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Infertility as a Contemporary Social and Therapeutic Challenge - A Literature Review

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ABSTRACT

INTRODUCTION: Infertility is a multifactorial condition affecting both women and men, with substantial social, psychological, and medical implications. It arises from hormonal, anatomical, genetic, infectious, and lifestyle-related factors.

AIM OF STUDY: This review aims to summarize current knowledge on the etiology, pathophysiology, and therapeutic approaches to infertility in both sexes, emphasizing major conditions.

MATERIAL AND METHODS: A literature review was conducted analyzing peer-reviewed studies on reproductive health from PubMed and GoogleScholar. Both male and female infertility were considered, focusing on factors influencing gametogenesis, fertilization, embryo implantation and pregnancy outcomes.

BASIC RESULTS: In women, infertility is influenced by endometriosis, which alters implantation through inflammatory and immunomodulatory mechanisms; PCOS, which disrupts hormonal balance and ovulation; and uterine fibroids, which impair myometrial contractility and endometrial receptivity. In men, infertility results from genetic and acquired causes, including azoospermia, varicocele, infections, and malignancies, with oxidative stress, antisperm antibodies, and dysbiosis contributing to impaired spermatogenesis and sperm transport. Lifestyle interventions, as well as surgical and pharmacological treatments, can improve reproductive outcomes.

CONCLUSION: Infertility is a complex, interrelated condition requiring multidisciplinary management. Understanding biological, genetic, immunological and lifestyle factors is essential to optimize therapy, enhance conception, and increase live birth rates. Targeting modifiable factors such as diet, physical activity, and body weight is a promising adjunct to conventional treatment.

KEYWORDS: infertility, endometrosis, immunological infertility, PCOS, testicular cancer

INTRODUCTION

Procreation is a natural phenomenon, the primary purpose of which is the continuation of the species. It occurs across various species, often proceeding in distinct ways depending on biological characteristics. In humans, sexual intercourse is frequently associated not only with the goal of reproduction but also with the fulfillment of intrinsic physical, psychological and, in some cases, cultural needs. An individual's health status is closely correlated with processes occurring both prior to sexual initiation and during attempts to conceive. It is often determined by the health condition of both partners, as well as by socio-demographic circumstances and the cultural background in which the partners were raised. Numerous factors influence health, thereby affecting the phenomenon of procreation and the difficulties associated with it.

Infertility is a disorder defined by the World Health Organization (WHO) as the inability to conceive within twelve months in women under the age of 35, despite regular unprotected sexual intercourse.

However, for women over the age of 35, this timeframe is reduced to six months and may be shortened further regardless of age [1–2]. This condition affects both sexes, and therefore any attempts to address infertility must involve coordinated therapeutic interventions targeting both partners. In Poland, depending on the source, approximately one million couples struggle with infertility [1]. Globally, the prevalence of infertility is estimated to affect between 12.6% and 17.5% of couples of reproductive age [2].

Endometriosis

Endometriosis is a chronic inflammatory disease affecting women, characterized by the implantation of endometrial-like tissue outside its normal anatomical location [3]. It is estimated that approximately 176 million women worldwide suffer from this condition [4]. One of the most widely accepted hypotheses explaining the pathogenesis of endometriosis is retrograde menstruation, in which menstrual blood containing viable endometrial cells refluxes into the pelvic cavity, where these cells may differentiate into endometrial-like tissue [5]. Such a mechanism is particularly likely in the presence of obstructive anomalies, including imperforate hymen, complete transverse vaginal septum, distal vaginal aplasia, Herlyn-Werner-Wunderlich syndrome or a non-communicating rudimentary uterine horn [6]. Animal studies have demonstrated that endometriosis may also develop de novo from bone marrow-derived stem cells [7]. The familial occurrence of the disease suggests a genetic component [8]. Examples include abnormal expression of the HOXA10 and HOXA11 genes, which are crucial for embryonic development and endometrial regeneration; decreased expression of these genes has been observed during the luteal phase in women with endometriosis [9–10]. Studies further indicate dysregulation of progesterone receptors and the development of progesterone resistance in endometrial tissue, both of which negatively affect implantation [11–12].

The most common symptoms reported by patients include pelvic pain, dyspareunia, dysmenorrhea, and infertility. However, the disease may also remain asymptomatic [13]. A strong association exists between endometriosis and infertility, with the condition estimated to affect 25–40% of infertile women [14]. Beyond the psychological consequences of infertility and chronic pain, the disease contributes to the formation of adhesions within the reproductive organs, impairing the release and transport of oocytes. Adhesion-related pelvic anatomical distortion, together with impaired uterine contractility, further affects the transport of both oocytes and spermatozoa. Moreover, the chronic inflammatory response characteristic of endometriosis influences ovulation and implantation processes [15–16].

