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REVIEW

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Environmental exposures and infertility

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ABSTRACT

The risk of infertility is increasing globally as a result of genetic factors as well as environmental factors. This review focuses on the complex relationship between environmental factors and infertility, a global issue affecting millions. It covers a wide range of environmental exposures, including air pollution and endocrine-disrupting chemicals (EDCs), which can interfere with various stages of reproductive physiology. In males, lifestyle choices, occupational hazards, and EDCs can negatively impact sperm quality and hormonal balance. Similarly, these chemicals can disrupt ovarian function and menstrual regularity in females. Furthermore, this review discusses how environmental exposures can affect the success of Assisted Reproductive Technologies (ART), influencing ovarian response and embryo quality. It highlights the role of epigenetic mechanisms, where changes induced by environmental exposures can be passed down to future generations. Despite existing regulations to lower environmental risks, challenges remain. It also emphasizes the importance of public awareness and education in addressing these risks. The mini-review concludes by demanding future research to identify new environmental threats, understand their molecular mechanisms, evaluate their long-term effects, and develop new biomarkers and models for risk assessment. In addition, emphasizes the importance of environmental factors and interdisciplinary approaches to human fertility and ART outcomes.

KEYWORDS

Infertility; EDCs; ART; Environmental exposures; Pollution; Epigenetics

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Introduction

Infertility is a complex and multifactorial condition (especially genetic or environmental factors) that affects millions of couples worldwide. It is the inability to conceive after 12 months of regular unprotected sexual intercourse [1,2]. According to the World Health Organization (WHO), infertility affects about 17.5% of women of reproductive age globally, roughly 1 in 6 [3]. The link between environmental exposures and infertility is a topic of growing interest and concern, as many studies have suggested that various natural and anthropogenic agents can affect human reproductive function and contribute to infertility [4,5]. Environmental factors include various substances and conditions that can influence human health and well-being, such as air pollution, water contamination, pesticides, heavy metals, endocrine-disrupting chemicals (EDCs), electromagnetic radiation, noise, temperature, and stress. These factors can be exposed through various routes, such as inhalation, ingestion, dermal contact, or transplacental transfer.Environmental factors can interfere with various aspects of reproductive physiology and function, such as gametogenesis, fertilization, implantation, embryonic development, placentation, and fetal growth [4,5].

Understanding and addressing the role of environmental factors in infertility is crucial for several reasons. First, environmental exposures are ubiquitous and often unavoidable in modern society [1]. Second, environmental factors can have cumulative and synergistic effects on reproductive health [4,6]. Third, environmental factors can influence the efficacy and safety of assisted reproductive technologies (ARTs), which are increasingly used to treat infertility [7]. Fourth, environmental factors can have transgenerational effects on fertility by affecting the epigenetic programming of the offspring [8]. Fifth, environmental factors can interact with genetic and epigenetic susceptibility to modulate the risk of infertility [9].

Air pollution, pesticides, electromagnetic radiation, and heavy metals can affect reproductive function by inducing oxidative stress, inflammation, DNA damage, endocrine disruption, apoptosis, and epigenetic modifications in the gametes and reproductive organs. It has been associated with reduced sperm quality and quantity, increased risk of miscarriage, preterm birth, low birth weight, congenital anomalies, and impaired neurodevelopment [10,11]. EDCs can affect reproductive function by altering the feedback mechanisms of the hypothalamic-pituitary-gonadal axis (HPG axis), disrupting the synthesis and secretion of gonadotropins and sex steroids, modulating the expression of hormone receptors and transporters, affecting the maturation and function of gametes and reproductive organs and influencing the implantation and development of embryos [10,11]. These are some of the main environmental factors affecting human fertility and reproductive health. However, there are many other factors that can also play a role, such as

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noise, temperature, stress, diet, lifestyle, genetics, epigenetics, and interactions among these factors.

Therefore, the aim of this mini-review is to provide a comprehensive overview of the intricate relationship between environmental factors and infertility, a leading global issue impacting millions of individuals and couples. We discussed diverse exposures, such as air pollution, EDCs, pesticides, electromagnetic radiation, and heavy metals, and their impact on male and female reproductive health, including sperm quality, hormonal balance, ovarian function, and menstrual regularity. Additionally, it explores how these environmental factors influence the success of ART and underscores their role in epigenetic transgenerational effects. Furthermore, it highlights regulatory challenges, advocates for public awareness, and calls for continued interdisciplinary research to identify emerging threats and develop novel risk assessment tools, collectively addressing the global issue of infertility exacerbated by environmental exposures.

Environmental Factors Affecting Male Fertility

According to Kumar et al., environmental factors are external influences that can affect the quality and quantity of sperm men produce. Some of these factors include air pollution, chemicals, radiation, heat, and lifestyle choices. Exposure to these factors can cause hormonal imbalances, oxidative stress, DNA damage, and reduced sperm motility and morphology [12].

