Conditions Determining Male Infertility

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The lack of knowledge of the causes of impaired reproductive potential results in an inability to implement specific treatment, which is associated with the lack of positive outcomes (pregnancy). This review will make relevant environmental comparisons. It will allow an understanding of the importance of environmental factors in shaping the body's defense and capabilities in the field of reproductive condition. The results can be used in enhancing diagnosis and deciding on appropriate infertility treatment.

Keywords: male infertility ; environmental pollution ; polymorphisms ; oxidative stress ; antioxidants ; azoospermia ; cystic fibrosis ; CBAVD ; Klinefelter syndrome ; Kallmann syndrome

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We explain environmental and genetic factors determining male genetic conditions and infertility and evaluate the significance of environmental stressors in shaping defensive responses, which is used in the diagnosis and treatment of male infertility. This is done through the impact of external and internal stressors and their instability on sperm parameters and their contribution to immunogenetic disorders and hazardous DNA mutations. As chemical compounds and physical factors play an important role in the induction of immunogenetic disorders and affect the activity of enzymatic and non-enzymatic responses, causing oxidative stress, and leading to apoptosis, they downgrade semen quality. These factors are closely connected with male reproductive potential since genetic polymorphisms and mutations in chromosomes 7, X, and Y critically impact on spermatogenesis. Microdeletions in the Azoospermic Factor AZF region directly cause defective sperm production. Among mutations in chromosome 7, impairments in the cystic fibrosis transmembrane conductance regulator *CFTR* gene are destructive for fertility in cystic fibrosis, when spermatic ducts undergo complete obstruction. This problem was not previously analyzed in such a form. Alongside karyotype abnormalities AZF microdeletions are the reason of spermatogenic failure. Amongst *AZF* genes, the deleted in azoospermia *DAZ* gene family is reported as most frequently deleted AZF. Screening of AZF microdeletions is useful in explaining idiopathic cases of male infertility as well as in genetic consulting prior to assisted reproduction. Based on the current state of research we answer the following questions: (1) How do environmental stressors lessen the quality of sperm and reduce male fertility; (2) which chemical elements induce oxidative stress and immunogenetic changes in the male reproductive system; (3) how do polymorphisms correlate with changes in reproductive potential and pro-antioxidative mechanisms as markers of pathophysiological disturbances of the male reproductive condition; (4) how do environmental stressors of immunogenetic disorders accompany male infertility and responses; and (5) what is the distribution and prevalence of environmental and genetic risk factors.

1. Introduction

Nowadays a large pool of substances potentially harmful for human health is incessantly present in the natural environment. Toxic metals (Cd, Pb, Hg, As, Be, V, Ni), dioxins, anti-metabolites, dyes, herbicides, fungicides, or even house dust constitute a detrimental mixture that people are exposed to practically every day [1][2][3][4]. Therefore, essential systems of the human organism are continually subjected to potential damage. Among them, the reproductive system, especially spermatogenesis, appears to be affected, too [5]. Long-term exposure to destructive factors may lead to occupational diseases, irreversible changes in the reproductive system (worsening of sperm quality, disorders in spermatogenesis), or even to infertility [6]. In this respect, toxic heavy metals and certain chemical pollutants (dichloro-diphenyl-dichloro-ethane DDT or methoxychlor) are considered as oxidative stress inducers [7]. Oxidative stress is defined as a lack of balance between per-oxidation and anti-oxidation, directly connected with overproduction of reactive oxygen species ROS [8]. It is difficult to avoid certain factors that induce oxidative stress, especially in cities due to traffic and industrial activity (smog, traffic fumes), but other sources of ROS may remain under control. Cessation of smoking, introducing a low-fat diet, or regular physical activity can be simple strategies against oxidation [9]. One of the causes of oxidative stress is the decrease of antioxidant enzymes (superoxide dismutase SOD, catalase CAT or glutathione peroxidase GPx) which erodes the line of defense against reactive forms of oxygen [10]. Thus, introducing an anti-oxidative diet consisting, e.g., of fruits and vegetables rich in vitamins A, C, E, and B, is recommended and beneficial for

strengthening the anti-oxidative potential of the body [11][12][13]. The male reproductive condition can be improved by supplementation of beneficial elements such as zinc or selenium that cause positive changes in sperm count and motility [14]. Melatonin, beta-carotene, or luteine also contribute to maintaining high semen quality [15][16].

