



The Potential Relationship Between Different Human Female Reproductive Disorders and Sperm Quality in Female Genital Tract

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Abstract

Spermatozoa should travel throughout the female reproductive tract to reach its ultimate goal, fertilization of the oocyte. At the ejaculation moment, millions of sperm within a few milliliters of the ejaculate are deposited at the cranial segment of vagina and make their journey to the fertilization site. This is done by means of various factors, such as sperm motility, the uterine and fallopian tubes contractility, and the ciliary movement of the lining cells. During this migration, spermatozoa interact with the female microenvironment both physically and molecularly. In this regard, the quality of the environmental conditions may affect this interaction. Therefore, some alterations in women's genital tract microenvironment, such as conditions that occur in female reproductive disorders, may have detrimental effects on sperm reproductive function. In this review, human sperm migration through the female tract is described, and the potential effects of different reproductive disorders at reproductive organs, such as vagina, uterine cervix, uterus, fallopian tubes, and ovary on sperm survival and quality, are also argued. The understanding of those conditions that may impair sperm fertility in the female genital tract can provide a more accurate diagnosis of the causes of infertility in couples. This can ultimately lead to the discovery of effective treatment approaches.

Keywords Sperm quality · Female reproductive disorders · Vagina · Cervical mucus · Uterus · Fallopian tube · Polycystic ovary syndrome
Review

Introduction

Successful fertilization is a complex process whose prerequisite is the entrance of maternal gamete (oocyte) into the fallopian tube after ovulation. Moreover, in this process, paternal gametes (sperm) should have the ability to migrate throughout the female reproductive tract and reach the fertilization site. In order to maximize the chance of sperm to

meet the egg, the journey of sperm through the female reproductive tract is entirely regulated. During this journey, the spermatozoa are propelled towards the oocyte by the beating force of their flagellum and with the assistance of muscle contractions, as well as the ciliary movements and the fluid flow of the female tract [1]. From ejaculation to the fertilization site, the female tract has various physical and molecular interactions with sperm to keep sperm alive,

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facilitate their migration, and provide high-quality spermatozoa for successful fertilization [2].

Evidence suggests that spermatozoa retain their fertility in the female reproductive tract for about 5 days [3]. Spermatozoa are indeed the highly specialized cells with minimal organelles and cytoplasm; thus, they approximately lack the transcription, translation, and cellular repair equipment found in common somatic cells [4]. Hence, any alterations in the female reproductive environment like anatomical or molecular disorder, which may cause female infertility, can have a direct influence on sperm quality and ultimately on fertilization. In this paper, sperm migration through the female reproductive tract was reviewed. In addition, various reproductive disorders in the female genital tract and seminal fluid that can interfere with sperm migration through the vagina, cervix, cervical mucus, uterus, fallopian tubes, and ovary were examined. In fact, it was aimed to learn more about the conditions that may synergically affect the female fertility and sperm quality and may be involved in the pathophysiology of unexplained infertility.

Vagina

Vaginal pH

Vagina is an internal female reproductive organ that connects the external genitalia (vulva) to the uterine cervix. Upon puberty, the rising levels of estrogen induce the accumulation of high amounts of glycogen in the multilayered stratified squamous epithelial cells of the vagina. These cells are covered by a mucosal layer and some cervicovaginal fluids [5, 6]. Glycogen is hydrolyzed by human α -amylase to maltose (disaccharide), maltotriose (trisaccharide), and α -dextrins (oligosaccharides), which are metabolized by lactobacillus species to lactic acid [7, 8]. This metabolic process leads to acidic vaginal pH. Some species of *Lactobacillus* also produce hydrogen peroxide (H₂O₂), bacteriocins [9], and presumably biosurfactants [10], which are toxic to other microorganisms. In combination with immunological responses, this acidic environment is considered a physical and biochemical barrier against the overgrowth of bacteria and sperm cells [11].

Upon ejaculation, millions of sperm are inseminated at the upper vaginal segment and undergo a long journey through the female reproductive tract to reach the fertilization site [12]. It has been demonstrated that the optimal pH for sperm survival and function is between 7.5 and 8 and sperm motility significantly decreases in PHs lower than 6 [13, 14]. Under normal circumstances, vaginal pH is maintained between 3.8 and 4.2, which is toxic to sperm. Due to alkaline vaginal secretions during sexual arousal and intercourse, along with the alkaline components of semen obtained from the seminal vesicle glands, the vaginal pH temporarily gets elevated from

4.3 to 7.2 in up to 8 s. This can protect spermatozoa against the acidic environment [1, 15, 16].

Female-Related Factors Affecting Sperm Quality in Vagina

Several factors can lead to the variability of vaginal pH and consequently sperm quality by having an impact on lactobacillus populations. These factors may include infections, smoking, stress, pregnancy, menstruation, hormonal disorders, aging, changes in estrogen levels during the lifespan, cancer, and antibiotic consumption [17, 18]. Due to changes in vaginal pH, defense mechanisms are diminished, and vagina becomes more susceptible to infection. Infectious conditions in vagina, such as trichomoniasis, bacterial vaginosis, and cytolytic vaginosis alter the vaginal pH through the disruption of the lactobacillus microflora. This may affect sperm motility and capacitation [19] or may even result in infertility [20]. In this line, research findings have revealed that the alkalization above 6.5 may increase the risk of vaginal infection [21, 22], and such infections can elevate the number of leukocytes in vagina. Here, owing to the increasing trend of sperm phagocytosis, sperm count is reduced [23]. Besides, some studies have demonstrated that the rising vaginal acidity has a negative effect on cervical mucus and sperm motility, which results in infertility [24, 25]. Smoking is considered to be another factor affecting the activity of lactobacilli. A study carried out in 2014 showed that the proportion of vaginal lactobacillus was lower in smokers than that in non-smokers. These conditions probably arise from the anti-estrogenic effects of smoking and the presence of benzo[a]pyrene diol epoxide in the secretions of smoking women [26]. Moreover, stressful conditions release the corticotrophin-releasing hormone from the hypothalamus, which activates the secretion of cortisol hormone from the adrenal cortex [27]. Cortisol inhibits the accumulation of estrogen in vaginal epithelial cells, and this contributes to a decreasing in the population of lactobacillus. As a result, vaginal infection may occur [28]. The elevated levels of estrogen during pregnancy also change the normal pH of vagina [29] by increasing the accumulation of glycogen in vaginal epithelial cells [30] and menstruation as the microbial diversity of vagina undergoes some changes [26].

