Research Article

Rule of ٣-dimensional ultrasonography in evaluation of patients with previous ICSI failure.

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Abstract

Background: The incidence of undiagnosed intrauterine abnormalities, prior to ICSI, has been described to be ١١–٤٥٪. Therefore, it is advocated to diagnose and treat these abnormalities in order to optimize the condition of the uterine environment and thereby the outcome of ICSI treatment. However, high-quality evidence that defines the influence of screening for intrauterine pathology on reproductive outcome is absent. **The aim of is study:** To assess the incidence of undiagnosed intrauterine pathology based on screening by ٣ – dimensional transvaginal ultrasonograghy in women with previous ICSI faillure. **Patients and methods:** ٩٣ women with previous ICSI failure subjected to detailed history, general and local examination, two-dimension ultrasound and then three-dimension ultrasound. Then data collected for statistical analysis. **Results:** revealed that three-dimension ultrasound was normal in ٥٢(٥٥.٩٪), Endometrial polyp in ٨ (٨.٦٪), Endometrial hyperplasia in ٣(٣.٢٪), Asherman syndrome in ١ (١.١٪), Endometritis in ٤(٤.٣٪), Endo cervical polyp (٤.٣٪), Subseptate uterus ٢(٢.٢٪), Unicorniate uterus ١(١.١٪), submucous fibroid ١(١.١٪), Arcuate uterus ٧(٧.٥٪), Bicornuate uetrus ٢(٢.٢٪), Intramural fibroid ٨(٨.٦٪). **Conclusions:** Three Dimensional Ultrasound is a reliable diagnostic tool in cases of recurrent implantation failure with results comparable to hysteroscopy. Regarding the Three Dimensional Ultrasound which is completely non invasive, carry no risk of anesthesia and also no risk of ionized radiation (compared to HSG). So, when compared to the minimal invasive tool (hysteroscope), it is much simple, more acceptable with no surgical risk.
Key words: ICSI failure, recurrent implantation failure, ٣D ultrasound.

Introduction

Despite progressing improvement of ICSI, the maximum implantation rate per embryo transferred does not exceed ٣٠٪ (Andersen et al., ٢٠٠٨). Even if both ovum retrieval and fertilization occur successfully in the process of ICSI, there is a large unexplained drop between embryo transfer and occurrence of pregnancy. Implantation failure presents a major clinical challenge and is a cause of considerable stress to patients and their carers in assisted reproductive technology. Next to the physiological and physical burden that comes with every ICSI cycle, implantation failure also adds up to the costs associated with fertility treatment (Bouwmans et al., ٢٠٠٨).

Implantation failure could be due to the embryo, uterine environment or a combination of both. Even minor uterine cavity abnormalities, such as endometrial polyps, small submucous myomas, adhesions and septa, are considered to have a bad impact on the results of ICSI cycles (Rogers et al., ١٩٨٦).

The incidence of unsuspected intrauterine abnormalities, diagnosed by hysteroscopy prior to ICSI, has been described to be ١١– ٤٥٪ (Fatemi et al, ٢٠١٠).

Therefore, it is logic to diagnose and treat these abnormalities in order to optimize the condition of the uterine environment and thereby the outcome of ICSI treatment.

However, high-quality evidence that defines the influence of screening for intrauterine pathology on reproductive outcome is absent (Demirol and Gurgan, ٢٠٠٤).

At present, the basic work up for evaluation of the uterine cavity prior to ICSI consists of transvaginal ultrasound (TVS), possibly followed by gel or saline infusion sonography (GIS or SIS), hysterosalpingo-graphy (HSG) or hysteroscopy. The accuracy of HSG in evaluation of the uterine cavity abnormality in infertile patients has been reported to be rather disappointing (Gaglione et al, ١٩٩٦ and Golan et al, ١٩٩٦).

Whereas gel or saline infusion sonography (GIS or SIS) are increasingly considered to be useful in diagnosing intrauterine abnormalities, hysteroscopy is still known as the gold standard (Bozdag et al., ٢٠٠٨). It is easy to perform in an outpatient clinic without anesthesia. Advanced evaluation of the uterine cavity besides TVS is not recommended till now as routine fertility work up (Royal College of Obstetricians and Gynaecologists, ٢٠٠٤).