Since oxidative stress contributes to serious impairments in genetic composition, such as damage of chromosomes or breakages in the deoxyribonucleic acid DNA , it is valuable to analyze genetic reasons for male infertility. On chromosome Y, microdeletions in the AZF-region (called the azoospermic factor) result in spermatogenic failure and a lack of sperm cells in semen [17][18]. The world frequency of AZF microdeletions is estimated in the range of 1–15% of cases of azoospermic infertile men [19][20]. Other common reason for male infertility is cystic fibrosis, i.e., a recessive disease with a frequency of occurrence of 1/2500 live births, is caused by mutations in the *CFTR* gene on chromosome 7 [21]. Overproduction of thick, sticky mucus in organs with mucous glands is a typical symptom of the disease. In addition to pathological changes in the alimentary or respiratory systems, cystic fibrosis also contributes to infertility through clogging spermatic ducts with mucus [22][23]. The condition often accompanying cystic fibrosis is a congenital bilateral absence of the vas deferens, manifested as aplasia of spermatic ducts and an obstruction of sperm outflow into the urethra. Similarly to cystic fibrosis, congenital bilateral absence of the vas deferens is caused by mutations in the *CFTR* gene [24][25]. Finally, impairments on the X chromosome play an essential role in pathogenesis of Klinefelter syndrome KS (the presence of an extra X chromosome in the male karyotype) and Kallmann KAL syndrome (mutations in the KAL1 gene on the X chromosome; KAL1 is a human gene which is located on the X chromosome at Xp22.3 and is affected in some male individuals with Kallmann syndrome). The former is manifested by small testicles, degenerative changes in spermatic ducts, azoospermia, and decay of potency [26][27][28][29][30], while the latter is manifested in a deficiency in the sense of smell, delayed maturation, small testicles, and underdevelopment of the penis [31][32][33][34].

We reviewed the recent data in an effort (1) to estimate the diversification of potentially harmful factors accumulated in the modern environment (from heavy metals to domestic dust) and their influence on human fertility; (2) to establish the relationship between various pollutants and oxidative stress intensification; (3) to find effective strategies in overcoming oxidative stress in everyday human life, thereby improving reproductive conditions; (4) to analyze common genetic factors underlying male infertility associated with chromosome Y (AZF region); and (5) to analyze the most common factors underlying male infertility associated with chromosome 7 and the X chromosome.

This review of existing research will broaden our knowledge of the impact of environmental stressors on antioxidant reactions, and changes of lipoperoxidation and immunogenetic disorders in patients with symptoms of infertility. The results can be used in the prophylaxis of male infertility among patients inhabiting degraded areas. It will also answer some questions about the causes of infertility in men in whom it was previously unknown. Linking the biochemical and morphological parameters of semen with immunogenetic disorders will bring clarification to the role of environmental factors in shaping responses to various stressors. Analysis of the activity of enzymatic antioxidative mechanisms, lipoperoxidation intensity, and the levels of stress proteins and non-enzymatic mechanisms jointly can give a more complete picture of conditions shaping the response of an organism to environmentally diversified stress. Simultaneous analysis of the degree of the accumulation of different physiological elements in the semen of men from polluted areas, as well as lipoperoxidation processes and reactions from oxidative enzymatic and non-enzymatic systems, will map the causal connections with the reproductive condition of particular patients.

