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Complementary roles of hysteroscopy and saline infusion hysterosonography in uterine cavity assessment before *in vitro* fertilization

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ABSTRACT

Objective: This comparative study was designed to assess the role of saline infusion hysterosonography in refining the diagnosis of uterine cavity abnormalities diagnosed by hysteroscopy in infertile, asymptomatic women before *in vitro* fertilization/intra-cytoplasmic sperm injection (IVF/ICSI) treatment. **Methods:** One hundred and twenty four asymptomatic infertile women were included in this study before IVF/ICSI treatment. Hysteroscopy was done as routine procedure for uterine cavity assessment before the first attempt of IVF/ICSI treatment. Patients agreed to have an ultrasound assessment of uterine cavity with the use of saline as the contrast medium (Saline infusion hysterosonography, SIHS) beside the hysteroscopic assessment. Both hysteroscopy & SIHS procedures were scheduled post menstrual period in the early-mid follicular phase of a cycle of the same menstrual cycle, 1-3 months before starting the IVF/ICSI treatment. **Results:** The uterine cavity abnormalities were detected in 40.3% of the patients included in this study before IVF/ICSI treatment (17.7% endometrial polyps, 10.5% sub-mucous fibroid, 4.8% uterine septum, 3.2% uterine adhesions, 2.4% endometrial hyperplasia and 1.6% thin or atrophic endometrium). In this study, the hysteroscopy was more sensitive (98.0% versus 96.2%), more specific (100.0% versus 98.7%) and more accurate (99.2% versus 97.6%) than SIHS, and the hysteroscopy also had higher predictive values (100% versus 98% positive predictive value; 98.7% versus 97.4% negative predictive value) than SIHS during uterine cavity assessment before IVF/ICSI treatment. **Conclusions:** Infertile asymptomatic women should be screened for possible uterine cavity abnormalities before IVF/ICSI; SIHS is a simple, well tolerated procedure that can be used as a complementary tool to confirm the diagnosis of uterine cavity abnormalities detected by hysteroscopy.

1. Introduction

Evaluation of the uterine cavity is a basic step in the investigation of infertile women[1,2]. Both the condition of the endometrium as well as the uterine cavity are thought to be important factors in determining receptivity for embryo implantation[3,4]. It has been suggested that unsuspected intrauterine abnormalities may negatively affect the uterine environment and thereby the likelihood of achieving an ongoing pregnancy[5]. Hence, it is recommended to diagnose and treat these abnormalities, in order to optimize the uterine conditions and subsequent *in vitro* fertilization (IVF) success rates[6-9].

Transvaginal ultrasonography (TVS) is the standard method applied to screen for possible endometrium or uterine cavity abnormalities in the work up of infertility patients. When indicated, this evaluation of the uterine cavity lining can be expanded with saline/gel infusion sonography (SIS), hysterosalpingography (SIHS) or hysteroscopy[10].

Hysteroscopy is known as the gold standard procedure for uterine cavity assessment. It enables diagnosis and treatment of intrauterine pathology in the same outpatient setting. Hysteroscopy is quick, safe and well-tolerated procedure[11]. Therefore, it has become an excellent tool for the diagnostic and therapeutic infertility work-up. It has been frequently advised to perform hysteroscopy as a routine procedure prior to IVF/ICSI (*In vitro* fertilization/

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intra-cytoplasmic sperm injection) treatment[12,13]. The reported prevalence of minor intrauterine abnormalities detected by hysteroscopy prior to IVF/ICSI differs considerably between studies[13,14].

Although, hysteroscopy is known as the gold standard procedure for uterine cavity assessment[15], the periovulatory TVS had positive predictive value (PPV) as high as 85%-95% for uterine abnormalities detected at hysteroscopy in an infertile population[16], and it has been reported that the expansion of uterine cavity with saline during transvaginal sonography improves the delineation of uterine cavity abnormalities[17-19]. Therefore, this study was designed to assess the role of saline infusion hysterosonography in refining the diagnosis of uterine cavity abnormalities diagnosed by hysteroscopy in infertile asymptomatic women before IVF/ICSI treatment.

