Use of hysteroscopy before ICSI

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ABSTRACT: What problem was addressed? There is need to define use of diagnostic and operative hysteroscopy before ICSI in evaluating, treating abnormalities of uterine cavity, and to evaluate sensitivity and specificity of hysteroscopy in diagnosis of endometritis, in infertile women attending National infertility center, Misurata Libya. Use of hysteroscopy before ICSI helps in tackling of uterine factors, and can improve the outcomes, reduce the costs, and alleviate anxiety due to failure of ICSI.

What was tried? Interventional prospective study of 208 infertile cases candidate for ICSI. Hysteroscopy used to diagnose and treat abnormalities detected before ICSI. Evaluation of sensitivity, specificity, calculated to assess diagnostic hysteroscopy for detecting endometritis in infertile female.

What lessons were learned? Abnormal uterine findings were detected in 89.2% of cases, treated before starting ICSI. Hysteroscopy showed 90.2% sensitivity and 90% specificity in evaluation of endometritis. After use of diagnostic hysteroscopy pregnancy occurred spontaneously in 12.9% of cases and in 26.9% after ICSI. Between the two groups there was significant difference statistically only in the duration of infertility and presence of adhesions.

Use of hysteroscopy before ICSI has high sensitivity and specificity in detecting endometritis. Hysteroscopic use can by itself improve the chances of spontaneous pregnancy.

Keywords: Hysteroscopy, infertility, Uterine factors, failure of ICSI.

1 Introduction

When it comes to predicting IVF outcomes, we know that oocyte biology, embryonic development and endometrial receptivity contribute significantly to predictive models of outcome. Several factors are responsible for recurrent assisted reproductive failure (RIF). They are related to either maternal or embryonic causes. Maternal factors include uterine anatomic abnormalities, thrombophilia, non-receptive endometrium, and immunological factors. Failure of implantation due to embryonic causes is associated with either genetic abnormalities or other factors intrinsic to the embryo that impair its ability to develop in utero, to hatch and to implant. [1]

Uterine endometrial receptivity of the embryos is an important factor to the IVF success. Treatment of RIF should be targeted to the abnormality detected, and the correction of any potential malfunction of the uterus that might contribute to the failure of implantation. [2].

Maternal uterine factors that affect implantation adversely involve: anatomical defects (septa polyps, fibroids, and adhesions), endometritis could cause defective endometrial receptivity. Thrombophilia, connective tissue disease, and immunologic factor all contribute negatively to the implantation process. no formal criteria defining the number of failed cycles or the

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total number of embryos transferred in these IVF attempters. [3,4]. Evaluation of the uterine cavity by noninvasive methods which allow visualization of uterine cavity, measurement of endometrial thickness using ultrasonography, sonohysterography. [5]

Hysterosalpingography helps in detection of tubal patency, and detection of tubal abnormalities. Hysteroscopy can evaluate and easily treat uterine cavity abnormalities with the application of operative hysteroscopic techniques. Ideally, a relatively simple and straightforward procedure, such as office hysteroscopy, could be adopted in the routine initial work-up of infertile couples, especially in patients with repeated IVF failures. [6]

World Health Organization) recommends hysterosalpingography alone for management of infertile women, as it provides information on tubal patency or blockage. The WHO only recommends Office hysteroscopy when clinical or complementary exams (ultrasound, HSG) suggest intrauterine abnormality or IVF failure. Many specialists feel that hysteroscopy is a more accurate tool because of the high false-positive and false negative rates of intrauterine abnormality with HSG. They use hysteroscopy as a first-line routine exam for infertility patients regardless of guidelines. [7].

1. The objective: aim of this study was to define the diagnostic and operative use of hysteroscopy in evaluating and treating abnormalities of the uterine cavity, before ICSI and to evaluate the sensitivity and specificity of hysteroscopy in the diagnosis of endometritis, in infertile women.

2. Participants and methods:
2.1 Patients selection: The study was conducted in Misurata National Infertility Management Center. Interventional prospective study, all patients (208 patients) who were candidate for ICSI due to primary and secondary infertility, from September 2013 till January 2014 (5 months duration) were enrolled in the study. In one hundred twenty-seven (61%) patients, it was their first or second trial of ICSI, and eighty-one (39%) patients with previous failed trials (2-10 trials). Mean age group (33.4 years), they were eligible to receive ovarian stimulation by antagonist or agonist protocols. Before starting ICSI, they all underwent hysteroscopic examination of the uterine cavity, after explanation of the procedure, and signing a consent. Patients were followed for two months after performing the hysteroscopy. The study and procedure were explained to the patients, explanation of treatments options if needed, Written Consents of patients were obtained before the procedure.

