

## Diagnostic accuracy of Saline Infusion sonohystero-salpingography (SIS) as compared to Hystero-salpingography (HSG) in the assessment of sub-fertile women

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### Abstract

**Objectives:** To compare the sensitivity and specificity of saline infusion sonohysterography with hystero-salpingography as diagnostic tool in the assessment of infertile women.

**Methods:** The comparative cross-sectional study was carried out at a private infertility clinic in Karachi, and comprised women who registered for assessment of infertility from June 2011 to May 2013. Uterine and tubal pathology was assessed as a possible cause of infertility by using saline infusion sonohysterography as an index test and hystero-salpingography as the standard reference. The diagnostic accuracy of the two tests was compared. Sub-fertile patients were followed up for 2 weeks after the tests for any possible adverse effects of the procedures. Data was analysed using SPSS 19.

**Results:** Of the 256 subjects, 184 (72%) presented with primary and 72 (28%) with secondary infertility. Overall mean age of the sample was 28±8 years. The mean BMI was 29.8±4.1 in primary infertile compared to 28.2±5 in women with secondary sub-fertility. The sensitivity of saline infusion sonohysterography for detecting patency of the tubes was 100% and the specificity was 91% whereas positive predictive value was 69.8% and negative predictive value was 100% (Kappa: 0.61). For large uterine polyps, sensitivity and specificity was 100% and for small polyps sono-hystero-salpingography showed 14% false positive results (Kappa: 0.21).

**Conclusion:** Saline infusion sono-hysterography was found to be a more reliable method of diagnosing tubal or uterine pathologies compared to hystero-salpingography for cases of infertility.

**Keywords:** Saline infusion salpingography, Infertility, Hysterosalpingography. (JPMA 69: 777; 2019)

### Introduction

The prevalence rate of primary infertility in the world ranges from 2% to 5%, and it is reported to be 20% for secondary infertility among both genders. In Pakistan, the overall rate of infertility is 7%. The incidence is reported to be 3.5% in the primary group and 18.9% for secondary infertility.<sup>1</sup> The incidence of infertility differs widely between countries, gender and cultures because of issues such as accessibility of specific care, cost of care and cultural myths.<sup>2</sup> It is found to be higher in males when compared to females in Scandinavian countries.<sup>3</sup> There is evidence to show that intra-uterine anomalies are far more common among infertile women when compared to those with dysfunctional uterine bleeding (DUB).<sup>4</sup> Tubal factors have been shown to be responsible for sub-fertility in at least one-third of cases. According to the latest National Institute for Health and Care Excellence (NICE) guidelines, infertility due to uterine factors has been estimated to be the cause in 10% of cases.<sup>6</sup>

However, this factor is not usually incorporated, due to paucity of evidence, into the investigation algorithm produced.

The uterine factor is usually assessed by hysteroscopy, which is the gold standard investigation for assessing uterine cavity blemishes as well as structural abnormalities. Hystero-salpingography (HSG), whilst still convenient for the investigator where the facilities are available, has been relegated into second place as the definitive investigation of choice, partly because of the use of ionizing radiation and the limitations of the information discernible from the investigation.

Trans-vaginal sonography may be used initially in the detection of endometrial polyps and other uterine pathology.<sup>5</sup> However, polyps may be better visualised during saline infusion sono-hysterography (SIS), in which saline is used to distend the uterine cavity to readily reveal polyps as smoothly margined focal lesions that protrude into the endometrial cavity.