Male-Related Factors Affecting Sperm Quality in Vagina

Semen is composed of two components, namely, sperm and seminal plasma, which originate from testes, epididymis, and accessory glands. Seminal plasma is a complex mixture of several biochemical compounds, such as sugars, lipids, proteins, metabolites, antioxidants, energy substrates, hormones, cytokines, organic acids, polyamines, ions, and HCO₃⁻/CO₂

[31, 32]. Thus, semen has a high buffering capacity, which is referred to as a defense mechanism against endogenous factors like sperm fructolysis and exogenous factors like vaginal acidic pH [33]. If semen is unable to raise the pH of vagina, it can lead to sperm immobilization and death [33]. For example, in such conditions as hypospermia where the volume of semen is smaller than the normal ejaculation volume, the buffering capacity of semen is unable to neutralize the vaginal acidity. Furthermore, such pathological conditions as the congenital absence of seminal vesicles, or obstruction of one or both ejaculatory ducts that cause the lack of alkaline secretions, result in the acidification of the ejaculatory fluid [15, 34]. In addition, another factor that damages sperm after ejaculation in vagina is semen hyperviscosity. The hypofunction of prostate, infection, the high number of seminal leukocytes, and oxidative stress may contribute to seminal hyperviscosity [35]. As a result, spermatozoa are trapped in the very viscous seminal coagulum, and, thereby, the normal sperm movement in the female tract is prevented [35].

Figure 1 summarizes the female- and male-related factors that may affect sperm quality in the female genital tract.

Cervix

Cervical Physiology and Function

Cervix is the lower part of uterus and connects the vaginal lumen to the uterine cavity. Several hundred endocervical glands secrete variable amounts of cervical mucus during the women's reproductive lifespan. Through mucus production, the cervix protects sperm against the vaginal acidic environment and phagocytosis by leukocytes, filters out the abnormal spermatozoa in motility or morphology [36], and creates an appropriate environment for sperm storage, capacitation, and migration into the uterus [12, 37, 38]. The cervical mucus acts as a barrier against sperm migration; thus, the penetration of sperm into the mucus depends on the seminal enzymes, external forces (e.g., the cervix contractions) [39], the hydration status of the mucus [40], and the number and motility of spermatozoa. The viscoelastic properties of human cervical mucus throughout the menstrual cycle are influenced by ovarian steroid hormones. This behavior of mucus plays an important role in female fertility and the passage of sperm and is measured by microrheometry [41, 42]. Related studies have shown that there is an inverse relationship between penetrability and viscoelasticity of cervical mucus [41]. During the periovulatory period, under the estrogen stimulation, cervix secretes a hydrate (more than 96% water) and clear mucus with low viscoelasticity [43]. This allows more sperm to penetrate into the mucus [44]. After ovulation, progesterone provides a thick and viscous mucus in the cervix to prevent the penetration of microorganisms and sperm into uterus [45–47].

Cervix generally acts as an effective factor in sperm selection; for this reason, the adequate production of cervical mucus is necessary to transfer sperm from vagina to the uterine cavity. As a result, any problem in the structure and anatomy of cervix or during the production and quality of mucus can impede this process.