2. Patients and methods

One hundred and twenty four asymptomatic infertile women were scheduled for IVF/ICSI treatments and were included in this study after informed consent & approval of the study protocol by the institute ethical committee of Ahmadi Hospital. Hysteroscopy was done as routine procedure for uterine cavity assessment before the first attempt of IVF/ICSI treatment, the patients agreed to have an ultrasound assessment of uterine cavity with the use of saline as the contrast medium (SIHS) beside the hysteroscopic assessment.

Patients included in this study were nulliparous; the mean age was (30.3±3.4) years (range from 25.0 to 35.0). Both hysteroscopy & SIHS procedures were scheduled post menstrual period in the early-mid follicular phase of a cycle of the same menstrual cycle, 1-3 months before starting the IVF/ICSI treatment. All patients received non-steroidal analgesic 30 min before the two procedures and prophylactic antibiotics (200 mg of doxycycline before & 100 mg twice daily for 5 d after). The findings during hysteroscopy & SIHS were recorded on DVD and reviewed by senior gynecologists.

Any uterine abnormalities diagnosed in the studied cases were treated using operative hysteroscopy under general anaesthesia and specimens obtained were sent for histopathological examination.

The diagnosis of endometrial polyps, sub-mucous myoma, endometrial hyperplasia and thin or atrophic endometrium were confirmed after the histopathological results of the specimens taken during operative hysteroscopy, while the diagnosis of the intrauterine adhesions was based on the hysteroscopic findings reviewed by senior gynecologists.

Hysteroscopy: office hysteroscopies were carried out in a standardized manner, using a 5-mm outer-diameter continuous flow Bettocchi hysteroscope with 30° direction of view (Karl Storz Endoscopy, Utrecht, Netherlands). Normal sterile, isotonic saline solution was used for distension of the uterine cavity. The uterine cavity was assessed on its shape (normal, arcuate or septate) and the presence or absence of abnormalities (endometrial polyps, myomas, adhesions and septa). Any uterine abnormalities diagnosed in the studied cases were treated using operative hysteroscopy under general anaesthesia and specimens obtained were sent for histopathological examination.

SIHS: TVS examinations were done by an expert sonographer, who was blinded to the patients' data, using Philips HD9 with 2D convex probe 4-9 MHz. Initially, the myometrium and endometrium were examined in longitudinal & transverse planes. Irregularities and any distortion of the endometrial echo were noted. The SIHS was then performed by insertion of pediatric Foley's catheter (No. 5) through the cervix, 1-2 mL of saline used to inflate the self-retaining balloon. Then, 5-15 mL of physiologic saline solution was slowly infused to distend the uterine cavity during continuous scanning. The uterine cavity was evaluated with attention to its contour, dimensions, regularity, and thickness of the endometrium and presence of endometrial polyps or fibroids in at least two planes during the distension and by the end of it.

Data was collected, tabulated and then statistically analyzed using Statistical Package for Social Sciences (SPSS); computer software version (15). Numerical variables were presented as mean±SD, while categorical variables were presented as number and percentage. Student (t) test was used for comparison between groups as regard numerical variables. A difference with P value <0.05 was considered statistically significant, otherwise it was insignificant. Sensitivity is the proportional detection of individuals with the disease of interest in the population. Specificity is the proportional detection of individuals without the disease of interest in the population. PPV is the proportion of all individuals with positive tests, who have the disease. Negative predictive value (NPV) is the proportion of all individuals with negative tests who are non-diseased. The sensitivity, specificity, accuracy and the predictive values of the hysteroscopy & SIHS were calculated using the following formulas:

Sensitivity=True positive/(True positive+False negative)×100% (1)

Specificity=True negative/(True negative+False positive)×100% (2)

PPV=True positive/(True positive+False positive)×100% (3)

NPV=True negative/(True negative+False negative)×100% (4)

Accuracy=(True positive+true negative)/(True positive+True negative+False positive+False negative)×100% (5)

3. Results

The uterine cavity abnormalities were diagnosed in 40.3% of the patients included in this study (17.7% endometrial polyps, 10.5% sub-mucous fibroid, 4.8% uterine septum, 3.2% uterine adhesions, 2.4% endometrial hyperplasia and 1.6% thin or atrophic endometrium) (Table 1). As shown in Table 1, during hysteroscopic evaluation of the uterine cavity of the studied cases, one case of small sub-mucous fibroid was diagnosed as normal uterine cavity (false negative), while during SIHS evaluation of the uterine cavity of the studied cases, two cases were diagnosed as normal uterine cavity (one cases of endometrial polyp and one case of Ascherman syndrome were false negative) and one case of endometrial polyp was diagnosed as endometrial hyperplasia (false positive).

