Screening Saline Infusion Sonohysterography before ICSI and Its Effect on Success Rate of Assisted Reproduction  
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Abstract  
The aim of this work was to evaluate the diagnostic value of screening Saline Infusion Sonohysterography in diagnosing bilateral tubal blockage in patients with normal transvaginal ultrasonography, before undergoing ICSI treatment and its impact on success rate of ICSI in terms of pregnancy rate, miscarriage rate and ongoing pregnancy rate. In this prospective randomized controlled study, 80 consenting patients with primary or secondary infertility scheduled for ICSI treatment cycle at Dar Elteb infertility Centre, with normal transvaginal ultrasound, were considered eligible for this study after taking an informed consent. The patients underwent ovarian stimulation with standard long protocol. Patients were divided into two groups; Group 1: 40 underwent ICSI with a prior saline sonohysterography and, Group 2: 40 underwent ICSI without a prior saline Sonohysterography. Demographic data of patients included Age (years), Weight (kg) and BMI (kg/m2). Type and duration of infertility in the two groups was also studied. Main outcome measures were; measuring the sensitivity, specificity, positive predictive value, negative predictive value, false positive rate and false negative rate of SIS and TVS as well as the pregnancy rate, miscarriage rate and ongoing pregnancy rate. Comparison of accuracy of TVS and saline sonohysterography in diagnosing the bilateral tubal block was also performed in infertile patients. A total of 80 eligible women were included in the final analysis. Comparison of accuracy of TVS and saline sonohysterography was done in diagnosing bilateral tubal block in the infertile patients. TVS was diagnostic of bilateral tubal block with a sensitivity of 63%, a specificity of 72.5%, a positive predictive value PPV of 60.5%, a negative predictive value NPV of 52.5%, a false positive rate FPR of 29.1% and a false negative rate FNR of 28%. Saline sonohysterography was diagnostic of bilateral tubal block with a sensitivity of 100%, a specificity of 91.3%, a PPV of 71.9%, an NPV of 93.4%, a FPR of 10.2% and a FNR of 7%. Our study results indicated, 49% pregnancy rate, 12% miscarriage rate and, 37% ongoing pregnancy rate in group I (who underwent ICSI with a prior saline sonohysterography) compared to 36 % pregnancy rate, 10% miscarriage rate and 26% ongoing
pregnancy rate in group II (who underwent ICSI without a prior saline sonohysterosgraphy). There was a statistically significant difference between the two groups as regards the overall pregnancy and ongoing pregnancy rates while there was no significant difference between the two groups as regards the miscarriage rate.

Keywords

Intracytoplasmic Sperm Injection (ICSI), Embryo Transfer (ET), Saline infusion Sonohysterosgraphy (SIS), Transvaginal ultrasound (TVS)

I. Introduction

The uterus along with the fallopian tubes plays an essential role in reproduction. In 3–10% of women with fertility disorders, a so-called “uterine factor” might be a cause of their reproduction problems [1]. The fallopian tube plays an important role in the mechanical transport and physiological sustenance of the gametes and early conceptus. Tubal stenocclusive and dilative disease is an important cause of infertility and should be specifically looked for. Tubal disease with blockages can involve the proximal part, the mid part or the distal part. The diagnostic modalities that are commonly employed to evaluate the regularity and shape of the uterine cavity include a conventional 2-D and 3-D transvaginal scan, saline infusion sonography (SIS), hysterosalpingogram (HSG) and hysteroscopy [2].

Implantation failure presents a major clinical challenge and is a cause of considerable stress to patients and clinicians in assisted reproductive technology (ART). Even minor uterine cavity abnormalities, such as endometrial polyps, small submucous myomas, adhesions, and septa are considered to have a negative impact on the chance to conceive through IVF [3]. The prevalence of unsuspected intrauterine abnormalities, diagnosed by hysteroscopy prior to IVF, has been reported to be 11–45% [4]. Therefore, it has been proposed that these abnormalities should be diagnosed and treated in order to optimize the condition of the uterine environment and thus the outcome of IVF treatment. However, this recommendation is not based on high quality evidence [5]. In addition, the benefits of hysteroscopy in patients who will undergo a first IVF/ICSI treatment have not yet been investigated.

