ECOLOGIA BALKANICA

2023, Vol. 15, Issue 1 June 2023 pp. 95-108

Main factors causing male infertility: A review

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Abstract. Human infertility affects millions of people of reproductive age worldwide and impacts their families and communities. Approximately half of the cases of childless couples are due to problems with male fertility (male factor). In this review, a complex of factors that affect the quality of male fertility is presented. Particular attention is paid to the main factors in the organism representing endogenous factors and to the influence of the professional environment and lifestyle, which represent the exogenous factors. In regard to the exogenous factors, it is important to establish the effect of different environmental factors, such as air pollution, presence of various contaminants, such as chemicals, pesticides, and heavy metals, radiation, etc. The exogenous factors also include lifestyle features such as intake of alcohol, smoking, drugs, hazards in the professional working environment, social and psychological aspects, etc. Moreover, with reference to the impact of harmful effects in the professional work environment, the negative factors could be the increased levels of the radiation fund, temperature fluctuations, dustiness, immobility and sitting in the same place for a long time, etc. Obesity and dietary disorders are also associated with the expression of the male factor. In conclusion, it is suggested that for the definition and implementation of adequate and correct treatment of the problems with male fertility, the whole complex of factors should be considered in order to achieve the best results in the procedures associated with *in vitro* fertilization (IVF).

Key words: male infertility, endogenous factors, exogenous factors.

Introduction

Currently, fertility problems are observed both in men and women. It is established that approximately half of the disorders in childless couples are due to male infertility - the so-called "male factor" (Kumar & Singh, 2015; Yu et al., 2015). Unfortunately, in recent years, problems with male fertility, also known as male infertility, are of increasing importance. In this regard, in the recent years in Bulgaria, the statistical data showed a negative population growth, the work of reproductive health specialists is essential and responsible. Thanks to the widespread *in vitro* clinics in Bulgaria, the infertility treatment is more reliable and turns out to be one of the main ways to help solve the problem with infertility. According to data from the National Statistical Institute in Bulgaria from 2013, there are more than 145,000 people with problems related to reproductive health. In the last decade, the problem continues to deepen, and currently, according to unofficial data, there are between 300 – 400,000 young people with impaired fertility. In this regard, the *in vitro* clinics must carry out the responsible and in-depth analyzes for diagnosis, which will determine the exact and adequate treatment. Along with this, additional measures could be applied to inform society about male infertility, and ways to limit the development of the infertility. In the presence of problems with male fertility, it is essential to establish the diagnosis, which determines the need to study the factors causing a disorder in the male reproductive system.

Therefore, the main aim of the present review is to summarize the effects of different endogenous and exogenous factors on male fertility.

Causes and factors for the occurrence of male fertility problems

According to WHO (2010) "infertility is a disease of the male or female reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse". The reasons for the development of infertility in couples are often complex. They can be influenced by various factors from the external environment and from the body. The male infertility may be caused by anomalies in the anatomical structure of the reproductive system, inflammatory processes of the urogenital system, age, overweight and obesity, changes in the normal hormonal status and its regulation, anomalies in the morphological and functional indicators of the gametes. The additional factors are related to the expression of genetic disorders, such as genomic, chromosomal and molecular. In this regards, histopathological studies can reveal defects in the normal development of the reproductive system (eg. Sertoli cells in the seminiferous tubules, disorders in spermatogenesis, etc.). Traumatological conditions that have occurred can also impair male fertility (Nikolaidis, 2017). The above-mentioned factors usually affect reproductive processes directly or indirectly.

According to Merzenich et al. (2010) some exogenous factors, such as lifestyle, have been considered as prerequisite for the deterioration of fertility and the occurrence of male infertility as well. Some environmental factors, such as air pollution, exposure to chemicals and other toxic agents may be responsible for the decreased sperm quality at the population level. Brezina et al. (2012), Tournaye & Cohlen (2012), Yu et al. (2015) consider exogenous factors such as lifestyle features, alcohol intake, smoking, pharmaceuticals, narcotic substances, and professional working environment, as well as social and psychological aspects.

Regarding the impact of harmful effects in the professional working environment with a negative effect on male fertility, it is considered that daily exposure to various toxicants increased levels of the radiation fund, temperature fluctuations, dustiness, lack of physical activity and sitting in the same place for a long time, etc. Disorders in dietary intake and obesity are also presented as factors in the occurrence of disorders in male fertility and they are associated with the expression of the male factor. Li et al. (2011), Brezina et al. (2012), and Yu et al. (2015) also pay attention to the negative influence of various social, psychological and behavioral characteristics, as well as stress factors on male fertility. Along with this, there are studies with conflicting data regarding the relationship between harmful habits, male reproductive status and the quality of sperm parameters (Dikshit et al., 1987; Trummer et al., 2002). Based on that, additional studies on the causes of infertility are very much needed.

Common anatomical reproductive factors with a negative impact on male fertility

Impaired reproduction in men is often associated with the anatomical disorders of their reproductive system. The most common are varicocele, cryptorchidism, hydrocele, and testicular torsion. These anatomical disorders are due to abnormal development or traumatological processes. The above-mentioned conditions have a direct impact on the normal development of the testes, which affects spermatogenesis and the morpho-functional characteristics of the spermatozoa.

Varicocele is among the most frequently diagnosed anatomical factors with a negative impact on male fertility. This male pathology is an abnormal dilatation of the veins of *plexus pampiniformis*. Shiraishi et al. (2012) stated that this factor affects 15% of men of reproductive age, reaching 35% in primary infertility and 80% in secondary infertility. Furthermore, varicocele is mostly associated with changes in sperm indicators and development of male infertility. The development of varicocele is a result of weakness in the vascular wall and insufficiency in the valves of the veins of the testes. This change impairs venous drainage, increases testicular temperature, which contributes to disturbances in normal spermatogenesis and Leydig cell function. The consequences of varicocele are related to both a decrease in sperm concentration and motility, as well as lead to an increase in the abnormal morphology of the spermatozoa. Moreover, advanced and chronic varicocele leads to testicular atrophy and infertility. In this regard, Pastuszak & Wang (2015) stated that the negative role of the disease on the sperm parameters could be related to increased number of immature sperm cells, amorphous cells and impaired testicular functional potential as well. The authors also found significantly higher levels of reactive oxygen species (ROS), which were associated with disruptions in nuclear chromatin integrity and high levels of DNA fragmentation.

According to Boisen et al. (2004) cryptorchidism is one of the most common birth defects of the male reproductive system. It affects between 2% and 9% of boys, who are often born prematurely. Cryptorchidism is associated with the failure of one or both testes to descend into the scrotum prenatally as a part of impaired testicular dysgenesis. As a result of an atypical position, its functions are irreversibly disturbed, which in turn leads to the appearance of infertility. In this regard, cryptorchidism is considered a risk factor for the occurrence of male infertility, testicular cancer and hypospadias in relation to the appearance of testicular dysgenesis syndrome (TDS) (Schnack et al., 2008; Schnack et al., 2010).