A meta-analysis of patients diagnosed with endometriosis demonstrated that surgical laparoscopy or treatment with gonadotropin-releasing hormone (GnRH) agonists significantly increased pregnancy rates compared with placebo [17]. Pharmacological therapies commonly employed in the management of endometriosis include gestrinone, danazol, norethisterone acetate, leuprorelin acetate, levonorgestrel, and etonogestrel [18–19]. Clinical studies have reported improved pregnancy outcomes following pharmacotherapy [19].

Polycystic Ovary Syndrome

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting a substantial proportion of women. Its prevalence is estimated at 5–10%, although some reports suggest it may affect up to 26% of the female population [20]. Diagnosis is established when at least two of the following three criteria are met, after excluding other potential causes: (1) clinical and/or biochemical features of hyperandrogenism; (2) polycystic ovarian morphology identified on ultrasound; (3) menstrual irregularities and ovarian dysfunction persisting for more than six months, manifested as amenorrhea or cycle lengths shorter than 21 days or longer than 35 days. Interestingly, studies have demonstrated that lifestyle modifications, such as weight reduction, exert a beneficial impact on ovulation rates, conception, and live birth outcomes among women with PCOS [21–22].

Uterine Fibroids

Uterine fibroids are benign tumors composed of smooth muscle cells that histologically resemble normal myometrial tissue. While many fibroids remain asymptomatic, symptomatic cases are often characterized by heavy menstrual bleeding, pelvic or lower back pain, dyspareunia, constipation, or urinary incontinence, all of which may themselves contribute to reduced sexual arousal [23]. The role of fibroids in infertility is largely determined by their location, size, and number. Studies have demonstrated that larger fibroid diameters are associated with poorer implantation outcomes and impaired embryonic development [24]. The modulatory influence of fibroid location on the uterine wall plays a particularly significant role in infertility, with the strongest association observed in submucosal fibroids [25].

Fibroid growth can markedly impair normal myometrial contractility, disrupting sperm transport, embryo implantation, and increasing the risk of miscarriage. Submucosal and intramural fibroids, in particular, exhibit a higher propensity to interfere with uterine motility [26–27]. In addition, fibroids exert immunomodulatory effects by reducing the levels of cytokines essential for implantation, such as leukemia inhibitory factor (LIF) and cell adhesion molecules. A deficiency in LIF has been directly linked to implantation failure [28]. Elevated concentrations of transforming growth factor (TGF)-β3 in women with fibroids suppress the expression of bone morphogenetic protein receptor type II (BMPR-II) in the endometrium, subsequently leading to decreased HOXA10 and LIF expression [29].

Although numerous factors may determine the impact of fibroids on reproductive potential, the available evidence does not unequivocally confirm a direct causal relationship between fibroids and infertility. However, there are indications that fibroids may modulate fertility processes. Further research and analysis are required to clarify the extent and mechanisms of this association [30].

Male Infertility

Infertility affects both women and men, with male factors estimated to account for 30–50% of all infertility cases [31–32]. According to the World Health Organization (WHO), the reference values associated with a statistically significant probability of achieving pregnancy within one year of unprotected intercourse are as follows:

sperm vitality: ≥ 58% live spermatozoa,

sperm motility: ≥ 32% with progressive motility,

sperm concentration: ≥ 15 million/ml or ≥ 39 million per ejaculate,

sperm morphology: ≥ 4% with normal morphology,

pH: ≥ 7.2,

ejaculate volume: ≥ 1.5 ml [1].

Testicular and Excretory Duct Dysfunction

Azoospermia, defined as the complete absence of spermatozoa in the ejaculate, is reported to affect between 1% and up to 20% of infertile men, depending on the study [33–34]. It can be classified as obstructive or non-obstructive. The former results from physical blockage of the seminal outflow tract [34]. Approximately 50–80% of cases of non-obstructive azoospermia have no identifiable cause and are considered idiopathic. Genetic factors include Kallmann syndrome, Klinefelter syndrome, mild androgen insensitivity syndrome, TEX11 mutations, and Y chromosome deletions or translocations [33–34].

Acquired causes encompass varicocele, chemotherapy, radiotherapy, orchitis, infections, and trauma [35]. Infections are responsible for 10–15% of male infertility cases. Among infectious etiologies, Chlamydia trachomatis and Neisseria gonorrhoeae are the most common pathogens, often remaining asymptomatic and diagnosed incidentally during testicular biopsy [35–37]. Human papillomavirus (HPV) is also frequently discussed in the literature, with evidence suggesting both direct effects on sperm count, motility, and viability, as well as indirect effects via the induction of antisperm antibodies [38]. Vaccination thus plays a key role in preventing HPV transmission and its sequelae, including infertility. Moreover, coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, may damage the testes and induce inflammatory destruction due to the abundance of ACE2 receptors on Leydig and Sertoli cells, which facilitates viral entry [39–40].