Insufficient knowledge about the causes of impaired reproductive potential results in an inability to implement specific treatments, which is associated with a lack of positive outcomes [35]. This review allows an understanding of the role of environmental factors in shaping the body’s defense capabilities in the area of reproductive condition. In stress conditions physiological responses of the reproductive system can be estimated based on the changes in the activity of antioxidant enzymes, biochemical and structural modifications of proteins caused by oxidative stress involving products of advanced oxidation protein, assessment of oxidative stress by changing the quantity of products of advanced oxidation protein, or changes in the lipoperoxidation and pro-antioxidant mechanisms inactivation of ROS. The lack of knowledge of the causes of impaired reproductive potential results in an inability to implement specific treatment, which is associated with the lack of positive outcomes (pregnancy). This review will make relevant environmental comparisons. It will allow an understanding of the importance of environmental factors in shaping the body’s defenses and capabilities in the field of reproductive condition. The results can be used in enhancing diagnosis and deciding on appropriate infertility treatment. Physiological responses in the semen and blood of patients (specified above) are indicative of changes in the reaction to stress conditions.

A further purpose of this review is to analyze the immunological mechanisms that determine male reproductive potential and the impact of environmental stress on semen quality parameters. This is of major significance since bioaccumulation of toxic metals causes oxidative stress, which negatively impacts the condition of the semen. These events lead to alterations in the activity of caspase proteins leading to apoptosis in the germ cells . Most of the negative changes

mentioned above result from degradation of the natural environment with toxic metals, pesticides, or chemicals used in the industry. Since oxidative stress may contribute to DNA damage, the connected causes of human infertility appear at the genetic level. Mutations responsible for pathophysiological changes in the human reproductive system occur in Down syndrome (trisomy of autosome 21), Edwards syndrome (trisomy of autosome 18), Patau syndrome (trisomy of autosome 13), Klinefelter syndrome, Turner syndrome (complete or partial absence of one of the X chromosomes in all cells of the body or a portion thereof), or cystic fibrosis (mucoviscidosis) [36]. These mutations may create a serious, usually irreversible threat to male fertility with diverse prevalence. Simultaneous analysis of the degree of accumulation of different physiological elements in the semen of men from polluted sites will trace the causal connections listed above in parallel with the reactions of the biochemical systems and the level of elements, lipoperoxidation, and oxidative enzymatic and non-enzymatic systems. Here it is important to take account of links between environmental elements and conventional pathologies associated with male infertility in correlation with selected biochemistry (total protein, albumin, cholesterol, glucose, fructose, bilirubin, alanino-aminotransferase ALAT, aspartat-aminotransferase ASPAT, urea, enzymes (akrosine, alkaline, and acid phosphatase), and thioneins. Complementing this evaluation is the analysis of the extracellular matrix, the components of which also mediate intercellular communication through (1) binding of cytokines or concentrate them in certain locations; (2) presentation of cells; and (3) direct binding of the individual components with specific cell receptors, which causes specific changes in the cell metabolism.

