CHROMOHYSTROSCOPY AFTER FAILED INTRACYTOPLASMIC SPERM INJECTION (ICSI)

Thesis

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By

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LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Intra-cytoplasmic sperm injection (ICSI)

As the name implies, ICSI is the injection of a single sperm directly into the cytoplasm of the oocyte. The first clinical success of ICSI, in 1992, lead to worldwide adoption of this procedure as the ultimate micro-assisted fertilization approach. This procedure by-passes most natural barriers that the sperm has to encounter In recent times it was developed to procure conception and pregnancy, which resulted in live offspring in domestic and laboratory animal species. (1)

Indications of ICSI:

There are two main groups of patients that may require ICSI:

1. Patients who have a severe sperm problem, which prevents them from even attempting conventional or a modified form of in-vitro fertilization(IVF) (2)
2. Patients who have previously attempted IVF due to any cause of infertility, but have failed to achieve fertilization (generally on more than one occasion).

Infertility:

The standard medical definition of Infertility is the inability of a couple to conceive after 12 months of sexual intercourse without the use of contraception. The terms primary or secondary infertility are used depending upon whether the couple has not or has previously achieved a pregnancy respectively. Infertility affects approximately 10-15 % of the couples in the reproductive age group, which makes it an important component of gynecological practice. (3)

Causes of Infertility:

The causes of infertility can be divided into four major categories: female factors including anovulation, luteal phase defects, tubal or peritoneal factor, cervical factor, uterine factor, and vaginal factor, male factors, combined factors, and unexplained infertility. It is difficult to assign exact percentage to each of these categories; however, it is generally reported that in approximately 45% of cases, infertility is mainly due to a female factor, 30% to a male factor, in 20% to abnormalities detected in both partners, and 5% of cases no diagnosis can be made after a complete investigation. (4)

Causes of Female Infertility:(5)

1. Causes of Failure to Ovulate account for 30% of women's infertility.
2. Causes of Poorly Functioning Fallopian Tubes affect approximately 25% of infertile couples.
3. Endometriosis approximately 10% of infertile couples is affected by endometriosis.
4. Uterine causes at least 10% of all cases of female infertility are caused by an abnormal uterus.

5. Behavioral Factors:

   It is well-known that certain personal habits and lifestyle factors impact health; many of these same factors may limit a couple's ability to conceive for example (Diet, Exercise, Smoking, Alcohol, and Drugs).

6. Environmental and Occupational Factors:

   The ability to conceive may be affected by exposure to various toxins or chemicals in the workplace or the surrounding environment. Substances that can cause mutations, birth defects, abortions, infertility or sterility are called reproductive toxins; four chemicals are now being regulated based on their documented infringements on conception which are (Lead, Medical Treatments and Materials, Ethylene Oxide, and Dibromochloropropane (DBCP).

Uterine Causes of Infertility:

Many women who have uterine problems may have no problems getting pregnant, but they may have difficulty in keeping the pregnancy as they tend to miscarry. Most women have no symptoms, some women will have scanty periods, some patients may also complain of heavy periods (due to fibroids). [6]

1. Fibroids:

Fibroids are benign growths of the muscle of the uterus; they are very common especially in late reproductive life. Many women who have fibroids are fertile and have no problems with keeping the pregnancy. However, if the fibroid significantly distorts the cavity of the uterus, it may interfere with embryo implantation.

2. Intrauterine adhesions:

Adhesions in the uterine cavity may be a consequence of infection (endometritis) or surgery such as D&C (scraping of the uterus).

3. Asherman's syndrome:

In Asherman's Syndrome, scar tissue forms inside the uterus causing cessation of menstrual bleeding and infertility. It has been believed that the cessation of bleeding is directly due to the scar tissue damaging the normal endometrial lining tissue. [7]

4. Congenital anomalies:

Congenital anomalies of the uterus may result from Mullerian agenesis (aplasia), insufficiently developed uterus (uterine hypoplasia), or failure of fusion Mullerian halves, e.g. bicornuate or septate uterus.

Evaluation of uterine factor before ICSI is done by:

Obtaining a history from the patient is the most important diagnostic tool. A history of recurrent abortions, uterine surgery, postpartum uterine infections, retained products of conception, or postpartum curettage should alert the clinician to a possible uterine factor, a history of abnormal bleeding, such as midcycle spotting, may represent an intrauterine

polyp or fibroid. Recurrent malpresentation during pregnancy or recurrent pregnancy loss often suggests a uterine anomaly, such as a septum or bicornuate uterus. [8, 9]

Tests used for diagnosis are:

- Hysterosalpingogram(HSG)
- Hysteroscopy and laparoscopy
- Ultrasound (abdominal &trans vaginal)
- Saline infusion sonohysterography(SIS)
- Endometrial biopsy
- Some consider MRI useful for evaluating intrauterine pathology, but MRI is a relatively expensive test.

Hysteroscopy:

Hysteroscopy is the process of viewing and operating in the endometrial cavity from a trans-cervical approach.

Procedure:

It is best done when the endometrium is relatively thin, that is after menstruation, and patient is in a lithotomy position.

Local anesthesia can be used. Simple operative hysteroscopy can also be done in an office or clinic setting. Hysteroscopic intervention can also be done under general anesthesia (endotracheal or laryngeal mask) or Monitored Anesthesia Care (MAC), but a short diagnostic procedure can be performed with just a Para cervical block using the Lidocaine injection in the upper part of the cervix. [10]

Indications of Hysteroscopy:

- **Abnormal uterine bleeding**[11]

Hysteroscopy has nearly replaced standard D&C for the management of abnormal uterine bleeding (AUB), as it allows for direct visualization, diagnosis and treatment of intrauterine abnormalities, and it often offers an opportunity for simultaneous treatment. Uterine sampling can be done by means of endometrial biopsy, D&C, or direct visualization with hysteroscopy and specific biopsy procedures. Evaluation of the uterine cavity with sonohysterography or diagnostic hysteroscopy is up to 88% effective in identifying polyps and sub mucosal fibroids.

- **Infertility**

Hysteroscopy is not part of the routine workup for infertility, but when compared with Hysterosalpingography, hysteroscopy is equivalent for evaluating the uterine cavity, and it increases accuracy in diagnosing the cause of intrauterine filling defects. In unexplained infertility, hysteroscopy may be performed simultaneously with laparoscopy to evaluate the uterine cavity and cervix. But for patients with recurrent miscarriage and intracavitary fibroids, surgery increases rates of viable pregnancy outcomes. [12]

- **Mullerian anomalies:**

Approximately 1-2% of all women, 4% of infertile women, and 10-15% of patients with recurrent miscarriage have Mullerian anomalies. These anomalies range from didelphys to Mullerian agenesis. Uterine septum and in utero diethylstilbestrol (DES) exposure are more likely to be associated with miscarriage than is uterus didelphys. Patients with a bicornuate uterus have a >50% live birth rate compared with those with a uterine septum, who has a <30% live birth rate. Patients with in utero DES exposure are likely to have a T-shaped uterus with corneal restriction bands, pretubal bulges, lower-uterine-segment dilation, and a small and irregular cavity with borders resembling adhesions. [13, 14]

- **Polyps and fibroids:**

Polyps and sub mucosal fibroids can be definitively diagnosed with hysteroscopy; the advantages of hysteroscopic resection are numerous and include treating irregular bleeding and obtaining tissue diagnosis. If a fibroid is predominantly sub mucosal, complete resection is possible.

In patients desiring to maintain fertility, hysteroscopic myomectomy for sub mucous fibroids is a reasonable option; minimal cauterization should be used to decrease damage to otherwise healthy endometrium. [15, 16]

- **Intrauterine adhesions:**

Intrauterine adhesions are often associated with amenorrhea and infertility. Hysteroscopy can be used to diagnose and treat these adhesions; filmy adhesions can be often broken by distention alone, whereas the dense adhesions often require cutting or excision with blunt, sharp, electro cautery, or laser techniques.

- **Proximal tubal obstruction:**

In Many cases proximal tubal obstruction may simply be due to spasm., and cannulation of the tubes can be performed at the same time.

Contraindications of Hysteroscopy: [17]

In general, hysteroscopy is avoided in patients with the following findings:

- Active cervical or uterine infection.
- A large uterine cavity, i.e., longer than 10 cm in length (clinically similar to a 12-week pregnant uterus.
- Severe medical conditions precluding surgery.
- Pregnancy.

Complications of hysteroscopy:

Mechanical complications:

Perforation and cervical trauma are 2 of the most common complications of hysteroscopy, with uterine perforation rates of approximately 0.7-0.8%. Risk factors for perforation include cervical stenosis, severe uterine ante flexion or retro flexion, infection, myomas of lower uterine segments, and synechiae. Most cervical traumas and uterine perforations occur during dilation of the cervix. [18]

Media-related complications:

The risk of gas embolism is the primary complication associated with the use of CO2 as the distention medium. Intrauterine pressures should be maintained below 100 mm Hg, with maximal flow rates less than 100 mL/min. The risk of absorption of media is minimal under normal operative conditions.

Risk factors for clinically significant intravasation of fluid include prolonged operative procedures, the use of large volumes of low-viscosity media, or the resection of fibroids or myometrial trauma that results in open uterine venous channels or unidentified perforations. When large volumes of non-electrolyte solutions are absorbed, subsequent hyponatremia, hypervolemia, hypotension, pulmonary edema, cerebral edema, and cardiovascular collapse can occur. Absorption (or deficit) of nonelectrolyte solutions must be closely monitored throughout operative hysteroscopy. Some suggest that of all nonelectrolyte media, 5% mannitol has the safest adverse-effect profile because it can maintain a patient's osmolality despite hyponatremia, improving neurologic outcomes**.** [19]

Bleeding:

Bleeding during or after surgery is the second most common complication of hysteroscopy (0.25% of all cases). Myomectomy is the procedure with the highest complication rate (2-3%).

Infection:

Infection is an uncommon complication of hysteroscopy. Even with Dextran 70, which is a polymerized sucrose, infection is rare in a patient who is preoperatively screened. If a patient has a preoperative infection or a significant history of pelvic inflammatory disease, treatment before surgery is recommended. [20]

Office hysteroscopy (OH):

OH is well-tolerated minimally-invasive procedure, which allows reliable visual assessment of the cervical canal and uterine cavity and provides the opportunity to perform therapy in the same setting with low cost, minimal morbidity and inconvenience to the patient, and some lesions diagnosed can be operated easily using different equipment introduced through the operative channel of the hysteroscope. With the technical developments (video camera, mini-hysteroscopes, photo documentation, distention medium), it was believed that the requirements are fulfilled for the establishments of office hysteroscopy in daily gynecology practice.

Technique of atraumatic diagnostic hysteroscopy (the vaginoscopic approach) [21]

1. No cervical dilatation.
2. No blind insertion of instruments into the uterine cavity.
3. No use of tenaculum.
4. Atraumatic and sight controlled insertion of the hysteroscope.
5. Use non irritating distention medium (ionic watery solution).
6. No anesthesia or analgesia necessary.

Mini-hysteroscopy with optics <3 mm in diameter has reduced invasiveness and allows faster evaluation without dilatation.