While the transvaginal scan is generally performed to screen for uterine pathologies, its diagnostic accuracy is poor with pathologies like polyps, adhesions, and submucous fibroids being missed. Recent studies have reported saline infusion SIS via this cathether an easy to perform, safe and well-tolerated procedure yielding high diagnostic accuracy and, seems to be superior to TVS and very close to hysteroscopy [6]. SIS is a minimally
invasive, cost-effective and acceptable diagnostic modality. Saline infusion helps to define better intracavitary structures, thereby improving the diagnostic accuracy. SIS is increasingly considered to be useful in diagnosing intrauterine abnormalities. It is an inexpensive, non-invasive diagnostic test, and has been proven to be very accurate [7]. For a few years ultrasonography has been a basic diagnostic method used in gynecology. It is a quick and relatively cheap way of diagnosing anomalies of reproductive organs, including pathological states inside the uterine cavity. Thanks to a contrast medium or colorful Doppler used in sonohysterography it is possible to see a contour of the uterine cavity [8]. Moreover, it also allows for confirming the patency of Fallopian tubes. In addition to that, the examination is safe and well tolerated by patients [9]. The SIS procedure makes the whole cross section visible as well as facilitating the observation of the external outline of the uterus. The presented method does not require any extra specialist equipment, except for an ultrasonography with a transvaginal probe. Such equipment can be found in every gynecological office.

Yet hysteroscopy is still considered to be the gold standard. It has become easy to perform in an outpatient clinic without anesthesia. Moreover, hysteroscopy enables diagnosis and treatment of intrauterine pathology in the same setting. An alternative to diagnostic hysteroscopy could be saline infusion sonography, which is used to evaluate the uterine cavity and patency of Fallopian tubes after application of fluid medium. The advantage of the examination is the possibility of observing the cross section and outline of the uterine cavity as well as a more detailed observation of Fallopian tubes to check whether they are blocked without using some other specialist equipment. The examination is safe and well tolerated by patients [9].

The NVOG (Dutch society of Obstetrics and Gynaecology) as well as the ESHRE (European Society for Human Reproduction and Embryology) and RCOG (Royal College of Obstetricians and Gynaecologists) do not recommend SIS nor hysteroscopy as initial investigation prior to starting IVF [10]. It has been argued that the significance of treating unsuspected intrauterine abnormalities has not yet been proven. So far, none of the guidelines considered the most recent literature on this topic.

In a retrospective cohort analysis, Gera et al. compared the pregnancy rate after operative hysteroscopy of patients with intrauterine abnormalities at SIS to the pregnancy rate of patients with a normal uterine cavity. A 31.6% increase in pregnancy rate was observed after treatment of detected abnormalities [11]. Furthermore, two randomized trials reported exceptional improvements in pregnancy rates after office hysteroscopy and instant treatment of detected pathology in patients after two failed IVF attempts. Intervention resulted in a 9–13% increase in clinical pregnancy rate in the subsequent IVF cycle [12]. These results endorsed the findings of other previously published prospective studies. Despite some methodological weaknesses in the study design, the results of these studies indicate a trend towards a beneficial effect of screening hysteroscopy on IVF outcome. This finding, combined with the observed high prevalence of intrauterine abnormalities, has led to a general debate on the beneficial effect of pre-IVF work-up of the uterine cavity [13].

The aim of this work was to evaluate the diagnostic value of screening Saline Infusion
Sonohysterography in diagnosing bilateral tubal blockage in patients with normal transvaginal ultrasonography, before undergoing ICSI treatment and its impact on success rate of ICSI in terms of pregnancy rate, miscarriage rate and ongoing pregnancy rate.

II. Patients and Methods

Design:
Prospective randomized controlled study

Setting:
Dar Elteb infertility centre

Patients:
80 consenting patients with primary or secondary infertility scheduled for ICSI treatment cycle at Dar Elteb infertility centre from January 2015 till August 2016, who had normal transvaginal ultrasound, were considered to be eligible for inclusion. An informed consent was taken from each patient included in the study.

Inclusion criteria:
• All patients included, had normal transvaginal ultrasound that is defined as no visible intracavitary pathology (e.g. sub mucous myomas, polyps or septa) and was performed in the follicular phase of the menstrual cycle. Intramural myomas without impression or deformation of the uterine cavity were incorporated in the definition of a normal ultrasound.
• Patient’s age ranging from 25 to 30 years.