The use of Three-dimensional ultrasound in the field of gynecology has been a steady increase in the number of papers published in the last few years. These applications include: imaging the uterus, uterine cavity, adnexa, and pelvic floor as well as reproductive medicine, such as the prediction of ICSI success or ovarian hyperstimulation syndrome (Nelson et al., ١٩٩٩).

Patients and methods

This prospective study was done in the department of Obstetrics and Gynecology, Minia Maternity University Hospital in the period of Nov. ٢٠١٢ to January ٢٠١٦.

All patients presented with recurrent ICSI failure were subjected to detailed history taking, two Dimensional Ultrasound, Three Dimensional Ultrasound and Hysteroscopy. Prior to the procedures all benefits, risks and possible complications of the procedure were clearly explained to the patients and an informed consents were taken from all patients.

The study protocol was approved by scientific ethical committee research of the Department of Obstetrics and Gynecology, Faculty of Medicine, Minia University at its monthly meeting. Also approval was ascertained from the Institutional Review Board of the University Hospital- Quality Control Unit-of the Faculty of Medicine, Minia University.

Inclusion Criteria was Age bellow ٣٨ years old, At least ٢ cycles of ICSI failure, History of transfer of at least ٢ good quality embryos in each trial, No history of recent hysteroscopy within one year at least

Exclusion criteria was Age more than ٣٨ years, Cases with untreated tubal pathology, Patient known with immunological disorder, Patients with thrombophylia, Patients known with poor endometrial development at time of embryo transfer.
Women with recurrent ICSI failure visited infertility clinic at Minia Maternity University Hospital were subjected to:
Detailed history was taken in all cases, Evaluation of the present investigations as HSG, hormonal profile, immunological investigations, thrombophilias investi-gations, history of previous laparoscopy and / or hysteroscopy.

Examination:
General and local examination was done.

Investigation:
١- ٢D Trans-vaginal ultrasound:
Trans-vaginal ultrasonography was done using Voluson S٨ (RIC٥-٩ RS ٥ to ١٠ MHZ Trans-vaginal probe) All scans were done at post menstrual period. The patients were instructed to evacuate the bladder before the procedure, patient lied at lithotomy position .The probe was covered with a thin layer of gel and loaded in a disposable glove or condom and inserted slowly into the vagina. The vaginal cavity, cervix, bladder and then the uterus were identified; a slow movement of the probe from side to side, and then pointing posterior was made. Once the uterus has

been located, its position (anteverted or retroverted) and its size were noted.

The uterus was evaluated initially in the sagittal plane. The uterine cavity was completely imaged from the ectocervix to the fundus of the uterus. After complete sagittal evaluation was made, the transducer was rotated ninety degrees perpendicular to the sagittal plane to evaluate the uterus through its coronal image. Again, the uterine cavity was completely assessed from the external os to the endocervical canal into the endometrial cavity till the fundus and from the cornu to the other one.

Measurements were then taken. The size of the uterus was measured in the longitudinal, transverse and anteroposterior diameters. The measurements of the endometrium were taken at its thickest part in the longitudinal plane and included both endometrial layers. If an intracavitry abnormality such as a polyp or submucosal myoma was present, it was included in the measurement.

Specific observations were made to ascertain the normality of the endometrium, myometrium and endometrial-myometrial interface. Similar observations were made for the cervix and endocervical canal. Scanning for both adnexa was done to detect any pathology that could have been missed during clinical examination. The endometrium and uterine cavity were considered normal if TVUS showed a hyperechoic line in the middle of the uterus with a homogenous endometrial lining and distinct margins to the myometrium

All other findings such as deformities of the endometrial lining, absence of the central hyperechoic line, and the appearance of any structure with or without well-defined margins or variable echogenicity, were considered abnormal.

۲- ۳D ultrasound trans-vaginal examination:
After ۲d ultrasound, select (new patient) button to start exam for the patient & to save her ID & images captured, then ۳D ultrasound was performed by pressing (۳D)

button on console, angulation & rotation of probe to get best view in which uterus was clearly viewed from fundus to cervix with continuous endometrial line, using trackball &top trackball adjust ROI (Region of interest) box position &size to include area of interest.

