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Environmental Factors and Male Infertility

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Abstract

A significant decrease in human fertility has been observed in the last 50 years. Approximately 15% of couples of reproductive age have fertility problems and about half of these cases are because of male factors. A growing body of evidence suggests that environmental factors play an important role in the causes of male infertility. Our environment is contaminated by natural and synthetic chemicals, which could interact with the endocrine system, resulting in the reduction of human fertility. Studies carried out in recent years have proven that endocrine-disrupting chemicals may disturb fertility of men. Improper lifestyle factors such as smoking, alcohol consumption, high temperature, radiation also have negative impact on male fertility. This chapter is an overview of recent developments about the importance of endocrine-disrupting chemicals and lifestyle factors' effects on sperm counts and male fertility in human.

Keywords: male infertility, endocrine-disrupting chemicals, EDCs, lifestyle factors, spermatogenic failure

1. Introduction

Approximately, 10–15% of human couples of reproductive age have impaired fertility and male factor is responsible in 50% of these cases. As is well-known, human reproduction is precisely regulated and extremely fragile to the environmental changes. Let alone harmful chemicals, even body temperature could affect sperm quality. In this chapter, we discuss two well-known major aspects that contribute to male infertility such as endocrine-disrupting chemicals (EDCs) and lifestyle factors.

2. EDCs and male infertility

The focus of male infertility is that our environment is contaminated by natural and synthetic chemicals. These chemicals could interact with the endocrine system [1]. People's exposure to chemicals is thought to be extensive, especially to EDCs, which supposed to alter the male reproductive tract. Mass industrial production and widespread use of EDCs have resulted in worldwide contamination.

EDCs are exogenous agents with the ability to mimic endogenous hormones, interfering with their biosynthesis, metabolism, and normal functions. These natural hormones are responsible for self-balance, reproduction, development and behavior of natural hormone synthesis, secretion, and transport. They mimic and inhibit the action of natural endogenous hormones or alter the normal regulatory function of the endocrine system and have potential hazardous effects on male reproductive axis causing infertility [2]. EDCs are estrogen-like and anti-androgenic chemicals in the environment. Bisphenol A (BPA), phthalates, polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT), dioxin, and some pesticides are the representatives of EDCs [2]. The first estrogenic and antiandrogenic endocrine disruptors that were reported to have transgenerational effects of spermatogenic failure were methoxychlor and vinclozolin [3].

2.1. Bisphenol A (BPA)

BPA is used in industries to synthesize polycarbonate and epoxy resins. Since the 1960s, it has been used in the manufacturing of plastic bottles, suction cup, inner coating of food and beverage cans, and so on. BPA is ubiquitous, from mineral water bottles, medical devices to food packaging, and has its shadow. This widespread chemical can do great harm to male fertility, having the potential of causing cryptorchidism, hypospadias, low sperm counts, or even testicular cancer [4–6]. It was also one of the important causes of occupational infertility [7]. Acting as an endocrine and metabolic disruptor, BPA can mimic the effect of endogenic estrogen. Even a very low dose of BPA can make the animals develop precocious puberty, low sperm count, prostatic hyperplasia, and so on [8]. It was reported that BPA could have greater impact on the development of human fetal testis [9]. Due to its potential harm to not only the reproductive ability but also the functions of other organs, BPA was banned from being used in baby care in many countries.

2.2. DDT

As an effective pesticide, DDT was widely used in agriculture and forestry. Its metabolites (*p,p'*-DDT, and *p,p'*-DDE) have estrogenic effects in males by blocking the androgen receptors [10]. DDT exposure was estimated by the level of *p,p'*-dichlorodiphenyl dichloroethylene in blood plasma, the major metabolite of DDT. Crude regression analysis showed that several sperm motion parameters, including the percentage of motile sperm and sperm with

morphological tail defects, decreased and increased respectively with higher plasma p,p'-DDE concentration. Insufficient sperm chromatin condensation was observed in 46.6% of participants and the most severe category of incomplete DNA condensation was also positively correlated with p,p'-DDE concentration [11]. Therefore, nonoccupational exposure to DDT, as assessed by plasma p,p'-DDE concentrations, is associated with poorer semen parameters in men, indicating adverse effects on testicular function and/or the regulation of reproductive hormones.