Most references suggest that office hysteroscopy is a well-tolerated procedure and recommend analgesic use only in selected patients. [22]

Beside the diagnostic and therapeutic effect of office hysteroscopy on the endometrium, it has been reported by Karimzadeh 2009, that local endometrial injury by office hysteroscopy increases the implantation rate through the release of chemical mediators such as histamine and growth factor. Also another paper published by Gnainsky 2010 mentioned that local injury of the endometrium induces an inflammatory response that promotes successful implantation. [23]

Indications [24, 25]

- Abnormal uterine bleeding
- Infertility
- Abnormal findings by other diagnostic tools e.g. ultrasound, Hysterosalpingography (HSG), magnetic resonance imaging (MRI), and blind biopsy.
- Repeated pregnancy loss.
- Suspicious of uterine congenital anomalies
- Suspicious of intrauterine adhesions.
- Misplaced foreign bodies' e.g.IUD.
- Follow up of medical (e.g. tamoxifen) or surgical treatment

Chromohystroscopy:

Chromo endoscopy is a widely used technique in gastrointestinal imaging. Over the last decade; endoscopic systems have acquired great power due to high-resolution images, Chromohystroscopy was first introduced after the study by Kucuk and Safali in 2008, where they combined Chromo endoscopy and hysteroscopy as a new avenue to improve the diagnostic value of hysteroscopy (by using methylene blue dye) in the setting of assisted reproduction. [26]

Methylene blue (CI 52015): [27, 28]

Methylene blue is a heterocyclic aromatic chemical compound with the molecular formula $C_{16}H_{18}N_3SCl$. It has many uses in a range of different fields, such as biology , chemistry, and medicine such as:

- Combined with light(phototherapy)
- Methemoglobinemia
- Cyanide poisoning
- Dye or stain
- Placebo
- Ifosfamide neurotoxicity
- Vasoplegic syndrome after cardiac surgery

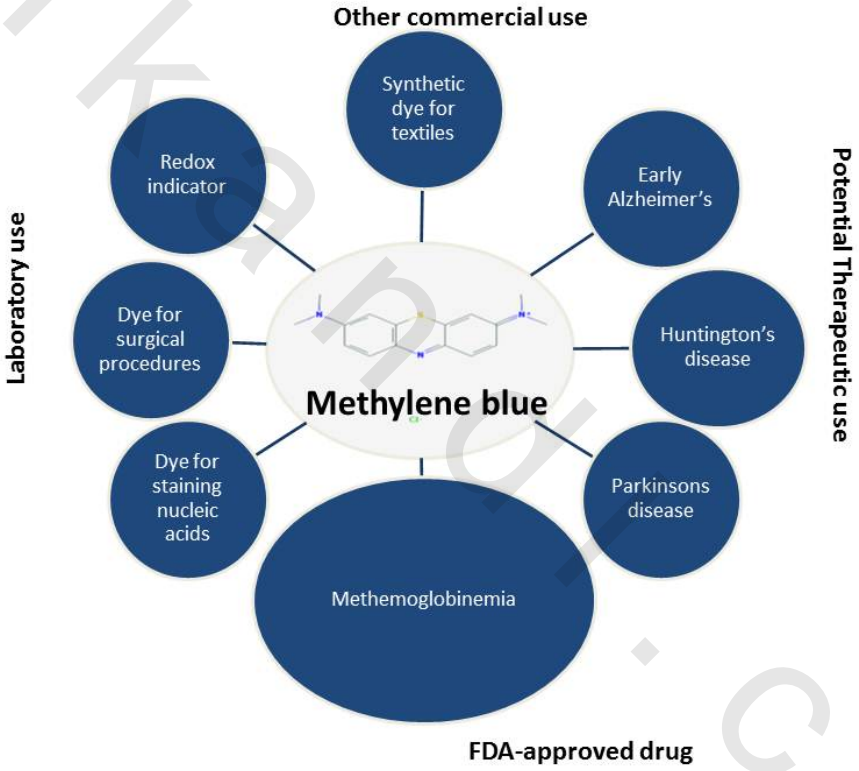

Figure (1): Uses of methylene blue.

Implantation failure:

Clinicians have yet to agree the definition of implantation failure, and in many studies no definition is described in the methodology section. Some investigators consider it to indicate a negative pregnancy test 2 weeks after embryo transfer (i.e. IVF\ICSI failure). Others use the term to indicate either absence of a gestational sac on ultrasound 5 weeks after transfer or of a fetal heartbeat at or beyond 3 weeks of pregnancy, and some even consider failure as absence of a live birth after IVF (Munné et al., 2003; Takahashi et al., 2004; Check et al., 2005; Thornhill et al., 2005). [29, 30]

Table (I): Etiological factors in implantation failure during IVF. [31]

Factors	
Maternal age, oocyte and embryo quality	Poor ovarian reserve and age related chromosomal aneuploidies Parental balanced translocation.
Immunological factors	Antiphospholipid antibodies Abnormal expression of endometrial cytokines and natural killer cells Shared parental human leukocyte antigens
Endometrial receptivity	Abnormal expression of endometrial estrogen and progesterone receptors Abnormal expression of endometrial integrins and pinopods Luteal phase defects
Uterine, tubal and peritoneal factors	Endometrial polyps and sub mucous fibroids Intramural fibroids Hydrosalpinges Endometriosis Infection

Causes of Failure of Implantation after ICSI:

The cellular and molecular interactions between the endometrium and implanting blastocyst remain poorly understood. Implantation failure is therefore an important rate-limiting step during IVF. The definition of implantation failure varies from place to place. The most frequently used criteria, however, are repeated, consecutive failure of embryos to implant following IVF.

Poor ovarian reserve and age related chromosomal aneuploidies:

Increasing maternal age is a proven adverse factor in reproductive performance. Ovarian reserve decreases progressively after the age of 35 years and such women undergoing IVF become increasingly more prone to aneuploidies and mosaicisms involving the sex chromosomes and autosomes 13,16,18,21, and 22. [32]

Antiphospholipid Syndrome:

Antiphospholipid syndrome is now well recognized as an etiological factor in recurrent miscarriage and the treatment with low dose aspirin or low-molecular weight heparin is now well established.[33] Unfortunately, the same success story cannot yet be said for implantation failure. A few observational studies have reported a higher prevalence of antiphospholipid antibodies in women with repeated implantation failure. [34]

Abnormal expression of cytokines and natural killer cells:

An increased expression of the 2endometrial cells and production of interleukins (IL-4, IL-6, IL-11 and IL 10) are believed to enhance reproductive outcome, [35] whereas a high level of endometrial pro-inflammatory Thl cells and production of tumor necrosis factor-α and IFN-g are associated with impaired implantation. The relative concentrations within the decidua basalis are also being studied. But some cases of RIF were related to local dys-regulation of the normal expression or action of various cytokines and elevated endometrial NK cells. [36]

Shared parental human leukocyte antigens:

Human leukocyte antigens (HLAs) are proteins located on the surface of the white blood cells and other tissues in the body. When two individuals share the same HLAs, their tissues are immunologically compatible. Early reports proposed that recurrent pregnancy losses may result from impaired immune responses leading to the absence of maternal leukocytotoxic antibodies, maternal blocking antibodies and defects in molecular immunosuppressive factors (cytokines and growth factors) at the local decidual/trophoblastic level. (37)

Endometrial receptivity and luteal phase defects:

Endometrial receptivity is dependent on adequate stimulation of estrogen and progesterone receptors in glandular and stromal cells. These steroid actions are mediated either by direct action on receptors or via paracrine mediators. Progesterone stimulation of an estrogenized endometrium leads to the production of proteins and other substances like integrin adhesion molecules and special markers called pinopods, which are thought to represent the implantation window. (38)

Uterine, tubal and peritoneal factors:

There are reports of undiagnosed endometrial pathologies like polyps, sub mucous fibroids, endometritis and synechiae causing repeat IVF\ICSI failures. There may be a link between intramural uterine fibroids and implantation failure, as small prospective controlled trials have suggested that fibroids may have adverse effects on outcome of IVF. One of these showed a halving of live birth rates in women with intra-mural fibroids of less than 5 cm, who underwent IVF without prior myomectomy. Similarly, there is evidence that hydrosalpinges halves IVF success rate. . Hydrosalpinx fluid is commonly slightly alkaline and may contain cytokines, prostaglandins or other inflammatory compounds. These compounds may have either direct embryo-toxicity or adversely affect the endometrium. Reflux of hydrosalpinx fluid into the uterine cavity may result in diminishing embryonic endometrial apposition. Current evidence-based-practice is therefore to offer unilateral or bilateral salpingectomies prior to IVF. (39)

Defective embryonic development:

Using fluorescence in-situ hybridization (FISH) for chromosomes 13, 16, 18, 21, 22, X and Y on blastomeres from biopsied embryos, Gianaroli and later Pehlivan et al found that the percentage of embryonic aneuploidy was higher in RIF (54–57%) compared with controls (36%). Thus, it can be assumed that many patients with RIF develop a high percentage of chromosomally abnormal embryos that fail to implant despite good morphology and developmental rate. Thus, it can be assumed that many patients with RIF develop a high percentage of chromosomally abnormal embryos that fail to implant despite good morphology and developmental rate. (40)

The zona pellucida, which surrounds the mammalian oocyte, hardens naturally after fertilization to prevent polyspermic fertilization and to protect the integrity of the pre-implantation embryo. Increased zona thickness was associated with lower implantation rates. Zona hardening, which may be induced by in vitro culture or by in vivo ageing, can also affect hatching **(**De Vos A, Van Steirteghem A 2000). Thus, failure of the zona to rupture has been suggested as a possible cause of RIF. (41)

Culture media and stimulation protocols:

It is now well known blastocyst transfer programs generally outperform zygote or embryo stage transfers. Yet, a controlled trial suggested that culture media have a variable effect on pregnancy rates after IVF. When clinics, rather than apply a blanket protocol to all, modify their treatment protocols to suit individual clinical findings based on past reproductive performances, results are generally better. There are no controlled studies to prove that changing any specific medication or stimulation protocol can improve treatment outcome. [42]

Endometrial pathologies [39, 40] can contribute to a less nutritive and/or to a hostile environment for the implanting blastocyst, placentation and growth of the fetus. Additionally, any coexisting abnormal myometrial activity and any abnormal uterine cavity can result in premature expulsion of the products of conception Examples include: endometritis, endometrial atrophy, endometrial sclerosis, poorly developed endometrial vessels and glands, asynchronous endometrial development, endometrial polyps, sub mucous fibroids, endometrial synechiae and malformations of the uterus.

Higher live birth rates were reported following treatment of these uterine pathologies in a number of case-controlled studies. It has been estimated that up to 33% of women would benefit from routine screening, diagnosis and selective treatment of relevant uterine pathologies before undergoing IVF treatment, and up to 22% of women after repeated unsuccessful IVF treatments.

Office hysteroscopy and implantation failure:

Embryo transfer is the stage of the in vitro fertilization treatment cycle that has the highest failure rate. Recurrent implantation failure (RIF) may be due to unrecognized uterine pathology. Hysterosalpingography, transvaginal ultrasonography and saline infusion sonography are the tools to assess the inner architecture of the uterus while hysteroscopy is considered to be the gold standard. [43]

In many practices, diagnostic hysteroscopy is the preferred procedure for the diagnosis of uterine pathology in infertile patients especially since office hysteroscopy has been proven to have superior sensitivity and specificity in evaluating the endometrial cavity. [44]

Endometritis:

Endometritis is inflammation of the endometrial lining of the uterus. In addition to the endometrium, inflammation may involve the myometrium and, occasionally, the parametrium.

Endometritis can be divided into pregnancy-related endometritis and endometritis unrelated to pregnancy. When the condition is unrelated to pregnancy, it is referred to as pelvic inflammatory disease (PID).

