Role of Hysteroscopy in Unexplained Infertility

Thesis

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List of Abbreviations

2D US	Two dimensional ultrasound
3D US	Three dimensional ultrasound
AAGL	American Associates of gynecologic laparoscopists
APA	Antiphospholipid antibodies
ANA	Anti DNA
AOA	Anti Zona and Anti ovarian
ART	Assisted reproductive technologies
ASA	Anti Sperm
aCL	Anticardiolipin
aPS	Anti-Phosphatidylserine
aPE	Anti Phosphatidylethanolamine
AUB	Abnormal uterine bleeding
CAM	Cell adhesion molecules
CD	Cycle day
CI	Confidence interval
D&C	Dilatation and curettage.
DVT	Deep venous thrombosis
ET	Embryo transfer
ebaf	Endometrial bleeding associated factor
ECM	Extracellular matrix
ESHRE	European society for human reproduction and embryology

FISH	Fluorescence *in situ* hybridization
FSH	Follicle-stimulating hormone
HSG	Hysterosalpingography
ICSI	Intra Cytoplasmic Sperm Injection
IL12	Interleukin 12
IL18	Interleukin 18
IUA	Intrauterine adhesions
IUI	Intrauterine insemination
IVF	In vitro fertilisation
LA	Lupus anticoagulant
LH	Lutenizing hormone
MRI	Magnetic resonance imaging
NICE	National institute of clinical evidence
OD	Outside diameter
OH	Office Hysteroscopy
PCO	Polycystic ovary syndrome
PGD	Preimplantation genetic diagnosis
PID	Pelvic inflammatory disease
RCOG	Royal college of obstetricians and gynecologists
RM	Recurrent miscarriage
RVF	Retroverted flexed Uterus.
ROC	Receiver-operating characteristics.

SIS	Saline infusion sonography.
SUA	Structural uterine anomalies
TSH	Thyroid-stimulating hormone.
TURP	Transurethral resection of the prostate.
TVS	Trans vaginal ultrasound
UI	Unexplained infertility
UK	United Kingdom.
USA	United States of America.
WHO	World Health Organization

List of Tables and Figures

1. Tables:

2. Figures :

Index

Abstract

One of the basic steps of the infertility workup is to assess the shape and regularity of the uterine cavity. Historically, and still today as it turns out, the HSG has been the most commonly used test for this purpose. During the last two decades, however, several studies have demonstrated that when the uterine cavity has to be investigated within the infertility workup, hysteroscopy is much more accurate than HSG. Our study was conducted on 50 females who attended the outpatient clinical Cairo University hospital. Its objective was to assess the role of hysteroscopy in investigation of infertile women. The study was designed to investigate the role of hysteroscopy in determining the uterine cavity abnormalities that were missed during routine investigations of infertility as ultrasound and hysterosalpingography which were reported as normal.

The study revealed presence of intrauterine polyps, submucous fibroids, intrauterine adhesions, Mullerian anomalies that were missed by standard infertility investigations. These lesions can be treated during hysteroscopy and their treatment may lead to successful conception as reported by some authors. Outpatient investigation is a comparatively new concept in gynecology. Patients may favor the outpatient approach because they spend less time in hospital. However, it is important to tailor the outpatient investigation to suit the particular patient, realizing that all methods of endometrial evaluation are complementary rather than competitive and that combining several modalities would yield more information than a single approach. HSG is still a useful screening test for the evaluation of the uterine cavity in the study of primary or secondary infertility. In addition, HSG provides information concerning the assessment of tubal morphology and patency. We believe that these two procedures are complementary in the evaluation of the uterine cavity.

Keywords:

Hysteroscopy
Infertility
Hysterosalpingography

Introduction

The state of the art of the infertility workup, strange as it may appear, has never been accurately defined. A recent survey, that was designed to determine how reproductive endocrinologists practice on a daily basis, demonstrated that the five basic tests that were regarded as the cornerstone of the infertility evaluation were: semen analysis, assessment of ovulation, hysterosalpingogram, laparoscopy, and post-coital test **(Glatstein et al, 1997).**

Uterine cavity pathologies may interfere with embryo implantation (**Mittal et al., 1994**). Therefore, the evaluation of the uterine cavity is one of the basic steps in work-up of infertile women, especially before an IVF program.

