

ORIGINAL ARTICLE

Spontaneous pregnancy rate after hysterosalpingography versus saline infusion sonogram done under high pressure: a randomized controlled trial

Short title: SIStreat

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ABSTRACT

Objective. A prospective, randomized controlled clinical trial was conducted from March 2020 till April 2021 on 183 eligible women recruited from the infertility outpatient Clinic of El-Shatby University Hospital, Alexandria, Egypt.

Materials and Methods. Patients were randomized into two main groups; "group A"

did HSG and "group B" did conventional SIS. Patients with tubes patent under low pressure were assigned as "group B1" and patients with tubes which were occluded under low pressure were assigned as "group B2" and subjected to SISStreat. The results of tubal patency were observed and recorded in groups A and B2, either open or occluded. Pregnancy was diagnosed by serum B-HCG and with ultrasonic diagnosis of intact intrauterine gestational sac one week afterwards.

Results. Out of 93 cases performed HSG (group A); the Number of opened tubes = 79 (84.9%); the Number of occluded tubes = 14 (15.1%) cases, and pregnancy rate = 13 (14%) cases. Regarding 71 cases performed SISStreat (group B2), the Number of opened tubes = 62 (87.3%); the Number of occluded tubes = 9 (12.7%) cases, and pregnancy rate = 27 (38%) cases. There was no statistical significance difference between the two groups in rate of (opened/ occluded tubes) diagnosis ($P = 0.664$), but the rate of spontaneous pregnancy after 6 months was statistically significant when compared between both groups ($P = <0.001$), in favor of the SISStreat group.

Conclusions. SISStreat is equal to the conventional HSG in diagnosis of tubal patency. Also, this method increases the rate of post-procedure pregnancy rate.

Key words

SISStreat, Saline infusion sonogram, Tubal factor Infertility, Transvaginal ultrasound.

Introduction

According to the World Health Organization (WHO), between 8% and 12% of all couples in the world experience some kind of infertility during their reproductive period. This means that 50 to 80 million people worldwide are infertile or sub-fertile [1]. As considered one of the most common causes of subfertility, tubal factor has increased since the last decade, reaching up to 30-35% of cases suffering from delayed conception [2].

Screening for tubal occlusion is part of the investigation of subfertile couples and is classically performed using hysterosalpingography (HSG) or laparoscopy with chromo-tubation [3]. Hysterosalpingography uses a real-time form of X-ray called fluoroscopy to examine the uterus and fallopian tubes. It is performed in the early stage of the menstrual period (6th-12th day of menstrual period) and usually is done in radiology clinics [4]. Diagnostic laparoscopy (DL) is a painful procedure, with well-known possible anesthesia or operative complications [5].

Initially, Saline infusion sonohysterography (SIS) has been used for assessment of the uterine cavity. Afterwards, SIS was used as an initial step for the assessment of fallopian tube patency because it is a safe and well tolerated method with a low risk of complications [6,7]. Additive to this, SIS is considered an outpatient procedure which is done by the gynecologist himself. It has almost equal specificity and sensitivity when compared to the golden standard for tubal patency testing; laparoscopy [8].

Many studies have examined whether a patency test –by itself- promotes a spontaneous pregnancy or not. Recently, SIS done under high pressure (SIS-treat) was introduced as a treatment procedure to relieve simple obstruction of the tubes, and was associated with increased post-procedure pregnancy rates. [9] The aim of this study was to compare Spontaneous pregnancy rates after

hysterosalpingography (HSG) versus saline infusion sonogram done under high pressure (SIS) in women suffering from primary or secondary infertility.

Materials and Methods

This is a prospective, randomized controlled clinical trial, performed in the period from March 2020 till April 2021. Patients were recruited from the infertility outpatient Clinic of El-Shatby University Hospital, Alexandria, Egypt. The trial was registered at Pan African Clinical Trial Registry (www.pactr.org) database, the number for the registry is **PACTR202210557026698**. According to the test validity parameters of HSG in comparison to SIS in literature, we calculated the appropriate sample size to be 90 participants in each group, required at $\alpha = 0.05$ and a study power of 80%.

227 eligible women were recruited. 183 patients completed the study. The main cause of exclusion was lack of follow-up and patients' drop-out. They were randomized into two main groups; "group A" did HSG and "group B" did conventional SIS. We used the closed envelop method for randomization. A brief description of the procedure was given and informed consent was taken from each patient.

Inclusion criteria: women suffering from primary or secondary infertility for one year or more, normal ovarian and uterine factors and Normal semen analysis.