SIS or saline-induced ultrasonography or hydro-sonography ('water scan'), is being used with increasing frequency for investigation of infertility and other

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gynaecological indications. It is effective in distinguishing diffuse endometrial changes and focal intra-cavity protuberances. However, it is limited in its ability to differentiate between endometrial hyperplasia (pre-malignant polyps) and endometrial carcinoma.<sup>6</sup>

SIS is similar to HSG in its effectiveness for evaluating tubal patency, but superior to HSG for assessing intra-uterine abnormalities. The advantages of sono-hysterosalpingography (SIS) over HSG also include the ability to assess nearby extra-uterine structures, the lack of ionizing radiation and, often, better tolerability by the women being examined. SIS can offer a detailed assessment of the internal reproductive organs within the female pelvis, and therefore has the potential to replace HSG as a routine, first-line infertility investigation.<sup>7</sup>

Hystero-salpingogram can reveal major defects such as polyps and septae, but it often fails to diagnose smaller lesions.<sup>9</sup> It will not be wrong to say that while diagnosing unexplained sub-fertility, the part played by the uterine cavity is totally ignored. SIS can assess tubal patency and at the same time it offers an adequate examination of the uterine cavity and is therefore a useful tool in explaining cases of 'unexplained sub-fertility'.<sup>10</sup>

Over the last three decades, assisted reproductive techniques have made tremendous progress. The live birth rate from in vitro fertilisation (IVF) is around 30%. Attachment to and implantation of the embryo to the endometrium remains a major stumbling block to higher success rates and research into this problem continues apace.

In the developing world, the cost of specialised examination room facilities for the use of ionizing radiation is an important additional financial consideration.

Benign uterine cavity pathology such as endometrial polyp is common and is often diagnosed during the fertility workup process prior to IVF treatment. They alter the potential of endometrial receptivity in various ways. A meta-analysis has showed that removal of such polyps at hysteroscopy leads to a four-fold increase in pregnancy rates.

Hysteroscopic polypectomy is a minimally invasive procedure with little risk of complications and therefore should be performed prior to IVF to optimise the chances of successful implantation.<sup>13</sup>

The current study was planned to investigate the potential of differentiating between different structural

causes of infertility using saline infusion SIS and HSG.

## Patients and Methods

The comparative cross-sectional study was conducted at a private infertility clinic in Karachi, and comprised subjects from June 2011 to May 2013 who reported with primary or secondary infertility regardless of time duration. Permission was obtained from the ethical review board of City District Government, Karachi (CDGK).

The subjects were enrolled through non-probability purposive sampling from the out-patient department (OPD) after taking written informed consent from each of them. The sample size was calculated out to be 243 (with  $P=0.2$ )<sup>1</sup> by using open Epi and 5% sample was increased to ensure effect size, making it 256. In this study a non-probability purposive sampling technique was used.

Cases in which sterility of male partner had been established or was unclear were excluded and so were patients who were found to have stenosis of the cervix and required dilatation under local or general anaesthesia.

The SIS procedure was carried out in OPD without anaesthesia. The cervix was visualised using a sterile Cusco's speculum. A Foley's catheter French size 6 was inserted through cervical orifice (os) and its balloon was inflated in the uterine cavity with 1.5-2ml normal saline. Sterile normal saline solution was instilled through the catheter. The uterine cavity was distended with fluid and any polyp or abnormality in uterine cavity was clearly seen against the fluid background and recorded. The amount of saline solution instilled varied between individual patients but was usually between 10-50 ml of saline. Simultaneously, transvaginal sonography (TVS) was carried out to look at the uterus and ovaries. Presence or absence of free fluid in the pelvis was noted. Observation of a collection of fluid in the pouch of Douglas was taken as evidence of tubal patency (Figures 1-2).

The findings of HSG and SIS were recorded on a proforma for each patient. Patients were asked to describe the pain experienced during each procedure on a scale of 1 to 10, with 1 being minimal and 10 being severe discomfort. The patients' opinion was taken for their preference between the two procedures, if given a choice.

All patients were initially followed up for one week after the procedure through telephone calls, and inquiries were made about discomfort and need for analgesia.

Any visit to the hospital and requirement of parenteral analgesia were also recorded. All patients were seen for a

final follow up in the OPD for 2 weeks after the procedures.