This review analyzes the immunological mechanisms that determine male reproductive potential and the impact of environmental stress on semen quality parameters. The influence of chemical elements with different physiological groups on the morphometry of semen of people living in areas with varying degrees of contamination and degradation changes (acidification, salinity, increased levels of Ca, Fe, Mg, and trace elements) is discussed. Bioaccumulation of many elements causes oxidative stress, which leads to apoptosis and determines the condition of the semen. These events lead to alterations in the activity of caspases and induction of apoptosis in the germ cells. We examine the activity of antioxidant enzymes, which may differ significantly to the control group. Chemical elements, not yet analyzed in the study of infertility (Al, Ni, Cr, Mn, As, Se, Si), play an important role in the induction of immunogenetic changes and affect the activity of antioxidant enzymes. The changes may result from degradation of the environment with heavy metals, pesticides, and chemicals used in industry. These genetic mutations are responsible for the genetic pathophysiological changes (as above). Simultaneously, one of the causes of male infertility is immunogenetical change. Therefore, we should consider the cumulative impact of xenobiotics in the semen on the occurrence of mutations responsible for these diseases and disorders of spermatogenesis, in the form of the expression and deletion of genes. Previous studies give conflicting results about the effects of chemical elements on sperm. Much of the work relates to their direct impact or has been carried out on the seed derived from persons occupationally exposed [37]. This knowledge is incomplete and needs to be reviewed, but the condition of human sperm deteriorates significantly. Further research should broaden the understanding of the impact of elements on immunogenetic disorders in male infertility, both in lipoperoxidation and antioxidant activity, as well as reactions with reductases and stress proteins. This will determine the distribution of the prevalence of these changes in regions where such research has not been conducted. This will enable the mapping of the distribution of immunogenetic changes, the dangerous mutation of DNA, semen biochemical parameters, and concentrations of chemical elements in it. The results can be used in the prevention of infertility in women living in degraded areas. They will also shed light on the causes of infertility in those men who were previously fertile. Linking biochemical analysis of semen and immunogenetic changes elucidates the mechanisms and clarifies the role of heredity factors in shaping the response to environmental stress by oxidative enzyme systems. The results can be used in the diagnosis of male infertility undergoing environmental weakening. In addition, the levels of oxidative enzyme activity circuits and an analysis of the lipoperoxidation intensity and protein levels of stress can give an index of sperm health conditions in humans.

2. Molecules Affecting Male Infertility

Currently, 30% of men suffer from idiopathic infertility [38]. The standard semen analysis is still the most important clinical assessment of male reproductive potential. The results of this analysis determine ejaculate capacity, sperm count, motility, and morphology. Among the basic components of the sperm plasma ions Na, K, Mg, Ca, Fe, Cu, Zn, and Se are the most significant [39]. The potassium concentration in the sperm plasma should be 27 ± 5 µmol (1.1 mg × mL^{-1}). When the ratio of Na/K exceeds 1:2.5, it affects sperm motility and an increased concentration of potassium cations increases the electrical charge of the sperm cell membrane decreasing the motility of cell [40]. Each element plays a different role in the body, thus destabilizating their level has serious consequences. Ca, Mg, and other electrolytes maintain osmotic equilibrium and are involved in the transport of nutrients. Zn and Fe are involved in redox processes. Zn and Mg are stabilizers of cellular membranes and coenzymes of SOD, which prevents the harmful effects of free radicals on sperm . Zinc, as one of the most important factors influencing male sexuality, is involved in processes of reproduction, in both

hormone metabolism and sperm formation, as well as in the regulation of sperm viability and motility . Zn deficiency results in decreased levels of testosterone and decreased sperm count, potency disorders, reduced sperm viability and even infertility [41]. Zinc, as an antioxidant plays an important role in the protection of spermatozoa from the attack of free radicals. High levels of Zn in the semen decrease the activity of oxygen radicals, maintaining sperm in a relatively quiet and less motile state, resulting in a lower consumption of oxygen which allows the storage of energy needed during the passage through the genital tract. Zn also has a protective effect against too high a concentration of Pb (contributing to reduction of fertility). Even with a high Pb accumulation, elevated Zn concentration has a protective effect, reducing the harmful effects of this element[42][43]. Chia et al. (2001) [44] have demonstrated a correlation between the concentration of Zn in the blood and semen plasma, and the quality of sperm from fertile and infertile men. The results showed lower Zn levels (accompanying lower morphologic parameters) in patients with impaired fertility (183.6 mg·L^{-1}). In fertile patients Zn level was much higher (274.6 mg × L^{-1}). Thus, Zn has a positive impact on fertility and potency through participation in spermatogenesis [44]. An important role of Zn was also described by Giller (1994)[45], indicating that semen volume decreases by 30% at a low Zn concentration. Similarly, Mohan et al. (1997) [46] have shown that men with low daily Zn intake (only 1.4 mg) displayed a significant decline in semen capacity and concentration of testosterone in serum. A relationship was also shown between the level of Zn in serum and semen in oligozoospermic infertile men, with significantly lower levels of Zn in serum and semen of men with fertility problems [46].