2.2 Ethical approval: The study protocol was approved by the scientific committee, research department of the National Infertility Management Center, Assisted Reproductive Technique Unit, Faculty of Medicine Misurata University.

2.3 Hysteroscopic technique: Under aseptic conditions, general anesthesia administered, hysteroscopic examination were performed during follicular phase of the menstrual cycle, usually within week after the end of menstruation. All cases received 400 μg vaginal misoprostol 10 hour before the procedure. An initial transvaginal ultrasound scan done, cervix visualized, the anterior lip was grasped with a single toothed tenaculum. Rigid 30° hysteroscopy Karl Storz (KARL STORZ GmbH and Co. KG, Tuttlingen, Germany) with a 3.5 mm outer diameter of the sheath used. Normal saline used as distension medium, keeping the uterine pressure (100-150 mm of mercury) was maintained using an electronic pomp (Karl Storz), light source was (Karl Storz, 300). The endocervical canal, uterine cavity, endometrium, tubal ostia, were inspected methodically. At the end of diagnostic hysteroscopy, if polyps, leiomyomas, or adhesions were found, the patient under-gone immediate hysteroscopic resection or adhesiolysis. Septoplasty done by bipolar cautery and scissor for resecting the septa. Electrocautery used to coagulate bleeding from small vessels. Chronic endometritis: defined as areas of hyperemia, edema, and small polyps. Endometritis was found in 119 (63.64%), either alone or mixed with other finding i.e. with septum, polyps, and adhesions. Endometritis was detected alone in 21
(11.22%) of cases endometrial tissue samples were obtained from these cases endometritis. All samples fixed in formaldehyde and sent for histopathological examination. Prophylactic antibiotic routinely given for all patients (vibramycin tablets 100mg and vaginal flagyl suppositories twice daily for 10 days). Additionally, in cases of septum resection patients discharged on estrogen tablet 2mg for 10 days. All patients (208) were discharged in the same day of the procedure without any complication.

2.4 The controlled ovarian stimulation (COS) protocol: Spontaneous pregnancy occurred in 27 cases (12.9%) during the same cycle after performing the hysteroscopic procedure. The remaining patients 181 cases, (87.1%) had ICSI trials within two months after hysteroscopy, either by agonist or antagonist protocols according to patient criteria.  

**Agonist protocol:** down-regulation was started using triptorelin acetate (Decapeptyl, Ferring) 0.1 mg subcutaneously daily on day 20 of the cycle. Adequacy of down regulation by measuring E2 (<50 pg./ml) at 2ed or 3rd day of menstrual cycle. Ovarian stimulation started using menotrophin (menogon.75 IU, ferring) and recombined FSH (Gonal f 75 IU 5.5 micrograms merch Serono), dose was adjusted on basis of individual response. GnRH antagonist protocol, ovarian stimulation started at day 2 or 3 of menstrual cycle and (Cetrorelix acetate) cetrotide 0.25 mg/daily started at day 6 of stimulation. Follow-up using transvaginal ultrasound and serum estradiol was done on day 6,8, and 10 of stimulation and repeated as indicated. Human chorionic gonadotropin (hCG) measured, followed by sonography two weeks later to confirm of pregnancy.

2.6 Statistical analysis: Data entry and analysis were done, using software SPSS version 13. Chi square test and student t-test used. The probability of less than 0.05 was used as a cut off for all significant tests. The overall performance of sensitivity and specificity by using ROC AUC as a measure of overall performance of these tests. Pie charts were used for comparing the results (positive pregnancy results) between two groups of the study.

3. Results:

A total of 208 infertile women the mean age was (33.47+4.98) years (range 18-40) years, the mean duration of infertility was (6.30± 3.88) years (range1-21) years. Most of the studied group had history of primary infertility in120 cases (57.7%) and secondary infertility was reported in 88 cases (42.3%). Studied group divided to two group, first group, one hundred twenty-seven (61%) patients, it was their first or second trial of ICSI, and eighty-one (39%) patients with previous failed trials (2-10 trials). Their mean age was (33.47 + 4.9 SD), as shown in (Table 1).

