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MINI REVIEW

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Ovarian diseases leading to female infertility: a mini-review

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ABSTRACT

Infertility has become a significant global health issue impacting people's lives. Among the multiple factors, including age, lifestyle, environment, ovulatory dysfunctions, etc., the current mini-review focuses on major ovarian disorders, including polycystic ovarian syndrome (PCOS), endometriosis, pelvic adhesion, uterine fibrosis, tubal factor, and hyperprolactinemia, which are strongly associated with female infertility. This mini-review showcased the cause, symptoms, and treatment of these ovulatory dysfunctions, which might help relieve infertility, and patients would have clinical benefits by following proper treatment protocol.

KEYWORDS

Infertility; Ovarian obstruction; Polycystic ovarian syndrome; Endometriosis; Fallopian tubal blockage; Uterine fibrosis

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Introduction

Female infertility has become the most common and predominant issue at both social and economic stages due to the modern lifestyle, which is mostly reported in developed and developing countries in the present scenario [1-3]. Approximately 80 million people were affected with infertility worldwide in 2002, and the increased cases led to the term "the civilization disease of the 21st century" by the World Health Organization (WHO) [3,4]. Advances in assisted reproductive technology (ART) have been unable to minimize the increasing rate of infertility and make it a global public health concern [5]. It can damage the patients' psychological, physical, mental, spiritual, and medical conditions, leading to chronic health conditions [6]. According to WHO, 37% of infertile cases are due to female infertility, whereas 35% include both male and female [7].

Infertility is multifactorial, including the most common causes of ovulatory dysfunction and tubal diseases [7,8]. About 25% of infertility diagnoses are due to ovulatory disorders, while 70% of anovulation is because of polycystic ovarian syndrome (PCOS) [8]. Other causative factors include endometriosis (15%), pelvic adhesions (12%), tubal blockage (11%), uterine abnormalities (11%), and hyperprolactinemia (7%) [7]. However, a female's age, lifestyle, and environment are also considered as contributing factors for infertility. Although various advanced treatment options like laparoscopy surgical implications, in vitro fertilization (IVF), and clinical medications and therapies have improved fertilization in women, the varied ages and symptoms pose challenges to diagnose and manage for each female [9]. This mini-review discussed the six most commonly associated ovarian disorders in female infertility, which will provide beneficial insights on causes, symptoms, and available treatment options to overcome infertility in the future as per the clinician's advice.

Ovarian Diseases Leading to Female Infertility

Polycystic ovary syndrome (PCOS)

Polycystic Ovary Syndrome (PCOS) is considered the most well-known endocrine and reproductive disorder affecting the reproductive capacity of females and leading to 70-80% of infertility cases in women [10-12]. It represented the major cause for hyperandrogenism and oligo-anovulation during a female's reproductive age [11], in which anovulation or ovulatory dysfunction is the key cause of infertility. Defective endometrium-like oocyte alterations, embryo quality, abnormal trophoblast invasion, and placentation significantly increase complicated pregnancies, miscarriages, and failed implantation [12,13]. The signs and symptoms may vary, but the three most commonly associated factors with PCOS are irregular ovulation, enhanced androgen levels, and cystic ovaries. Additional symptoms include irregular menstrual cycles, pelvic pain, hirsutism, alopecia, acne, acanthosis nigricans, skin tags, etc., which may be noticed in PCOS cases [14]. To optimize the treatment methods in PCOS cases, multiple approaches, such as lifestyle changes and weight loss, have been considered the first-line of treatment for women with infertility. Likely, the second-line treatments include exogenous gonadotropins or laparoscopic ovarian drilling, which has benefitted approximately 50% of cases, whereas the third-line treatment is considered IVF [11,14]. According to the reports, Clomiphera has shown the best results [14]. However, the appropriate treatment option should be chosen based on the patient's age, level of anxiety, previous treatment record, and other clinical factors [11].

Endometriosis

Endometriosis is a common chronic uterine inflammatory disease observed in females during their reproductive age that alters the pelvic anatomy and is known to cause frequent infertility [15,16]. It can cause infertility when combined with

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other fertility-reducing factors [16]. Endometriosis occurs in 10-15% of the reproductive-aged, i.e., <35-year-old female population with a 35-50% increased risk of pain and infertility [16,17], whereas 25-50% of endometriotic women are fertile [15]. However, the association between endometriosis and infertility is controversial even after years of research. Still, the fecundity rate in females during endometriosis is lower, i.e., 2-10%, than the normal fertile women, i.e., 15-20%. According to the IVF analysis, poor ovarian reserve, implantation with low oocyte and embryo quality are observed in the endometriotic women [17]. In addition to infertility, patients with endometriosis complain regarding associated symptoms, including pelvic pain, nausea, lethargy, chronic fatigue, hemoptysis, thoracic pain, acute abdomen, bladder/bowel pain, dysmenorrhea, and dyspareunia [15,17]. These symptoms can damage pelvic anatomy, causing abnormalities or complications in endocrine and ovulatory organs. It may also alter the immunity of peritoneal, hormonal, and cell-mediated functions, which affect the patient's physical, mental, and social life [15]. Laparoscopy for uterine nerve ablation, peritoneal endometriosis excision, ovarian surgery, deep infiltrating endometriosis excision, hysterectomy, adhesiolysis, presacral neurectomy are surgical options for endometriosis patients. Clinical medications such as progestins, combined oral contraceptives pills, non-steroid anti-inflammatory drugs (NSAIDs), gonadotropin-releasing hormones (GnRH), selective estrogen receptor modulators (SERM), vitamins etc., are prescribed for endometriosis patients. Some complementary therapies like acupuncture and electrotherapy have also been followed [18].