Female-Related Causes of Sperm Impairment in Cervix

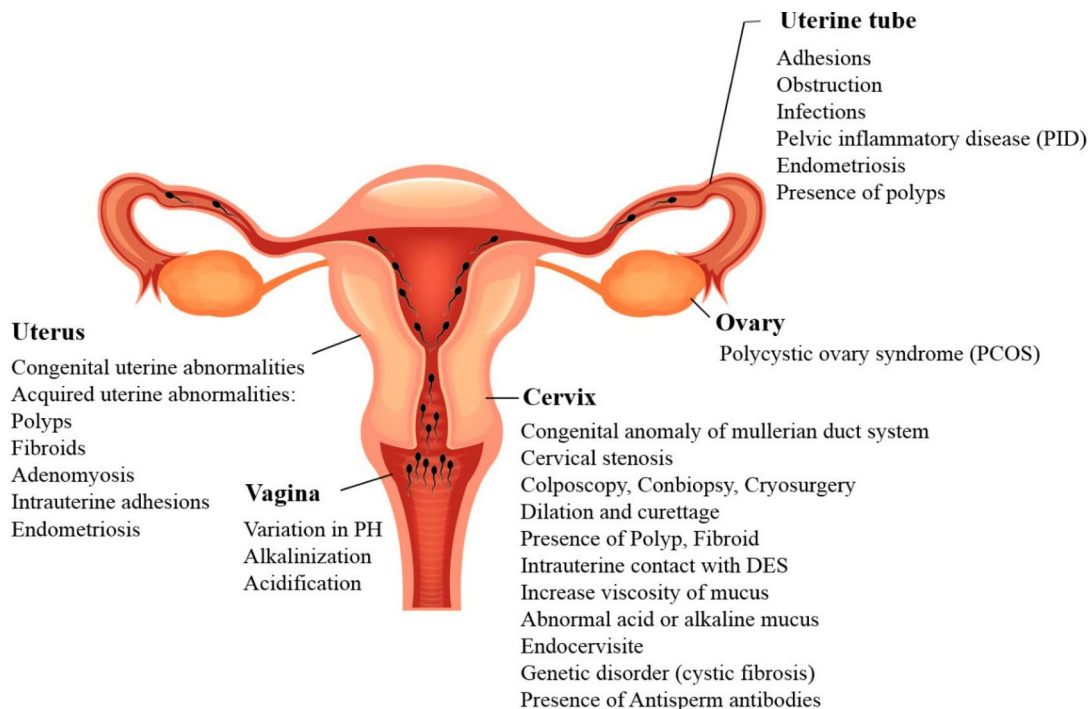
Anatomical and Organic Causes

One of the causes of sperm impairment in the cervix is the structural/anatomical defect of cervix. Congenital anomalies of the müllerian duct system that occurs during embryogenesis can disrupt any part of the müllerian ducts, such as fallopian tubes, uterus, cervix, and the upper part of vagina [48]. Although some of these disorders are diagnosed at birth, others are not diagnosed until postpuberty. The range of disorders varies from the agenesis or duplication of uterus, cervix, and vagina to small uterine abnormalities [49]. Any disorder in each part of these areas may impair the sperm migration into the women's reproductive tract, and, thereby, infertility may arise [45]. Cervical stenosis, in which the endocervical canal is partially or completely blocked, may also prevent the normal fertility by impeding the passage of sperm into the uterus [50]. Cervical stenosis may be congenital or can be acquired by a scar created arising from infection or surgical manipulations (e.g., colposcopy, cone biopsy, or cryosurgery procedure). As a result, mucus production may be disrupted owing to the removal of mucus-secreting cells lining the endocervix and cervical crypts [51]. The less likely stenosis can possibly occur due to the obstructions produced by a polyp, fibroid, or neoplasm [52]. Similarly, cervix may be damaged due to interfering processes, such as dilation and curettage (D&C) or instrument passage [53]. Besides, it has been demonstrated that the intrauterine contact with diethylstilbestrol (DES), a nonsteroidal estrogen that was widely used during 1940–1971 to reduce pregnancy complications, can induce cancer and various abnormalities in cervix and uterus [52].

Cervical Mucus

Cervical mucus is a glycoprotein gel composed of an aqueous phase and an insoluble mucin phase [54]. Mucins are the large glycosylated polymers that are linked together by disulfide bonds in order to form a complex network of interconnected micelles, which can support the aqueous phase. The aqueous phase consists of soluble proteins (e.g., albumin), trace metals (e.g., iron), and some organic elements (e.g., fatty acid). The protein content of cervical mucus is considered a proper index for evaluating the sperm penetrability of mucus [41, 55]. The

a Female-related causes of sperm impairment in female genital tract



b Male-related causes of sperm impairment in female genital tract

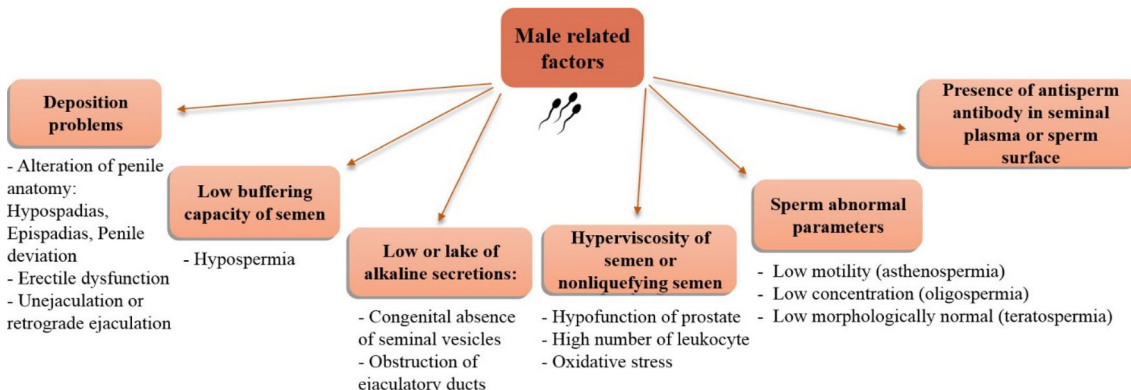


Fig. 1 Factors affecting sperm quality in female genital tract. **a** Female-related causes of sperm impairment in female genital tract. **b** Male-related causes of sperm impairment in female genital tract

structure of the cervical mucus plays an important role in female fertility. The increased viscosity of cervical mucus is one of the most important barriers to the sperm passage. Viscous mucus during the preovulatory phase is abnormal and may be the result of an insufficient stimulation of estrogen, chronic cervicitis, or the abnormal function of mucin-producing cells [37]. Abnormalities, such as severe endocervicitis and acute inflammatory conditions, also have an effect on mucus production and disrupt the sperm passage with the increase of leukocytes, exogenous proteins, and bacterial toxins [37, 56, 57]. Additionally, abnormal acid (less than pH 6) and alkaline (over pH 8.5) mucus of cervix can

also have detrimental effects on the sperm viability and motility [58]. Besides, the presence of antisperm antibodies like IgA and IgG in the cervical mucus can impair the sperm power to penetrate into the cervical mucus. In this process, immunoglobulin A can prevent the progressive penetration of sperm in the mucus, and immunoglobulin G also causes sperm death [59]. In addition, cystic fibrosis is a genetic disorder that adversely affects sperm penetration by changing the mucus quality. Cystic fibrosis is caused by mutations in the gene encoding a cAMP-regulated chloride channel, the cystic fibrosis transmembrane conductance regulator (CFTR), affecting the passage of sperm by producing a viscous and low-water

cervical mucus [60–62]. Hormonal fluctuation in the reproductive lifespan of a woman also affects the mucus secretion, composition, and quality as well as the sperm penetration into mucus [46, 57]. Hormonal dysfunction during the late follicular phase is mainly caused by low estrogen production and premature progesterone elevation. This dysfunction can make the cervical mucus improper for sperm penetration, and, consequently, it may lead to infertility [38].