The Centers for Disease Control and Prevention (CDC) 2010 sexually transmitted diseases treatment guideline defines PID as any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis.[45]

Pathophysiology:

Infection of the endometrium, or decidua, usually results from an ascending infection from the lower genital tract. From a pathologic perspective, endometritis can be classified as acute versus chronic. Acute endometritis is characterized by the presence of neutrophils within the endometrial glands. Chronic endometritis is characterized by the presence of plasma cells and lymphocytes within the endometrial stroma.

In the non-obstetric population, pelvic inflammatory disease and invasive gynecologic procedures are the most common precursors to acute endometritis. In the obstetric population, postpartum infection is the most common predecessor.

Chronic endometritis in the obstetric population is usually associated with retained products of conception after delivery or elective abortion. In the non-obstetric population, chronic endometritis has been seen with infections, and the presence of an intrauterine device.

Etiology:

Endometritis is a poly microbial disease involving, on average, 2-3 organisms. In most cases, it arises from an ascending infection from organisms found in the normal vaginal flora. Commonly isolated organisms include Ureaplasma urealyticum, Peptostreptococcus, Gardnerella vaginalis, Bacteroides bivius, and group B Streptococcus. Chlamydia has been associated with late-onset postpartum endometritis. Enterococcus is identified in up to 25% of women who have received cephalosporin prophylaxis.

Herpes and tuberculosis are rare causes, although in some countries tuberculosis is not an uncommon etiologic agent.[46, 47, 48]

Signs and symptoms of endometritis:

- Fever, usually occurring within 36 hours of delivery, in the obstetric population
- Lower abdominal pain
- Abnormal vaginal bleeding or discharge
- Dyspareunia (may be present in patients with pelvic inflammatory disease (PID)
- Dysuria (may be present in patients with PID)
- Malaise
- Adnexal tenderness if there is an associated salpingitis
- Foul-smelling lochia
- Tachycardia
- Uterine tenderness is the hallmark of the disease.

Risk Factors

Women are particularly vulnerable to endometritis after birth or abortion. In both the postpartum and postabortal state, risk is increased because of the open cervical os, presence of large amounts of blood and debris, and uterine instrumentation.

Major risk factors for obstetric endometritis include the following:

- Cesarean delivery (especially if before 28 weeks' gestation)
- Prolonged rupture of membranes
- Long labor with multiple vaginal examinations
- Severely meconium-stained amniotic fluid
- Manual placental removal[49]
- Extremes of patient age
- Low socioeconomic status

Minor risk factors include the following:

- Absence of the normal cervical mucus plug
- Administration of multiple courses of corticosteroids for prevention of premature delivery
- Prolonged internal fetal monitoring
- Prolonged surgery
- General anesthesia
- Postpartum anemia

The following factors increase the risk for endometritis in general: [50, 51]

- Presence of an intrauterine device: the vaginal part of the device may serve as a track for the organisms to ascend into the uterus
- Presence of menstrual fluid in the uterus
- Associated cervicitis secondary to gonorrhea or Chlamydia infection
- Associated bacterial vaginosis
- Frequent douching
- Unprotected sexual activity
- Multiple sexual partners
- Cervical ectopy

Potential Complications:

Potential complications of endometritis include the following:

- Wound infection
- Peritonitis
- Adnexal infection
- Parametrial phlegmon
- Pelvic abscess

- Pelvic hematoma
- Septic pelvic thrombophlebitis
- Septicemia
- Septic shock
- Infertility

Differential Diagnosis

- Appendicitis
- Pelvic Inflammatory Disease
- Urinary Tract Infection
- Pyelonephritis
- Viral syndrome
- Pelvic thrombophlebitis
- Chorioamnionitis

Endometritis diagnosis:

- Although the diagnosis of endometritis is principally made on clinical grounds, laboratory studies can be helpful for supporting the diagnosis and excluding or identifying other diagnostic possibilities.
- Complete Blood Cell Count (CBC) typically reveals leukocytosis. However, in the postpartum period, this finding may reflect the physiological leukocytosis of pregnancy and it is therefore unreliable for diagnosis.
- Anemia (may be risk factor).
- ESR (sedimentation rate)
- Laparoscopy and hysteroscopy.
- Wet prep (microscopic exam of any discharge)
- Endometrial biopsy can be obtained to assess chronic endometritis. The diagnosis is ultimately based on the presence of plasma cells in the endometrial stroma upon histopathological examination.

Pathologically, endometritis is defined as the presence of 5 or more neutrophils per high-power field (400×) in the superficial endometrium and 1 or more plasma cells per high-power field (120×) in the endometrial stroma.

- Blood culture is positive in 10-30% of cases, and a urine culture should be ordered.
- The role of endocervical cultures is controversial. They are not generally helpful in management, as positive results are usually the result of contamination from normal resident cervicovaginal flora. However, endocervical cultures (or DNA probe) are obtained for gonorrhea and chlamydia when appropriate.

- Gram stain or wet mount of the vaginal discharge may be useful in ruling out endometritis. If no pus cells are observed in the Gram stain, the negative predictive value for endometritis is 95%.
- CT scanning of the abdomen and pelvis may be helpful for excluding broad ligament masses, septic pelvic thrombophlebitis, ovarian vein thrombosis, and phlegmon.
- Ultrasonography of the abdomen and pelvis may yield normal findings in patients with a clinical diagnosis of endometritis.

Endometritis treatment:

After making the diagnosis of endometritis and excluding other sources of infection, the physician should promptly initiate broad-spectrum antibiotics. Improvement will be noted within 48-72 hours in nearly 90% of women treated with an approved regimen.

Dilation and curettage may be advised for retained products of conception, however. In rare instances of overwhelming infection nonresponsive to conservative therapy, hysterectomy may be necessary as a life-saving intervention.[52]

Antibiotic Therapy*:*

The combination of clindamycin and gentamicin administered intravenously every 8 hours has been considered the criterion standard treatment. Some studies have revealed adequate efficacy with once-daily dosing, as well.[53, 54, 55]The combination of a second- or third-generation cephalosporin with metronidazole is another popular choice.

Sexual partners may need to be treated if the condition is caused by a sexually transmitted infection.

Prophylaxis:

Prophylactic antibiotics reduce the incidence of postpartum febrile morbidity in patients undergoing cesarean delivery. Current research supports the use of preoperative administration of prophylactic antibiotics.[56, 57, 58] Single-agent therapy with a first- or second-generation cephalosporin (e.g., cefazolin) has been considered the best choice.

A combination therapy with clindamycin and an aminoglycoside is considered the criterion standard by which most antibiotic clinical trials are judged. A combination regimen of ampicillin, gentamicin, and metronidazole provides coverage against most of the organisms that are encountered in serious pelvic infections. Doxycycline should be used if Chlamydia is the cause of the endometritis.

Ampicillin sulbactam can be used as monotherapy. Single-agent therapies have been found to be effective in 80-90% of patients.[59, 60]

Endometritis ICD-9 and ICD-10 Codes

The ICD-9 code for endometritis is 615.9 while its ICD-10s code is N71.

AIM OF THE WORK

The aim of the work was to assess the value of adding methylene blue dye to conventional office hysteroscopy in evaluating the uterine cavity after failed trial of ICSI, and detecting any signs of endometritis.

MATERIALS

This was a case- control study in which 25 infertile women that had a failed trial of intracytoplasmic sperm injection, the second group include 25 control cases from patients seeking for fertility treatment with no history of anatomic uterine abnormalities accepting and consenting to do Chromohystroscopy procedure.

Inclusion criteria:

- Age between 20-38 years.
- Nullipara or multipara.
- Failed ICSI cycle in spite of good embryos in group one.
- Time of hysteroscopy was between 30 and 120 days after the IVF cycle (3 or 4 days) post menstrual.

Exclusion criteria:

- A known or detected uterine anatomical abnormality.
- Cancelled cycles or no embryo transfer.
- Evidence of hormonal disturbance.
- Repeated curettage more than 3 times and /or evidence of Asherman, s syndrome.

METHODS

After approval of medical ethics committee and after taking informed consent, all cases in this study were subjected to the following:

A) Detailed history taking including complete obstetric and gynecologic history.

B) History of previous ICSI cycles, number of embryos transferred ,quality of embryos ,and presence of any associated pelvic pathology that was present during the ICSI cycle (hydrosalpinx ,endometriosis ,……).

C) Complete general and gynecological examination.

D) Transvaginal ultrasonography was done for evaluation of uterus &ovaries and detects any pelvic pathology.

E) All hysteroscopic operations were performed in the early follicular phase (3 or 4 days post menstrual) as conventional hysteroscopy and documentation of the findings was done.

F) Dorsal lithotomy position was used for all hysteroscopic procedures. 2.9 mm, 30° rigid telescope with an operative sheath of 3.5 mm was used for examination and intraoperative antibiotics prophylaxis with 1 g ceftriaxone was given to all patients.

G) All procedures were done in an out-patient setting with paracervical block if needed, using xylocaine 5 ml to be injected at 3 and 9 o'clock.

H) Chromohystroscopy was done:

- Five milliliter of 1% methylene blue dye was introduced through the hysteroscopic inlet. After 5 min of waiting distending medium flow was start again and let wash the endometrium.

- Uterine cavity was visualized for staining pattern. Diffuse light hallow (no staining) was considered normal. Focal, dark blue staining above the internal cervical ostium, regardless of size and number of stained areas, was considered positive finding.

Statistical analysis of the data:[61]

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. [62] Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's exact test or Monte Carlo correction. For normally distributed data, comparison between two independent populations were done using independent t-test, also paired t-test is used to analyze two paired data. For abnormally distributed data, comparison between two independent population were done using Mann Whitney test The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, Shapiro-Wilk test and D'Agstino test, also Histogram and QQ plot were used for vision test. If it reveals normal data distribution, parametric tests was applied. If the data were abnormally distributed, non-parametric tests were used.

RESULTS

This study was conducted on 50 infertile female patients, conducted from El-Shatby University Maternity Hospital during the period between March 2013 and May 2014, undergoing infertility management workup.

As regard to patient's age, in the study group it ranged between 22-38 years with mean ± S.D. 30.84±4.732 years while in the control group it ranged between 20-38 years with mean ± S.D. 29.36±5.171 years. There was no statistically significant difference between the two groups P=0.296 (P significant level where $P \leq 0.05$).

