INTRODUCTION

Infertility affects about 10-15% of reproductive age couples ***(Boivin et al., 2007)***. Experience has shown that majority of pelvic pathology in infertile women is frequently not well appreciated by routine pelvic examinations and the usual diagnostic procedures ***(Miller et al., 1999)***.

Visualizing the uterine cavity and identifying the possible pathology has made hysteroscopy an important tool in infertility evaluation ***(Nayak et al., 2013)***. The possibility to perform hysteroscopy using no anesthetic or local anesthesia allows use of outpatient settings and speeds recovery ***(Stefanscu and Marinescu, 2012)***.

Hysteroscopy is performed for evaluation or treatment of different pathologies of the endometrial cavity, tubal ostia, or endocervical canal for diagnosis alone or for diagnosis and treatment in the same operative setting ***(Koskas et al., 2010)***.

Treatment for some abnormalities seen during hysteroscopy are suspected beneficial in infertile women. These are uterine myomas, congenital uterine malformations and intrauterine adhesions ***(Sanders, 2006)***.

The impact of fibroids on fertility remains controversial ***(Pritts et al., 2009)***. Fibroids are believed to interfere with sperm

migration, ovum transport and embryo implantation ***(Richards et al., 1998)***. This may be caused by altered contours of the uterine cavity resulting in altered mechanical pressure or abnormal uterine contractility ***(Oliveira et al., 2004)***.

Hysteroscopic septoplasty is frequently performed in patients with recurrent miscarriage because a uterine septum is associated with an adverse pregnancy outcome ***(Homer et al., 2000)***. The precise mechanism through which a uterine septum may cause subfertility is not fully understood ***(Fedele et al., 1996)***. It is biologically plausible that the endometrium of the septum may be unsuitable for blastocyst implantation ***(Grimbizis et al., 1998)***. The association between septate uterus and endometriosis may explain the subfertility of at least some patients with septate uterus but requires further research ***(Nawroth et al., 2006)***.

Intrauterine adhesions frequently occur as a result of trauma to the basal layer of endometrium following pregnancy-related curettage such as incomplete abortion, postpartum hemorrhage, and elective abortion ***(Robinson et al., 2008)***. Basal layer damage leads to partial or complete obliteration of the uterine cavity with surface deficiencies of the endometrium by fibrous bridges between the uterine walls ***(March, 2011)***. Patients with intrauterine adhesions usually present with menstrual disturbances such as amenorrhea or hypomenorrhea,

infertility, or recurrent pregnancy loss ***(Kodaman and Arici, 2007)***.

The position of hysteroscopy in current fertility practice is under debate ***(Shushan and Rojansky, 1999)***. Although there are many randomized controlled trials on technical feasibility and patient compliance demonstrating that the procedure is well tolerated, there is no consensus on the effectiveness of hysteroscopy in improving the prognosis of subfertile women ***(Kabli and Tulandi, 2008)***. Many studies describe the incidence of abnormal findings with hysteroscopy in infertile women or prior to IVF, but none give the proportion of these women who could benefit from an adapted treatment based on hysteroscopic findings. It is difficult to draw direct connections between hysteroscopic findings and benefits from a specific treatment based on these findings ***(Koskas et al., 2010)***.

AIM OF THE WORK

The aim of this study is to assess the reproductive outcome after operative hysteroscopy in patients with history of infertility or recurrent miscarriage at Ain Shams University Maternity hospital; early cancer detection unit over a period of 6 years (2007-2013).

INFERTILITY

Infertility is a disease, defined by the failure to achieve a successful pregnancy after 12 months or more of appropriate, timed unprotected intercourse or therapeutic donor insemination ***(Practice Committee of the American Society for Reproductive Medicine, 2013)***.

Epidemiology

About 15% of couples do not achieve pregnancy within 1 year; almost 50% of them do so spontaneously in the second year of unprotected intercourse, and another 14% in the third year, ultimately, <5% remain childless ***(Te Velde and Pearson, 2002)***. No cause of infertility can be found using routine diagnostic work-up in 10–15% of couples ***(Jungwirth et al., 2012)***.