Hysteroscopy has traditionally been performed as an adjunct tool to evaluate abnormalities suspected as a result of hysterosalpingography(HSG) evaluation. Recent studies have shown increased benefit from combining hysteroscopy and HSG in the evaluation of female infertility. Moreover, hysteroscopy is useful in identifying endometrial abnormalities not detectable on HSG **(Brown et al., 2000)**.

During the last two decades, hysteroscopy has increasingly been gaining acceptance and is today a necessary tool in the investigation of female infertility. Hysteroscopy permits direct visualization of the cervical canal and the uterine cavity, enabling observation of the shape and vascular pattern of any abnormality **(Roma et al., 2004).** Since nowadays it is performed in the office, so it can be offered as a first-line diagnostic tool for evaluation of uterine abnormalities in patients with abnormal uterine bleeding and/or infertility. In addition, the hysteroscopic approach offers the possibility of obtaining endometrial/myometrial biopsies under visual control (**Molinas and Campo, 2006)**.

Makris et al., 1999 performed hysteroscopy in patients with history of abortions, infertility and repeated failure of IVF. They showed that abnormal hysteroscopic findings were observed in 40.5% of cases in which intrauterine adhesions, endometrial hyperplasia and polyps were the most common. **Faghali et al, 2003** evaluated the benefits of a diagnostic hysteroscopy prior to IVF which shows that systematic hysteroscopy prior to IVF could improve the pregnancy rate. La Sala and Oliveira and their colleagues showed relation between IVF-ET failure and unsuspected intrauterine abnormalities **(La Sala et al., 1998 and Oliveira et al., 2003).**

Up to 30% of couples who are unable to conceive are eventually determined to have unexplained infertility.Traditionally; this diagnosis is made only after the basic infertility evaluation fails to reveal an obvious abnormality. The basic evaluation should provide evidence of ovulation, adequate sperm production, and fallopian tube patency. It remains unclear whether the basic infertility assessment should test for anti-sperm antibody, adequate cervical mucous production, timely development of secretory phase endometrial responses, presence of adhesions, and evidence of pelvic endometriosis. At present, even the most sophisticated diagnostic assessment can't reveal all of the possible abnormalities. Therefore unexplained infertility appears to represent either the lower extreme of the normal distribution of infertility, or it arises from a defect in fecundity which can't be detected by the routine infertility evaluation (**Silverberg et al, 1996).**

Couples with unexplained infertility suffer from both diminished and delayed fecundity, compared with the 20% to 25% that would be expected in normal fertile couples. In a review of unexplained infertility studies, the average cycle fecundity in the untreated control groups was 1.8% in eleven non-randomized studies and 3.8% in six randomized studies (**Guzick et al, 1998**). Pregnancy rates are lower with increasing age of the female partner and duration of infertility (**Collins et al, 1989).**

Review of Literature

Hysteroscopy

For more than one hundred years, investigators all over the world have been trying to develop techniques by which the visualization of the uterine cavity would be possible. Before the advent of hysteroscopy, gynecologists could investigate the uterine cavity only indirectly (**Valle, 1999; Serden, 2000).**

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Intra-uterine pathology, including submucous myomas, polyps, and hyperplasia, may occur in a relatively high percentage of asymptomatic, infertile patients **(Balmaceda and Ciuffardi, 1995).** These conditions can be easily identified and classified through hysteroscopy.

Additional pathology which can interfere with embryo implantation and development are uterine malformations, particularly a septate uterus, although uterine malformations are usually associated with pregnancy wastage, not infertility. Hysteroscopy and laparoscopy allow precise classification and consequently appropriate treatment of uterine malformations. When facing the problem of recurrent abortion, visualization of the uterine cavity becomes indispensable for a correct diagnosis, and forms the basis for an appropriate therapy **(Raziel et al., 1994).**

Contraindications

Usually, hysteroscopy is an endoscopic procedure free of complications. Faulty techniques and selection of inappropriate patients are the most frequent causes of sequelae**.** Hence, it is important to know the absolute and relative contraindications of hysteroscopy. Most of the classic contraindications of diagnostic hysteroscopy, such as the presence of an active pelvic infection or cervical cancer, are not considered any more as absolute, but rather as relative.