Table (II): Comparison between the two groups as regard to age

Age	Study Group	Control Group	P value
Min.	22	20	0.296
Max.	38	38	
Mean	30.84	29.36	
S.D.	4.732	5.171	

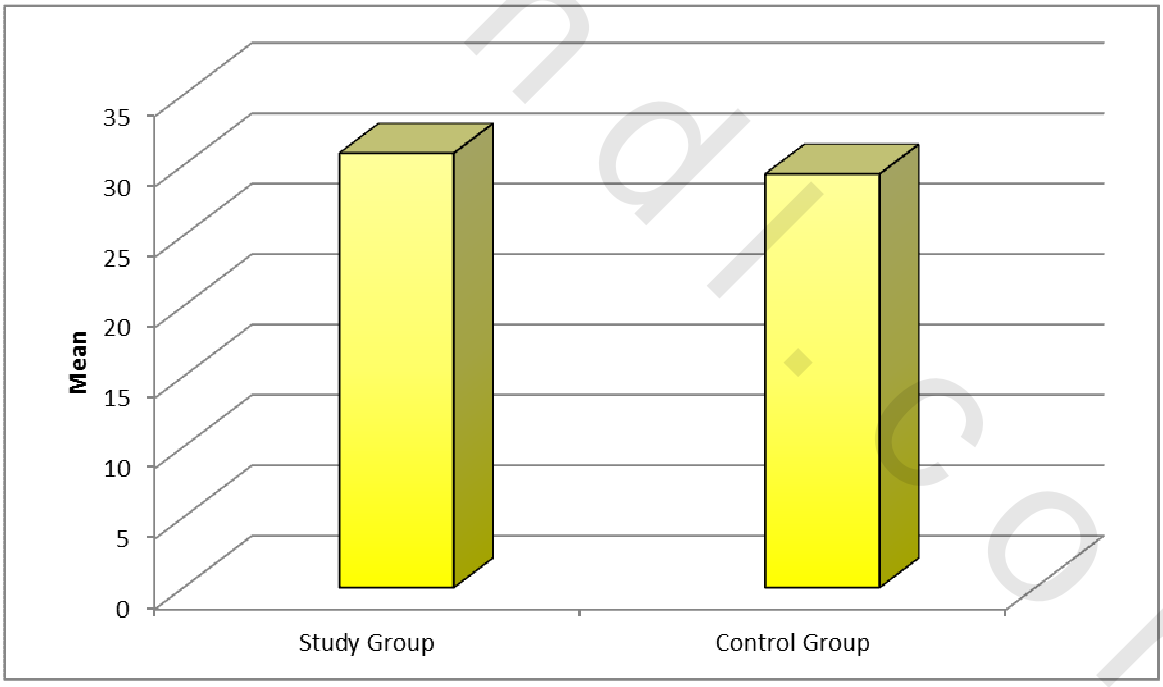

Figure (2): Comparison between the two groups as regard to age

As regard to infertility type, in the study group 22(88%) out of the patients had primary and 3(12%) out of the patients had secondary and the same in the control group 22(88%) out of the patients had primary and 3(12%) out of the patients had secondary. There was no statistically significant difference between the two groups P=1.000 (P significant level where $P \leq 0.05$).

Table (III): Comparison between the two groups as regard to infertility type

Infertility type	Study Group		Control Group		P Value
	No.	%	No.	%	
Primary	22	88	22	88	1.000
Secondary	3	12	3	12	
Total	25	100	25	100	

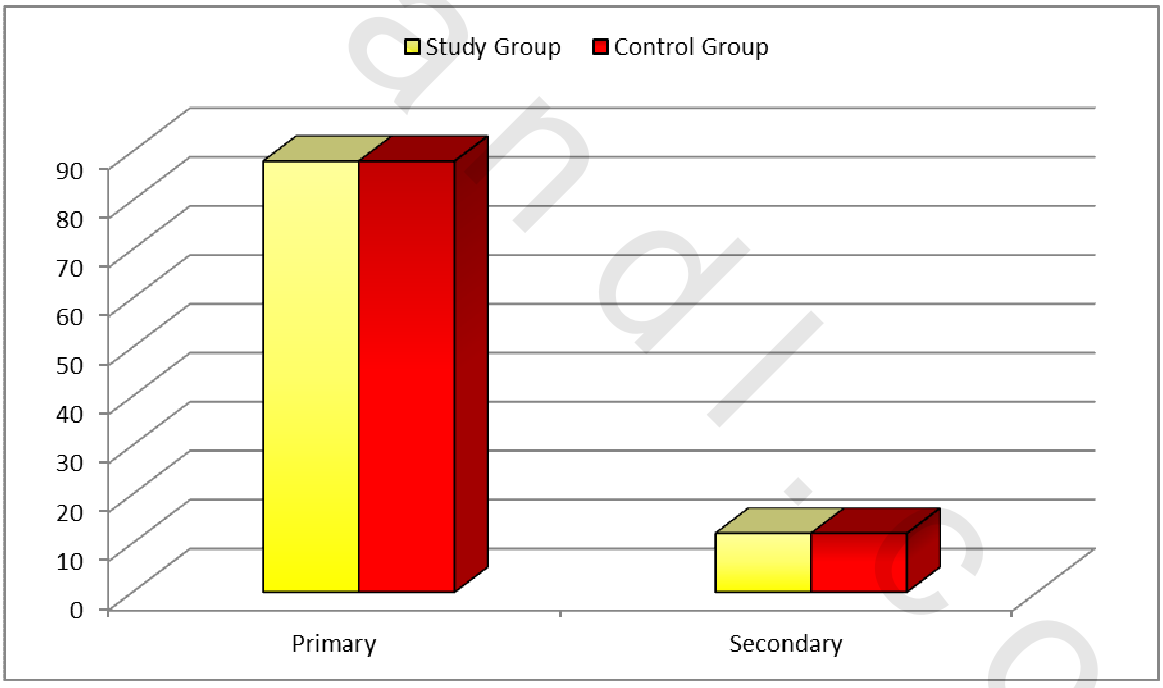

Figure (3): Comparison between the two groups as regard to infertility type

As regard to cause of infertility, in the study group 7(28%) out of the patients had male factor, 5(20%) out of the patients had ovulatory problem, 3(12%) out of the patients had endometriosis, 5(20%) out of the patients had tubal factor and 5(20%) out of the patients had unexplained infertility while in the control group 10(40%) out of the patients had male factor, 6(24%) out of the patients had ovulatory problem, 3(12%) out of the patients had endometriosis, 2(8%) out of the patients had tubal factor and 4(16%) out of the patients had unexplained infertility. There was no statistically significant difference between the two groups P=0.837 (P significant level where $P \leq 0.05$).

Table (IV): Comparison between the two groups as regard to cause of infertility

cause of infertility	Study Group		Control Group		P Value
	No.	%	No.	%	
Male factor	7	28	10	40	
Ovulatory problem	5	20	6	24	
Endometriosis	3	12	3	12	
Tubal factor	5	20	2	8	
Unexplained infertility	5	20	4	16	
Total	25	100	25	100	

As regard to ultra sound findings, in the study group 21(84%) out of the patients had normal ultrasound findings, 1(4%) out of the patients had acute AVF and 3(12%) out of the patients had RVF while in the control group 22(88%) out of the patients had normal ultrasound findings and 3(12%) out of the patients had RVF. There was no statistically significant difference between the two groups P=0.600 (P significant level where P ≤ 0.05).

Table (V): Comparison between the two groups as regard to ultrasound findings

Ultrasound findings	Study Group		Control Group		P Value
	No.	%	No.	%	
Normal	21	84	22	88	0.600
Acute AVF	1	4	0	0	
RVF	3	12	3	12	
Total	25	100	25	100	

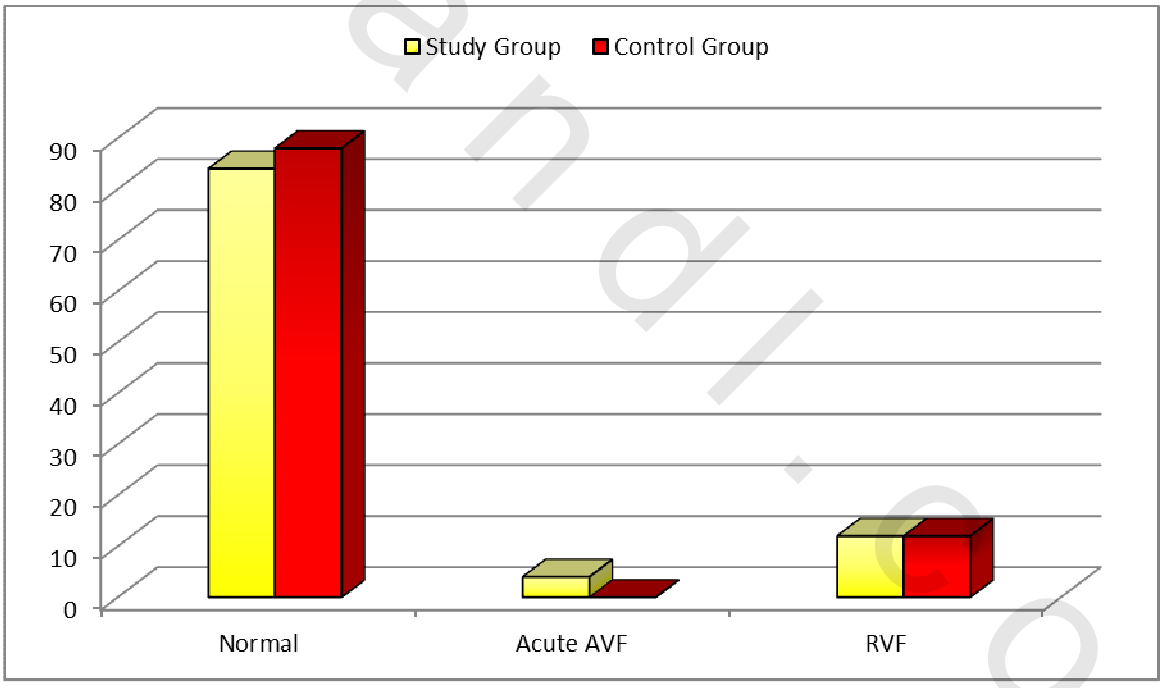

Figure (4): Comparison between the two groups as regard to ultrasound findings

As regard to condition of tubal ostea, in the study group 17(68%) out of the patients was healthy, 3(12%) out of the patients was not seen and 5(20%) out of the patients was not patent while in the control group 23(92%) out of the patients was healthy, 1(4%) out of the patients was not at same level and 1(4%) out of the patients was not patent. There was a statistically significant difference between the two groups P=0.028 (P significant level where $P \leq 0.05$).

Table (VI): Comparison between the two groups as regard to condition of tubal Ostea

Condition of tubal ostea	Study Group		Control Group		P Value
	No.	%	No.	%	
Healthy	17	68	23	92	0.028
Not at same level	0	0	1	4	
Not patent	5	20	1	4	
Not seen	3	12	0	0	
Total	25	100	25	100	

As regard to cavity condition, in the study group 23(92%) out of the patients was normal, 1(4%) out of the patients was lateral constriction and 1(4%) out of the patients was T shape while in the control group 23(92%) out of the patients was normal, 1(4%) out of the patients was arcuate uterus and 1(4%) out of the patients was obliterated rudimentary segment. There was no statistically significant differences between the two groups while P=0.406 (P significant level where P ≤ 0.05).