Male-Related Causes of Sperm Impairment in Cervix

The progressive movement of sperm through the mucin network depends on the size of the interstitial space between the mucin micelles. Since the size of these spaces is smaller than the head of the sperm, the sperm must have a progressive motility to push their way through the mucus [63]. Therefore, any abnormality in sperm motility like asthenozoospermia can interfere with the movement of spermatozoa through the mucus [12]. Moreover, oligozoospermia (low concentration of spermatozoa), teratozoospermia (morphologically abnormal spermatozoa), and abnormal liquefaction are correlated with sperm inability to penetrate into the cervical mucus [37]. The presence of antisperm antibodies in the semen and on the sperm surface can also prevent sperm penetration into the cervical mucus [64].

Other Factors

Some factors change the production or quality of cervical mucus and, thereby, can have multiple effects on sperm penetration. Numerous studies have shown that two common drugs, namely, clomiphene citrate and propranolol, can be included in this category. Several studies have reported that the use of clomiphene citrate with the aim of improving ovulatory dysfunction has a significant anti-estrogenic effect on the cervical mucus [65–68] and increases the viscosity and opacity of mucus. Propranolol is another drug that is widely taken to treat heart problems. It has been shown that propranolol brings about sperm damage after oral administration due to a 4-fold increase in the accumulation of the cervicovaginal mucus compared to blood [69]. Propranolol accumulation can disrupt sperm motility as it affects the production pathways of glycolysis energy [70, 71]. Another factor is nicotine, and its metabolite cotinine has been demonstrated to have an anti-estrogenic effect. This can get accumulated in the cervical mucus of smoking woman [72–74]. With regard to the effect of nicotine on sperm, the results of an *in vitro* study suggested that, when being placed at a concentration similar to the seminal plasma of smokers (70 ng/ml), nicotine suppresses sperm progressive motility, reduces the percentage of viable spermatozoa, and increases the fragmentation of DNA in a dose-dependent manner [75]. In the same way, an animal study indicated that nicotine has a dose-dependent detrimental

effect on sperm parameters (e.g., reduced sperm viability, motility, count, and normal morphology) and fertility profile in male rats [76, 77].

Uterus

The uterine cavity is only a few centimeters in length (approximately 3 cm). It is estimated that sperm can travel through it in less than 10 min at the swimming speed of 5 mm/min [78]. In the uterus, spermatozoa move to the fallopian tube actively with their progressive motility and passively with the peristaltic contractions of the uterine myometrium. It has been shown that cranially directed contractions of uterine smooth muscle exist in uterine ultrasound whose intensity increases during the late follicular phase [64, 79]. There are several disorders in the uterus that can affect the sperm quality by changing the structure and anatomy or changing the uterus microenvironment. Uterine abnormalities are often classified into congenital or acquired. Arcuate uterus, complete or partial uterine septate, unicornuate or bicornuate uterus, uterine didelphys, and müllerian duct atresia constitute the most common congenital uterine abnormalities. In the congenital malformations of uterus, infertility is more likely to arise from the recurrent pregnancy loss. Except for the agenesis of müllerian ducts wherein uterus, fallopian tubes, cervix, and upper vaginal part are absent, no data about the interfering migration of sperm have been reported.

Acquired Disorders

Polyps

Endometrial polyps are a hyperplastic overgrowth of the endometrium consisting of uterine glands, stroma, and blood vessels that have been extruded into the uterine cavity. Aging generally increases polyps. They are rare in women younger than 30 years but are found in 5% of women aged 30–39 years and 10% of women over 40 years of age. Besides, they are more likely to occur in infertile women [80]. The frequency of polyps determined by hysteroscopy has been reported to be between 16.5 and 26.5% in patients with unexplained infertility and up to 46.7% in endometriosis patients [81, 82]. A study conducted on 1000 women undergoing hysterectomy before IVF revealed that 32% of them had a polyp in their uterus [83]. However, polyps may be considered to be a cause of infertility due to their mechanical interference with sperm and embryo transfer, implantation intervention, intrauterine inflammation, alteration uterine receptivity, and possibly the elevated production of inhibitory factors like glycodein [84, 85]. Shokeir et al. reported that the polyps located in the utero-tubal junction (UTJ) may lead to the loss of ostium function and affect the sperm migration to the fallopian tube [86, 87]. Research findings have shown that

the surgical removal of UTJ polyps has a positive effect on pregnancy results in ovulation induction and intrauterine insemination (IUI) cycles [88]. Richlin et al. also reported that glycodelin levels, the receptivity endometrial marker in plasma, and uterine flushings increased in patients with polyps and leiomyomas during the proliferative and preovulatory phase compared to the control group [89]. It should be noted that glycodelin is a glycoprotein with a very low level in the uterus during the follicular and periovulatory phases and reaches its peak 12 days after ovulation in order to prepare the uterus for implantation [90]. It has been shown that it inhibits the binding of sperm with oocyte zona pellucida and the activity of natural killer cells in a dose-dependent manner [91, 92]. Therefore, its low level around the time of ovulation contributes to successful fertilization, whereas the elevated levels of glycodelin may disrupt fertilization and implantation [93].