Pregnancy after treatment of uterine abnormalities, occurred either immediately in the same cycle after hysteroscopic procedure (spontaneous pregnancy, without ICSI), or in the cycle following procedure. The highest rate of pregnancy was among patients treated by adhesiolysis, and endometritis. (50% and 47.6% respectively. (Table 2)

Regarding distribution of admission characteristics, pregnancy rate and Hysteroscopic findings based on patients’ previous ICSI cycles, there were no significant differences between the two groups, (age, type of infertility, pregnancy rate after hysteroscopic procedure). Significant statistical differences were detected in cases of adhesions, and duration of infertility which were significantly more in the second group cases, previous (2-10 trials). Endometritis was found in 119 (63.64%). Present alone in 21(11.22%) of cases and mixed with other
findings i.e. with septum, polyps and adhesions in 98 (52.42%) of cases. (Table 3).

**Table 1**: Shows mean age, duration of infertility and number of failed IVF cycles

<table>
<thead>
<tr>
<th></th>
<th>208</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>33.47 ± 4.98</td>
</tr>
<tr>
<td>Duration of infertility (years), mean ± SD</td>
<td>6.30 ± 3.88</td>
</tr>
<tr>
<td>Number of failed IVF cycles</td>
<td>2.24 ± 1.66</td>
</tr>
</tbody>
</table>

**Table 2**: Uterine abnormalities and occurrence of pregnancy (spontaneous or after ICSI) after hysteroscopic treatment

<table>
<thead>
<tr>
<th></th>
<th>Spontaneous pregnancy</th>
<th>Pregnancy after ICSI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septum</td>
<td>9 (10.50%)</td>
<td>27 (31.76%)</td>
<td>36 (42.55%)</td>
</tr>
<tr>
<td>Adhesions</td>
<td>11 (13.40%)</td>
<td>13 (15.65%)</td>
<td>24 (29.06%)</td>
</tr>
<tr>
<td>Polyps</td>
<td>4 (7.04%)</td>
<td>0 (0.00%)</td>
<td>13 (25.40%)</td>
</tr>
<tr>
<td>Endometritis</td>
<td>3 (14.28%)</td>
<td>2 (13.33%)</td>
<td>10 (47.06%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Previous ICSI cycle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=117 (61%)</td>
<td>N=81 (59%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average age</td>
<td>33</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>56 (44%)</td>
<td>27 (33%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of infertility:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary infertility</td>
<td>73 (57.48%)</td>
<td>47 (58%)</td>
<td>NS</td>
</tr>
<tr>
<td>Secondary infertility</td>
<td>54 (42.52%)</td>
<td>34 (42%)</td>
<td>NS</td>
</tr>
<tr>
<td>Average Duration of infertility (years)</td>
<td>5.4</td>
<td>7.7</td>
<td>S</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Hysteroscopy findings</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine septum</td>
<td>52 (41%)</td>
<td>33 (40.74%)</td>
<td>NS</td>
</tr>
<tr>
<td>Arcuate uterus</td>
<td>7 (5.51%)</td>
<td>5 (6.17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Endometritis</td>
<td>73 (61.34%)</td>
<td>52 (71.23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Uterine polyps</td>
<td>32 (25.20%)</td>
<td>19 (25.68%)</td>
<td>NS</td>
</tr>
<tr>
<td>Submucous fibroid</td>
<td>0 (0.00%)</td>
<td>2 (2.47%)</td>
<td>NS</td>
</tr>
<tr>
<td>Adhesion</td>
<td>21 (16.54%)</td>
<td>26 (32.10%)</td>
<td>S</td>
</tr>
<tr>
<td>Bicornuate uterus</td>
<td>10 (0.00%)</td>
<td>0 (0.00%)</td>
<td>NS</td>
</tr>
<tr>
<td>Uniborn uterus</td>
<td>10 (0.79%)</td>
<td>1 (1.23%)</td>
<td>NS</td>
</tr>
<tr>
<td>Atrophic Endometrium</td>
<td>2 (1.57%)</td>
<td>2 (2.47%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Figure 1**: ICSI Test chart.

In group 1 nearly half of them (44%) become pregnant either spontaneously or after ICSI, within one month after use of hysteroscopy. Patients with previous ICSI trials (2-10 failed trials, group 2), one-third of them (44%) became pregnant either spontaneously or after ICSI, within one month after use of hysteroscopy, (Figure 1).

Sensitivity is the probability that a test will indicate 'disease' among those with the disease. Specificity is the fraction of those without disease who will have a negative test result. (Table 4).
Figure 2 Hysteroscopic examination.