Hydrocele is defined as an abnormal free-fluid collection between the visceral and parietal layers of *tunica vaginalis*, which occurs as a result of fluid secretion and reabsorption imbalance. This in turn leads to excessive pressure that adversely affects its normal blood supply and thermoregulation and a disorder in the development of spermatozoa during the process of spermatogenesis (Dagur et al., 2017).

Another factor that may cause male infertility is the testicular torsion, which includes twisting of the testis around the spermatic cord causing ischemia, thus the condition should be treated with acute surgery (Törzsök et al., 2022). According to Jacobsen et al. (2020) this alteration is expressed in two forms, such as rotation of the *tunica vaginalis* (extravaginal torsion) around the spermatic cord and rotation within the *tunica vaginalis* (intravaginal torsion).

Other factors that negatively affect male fertility

Germ spermatogenic cells are vulnerable to external stressors during all stages of spermatogenesis. Human genetic patterns (Lottrup et al., 2013) and experimental findings with animal models showed that the process of differentiation of pluripotent fetal germ cells into spermatogonia is particularly sensitive to toxically induced changes in Sertoli and Leydig cells (Sharpe & Skakkebaek, 2008). Seminomas (germ cell tumors) and non-seminomas, which originate from fetal pluripotent germ cells, have differentiation disturbances during the perinatal period (from 28 week of prenatal development to 7 days after birth). According to Skakkebaek et al. (2016) the fetal hypothesis also associated cell carcinoma with other symptoms of testicular dysgenesis syndrome, such as cryptorchidism, hypospadias, and decreased spermatogenesis.

Moreover, various microorganisms, such as different viruses and bacteria, can cause infections in the male reproductive system. Inflammatory processes are characterized by the appearance of leukocytospermia (the concentration of white blood cells is >106/ml and/or expression of ROS overproduction). The increased number of leukocytes in semen may persist even after antibiotic treatment. This can be seen with established microbiological pathogens, in some patients with complicated infection of epididymis such as prostato-vesiculo-epididymitis (PVE). In addition to the leukocytospermia (WHO, 2010), the patients often have established disturbances in the conventional sperm parameters, such as concentration, motility and morphology (Yanushpolsky et al., 1996). Furthermore, an important post-factor, which leads to change in sperm parameters, is the oxidative stress (OS). It develops as a result of increased production of ROS, as a by-product of aerobic conditions. As stated Jung & Seo (2014), ROS production and total antioxidant capacity remain balanced in fertile men. However, infections, autoimmune, and chronic diseases, advanced age, alcohol consumption, smoking, stress and obesity can counteract and alter this balance by the increased levels of ROS. On the other hand, regarding the functional abilities of spermatozoa, in a small amount, ROS produced in the earliest stages of spermatogenesis, have a physiological and beneficial role (Agarwal et al., 2004). In this regard, ROS are involved in the process of sperm chromatin condensation, apoptosis and proliferation of spermatogonia, which in term regulates the number of sperm cells (Fisher & Aitken, 1997). In mature spermatozoa, ROS are a necessary factor to accelerate the process of condensation and acrosome reaction. Moreover, they are involved in mitochondrial membrane stability and sperm motility. Sperm with abnormal morphology, mainly those with cytoplasmic debris, indicate immaturity and reduced fertilizing potential. In addition, they were found to produce a greater amount of ROS than normally mature spermatozoa (Gomez et al., 1996; Aitken, 1999).

According to Opuwari & Henkel (2016), seminal plasma contains natural antioxidants, such as vitamins C and E, superoxide dismutase (SOD), glutathione, uric acid, and the polyamine spermine, which counteract free radicals. However, the high concentration of unsaturated lipids in the plasma membrane and relatively lower levels of natural antioxidants, expose mature spermatozoa to OS and impairments.

Overweight and obesity as a factor in male fertility problems

When determining overweight as the main indicator, body weight is most often measured in relation to the person's height, which determines body mass index (BMI). Increasing body weight and obesity is becoming a global health problem that is reaching epidemic levels (Maghsoumi-Norouzabad et al., 2020). Changes in the health status is often associated with increased BMI levels and obesity, which has adverse effects mainly on the cardiovascular, neuroendocrine, and reproductive systems. Important emphasis in the human ontogenetic period, when the rapid growth, development, and sexual maturation processes occur, is the state of body weight. In this regard, researchers in Bulgaria studied the physical development by using some anthropometric indicators for body composition, muscle-fat ratio and body type at different ages of development (Boukov et al., 2000; Nikolova & Mladenova, 2005; Nikolova et al., 2005, 2009; Andreenko & Nikolova, 2008, 2010). Intragroup differences were proven in morphological characteristics in children and adolescents based on social and economic factors for Smolyan region, Bulgaria (Mladenova & Nikolova, 2002). Moreover, body composition and anthropological characteristics in children and adolescents from the city of Plovdiv, Bulgaria, were studied (Nikolova et al., 2005; Tineshev & Nikolova, 2010). Physical development and nutritional status during the period of growth in children and adolescents were monitored in relation to components of body mass (Mladenova et al., 2005; Mladenova & Nikolova, 2005, Nikolova et al., 2009). Body fat and BMI indices in Bulgarian children and adolescents were also measured by Nikolova & Tineshev (2010). Comparative analyzes were carried out regarding the height, weight and BMI of children by Nikolova et al. (2010). Nikolova & Boyadjiev (2011) clarified the relationship between body composition and some social factors and habits in children. In earlier studies, an influence of exogenous and endogenous factors was established on the phenotypic formation of girls from the city of Plovdiv between the ages of 7 and 22 (Nikolova & Petrov, 1982).

In recent decades, there has been an excessive interest in proving the association between increased levels of body weight and increased cases of male fertility problems. Authors concluded that sperm concentration was the only sperm parameter that showed a significant decrease at higher BMI index in the infertile men. Kozopas et al. (2020) stated that decreased semen quality is due to increased BMI levels. According to the authors, the group with obesity showed lower sperm concentration, total sperm count and progressive motility. Thus, BMI has a negative correlation with most sperm parameters. Moreover, decreased fructose levels and increased concentration of citric acid and zinc were observed in the overweight group. As the authors stated, obesity could be considered as a negative factor for male fertility.

According to retrospective study by Ramírez et al. (2021) with 9464 patients, the increased BMI index caused alteration in sperm concentration and total sperm count, which was also confirmed by logistic prediction analysis.

Hormonal condition of male infertility

The normal development and functionality of male reproduction also depends on the hormonal status and the processes related to its regulation. Therefore, the condition of the hormonal status is also accepted as an important factor that significantly affects male fertility.

Laboratory studies on the levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, estradiol, and inhibin identified disturbances in the hypothalamic-pituitary-testicular (HPG) axis, which in turn controls reproduction and the identification of primary to secondary hypogonadism were carry out by Chapin & Creasy (2012). Semen function and spermatogenesis are directly dependent on gonadal testosterone production and they are under the direct regulation of the hypothalamic-pituitary-gonadal axis (O'Donnell et al., 2017). Spermatogenesis depends on high levels of intratesticular testosterone and FSH in relation to the stimulation of Sertoli cells (Jarow & Zirkin, 2005). In men, LH primarily stimulates testosterone production, while FSH stimulates semen production. In addition, epididymal function and accessory glands should function normally to produce normal seminal plasma.