The post-procedural pain was classified as 'severe' pain when requiring more than 2 doses of oral analgesics (diclofenac sodium) or parenteral analgesics or visit to emergency room; whereas 'moderate' pain was when it required up to 2 doses of oral analgesics (diclofenac sodium), and 'mild' pain stood for any slight discomfort not requiring analgesics.

The statistical analysis was done by using SPSS-19. Data was initially explored for its normality by using Shapiro-Wilk test ( $p=0.35$ ). Therefore, the mean and standard deviation and t test were applied for quantitative inferential analysis like comparison of pain score; whereas for qualitative variables like sensitivity & specificity, absolute frequencies, percentage values and subsequently  $\chi^2$  test was applied, with the level of significance fixed at 5%. Kappa statistics calculated to measure the agreement on predictability between these two tests HSG & SIS.

The study was duly approved by the Ethical Review Board of City District Government of Karachi.

### Results

Of the 256 subjects, 184 (72%) presented with primary and 72 (28%) with secondary infertility. Overall mean age of the sample was  $28 \pm 8$  years. The mean BMI was  $29.8 \pm 4.1$  in primary infertile compared to  $28.2 \pm 5$  in women with

**Table-1:** Presentation of subjects n=166.

| Symptoms           | Frequency | %    |
|--------------------|-----------|------|
| Dysmenorrhoea      | 40        | 24.1 |
| Irregular bleeding | 45        | 27   |
| Oligomenorrhoea    | 30        | 18   |
| Hypermenorrhoea    | 12        | 7.2  |
| Dyspareunia        | 23        | 13.8 |
| Miscellaneous      | 16        | 9.6  |

**Table-2:** Comparing Pain score during two procedures (at scale 1-10).

| Pain scale | SIS (%)    | HSG       | P value* |
|------------|------------|-----------|----------|
| 1-2        | 12 (4.6)   | 00        | <.000    |
| 3-4        | 184 (71.8) | 02 (.8)   | <.000    |
| 5-6        | 30 (11.7)  | 09 (3.5)  | <.000    |
| 7-8        | 21(8.2)    | 51 (19.9) | <.05     |
| 9-10       | 09(3.5)    | 194(75.7) | <.005    |

\*Student Independent t -test

SIS: Sono-hystero-salpingography

HSG: Hystero-salpingography.



**Figure-1:** Polyp distorting uterine cavity as seen on sono-hystero-salpingography (SIS).

secondary sub-fertility. Overall, 90(35%) patients did not report any symptoms. Symptoms reported included dysmenorrhea in 40(24.1%), irregular bleeding in 45(27%), oligomenorrhea in 30(18%), hypermenorrhoea in 12(7.2%), dyspareunia in 23(13.8%) and vague complaints in 16 (9.6%) cases (Table-1). All the HSG and SIS procedures were performed with no concomitant complications.

Large polyps were found in 34(13.2%) patients and detected by both HSG and SIS. In 42 (16.4%) cases SIS showed small polyps which an HSG had failed to detect or radiologist disregarded them as artefacts. Later, 36(85.7%) of these polyps were confirmed on histopathology. Sensitivity of SIS in detecting small polyps was significantly higher than that of HSG ( $p < .0001$ ).

Other structural uterine anomalies were detected in 5 cases on HSG but 4 were obvious on SIS ( $p > 0.05$ ).

The sensitivity of SIS for detecting large uterine polyps was 100%, whereas the false positive rate for small polyps was 14%.

Blocked tubes were diagnosed on SIS in 63 (24.6%) cases. HSG showed that out of these, 19 had free spill whereas in 44 (17.2%) cases tubes were actually blocked ( $p=0.22$ ).

In 193(75.3%) cases SIS showed spill, while HSG confirmed patent tubes in 212(82.8%) patients.