2.3. Dioxins and dioxin-like compounds

Dioxins had been shown to exhibit antiestrogenic activity [12]. The association between dioxins/dioxin-like compounds exposure and impaired reproductive function had been strengthened by both epidemiological evidence and experimental studies [13–15]. Sexually mature laboratory animals exposed to relatively high doses of dioxin displayed decreased spermatogenesis, decreased testicular weight, and abnormal testes with reduced fertility [11]. By using gas chromatography/high-resolution mass spectrometry (GC/HRMS), Galimova et al. examined the concentration of dioxin-like compounds in semen of infertile males and fertile controls [14]. They found the dioxin/furan level in seminal fluid of infertile males was higher than that of fertile controls. The toxicity of dioxins is mediated by the AhR/ARNT receptor complex. The effects of high exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and "TCDD-like" compounds on important sites for the development and reproduction have been recognized for years. The reproductive system has even been thought as the most sensitive "end point" for dioxin.

2.4. Heavy metal

It is beyond argument that cadmium and lead can induce male reproductive toxicity. World Health Organization (WHO) indicated that even low-level exposure to lead and cadmium (400 µg/l and 10 µg/l, respectively) can enable the semen has a significant quality descend, although it did not show conclusive evidence of male hormonal changes in reproduction.

Typically, testicular toxins and various derivatives in the animal model do harm to the testis by causing a severe damage to the seminiferous epithelium. However, cadmium prefers the way of damaging the Sertoli cells, causing testicular damage directly. The morphological changes under the scanning electron microscopy can account for this mechanism. It also works in a way by interfering with the normal functioning of mitochondrial enzymes [16].

Results from testicular biopsies, such as vacuolation, peritubular fibrosis, and oligospermia, prove that lead has direct testicular toxicity, and some researchers found that lead exposure can also have an effect on hormonal feedback mechanism at the hypothalamic pituitary level. But further investigation should be done as these studies are insufficient to make detailed evaluations in humans.

2.5. Phthalates

Phthalates are substances used in the manufacturing of automobiles, medical supplies, plastics, beverage containers, coating of metal cans, and so on. Data have demonstrated that perinatal exposure to a variety of phthalate esters alters the development of the male reproductive tract in an antiandrogenic way, causing underdevelopment and agenesis of the epididymis at relatively low doses [16]. Environmental exposure to di-n-butyl phthalate (DBP) and di-2-ethylhexyl phthalate (DEHP) may contribute to a decline in semen quality [17]. Additionally, our recent study demonstrated that prenatal exposure to DBP has transgenerational effects of impaired spermatogenesis. We also revealed that metabolic and epigenetic changes induced by the aberrant expression of betaine homocysteine S-methyltransferase (BHMT) represent a novel mechanism linking in utero DBP exposure to transgenerational spermatogenesis failure [18].

2.6. Mechanism(s) of action of endocrine disruptions on hypothalamic-pituitary-gonadal (HPG) axis

A large amount of substances has the ability to inhibit the biosynthesis of a variety of hormones. Some substances can inhibit the specific enzymes in steroidogenesis such as aminoglutethimide, cyanoketone, and ketoconazole. Some fungicides inhibit estrogen synthesis by inhibiting aromatase activity in the testis, which has an effect on testosterone to estrogen. Through a set of signals at transcriptional and translational levels, EDCs make further efforts to transform the biosynthesis of protein mediated by gonadal steroids [19].

Hormones react with their target tissues directly by interacting with membrane-bound receptors or intracellular receptors. The vital procedure in the function of hormones is the specific binding of natural ligand to its receptors. Intracellular or nuclear receptors interact with specific DNA sequences regulating gene transcription in a ligand-dependent pattern. This procedure might be changed by many environmental factors through mimicking the natural ligand and serving as an agonist or inhibiting the binding and serving as an antagonist. The most notable examples are methoxychlor, chlordecone, DDT, some polychlorinated biphenyls, and alkylphenols, which can disturb the function of estrogen receptors [20].

Epigenetic modifications characterized by DNA methylation, histone modifications, and chromatin remodeling are important regulators in spermatogenesis. Studies have shown that aberrant epigenetic modifications are associated with disturbed spermatogenesis and male infertility [21–23]. Exposure of gametes to environmental factors may cause alterations in sperm. In addition, more and more studies have demonstrated that many EDCs have transgenerational effect of spermatogenic failure through epigenetic mechanism [3, 24].