Negative factors from the environment and lifestyle, which negatively affecting male fertility

In modern society, environment, etiologic behavior, and diet affect various levels of organization, including the process of spermatogenesis and reproductive capacity. In some cases, when there was a long term exposure with high levels of toxicants, chemotherapy or radiotherapy, disorders in spermatogenesis and morpho-physiological indicators of spermatozoa were observed. As stated by Milachich & Dyulgerova-Nikolova (2020) the regenerative process of spermatogenesis takes a long period to recover and irreversible consequence may occur.

Smoking

Smoking is one of the harmful lifestyle habits that has been associated with male infertility and has been studied for many years. Moreover, mainly retrospective studies, regarding to the effects of smoking on the sperm parameters (Kovac et al., 2015), were associated with sub/infertility in men leading to decrease in sperm concentration, motility and morphology (Zinaman et al., 2000). Vine (1996) found that testosterone levels in smokers can remain unchanged, while the level of estradiol often showed an increase. In addition, Zinaman et al. (2000) studied the negative impact of this factor on a significant decrease in the number of pregnancies in relation to the changes in sperm parameters in the test group of male smokers. A significant increase in leukocytes in the peripheral blood of smokers has been found (Parry et al., 1997), as well as, an increase in their number in the ejaculate in 20% of the examined male smokers (Wolff, 1995). Sharma & Agarwal (1996) identified smoking as a major source of ROS in the ejaculate. ROS have a detrimental effect on the sperm DNA chain and membrane phospholipids (Kim & Parthasarathy, 1998), due to the increased oxidetive stress. Hamad et al. (2014) summarized that a negative factor, such as smoking affects male fertility. The authors studied the relation between smoking and abnormalities in the process of chromatin condensation and packaging, as well as changes in the expression of sperm protamine. The relationship between decreased sperm count and the presence of DNA fragmentation in sperm nuclei in fertile and infertile men who smoke cigarettes was also investigated by Sudhagar et al. (2012). The study included four groups of men depending on the number of cigarettes smoked for a different period. Sudhagar et al. (2012) observed a significant decrease in sperm parameters – concentration, motility and morphology, as well as a statistical dependence on the pack-years of tobacco smoking. As stated by Trummer et al. (2002), smoking is a cellular mutagen and carcinogen, adversely affecting fertility. Cigarette smoke contains numerous toxicants, which have adverse effects on fertility in men and women. In this regard, smokers should be encouraged to stop this harmful habit in order to improve their general health, especially if they plan future pregnancies.

Alcohol abuse and its effect on male fertility

Alcohol consumption has a negative effect on the male reproductive hormones and sperm quality, which is proven by several studies (Muthusami & Chinnaswamy, 2005; Gaur et al., 2010). On the other hand, other studies did not confirm these findings (Kunzle et al., 2003; Lopez Teijon et al., 2007). In addition to the studies that show the negative effects, Muthusami et al. (2005) found that chronic alcohol consumption has adverse effects on male reproductive hormones, sperm quality, as well as Wdowiak et al. (2016) established increases levels of DNA fragmentation in spermatozoa nuclei, which in turn lead to a decrease of effectiveness in the treatment of infertility.

Medication intake and their impact on male reproduction

Various medications have an indirect effect on reproduction. In this regard, studies have been carried out on the influence of some frequently and more widely used classes of medicinal products. Ali & Lam (2011) stated that some antidepressants used as a treatment for depressive conditions and have a male factor effect. In some reports, depressive conditions, even without the use of medications, affect testosterone levels, which in turn may be associated with male infertility. On the other hand, Tanrikut et al. (2010) did not find a negative effect on conventional sperm parameters (volume, sperm concentration, motility, and morphology) in test group of men, which take antidepressants, but with regard to the state of the DNA integrity of the spermatozoa, the patients showed significantly higher values (30.3%) compared to the control group (13.8%). Calcium channel blocker therapy is used for a variety of medical conditions, including hypertension and heart failure. Their action is based on blocking the movement of free calcium ions (Ferri et al., 2008). Aaberg et al. (1989) showed that calcium antagonists produced a dose-dependent effects on sperm motility under in vitro conditions. The authors demonstrated structural changes in both the cephalic and caudal regions of spermatozoa studied by using electron microscopy. Benoff et al. (1994) showed that calcium channel blockers (CCBs) negatively affect the ability of spermatozoa to bind to an egg by altering the lipid bilayer of their plasma membrane. Studies of antiepileptic medications, including carbamazepine, phenytoin, and valproate, have suggested drug side effects including abnormal sperm morphology, decreased sperm motility, lower sperm count, and decreased testicular volume. Herzog et al. (1986) suggested that the mechanism for these adverse reactions could be an interaction between antiepileptic medications and reproductive hormones that interferes with the normal functioning of the hypothalamic-pituitary-gonadal axis pathway. However, many studies are inconclusive as to whether these effects are symptoms of epilepsy itself or side effects of long-term use of antiepileptic medications (Shechter-Amir et al., 1993; Taneja et al., 1994). Many authors documented the beneficial effect of antibiotics on sperm quality in the setting of testicular infection, especially epididymitis (Yániz et al., 2010; Cai et al., 2012). However, data from animal models suggests that some antibiotics, such as tetracycline, may have independent deleterious effects on sperm quality if they are not taken in the context of testicular infection (Farombi et al., 2008). A significant negative effect, even at low doses, of chemotherapy agents and radiation treatment on sperm parameters were found by Marquis et al. (2010) and Drumond et al. (2011). Moreover, alkylating agents, such as cyclophosphamide have a long-lasting effect on spermatogenesis and can cause persistent oligo or azoospermia (Drumond et al., 2011).

Drug use and male fertility

Marijuana, as one of the most common narcotic substances, has a direct and indirect effect on male fertility. Marijuana contains cannabinoids that bind to receptors on the ductus deferens and sperm. Gundersen et al. (2015) found that activation of sperm endocannabinoid receptors induced dose-dependent asthenozoospermia, as well as inhibition of sperm capacitation and the acrosome reaction at fertilization. Cannabinoids also indice Sertoli cell apoptosis. The use of cannabis affects the reduction of serum LH levels, as well as induces the development of oligozoospermia (Fronczak et al., 2012). Along with this, Bracken (1990) observed a state of hyperprolactinemia and hypotestosteronemia leading to inhibition of spermatogenesis. The studied effect depended on the dose and duration of drug use. Studies showed that cocaine use for more than five years led to abnormalities and changes in sperm concentration, motility and morphology (Rizk et al., 1996; Joo et al., 2012). Fronczak et al. (2012) studied the effect of amphetamines and ecstasy (3,4-methylenedioxy-N-methylamphetamine) on the quality and functional relationship of sperm using rat models. Amphetamines caused a dose-dependent reduction in plasma testosterone and DNA damage. Ecstasy produced a similar effect, but it is associated with higher levels of DNA damage, tubular degeneration, and interstitial edema. Furthermore, Joo et al. (2012) and Fronczak et al. (2012) found that drugs, such as methadone and heroin, induced lower serum testosterone concentrations, affected sperm motility, and caused lower semen volumes. Secondary effects result from their alpha-adrenergic blocking properties, such as abnormal sexual dysfunction, which was expressed with a long-term effect even after discontinuation of their use. According to Fronczak et al. (2012), men who were on long-term morphine therapy (oral, transdermal, or intrathecal) had lower serum LH and testosterone levels, a higher incidence of erectile dysfunction, and reduced libido. Safarinejad et al. (2013) showed that drug intake, sperm concentration and quality as well as, catalase and superoxide dismutase activity were decreased, while the frequency of spermatozoa with nuclear DNA fragmentation was increased.