The second element of fundamental importance for semen quality is selenium, which occurs in high concentrations in semen and plays an important role in maintaining reproductive condition. Selenium is an essential microelement at low levels of intake and produces toxic symptoms when ingested at level only 3–5 times higher than those required for adequate intake. Se-counteract the toxicity of heavy metals such as Cd, inorganic mercury, methylmercury, thallium and to a limited Ag extent. Although not as effective as Se, vitamin E significantly alters methylmercury toxicity and is more effective than Se against silver toxicity. Selenium can particularly counteract Hg toxicity, and is the key to understanding Hg exposure risks. Selenium compound selenide binds mercury by forming mercury selenide, which neutralizes the harmful effect of Hg. However, once that bond is made, Se is no longer available to react with selenoproteins that depend on it. Human studies have demonstrated that selenium may reduce As accumulation in the organism and protect against As-related skin lesions. Se was found to antagonize the prooxidant and genotoxic effects of As. From epidemiological point of view Se interaction with heavy metals raises a large interest. Although antagonistic influence of Se on the bioaccumulation of Hg, Cd, and As is well known, interaction mechanism between those elements in humans remain unexplained [47]. Selenium takes part in the constitution of the mitochondrial shield in sperm cells and influences the condition and function of sperm, and is effective in the treatment of impaired fertility[47]. Simultaneously, selenium as part of selenoproteins, playing a key role in defending the body against oxidative stress[48]. Phospholipid hydroperoxide glutathione peroxidase PHGPx changes the physical properties and biological activity during the maturation of sperm. In spermatids it displays enzymatic activity and is soluble, while in mature sperm it is present as an inactive and insoluble protein. Inside the mature sperm PHGPx protein constitutes at least 50% of the material of the shield [49]. However, toxic heavy metals (Cd, Pb, Hg, Ni, Cr, B, V) impair testicular function and the mechanisms of their toxic activity in the nucleus include damage of the vascular endothelium of the Leydig' and Sertoli' cells but these heavy metals not only damage the vascular endothelium but as stated for example, in[50][51], Cd and Pb cause an alteration in the functionality of the Sertoli cell even at subtoxic doses. Oxidative stress occurs as a result of their accumulation due to impairment of antioxidative defensive mechanisms and intensification of the inflammatory reaction leading to changes in the morphology and function of the testes [52][53]. The effect of these changes can be necrosis of the seminiferous tubules, which inhibits the synthesis of testosterone and impairs spermatogenesis. Short-term exposure to these metals increases the activity of SOD, CAT, GPx, and glutathione reductase GR, which is indicative of the activation of defense mechanisms and the adaptive response of cells [54].

In order to fully analyze the problem, we should distinguish precisely the functions of individual forms of GPx and their importance for the male reproductive system. Glutathione peroxidases are composed of eight forms that are distributed in different tissues with differences among species [55]. They catalyze the reaction needed to remove hydrogen peroxide H_2O_2 and other hydroperoxides using reduced glutathione GSH. In order to keep removing hydroperoxides, the oxidized glutathione disulfide GSSG must be reduced back to GSH by the GR enzyme using NADPH as reducing agent. There are selenium-dependent and selenium-independent GPx forms. The first group is represented by GPx1–4 and the second group by GPx5–8. GPx forms can also reduce peroxynitrites $ONOO^-$, a very reactive ROS capable of harming cells promoting tyrosine nitration in proteins involved in motility and sperm capacitation [55]. Of great importance for spermatozoa is the presence of the selenoprotein phospholipid hydroperoxide GPx4 (PHGPx), a structural protein which is essential for normal formation of the mitochondrial sheath and constitutes about 50% of the sperm midpiece protein content localized in the mitochondrial helix. The need for mitochondrial PHGPx (mGPx4) to assure normal sperm function has been demonstrated in humans since infertile men have shown low sperm motility with abnormal morphology [55]. It is important to highlight that what is relevant for fertility is the ability of mGPx4 to interact with hydroperoxides to form the

mitochondrial sheath during spermiogenesis and not its antioxidant activity which is less than 3% of the total PHGPx protein content in ejaculated spermatozoa. Selenium is essential to assure normal GPx4 function during spermiogenesis as it was confirmed by the presence of abnormal spermatozoa with poor motility [55].