Fibroids

Uterine myomas, also known as fibroids, are the most common benign uterine smooth muscle tumors that originate from the myometrium and are classified based on their location. From among all the uterine neoplasms, leiomyoma has the maximum interference with fertility [94]. Interfering mechanisms with fertility in the presence of myoma are closely related to the number, size, and location of myoma. A systemic review on this subject suggested that submucosal fibroids reduce pregnancy, implantation, ongoing pregnancy, and live birth rate [95]. Fibroids are supposed to interfere with sperm motility and fertility through a number of pathways, such as the enlargement and deformation of the uterine cavity, as well as the cervical displacement. Alterations in uterine contractions occur in the uterus with myoma due to changes in the endometrial and myometrial blood supply. Similarly, the persistence of menstrual efflux resulting from the deformity of the uterine cavity may interfere with sperm transfer and implantation [96, 97]. Moreover, inflammatory changes and immunological factors in the endometrium and secretions of the uterus with myoma can engender the conditions that may damage spermatozoa [94].

Adenomyosis

Adenomyosis is a benign nonneoplastic disorder of the uterus that is caused by an invasion of the endometrium (glands and stroma) into the myometrium. Despite the availability of conflicting evidence, adenomyosis appears to have a generally negative effect on infertility and IVF results [98, 99]. Adenomyosis may change the normal peristaltic contractions of the uterus by altering the structure and function of the myometrium, and, thereby, the rapid and directed sperm transfer gets disrupted [100]. The ultrastructure of uterine smooth muscle cells (myocytes) in patients with adenomyosis is

different from that of the smooth muscle cells of normal uteri, which probably influence the normal rhythmic myometrial contractility [101]. The endometrium also shows an extensive alteration in molecular expression levels among women with adenomyosis. In this regard, it has been reported that the expression of the key endometrial receptivity gene (i.e., Hox-A10) is reduced in the endometrial secretory phase of patients with adenomyosis [102, 103]. Numerous studies have suggested that alteration in the expression profile of inflammatory markers, cytokines, and growth factors in the endometrium is associated with infertility in adenomyosis. Patients with adenomyosis often show the elevated levels of corticotropin-releasing hormone [104], hypoxia-inducible factor 1 α (HIF-1 α), IL-1 β , IL-6, IL-8, IL-10, matrix metalloproteinase MMP2 and MMP9, vascular endothelial growth factor (VEGF) [97], β -catenin [105], L-selectin [106], and an elevated number of NK cells and macrophages [107] in comparison with normal fertile women. Also, some other factors, including leukemia-inhibiting factor (LIF), LIF receptor α , IL-11, integrin beta-3, and osteopontin, have been reported to experience a decrease in women with adenomyosis [97, 108]. Therefore, the altered uterine microenvironment in the presence of adenomyosis may interfere with the sperm quality and motility. This claim has been reported in some in vitro studies where the addition of IL-6 to sperm reduced the progressive motility in a dose-dependent manner [109, 110].

Intrauterine Adhesions

Intrauterine adhesions (IUAs) are defined as the formation of fibrous strands inside the uterine cavity and/or cervix that cause a partial or complete obstruction of the uterine cavity [111]. It is believed that IUAs are caused by trauma to the uterine wall, which induces some uterine wall adhesions during the wound healing process [112, 113]. IUAs are known as Asherman's syndrome when they are associated with such symptoms as painful cyclic hypomenorrhea, secondary amenorrhea, and infertility [114]. A systematic meta-analysis review examining post-miscarriage adhesions reported that 19.1% of women developed IUAs after dilatation with blunt or suction curettage for miscarriage [115]. Adhesions are usually produced after postpartum hemorrhage or endometrial infection resulting from uterine manipulation by dilation and aggressive curettage (D&C) [96]. The possible mechanism of infertility due to IUAs is not known, but it may be related to interference with sperm and embryo transfer or implantation resulting from the defective endometrial function [111, 112, 116, 117].

Endometriosis

Endometriosis is a complex multifactorial disease characterized by the presence of endometrial glands and stromal cells outside the endometrial environment [118]. These external

tissues, called endometriotic lesions, can be found in the fallopian tube, on the surface of the ovary, and on the surface of the pelvic organs, which result in pain and infertility [119, 120]. It is estimated that 10–15% of women are affected by endometriosis at the time of childbearing [120, 121]. About 50% of the patients with endometriosis appear to be subfertile [122]. Studies have shown that women with endometriosis have a lower fertility rate in assisted reproductive technology (ART) outcomes [121–123] and even have a lower rate of ART success in stage III/IV than patients with stage I/II [121]. However, the rates of embryo cleavage, implantation, and pregnancy were approximately similar in both groups [123, 124]. The mechanism through which endometriosis causes infertility in women is contingent upon the disease stage. In general, some factors, such as anatomical distortion of the fallopian tube and/or ovary, ovulatory dysfunction, altered peritoneal microenvironment, deleterious effect on sperm motility, decreased fertilization, and implantation, are correlated with infertility in this disorder [125].

Numerous factors lead to the decline of sperm quality and inability to fertilize oocytes in women with endometriosis. In this domain, Mansour et al. observed that the peritoneal fluid of women with endometriosis causes a significant increase in the DNA damage of normal sperm, which is directly related to the endometriosis stage and infertility duration [126]. They described this observation as one of the mechanisms of infertility in endometriosis. Recently, Sáez-Espinosa et al. cultured peritoneal fluid of women with endometriosis with normal sperm and showed that the long-term (48 h) culture of sperm with peritoneal fluid had a negative effect on sperm motility, protein tyrosine phosphorylation, and relocation of glycocalyx sugars, while it had no effect on the viability and acrosome reaction of spermatozoa [127]. They explained that the high concentration of cytokines in peritoneal fluid may reduce tyrosine phosphorylation and result in the decreased motility and capacitation. The correct redistribution of sugars in the sperm plasma membrane is a major requirement for spermatozoa capacitation. This feature has been shown to be significantly impacted during the long-term (48 h) culture of spermatozoa with the peritoneal fluid of endometriosis patients [127].