The sensitivity of SIS for detecting patency of tubes was 100% and specificity was 91%, whereas positive predictive value (PPV) was 64% and negative predictive value (NPV) was 95%. The false positive rate for tubal



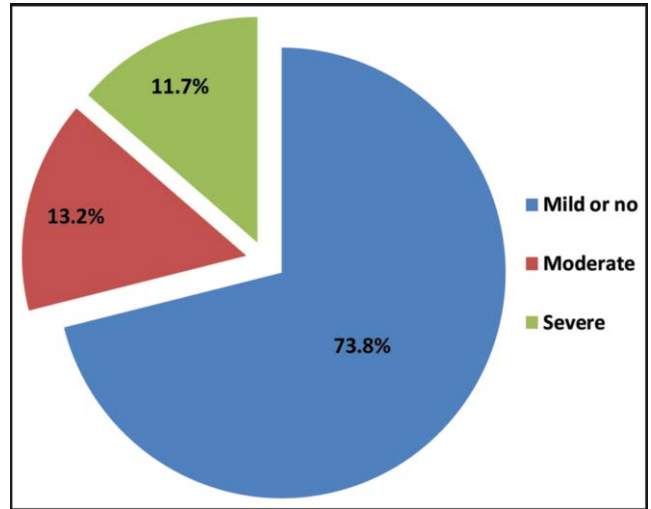
**Figure-2A-B:** Sono-hystero-salpingography (SIS) showing a small polyp in uterine cavity and an artefact.

blockade was 30.1% and 100% NPV.

Kappa statistics of 0.29 was calculated between HSG and SIS as agreement on uterine polyps while for tubal patency it was 0.61

In the HSG group, 194 (75.7%) patients experienced severe pain (pain score 9-10) and in 51(19.9%) patients, the pain score was 7-8. In the SIS group, only 30(11.7%) patients experienced severe discomfort (pain score 7-10).

During SIS, the pain score was 3-4 in 184(71.8%) women, indicating mild to moderate discomfort, while only 2 (.8%) patients fell in this category during HSG (Table-2). The



**Figure-3:** Sono-hystero-salpingography (SIS) pain score during 2-week follow-up.

pain scores during the procedure were found to be significantly higher in HSG ( $p < 0.0001$ ).

Pain and discomfort during the week following the procedure was also significantly more severe in HSG ( $p < 0.05$ ). A total of 194 (75.7%) patients complained of severe pain lasting more than a week, requiring more than 2 doses of analgesics or parenteral analgesics or necessitating a visit to an emergency room. During SIS, only 2 (.8%) women had a similar experience.

In HSG, 75 (30%) and in SIS 39 (15%) patients required 1-2 doses of oral analgesics. In SIS 182(71%) and in HSG only 2 (.8%) women complained of mild or no discomfort lasting for 2-3 days after the procedure (Figure-3).

**Discussion**

The sensitivity of SIS for detecting large and small uterine polyps in our study was 100% and 86% respectively. A recent meta-analysis that reviewed SIS as a diagnostic modality in sub-fertile women also concluded that SIS has a high degree of diagnostic accuracy in the detection of all types of intrauterine abnormalities with a sensitivity and specificity of 88% and 94% respectively. The positive and negative likelihood ratios were 20.93 (95% confidence interval [CI]: 9.06-48.34) and 0.15 (95% CI: 0.10-0.22), respectively.<sup>14</sup> In this systematic review, the authors had combined the analysis for all uterine anomalies whereas we analysed specifically for large and small polyps etc.

Furthermore, this diagnostic accuracy of SIS was compared with HSG in a longitudinal study which demonstrated high specificity (92.8%) in the detection of uterine polyps, and both high sensitivity (92.9%) and

specificity (96.8%) in the diagnosis of endometrial hyperplasia. In addition it showed high sensitivity (90%), specificity (99%), PPV (92.2%), and NPV (99%) for detection of submucous myomas.<sup>18</sup>

The false positive rate for small polyps, which was 14% in our study, is high but this can be offset by other obvious advantages that saline contrast sonography has over laparoscopy and hysteroscopy. The sensitivity of SIS could be further improved if three-dimensional ultrasound is utilised.<sup>15</sup>

In this study, blocked tubes were diagnosed by SIS in 63 (24.6%) cases. HSG showed that out of these cases, 19 had free spill from the fallopian tubes (or at least from one tube) whereas in 44 (17.2%) cases, the tubes were actually blocked.