Clearly, there should be more studies to explore the data gaps. In addition to a few exceptions (e.g., diethylstilbestrol [DES]), the causal relationship between exposure to specific agents and endocrine disruptor-mediated adverse health effects has not been determined. The development and validation of short-term screening studies should be used to clarify the mechanism.

It is possible that these environmental agents such as alkyl phenol ethylate and their degradation products, chlorinated dibenzodioxins, and PCBs can induce irreversible decline in male fertility [2].

3. Lifestyle factors and male infertility

In general, lifestyle factors affect male reproductive system in various ways. In today's society, male infertility has become a more and more important problem. People's unhealthy lifestyle may be one of the great reasons. Sperm needs a suitable internal and external environment to complete several physiological links such as occurrence, development, maturity, and transportation. Some physical and chemical factors can lead to the damage of the testis and accessory glands, the disorders of the internal environment, and spermatogenesis dysfunction to some extent. Several studies have found that occupation, behavioral habit, dietary habit, and other factors can play a role in the decreased fertility. The following discussion focuses on the association between male infertility and lifestyle factors such as smoking, alcohol consumption, and diet.

3.1. Smoking

As we know, smoking is associated with variable diseases, including respiratory diseases, cardiovascular diseases and cancer of the lung, kidney, urinary bladder, pancreas, and so on [25, 26]. The relationship between smoking and infertilities has been studied for several years.

A vast amount of studies showed the negative effects of smoking on various parameters of semen analysis. In an experiment conducted in Denmark from 1987 to 2004, 2562 men participated; researchers found that heavy smokers had a 19% lower sperm concentration than nonsmokers [27]. Moreover, in another cohort study which involves 1786 men, researchers proved that smoking was associated with a significant decrease in sperm density, total sperm count, total number of motile sperm, and citrate concentration. In addition, sperm vitality, ejaculate volume, and fructose concentration were slightly but nonsignificantly affected [28]. In other aspects, smokers had a significantly decreased semen volumes, sperm motility, and viability compared with nonsmokers. All sperm motion parameters were lower in the smokers except for beat-cross frequency (Hz). Further, the percentage of normal morphology sperm was decreased significantly in smokers, and the sperm morphology was worse with increasing degree of smoking [29]. The experiments have already shown that smoking in daily life damages the semen quality.

Existing data indicate that varicocele plays an important role in male infertility. There are also experiments trying to figure out the relationship between varicocele and smoking. In a study conducted in Iran, percentage of varicocele was significantly higher in smokers compared with nonsmokers [30].

The mechanism behind the negative effect of smoking on semen quality remains vague until today. There are evidences showing that people who smoke possess a higher proportion

of spermatozoa with an alteration of the histone to protamine ratio than those who do not smoke, which may lead to male infertility [31]. Also there was a research that revealed the relationship between smoking and seminal plasma zinc level. Semen parameters were also significantly decreased among smokers with abnormal zinc levels, while there was no significant difference between nonsmokers with normal zinc and nonsmokers with abnormal zinc levels [32]. In addition, DNA methylation pattern in sperm DNA can be influenced by cigarette smoking [33]. Aberrant DNA methylation had been shown to be associated with male infertility [34].

3.2. Alcohol consumption

Excessive alcohol intake is always thought of as a cause of liver diseases, kidney diseases, and so on. In addition, alcohol consumption is considered to have an adverse impact on reproductive function. We discuss about its negative influence on the sperm parameters and the endocrine.

There was an interesting case report showing that an azoospermic patient regained normal sperm parameters 3 months after the discontinuation of alcohol consumption, which strongly supported the negative impact of alcohol consumption on male infertility [35]. Firstly, available literatures stated that alcohol consumption may give rise to spermatozoon morphological changes and the changes including breakage of the sperm head, distention of the midsection, and curling of its tail [36]. Moreover, in an experiment conducted by researchers in Argentina, which involved 537 men, it was found that alcohol consumption evoked a tendency toward diminished sperm concentration, motility, viability, and normal morphology [37].

As for its effect on the endocrine, there are masses of such studies reminding people of the impact of alcohol consumption that might cause structural testicular changes, decreased level of testosterone, which might be involved in the phenotype of hypogonadism and feminization. Alcohol and its metabolite acetaldehyde can cause a reduction in luteinizing hormone (LH) binding to Leydig cells, which may inhibit the enzymes involved in the formation of sex hormones [38]. With regard to the mechanism of its negative effects, alcohol seems to exert a dual effect on the HPG axis by directly inhibiting testicular steroidogenesis and by blocking the release of LH-releasing hormone/LH from the hypothalamic-pituitary axis [39].