Exclusion criteria: women elder than 40 or less than 18 years old, any uterine abnormalities, Ovulation failure, $\text{FSH} > 15 \text{ mIU/ mL}$, Known tubal occlusion and Abnormal semen analysis. All patients were asked to attend the clinic in the early postmenstrual period to perform the test. Routine history taking, physical examination, vaginal ultrasound evaluation of the uterus and adnexa were performed for each participant.

93 cases of group A did HSG in radiology department, using water-soluble contrast material WSCM (52.7% diatrizoate meglumine and 26.8% iodipamide meglumine, Sinografin; Bracco Diagnostics, New Brunswick, NJ). Balloon catheters were placed in the uterus and the mean amount of WSCM used was 20 mL (range, 10–35 mL). The tubal status was checked and recorded as patent (one or both tubes) or occluded (both tubes).

As regard group B, all patients started to perform the conventional SIS, using a sterile pediatric Foley catheter (10 f) inserted through cervical canal, a Toomey syringe attached to the outer end of the catheter, filled with 60 ml of sterile saline solution then a transvaginal ultrasonic probe was inserted into the posterior vaginal fornix. In the beginning, classical SIS was performed: saline was slowly infused to the extent that would distend the uterus. Tubal patency was checked under low pressure that just permitted proper visualization. Observation of free fluid in the cul de sac was considered an indication of tubal patency (at least one tube) and the condition of the tubes were recorded as patent under low pressure. Patients with tubes patent under low pressure were identified as "group B1". Otherwise, women with tubes recorded as occluded under low pressure were subjected to (SIS treat) immediately, by gradual increasing the infusion pressure using the Toomey syringe [9], until fluid appeared in the cul de sac or the pressure was maintained for 5 minutes. If no free fluid appeared in the cul de sac, the tubes were recorded as occluded under high pressure.

For all patients, a prophylactic antimicrobial agent (100mg of doxycycline twice daily for 5 days) was prescribed. Some patients needed an analgesic post procedure.

All were advised to have regular intercourse during the following 6 months. Pregnancy was diagnosed by serum B-HCG after a missing period, then confirmed

with ultrasonographic diagnosis of an intact intrauterine gestational sac one week later.

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using numbers and percent. The chi-square tests, Fisher exact test, and independent T-test were used to determine the relationship between variables. Significance of the obtained results was judged at the 5% level [10].

Results

Our primary outcome was opening the oviducts using HSG or SIS treat, evidenced by the presence of dye or saline in the pouch of Douglas that would be detected by X-ray or TV-US respectively. Secondary outcome was the existence of spontaneous clinical pregnancy within the follow-up period of six months. The diagnosis was confirmed by a sonographically visible intrauterine gestational sac.

Patients' characteristics were shown in table (1); the mean age of group A was 31.5 years, and in group B, B2 was 32.2 years. Primary infertility was present in 30.1% of group A, 37.7% in group B, and 39.4% in group B2. Caesarian section was the most common mode of delivery in all groups; 48.3%, 55.5% and 56.3% in group A, B and B2, respectively. As shown in table (1)

As regards group A, out of 93 cases performed HSG, the Number of opened tubes (at least one) = 79 (84.9%); the number of occluded tubes = 14 (15.1%) cases, and pregnancy rate = 13 (14%) cases.

Group B (90 cases), had 19 (27%) cases with opened tubes under low pressure, those were assigned as group B1. The remaining cases (71 cases), did not show evidence of patent tubes under low pressure, and were exposed to the gradual increased pressure while injecting saline; group B2 (SIS treat). In 62 (87%) cases, at least one tube was opened and saline was observed in DP using TV-US. In the

remaining 9 (13%) cases, no changes occurred and were diagnosed as occluded under high pressure. Pregnancy rate in this group = 27 (38%) cases; only one of them was previously diagnosed as occluded under high pressure.

Comparing women of group A -the patients subjected to (HSG) - to women of group B2 -the patients subjected to SIS-treat- we found that: (table 2)

As regards the condition of the tubes (opened or closed), there was no statistical significant difference between the two groups ($P= 0.664$), $OR=0.819$ (95% $CI=0.333-0.664$).

As regards the pregnancy rate (pregnant or not pregnant), there was a statistical significance between the two groups ($P = <0.001$), $OR=0.265$ (95% $CI=0.124-0.565$), in favor of the SIS-treat group.

Discussion

To test tubal patency, you have to push a substance (air, dye or fluid) to pass through it. That is why all available procedures are considered more or less invasive, ranging from HSG or SIS up to laparoscopy [11].

Mimicking chromo-tubation done during DL, the new idea originated from using SIS as a simple therapeutic procedure for tubal factor subfertility, by elevating saline infusion pressure gradually to wash out any mucous, debris or break minor tubal adhesions that may hinder pregnancy, and it was named "SIS-treat."