The sperm chromatin formation during spermiogenesis is accomplished in part by the nuclear isoform of GPx4 (snGPx4); this enzyme mediates the oxidation of S–H groups of protamines by hydroperoxides. It is possible then that other proteins are involved in the sperm chromatin re-modelling and potential candidates are peroxiredoxins. The contribution of GPx to the protection against ROS is limited in human spermatozoa since human spermatozoa, testes, or seminal plasma lacks GPx2, GPx3, and GPx5 and GPx4 are insoluble and enzymatically inactive in mature ejaculated spermatozoa[55]. It seems that the role of GPx1 as important antioxidant enzyme is questionable because $Gpx1^{-/-}$ males are fertile and they are not susceptible to oxidative stress and lipid peroxidation does not increase in human spermatozoa incubated with H_2O_2 in the presence of carmustine (GR inhibitor) or diethyl maleate (binds to GSH making it non-accessible for GPx/GR system) that affects the GPx/GR system activity [55].

In turn, Gladyshev et al. (2016) [56] indicates that the human genome contains genes coding for selenocysteine-containing proteins (selenoproteins). These proteins are involved in a variety of functions, most notably redox homeostasis. Selenoprotein enzymes with known functions are designated according to these ones. Selenoproteins with no known function appear to be important but require further research.

A particularly dangerous heavy metal for semen quality is lead. It is increasingly recognized that impaired fertility in men can be associated with environmental and occupational exposure to lead [57]. The mechanism of action of lead on male gonads is complex and includes effects on spermatogenesis, steroidogenesis, the redox system, and damage of the vascular endothelium of the gonads by free radicals, resulting in morphological changes (weight changes of the testes and seminal vesicles, their fibrosis, a reduction in the diameter of the seminiferous tubules, and a reduction in the population of reproductive cells by apoptosis) and functional changes (decreased testosterone synthesis). Lead may affect the function of Leydig' cells impairing steroidogenesis, decreasing the levels of testosterone and worsening the quality of sperm" but this observation is valid not only for Leydig cells but also for Sertoli cells that are the sentinel of spermatogenesis . The phenomenon of oxidative stress in animals poisoned with lead confirms an increase in lipid peroxides and decomposition of thiobarbituric acid reactive substances TBARS [58].

3. Antioxidant Mechanisms

A significant role in the pathogenesis of infertility involves redox reactions because the germ cells are capable of producing ROS. A certain physiological amount of reactive metabolites of oxygen, rising in the respiratory chain, is necessary to maintain normal sperm functionality. However, due to overproduction of ROS or the exhaustion of the compensating possibilities of antioxidative mechanisms in sperm, oxidative stress begins to increase . Subsequently, it leads to changes in peroxidation of lipid membranes of sperm, impairing the structure of membrane receptors, enzymes, transport proteins, and leads to an increase in the level of DNA fragmentation of sperm [59][60][61]. The balance between ROS formation and the protective actions of antioxidative system is necessary to sustain normal functions of an organism . The important area of influence of essential elements are metabolic mechanisms, i.e., reactions involving compounds quenching excited molecules, non-enzymatic mechanisms (ceruloplasmin, transferrin, polyamides, transitional metals, sequestration of metals, thioneins), antioxidant enzymatic mechanisms (SOD, CAT, GPx, GR, glutathione S-transferase GST, secretory phospholipase A2 sPLA2, reactions involving heat shock protein HSP, chaperones, and proteases [59][60][61]. Due to the particular sensitivity of male reproductive cells to the oxidative action of ROS, mammalian semen is equipped with a variety of enzymatic and non-enzymatic compounds, which neutralize the excess of ROS, localized in the seminal plasma and inside sperm cells [59][60][61]. A direct relationship between the SOD activity and sperm damage and sperm motility was confirmed by numerous researchers . The addition of exogenous SOD to a suspension of sperm cells protected their vitality and significantly affected motility by inhibiting the destruction of biological membranes. However, some researchers could not confirm the effect of SOD on semen quality and sperm fertilizing potential [62][63].

