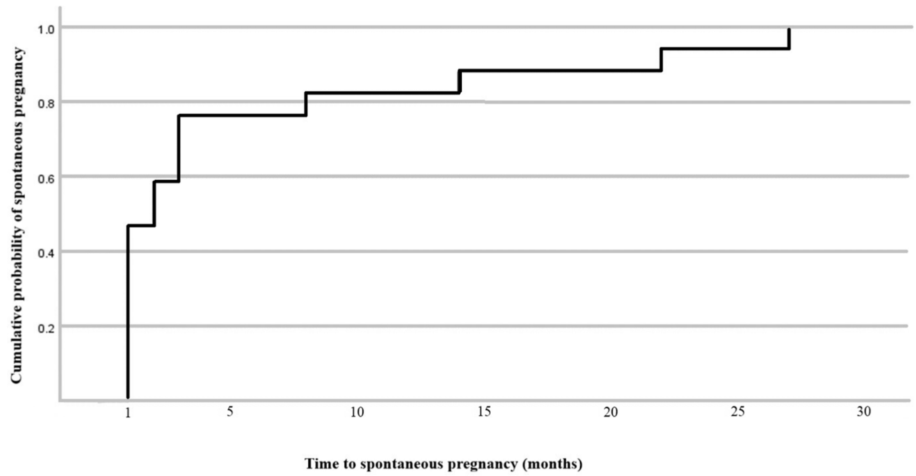

Fig. 3. Kaplan-Meier curve of the spontaneous pregnancy rate.

conducted in the doctor's office, there is no exposure to radiation, and patients report less discomfort than with HSG [4]. The office setting may be more welcoming than a radiology department where the HSG is performed on a hard flat X-ray table [4]. Beyond tubal patency, both hydrosonography and HyFoSy have the advantage of providing information on the pelvic anatomy, including the uterus and the ovaries, and may help detect pelvic pathologies such as endometriosis, adenomyosis, uterine abnormalities and ovarian findings. Most women tolerate HyFoSy well and there are few reported adverse effects [4] such as pain which are often reported for HSG [15,21].

The current study has several limitations. The statistical analysis was based on data collected by telephone, which may be subject to recall bias. Furthermore, 150 cases are a fairly small cohort, which may not be clinically relevant. Since there are no data in the literature on this important issue, further studies are needed to confirm these results.

In conclusion, sequential hydrosonography and HyFoSy can be considered a promising diagnostic test for tubal patency in women undergoing a routine infertility workup. Our findings suggest that there may be an additional effect after the procedure in enhancing spontaneous pregnancies. In light of the advantages of sequential hydrosonography and HyFoSy, this test should be considered in the initial workup for infertile patients. Future work is needed to confirm an enhanced spontaneous pregnancies rate after sequential hydrosonography and HyFoSy.

CRediT authorship contribution statement

Yaakov Melcer: Writing – original draft. **Neta Shamir-Kaholi:** Investigation. **Shirah Vainer-Rotbart:** Formal analysis. **Marina Pekar-Zlotin:** Formal analysis. **Michal Youngster:** Writing – review & editing. **Itai Gat:** Methodology. **Ron Maymon:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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