An interventional prospective clinical trial was done between the period from October 2017 and November 2018. During the performance of regular SIS, and when saline did not appear in DP, we tried "SIS-treat" immediately in the same sitting. A full description of the new procedure was given to the patient before she participated. Our early observations were; 1) a high success in opening tubes and 2) an increased pregnancy rate among these patients. The results were published

in 2020 [9]. So, a well-designed prospective, randomized controlled clinical trial was needed to evaluate this new technique as a treatment option for simple tubal block, and to compare the post-procedure pregnancy rate with a standard, closely related method; hystrosalpingiogram.

In the group of Cases who performed HSG (group A), the diagnosis of opened tubes equaled 84.9%, which was comparable to the same diagnosis of group B2 (the SIS treat group) = 87%, the difference was statistically insignificant ($P = 0.664$), which means that SIS treat is an effective diagnostic method for tubal patency. Rezk et. Al [12], studied in a prospective study, 104 consecutive infertile women that underwent SIS and HSG for tubal patency followed by laparoscopy with dye test. They confirmed the higher sensitivity, safety, and acceptability of SIS compared to HSG for the evaluation of tubal patency in infertile women [12].

Noteworthy, in a recent study, the new technique was applied on 99 post-slaughtering genital tracts of multiparous buffaloes. The author reported passage of secretions, debris, and mucous after application of high pressure saline infusion through the occluded oviducts [13].

Again, when comparing both groups for post-procedure pregnancy rates, it was 14% in group A, and 38% in group B2. Statistically, the difference was significant and $P = <0.001$ in favor of the SIS treat group. Although HSG was never described to be a treatment option for tubal factor infertility, but it is also well-known that Spontaneous pregnancy rates increased following HSG . This may be due to the effect of tubal irrigation that breaks filmy adhesions or sweeps mucus and cellular debris through the oviducts [14].

In 2019, a meta-analysis had reported that using an oil-soluble contrast medium (OSCM) revealed a significantly higher spontaneous pregnancy rate in 6 months of follow up, than a water-soluble contrast medium (WSCM) did or no flushing at

all. But oil-soluble contrast material (OSCM) may promote granulomatous inflammation in the presence of obstructed or inflamed fallopian tubes [15].

On the other side, the conventional Saline infusion sonogram was reported to increase pregnancy rates when it was performed just before ICSI cycles, if there were no associating uterine pathologies [16].

Similar to what HSG was approved to do, SIS treat can break simple adhesions, remove cell debris, and cleans mucous plugs. Other explanation; SIS treat might cause endometrial damage due to cavity distension and/or catheterization process, which may cause growth factors and cytokines secretion (e.g., interleukin-11, leukemia inhibitory factor, and heparin-binding endothelial growth factor). These cytokines are essential for embryo implantation [17]. In a closely related clinical trial, Emad M. Siam [14] studied whether the use of a homogenously mixed saline and air contrast sonography (HyCoSy) could enhance the chance of spontaneous clinical pregnancy in women undergoing subfertility investigation, and this was compared with other contrast media used for Hysterosalpingography (HSG). The pregnancy rates of the HyCoSy group were nearly the same as those following HSG using different contrasts [14].

Recent studies have considered hysterosalpingo-foam sonography (HyFoSy) procedure as a new technique used for evaluation of tubal function. It is largely used to test tubal patency, but it is not completely clear the role of this technique as a treatment option. Maria G Piccioni et. Al. [18], conducted a systemic review of the literature and included all the studies addressed that issue from 2010 to 2019. They concluded that HyFoSy, similar to other tubal flushing techniques, actually improves the chance of implantation and establishment of a spontaneous pregnancy [18].

During the study, the main side effects of SIS treat were comparable to those of HSG, but the procedure lacks risk of exposure to ionizing radiation or dyes, it can be done in a gynecology outpatient clinic, it is safe, tolerable, and not expensive. It has a relatively short learning curve 2-9 times for doctors. The clinical implications of this study: SIS treat can be used for the diagnosis and treatment in one clinic visit, without wasting time and money in many visits or high cost procedures

Study Strength and limitations

To the best of our knowledge, this is the first randomized controlled study to address the utilization of high pressure SIS in clearing up simple tubal block.

During this study, SIS treat could not differentiate between simple tubal block and temporary tubal spasm, which might have occurred during performing the procedure. Also, we were not able to define the "high pressure" needed or measure that pressure precisely. When comparing results of SIS treat with those of HSG, we were not able to diagnose a single tubal block and/or record the exact site of tubal obstruction (proximal or distal).