Causes of infertility

Ovulatory Factor

Disorders of ovulation are the most common cause of primary infertility and account for about 30% to 40% of all cases of female infertility ***(Burney et al., 2007)***. It is identified in approximately 15% of all infertile couples and accounts for up to 40% of infertility in women ***(Mosher and Pratt, 1991, ASRM, 2012)***.

Tubal Factors

Tubal factors are the most common cause for secondary infertility and account for 30% to 40% of cases of female infertility including damage or obstruction of the fallopian tubes and usually are associated with previous pelvic inflammatory disease or previous pelvic or tubal surgery. Tubal disease is an important cause of infertility and should be specifically excluded ***(Practice Committee of the American Society for Reproductive Medicine, 2012)***.

Infectious Factors

The relationship between subclinical infection and fertility has received considerable attention with particular interest has focused on two potential pathogens: Chlamydia trachomatis and Mycoplasma species ***(Burney et al., 2007)***.

Uterine Factors

Abnormalities of uterine anatomy or function are relatively uncommon causes of infertility in women, but should be excluded ***(The Practice Committee of the American Society for Reproductive Medicine, 2012)***.

Uterine pathologies are the cause of infertility in as many as 15% of couples seeking treatment and are diagnosed in as many as 50% of infertile patients ***(Mooney and Milki, 2003)***. For patients undergoing in vitro fertilization, lower pregnancy

rates are observed in the presence of uterine cavity anomalies ***(Kupesic et al., 2002)***. The correction of these anomalies has been associated with improved pregnancy rates ***(Mooney and Milki, 2003)***.

Cervical and Immunologic Factors

Abnormalities of cervical mucus production or sperm/mucus interaction rarely are the sole or principal cause of infertility ***(The Practice Committee of the American Society for Reproductive Medicine, 2012)***.

Antisperm Antibodies

The mechanisms by which antisperm antibodies might adversely affect fertility remain a subject of debate and ongoing investigation ***(Falcone et al., 2000)***.

Peritoneal factors

Peritoneal factors such as endometriosis and pelvic or adnexal adhesions may cause or contribute to infertility. History and/or physical examination findings may raise suspicion but rarely are sufficient for diagnosis ***(The Practice Committee of the American Society for Reproductive Medicine, 2012)***.

Endometriosis

Endometriosis is characterized by the presence of endometrial like glands and stroma outside the uterine cavity ***(Giudice and Kao, 2004)***. It is estimated that 5% to 15% of women of reproductive age have endometriosis ***(Abrao et al., 2013)***. Dysmenorrhea, deep dyspareunia, chronic pelvic pain, abnormal uterine bleeding, intestinal disorders, and infertility are the main symptoms associated with endometriosis ***(Giudice and Kao, 2004)***. The prevalence of endometriosis is higher among women with chronic pelvic pain or infertility than among women without these symptoms (40%–60% vs 20%–30%) ***(Ajossa et al., 1994)***. The gold standard for diagnosis is direct visualization of endometriosis by laparoscopy, which can be confirmed by histologic analysis ***(Abrao et al., 2003)***.

Anatomical causes

Anatomical causes of female infertility include tuboperitoneal abnormalities, endometriosis, myomas distorting the uterine cavity, congenital uterine anomalies, and other, less frequent anomalies of the reproductive tract ***(Abrao et al., 2013)***.

Systemic Illness

In general, any severe systemic illness, such as renal failure, liver failure, or metastatic cancer, can lead to disruption of the hypothalamic–pituitary–ovarian axis and cause

infertility. The association of antiphospholipid antibodies, particularly anticardiolipin antibodies and the lupus anticoagulant, with recurrent pregnancy loss led to the investigation of a role for these antibodies in infertility and it was reported that these antibodies are more prevalent in the infertility population ***(Roussev et al., 1996)***. However, the presence of antiphospholipid antibodies has not been found to adversely affect IVF outcomes in a prospective study ***(Chilcott et al., 2000)*** or in a meta–analysis of seven studies ***(Hornstein et al., 2000)***.