Evidence suggests that these adverse effects of endometriosis on sperm result from the changes occurring in the peritoneal fluid microenvironment, which is directed towards an inflammatory state. It has been reported that the levels of tumor necrosis factor α (TNF- α), IL-1 β , macrophage inhibitory factor (MIF), interleukin-8, and interleukin-6 (IL-6) cytokines witness an increase in the peritoneal fluid of endometriosis patients [128–130]. Yoshida et al. showed that IL-6 and its soluble receptor, which are present in the peritoneal fluid of endometriosis patients, reduce sperm motility in a dose-dependent manner and are possibly in correlation with GP130 [110]. TNF- α is a cytokine that is used as a marker for the non-surgical diagnosis of endometriosis [131]. In this light, Said et al. argued that TNF- α at pathophysiological

concentrations, similar to that present in endometriosis, reduce the motility, plasma membrane integrity, and DNA damage of spermatozoa [132]. In another study, they found that anti-inflammatory drug infliximab could reverse the influence of TNF- α on sperm [133]. Carli et al. also examined the dose-dependent effect of cytokine MIF on normal sperm quality. They showed that MIF at the pathophysiological concentration levels had a negative effect on sperm capacitation and motility; therefore, cytokine MIF has a role in endometriosis-related infertility in women [134]. The results of a similar study revealed that the elevated number of macrophages in the peritoneal fluid of endometriosis women can result in the increase of phagocytosis of healthy sperm and the decrease of their number and motility [135]. Osborn et al. also found that the macrophages in infertile women with endometriosis produce more NO than that in normal fertile women, which had adverse effects on embryo, sperm, and implantation [136].

Autoimmunity also plays an important role in the pathophysiology of endometriosis. It has been found that the levels of endometrial autoantigen increase for both transferrin and alpha 2-HS glycoprotein in the peritoneal fluid of women with endometriosis [137, 138]. Mathur et al. added two transferrin and alpha 2-H glycoprotein antibodies in various dilutions to washed sperm and identified that both anti-transferrin and anti-alpha 2-H glycoprotein reduce the survival and motility of spermatozoa [137].

Moreover, the related data suggest that endometriosis can interfere with utero-tubal sperm transport [139–141]. In this regard, the results of *in vitro* experiments demonstrate that the peritoneal fluid of endometriosis patients has a negative impact on sperm binding to the zona pellucida of oocyte [142]. In addition, a recent study done by Grande et al. [143] revealed that endometriosis may play a role in reducing sperm quality. In this study, the cervical mucus proteome of patients with endometriosis was examined, and the results showed that the expression profile of several proteins was altered compared to the normal counterparts. The expression of six proteins also increased where almost all of them had a key role in inflammation. Nine proteins, including the ones relating to local innate immunity and protection against oxidative stress, showed a decreased expression. In addition, fifteen proteins, including the ones involved in antimicrobial activities and seminal plasma liquefaction proteins (i.e., human kallikreins 13 genes (KLK13)) were not detected in the cervical mucus of endometriosis patients. It is argued that kallikreins are important in controlling semen liquefaction and sperm motility. Thus, the decreased expression of these proteins is likely to contribute to sperm infertility [144].

Other Factors

It is claimed that there may be an association between cystic fibrosis in women and the decreased sperm quality in the

uterus. A study in the domain maintained that the co-culture of sperm cells with endometrial cells treated with antisense oligonucleotide against CFTR or with bicarbonate secretion-defective cystic fibrosis epithelial cells reduced the sperm capacitation and the ability to fertilize eggs. This result confirmed the role of CFTR in controlling uterine bicarbonate secretion and the presence of a link between the defective CFTR and lower fertility levels in cystic fibrosis patients [145].

Fallopian Tubes

Fallopian tubes are approximately 10–12 cm long and connect the uterine cavity to ovaries. They can be subdivided into four parts, namely, intramural, isthmus, ampulla, and infundibulum parts. After taking a long journey, only a few thousand sperm finally reach the fallopian tubes [146], and the majority of these sperm enter the tube which contains the ovulated oocyte. The fallopian tube microenvironment plays an important role in several primary processes of a successful pregnancy, including sperm capacitation and transfer, capture and transfer of oocyte, fertilization, and early embryonic development [147]. In isthmus, spermatozoa get attached to the lining epithelium and undergo the capacitation process under the influence of tubular secretions. Isthmus is also considered a sperm reservoir that releases only a limited number of sperm at a time to prevent polyspermy by reducing the available sperm for oocyte [148]. After the capacitation, spermatozoa acquire a hyperactive movement and get detached from the epithelium. Hyperactivation helps sperm overcome the barriers, including the mucus of the isthmus, the corona radiata, and the zona pellucida around the oocyte to reach the oocyte. In some species (e.g., rabbits, cattle, pigs, and humans), the UTJ is filled with a viscous mucus that may filter out pathogens and abnormal sperm cells in morphology and motility [149, 150]. In this respect, isthmus is analogous to cervix. The human spermatozoa must travel a long distance (3–5 cm) from reservoir to the fertilization site [151]. The capacitated sperm cells move this long way undergoing a combination of sperm swimming and peristaltic contractions of the tube [1]. Moreover, the capacitated sperm movement is influenced by thermotaxis (long-range) and chemotaxis (short-range) mechanisms. In thermotaxis, the thermotactically active spermatozoa acquire the ability to sense and respond to a temperature gradient and change their swimming directions towards the fertilization site (i.e., a warmer place) [152, 153]. Also, chemotaxis is a mechanism wherein the capacitated-spermatozoa have the capability of swimming up along with a concentration of chemoattractant gradient secreted by the oocyte and its surrounding cumulus cells [154]. It seems that the ciliary motion of fallopian tube may also have some part in the transfer of sperm since the co-culture of sperm with epithelial cells of

the fallopian tube increases the ciliary beat frequency (CBF) [155]. Every factor that may disrupt the function of the fallopian tube can lead to the incomplete transmission of gametes, fertilization failure, and, ultimately, infertility.