The most effective antioxidative enzyme in sperm apart from SOD is CAT . It was found inside sperm cells and seminal plasma, with activity significantly reduced in infertile men [64]. Another important enzyme that protects cells from the toxic effects of H_2O_2 is GPx. The sperm GPx is located in the mitochondrial matrix. Its activity is largely related to the level of Se in semen. The important protective role of GPx in counteracting the loss of sperm motility as a result of spontaneous lipoperoxidation has been widely confirmed. Many researchers have proved the relationship between peroxidative damage of sperm and male infertility [62], because lipoperoxidation is one of the most important processes related to the action of ROS. The accumulation of damaged lipid molecules lowers the fluidity of biological membranes and the structural damage of membranes has a direct impact on their receptor and transport functions.

4. Genetic Effects

The accumulation of heavy metals in an organism and the impact of free radicals can cause immunogenetic disorders, chromosomal aberrations and consequently lead to serious genetic defects, causing infertility include numerical and structural aberrations that may affect autosomes or sex chromosomes [65][66][67][68]. Chromosomal aberrations appear in 7% of infertile men, that is 30 times more frequently than in the general population [69][70]. The most common chromosomal cause of male infertility is Klinefelter syndrome (>4%) [71]. In this disease, similarly to Turner syndrome, partial fertility is maintained only in mosaicism [72]. In Klinefelter syndrome changes in nuclear structure leading to infertility may be a result of the presence of two alleles of many genes associated with the X chromosome, which typically operate on the principle of disomy and do not undergo inactivation during lyonization of extra chromosome. In 15% of males with azoospermia and 5% with oligozoospermia display an abnormal karyotype [73]. Another cause of male infertility is microdeletions of the Y chromosome or aberrations and mutations of genes responsible for male sexual development, e.g., located in the short arms of the Y chromosome in the region Yp11.2 (the Yp11.2 region containing the amelogenin gene on the Y chromosome *AMELY* locus). The amelogenin gene on the Y chromosome, *AMELY*, is a homolog of the X chromosome amelogenin gene *AMELX*, and the marker is employed for sexing in forensic casework, *SRY* gene (a sex-determining gene on the Y chromosome). *SRY* gene, as a sex-determining gene on the Y chromosome in mammals that determines maleness and is essential for development of the testes; testis-determining factor TDF, known as sex-determining region Y SRY protein, is a DNA-binding protein (known as gene-regulatory protein/transcription factor) encoded by the *SRY* gene that is responsible for the initiation of male sex determination in humans). Another reason for male infertility is the partially symptomatical form of cystic fibrosis, responsible for 60% of the so-called obstructive azoospermy. The true symptomatic form of cystic fibrosis is the result of mutations in the *CFTR* gene and in 95% cases of men leads to infertility [74][75].

The current state of knowledge about male fertility conditions does not give clear and unambiguous answers to the cause of the growing problem of infertility. We cannot determine unambiguously which environmental factors have the greatest impact on human fertility. It is, therefore, necessary to continue research in the field of concentration of elements, oxidative enzyme activity, and the incidence of immunogenetic disorders in the seed. These analyses are a benchmark in project design, making it possible to verify the views on the impact of environmental stressors on male fertility. The results of these studies can be applied in the prevention of infertility and contribute to the development of new diagnostics.

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