PharmacologyOnLine

Archives • 2021 • vol.3 • 265-274

MALE INFERTILITY AS A CONSEQUENCE OF ENDOGENOUS AND EXOGENOUS FACTORS

Konovalenko, Serhii[1]; Kritsak, Myroslav[1]; Stechyshyn, Iryna[2]; Pavliuk, Bohdana[2*]

1Department of Operative Surgery and Clinical Anatomy, I. Horbachevsky Ternopil National Medical University, Maidan Voli 1, 46001 Ternopil, Ukraine

2Department of Pharmacy Management, Economics and Technology, I. Horbachevsky Ternopil National Medical University, Maidan Voli 1, 46001 Ternopil, Ukraine

*vons@tdmu.edu.ua

Abstract

Nowadays, infertility in marriage is a pathology that is widespread in the world. The male component of this pathological process has been given close attention in recent years in many countries. With age in men, the content of bioavailable testosterone in the serum decreases, which leads to a decrease in muscle tone and decreased libido in combination with a range of other clinical symptoms and signs. The number of sperm does not decrease significantly with aging, but their quality decreases. Elderly men often have systemic diseases (obesity, diabetes, atherosclerosis, cardiovascular and cerebrovascular diseases, etc.), in connection with which they take medication. It can also adversely affect fertility and exacerbate age-related changes. The pathogenesis of male infertility is associated with testicular overheating, hemodynamic changes, and increased production of active oxygen radicals, decreased antioxidant activity, autoimmune reactions against sperm, and some other mechanisms. Given the above, we can assume that this study is devoted to topical from a theoretical and practical point of view the problem of medicine, which concerns the in-depth study of patterns of remodeling of structures and vascular bed of testes under the influence of endogenous and exogenous harmful factors.

Keywords: *infertility, testicles, endogenous and exogenous factors*

Introduction

It is known that in the structure of infertility, the male factor is 40-50%, the reproductive function of both partners - 25-30%, in 15-20% - the cause of infertility is unknown. It should be emphasized that most researchers claim that acute and chronic circulatory disorders in the testes significantly affect the spermatogenic and hormonal functions of this organ, significantly reducing them. Significant disturbances of testicular blood supply can occur when the body is exposed to endogenous and exogenous toxic factors, leading to circulatory hypoxia of the testis, structural changes in the tortuous seminiferous tubules, and disorders of spermatogenesis [4, 5, 19, 20, 41, 49].

Methods

Data from more than 112 sources were analyzed and summarized, 55 sources of modern literature on the erectile dysfunction, male infertility, immunological infertility, dysfunction of the reproductive system, herminogenic tumors, in medicine were used in this review. The study examines the scientific publications of the last decade, which are available on the internet the key words were "male infertility", "disorders of spermatogenesis", "testicular dysfunction", "spermatogenic cells" and "Immunological infertility".

Results and Discussion

ACUTE AND CHRONIC BLOOD CIRCULATION DISORDERS

An important place among the disorders of spermatogenesis when exposed to the testicle belongs to acute and chronic circulatory disorders that occur in varicocele, inguinal hernias, after inguinal canal plastic surgery as a result of compression of blood vessels of the spermatic cord, as well as inflammatory diseases, testicular injuries [21, 22, 23, 28].

According to the literature, inguinal hernias lead to temporary or permanent circulatory disorders in the testis, followed by degenerative changes in the seminal vesicles, resulting in the pressure of the hernia sac on the blood vessels of a homogeneous canal [23, 53].

There are causes of testicular dysfunction in an inguinal hernia, namely chronic testicular hypoxia due to compression of the arteries and veins of the spermatic cord by the contents of the hernia sac and an increase in temperature in the scrotum on the side of the inguinal hernia. They primarily cause hemodynamic disorders in the testis, which adversely affect spermatogenic and endocrine function. The severity of chronic testicular ischemia in inguinal hernia depends on the timing, shape, and capacity of the hernia. Chronic testicular ischemia plays a leading role in the pathogenesis of the testicular form of male infertility [23].

The results of scientific experiments [19, 21, 24, 30] confirm the high sensitivity of spermatogenic epithelium to circulatory hypoxia. Spermatogenesis normally occurs at a temperature 3-4 °C below body temperature [39]. Negatively affects the spermatogenesis of increased testicular temperature in violation of venous outflow due to blood deposition in the pampiniform venous plexus [25, 39].