Androgen supplement abuse

Steroid use has been reported to affect muscle function (Parr et al., 2010). Anabolic androgenic steroids include not only testosterone, but also its synthetic derivatives in which there are additional structural changes to maximize its anabolic function and reduce the androgenic effects. Ding et al. (2017) reported that anabolic effects, which include promotion of growth, protein and collagen synthesis, usually occur when physiological testosterone levels (> 1000 ng/dl) were increased, but also induced hypogonadotrophic hypogonadism leading to reduced serum testosterone concentrations. According to the authors, abuse of anabolic derivatives can lead to testicular atrophy, impaired spermatogenesis with oligoastenotheratozoospermia or azoospermia.

Professional environment with a negative impact on male fertility

Harmful conditions in the working environment are considered as factors that can have a negative impact on the fertilizing ability of sperm. Prevention of the negative effects on the male reproductive system is a priority for health professsionals and could be supported by promoting employee awareness and taking appropriate preventive measures for the negative factors. In this regard, Vaziri et al. (2011) reported a list of work-places that are associated with exogenous harmful exposure in professional environment and their possible relation with male infertility. Hauser & Sokol (2008) added that toxic substances, which affect reproductive health could be categorized into several groups, such as heavy metals, agricultural and industrial chemicals, derivatives of petroleum products, substances in various aggregate states separated from the industry, including paints, acetones, acids, alcohols, nitrogen compounds, and pesticides, etc. Studies on the impact and exposure of occupational chemical and physical hazards on sperm quality showed a negative relation between the exposure to solvents or pesticides, and sperm concentration and motility (Petrelli & Mantovani, 2002; Swan et al., 2003), as well as between high heat exposure and conventional sperm parameters (Torabizadeh, 2002).

Sadighi et al. (2003) found that certain environmental factors, as well as certain working conditions (occupational and environmental exposures) had harmful effect on the human reproductive system. The authors studied group of 500 people and 164 of them were exposed to negative factors, which affected the process of spermatogenesis. Sadighi et al. (2003) divided the main group according to the negative factor - 22% were affected by the action of insecticides; 28% - by solvents; 34.1% - by heat and 15.9% - affected by a combination of these factors; and according to their profession - 6.8% agricultural producers, 7.8% - drivers, and 4.4% - welders. Overall, the authors found that agrochemical products had caused decrease in the sperm count and sperm motility was significantly lower among welders. Moreover, the artists exposed to different toxic solvents were three times more affected by oligozoospermia. According to Woldemeskel (2017) and Creasy & Chapin (2018), the evaluation of the impact of lead oxide, heavy metals, agrochemicals on the reproductive system was carry out by applying various methods, such as levels of reproductive hormones, sperm analysis, functional analysis of spermatozoa, biochemical, and genetic approaches. The authors explained that alterations in somatic cell develop-ment and function, or apoptotic exposure to toxic compounds had adverse effects on the male reproductive system. This reflected in different systems and organs essential to reproductive functions. Under normal conditions, somatic cells provide structural support and nutrition and regulate endocrine functions necessary for normal spermatogenesis and fertility. Substances that interfere with sperm development, integrity, and function could have toxics effects on male fertility (Scott et al. 2009; Sansone et al., 2018). Human spermatogenesis could be impaired by exposure to chemicals and radiation (Brennemann et al., 1997). Chemicals, such as hydrocarbons, cadmium, and some phthalate esters showed induce cell apop-tosis in Sertoli cells, which in turn lead to changes in the cytoskeleton and their intercellular con-nections, while at the same time reflected in a decrease in the steroidogenesis of Leydig cells. In addition, local macrophages that interact with Leydig cells, as well as endothelial cells were present in the testicular interstitial space and may become targets for toxin-induced injury (Zheng et al., 2010; Harris et al., 2016). Furthermore, normal reproductive functions could be altered by expo-sure to reproductive toxicants, such as vinclozolin and flutamide (Dent et al., 2015).

The negative impact of high temperature as an occupational negative factor on male reproductive health was investigated by Dada et al. (2001). The authors noted that under normal conditions the testicular temperature is approximately 3°C lower than that of the body, which is an important prerequisite for the efficiency of spermatogenesis. They emphasized that germ cells and Sertoli cells are extremely sensitive to elevated temperature, and as a result, various occupational hazards and agents from the environment could have a negative impact on the male reproductive functions. The analysis was based on comparison between an experimental group of infertile men and a control group of healthy men. The obtained results indicated that intratesticular hyperthermia lead to disturbances in spermatogenesis and to an increased frequency of morphological abnormalities in spermatozoa, as well as, decreased sperm motility and azoospermia. Sheynkin et al. (2011) concluded that long-term and frequent use of a laptop in a sitting position leads to transient scrotal hyperthermia, which in turn could cause disturbances in the process of spermatogenesis, especially in young men and adolescent boys. Numerous studies confirm the importance of occupational exposure and its negative impact on fertility, which indicates the need to conduct in-depth descriptive studies on the occupational factors affecting male infertility and also subsequently should be limited (Torabizadeh, 2002; Li et al., 2011).

Stress as a factor with a negative impact on male fertility

The influence of stress on the human organism is increasingly emphasized. According to Nargund (2015), stress could lead to a variety of neuro-endocrine, immune, and behavioral responses. In this regard, it is necessary to study its negative impact on the human reproductive system. The diagnosis of infertility in partners in a reproductive couple is also a stressful factor, due to the social pressure, the number of tests and treatments, failures and even economic costs associated with diagnosis (Anderson et al., 2010). Thus, stress can decrease luteinizing hormone (LH) and testosterone secretion by affecting spermatogenesis and sperm quality (Corona et al., 2016). Preclinical data suggest that acute stress could impair the testicular function.

Conclusions

In order to clarifying the mechanisms of expression of male infertility, the specialists in the reproductive health pay attention to problems not only related to the organism itself, but also the additional influence of exogenous factors such as the profess-sional environment and lifestyle. In this regard, it is important to establish the influence of some environmental factors, such as air pollution, chemicals, pesticides, heavy metals, radiation, etc. The specified group of factors includes lifestyle habits such as intake of: alcohol, smoking, drugs, narcotic substances, hazards in the professional working environment, social and psychological aspects. Application of adequate and correct treatment of male fertility problems, should be considered as a complex of factors in order to achieve the best possible results in *in vitro* clinics.