In this study, the hysteroscopy was more sensitive (98.0% versus 96.2%), more specific (100.0% versus 98.7%) and

Table 1
The hysteroscopic and saline infusion hysterosonography (SIHS) findings in the studied population (n=124).

Variables	Hysteroscopic findings	SIHS findings
Normal uterine cavity (n=74) (True negative)	75[a]	76[b]
Abnormal uterine cavity (n=50) (True positive)	49	48
Endometrial polyp (n=22)	22	20
Sub-mucous fibroid (n=13)	12	13
Uterine septum (n=6)	6	6
Intrauterine adhesions (Ascherman) (n=4)	4	3
Endometrial hyperplasia (Thick endometrium) (n=3)	3	4[c]
Thin (atrophic) endometrium (n=2)	2	2

The diagnosis of endometrial polyps, sub-mucous myoma, endometrial hyperplasia and thin (atrophic endometrium) were confirmed after the histopathological results (gold standard), while the diagnosis of intrauterine adhesions was based on the hysteroscopic findings reviewed by senior gynecologists. [a]One case of sub-mucous fibroid was diagnosed as normal cavity (false negative). [b]Two cases (one case of endometrial polyp and one case of Ascherman) were diagnosed as normal cavity (false negative). [c]One case of endometrial polyp was diagnosed as endometrial hyperplasia (false positive).

more accurate (99.2% versus 97.6%) than SIHS, and the hysteroscopy also had higher predictive values (100.0% versus 98.0% PPV; 98.7% versus 97.4% NPV) than SIHS during evaluation of uterine cavity before IVF/ICSI treatment.

4. Discussion

The reported prevalence of minor intrauterine abnormalities detected by hysteroscopy prior to IVF/ICSI differs considerably between studies applying a comparable set up (prevalence 11%-40%)[13,14]. Although hysteroscopy is known as the gold standard procedure for uterine cavity assessment[15], it has been reported that the expansion of uterine cavity with saline during transvaginal sonography improves the delineation of uterine cavity and increases the detection of the uterine cavity abnormalities.

One hundred and twenty four asymptomatic infertile women agreed to have SIHS beside the routine hysteroscopy for uterine cavity assessment before the first attempt of IVF/ICSI treatment. The uterine cavity abnormalities were diagnosed in 40.3% of the patients included in this study before IVF/ICSI treatment (17.7% endometrial polyps, 10.5% sub-mucous fibroid, 4.8% uterine septum, 3.2% uterine adhesions, 2.4% endometrial hyperplasia and 1.6% thin or atrophic endometrium).

A total of 678 asymptomatic infertile women before IVF/ICSI treatment underwent office hysteroscopy (asymptomatic patients, with a normal TVS and no previous hysteroscopy) to detect the prevalence of unsuspected intrauterine abnormalities in an asymptomatic population before IVF/ICSI by Fatemi *et al*[14]. They found that the overall prevalence of unsuspected intrauterine abnormalities in asymptomatic patients before IVF/ICSI was 11%, and the most common abnormalities detected was endometrial polyps (6% women) and submucous myomas (1% women)[14].