At a young age, the most common type of testicular abnormality is a congenital inguinal hernia. Studies have shown morphological changes in the testis in most patients with congenital inguinal hernia, up to complete aplasia of spermatogenic cells, thickening of the tubular walls, development of interstitial fibrosis, Leydig cell hyperplasia, oligospermia and azoospermia [7, 12, 26, 27, 54]. Morphometric analysis of histological preparations [21] from testicular biopsies obtained in patients with congenital inguinal hernia revealed fibrosis in the connective tissue, thickening of the convoluted seminal vesicles, reducing their diameter and slowing spermatogenesis to the stage of spermatozoa, reducing the number of spermatids. The diameter of the capillaries of the interstitial tissue of the testis decreases, which disrupts the trophism of the tortuous seminal tubules and Leydig cells.

Testicular circulatory disorders in more than 40% of patients are due to the presence of recurrent inguinal hernia and are accompanied by significant swelling of the tissues of the spermatic cord in 70-80% of cases, which leads to the development of ischemic syndrome in the testicle. Suppression of spermatogenic function is determined by the duration of the hernia, its shape and capacity [23].

According to scientific studies of clinicians [7, 15, 19, 21] to circulatory disorders in the testicle with spermatogenic and endocrine impaired function can be caused by surgery on the spermatic cord, due to postoperative testicular edema, which leads to partial atrophy of the gonad. Surgical interventions performed on the testicle at a young age increase the percentage of male infertility [40, 49].

Isolation of the hernia sac in oblique hernia from the surrounding tissues and its excision is accompanied by damage to the blood and lymphatic vessels of the spermatic cord, which requires special care for him and the gonad in children and young people.

After inguinal canal plastics, arterial circulation is disrupted in the traditional way, which leads to chronic ischemia and according to ultrasonography studies of the vessels of the spermatic cord in 25 % of cases is accompanied by a decrease in blood flow to the testicle by 2.2-2.5 times. Blood flow in the vessels of the spermatic cord does not change after 6 months. At the level of the spermatic cord, a decrease in testicular blood and lymph flow exacerbates hypoxia of the gonad, as well as changes in the thermoregulation of the scrotum and contributes to the violation of the postoperative condition of the testis. At the same time in 2.5-3% of cases there are ischemic orchitis [14, 25].

It has been experimentally established that acute cessation of blood flow in the testicular artery for 5 min causes minor changes in the testis, 15-30 min ischemia is accompanied by pronounced morphological changes, characterized by an increase in the volume of Leydig cell nuclei, edema of the own capsule of the seminal vesicles. After hernioplasty, chronic testicular ischemia often occurs, which is accompanied by a decrease in the content of testosterone in the serum of patients [49].

7.1-39% of cases of male infertility, there are varicocele-varicose veins of the pampiniform venous plexus of the spermatic cord. This problem is due to its high prevalence and negative impact on spermatogenesis. In this disease, there is a slowing of blood flow, hypoxia, and local fever. The peak incidence occurs in adolescents aged 14-15 years. Varicose orchopathy in children and adolescents with varicocele proceeds according to the type of focal aseptic orchitis and is morphologically manifested by destructive changes in the seminiferous tubules, which lead to inhibition of spermatogenesis. The cause of such changes is circulatory hypoxia [11, 15-17].

In the ejaculate in patients with varicocele, the number of sperm, decreases their motility decreases, and the number of pathological forms increases. Their delay in the ducts can cause a decrease or loss of their biological properties, violation of antisperm immunity.

With varicocele, hypoxia has a negative effect on the concentration, motility and morphological structure of sperm [15, 32, 35, 55]. It can be a source of autoantibodies against sperm, which are found in 8% of infertile men. As a result, there is a stable oligozoospermia or azoospermia, a small amount of sperm, a low concentration of fructose in it. Obstructive azoospermia revealed abnormalities in the structure of sperm an increase in the number of sperm with a small head, with a small acrosome [15].

A testicular biopsy in 1,053 patients with infertility caused by varicocele showed changes in the complexes of specialized connections between supporting cells as well as developing germ cells [18, 23, 40].

Research in recent year's shows that disorders of spermatogenesis in varicocele occur due to autoimmune reactions, due to the violation of the integrity of the components of the hematotesticular barrier. Among the causes of male infertility, 40-60% is varicocele [29, 49].

Low-effective (36-42%) treatment of infertility in men of reproductive age is due to its multifactorial development, which requires a detailed study of the pathogenesis of male infertility. There is a global trend to reduce the activity of spermatogenesis in men of reproductive age [4, 19, 20, 49].