References

Aaberg, R.A., Sauer, M.V., Sikka, S. & Rajfer, J. (1989). Effects of extracellular ionized calcium, diltiazem and cAMP on motility of human spermatozoa. Journal of Urology, 141(5), 1221–1224. doi: 10.1016/S0022-5347(17)41225-0

Agarwal, A. & Said, T.M. (2004a). Carnitines and male infertility. Reproductive BioMedicine Online, 8(4), 376-384. doi: 10.1016/S1472-6483(10)60920-0

Agarwal, A., Virk, G., Ong, C. & du Plessis, S. (2014b). Effect of oxidative stress on male reproduction.

The World Journal of Men's Health, 32(1), 1-17. doi: 10.5534/wjmh.2014.32.1.1

Aitken, R.J. (1999). The Amoroso Lecture. the human spermatozoon— a cell in crisis? Journal of Reproduction and Fertility, 115(1), 1–7. doi: 10.1530/jrf.0.1150001

Ali, M.K. & Lam, R.W. (2011). Comparative efficacy of escitalopram in the treatment of major depressive disorder. Neuropsychiatric Disease and Treatment, 7, 39–49. doi: 10.2147/NDT.S12531

Anderson, K., Niesenblat, V. & Norman, R. (2010). Lifestyle factors in people seeking infertility treatment. A review. Australian and New Zealand Journal of Obstetrics and Gynaecology, 50, 8–20. doi: 10.1111/j.1479-828X.2009.01119.x.

Andreenko, E. & Nikolova, M. (2008). Age features in the development of the subcutaneous fat tissue, muscularity and muscle-fat rations in men with different physical activity. Glasnik, Antropološkog društva Srbije, 43, 478-487.

Andreenko, E. & Nikolova, M. (2010). Topical distribution of the subcutaneous fat tissue on some parts and regions of the body in children and adolescents from South Bulgaria. Biotechnology and Biotechnological Equipment, 24, 342-346. doi: 10.1080/13102818.2010.10817859.

Benoff, S., Cooper, G.W, Hurley, I., Mandel, F.S, Rosenfeld, D.L, Scholl, G.M, Gilbert, B.R. & Hershlag, A. (1994). The effect of calcium ion channel blockers on sperm fertilization potential. Fertility and Sterility, 62(3), 606–617.

Boisen, K.A., Kaleva, M., Main, K.M., Virtanen, H.E., Haavisto, A.M., Schmidt, I.M., Chellakooty, M., Damgaard, I.N., Mau, C., Reunanen, M., Skakkebaek, N.E. & Toppari, J. (2004). Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. Lancet, 363, 1264–1269. doi: 10.1016/S0140-6736(04)15998-9.

Boukov, Y., Nikolova, M., Baltadgiev, G. & Matev, T. (2000). Basic somatometric indices in three generations of children from Plovdiv. Journal of Antrhopology, 3, 41-49.

Bracken, M.B. (1990). Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. Obstetrics & Gynecology, 76(2), 552-557.

Brennemann, W., Stoffel-Wagner, B., Helmers, A., Mezger, J., Jäger, N. & Klingmüller, D. (1997). Gonadal function of patients treated with cisplatin based chemotherapy for germ cell cancer. Journal of Urology, 158(3), 844–850.

Brezina, P.R., Yunus, F.N. & Zhao, Y. (2012). Effects of pharmaceutical medications on male fertility. Journal of Reproduction and Infertility, 13(1), 3-11.

Cai, T., Wagenlehner, F.M., Mazzoli, S., Meacci, F., Mondaini, N, Nesi, G., Tiscione, D., Malossini, G. & Bartoletti, R. (2012). Semen quality in patients with *Chlamydia trachomatis* genital infection treated concurrently with prulifloxacin and a phytotherapeutic agent. Journal of Andrology, 33(4), 615-623.

Chapin, R.E. & Creasy, D.M. (2012). Assessment of circulating hormones in regulatory toxicity studies II. Male reproductive hormones. Toxicologic Pathology, 40(7), 1063–1078.

Corona, G., Giagulli, V.A., Maseroli, E., Vignozzi, L., Aversa, A., Zitzmann, M., Saad, F, Mannucci, E. & Maggi, M. (2016). Testosterone supplementation and body composition: results from a meta-analysis study. European Journal of Endocrinology, 174, 99–116. doi: 10.1007/s40618-016-0480-2.

Creasy, D.M. & Chapin, R.E. (2018). Fundamentals of Toxicologic Pathology (Third Edition, pp. 459-516). London, UK: Academic Press of Elsevier. doi: 10.1016/B978-0-12-809841-7.00017-4.

Dada, R., Gupta, N.P. & Kucheria, K. (2001). Deterioration of sperm morphology in men exposed to high temperature. Journal of the Anatomical Society of India, 50(2), 107–111.

Dagur, G., Gandhi, J., Suh, Y., Weissbart, S., Sheynkin, Y.R., Smith, N.L., Joshi, G. & Khan, S.A. (2017). Classifying hydroceles of the pelvis and groin: an overview of etiology, secondary complications, evaluation, and management. Current Urology, 10(1), 1-14.

Dent, M.P., Carmichael, P.L., Jones, K.C. & Martin, F.L. (2015). Towards a non-animal risk assessment for anti-androgenic effects in humans. Environment International, 83, 94–106. doi: 10.1016/j.envint.2015.06.009.

Dikshit, R.K., Buch, J.B. & Mansuri, S.M. (1987). Effect of tobacco consumption on semen quality of a population of hypofertile males. Fertility and Sterility, (48), 334-336. doi: 10.1016/s0015-0282(16)59369-8.

Ding, J., Shang, X., Zhang, Z., Jing, H., Shao, J., Fei, Q., Rayburn, E.R., Li, H. (2017). FDAapproved medications that impair human spermatogenesis. Oncotarget, 8(6), 10714-10725. doi: 10.18632/oncotarget.12956.

Drumond, A.L., Weng, C.C., Wang, G., Chiarini-Garcia, H., Eras-Garcia, L. & Meistrich, M.L. (2011). Effects of multiple doses of cyclophosphamide on mouse testes: Accessing the germ cells lost, and the functional damage of stem cells. Reproductive Toxicology, 32(4), 395–406. doi: 0.1016/j.reprotox.2011.09.010.

Farombi, E.O, Ugwuezunmba, M.C, Ezenwadu, T.T, Oyeyemi, M.O & Ekor, M. (2008). Tetracycline-induced reproductive toxicity in male rats: effects of vitamin C and N-acetylcysteine. Experimental and Toxicologic Pathology, 60(1), 77–85.

Ferri, C., Croce, G. & Desideri, G. (2008). Role of combination therapy in the treatment of hypertension: focus on valsartan plus amlodipine. Advances in Therapy, 25(4), 300–320. doi: 10.1007/s12325-008-0042-x.

Fisher, H.M. & Aitken, R.J. (1997). Comparative analysis of the ability of precursor germ cells and epididymal spermatozoa to generate reactive oxygen metabolites. Journal of Experimental Zoology, 277(5), 390–400. doi: 10.1002/(sici)1097-010x(19970401)277:5.