In performing surface rendering the camera line (green line) should be adjusted to be just above the area of interest, it is remarkable that a fluid interface is helpful when performing surface rendering. start acquisition by using right trackball or freeze key, acquisition is automatic so transducer shouldn't be moved during acquisition .after acquisition of dataset multiple displays are possible, display divides the screen into four sections: A plane (initial acquisition plane), B plane (۹۰ degrees clockwise to A plane), C plane (orthogonal to A and B planes) & finally the composite image (۳D image) of the acquired volume.

Any change to the three planes (A, B, C) will be reflected to the ۳D image, fine adjustment to the rendered box & to camera line can be done to render the uterus clearly viewed with its endometrium showing any possible abnormality in the cavity or myometrium, single, dual or quad screen display is available .Any plane is available in a single screen by selecting single screen from the console; the active/reference image will be displayed.

Quad format displays all three orthogonal planes simultaneously. The volume dataset is not limited to the initial ۳ planes displayed, each plane can be rotated on the X, Y or Z axis as well as shifting through an individual plane in a parallel fashion (parallel shift). By manipulating the volume, any plane necessary within the volume can be displayed, whereas X Axis rotates the active image on the horizontal axis, Y Axis rotates the active image on the vertical axis, Z Axis rotates the active image in a clockwise or counter-clockwise motion, Parallel Shift moves in/out of the dataset without rotating on an axis. After capturing the desired image it is saved to the database by pressing (p۱) button. (D. Jurkovic., ۲۰۰۲)

Results

This study includes ٩٣ patients complaining of recurrent implantation failure. All data collected were analysed and these tables show the results gained.

Table ١: descriptive analysis of patient's characteristics.
Data colleced as regard age, duration of marriage, body mass index (BMI), type and cause of infertility shown in this table.

Variables	Descriptive statistics
Age Range Mean ± SD	(٢٢-٣٨) ٣٠.٢٦ ± ٤.٤٣
Duration of marriage Range Mean ± SD	(٢-٢٢) ٩.٩١ ± ٤.٣
BMI Range Mean ± SD	(١٦-٢٩) ٢٠.٩٨ ± ٣.٣٨
Type of infertility ١ ry ٢ ry	٦٠ (٦٤.٥٪) ٣٣ (٣٥.٥٪)
Infertility cause Male factor Female factor Combined Unexplained	٣٦ (٣٨.٧٪) ٢٠ (٢١.٥٪) ٦ (٦.٥٪) ٣١ (٣٣.٣٪)

Table ٢: Descriptive analysis of patient's previous investigations and data of previous ICSI trials.

Variables	Descriptive statistics
Previous HSG Not done Done	٣١ (٣٣.٣٪) ٦٢ (٦٦.٧٪)
Previous laparoscopy Not done Done	٤٩ (٥٢.٧٪) ٤٤ (٤٧.٣٪)
Previous Hysteroscopy Not done Done	٨١ (٨٧.١٪) ١٢ (١٢.٩٪)
FSH Range Mean ± SD	(٥.٧-١٦) ٨.٩١ ± ٢.٠٣
AMH Range Mean ± SD	(٠.٦-٥.١) ٢.٥٨ ± ٠.٩٩
AFC Range Mean ± SD	(٩-٣٥) ٢١.٠١ ± ٥.٧٥

Table ٣: findings diagnosed by three-dimension ultrasound.

Findings	٣D/US (n=٩٣)
Normal	٥٢ (٥٥.٩٪)
Endometrial polyp	٨ (٨.٦٪)
Endometrial hyperplasia	٣ (٣.٢٪)
Asherman syndrome	١ (١.١٪)
Endometritis	٤ (٤.٣٪)
Endo cervical polyp	٤ (٤.٣٪)
Subseptate uterus	٢ (٢.٢٪)
Unicorniate uterus	١ (١.١٪)
SM fibroid	١ (١.١٪)
Arcuate uterus	٧ (٧.٥٪)
Bicornuate uterus	٢ (٢.٢٪)
Intramural fibroid	٨ (٨.٦٪)

Discussion

In the present study the age of patients was ٢٢ to ٣٨ years, duration of marriage was ٢ to ٢٢ years, body mass index was ١٦ to ٢٩ kg/m٢, ٦٠ cases was primary infertility, ٣٣ case was secondary infertility, ٣٦ cases were male factor, ٢٠ cases were female factor, ٦ cases were combined male and female factors and ٣١ cases were unexplained infertility.