Female-Related Cause of Sperm Impairment in Fallopian Tubes

The major causes of tubal factor infertility can be referred to as pelvic-peritoneal adhesions, tubal obstruction [156], infections, pelvic inflammatory disease (PID) mostly arising from chlamydia [157], endometriosis [158], ectopic pregnancy [159], abdomino-pelvic surgery, presence of polyps, and manipulation by intrauterine devices [160]. The tubal disease may involve the proximal, distal, or entire tubal areas and is responsible for about 25–30% of female infertility cases [161]. Both chlamydia and gonorrhea are among the most common causes of sexually transmitted diseases and result in fallopian tube infections and consequent infertility. About 40% of chlamydial infections cause PID, which is the most common cause of tubal infertility and may involve several parts of tubes. More than 50% of the cases suffer from this condition [162, 163]. PID may result in adhesions, scarring, obstruction, tubal damage, ectopic pregnancy, and, consequently, infertility [164]. If infections remain untreated, they can bring about chronic salpingitis. In this case, the creating scar blocks the tube and disrupts the normal activity of the tubular cells. Endometriosis is another source of pelvic and peritoneal adhesions that may interfere with the tubal function. Intraluminal endometriosis may occasion the anatomical obstruction of the lumen, and, thereby, the passage of sperm, oocyte, and embryo is likely to get blocked. As a result of environmental cytokines, sperm interactions with isthmus are reduced, and, thereby, sperm pooling in this area is declined, as well. Endometriosis has a negative influence on sperm attachment to the epithelium of the oviduct [165]. Also, endometriosis can change the CBF of the lining epithelial cells. In an *in vitro* study, Lyons et al. examined the effect of peritoneal fluid in six women with early stages of endometriosis on CBF of fallopian tube epithelial cells. After 24 h of incubation, the CBF was significantly reduced in contact with the endometriosis peritoneal fluid [166]. In addition, after abdomino-pelvic surgery, pelvic adhesions and scarring may develop and restrict the movement of the ovaries and fallopian tubes where the final result can be infertility. Uterine polyps, found in approximately 11% of hysterectomy specimens, can also lead to the temporary obstruction of the fallopian tube. In a study on 323 women, hysteroscopy, conventional histology, and 4-dimensional hysterosalpingo-contrast sonography (4D-HyCoSy) were used to assess the relationship between endometrial polyps and fallopian tube patency. The results showed that the prevalence of endometrial polyps was significantly higher in infertile patients with bilateral fallopian tube

obstruction than that in patients with bilateral fallopian tube patency (42.9% vs. 1.20%) [167]. Thus could create mechanical obstruction depending on location and size. According to animal studies, smoking may also be an effective factor in tubal infertility. The culture of hamster infundibulum with the smoke solution brought about a dose-dependent reduction in CBF where the CBF was reversible after washing [168]. This group also showed that contact with the smoke solution can disrupt the oocyte cumulus pick up rate and ciliary beat frequency in a dose-dependent manner [169].

Male-Related Cause of Sperm Impairment in Fallopian Tubes

The research data on animal studies suggested that there may be a link between cystic fibrosis in men and the ability of sperm to undergo capacitation. In one study, the addition of a CFTR inhibitor to mouse sperm significantly reduced the capacitation and the events associated with HCO_3^- in sperm [170]. This result suggests that the CFTR gene plays an essential role in the process of capacitation and regulation of the entry of bicarbonate ions and subsequent events. The conduct of more research is required to establish the role of this gene in human infertility. In another study, the expression of the CFTR gene in sperm of male three groups (20–40, 40–60, and 60 years) was investigated. The results showed that the CFTR expression decreased in the equatorial segment and neck as an age-dependent manner. The reduction in the expression of CFTR is found to be associated with a decrease in the forward motility and HCO_3^- sensitivity required for sperm capacitation [171].

Ovary

Potential Role of Polycystic Ovary Syndrome in Sperm Impairment

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a common hormonal disorder that affects 5–10% of women at the childbearing age; besides, this disorder is associated with significant ovulatory dysfunctions [172, 173]. PCOS is characterized by a variety of signs and clinical and biochemical disorders, including ovulatory dysfunction, hyperandrogenism, hypertension, insulin resistance, type 2 diabetes, visceral obesity, cardiovascular disease, and infertility [174–177]. PCOS patients often show an elevated number of impaired oocyte qualities. This is likely to result in the decreased fertilization and implantation rate and the increased miscarriage rate, which are possibly associated with abnormal paracrine and endocrine factors like hormones, growth factors, and cytokines in the intra- and extra-

follicular microenvironment [178–180]. The direct effect of PCOS on sperm quality in the female reproductive tract has not been studied yet; therefore, it is felt necessary to study the alterations of the female tract microenvironment in this pathologic disease that may affect the survival and quality of spermatozoa.