Unexplained Infertility

Unexplained infertility is present in approximately 10% of couples, with no easily identifiable cause for infertility ***(ASRM, 2012)***.

Male factor

A male contribution to infertility is found in 45–50% of infertile couples ***(Jungwirth et al., 2012)***.

UTERINE FIBROID

Uterine fibroids (also known as leiomyomas or myomas) are the commonest benign uterine tumors ***(Wallach and Vlahos, 2004; Ryan et al., 2005)***. It disrupts the functions of the uterus causing excessive uterine bleeding, anemia, defective implantation of an embryo, recurrent pregnancy loss, preterm labor, obstruction of labor, pelvic discomfort, and urinary incontinence and may mimic or mask malignant tumors ***(Baird et al., 2003; Catherino et al., 2011)***.

They are monoclonal tumors of the uterine smooth muscle cells and consist of large amounts of extracellular matrix that contain collagen, fibronectin, and proteoglycan ***(Parker, 2007; Sankaran and Manyonda, 2008)***.

Epidemiology and etiology

Race and age

The incidence of uterine fibroids by age 35 was 60% among African-American women, increasing to 80% by age 50, whereas it was 40% and 70% respectively in Caucasian women ***(Day Baird et al., 2003)***. The cumulative incidence increases with age, but the rate of increase slows at older ages suggesting that the older premenopausal uterus is less susceptible to fibroid development ***(Laughlin et al., 2010)***.

Early menarche

Most of the older studies had reported an increased risk of fibroids with earlier age of menarche and later data confirm these findings ***(Schwartz, 2001)***.

Parity and pregnancy

Parity has been inversely associated with a risk of fibroid development ***(Baird and Dunson, 2003; Parazzini, 2006)***. Although a direct protective effect of pregnancy has been demonstrated, little is known of the mechanism ***(Baird and Dunson, 2003; Burbank, 2004)***. There have been some suggestions that during postpartum uterine remodeling, there could be selective apoptosis of small lesions ***(Baird and Dunson, 2003)***. Ischemia during parturition has also been proposed as a mechanism ***(Burbank, 2004)***. Thus, it may be implied that fibroid tissue could be highly susceptible to ischemia during both parturition and remodeling ***(Laughlin et al., 2010)***.

Alcohol and Caffeine intake

Current drinkers had been shown to have significantly higher risks than women who had never consumed alcohol and there appears to be a dose response for both duration of alcohol consumption and number of drinks per day ***(Wise et al., 2004)***. With regards to caffeine, the highest categories of caffeinated coffee and caffeine intake were both associated with increased fibroid risk ***(Laughlin et al., 2010)***.

Pathogenesis

Cellular origins

The cellular origin of uterine fibroids remains unknown. Several observations support the theory that each fibroid originates from the transformation of a single somatic stem cell of the myometrium under the influence of ovarian hormones ***(Arango et al., 2005)***. Genetic studies suggest that fibroids are monoclonal tumors ***(Szotek et al., 2007)***.

Human uterine fibroid tissue contains fewer stem cells than normal myometrium ***(Chang et al., 2010)***. However, stem cells derived from fibroid tissue carry mediator complex subunit 12 (MED12) mutations, which suggests that at least one genetic hit initially transforms a myometrial stem cell, which subsequently interacts with the surrounding myometrial tissue to give rise to a fibroid tumor ***(Ono et al., 2012)***.

In vivo experimental models reveal that the growth of human fibroid tumors that are dependent on estrogen and progesterone requires the presence of multipotent somatic stem cells; as compared with the main fibroid-cell population or with normal myometrial cells, fibroid stem cells express remarkably low levels of receptors for estrogen and progesterone ***(Mas et al., 2012)***.