ERECTILE DYSFUNCTION

With regard to sexual function, without ignoring a large number of factors that may play a role (eg, psychological problems, medication), there is evidence that with age, sexual function decreases (including sexual desire and fertility) [3, 21, 26]. Erectile dysfunction, the inability to achieve or maintain an erection during intercourse, is largely related to age and occurs mainly in men over the age of 50 years [3, 5]. Homeostasis of the erectile

process depends on the level of androgens, which decreases with aging. In addition, erectile dysfunction can be caused by atherosclerosis of the penile arteries, or a decrease in the formation of nitric oxide as a result of aging. The prostate is also prone to age-related changes. Benign hyperplasia and prostate cancer are classic diseases that occur in old age, and due to their high frequency are the cause of increasing clinical and socio-economic problems. Moreover, with aging there is an involution of the genital system, decreases the excretory and incretory function of the testes and Leydig cells, hypoandrogenism develops, estrogen content increases, androgen-estrogen balance is disturbed.

One of the main pathogenetic causes of dysfunction of the male reproductive system during aging is oxidative stress, which occurs under conditions of increased formation of reactive oxygen species in the absence of antioxidant protection [8, 9, 13, 36, 42, 43, 45, 55]. Against the background of age-related pathobiochemical changes, Astheno-depressive syndrome memory and sleep disorders develop, and efficiency is reduced. Age-related androgen deficiency is manifested not only by sexual dysfunction, but also associated with age-related diseases (obesity, diabetes, coronary heart disease, osteoporosis, etc.), which exacerbate dysfunction of the male reproductive system [1, 6, 13, 43, 44, 46, 48, 55].

Thus, in the process of spermatogenesis an important place belongs to the interaction of many factors, first – hormonal, as well as nervous, immune, genetic, which are based on subtle, still little studied molecular mechanisms of regulation.

EFFECT OF IONIZING RADIATION

Recently, many researchers have drawn attention to the problem of radiation-induced genome instability (RIGI) [33]. In particular, special attention is paid to the problems of genome instability induced by low doses of radiation, the role of "bystander effect" in the formation of radiation-induced genome instability and its connection with individual radiation sensitivity and, in particular, prove that RIGI is etiological factor of radiation carcinogenesis [31, 37].

RIGI can be manifested by DNA breaks, chromatin recompacting, chromosome aberrations, sister chromatid exchanges, aneu- and polyploidies, spontaneous gene expression, gene and chromosomal mutations, accompanied by disruption of cellular functions, malignancy, induction of apoptosis [2, 37, 53, 54]. Nowadays, it has been proven that the stability of the genome is ensured by the efficiency of functioning in the cell of the so-called DNA damage response system (DRS). DRS – is a universal system for repairing damage to the genome of the cell, arising as a result of endogenous processes (eg, replication errors), and under the influence of external stressors, including radiation. The main elements of this system include activation and modification of many protein sensors of DNA molecule damage, transducers and effectors of cellular signals, providing control of the cell cycle at determining points, its arrest, and repair or programmed death of damaged cells and the like. Modern scientists emphasize the crucial importance of repairing radiation-induced DNA breaks for the survival of the cell and its offspring. H Unrepaired damage is either realized in mutations in genes or chromosomes, or remains in the form of potential for a long time existing damage, which is the source material for the induction of RIGI [2, 52].

Many scientific articles published over the past 15 years by scientists in Japan, Sweden and Spain have confirmed that the chronic long-term effects of low-dose ionizing radiation induce the development of bladder, kidney and prostate cancer.

To study the effect of ionizing radiation on spermatogenesis, separate morphological studies of the effect of radiation on the spermatogenic epithelium of laboratory animals. It was found that exposure to small doses of radiation (0.25 and 1 Gy) causes profound changes in the spermatogenic epithelium of mice in the form of a decrease in the number of spermatogenic cells and an increase in multinucleated spermatocytes and spermatids. The appearance of multinucleated cells indicates delayed maturation and differentiation of cells at some stages of spermatogenesis, which reduces the number of cells in spermatogenesis [55].

Ultrastructural, immunohistochemically and molecular studies have shown that ionizing radiation affects, above all, the subtle mechanisms of spermatogenesis and can subsequently lead to defects in the male reproductive system.

GENETIC FACTORS

One of the causes of developmental abnormalities and dysfunction of the reproductive system are genetic factors [1, 2, 38, 50]. Their frequency correlates with the severity of reproductive pathology. Thus, some researchers believe that 30 % of cases of severe male infertility are due to genetic factors [37, 50]. Causes of male infertility can be chromosomal abnormalities, microstructural rearrangements and gene mutations that lead to impaired sex determination, differentiation or development of the reproductive system, its hormonal dysregulation, impaired spermatogenesis and sperm function [13].