3.3. Diet

3.3.1. Dietary bias

Scientists found that our daily consumption of cereals, fruits, and each meal a day had a strong bearing on semen quality. Taking proper amounts of minerals, antioxidant vitamins, and essential amino acids can maintain and improve it effectively [40]. There was also a case report conducted in Spain which showed that frequent intake of lipophilic foods like meat products or milk may negatively affect the semen quality in humans, whereas some fruits or vegetables may maintain or improve semen quality [41].

3.3.2. High-energy diets

High-energy diets, especially poor nutritional food intake with lots of unhealthy fat negatively affect semen parameters and fertility. It was described that the intake of processed meat, a source of saturated fats, is associated with poor semen quality [42]. In a cohort study conducted in the America, researchers found high intake of saturated fats was negatively related to sperm concentration whereas higher intake of omega-3 fats was positively related to sperm morphology [43]. However, studies with larger sample size are required to confirm these findings.

High-energy diets may alter testicular metabolism. Testis provides an environment that nurtures the germs cells, ultimately ensuring spermatogenesis and fertility. However, the over-consumption of high-energy diets enables the increase of fatty acid supply within testicular milieu and consequently compromises the key testicular metabolic mechanisms that ultimately compromise germ cells fate [44, 45]. High-energy diets intake disturbs whole-body metabolism and the normal function of the male reproductive axis. Existing data showed that metabolism and reproduction are closely connected [46]. Obesity toxicant from the high-energy foods can promote the development of obesity and the storage of lipid-soluble toxicants in the body. Thereafter, the molecular mechanisms that regulate appetite and energy intake will gradually be disrupted. The abovementioned process cannot be separated from the mediation of gut and adipose hormones. While the major function of gut and adipose tissues is to perceive the energy status of the body, recently, some gut and fat derived hormones are thought to be a regulatory factor in reproductive events. Hence, disruption of the endocrine activity of these tissues may affect the reproductive function [45].

3.4. Other factors

3.4.1. High temperature

Some people who work under an environment with a high temperature such as blacksmith and kettleman or who had to wear clothes which are too tight for them, both factors bring about heat stress to men's testis. The process of spermatogenesis is closely related to the appropriate temperature and occurs optimally at temperature slightly lower than that of the body. Adequate adjustment of the temperature is imperative to maintain a proper testicular temperature. Raised testicular temperature has a harmful effect on spermatogenesis and the resultant spermatozoa. Therefore, thermoregulatory failure leading to heat stress can compromise the sperm quality and increase the risk of infertility [47]. Both the epididymal sperm and testicular germ cells are sensitive to damage by heat stress, which leads to the apoptosis and the damage of DNA [48, 49].

3.4.2. Radiation

Cell phone usage is an indispensable part in people's daily life. As a result of which, several researchers have conducted a lot of experiments. There is a study investigating an association

between characteristics of cell phone usage and semen quality [50]. It showed that talking for ≥ 1 h/day and during device charging was associated with higher rate of abnormal semen concentration. Among men who reported holding their phones ≤ 50 cm from the groin, a non-significantly higher rate of abnormal sperm concentration was found. Multivariate analysis revealed that talking while charging the device and smoking were risk factors for abnormal sperm concentration. It suggests that certain aspects of cell phone usage may bear adverse effects on sperm concentration.

Concerning the usage of wireless internet, researchers have demonstrated that continuous Wi-Fi exposure with 2.45 GHz affected the testes of growing rats. Avendano et al. divided the motile spermatozoa, from 29 healthy donors, into two aliquots and one of them was exposed to a Wi-Fi computer but not the other. 4 h later, research findings showed that the sperm motility and the sperm DNA fragmentation in Wi-Fi group were significantly decreased and increased, respectively [51]. However, current studies are not able to reveal the relationship well enough, and, therefore, larger scales of studies concerned about this aspect are needed.