In the present ٥٢ cases are normal with three-dimension ultrasonography. While ٨ cases with endometrial polyps, Endometrial hyperplasia were ٣ cases, Endo cervical polyp were ٤ cases, subseptate uterus were ٢ cases, Unicorniate uterus was ١, sub-mucous fibroid was ١ case, Arcuate uterus were ٧ cases, Bicornuate uetrus were ٢ cases. endometritis were ٤ cases, Asherman syndrome was one case.

(Hosseini et al., ٢٠١٤) Study the rule of hysteroscopy in patients with repeated implantation failure to improves the outcome of assisted reproductive technology in fresh and frozen cycles; this was a cohort study with historical controls conducted in Tehran University of medical sciences, Tehran, Iran. A total of ٣٥٣ women with RIF undergoing ART with normal hysterosalpingography and transvaginal ultrasound were evaluated. The intervention group underwent hysteroscopy with a rigid, ٣٠°, ٤-mm hysteroscope in the menstrual cycle just before ART; in the control group hysteroscopy was not performed. Basal characteristics, stimulation parameters and pregnancy rates were compared between the two groups.

In (Hosseini et al., ٢٠١٤) the results of hysteroscopy were normal in ١٠٣ women (٧٢.٥٪), and they revealed inflammation in ٢٢(١٥.٥٪), polyp in ١٦(١١.٣٪) and Asherman syndrome in one patient (٠.٧٪). This agree with the present study in the presence or absence of uterine pathology but not in the types and percentages of pathologies as it revealed that three-dimension ultrasound was normal in ٥٢(٥٥.٩٪), Endometrial polyp in ٨(٨.٦٪), Endometrial hyperplasia in ٣(٣.٢٪), Asherman syndrome in ١(٢.٢٪), Endometritis in ٤(٤.٣٪), Endo cervical polyp (٤.٣٪), Subseptate uterus ٢(٢.٢٪), Unicorniate uterus ١(١.١٪), submucous fibroid ١(١.١٪), Arcuate uterus ٧(٧.٥٪), Bicornuate uetrus ٢(٢.٢٪), Intramural fibroid ٨(٨.٦٪).

(Soheila Arefi et al., ٢٠٠٨) did observational study in which the hysteroscopy findings and the outcomes of subsequent IVF/ICSI were evaluated in ٨٩ infertile women admitted in Avicenna Infertility Clinic, with previous repeated (more than two) failed IVF/ICSIETs, including the patients with normal Hysterosalpinography (HSG) and excluding

severe male factor infertility and also thrombophilia, genetic and immunologic problems.

In ٥٢(٥٩.٥٪) cases, hysteroscopy revealed abnormal intrauterine findings including adhesions ٧(١٣.٧٪), single polyp ١١ (٢٠.٧٪), endometrial polyposis ١٠ (١٨.٨٪), endometrial hyperplasia ١٠(١٨.٨٪), uterine cavity hypoplasia ٤(٧.٨٪) and myoma ٥(٩.٨٪).

According to this study, they strongly suggest evaluation of endometrial integrity by hysteroscopy in patients with repeated IVF/ICSI-ETs failure, before entering any other fertilization procedures.

The present study agree the study of (Soheila Arefi et al., ٢٠٠٨) in the presence or absence of uterine pathology but not in the types and percentages of pathologies as it revealed that three-dimension ultrasound was normal in ٥٢(٥٥.٩٪), Endometrial polyp in ٨(٨.٦٪), Endometrial hyperplasia in ٣(٣.٢٪), Asherman syndrome in ١(٢.٢٪), Endometritis in ٤(٤.٣٪), Endo cervical polyp (٤.٣٪), Subseptate uterus ٢(٢.٢٪), Unicorniate uterus ١(١.١٪), submucous fibroid ١(١.١٪), Arcuate uterus ٧(٧.٥٪), Bicornuate uetrus ٢(٢.٢٪), Intramural fibroid ٨(٨.٦٪).