Exclusion criteria:
• Abnormal transvaginal ultrasound as those with visible intracavitary pathology (e.g. sub mucous myomas, polyps or septa), ovarian cysts or endometrioma.
• Recurrent miscarriage, defined as 2 or more miscarriages prior to the 20th week of gestation.
• Prior hysteroscopy treatment and intermenstrual blood loss.
• Age below 25 or above 30 years.

The patients were divided into two groups:
Group 1: 40 underwent ICSI with a prior saline sonohysterography
Group 2: 40 underwent ICSI without a prior saline sonohysterography

Sonohysterography:
A speculum was inserted vaginally and up to 20 ml of sterile saline solution was infused into the uterine cavity, through pediatric Foley’s catheter with its guide, to distend the endometrial cavity. A transvaginal transducer of ultrasound machine (Medison x6) was used to scan the uterine cavity. The findings at SIS were recorded in a standardized manner on the case record form (CRF). The procedure was done between the 7th and 11th day of the cycle

Protocol of stimulation in subsequent IVF/ICSI attempt:
The patients underwent ovarian stimulation with standard long protocol. GnRH–agonist (lucrane: 10 units) was administered daily from the day 21 of the cycle. Then all the patients were treated with human menopausal gonadotropin (hMG: Merional , 150-300
IU/day) from day 2-3 of the next cycle, while continuing lucrine 10 units /day, with the close monitoring of follicular growth under ultrasonography every 3-4 days. HCG was administered 10000 IU when the minimum of 3 leading follicles reached 16-18 mm, and 36 hours later oocyte collection was performed.

Demographic data of patients included Age (years), Weight (kg) and BMI (kg/m2). Type and duration of infertility in the two groups was also studied. Main outcome measures were; measuring the sensitivity, specificity, positive predictive value, negative predictive value, false positive rate and false negative rate of SIS and TVS as well as the pregnancy rate, miscarriage rate and ongoing pregnancy rate. Comparison of accuracy of TVS and saline sonohysterography was also performed in diagnosing the bilateral tubal block in the infertile patients.

Statistical methods:
Statistical analysis was performed using SPSS for Windows version 20.0. Kolmogorov-Smirnov normality test was applied to all measured variables. Parametric variables were described as mean and standard deviation, and compared using independent student’s t-test. Non-parametric numeric variables were described as median and interquartile range, and compared using Mann-Whitney’s U-test. Categorical variables were described as number and percentage, and were compared using chi-squared test. Yates’ continuity correction was applied to the chi-squared test whenever one or more of the expected values were less than 5. Significance level was set less than 0.05 (P value < 0.05).

III. Results
The current study was conducted in Dar Elteb infertility centre during the period between January 2015 and August 2016. A total of 80 infertile patients were included in the study.
Table (1): Demographic data of the patients

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=40)</th>
<th>Group II (n=40)</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>25 – 30</td>
<td>25-30</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>22.71 ± 4.82</td>
<td>23.71 ± 3.85</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>50 – 105</td>
<td>45-105</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>71.8 ± 16.7</td>
<td>72.1 ± 15.6</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>17 – 34</td>
<td>17 – 35</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>28.21 ± 4.17</td>
<td>27.9±4.81</td>
<td></td>
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</table>

SD: standard deviation
Kg: Kilogram
BMI: body mass index [calculated as weight (in kilograms) divided by squared height (in meters)]
Data presented as range, mean ± SD

This table shows that the mean age in years was 22.71 ± 4.82 in group I compared to 23.71 ± 3.85 in group II, the mean weight in Kilograms was 71.8 ± 16.7 in group I compared to 72.1 ±15.6 in group II, the mean BMI in kilograms divided by squared height (in meters) was 28.21 ± 4.17 in group I compared to 27.9±4.81 in group II with no significant difference between the two groups as regards the 3 parameters

Table (2): Type and duration of infertility in the two groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (40)</th>
<th>Group II (n=40)</th>
<th>P- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Infertility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>30</td>
<td>28</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Secondary</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Duration of Infertility (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1 – 13</td>
<td>1-15</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>5.7 ± 2.6</td>
<td>5.15 ± 3.11</td>
<td></td>
</tr>
</tbody>
</table>

SD standard deviation
Data presented as number (percentage) or range, mean ± SD
This table shows that primary infertility was 30 women in group I and 28 women in group II with no significant difference between the two group. The mean duration of infertility was 5.7 ± 2.6 years in group I and 5.15 ± 3.11 years in group II with no significant difference between the two groups.