Hormones and Growth Factors

Differential expressions in two pituitary gonadotropins, namely, luteinizing hormone (LH) and follicle stimulating hormone (FSH), have been reported in PCOS patients. It is noteworthy that gonadotropins are fundamental to sexual development and reproduction. Numerous studies have reported that PCOS disorder is correlated with higher LH and lower FSH serum levels as compared to the women with normal menstrual cycles [181–183]. Women with PCOS also elevated some free circulating levels of androgens either due to the elevated production of ovary or due to the inhibition of sex hormone-binding globin synthesis by the liver [182, 184, 185]. Leptin is a peptide hormone secreted by adipose tissue, and its presence is essential for normal reproductive function. However, when the level of this hormone increases, it can have detrimental effects on the reproductive system. The high levels of leptin were found in follicular fluid and serum among women with PCOS, and they were directly associated with the reduced ovarian stimulation and responsiveness, decreased oocyte maturation, embryo quality, and pregnancy rate [186, 187]. Furthermore, the involvement of insulin resistance and compensatory hyperinsulinemia has been reported in women with PCOS. It has been also claimed that hyperinsulinemia is associated with the decreased oocyte quality, fertilization, implantation, and the increased rate of miscarriage [188–190]. In addition, numerous researches have lent support to the claim that the elevated serum and/or follicular fluid levels of some growth factors include epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin growth factor (IGF)-1, brain-derived neurotrophic factor (BDNF), transforming growth factor (TGF)- β family like anti-mullerian hormone (AMH), and vascular endothelial growth factor (VEGF). These factors are closely linked to the pathophysiology of PCOS patients [191–196].

Cytokines

The results of related studies have revealed that the metabolic signs and symptoms of PCOS can be associated with the presence of a chronic low-level inflammation state [197]. Kelly et al. reported that PCOS women had higher levels of C-reactive protein (CRP) than equal weight control women [198]. Similarly, it has been shown that the levels of pro-inflammatory IL-8 cytokine are significantly high in PCOS women [199]. There are more lymphocytes and macrophages

in the ovarian tissue of women with PCOS. This leads to the secretion of inflammatory cytokines, such as TNF- α and IL-6. Furthermore, the elevated levels of IL-1 α and IL-1 β [200] and a reduced level of IL-17 were reported in the serum of PCOS patients. Having evaluated the follicular fluid of PCOS women, Gallinelli et al. argued that the IL-12 levels in these women decreased significantly and IL-13 in them increased significantly compared to the women with a normal ovulation. In addition, they concluded that the total number of follicular fluid-activated T lymphocytes and the follicular fluid T helper/T suppressor ratio in normal women were higher than those in PCOS patients [201].

Other Factors

Another factor that experiences an increase in PCOS patients is the oxidative stress resulting from the production of excessive reactive oxygen species (ROS). In PCOS women, an increase in ROS levels, along with a decrease in antioxidant defense system, is directly related to poor oocyte quality, decreased fertilization, embryo quality, and success in clinical pregnancy. Moreover, it is noteworthy that the elevated homocysteine concentrations in serum and follicular fluid, a sulfur-containing amino acid, and the metabolite of essential amino acid methionine are adversely correlated with oocytes and embryo quality. These factors bring about a decreased fertilization and pregnancy rate and an increased recurrent spontaneous abortion in PCOS women [202–204].

Potential Relation of PCOS Pathophysiologic Condition with Sperm Impairment

Various studies have been conducted on subfertile or infertile men to determine the possible reasons for the decline of sperm quality and the correlation of infertility with different factors. It has been established that the elevated serum concentration of TNF- α , interferon-gamma (IFN- γ), IL-2, IL-4, IL-6, IL-8, and IL-21 cytokines are associated with the unexplained male infertility [205]. One study in this context showed that TNF- α and IL-6 levels have a significant correlation with the sperm lipid membrane peroxidation level [206]. Additionally, it has been demonstrated that sperm concentration and motility were inversely linked with IL-18 levels [207]. Likewise, it has been reported that testosterone concentrations in the semen of infertile men (75 ± 11 pg/100 μ L) was higher than that in the semen of fertile men (29 ± 3 pg/100 μ L). By the same token, the data of an *in vitro* study suggested that the incubation of semen with three different concentrations of testosterone (50, 150, and 300 pg) is associated with a dose-dependent reduction of sperm motility [208]. A case-controlled study also showed that the high concentrations of leptin and insulin in obese men can have detrimental effects on sperm parameters, including low sperm concentration and vitality, reduced

mitochondrial membrane potential, and high DNA fragmentation compared to non-obese men [209]. In another research, male Wistar rats were fed with a high-fat diet, and, after several weeks, an increase in obesity index and leptin came into being. In this way, sperm quality was also reduced with a decrease in motility as well as a decrease in their fertility potential (178). Furthermore, an increase in ROS levels is associated with decreased sperm motility and vitality, impaired sperm function and fertility, sperm DNA damage, and male factor infertility [210–212]. In fact, it has a negative effect on the formation of pronucleus, blastocyst formation, and pregnancy rate after ICSI [210, 213]. Eventually, hyperhomocysteinemia may affect male fertility by reducing the morphology, concentration, and motility of sperm [214, 215]. These studies suggest that the pathophysiological conditions that occur in the microenvironment of the female reproductive tract among PCOS patients may affect sperm survival, motility, and fertility.

Conclusions

The pathophysiological conditions discussed in this review were revealed to have the potential to alter the environment of the female reproductive tract by changing the population of immune cells, hormone and growth factors, inflammatory factors, and the gene expression or mechanical factors (e.g., obstruction). Thus, the sperm cells that pass through vagina, cervical mucus, uterus, and fallopian tubes to reach oocytes can also be affected by this inflammatory microenvironment. Therefore, it is recommended that physicians should pay special attention to the factors affecting sperm cells in the female tract, such as the buffering capacity and PH of the vagina, hormonal dysfunction and the quality of cervical mucus, the presence of any disorders in the uterus like polyp or fibroids, and disorders like endometriosis and PCOS. In addition, the male medical history and semen analysis should be assigned credit and taken into consideration. The evaluation of all the factors interfering with the quality of oocytes, sperm, and embryos in the female reproductive system could provide a more detailed outlook to understand the exact cause of infertility and find effective treatment approaches, such as laparoscopic surgery procedure or assisted reproduction technologies, such as intrauterine insemination (IUI), *in vitro* fertilization (IVF), and intracytoplasmic sperm injection (ICSI).

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Declarations

Conflict of Interest The authors declare no competing interests.

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