Area under the ROC curve is the probability that a randomly selected individual from the positive group has a test result indicating greater suspicion than that for a randomly chosen individual from the negative group. The ROC graph shows the accuracy of the hysteroscopy as a screening test depending on how well it separates the patients being tested into those with and without endometritis. Accuracy is measured by the area under the ROC curve. An area of 0.9072 represents an excellent test. In the present study, abnormal endometrial finding detected in 119/208 (63.64%) patients using hysteroscopy. When the diagnosis was compared with the results came out of the histopathology (i.e. golden rule) it showed statistically significant high sensitivity (90.4%) so hysteroscopy can detect 90.4% of the patients with endometritis, high specificity (91.04%) so only 9% test positive for endometritis by hysteroscopy which they do not had the disease, and diagnostic accuracy (90.72%). Hysteroscopy is highly valuable in diagnosing endometritis. Moreover, the main advantage of hysteroscopic examination is the ability to treat more than one abnormality in one procedure. (Figure: 2)

4. Discussion

Despite the rapid developments in the field of assisted reproduction, the implantation and pregnancy rates remain un-expectantly low. It was estimated that up to 85% of embryos transferred into the uterine cavity do not implant (8). Although endometrial receptivity is considered a major role for achievement of pregnancy, the evaluation of the uterine cavity for reproduction is an important step during infertility work-up, either during initial assessment or when any ART procedure is scheduled. Intrauterine lesions are more common in infertile women. [4,8]

In this study, the percentage of abnormality by hysteroscopy in patient for first and second trail ICSI was (88.97%), and in patients had previous ICSI failed (2-10) trial was (92.59%) statistically not significant. The pregnancy rates in both groups were (44.09% -33.33%) respectively. Septate uterus was
the most common anatomical abnormalities among the studied group and were present in nearly half of the cases (45.45%), followed by uterine polyp and uterine adhesions, which each were present in quarter of cases (27.27%-25.13% respectively).

Endometritis was identified in (63.64%) in all patients, either alone in (11.22%) or mixed with other finding. In our sample there were, 48 cases with both endometritis and uterine septum, with adhesions in 35 cases, and with polyp in 30 cases. Direct endometrial biopsies were taken under the visualization by hysteroscopy in cases of endometritis only due to limitation histopathological labs (technical and financial) and were sent for histopathological examinations and results showed high sensitivity (90.2%) of hysteroscopy in diagnosing endometritis

The highest rate of pregnancy occurred in patients treated for adhesiolysis, then patients treated for endometritis alone (47.61%), and by patients with uterine septa (51.06%)

Pregnancy rate after treatment by hysteroscope were reported in half of patients treated (42.35%) among patients treated by incision of uterine septa, and in (25.49%) cases treated by polypectomy.

Spontaneously pregnancy occurred in the same cycle after hysteroscopic procedure in 27 patients (12.9 %) without any ART procedure.

In normal finding hysteroscopy percentage of pregnancy was (38.1%), according to the role of mechanical endometrial injury [9], irrigation of the cavity with saline mechanically removes harmful anti-adhesive glycoprotein molecules on the endometrial surface, [10] as well as the possibility of studying the course and morphology of the cervical canal, to make the embryo transfer procedures easier [11]. All these have been considered as explanations for the improved implantation and pregnancy rates after hysteroscopic procedure.

For that all patient should be treated properly before going on ICSI because ignoring uterine abnormalities would increase the risk of implantation failure, abortion and prolonging the period of infertility.

5. Conclusion

The study identified that hysteroscopic use for diagnosis and treatment of infertile patients helped in achieving pregnancy either spontaneously or after ICSI trials, so it should be used routinely as an essential step of infertility work-up before ICSI, without regard to previous history of recurrent implantation failure (RIF). There is an association between hysteroscopic examination and the occurrence of spontaneous pregnancy in some cases including cases with normal findings and without hysteroscopic treatment. It also examined the sensitivity and specificity of hysteroscopy for diagnosis of endometritis. Studying these issues is critical to guard against the drastic outcome of recurrent implantation failure (RIF) due to uterine and endometrial receptivity factors.

6. Recommendations

Need for randomized controlled studies (RCT) with adequate controls to justify the use of hysteroscopy before ICSI and prove its effectiveness in the treatment of uterine abnormalities which can lead to improvement of the success rate of ICSI treatment.

Use of office hysteroscopy routinely for the diagnosis and treatment of minor uterine pathologies where there is no need to use general anesthesia or sedation, no major complications and reduced cost, can make its routine use easier to both medical staff and patients.

7. Limitations of the study:

The use of non-controlled trial affects the study.

Inability to perform histopathological examinations to all patients with uterine abnormalities and limiting it only to patients with endometritis due to deficiencies in technical procedure (trained staff, deficiency in lab materials),
and in some cases due to financial difficulty of the patients.

References


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Consent for publication

No conflict of interest was declared by the authors.

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