Table (3): Accuracy of TVS and saline sonohysterography in diagnosis of bilateral tubal block in the infertile patients

<table>
<thead>
<tr>
<th>Diagnosis of Bilateral Tubal Block†</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>FPR</th>
<th>FNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVS</td>
<td>63%</td>
<td>72.5%</td>
<td>60.5%</td>
<td>52.5%</td>
<td>29.1%</td>
<td>28%</td>
</tr>
<tr>
<td>Saline Sonohysterography</td>
<td>100%</td>
<td>91.3%</td>
<td>71.9%</td>
<td>93.4%</td>
<td>10.2%</td>
<td>7%</td>
</tr>
</tbody>
</table>

† PPV: positive predictive value  
NPV: negative predictive value  
FPR: false positive rate  
FNR: false negative rate

This table shows a comparison of accuracy of TVS and saline sonohysterography in diagnosis of bilateral tubal block in the infertile patients. TVS was diagnostic of bilateral tubal block with a sensitivity of 63%, a specificity of 72.5%, a positive predictive value PPV of 60.5%, a negative predictive value NPV of 52.5%, a false positive rate FPR of 29.1% and a false negative rate FNR of 28%. Saline sonohysterography was diagnostic of bilateral tubal block with a sensitivity of 100%, a specificity of 91.3%, a PPV of 71.9%, an NPV of 93.4%, a FPR of 10.2% and a FNR of 7%.

Table (4): Results of pregnancy rate in both groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Experimental group (n=40)</th>
<th>Control group (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy rate</td>
<td>49</td>
<td>36</td>
<td>&lt; 0.05*</td>
</tr>
<tr>
<td>Miscarriage rate</td>
<td>12</td>
<td>10</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Ongoing pregnancy rate</td>
<td>37</td>
<td>26</td>
<td>&lt;0.05*</td>
</tr>
</tbody>
</table>

All the parameters in this table are expressed in frequency (%) with Chi-square test. *p-value less than 0.05 was considered statistically significant.
This table shows the rate of pregnancy in both groups including those who experience miscarriages and those who continued their pregnancies. In group I the overall pregnancy rate was 49%, miscarriage rate was 12% while ongoing pregnancy rate was 37% compared to 36% women got pregnant in the control group with 10% miscarriage rate and 26% ongoing pregnancy rate. There was a statistically significant difference between the two groups as regards the overall pregnancy and ongoing pregnancy rates while there was no significant difference between the two groups as regards the miscarriage rate.

IV. Discussion

The fallopian tube, far from being a passive channel or conduit for gametes and early embryos, plays an important role in many reproductive functions such as sperm transport and capacitation, ova retrieval and transport, fertilization, embryo storage, nourishment and transport [14]. Tubal factor infertility is a common problem. Tubal dysfunction is responsible for approximately 30% of infertility cases [15]. The evaluation of tubal patency is traditionally considered fundamental in the study of causes of infertility. It represents one third of the total cost in the management of the infertile couple [16]. Several Fallopian tube assessment tests have been described but only few of them are currently in vogue in clinical practice [14], including Laparoscopy, Hysterosalpingogram, Selective salpingography and tubal catheterization, Salpingoscopy, Fallopscopy, Hystero-contrast sonography and Fertiloscopy.

Saline infusion sonohysterography is a safe, well-tolerated, quick and easy method for obtaining information on tubal status and the uterine cavity [17]. In the current study, evaluation of bilateral tubal patency was done using saline infusion sonohysterography in infertile patients before they underwent ICSI treatment and compared the results of SIS with those obtained from TVS. We found that the mean age in years was 22.71 ± 4.82 in group I compared to 23.71 ± 3.85 in group II, the mean weight in Kilograms was 71.8 ± 16.7 in group I compared to 72.1 ± 15.6 in group II, the mean BMI in kilograms divided by squared height (in meters) was 28.21 ± 4.17 in group I compared to 27.9 ± 4.81 in group II with no significant difference between the two groups as regards the 3 parameters. These results were similar to another two studies i.e., by Pujar et al. and Vaid et al., the majority of patients were in age group of 25-34 years and around 30 years (mean age 29.78 ± 4 years) respectively [18,19]. The results were inconsistent with other authors [20] who reported that the mean age is (31.21 ± 4.66) and this may be due to late age of marriage.