For successful in vitro fertilization, or Intra Cytoplasmic Sperm Injection, it is necessary to determine the etiology of the pathology. Along with chromosomal abnormalities, which are most often represented by Klinefelter's syndrome or its variants, one of the common genetic causes of nonobstructive azoospermia or oligozoospermia is microdeletion (loss of a site) of the Y chromosome [16, 25, 34].

Human Y-chromosome studies indicate that the region located at the AZF locus is the most complex region in the entire human genome, varies greatly in composition and repetitive composition, and has one of the highest mutation rates. Also was found that a partial deletion of the AZFc region may contribute to a complete deletion of this region. The study of only STS markers in this region does not always allow to accurately determine the type of rearrangement of the Y chromosome [34]. Performing this study allows you to more accurately determine the type of microstructural rearrangement of the Y chromosome.

In early studies, it was noted that the frequency of fertilization using sperm obtained from patients with Y-microdeletions and the development of embryos can be compared with the corresponding indicators when using sperm without deletions [2, 34]. Thus, the frequency of fertilization, fragmentation and pregnancy after intra cytoplasmic sperm injection among patients with azoospermia and Y-deletions was 47, 58 and 29 %, respectively, and in patients with the same diagnosis, but with an intact Y-chromosome, respectively – 42, 62 and 29 %. In oligozoospermia, these values were 64, 56 and 46 % in the intact Y chromosome, and 68, 65 and 50 % in the presence of Y microdeletions [34, 37].

According to the literature, the frequency of deletion of the AZF locus is from 7.5 % to 12 % in different populations [1, 37]. The low percentage of chromosomal abnormalities among the proven causes of male infertility reported in the literature probably suggests that in the pathogenesis of male infertility, genetic abnormalities in the deletion of the AZF Y-chromosome locus play an important but not necessarily decisive role. Further research may reveal the role of different types of Y-chromosome rearrangements in the pathogenesis of male infertility.

IMMUNOLOGICAL INFERTILITY

Immunological infertility is associated with the combined action of various antibodies to many sperm antigens [29, 41].

Various factors that disrupt the hematotesticular barrier also cause immune reactions with the formation of antibodies in the blood to the epithelium of the seminiferous tubules and the development of autoimmune infertility, as sperm appear during puberty after the formation of organism immune tissues. The mechanism of formation of antisperm antibodies is because the tolerance of the immune system to its own antigens is formed during embryonic development, when there are no sperm. However, sperm have a different chromosome set from somatic cells. As a result, sperm antigens are perceived by the immune system as foreign, so when they appear, they must be completely separated from it. For the testis, the hematotesticular barrier performs this function. Immunological disorders associated with autoimmune reactions against sperm with the formation of antisperm antibodies may cause a decrease in male fertility. Autoimmune disorders among infertile men, according to various data, range from 3 to 36 % [53]. According to one study, antisperm antibodies are found in 18 % of men of reproductive age. However, only when in the presence of a normal number of sperm more than 50% of them are covered with antibodies, as determined by a direct MAR-test, there may be impaired fertility of immune genesis.

Factors in the formation of antisperm antibodies are considered violations of the integrity of the epithelial layer or blood–testis barrier, which can occur as a result of mechanical, infectious and other damage. Antisperm antibodies can occur in obstruction of the ductus deferens, infections of the reproductive system, which are the most common potential risk factors for immune infertility [27, 29, 49].

Diagnosis of immune infertility today is laboratory confirmed by examination of blood and seminal fluid for antisperm antibodies – immunoglobulins G, A and M, which when interacting with sperm are able to immobilize, agglutinate, block the process of penetration into the ovum, preventing the process of fertilization, or to block the process of implantation of the embryo, even with the use of assisted reproductive technologies [29, 53]. Violation of the blood–testis barrier is always accompanied by the formation of antisperm antibodies. The blood-testis barrier performs a trophic function and provides a specific hormonal environment in the tubules necessary for spermatogenesis; therefore, the violation of the blood-testicular barrier is an important factor in the occurrence of disorders of spermatogenesis (oligo-, terato- and azoospermia). Thus, the condition of the blood-testis barrier is an important diagnostic and prognostic factor that must be considered in the treatment of male infertility.