These findings are consistent with other studies, supporting the view that saline SIS can replace the hystero-salpingogram as the initial investigation for fertility work. In cases of blocked tubes, HSG can also be performed.<sup>16</sup> Our study also found that there is slight agreement for uterine polyps ( $k=0.29$ ) and fair agreement for tubal patency ( $k=0.61$ ) among these two diagnostic procedures.

Our findings were in agreement with a study where TVS, SIS and HSG were compared. They found uterine pathologies in 25% of patients. TVS detected 6 (37.5%) and SIS revealed 11 (87.5%) of 13 intrauterine pathologies finally visualised at diagnostic hysteroscopy. TVS failed to visualise three submucous myomas, one endometrial polyp and two cases of septate uteri. All three cases of intrauterine synechiae were not detected with this method. One submucous myoma and one endometrial polyp were not identified with SIS. The study group was, however, too limited to show statistically significant differences in diagnostic accuracy among TVS, SIS and HSG.<sup>19</sup>

In the HSG group, 75.7% patients experienced severe pain (pain score 9-10) and in 19.9% of the patients; the pain score was 7-8. In the SIS group, about 1% of the women recorded pain scores of 7-8 or 9-10 (1.1%) with most (71.8%) recording pain scores of 3-4.

In a study comparing pain tolerance of hystero-salpingo-contrast sonography (HyCoSy) and X-ray hystero-salpingography, side-effects were assessed during the procedure at 2 hours, 24 hours and 28 days. The most common side-effect was pelvic pain which occurred in 56 out of 66 women (84%). This occurred during 19 out of 34 HyCoSy procedures (56%), 23 of 32 case during HSG (72%) and/or in the following 24 hours, 14 of the 34 HyCoSy

patients (41%) and 15 of the 32 HSG patients (47%) also experienced significant pain. Twelve of these 66 women required simple non-steroidal analgesia (HyCoSy 8/34 [24%], HSG 4/32 [13%]).<sup>17</sup>

These findings are similar to those encountered during our study. Pain and discomfort during the week following the procedure was also significantly more severe in the HSG group. It was seen that 179 (69.9%) patients complained of severe pain lasting for more than a week and these required more than 2 doses of analgesics or parenteral analgesics and required a visit to an emergency room. In the SIS group, only 2 women had a similar experience.

In HSG group 75 and in SIS group 39 patients required 1-2 doses of oral analgesics. In the SIS group 182 women complained of mild or no discomfort during the 2-3 days after the procedure. Of the HSG group, most had severe pain, with only 2 complaining of mild pain. SIS was clearly much better tolerated than HSG as an investigation to secure the same information.

The information provided by SIS is superior to that acquired from HSG, and much less discomfort is experienced by the women who had the former investigation.

This preliminary data is promising. Further analysis to establish cost-effectiveness would supplement its usefulness and uptake worldwide, and especially in developing countries where equipment costs are a major limiting factor.

The current study was a properly planned one and snapshot data was collected out of all eligible subjects during a stipulated time of two years for the required sample size.

Nevertheless, we found a limitation that if prevalence of blocked fallopian tubes would be known for our population then actual predictability of tubal blockade by SIS could have been calculated by using Bays Rule and, therefore, the study results would have been more conclusive clinically.

## Conclusion

SIS, a simple yet extremely valuable technique for investigating benign uterine pathology, was found to be a more reliable method of diagnosing tubal or uterine pathologies compared to HSG for cases of infertility. Although further research is warranted to establish its role as a first-line diagnostic modality in cases of sub-fertility, results and experience strongly suggest that it should be

considered favourably.

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**Conflict of Interest:** None.

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