Uterine fibrosis

Uterine fibroids or uterine leiomyomas are smooth muscle tumors in the uterus with highly heterogenous pathophysiology, size, location, and clinical symptoms affecting the females of reproductive age. Genetic and epigenetic factors like age, race, ethnicity, family history, body mass index, exposure to toxins, and vitamin D deficiency induce uterine fibroid development. Fibroids are one of the sole causes of 2-3% of women's infertility and may affect implantation by mechanisms like increased uterine contractility, deranged cytokine profile, abnormal vascularization, and chronic inflammation. The fibroids are divided into four types: intramural, submucosal, subserosal, and cervical. According to previous analysis, women with intramural fibroids may have significantly poor reproductive outcomes, such as lower pregnancy rates, live birth rates, and poor implantation than healthy women. In the same vein, women with submucosal fibroids may face a high risk of infertility and lower delivery and implantation rates. Meanwhile, subserosal fibroids do not affect fertility, pregnancy, implantation, abortion, and live birth rates as it is similar to normal patients (without fibroids). The symptoms of uterine fibroids may vary according to the size and location of the fibroids. The most common symptoms are heavy menstrual bleeding (hypermenorrhea) and painful periods or dysmenorrhea. Lower back and pelvic pain may also be associated with infertility, recurrent pregnancy loss, and adverse obstetric outcomes. Meanwhile, some women do not feel any symptoms of uterine fibroids. The treatment options for fibrosis include surgeries like hysteroscopic myomectomy for submucosal fibroids, laparoscopy or laparotomy with faster recovery and low postoperative pain, and blood loss for subserosal fibroids. In intramural fibroid cases, surgery may be done carefully as it may affect the uterus wall. Available medications for fibroids include gonadotropin-releasing hormone (GnRH), antagonists, anti-progestins, anti-fibrinolytic agents, and non-steroidal anti-inflammatory agents. Interventional radiology and IVF also help reduce the size of fibroids, control abnormal uterine bleeding, and treat the fibroids [2].

Fallopian tube obstruction

The fallopian tubes are the paired connectors of the ovary and the uterus and are essential for fertilization. Tubal obstruction is a basic cause of tubal factor infertility, which is induced by the inflamed reproductive system; in addition to this, endometriosis, congenital abnormalities, other pathologic factors like tubal, uterine, and pelvic infections, fallopian tube surgical injury, and tubal sperm, are also involved in fallopian tubal blockage and affect tubal patency [1,19]. A blocked fallopian tube leads to 30-40% of female infertility, whereas approximately 10-25% of women experience proximal fallopian tube obstruction [1]. The usual symptoms of fallopian tube obstruction are fever, abdominal pain, and vaginal bleeding. However, these symptoms have been classified as grade 1 (symptoms for <4 days), grade 2 (4-7 days), grade 3 (>7 days), grade 4 (4-7 days after drug treatment), and grade 5 (severe abdominal pain with fever for more than 7 days after drug therapy) as per the severity of the symptoms [19]. Tubal factors have been diagnosed with hysterosalpingography, insufflation test, laparoscopic chromopertubation, sonohysterosalpingography, and falloscopy. Among these diagnostic approaches, hysterosalpingography is a primary diagnosis method. The treatment methods include tuboscopy, IVF, and tubal cannulation under guided laparoscopy. Laparoscopy is more prominent for a detailed examination of infertility caused by pelvis-related diseases [1].

Pelvic adhesion

Pelvic adhesion is reported as the foremost public health problem [20], which usually occurs from former pelvic surgeries and pelvic infections. Endometriosis and intrauterine contraceptive complications can also lead to pelvic adhesions [21,22]. It is accountable for 15-20% of female infertility [22,23] and is associated with tubal occlusion, endometriosis, and other factors [23]. It is associated with symptoms of chronic pelvic pain, small bowel obstructions, and infertility [22]. The considered gold standard treatment for pelvic adhesion is laparoscopy. Meanwhile, transvaginal hydro-laparoscopy, also called fertiloscopy, has been incorporated as a safer and less expensive diagnostic method for pelvic adhesions. Recently, ozone has been introduced as a new therapeutic agent for infertility, as this therapy could reduce the rate of pelvic adhesions and induce fertility rate in females [22].

Hyperprolactinemia

Hyperprolactinemia (Hyper-PRL) is one of the typical endocrine disorders and an eminent cause of female infertility due to a preeminent level of prolactin, which may reduce the secretion of gonadotropins (GnRH) (hypogonadotropic hypogonadism), follicle-stimulating hormone (FSH) [24-26], involved in anovulatory cycles, sex hormone imbalance [27].

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Pituitary adenoma, intracranial tumors, prolactin stimulants, and pharmacological conditions cause hyper-PRL, which affects 8.7/100000 women annually [24]. Increased prolactin level is highly associated with anovulation, oligomenorrhea, amenorrhea, and galactorrhea [24,25]. Morphological changes of the follicles [24], functional alteration of the endometrium, altered implantation [26], menstrual disorders, sexual dysfunction, and reduced bone mineral density significantly induce infertility [28]. To treat or manage hyperprolactinemia, dopamine receptor agonists have been used as the primary therapy, which helps to restore the normal prolactin level and gonadotropin functions [24]. Still, discontinuation occurs in 10-20% of patients due to the intolerance effect of dopamine agonists [25].

Conclusions

The accurate and effective therapeutic diagnosis of associated causative factors of ovarian disorders may reduce the increased prevalence of female infertility. The association of discussed ovarian disease factors with increased infertility should be potentially studied to facilitate solutions for infertile females.

Disclosure statement

No potential conflict of interest was reported by the authors.

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