Table (VII): Comparison between the two groups as regard to cavity condition

Cavity condition	Study Group		Control Group		P Value
	No.	%	No.	%	
Normal	23	92	23	92	0.406
Arcuate uterus	0	0	1	4	
Lateral constriction	1	4	0	0	
Obliterated segment	0	0	1	4	
T shaped	1	4	0	0	
Total	25	100	25	100	

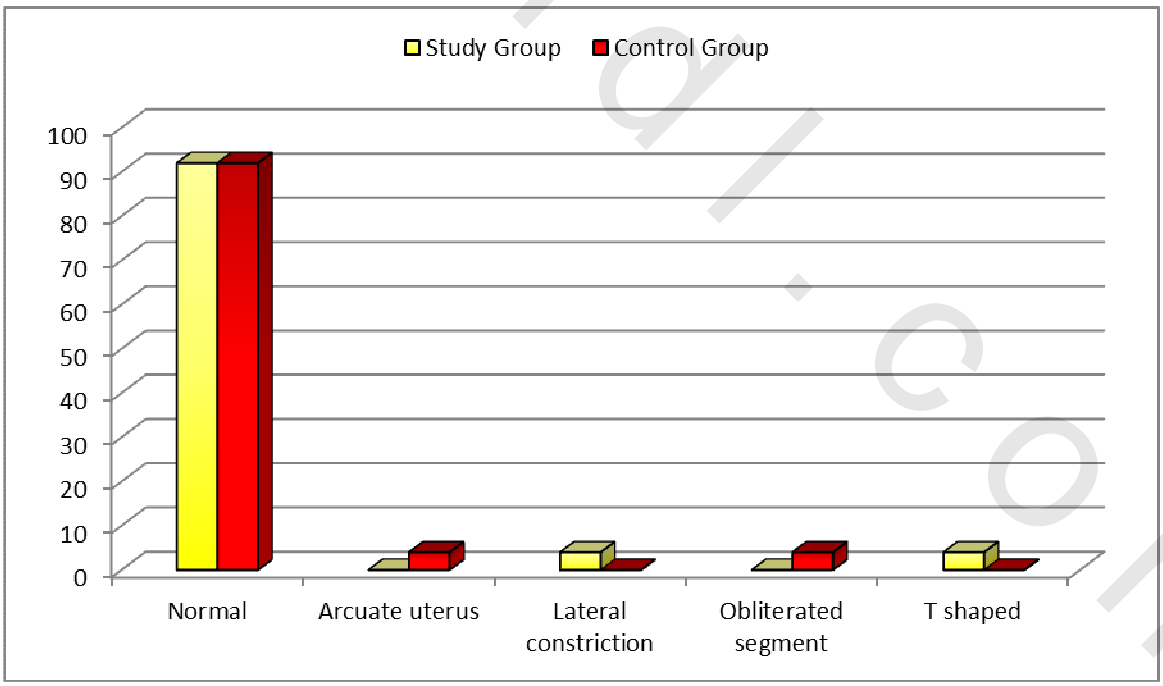

Figure (5): Comparison between the two groups as regard to cavity condition

As regard to condition of the endometrium, in the study group 21(84%) out of the patients was normal, 2(8%) out of the patients had atrophic, 1(4%) out of the patients had thick and 1(4%) out of the patients had thick polypoidal while in the control group 23(92%) out of the patients was normal, 1(4%) out of the patients had filmy adhesion and 1(4%) out of the patients was thick. There was no statistically significant difference between the two groups P=0.536 (P significant level where $P \leq 0.05$).

Table (VIII): Comparison between the two groups as regard to condition of the endometrium

Condition of the endometrium	Study Group		Control Group		P Value
	No.	%	No.	%	
Normal	21	84	23	92	0.394
Atrophic	2	8	0	0	
Filmy adhesion	0	0	1	4	
Thick	1	4	1	4	
Thick polypoidal	1	4	0	0	
Total	25	100	25	100	

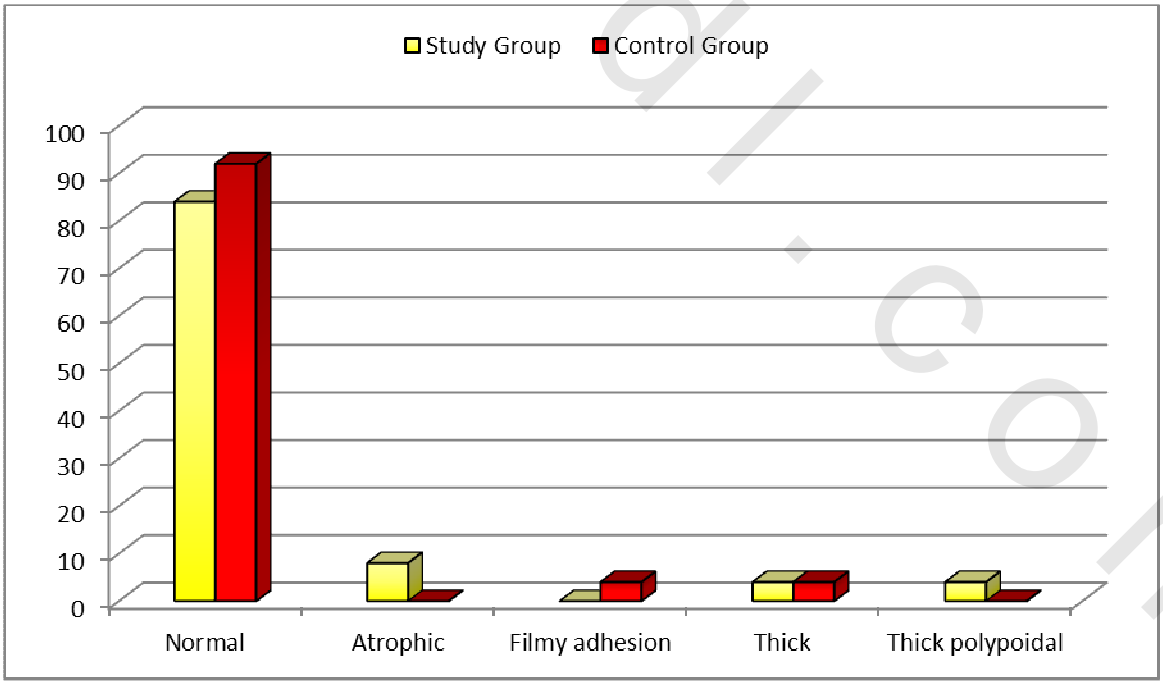

Figure (6): Comparison between the two groups as regard to condition of the endometrium

As regard to presence of endometritis, in the study group 8(32%) out of the patients had no presence of endometritis (diffuse light staining) and 17(68%) out of the patients had presence of endometritis (focal dark staining) while in the control group 21(84%) out of the patients had no presence of endometritis and 4(16%) out of the patients had presence of endometritis. There was statistically high significant difference between the two groups P=0.000 (P significant level where P ≤ 0.05).

Table (IX): Comparison between the two groups as regard to presence of endometritis

Presence of endometritis	Study Group		Control Group		P Value
	No.	%	No.	%	
No (diffuse light)	8	32	21	84	0.000*
Yes (focal dark)	17	68	4	16	
Total	25	100	25	100	

***P<0.001**

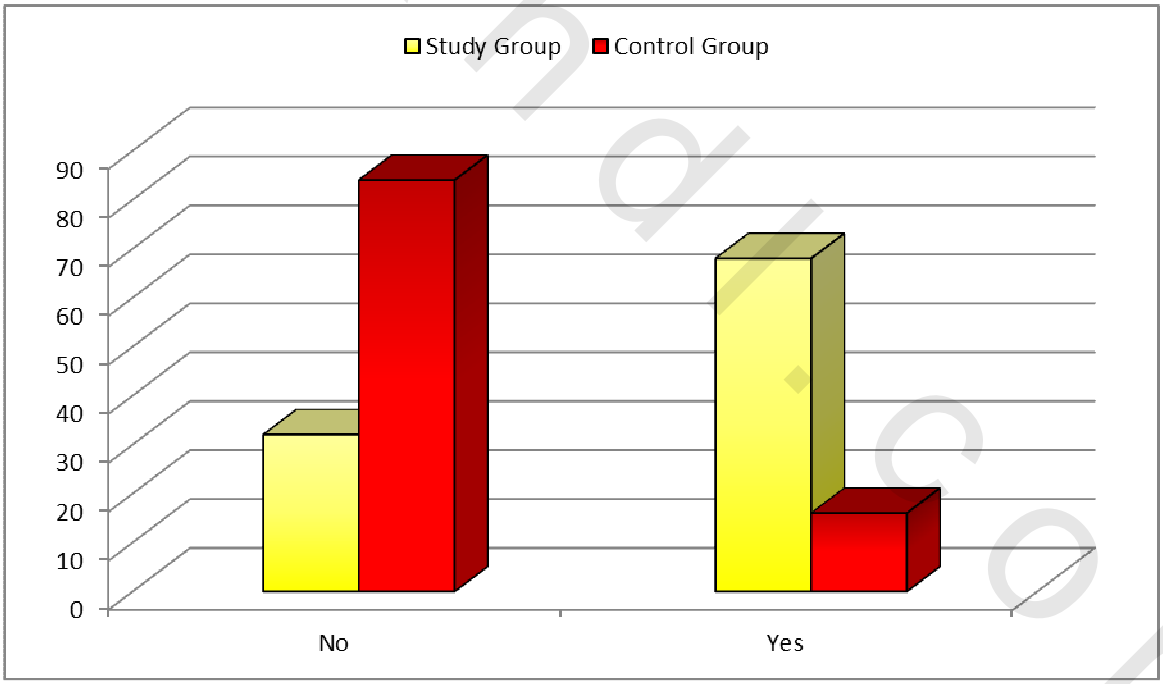

Figure (7): Comparison between the two groups as regard to presence of endometritis

As regard to presence of septum, in the study group 18(72%) out of the patients had no presence of septum and 7(28%) out of the patients had presence of septum while in the control group 16(64%) out of the patients had no presence of septum and 9(36%) out of the patients had presence of septum an the mean length of septum was 4mm. There was no statistically significant difference between the two groups P=0.762 (P significant level where $P \leq 0.05$).

Table (X): Comparison between the two groups as regard to presence of septum

Presence of septum	Study Group		Control Group		P Value	Mean Length of septum
	No.	%	No.	%		
No	18	72	16	64	0.762	4mm
Yes	7	28	9	36		
Total	25	100	25	100		

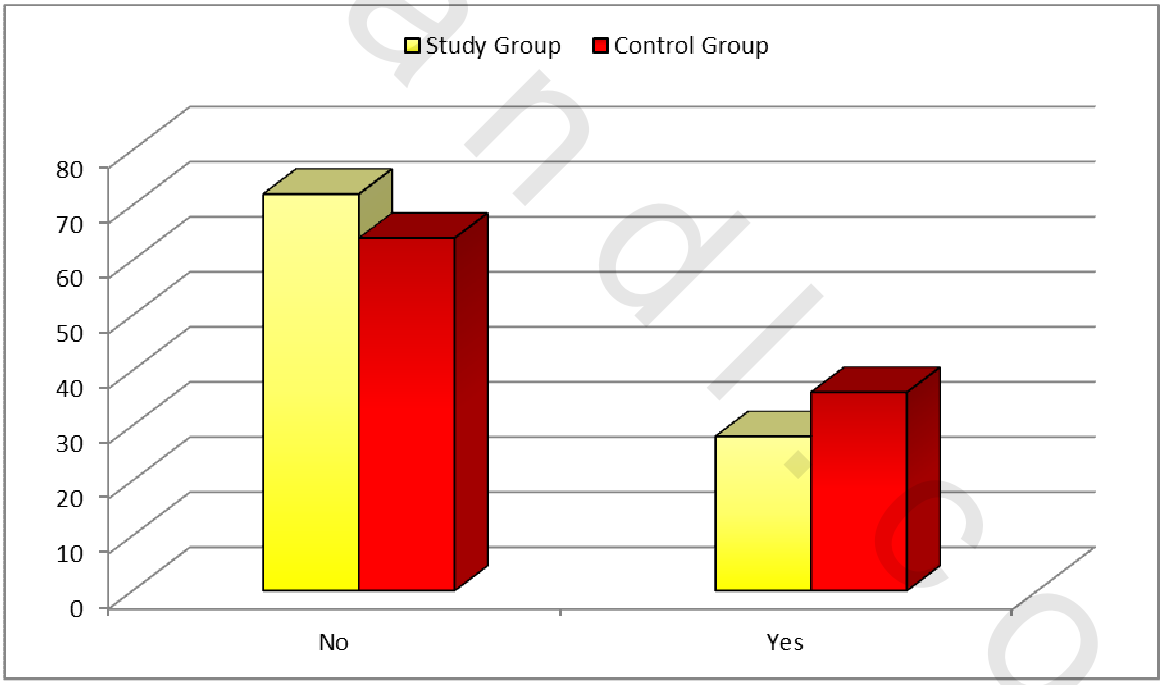

Figure (8): Comparison between the two groups as regard to presence of septum

As regard to presence of polypi, in the study group 23(92%) out of the patients had no polypi, 1(4%) out of the patients had single polyp and 1(4%) out of the patients had multiple polypi while in the control group 19(76%) out of the patients had no polypi, 4(16%) out of the patients had single polyp and 2(8%) out of the patients had multiple polypi. There was no statistically significant difference between the two groups P=0.247 (P significant level where $P \leq 0.05$).