Varicocele is observed in 35–40% of infertile men, most commonly on the left side. It contributes to hypoxia, oxidative stress through reactive oxygen species, and impaired thermoregulation [41–43]. Elevated interleukin-6 (IL-6) levels in these patients correlate with reduced sperm concentration and motility [44–45]. Given the high content of polyunsaturated fatty acids in sperm membranes, spermatozoa are particularly susceptible to lipid peroxidation. This process results in the formation of lipid peroxides and their degradation products, including isoprostanes, 4-hydroxynonenal, and malondialdehyde.

IL-6 concentrations above 30 pg/ml are associated with increased malondialdehyde levels both in seminal plasma and within sperm cells [46]. While varicocele itself is not a direct cause of antisperm antibody formation, it increases the risk of antibody production when coexisting with other pathological conditions [47].

Obstructive Azoospermia

Obstructive azoospermia results from blockage of the seminal ducts at various levels between the rete testis and the ejaculatory ducts [48]. The most frequent causes include vasectomy and iatrogenic injury, particularly following inguinal hernia repair or kidney transplantation [48–49]. Approximately 7% of men evaluated for obstructive azoospermia are found to have iatrogenic vas deferens damage leading to infertility [49]. Another important cause is cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations, which result in abnormal protein synthesis and increased viscosity of secretions. CFTR mutations are strongly associated with oligospermia, azoospermia, congenital bilateral absence of the vas deferens, epididymal obstruction, and ejaculatory duct obstruction [50–51]. Chronic epididymal obstruction may also increase intraluminal pressure, causing tubular damage [49].

Defects in Sperm Transport

Transport abnormalities due to defective ciliary motion are characteristic of primary ciliary dyskinesia (PCD) and Kartagener's syndrome. Both conditions are associated with recurrent respiratory tract infections, chronic otitis media, and sinusitis. Situs inversus distinguishes Kartagener's syndrome from PCD [52–53]. Another rare disorder with similar consequences is the Barry-Perkins-Young syndrome, in which azoospermia occurs despite normal spermatogenesis. Reduced fertility results from impaired sperm transport and the production of dense epididymal mucus that restricts motility [54–55]. Barry-Perkins-Young syndrome should also be differentiated from cystic fibrosis [49].

Cancers

The most common malignancies associated with infertility in men of reproductive age include leukemia, Hodgkin's lymphoma, testicular cancer, and germ cell tumors of the testes [56–57]. In cases of Hodgkin's lymphoma or testicular cancer, infertility may even precede the diagnosis of the disease [57, 59]. Male infertility is increasingly considered an early marker of urogenital malignancy, largely due to oxidative stress-induced DNA damage [58–60]. Among men diagnosed with germ cell tumors or testicular cancer, azoospermia or reduced sperm counts are frequently observed [61]. In addition to hematologic malignancies in men, infertility is also a characteristic feature of Fanconi anemia, alongside leukemias and Hodgkin's lymphoma [56, 62].

Antisperm Antibodies

Antibodies directed against spermatozoa are found in 5–15% of infertile men [63]. Varicocele has been shown to predispose infertile men to the development of antisperm antibodies compared with infertile men without varicocele. These antibodies, detected in serum and semen, are most commonly of the IgA and IgM classes [64–65]. Other causes of antisperm antibody formation include testicular trauma, genitourinary infections and epididymitis or orchitis [66].

Human Reproductive Tract Microbiota: Dysbiosis as a Key Factor in Infertility

The human microbiome comprises microbial communities inhabiting various body sites in contact with the external environment. In male infertility, infections often trigger inflammatory processes that disrupt spermatogenesis. Furthermore, immune activation may lead to the production of antisperm antibodies [67]. Studies investigating infertility related to varicocele have shown that colonization with Ureaplasma urealyticum is significantly more frequent among infertile men compared to fertile controls, both in those with and without varicocele [68]. A similar association has been reported with Toxoplasma gondii infection in men with varicocele, although this correlation was absent in patients without varicocele [69].

Negative correlations between viral infections and male infertility have also been observed. Cytomegalovirus (CMV), hepatitis B virus (HBV), and hepatitis C virus (HCV) have been implicated in infertility, while Epstein-Barr virus (EBV) shows no such association [70–71]. Among opportunistic bacteria, colonization of the prostate by Propionibacterium acnes has been linked to inflammatory changes and reduced semen quality [72]. Other bacterial pathogens implicated in male infertility include Escherichia coli, Corynebacterium spp., Clostridium spp., and Chlamydia trachomatis [73–75].

CONCLUSION

This article addresses selected aspects of infertility, which affects both women and men. Many of the conditions discussed warrant further research and in-depth analysis of the available literature. Improvements in socioeconomic conditions and modifications of lifestyle factors, such as increased physical activity, weight reduction and a balanced diet, can have a beneficial impact on reproductive outcomes.

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