Fronczak, C.M, Kim, E.D. & Barqawi, A.B. (2012). The insults of illicit drug use on male fertility. Journal of Andrology, 33, 515–528. doi: 10.2164/jandrol.110.011874.

Gaur, D.S, Talekar, M.S, Pathak, V.P. (2010). Alcohol intake and cigarette smoking: impact of two major lifestyle factors on male fertility. Indian Journal of Pathology and Microbiology, 53, 35–40. doi: 10.4103/0377-4929.59180.

Gomez, E., Buckingham, D.W., Brindle, J., Lanzafame, F., Irvine, D.S. & Aitken, R. J. (1996). Development of an image analysis system to monitor the retention of residual cytoplasm by human spermatozoa: correlation with biochemical markers of the cytoplasmic space, oxidative stress, and sperm function. Journal of Andrology, 17(3), 276–287.

Gundersen, T.D., Jorgensen, N., Andersson, A.M., Bang, A.K., Nordkap, L., Skakkebaek, N.E., Priskorn, L., Juul, A. & Jensen, T.K. (2015). Association between use of marijuana and male reproductive hormones and semen quality: a study among 1,215 healthy young men. American Journal of Epidemiology, 182(6), 473–481.

Hamad, M.F., Shelko, N., Kartarius, S., Montenarh, M. & Hammadeh, M.E. (2014). Impact of cigarette smoking on histone (H2B) to protamine ratio in human spermatozoa and its relation to sperm parameters. Andrology, 2, 666–677. doi: 10.1111/j.2047-2927.2014.00245.x.

Harris, S., Shubin, S.P., Wegner, S., Van Ness, K., Green, F., Hong, S.W. & Faustman, E.M. (2016). The presence of macrophages and inflammatory responses in an in vitro testicular co-culture model of male reproductive development enhance relevance to in vivo conditions. Toxicology in Vitro, 36, 210–215. doi: 10.1016/j.tiv.2016.08.003.

Hauser, R. & Sokol, R. (2008). Science linking environmental contaminant exposures with fertility and reproductive health impact in the adult male. Fertility and Sterility, 89, 59-65.

Herzog, A.G., Seibel, M.M., Schomer, D.L., Vaitukaitis, J.L. & Geschwind, N. (1986). Reproductive endocrine disorders in men with partial seizures of temporal lobe origin. Archives of Neurology, 43(4), 347–350. doi: 10.1001/archneur.1986.00520040035015.

Jacobsen, F.M., Rudlang, T.M., Fode, M., Østergren, P.B., Sønksen, J., Ohl, D.A. & Jensen, C.F.S.; CopMich Collaborative. (2020). The impact of testicular torsion on testicular function. The World Journal of Men's Health, 38(3), 298-307. doi: 10.5534/wjmh.190037.

Jarow, J.P. & Zirkin, B.R. (2005). The androgen microenvironment of the human testis and hormonal control of spermatogenesis. Annals of the New York Academy of Sciences, 1061, 208-220. doi: 10.1196/annals.1336.023.

Joo, K., Kwon, Y., Myung, S. & Kim, T. (2012). The effects of smoking and alcohol intake on sperm quality: light and transmission electron microscopy findings. Journal of International Medical Research, 40, 2327–2335. doi: 10.1177/030006051204000631.

Jung, J.H. & Seo, J.T. (2014). Empirical medical therapy in idiopathic male infertility: promise or panacea? Clinical and Experimental Reproductive Medicine, 41(3), 108–114. doi: 10.5653/cerm.2014.41.3.108.

Kim. J.G. & Parthasarathy. S. (1998). Oxidation and the spermatozoa. Seminars in Reproductive Endocrinology, 16, 235–239.

doi: 10.1016/j.fertnstert.2007.12.033.
Kovac, J.R., Khanna, A. & Lipshultz, L.I. (2015). The effects of cigarette smoking on male fertility. Postgraduate Medicine, 127(3), 338-341. doi: 10.1080/00325481.2015.1015928.
Kozopas, N.M., Chornenka, O.I., Vorobets, M.Z., Lapovets, L.Y. & Maksymyuk, H.V. (2020). Body mass index and sperm quality: is there a relationship? Journal of Human Reproductive Sciences, 13(2), 110-113. doi: 10.4103/jhrs.JHRS_15_20.
Kumar, N. & Singh, A.K. (2015). Trends of male factor infertility, an important cause of infertility: A review of literature. Journal of Human Reproductive Sciences, 8(4), 191-196. doi: 10.4103/0974-1208.170370.
Kunzle, R., Mueller, M.D., Hanggi, W., Birkhauser, M.H., Drescher, H. & Bersinger, N.A. (2003). Semen quality of male smokers and nonsmokers in infertile couples. Fertility and Sterility, 79(2), 287-291. doi: 10.1016/s0015-0282(02)04664-2.
Li, Y., Lin, H., Li, Y. & Cao, Y. (2011). Association between socio-psycho-behavioral factors and male semen quality: systematic review and meta-analyses. Fertility and Sterility, 95(1), 116-123. doi: 10.1016/j.fertnstert.2010.06.031.
Lopez Teijon, M., Garcia, F., Serra, O. Moragas, M., Rabanal, A., Olivares, R. & Alvarez, J.G. (2007). Semen quality in a population of volunteers from the province of Barcelona. Reproductive BioMedicine Online, 15, 434–44. doi: 10.1016/s1472-6483(10)60370-7.
Lottrup, G., Jørgensen, A., Nielsen, J.E., Jørgensen, N., Duno, M., Vinggaard, A.M., Skakkebæk, N.E., Rajpert-De Meyts, E. (2013). Identification of a novel androgen receptor mutation in a family with multiple components compatible with the testicular dysgenesis syndrome. The Journal of Clinical Endocrinology & Metabolism, 98(6), 2223–2229. doi: 10.1210/jc.2013-1278.
Maghsoumi-Norouzabad, L., Zare Javid, A., Aiiashi, S., Hosseini, S.A., Dadfar, M., Bazyar, H. & Dastoorpur, M. (2020). The impact of obesity on various semen parameters and sex hormones in Iranian men with infertility: a cross-sectional study. Research and Reports in Urology, 12, 357-365. doi: 10.2147/RRU.S258617.
Marquis, A., Kuehni, C.E., Strippoli, M.P., Kühne, T. & Brazzola, P. (2010). Swiss Pediatric Oncology Group. Sperm analysis of patients after successful treatment of childhood acute lymphoblastic leukemia with chemotherapy. Pediatric Blood & Cancer, 55(1), 208–210. doi: 10.1002/pbc.22475.
Merzenich, H., Zeeb, H. & Blettner, M. (2010). Decreasing sperm quality: a global problem? BMC Public Health, 10, 1–5. doi: 10.1186/1471-2458-10-24.
Milachich, T. & Dyulgerova-Nikolova, D. (2020). The Sperm: parameters and evaluation, innovations in assisted reproduction technology. In: Sharma, N. (Ed.), Innovations in assisted reproduction technology. IntechOpen, Rijeka. doi: 10.5772/intechopen.90677.
Mladenova, S. & Nikolova, M. (2002). Intragroup differences in morphological characteristics in children and adolescents from Smolyan region based on social and economic factors. Journal of Anthropology, 4, 55-58.
Mladenova, S. & Nikolova, M. (2005). Components of body mass and their relations during the growth period of the boys. Proceedings from Balkan Scientific Conference of Biology, Plovdiv University Press, 138-150.
Mladenova, S., Nikolova, M. & Boyadzhiev, D. (2005). Body mass index, some circumference indices and their ratios for monitoring of physical development and nutritional status of children and adolescents. Acta Morphologica et Anthropologica, 10, 226-229.
Muthusami, K.R. & Chinnaswamy, P. (2005). Effect of chronic alcoholism on male fertility hormones and semen quality. Fertility and Sterility, 84, 919–924.
Nargund, V.H. (2015). Effects of psychological stress on male fertility. Nature Reviews Urology, 12, 373-82. doi: 10.1038/nrurol.2015.112.
Nikolaidis, E. (2017). Chapter 12 - Relevance of animal testing and sensitivity of end points in reproductive and developmental toxicity. Reproductive and Developmental Toxicology (Second Edition), 211–224. doi: 10.1016/B978-0-12-804239-7.00012-3.
Nikolova, M. & Boyadjiev, D. (2011). Relation between body composition and some social factors and habits in children and adolescents. Acta Morphologica et Anthropologica, 17, 156-162.