Future study perspectives and recommendations: we need to design a study in which the pressure applied for SIS treat can be precisely measured, to try different pressure gradients and to determine the minimal pressure that will be needed to relief the simple tubal block. Researchers may try other methods with the same idea, like using color Doppler ultrasound during SIS treat, or air/saline HyCoSy infusion despite of simple SIS. Larger studies with bigger number of patients are needed to properly evaluate SIS treat as a simple, cheap and tolerable outpatient procedure for tubal factor infertility management.

Conclusion

SIS treat is equal to the conventional HSG in the diagnosis of tubal patency. Also, this method increases the rate of post-procedure pregnancy rate more than HSG

can do, with the well-known advantages of SIS, as it has no risk of radiation exposure and low cost consumables.

Compliance with Ethical Standards

Authors' contribution: S. E.: Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing.

S. A.: Data curation, Formal analysis, Software, Supervision

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Study registration: Pan African Clinical Trial Registry (www.pactr.org) database, identification number for the registry is PACTR202210557026698.

Disclosure of Interests: nothing to declare by both authors

Ethical Approval: the study was approved by the ethical committee of faculty of medicine Alexandria University.

Informed consent: consents were signed by each participant in this study

Data sharing: Data available on request due to privacy/ethical restrictions

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Figure legend

Figure 1. Schematic representation of various groups of the study.

Table legend

Table 1. Studied groups' characteristics: age, parity and mode of delivery.

Table 2. Comparison between group A and B2 according to tube condition/pregnancy

Table 1. Studied groups' characteristics: age, parity, and mode of delivery.

Patient characteristics	Group A (num = 93)	Group B (num = 90)	Group B2 (num = 71)
Age/ years Mean (SD)	31.5 (5.7)	32.2 (3.4)	32.2 (3.3)
Parity			
Nullipara %	28 (30.1%)	34 (37.7%)	28 (39.4%)
Multigravida %	65 (69.9%)	56 (62.2%)	43 (60.5%)
Mode of delivery			
vaginal %	20 (21.5%)	6 (6.6%)	3 (4.2%)
Cesarean section %	45 (48.3%)	50 (55.5%)	40 (56.3%)

Table 2. Comparison between group A and B2 according to tube condition/pregnancy.

	® HSG group A (n=93)	SIStreat group B2 (n = 71)	χ^2	p	OR (CI. 95%)
Opened/ Occluded					
® Opened	79 (84.9%)	62 (87.3%)	0.189	0.664	0.819 (0.333-0.664)
Occluded	14 (15.1%)	9 (12.7%)			
Pregnant +/- Not pregnant					
® Pregnant +	13 (14%)	27 (38%)	12.628*	< 0.001*	0.265 (0.124-0.565)
Not pregnant	80 (86%)	44 (62%)			

®: reference group

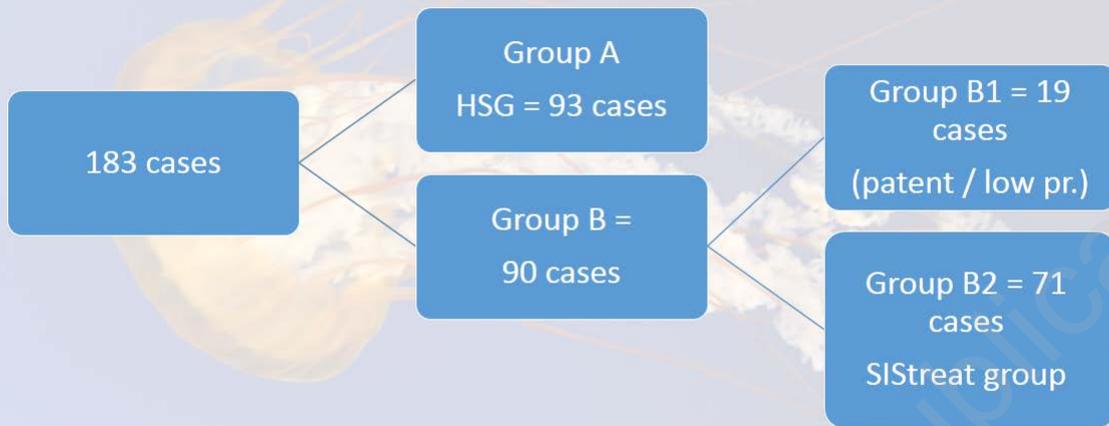
OR: Odds ratio

CI: Confidence interval

 χ^2 : Chi square test

p: p value for comparing between the two studied groups.

*: Statistically significant at $p \leq 0.05$



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