Fifty six infertile women with abnormal transvaginal ultrasound findings were included in a retrospective study, and a hysteroscopy was performed for them between the 6th and 10th day of the cycle by Devleta Balić & Adem Balić[20]. They found that the most frequent abnormalities during evaluation of uterine cavities were endometrial polyps (60.7% by TVS & 35.7% by hysteroscopy), septate uterus (14.3%), sub-mucosal myoma (12.5%), endometrial hyperplasia (8.9% by TVS & 33.9% by hysteroscopy) and Ascherman syndrome (3.6%)[20]. Also, Kasius and colleagues screened 107 asymptomatic infertile women for uterine cavity abnormalities before IVF/ICSI and they found that the most frequent abnormalities during evaluation of uterine cavities were endometrial polyps (11.2%), septate uterus (1.9%) and sub-mucosal myoma (1.9%)[21].

During hysteroscopic evaluation of the uterine cavity of the studied cases, one case of small sub-mucous fibroid was diagnosed as normal uterine cavity (one case = false negative), while during SIHS evaluation of the uterine cavity of the studied cases, two cases were diagnosed as normal uterine cavity (one cases of endometrial polyp + one case of Ascherman syndrome = false negative) and one case of endometrial polyp was diagnosed as endometrial hyperplasia (false positive). In this study, the hysteroscopy was more sensitive (98.0% versus 96.2%), more specific (100.0% versus 98.7%) and more accurate (99.2% versus 97.6%) than SIHS, and the hysteroscopy also had higher predictive values than SIHS during evaluation of uterine cavity before IVF/ICSI treatment. Devleta Balić & Adem Balić, concluded that the specificity was higher in hysteroscopy than in TVS in the diagnosis of endometrial polyps (92.3% versus 56.4%), while the sensitivity was identical (100.0%) and the sensitivity of TVS in the diagnosis of endometrial hyperplasia was higher than that of hysteroscopy (86.4% versus 22.7%), while specificity was identical (100.0%). Also, they concluded that hysteroscopy is more reliable in diagnosis of uterine cavity abnormalities than TVS and the use of a high frequency ultrasound probe leads to a lack of diagnostic clarity between endometrial polyps and hyperplasia[20].

Aydia *et al*. screened 44 patients by hysteroscopy and SCHS before IVF/ICSI, and SCHS was performed following a baseline transvaginal scan by injection of saline into the uterine cavity during continuous scanning. Hysteroscopy was performed with a flexible fiberscope with a 3.6-mm outer diameter. They diagnosed uterine cavity abnormalities in 16 women by hysteroscopy and the SCHS was in complete agreement with hysteroscopy in 13 out of 16 cases. They found that the SCHS had 87.5% sensitivity, 100.0% specificity, 100.0% PPV and 91.6% NPV during evaluation of uterine cavity abnormalities and they concluded that SCHS is a simple, well tolerated procedure that can be performed to avoid expensive diagnostic hysteroscopy and significant findings can be treated by operative hysteroscopy

prior to IVF/ICSI[22].

Two hundred and twenty three women with suspected uterine cavity abnormalities by TVS were evaluated by SIS and hysteroscopy (74% were premenopausal and 26% were postmenopausal) by Cepni and colleagues. To determine whether performing TVS and SIS before hysteroscopy could reduce the number of diagnostic hysteroscopies performed for the evaluation of uterine cavity abnormalities. They concluded that SIS and hysteroscopy are equally accurate in the diagnosis of endometrial polyps and sub-mucous fibroids in premenopausal patients, while hysteroscopy is the most accurate tool for diagnosis of polypoid lesions in the postmenopausal group, and they also concluded that performing TVS, SIS and dilatation & curettage could reduce the number of diagnostic hysteroscopies performed for the evaluation of uterine cavity abnormalities[23].

Eighty-three women with suspected endometrial cavity abnormalities were evaluated using SIS to evaluate the accuracy of SIS for the diagnosis of endometrial cavity abnormalities in patients with abnormal uterine bleeding by Gunes and colleagues. They concluded that SIS was a reliable and accurate method for detection of uterine cavity abnormalities and it can be a good alternative technique for the evaluation of uterine cavity abnormalities where office hysteroscopy is not available[15].

Infertile asymptomatic women should be screened for possible uterine cavity abnormalities before IVF/ICSI. SIHS is a simple, well tolerated procedure can be used as a complementary tool to confirm the diagnosis of uterine cavity abnormalities detected by hysteroscopy.

Conflict of interest statement

We declare that we have no conflict of interest.

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