In the present study, primary infertility was found in 30 women in group I and 28 women in group II with no significant difference between the two groups. The mean duration of infertility was 5.7 ± 2.6 years in group I and 5.15 ± 3.11 years in group II with no significant difference between the two groups. These results agreed with the result reported by other authors who published that (66%) of patients have primary infertility [19], and similar to that result reported by Pujar et al., 2010 [18] that reported (75%) of the patients have primary infertility.
Transvaginal ultrasonography has been used extensively in the evaluation of patients with infertility. Many previous studies in the literature have substantiated that TVS was quite a sensitive method to evaluate uterine, tubal and peritoneal factors. The diagnostic accuracy of TVS varies depending upon the expertise of the investigators. Our study results have indicated TVS was diagnostic of bilateral tubal block with a sensitivity of 63%, a specificity of 72.5%, a positive predictive value PPV of 60.5%, a negative predictive value NPV of 52.5%, a false positive rate FPR of 29.1% and a false negative rate FNR of 28%. Saline sonohysterography was diagnostic of bilateral tubal block with a sensitivity of 100%, a specificity of 91.3%, a PPV of 71.9%, an NPV of 93.4%, a FPR of 10.2% and a FNR of 7%.

Our study results indicated, 49% pregnancy rate, 12% miscarriage rate and, 37% ongoing pregnancy rate in group I (who underwent ICSI with a prior saline sonohysterography) compared to 36 % pregnancy rate, 10% miscarriage rate and 26% ongoing pregnancy rate in group II (who underwent ICSI without a prior saline sonohysterography). There was a statistically significant difference between the two groups as regards the overall pregnancy and ongoing pregnancy rates while there was no significant difference between the two groups as regards the miscarriage rate.

There were no procedural failures in the present study, but failure to complete the procedure has been mentioned in the literature due to an inability to complete the procedure because of a stenotic cervix and cervical scarring causing backflow of saline [21].

Cervical stenosis is common in elderly postmenopausal women. It was easy to catheterize the cervices of majority of our study population, as they were premenopausal. Similarly we did not encounter any complication related to SHG. Complications of SHG, in the literature are exceptional and include vasovagal syncope, endometrial shearing with catheter, bleeding, infection, perforation (due to instrumentation) and theoretical risk of spreading of carcinoma. SIS is virtually devoid of procedural complications as reported by Elsayes et al., 2009 except for potential intracavitary infection, which can generally be avoided if the procedure is performed under aseptic precautions [22]. In our study, patients underwent ovarian stimulation with standard long protocol. GnRH agonist (lucrine: 10 units) was administered daily from the day 21 of the cycle. Then all the patients were treated with human menopausal gonadotropin (hMG: Merional, 150-300 IU/day) from day 2-3 of the next cycle, while continuing lucrine 10 units /day, with the close monitoring of follicular growth under ultrasonography every 3-4 days. HCG was administered 10000 IU when the minimum of 3 leading follicles reached 16-18 mm, and 36 hours later oocyte collection was performed.

One of the limitations of our study was that we did not consider evaluating the other aspects of SIS as a screening method such as, its cost-effectiveness, time spent, patient’s preference and scoring the patient’s discomfort. Some studies in the literature are seen to address these issues. These studies are small in number and further work in this regard is needed in the future.
Our study found SIS an effective, easy, safe, accessible and non-invasive office procedure that can be offered as a screening method for the evaluation of the bilateral tubal patency in infertile women before undergoing ICSI treatment cycle.

V. Conclusion
Sonohysterography can be provided in an outpatient setting for diagnosing bilateral tubal blockage in patients with infertility before undergoing ICSI treatment. It is an effective, easy, safe, accessible and non-invasive office procedure that can be offered as a screening method for the evaluation of the bilateral tubal patency in this study population. This procedure is easy to perform in almost any medical setting because it does not require sedation or anesthesia, nor does it have any serious common adverse effects or severe related complications. Also interestingly, performance of SIS before ICSI-ET can increase the pregnancy rate.

VI. References


[15]. Allam IS et al. Role of hysteroscopy in the evaluation of tubal patency in infertile women, Middle East Fertil Soc J (2014).


Pan
Endoscopic Approach
“Hysterolaparoscopy” as an Initial Procedure in Selected Infertile Women


[22]. Elsayes KM, Pandya A, Platt JF, Bude RO. Technique and diagnostic utility of saline infusion sonohysterography. Int J Gynaecol...