Nikolova, M. & Godina, E. (2008). A comparison of Plovdiv and Moskow children's height, weight and BMI values. Acta Morphologica et Anthropologica, 14, 126-129.

Nikolova, M. & Mladenova, S. (2005). Anthropometric indicators for assessment of body composition. Acta Morphologica et Anthropologica, 10, 218-225.

Nikolova, M. & Petrov, I. (1982). Einfluss der exogenen und endogenen faktoren auf die phenotypische Ausbildung der plovdiver Madchen in Alter von 7 bis 22 Jahren. Human biology, Budapest, 12, 35-40.

Nikolova, M., Mollova, D. & Tineshev, Sl. (2009) Peculiarities in body composition of children. Comparison of Anthropometric and Bioelectrical impedance methods. Journal of Biomedical & Clinical Research, 2, 121-126.

Nikolova, M. & Tineshev, S. (2010). Comparison of the body mass index to other methods of body fat assessment in Bulgarian children and adolescent. Biotechnology and Biotechnological Equipment, 24, 329-337. doi: 10.1080/13102818.2010.10817857.

Nikolova, M., Godina, E. & Mollova, D. (2010). A comparison of Plovdiv and Moskow children's height, weight and BMI values. Acta morphologica et Anthropologica, 15, 212-216.

Nikolova, M., Sivkov, S., Akabaliev, V. & Mladenova, S. (2005). Body composition of children and adolescents in Plovdiv. Proceedings from Balkan Scientific Conference of Biology, Plovdiv University Press, 150-159.

O'Donnell, L., Stanton, P. & de Kretser, D.M. (2017). Endocrinology of the male reproductive system and spermatogenesis. In: L. O'Donnell, P. Stanton, D.M. de Kretser, K.R. Feingold, B. Anawalt, M.R. Blackman, A. Boyce, G. Chrousos, E. Corpas, W.W. de Herder, K. Dhatariya, K. Dungan, J. Hofland, S. Kalra, G. Kaltsas, N. Kapoor, C. Koch, P. Kopp, M. Korbonits, C.S. Kovacs, W. Kuohung, B. Laferrère, M. Levy, E. A. McGee, R. McLachlan, M. New, J. Purnell, R. Sahay, F. Singer, M.A. Sperling, C.A. Stratakis, D.L. Trence & D.P. Wilson (Eds.) Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK279031/

Opuwari, C.S. & Henkel, R.R. (2016). An update on oxidative damage to spermatozoa and oocytes. BioMed Research International, 11, 9540142. doi: 10.1155/2016/9540142.

Parr, M.K., Flenker, U. & Schänzer, W. (2010). Sportsrelated issues and biochemistry of natural and synthetic anabolic substances. Endocrinology and Metabolism Clinics of North America, 39, 45–57. doi: 10.1016/j.ecl.2009.11.004.

Parry, H., Cohen, S., Schlarb, J.E., Tyrrell, D.A., Fisher, A., Russell, M.A. & Jarvis, M.J. (1997). Smoking, alcohol consumption, and leukocyte counts. American Journal of Clinical Pathology, 107, 64–67. doi: 10.1093/ajcp/107.1.64.

Pastuszak, A.W. & Wang, R. (2015). Varicocele and testicular function. Asian Journal of Andrology, 17, 659-667. doi: 10.4103/1008-682X.153539.

Petrelli, G. & Mantovani, A. (2002). Environmental risk factors and male fertility and reproduction. Contraception, 65(4), 297–300. doi: 10.1016/s0010-7824(02)00298-6.

Ramírez, N., Estofán, G., Tissera, A., Molina, R., Luque, E.M., Torres, P.J., Mangeaud, A. & Martini, A.C. (2021). Do aging, drinking, and having unhealthy weight have a synergistic impact on semen quality? Journal of Assisted Reproduction and Genetics, 38(11), 2985-2994. doi: 10.1007/s10815-021-02274-2.

Rizk, B., Atterbury, J.L. & Groome, L.J. (1996). Reproductive risks of cocaine. Human Reproduction Update, 2, 43–55. doi: 10.1093/humupd/2.1.43.

Sadighi, M.A., Aminian, O. & Dehghan, F. (2003). Occupational exposure frequency in men with idiopathic abnormal spermatozoa visiting Royan Institute in 1998-2001. Journal of Reproduction & Infertility, 4(3), 203-212.

Safarinejad, M.R., Asgari, S.A., Farshi, A., Ghaedi, G., Kolahi, AA., Iravani, S. & Khoshdel, A.R. (2013). The effects of opiate consumption on serum reproductive hormone levels, sperm parameters, seminal plasma antioxidant capacity and sperm DNA integrity. Reproductive Toxicology, 36, 18-23. doi: 10.1016/j.reprotox.2012.11.010.

Sansone, A., Di Dato, C., de Angelis, C., Menafra, D., Pozza, C., Pivonello, R., Isidori, A. & Gianfrilli, D. (2018). Smoke, alcohol and drug addiction and male fertility.