Table (XI): Comparison between the two groups as regard to presence of polypi

Presence of polypi	Study Group		Control Group		P Value
	No.	%	No.	%	
No polypi	23	92	19	76	0.284
Single polyp	1	4	4	16	
Multiple polypi	1	4	2	8	
Total	25	100	25	100	

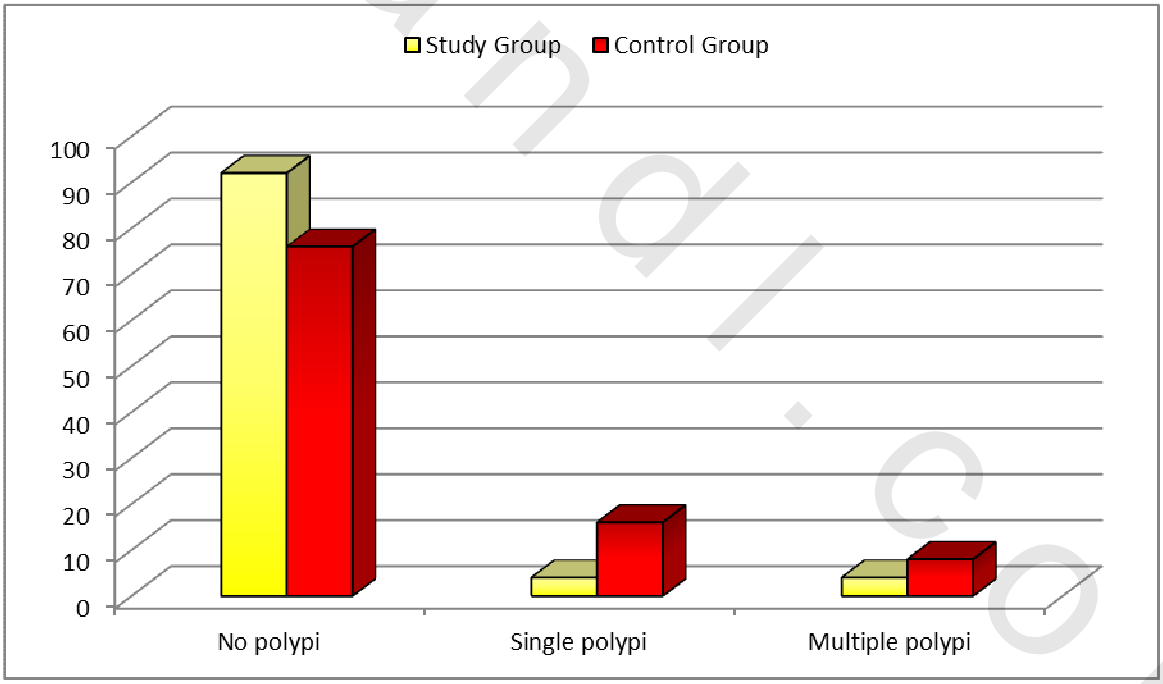

Figure (9): Comparison between the two groups as regard to presence of polypi

As regard to presence of hyperplasia, in the study group 23(92%) out of the patients had no presence of hyperplasia and 2(8%) out of the patients had presence of hyperplasia as well as in the control group 23(92%) out of the patients had no presence of hyperplasia and 2(8%) out of the patients had presence of hyperplasia. There was no statistically significant difference between the two groups P=1.000 (P significant level where P ≤ 0.05).

Table (XII): Comparison between the two groups as regard to presence of hyperplasia

Presence of hyperplasia	Study Group		Control Group		P Value
	No.	%	No.	%	
No	23	92	23	92	1.000
Yes	2	8	2	8	
Total	25	100	25	100	

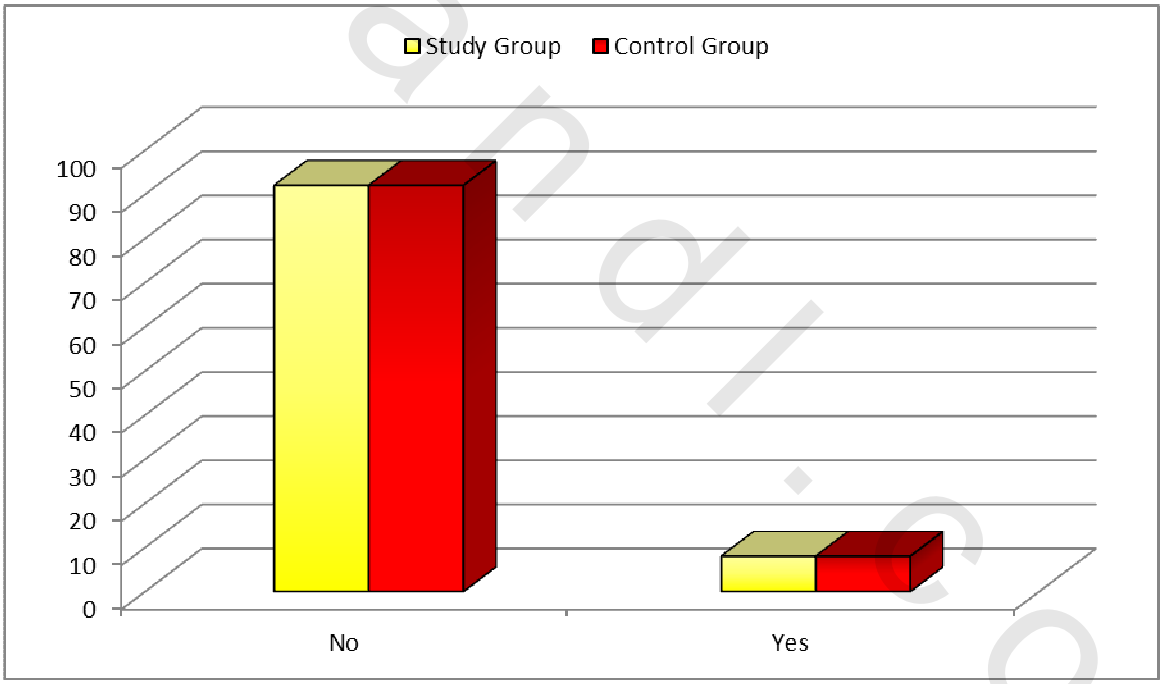

Figure (10): Comparison between the two groups as regard to presence of hyperplasia

As regard to hysteroscopic entry through the cervical os, in the study group 7(28%) out of the patients had difficulty and discomfort in entry and 18(72%) out of the patients had easy entry while in the control group 5(20%) out of the patients had difficulty in entry and 20(80%) out of the patients had easy entry but only on case that require anesthesia, and only 2 cases that require internal os dilatation by using a sound forceps. There was no statistically significant difference between the two groups P=0.742 (P significant level where $P \leq 0.05$).

Table (XIII): Comparison between the two groups as regard to hysteroscopic entry

Entry	Study Group		Control Group		P Value
	No.	%	No.	%	
Difficult	7	28	5	20	0.742
Easy	18	72	20	80	
Total	25	100	25	100	

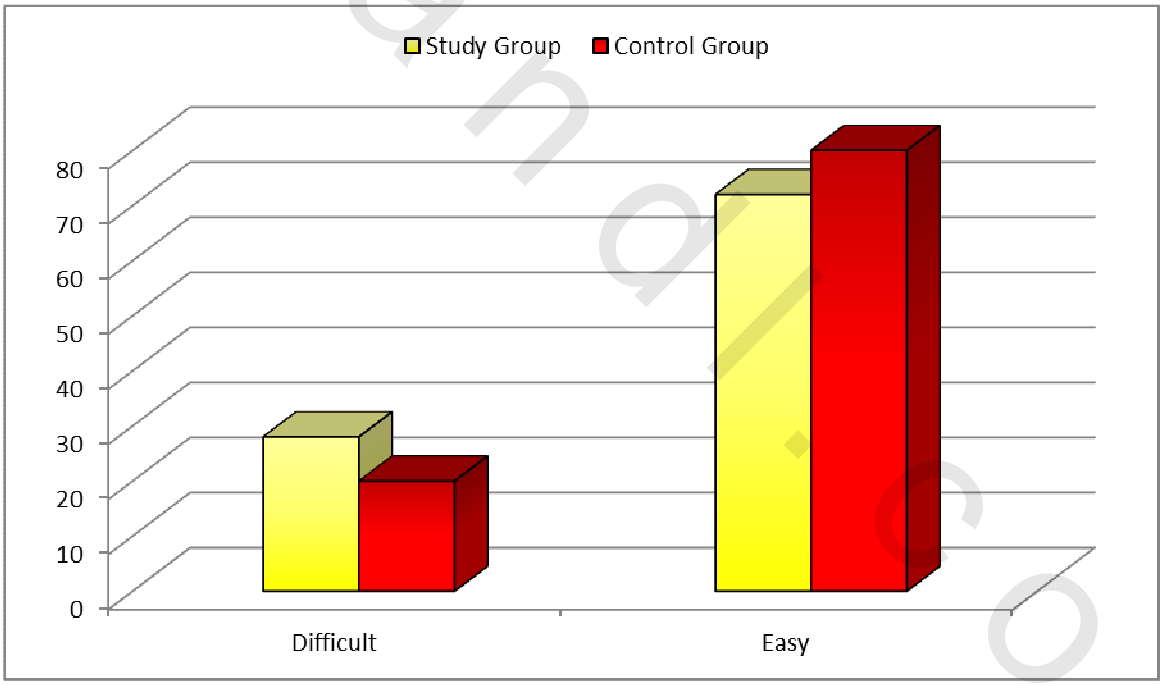

Figure (11): Comparison between the two groups as regard to hysteroscopic entry

As regard to days of menstrual cycle at the time of hysteroscopic procedure, in the study group it ranged between 5-15 with mean±S.D. 8.56±2.615 while in the control group it ranged between 5-14 with mean±S.D. 9.6±2.217. There was no statistically significant difference between the two groups P=0.068 (P significant level where P ≤ 0.05).