1- Absolute contraindications:

After a hysteroscopy, a patient with a history of recent pelvic inflammatory disease or adnexal tenderness, with or without pelvic mass, can develop salpingitis or peritonitis when either a gaseous or liquid medium was used for distension. Infection in the lower genital tract can spread to the fallopian tubes by direct extension from the endometruim, by the lymphatic system, or be transported through the blood system. Thereby, the vaginal area should be free of infection before conducting a hysteroscopic examination **(Mencaglia et al., 1987),**

2- Relative contraindications:

A- Profuse uterine bleeding:

Regardless of the distending medium used, hysteroscopy cannot be performed satisfactorily when bleeding is excessive**,** while scanty or mild uterine bleeding does not prevent adequate observation of the uterine cavity or predispose patients to complications, namely vascular intravasation **(Valle, 1983)**.

B- Medical Problems:

Because few women have such severe cardiovascular disease, hysteroscopy can be accomplished safely using local anesthesia. Hyskon and glycine are better avoided as a distension medium in patients with hepatic or renal impairment **(Serden, 2000).**

Technique of Hysteroscopy:

Instrumentation for hysteroscopy revolves around uterine distension. Although there was transient interest in contact hysteroscopy, all hysteroscopy systems in widespread use depend on adequate distension of the uterine cavity with an optically-clear medium. CO_2 has long been a favorite medium, but the difficulty in maintaining a clear view limits its use for operative procedures. The development of narrow diameter hysteroscopes with flow-through designs has simplified the use of low-viscosity fluids for diagnostic outpatient and office hysteroscopy, allowing clear vision in the presence of blood in the uterine cavity **(Indman, 2000).**

Basically, to examine and operate in the uterine cavity the followings are needed:

A- Transformation of the slit-shaped uterine cavity into a hollow cavity via a distending medium through special apparatus.

B- Illumination of the cavity by a suitable light source.

C- Viewing of the illuminated distended cavity by an endoscope.

D- Ancillary instruments for operative interventions.

The hysteroscope should enable the gynecologist to have an undistorted clear observation of the uterine cavity. It transmits light for illumination and carries the image to the viewer's eye. The optical components include lenses and prisms devised to utilize cold light generated from an appropriate source transmitting it through a fiberglass conductor. The illumination component is provided by fiberoptics (**Epstein, 1980**).

The telescope can be divided into 3 parts:

1- The objective lens: available in different focal lengths. The greater the focal length, the greater the size of field and the lower the magnification available.

2- The barrel (relay lens): long rod lenses whose thickness is larger than their diameter, with short air spaces in-between. Another system used is the graded refractory index system which includes a narrow rod of glass with a refractory index that progressively decreases from the axis to the periphery.

3- The ocular (eyepiece): This is a simple magnifying lens that allows stereoscopic vision. A prism is used with the ocular lens to reorient the image, which had been previously inverted by objective lens. A second prism is used in telescopes with an oblique lens.

The overall magnification of the endoscope is the product of the magnification of the objective lens and the eyepiece. The magnification is inversely proportional to the distance of the object to the lens. Hysteroscopes are monocular, providing little depth perception for the viewer; interpretation of depth comes with experience **(Siegler et al., 1990).**

The hysteroscopes most commonly used are 0 straight forward or 30 oblique. Others have a fore oblique lens that is offset from the horizontal by 12, 15, and 25 . The 30 scope is preferred in most diagnostic purposes because rotation of the instrument around its axis, using the light post as a guide, allows a panoramic view of the lateral walls and tubal ostia as well as the anterior and posterior endometrial surfaces. Modern rod-lens hysteroscopes have a beveled end that corresponds to the angle of viewing but also aids in instrument insertion into the uterine cavity (**Wieser et al., 1997**).

The angle of view also varies according to the refractory index of the medium used to distend the uterine cavity. If a gaseous medium is used the maximal angle of view is perceived through the optic, but when a liquid medium is used the angle is reduced. This coincides with the laws of reflection. Most commercial telescopes subtend a visual angle of 82°, although wide angle optics which provides a much larger field subtends an angle of 105° **(Siegler et al., 1990).**

With the use of fiber optics, thousands of small glass fibers (10 mm) produce a compact system of delivering brighter light efficiently and with minimal loss. The glass fibers are composed of two types of optical glass. The inner core is responsible for conveying light rays (or visual images) along the length of the fiber. This is surrounded by a thin layer of glass with a lower refractive index that acts like a covering insulation and is called *cladding.* The *cladding* prevents the reflected light rays from leaving the inner fiber to prevent loss of light. Light