Reproductive Biology and Endocrinology, 16(1), 3. doi: 10.1186/s12958-018-0320-7.
Schnack, T.H., Poulsen, G., Myrup, C., Wohlfahrt, J. & Melbye, M. (2010). Familial coaggregation of cryptorchidism, hypospadias, and testicular germ cell cancer: a nationwide cohort study. Journal of the National Cancer Institute, 102, 187–192. doi: 10.1093/jnci/djp457.
Schnack, T.H., Zdravkovic, S., Myrup, C., Westergaard, T., Wohlfahrt, J. & Melbye, M. (2008). Familial aggregation of cryptorchidism – A nationwide cohort study. American Journal of Epidemiology, 167, 1453–1457. doi: 10.1093/aje/kwn081.
Scott, H.M., Mason, J.I. & Sharpe, R.M. (2009). Steroidogenesis in the fetal testis and its susceptibility to disruption by exogenous compounds. Endocrine Reviews, 30(7), 883–925. doi: 10.1210/er.2009-0016.
Sharma, R.K. & Agarwal, A. (1996). Role of reactive oxygen species in male infertility. Urology, 48, 835–850.
doi: 10.1016/s0090-4295(96)00313-5.
Sharpe, R.M. & Skakkebaek, N.E. (2008). Testicular dysgenesis syndrome: mechanistic insights and potential new downstream effects. Fertility and Sterility, 89(2), 33–38.
Shechter-Amir, D., Yavetz, H., Homonnai, T.Z., Huberman, M., Cohn, D.F. (1993). Semen parameters among epileptic males treated with carbamazepine. Israel Journal of Medical Sciences, 29(10), 648–649.
Sheynkin, Y., Welliver, R., Winer, A., Hajimirzaee, F., Ahn, H. & Lee, K. (2011). Protection from scrotal hyperthermia in laptop computer users. Fertility and Sterility, 95(2), 647-651. doi: 10.1016/j.fertnstert.2010.10.013.
Shiraishi, K., Matsuyama, H. & Takihara, H. (2012). Pathophysiology of varicocele in male infertility in the era of assisted reproductive technology. International Journal of Urology, 19, 538-550.
doi: 10.1111/j.1442-2042.2012.02982.x.
Skakkebaek, N.E., Rajpert-De Meyts, E., Buck Louis, G.M., Toppari, J., Andersson, A.M., Eisenberg, M.L., Jensen, T.K., Jørgensen, N., Swan, S.H, Sapra, K.J., Ziebe, S., Priskorn, L. & Juul, A. (2016). Male reproductive disorders and fertility trends: influences of environment and genetic susceptibility. Physiological Reviews, 96(1), 55–97. doi: 10.1152/physrev.00017.2015.
Sudhagar, K., Balajee, R. & Rajan, D. (2012). Correlation between sperm parameters and sperm DNA fragmentation in fertile and infertile cigarette smoking patients. Fertility and Sterility, 97(2), 246-248.
Swan, S.H., Kruse, R.L., Liu, F., Barr, D.B., Drobnis, E.Z., Redmon, J.B., Wang, C., Brazil, C. & Overstreet, J.W. (2003). Semen quality in relation to biomarkers of pesticide exposure. Environmental Health Perspectives, 111(12), 1478–1484. doi: 10.1289/ehp.6417.
Taneja, N., Kucheria, K., Jain, S. & Maheshwari, M.C. (1994). Effect of phenytoin on semen. Epilepsia, 35(1), 136–140. doi: 10.1111/j.1528-1157.1994.tb02923.x.
Tanrikut, C., Feldman, A.S., Altemus, M., Paduch, D.A. & Schlegel, P.N. (2010). Adverse effect of paroxetine on sperm. Fertility and Sterility, 94(3), 1021–1026.
doi: 10.1016/j.fertnstert.2009.04.039.
Tineshev, S. & Nikolova, M. (2010). Anthropological characteristics of body composition in children and adolescents from Plovdiv. Biotechnology and Biotechnological Equipment, 24, 338-341.
doi: 10.1080/13102818.2010.10817858.
Torabizadeh, A. (2002). The relationship between occupation and male infertility. Proceedings of Environmental Factors and Infertility Seminar, 30-31.
Törzsök, P., Steiner, C., Pallauf, M., Abenhardt, M., Milinovic, L., Plank, B., Rückl, A., Sieberer, M., Lusuardi, L. & Deininger. S. (2022). Long-term follow-up after testicular torsion: prospective evaluation of endocrine and exocrine testicular function, fertility, oxidative stress and erectile function. Journal of Clinical Medicine, 11(21), 6507.
doi: 10.3390/jcm11216507.
Tournaye, H.J. & Cohlen, B.J. (2012). Management of male-factor infertility. Best Practice & Research Clinical Obstetrics & Gynaecology, 26, 769-775. doi: 10.1016/j.bpobgyn.2012.05.005.
Trummer, H., Habermann, H., Haas, J. & Pummer, K. (2002). The impact of cigarette smoking on human semen parameters and hormones. Human Reproduction, 17(6), 1554 –1559. doi: 10.1093/humrep/17.6.1554.

Vaziri, M.H., Sadighi Gilani, M.A., Kavousi, A., Firoozeh, M., Khani Jazani, R., Vosough Taqi Dizaj, A., Mohseni, H., Bagery Lankarani, N., Azizi, M. & Salman Yazdi, R. (2011). The relationship between occupation and semen quality. International Journal of Fertility and Sterility, 5(2), 66-71.

Vine, M.F. (1996). Smoking and male reproduction: a review. International Journal of Andrology, 19, 323–337. doi: 10.1111/j.1365-2605.1996.tb00523.x.

Wdowiak, A., Wdowiak, A., Bakalczuk, S. & Bakalczuk, G. (2016). Relationship between alcohol consumption and sperm nuclear DNA fragmentation and pregnancy. Advances in Andrology Online, 3(1), 14–21.

WHO. (2010). WHO Examination and processing of human semen 5 Edition. World Health Organization, pp. 286. Retrieved from: https://apps.who.int/iris/handle/10665/44261.

Woldemeskel M. (2017). Toxicologic pathology of the reproductive system. In Reproductive and Developmental Toxicology. (pp. 1209–1241). CA: Elsevier, Academic Press. doi: 10.1016/B978-0-12-804239-7.00064-0.

Wolff, H. (1995). The biologic significance of white blood cells in semen. Fertility and Sterility, 63, 1143–1157.
doi: 10.1016/s0015-0282(16)57588-8.

Yániz, J.L., Marco-Aguado, M.A., Mateos, J.A. & Santolaria, P. (2010). Bacterial contamination of ram semen, antibiotic sensitivities, and effects on sperm quality during storage at 15°C. Animal Reproduction Science, 122(1-2), 142–149. doi: 10.1016/j.anireprosci.2010.08.006.

Yanushpolsky, E.H., Politch, J.A., Hill, J.A. & Anderson, D.J. (1996). Is leukocytospermia clinically relevant? Fertility and Sterility, 66(5), 822–825.

Yu, X.W., Wei, Z.T., Jiang, Y.T. & Zhang, S.L. (2015). Y chromosome azoospermia factor region microdeletions and transmission characteristics in azoospermic and severe oligozoospermic patients. International Journal of Clinical and Experimental Medicine, 8(9), 14634-14646.

Zheng, S.J., Tian, H.J., Cao, J. & Gao, Y.Q. (2010). Exposure to di(n-butyl)phthalate and benzo(a)pyrenealtersIL-1β secretion and subset expression of testicular macrophages, resulting in decreased testosterone production in rats. Toxicology and Applied Pharmacology, 248(1), 28–37.
doi: 10.1016/j.taap.2010.07.008.

Zinaman, M.J., Brown, C.C., Selevan, S.G. & Clegg, E.D. (2000). Semen quality and human fertility: a prospective study with healthy couples. Journal of Andrology, 21, 145–153.

Received: 11.03.2023
Accepted: 04.04.2023