4. Conclusion

Accumulating evidence suggests that environmental factors are posing major threats to human reproductive health (Figure 1). Impaired spermatogenesis can be incurred by exposures in

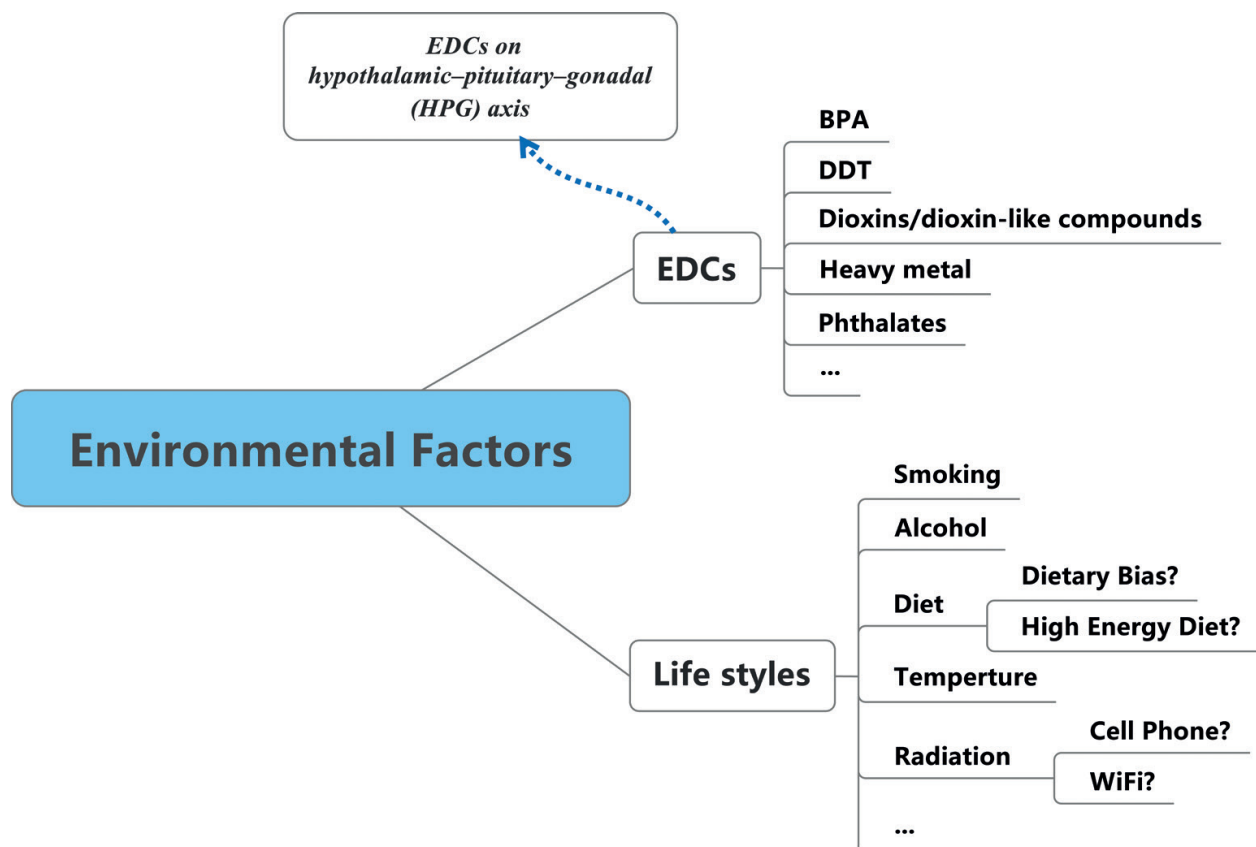


Figure 1. Schematic representation of environmental risk factors of male infertility.

utero, in the neonatal or adolescent periods, or in adulthood, and can have transgenerational effects. Despite promising discoveries, a causal relationship between male infertility and exposure to specific EDC or mixtures of EDCs is yet to be established, due to the degree of EDCs exposure, the sample size of the subjects examined, the complexity of the clinical protocols used, and the determination of the variables measured. Future studies are needed to focus on a uniform system of examining human populations with regard to the exposure to specific EDCs and its direct effect on male infertility. Considering all the lifestyle factors which result in the male infertility, to improve the severe situation of the male infertility, we should try to discontinue smoking and alcohol drinking, avoid high temperature and radiation, and maintain a balanced diet. From now on, if a good and healthy lifestyle is maintained, we will have offspring, bringing endless happiness.

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