In ٢٠١٠ Fatemi et al., study the prevalence of unsuspected intrauterine abnormalities in patients allocated for a randomized controlled trial was prospectively assessed at two tertiary infertility care units: Academic Hospital at the Dutch-speaking Brussels Free University and University Medical Center Utrecht. A total of ٦٧٨ unselected, asymptomatic, infertile women with a regular indication for a first IVF/ICSI treatment underwent office hysteroscopy. Only asymptomatic patients, aged ≤٤٢ years, with a normal TVS and no previous hysteroscopy were included. The presence of predefined intrauterine abnormalities was recorded and described in a standardized manner. (Fatemi et al., ٢٠١٠)

Endometrial polyps were identified in ٤١(٦٪) women and submucous myomas in ٦ women (١٪). Some women were also

diagnosed with intrauterine adhesions (٢٪) or septa (٢٪). The overall prevalence of any predefined intrauterine abnormality in this IVF/ICSI population was ١١٪. (Fatemi et al., ٢٠١٠)

The present study did not agree the results of (Fatemi et al., ٢٠١٠) in the overall prevalence of any predefined intrauterine abnormality in this IVF/ICSI population as being ٤٤.١٪ in the present study compared to ١١٪ (Fatemi et al., ٢٠١٠) and also in the type of intracavitary lesion.

In ٢٠١٥ Gao et al., did a prospective cohort study which was conducted involving ٦٧٢ asymptomatic recurrent implantation failure women from a Chinese university hospital. The incidence of intrauterine abnormalities in the hysteroscope group was ٣٧.١٣٪. The most common abnormalities included endometrial polyps or polypoid endo-metrium, endometrial hyperplasia and intrauterine adhesions.

In ٢٠١٥ Gao et al., Endometrial polyps or polypoid Endometrium ٦٤(١٩.١٦٪), Endometrial hyperplasia ٢٠(٥.٩٩٪) Intra-uterine adhesion ١٥(٤.٤٩٪), Endometritis ٩(٢.٦٩٪), Endocervical polyps ٧(٢.١٠٪), Cervical stenosis ٧(٢.١٠٪), Septate uterus ٦(١.٨٠٪) Unicornuate uterus ٢(٠.٦٠٪), Submucous fibroid ١(٠.٣٠٪).

The present study agree the study of (Gao et al., ٢٠١٥) in the presence or absence of uterine pathology and also in the types and percentages of pathologies as it revealed that three-dimension ultrasound was normal in ٥٢(٥٥.٩٪), Endometrial polyp in ٨(٨.٦٪), Endometrial hyperplasia in ٣(٣.٢٪), Asherman syndrome in ١(١.١%), Endometritis in ٤(٤.٣٪), Endo cervical polyp (٤.٣٪), Subseptate uterus ٢(٢.٢٪), Unicorniate uterus ١(١.١٪), submucous fibroid ١(١.١٪), Arcuate uterus ٧(٧.٥٪), Bicornuate uetrus ٢(٢.٢٪), Intramural fibroid ٨(٨.٦٪).

Conclusion and Recommendations:
Three Dimensional Ultrasound is a reliable diagnostic tool in cases of recurrent implantation failure with results comparable to hysteroscopy.

Regarding the Three Dimensional Ultrasound which is completely non invasive, carry no risk of anesthesia and also no risk of ionized radiation (compared to HSG). So, when compared to the minimal invasive tool (hysteroscope), it is much simple, more acceptable with no surgical risk.

Till now the role of hysteroscopic evaluation of all patients as a routine prior to ICSI cycles is a matter of debate. So, Three Dimensional Ultrasound being more accepted as a routine maneuver before any trial of ICSI not for evaluation of uterine abnormality only, but also fore evaluation of the tubes and ovaries with much more data gained compared to the two dimensional ultrasound.

Further researches are needed to show how to increase the diagnostic capability of ٣D ultrasound and also to increase number of patients to evaluate more lesions which not detected in this study as adenomyosis.

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