HERMINOGENIC TUMORS

In recent years, there has been a tendency to increase the incidence of germinal tumors, which occur in 3-4 cases per 100,000 male population and rank fourth among the causes of death from cancer among young men [44, 47]. While the incidence of testicular neoplasms in the United States is 3.1 %, in England and Canada – 2.5 %, in Japan – 0.97 % per 100,000 male population per year [14]. The increase in the incidence of germinal tumors occurs in men of reproductive age from 20 to 40 years [44].

According to scientists, the majority (90-95%) of testicular neoplasms have the structure of germinal tumor [2], which according to the WHO classification include seminomas, embryonic cancer, yolk sac tumors, chorionic carcinomas, teratomas, and testicular intratubular neoplasia.

The causes of testicular tumors have not been definitively elucidated, but factors are known to play an important role in their development. To date, it has been studied that the development of germinal tumors is associated with changes in the spermogram of patients in the form of oligozoospermia and azoospermia, indicating a violation of spermatogenesis in such patients. The data also suggest a possible link between impaired spermatogenesis and the development of germinal tumors [2, 44]. Therefore, a survey of 3,847 infertile men and an analysis of a similar group of men in the general population found that the number of cases of diagnosed testicular cancer in infertile men is 20 times higher than in the general population of men [14].

The testis is a hormonally active and hormone-dependent organ, and the literature suggests the influence of endocrine disorders in the etiology of testicular tumors. Moreover, it is known that the age peaks of tumors of this localization coincide with the rise of gonadotropins in the blood in the antenatal period, during puberty and age involution. In patients with germinal tumors, significant increases in pituitary gonadotropins are often observed, which disappear after tumor removal, which, according to researchers [2, 44], accelerates tumor development. Studies show that gonadotropins stimulate the growth of germinal tumors. Thus, some authors [2, 42] have long observed a patient who developed a typical seminoma on the background of hyperprolactinemia.

Semin has also been reported in Kallmann syndrome [3], the development of which is associated with inadequate synthesis and (or) secretion of gonadotropin-releasing factors. Similar hormonal changes occur in patients with male infertility, in particular, with secretory infertility. There are studies that report the development of germinal tumors in patients with male infertility, in which oligozoospermia was treated with chorionic gonadotropin or synthetic analogues of testosterone (clomiphene, mesterolone) [2, 10, 44].

Nowadays, specific genetic alterations characteristic of this group of tumors have been identified. Histologically, in all types of blood-testis barrier, the isochromosome of the short arm of chromosome 12, in the form and (12p), is detected

[13]. Testicular intratubular neoplasia showed similar chromosomal changes, as well as mutations in the p53 gene in 66 % of cases.

Testicular intratubular neoplasia is claimed to be a precursor to most germinal tumors except for spermatocytic seminoma in the elderly, yolk sac tumors, and mature teratoma in infants [14, 35]. In any case, Testicular intratubular neoplasia is a non-invasive cancer because the anaplastic cells are located within the seminiferous tubule.

Testicular intratubular neoplasia can be observed in the testicular tissue surrounding the tumor, according to some researchers in 90% of cases [2, 44, 50], and found in testicular tissue in men at risk for testicular cancer. Also include a history of cryptorchidism, Kleinfelter's syndrome, family history of testicular cancer (father or brother), contralateral testicular tumor, gonadal dysgenesis, and male infertility [50]. However, some researchers do not find a risk of developing germinogenic testicular tumors in disorders of spermatogenesis [44].

Today markers of testicular intratubular neoplasia are M2A C-KIT and OCT4/NANOG, PLAP [18, 31]. The existing theory of histogenesis of herminogenic testicular tumors is theoretically substantiated as to the fact that testicular intratubular neoplasia cells are pluripotent and can develop into any type of testicular tumor [44]. Therefore, immunohistochemical determination of OCT4 and PLAP levels in testicular tumor indicates a high level of OCT4 and PLAP in classical seminoma and testicular intratubular neoplasia compared with non-seminoma tumors, which demonstrates a close relationship between testicular intratubular neoplasia and typical seminoma and confirms the hypothesis neoplasia as a preinvasive stage of herminogenic tumors.

Numerous studies have been published in recent years that confirm the association of spermatogenesis disorders with the development of testicular tumors.

Conclusions

The analysis of the literature outlined the range of current and promising areas of research. But the polyetiological problem of infertility encourages the study of patterns of structural changes of the testis and vascular bed of the testes under the influence of endogenous and exogenous factors and requires knowledge in the light of the current state of medical science.

Conflict of interest

The authors declare that there are no conflicts of interest.

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