Table (XIV): Comparison between the two groups as regard to days of menstrual cycle

Days of menstrual cycle	Study Group	Control Group	P value
Min.	5	5	0.068
Max.	15	14	
Mean	8.56	9.60	
S.D.	2.615	2.217	

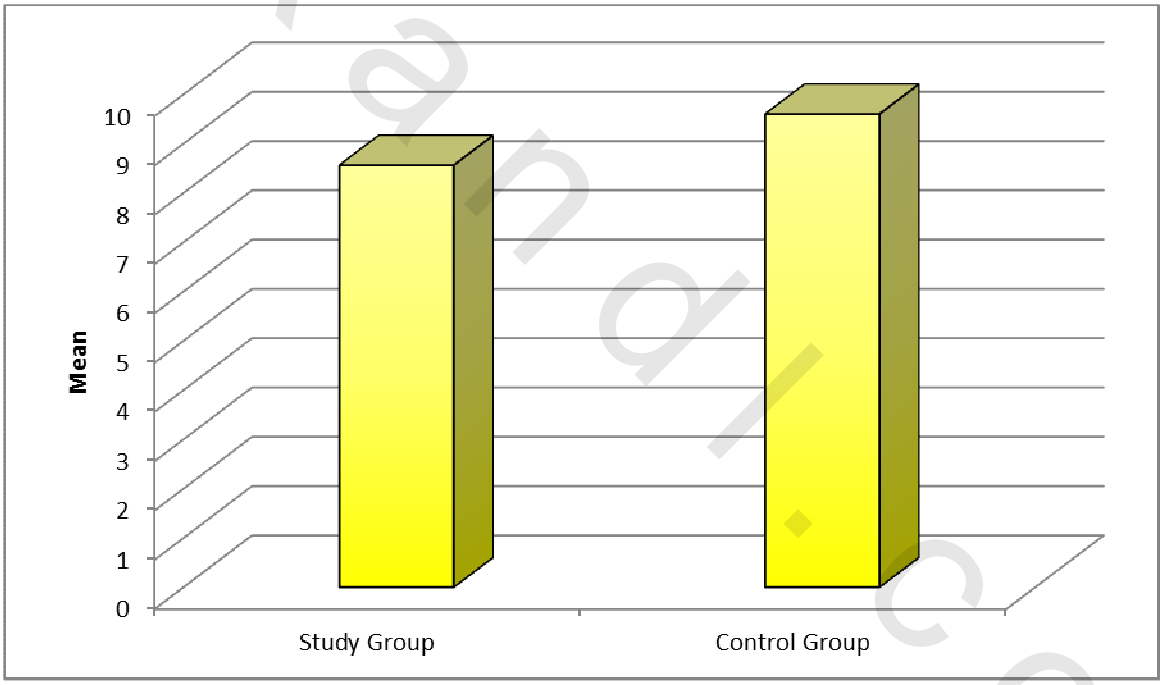

Figure (12): Comparison between the two groups as regard to days of menstrual cycle

As regard to duration of infertility, in the study group it ranged between 1-15 with mean±S.D. 6.60±3.231 while in the control group it ranged between 1-12 with mean±S.D. 4.5±3.024. There was statistically significant difference between the two groups P=0.008 (P significant level where P ≤ 0.05).

Table (XV): Comparison between the two groups as regard to duration of infertility

Duration of infertility	Study Group	Control Group	P value
Min.	1	1	0.008
Max.	15	12	
Mean	6.60	4.50	
S.D.	3.231	3.024	

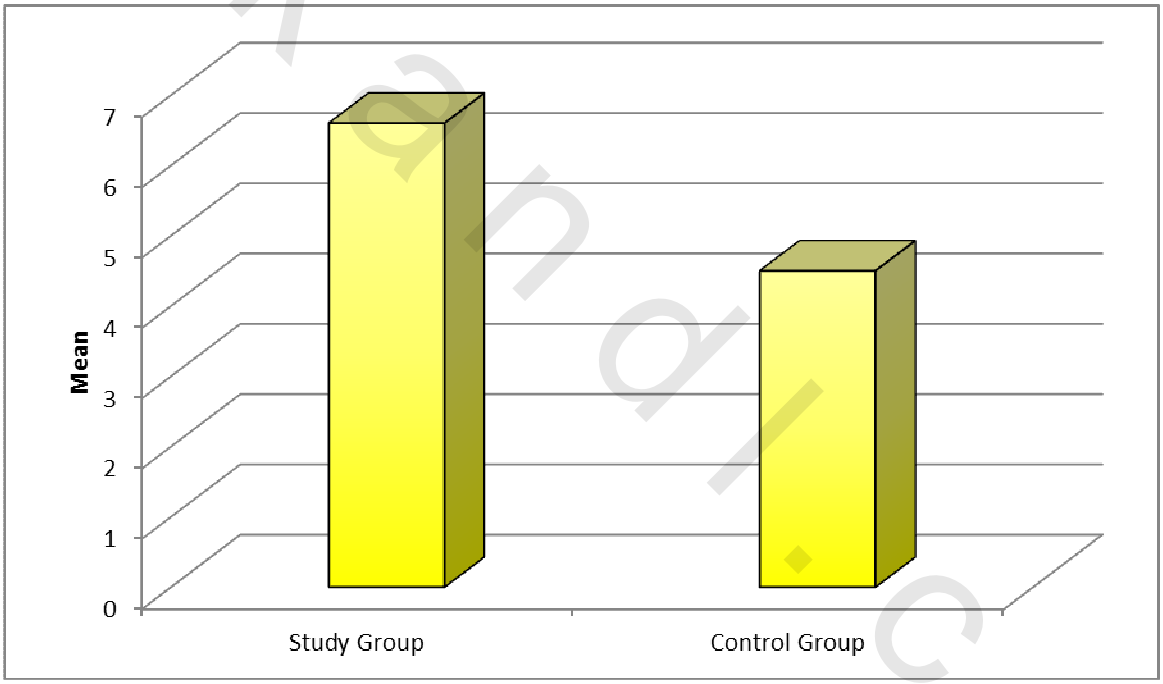

Figure (13): Comparison between the two groups as regard to duration of infertility

As regard to number of failed cycles in the study group it ranged between 1-3 with mean ±S.D. 1.44±0.651. (Table (**XVI**)

As regard to number of embryos transferred in the study group it ranged between 2-5 with mean ±S.D. 3.44±0.917. (Table (**XVI**)

Table (XVI): demographic data of no. of failed cycles and embryos transferred

	Min.	**Max.**	**Mean**	**S.D.**
Number of failed cycles	1	3	1.44	0.651
Number of embryos transferred	2	5	3.44	0.917

DISCUSSION

The evaluation of uterine factor of infertility can be accomplished using ultrasonography (abdominal, transvaginal (TVUS), or three-dimensional modalities), hysterosalpingography (HSG), saline infusion sonography (SIS) and hysteroscopy. When there is a macroscopic abnormality, it is hardly possible to miss the diagnosis. But when there is no apparent finding, uterus is accepted as normal, although endometrial cells still can be defective. Hysteroscopy has the advantage in its ability to establish a direct and closer visual diagnosis of endometrial anatomy and integrity. [(9)]

The value of hysteroscopy is limited for detection of subtle and/or local endometrial changes which has not produced a macroscopic finding. Endometrial biopsy is employed to diagnose cellular pathologies. La Sala et al. [(63)] reported an incidence of 2% endometritis among 100 women with two consecutive IVF failures.

Majority of papers in the current medical literature reported macroscopic endometrial pathologies like polyp, adhesion or sub mucous myomas in hysteroscopy after repetitive IVF failure. [(8)] When there is a macroscopic abnormality, eventually; it is detected and treated appropriately.

In our study we included 50 patients divided to 2 groups. A study group containing 25 patients and a control group containing another 25 patients.

The mean age for study group was 30.84 years while for control group was 29.36 years we had 88% of our patients in both groups suffering from primary infertility and only 12% of patients suffering from secondary infertility. In our study we had variable causes of infertility. In study group one had cervical factor, 6 had male factor, 5 had ovulatory problems, 3 had pelvic factor, 5 had tubal factor and 5 had un explained infertility while for the control group 1 had cervical factor, 9 male factor, 6 ovulatory problem 3 pelvic factor, 2 tubal factor, 4 un explained infertility.

Regarding the ultrasound finding for the study group 21 of our patients showed normal with no significant finding while one patient showed Acute AVF and 3 patients showed RVF while for the control group 22 patients showed normal result with no significant finding and we had no patients having Acute AVF and 3 patients having RVF. While regarding duration of infertility the study group showed a mean duration of 6.6 while control group showed 4.5.

The corner stone in our study was assessing the cavity condition we found in the study group 23 patients having a normal finding and one patient having a lateral constriction and another patient having a T-Shaped while in control group we had 23 patients having a negative finding and 1 patient having arcuate uterus 1 patient having obliterated segment.

Concerning the endometrial status we found in the study group 21 patients having a negative normal endometrial finding 2 atrophic 1 thick and another patient having thick poly poidal while in control group we had 23 negative patients.

Also, one patient having filmy adhesion and another having a thick endometrial. In our study we had 2 Patients in the study group having hyperplasia and also the same number was seen among the control group which is 8%.

The ease of the procedure was demonstrated in our study. That in study group 18 out of 25 Patients, the entry was easy 72% while this percentage was as 80% in the control group which prove the safety and the ease of the procedure within a short time interval.

Showing the marked increase in positive finding in the study group which is 68% while in control group is only 16% there was 7 patients in study group having a septum which is 28% while in control group there were 36% we had 2 patient in study group having polyps 8% while in control group we had 6 patients 24%?

Differey studies endometrial causes of infertility and found that, hysterographic and sonographic sensitivities were 48.9% and 48%, and false negative rates were 51.1% and 52%, respectively. So, sonography and hysterography were not accurate enough for uterine cavity evaluation. These women were mistakenly treated as women with normal uterine cavity who would probably undergo other unnecessary tests within the infertility workup, while the cause of their infertility might be a missed intra uterine lesion.

Anthey study showed that two thirds of hysteroscopic findings were not correlated with those found on hysterography. It was shown that 54.3% of intra uterine adhesions diagnosed on hysterography were not found on direct hysteroscopic examination. In another study, the most common pathologic finding in women with AUB and normal vaginal sonography was a polyp. Hysteroscopy is one of the best methods to detect polyp in this area. [16]

Zeyneloglu et al. [64] have reported that, observations of micropolyps in hysteroscopy were a significant predictor of miscarriage after IVF–ET. But, the incidence of endometritis was not stated in their abstract. Micro polyposis was reported to be associated with endometritis in another study, too. [65]

The novel technique of endometrial dying was not intended to be the sole procedure for diagnosis, but an adjunctive method to target the biopsy to correct site for an accurate diagnosis.

It was shown that local endometrial defects can cause miscarriage. [66] Removal of local endometrial defects may lead to replacement by healthy cells and receptivity is restored, eventually successful implantation is achieved. This theory is supported by the study of Barash et al. [67] who showed that local injury to the endometrium significantly increased the pregnancy rate in IVF.

The presences of uterine pathology was documented in 10–62% of women with infertility,[68] in 10–60% of women undergoing pretreatment assessment for IVF–ET,[69,70] and in 19–50% of women who failed to conceive following assisted reproductive technologies.[71] After exclusion of cases of abnormal uterine cavity by HSG and/or TVS, the researchers found that 45% of patients undergoing ART had abnormal endometrial findings on hysteroscopy, so hysteroscopy is highly valuable and should be applied to all such patients especially with failed ICSI but yet without sufficient evidence.[71]

Fatemi et al, [72] and Karayalcin et al, [73] demonstrated that uterine cavity abnormalities in their study population were low (11% for the 1st one and 22.9% for the 2nd one), while Gaviño-Gaviño et al,[74] found very high incidence of uterine pathology in their studies (64%) with repeated IVF failure.