Both myometrial and fibroid multipotent somatic stem cells lack markers for smooth-muscle cells, and in addition to their differentiation into smooth-muscle cells in vivo, they can be induced to differentiate into cells with adipogenic and osteogenic lineages ***(Ono et al., 2007)***.

Overall, total β-catenin levels in the myometrium and fibroid tissue are similar, but because the key effects of β-catenin are probably manifested at the level of stem cells, which make up a very small fraction of fibroid or myometrial tissue, differences in β-catenin levels would not be detected when whole fibroid and myometrial tissues are compared ***(Tai et al., 2003)***.

Fibroid-tissue–derived transforming growth factor β3 (TGF-β3) may also suppress the expression of local anticoagulant factors in adjacent endometrial cells, which results in the prolonged menstrual bleeding associated with fibroids, these observations indicate that there are critical interactions among activated WNT–β-catenin and TGF-β pathways, estrogen and progesterone, and stem-cell renewal and that these interactions ultimately give rise to the clonal formation of uterine fibroid tumors ***(Sinclair et al., 2011)***.

Genetic Mechanism Involved in Fibroids Etiology

The high-mobility group AT-hook 2 (HMGA2) gene was found in translocation 12:14, the most common cytogenetic abnormality that occurs in about 20% of chromosomally abnormal lesions, this gene encodes a high mobility group

DNA binding protein and embryonic proliferation modulator ***(Hodge et al., 2009)***. The HMGA2 gene is expressed in uterine leiomyoma and in other human tissues with a proliferative phenotype, such as fetal tissues, lung, and kidney, but not in the normal myometrium ***(Gattas et al., 1999)***. The antagonism of HMGA2 in vitro was found to decrease leiomyoma cell proliferation ***(Markowski et al., 2011)***.

Cha and colleagues (2011) genotyped 1607 individuals with uterine fibroids and identified 3 susceptibility loci associated with uterine fibroids and chromosome 10q24.33 seems to have the best association with leiomyomas.

Another gene product located in the region is A-kinase anchor protein-13 (AKAP13), associated with cytoskeletal filaments. Related mutations could alter the regulation of extracellular matrix deposition and, consequently, of the fibrotic phenotype of the leiomyoma ***(Rogers et al., 2008)***.

Several studies described that 70% of fibroids contained a series of mutations in a transcriptional regulator MED12 ***(Makinen et al., 2011; Je et al., 2012)***. ***Perot and associates (2012)*** reported that MED12 is frequently mutated in typical leiomyomas (66.6%) and also that mutations are not restricted to benign tumors since highly aggressive leiomyosarcomas were also mutated. However, no mutations were detected in non uterine leiomyosarcomas, this affirmed that MED12 seems to be specific to uterine smooth muscle tumors ***(Perot et al., 2012)***.

Micro RNA

Studies directed at identifying epigenetic abnormalities in fibroids demonstrated abnormally hypomethylated estrogen receptor (ER) α ***(Asada et al., 2008)***. Follow-up studies demonstrated globally abnormal genomic methylation in leiomyomas compared to myometrium, implicating possible epigenetic contributions to genetic susceptibility of leiomyoma development ***(Yamagata et al., 2009)***.

Estrogen

A large body of experimental data and circumstantial evidence suggests that estrogen stimulates the growth of uterine fibroids through ER α ***(Marsh and Bulun, 2006)***. The primary roles of estrogen and ER-α in fibroid growth are permissive in that they enable tissue to respond to progesterone by inducing the expression of progesterone receptor ***(Ishikawa et al., 2010)***. Fibroid tissue is exposed to ovarian estrogen and to estrogen produced locally through the aromatase activity in fibroid cells ***(Bulun et al., 1994)***.

Progesterone

Progesterone interacts with its receptors progesterone receptor (PR)-A and PR-B, playing a key role in myometrial and leiomyoma biologies ***(Maruo et al., 2010; Kimand and Sefton, 2011)***. Several studies have stressed that PR content and mRNA levels are higher in leiomyoma than those in