Despite these drawbacks, many IVF clinics were reluctant in use of hysteroscopy for uterine cavity evaluation. As hysteroscopy has traditionally in the past required general anesthesia, careful surveillance of fluid status to minimize complications of hyponatremia and fluid overload, physician experience which need a learning curve and high cost. However, now office hysteroscopy with small diameter sheath (3–5 mm), using the non-touch (vaginoscopic) technique without dilatation of the cervix (and consequently no anesthesia) with low pain score during or after the procedures. Saline was used as a distention making use of office hysteroscopy in IVF center easy, extremely safe, with no patients monitoring or laboratory studies for fluid overload.[75] In addition to the previous advantages, office-based operative hysteroscopy has been shown to be easily performed with excellent surgical results.[44]

Pathologic abnormalities were found in a significant number of patients and an improvement in clinical pregnancy rates in patients who have office hysteroscopy prior IVF or ICSI, particularly on those were endometrial pathology was found and corrected was obtained. While in the other hand Gaviño-Gaviño et al, [74] and Lorusso et al, [76] stated that hysteroscopy also seems to be the best way to repair the uterine cavity when pathological conditions are present. Demirol and Gurgan [9] in their randomized controlled trial although they found a significant difference in the clinical pregnancy rates ,They concluded that patients with normal HSG but recurrent IVF–embryo transfer failure should be evaluated prior to commencing IVF–embryo transfer cycle to improve the clinical pregnancy rate. In the same way Bozdag et al, [77] in their review found that there is paucity of data on the role of hysteroscopy in failed IVF cycles and in the available two randomized controlled trials, pregnancy rates appear to be increased when hysteroscopy is performed.

El-Toukhy et al, [78] in their meta-analysis, they found an evidence of benefit from outpatient hysteroscopy in improving the pregnancy rate in the subsequent IVF cycle.

The evidence from randomized trials was consistent with that from non-randomized controlled studies and future robust randomized trials comparing outpatient hysteroscopy or mini-hysteroscopy with no intervention before IVF treatment would be a useful addition to further guide clinical practice.[78]

Accumulating data from other studies and the present study proved that hysteroscopy is the gold standard for the investigation of uterine cavity. It is a safe test for the direct and accurate diagnosis of intrauterine abnormalities. It permits direct visualization of the uterine cavity, revealing the nature, location, shape, size and vascular pattern of any uterine cavity abnormalities. It also allows a directed biopsy and therapeutic intervention for the treatment of any pathology.

Chronic endometritis has been related to infertility and recurrent abortion. [8] Some authors reported that observation of micropolyps on micro hysteroscopy that was associated with 94% probability of chronic endometritis and considered it a reliable diagnostic sign.

Marconi et al. [26, 79] and Kucuk and Safali [80] reported that the endometrium is not an absorptive epithelium in normal circumstances and that structural damage of the cells allows passage of methylene blue dye into the cells. Dark blue staining represents structural damaged areas due to endometritis. [79, 80]

Different studies implies endometrial dyeing with methylene blue dye (inspired from gastroenterologists' approach) to improve the diagnostic value and to provide guided biopsy to diagnose chronic endometritis during hysteroscopy in the absence of macroscopic abnormalities. They showed a significant incidence for diagnosis of chronic endometritis higher than that in the study performed by La Sala et al, [63] where the incidence was 2%.

In our study we had in the study group 17 Patients suffering from endometritis and 8 normal patients while in the control group we had 21 normal Patients and only 4 suffering from endometritis which shows a significant increase in the incidence of endometritis among the study group which is 68% while it is only 16% in our control group.

The technique of endometrial dyeing was not intended to be the sole procedure for diagnosis, but an adjunctive method to target the biopsy to correct site for an acurate diagnosis. Hysteroscopy, with its current abilities, can never replace pathologist's eye, pathology is still the gold standard. Broader studies and/or a new vital dye can improve the diagnostic accuracy of Chromohystroscopy, [80] endometrial dyeing with methylene blue at hysteroscopy improves the detection of chronic endometritis.

SUMMARY

Hysteroscopy is the gold standard for the investigation of uterine cavity. It is a safe test for the direct and accurate diagnosis of intrauterine abnormalities. It permits direct visualization of the uterine cavity, revealing the nature, location, shape, size and vascular pattern of any uterine cavity abnormalities. And is the best technique for identifying macroscopic endometrial pathologies, it also allows a directed biopsy and therapeutic intervention for the treatment of any pathology.

This study is inspired from gastroenterologists' approach to enhance subtle mucosal changes. Conventional hysteroscopy has its limitation in evaluating endometrial integrity.

The aim of this study was to evaluate the uterine cavity after failed trial of ICSI, and detect any signs of endometritis.

This study was conducted on 25 infertile female patients from El-Shatby Maternity University Hospital that had failed trials of ICSI, and another 25 control cases from patients seeking for fertility treatment with no previous history of ICSI and with no history of anatomic uterine abnormalities.

Chromohystroscopy was performed for all cases for detection of signs of endometritis.

The results can be summarized as follows:

- The age of patients ranged from 20-38 years old.
- The day, procedure was conducted in ranged from 5^{th} -15^{th} day of menstrual cycle.
- Ultrasound findings were normal in 84% of the cases and 88% of the control group.
- There were non-significant differences between both groups as regard the presence of septum while P=0.762.
- There were non-significant differences between both groups as regard the presence of polypi while P=0.247.
- There was statistically significant differences between the two groups as P=0.000 regarding the presence of signs of endometritis.

CONCLUSION

- Chromohystroscopy is a safe and easy procedure which can help to improve the efficacy of hysteroscopy in diagnosing cases of endometritis and to increase the success rate of IVF and ICSI. It is highly recommended to be applied to cases of repeated ICSI or IVF failure.

RECOMMENDATION

- Adding methylene blue dye to conventional office hysteroscope (Chromohystroscopy) for endometrial dyeing, improve its diagnostic sensitivity to chronic endometritis in the absence of macroscopic abnormalities.
- Future randomized controlled trials are warranted to determine the proper timing, indications and technique of Chromohystroscopy.

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الملخص العربى

عدم صلاحية بطانة الرحم لزرع الأجنة يعد من أهم عوامل الفشل المتكررلعمليات الحقن المجهرى، علي الرغم من وجود الكثير من الوسائل التشخيصية لتقييم كفاءه بطانة الرحم مثل الأشعة التليفزيونية بأنواعها ومنها الفحص بعد حقن محلول الملح عن طريق المهبل،أو أشعة الصبغة(هستوسلبنجوجرام)،أو أشعة الرنين المغناطيسى ،أو عن طريق المنظار الرحمي، لكن إذا كان الخلل علي المستوي الخلوى والناتج في العديد من حالاته عن الإلتهاب المزمن لبطانة الرحم فإن أخذ عينه من بطانة الرحم وتحليلها هستوباثولوجيا يعد من أدق الوسائل التشخيصية المتاحة حاليا.

وقد جربت العديد من الاستراتيجيات التشخيصية لمحاولة الوصول إلي تشخيص الإلتهاب المزمن لبطانة الرحم بأقل الوسائل نفاذية قدر الإمكان ،كان منها أن يتم تحديد المكان المناسب لأخذ العينة وذلك بإستخدام المنظار الرحمي و الذي يعد في الوقت الحالي من أهم الوسائل المستخدمة لتقييم بطانة الرحم وخصوصا أن معظم الدراسات الحديثة توصي بضرورة إستخدام المنظار الرحمي بشكل روتيني قبل إجراء عمليات التلقيح الصناعي والحقن المجهري.

كان الهدف من هذه الدراسة محاوله زيادة كفاءه المنظار الرحمي في تشخيص الإلتهاب المزمن لبطانة الرحم وذلك بإستخدام صبغة الميثيلين الأزرق والذي سبق أن أثبتت كفاءته في جراحات مناظيرالجهاز الهضمى وقدرته علي الإتحاد مع الخلايا التالفه بسبب الإلتهابات المزمنة وبالتالي يمكن أن ترى تلك الخلايا بالعين المجردة أثناء التقييم الروتيني لبطانة الرحم بإستخدام المنظار الرحمي.

أجريت هذه الدراسة على ٥٠ مرضى إناث مصابين بالعقم من مستشفى الشاطبي الجامعى، تم تقسيمهم إلي مجموعتين إحداهما كانت الحالات تعرضوا سابقا لفشل عملية الحقن المجهري. تم إجراء عملية المنظار الرحمي لجميع الحالات ومن ثم البحث عن وجود دلالات الإلتهاب المزمن لبطانة الرحم.

ويمكن تلخيص النتائج على النحو التالي:

- تراوح عمر المرضى بين ٢٠-٣٨ عاماً.
- كانت نسبة العقم الأولي بين الحالات ٨٨%، وتراوحت مده العقم مابين ١-١٥ عام بمتوسط ٦.٦+\-٣.٢ في المجموعة التي تعرضت لفشل عملية الحقن المجهري ،ومابين ١-١٢ عام بمتوسط ٤.٥+\-٣.٠٢٤ مع وجود فارق ذا دلالة إحصائية بين المجموعتين.
- كانت أهم أسباب العقم في الحالات هو وجود سبب ذكري في(٢٤%و٣٦%)بين المجموعتين.
- كان متوسط فشل عمليات الحقن المجهري ١.٤٤+\-٠.٦٥١ عملية ومتوسط عدد الأجنة التي تم إرجاعها ٣.٤٤+\-٠.٩١٧ جنين.
- تم إجراء الفحص ما بين اليوم٥-١٥ و اليوم٥-١٤ من اليوم الأول للطمث مابين المجموعتين مع عدم وجود فارق ذا دلالة إحصائية بينهما.
- كانت نتيجة فحص الحالات بواسطة الأشعة التليفزيونية طبيعية في(٨٤%و٨٨%)بين المجموعتين.
- فتحات أنابيب فالوب داخل تجويف الرحم كانت طبيعية في(٦٨%و٩٢%)بين المجموعتين.
- تجويف الرحم طبيعي بنسبه٩٢%،وكذلك الشكل الظاهري لبطانة الرحم طبيعي بنسبة(٨٤%و٩٢%)بين المجموعتين،مع وجود زياده في حجم بطانة الرحم بنسبه٨%.
- عدم وجود فارق ذا دلالة احصائية بين المجموعتين فيما يتعلق بوجود حاجز رحمي بنسبه(٢٨%و٣٦%)بينهما.
- كذلك عدم وجود فارق ذا دلالة احصائية بين الحالات فيما يتعلق بوجود لحميات وزوائد ببطانة الرحم وذلك بنسبه(٨%و٢٤%)بين المجموعتين.
- كانت نسبه سهوله إدخال المنظار الرحمي بين المجموعتين(٧٢%و٨٠%) ولم يتم اللجوء إلي توسيع عنق الرحم بإستخدام المجس الرحمي إلا في٤%من الحالات فقط.
- وجدت دلالات الإلتهاب المزمن لبطانة الرحم وذلك بعد حقن صبغة الميثيلين الأزرق بنسبه (٦٨%و١٦%)بينها مع وجود فارق ذا دلالة احصائية بين المجموعتين.

دور المنظار الرحمي بإستخدام المثيلين الأزرق بعد الفشل المتكرر لحالات الحقن المجهري

رسالة علمية

مقدمة لكلية الطب – جامعة الاسكندرية
إيفاءاً جزئياً لشروط الحصول على درجة

الماجستير فى التوليد وأمراض النساء

مقدمة من

نهى صبحي محمود عابدين

بكالوريوس الطب والجراحة – جامعة الإسكندرية

كلية الطب
جامعة الإسكندرية
٢٠١٥

دورالمنظار الرحمي بإستخدام المثيلين الأزرق بعد الفشل المتكرر لحالات الحقن المجهري

مقدمة من

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للحصول على درجة

الماجستير فى التوليد وأمراض النساء

لجنة المناقشة والحكم على الرسالة	**موافقون**
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أ.د/ عماد الدين عبد الرحمن خليفة أستاذ التوليد و أمراض النساء كلية الطب جامعة الإسكندرية	.....
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