Endocrine-disrupting chemicals (EDCs)

EDCs are substances that interfere with the normal functioning of the endocrine system, which regulates the production and action of hormones in the body. EDCs can mimic, block, or alter the effects of natural hormones, leading to adverse health outcomes [13,14]. EDCs can be found in various sources, such as industrial products, pesticides, plastics, personal care products, pharmaceuticals, and environmental pollutants. Some of the most common EDCs are phthalates, bisphenol A (BPA), dioxins, polychlorinated biphenyls (PCBs), and metals [13,14]. EDCs can affect male fertility by disrupting the normal development and function of the male reproductive system. Several studies have shown that exposure to EDCs can impair sperm quality and quantity, reduce testosterone levels, alter the expression of genes involved in spermatogenesis, induce oxidative stress and DNA damage, cause structural abnormalities in the testis and epididymis, and increase the risk of testicular cancer [13,14].

Lifestyle and occupational exposures

Tobacco and alcohol are widely used substances that can harm the male reproductive system in various ways. Tobacco smoking and alcohol consumption can lower sperm count, motility, and morphology, as well as increase the risk of DNA damage, affect sexual performance, and hormonal imbalance. Both tobacco and alcohol can interact with other drugs and chemicals to worsen their effects on sperm health [15].

Chemical exposure

Certain chemicals commonly found in workplaces can affect male fertility. Prolonged exposure to solvents, heavy metals (lead, mercury, etc.), pesticides, and industrial chemicals like benzene and toluene can negatively impact sperm production, quality, and function [16].

Heat and radiation

Excessive heat and radiation can disrupt normal sperm production by increasing the scrotal temperature or damaging the testicular tissue [16].

Physical strain

Jobs involving prolonged sitting, driving, or heavy lifting can increase scrotal temperature and decrease sperm quality [16].

Air and water pollution

Air pollutants, such as particulate matter (PM), ozone (O3), nitrogen dioxide (NO2), sulfur dioxide (SO2), and polycyclic aromatic hydrocarbons (PAHs), can cause oxidative stress, inflammation, endocrine disruption, DNA damage, and epigenetic changes in the male reproductive system [12,17]. These effects can lead to reduced sperm count, motility, morphology, fertilization ability, and increased sperm DNA fragmentation and chromosomal abnormalities [12,17]. Water contaminants, such as heavy metals, pesticides, pharmaceuticals, and EDCs, can also interfere with the male reproductive function by altering the hormone levels, inducing oxidative stress, damaging the testicular tissue, and affecting sperm quality and function. These contaminants can also cause reproductive toxicity, such as decreased libido, erectile dysfunction, infertility, and testicular cancer [12].

Environmental Factors Affecting Female Fertility

Female fertility is influenced by various factors, such as genetics, hormones, age, and lifestyle. However, environmental factors can also affect female fertility, such as exposure to chemicals, pollutants, and radiation.

EDCs and female reproductive health

EDCs can affect the development and function of the ovaries, which are the main source of female sex hormones (estrogen and progesterone). EDCs can alter ovarian cells' hormone synthesis, secretion, transport, metabolism, and receptor binding [14]. This can lead to ovarian dysfunction, such as reduced ovarian reserve, poor oocyte quality, and premature ovarian insufficiency [18,19]. EDCs can also disrupt the feedback mechanisms between the ovaries and the hypothalamus-pituitary axis, which regulates the menstrual cycle and ovulation [14,18]. EDCs can cause menstrual irregularities, such as changes in the cycle length, frequency, and bleeding patterns [14,18]. Chattopadhyay et al. studied that these irregularities can affect the timing and occurrence of ovulation. EDCs can also impair the ovulation process by affecting the follicular development, maturation, rupture, and luteinization in the ovary [14,18]. These effects can lead to anovulation (absence of ovulation), oligoovulation (infrequent or irregular ovulation), or poor ovulation quality [18].

Lifestyle factors and female fertility

The review by Silvestris et al. found that diet and nutrition can significantly impact both female reproductive function and pregnancy outcomes. A healthy, balanced diet that provides all the necessary nutrients can help to maintain hormonal balance, promote healthy ovulation egg quality, and improve the chances of conception and implantation [20]. On the other hand, diets that are high in calories, fat, sugar, or processed foods can impair female fertility by causing metabolic

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disorders such as obesity, diabetes, and hyperlipidemia. These disorders can affect ovarian function, menstrual cycle, ovulation, and egg quality, as well as increase the risk of infertility, miscarriage, and pregnancy complications [20]. Therefore, women who are trying to conceive or maintain a healthy pregnancy should follow a balanced diet that includes adequate amounts of protein, fiber, antioxidants, vitamins, minerals, and omega-3 fatty acids.

Stress is a common factor that can affect female reproductive health in various ways. Stress can be caused by psychological, physical, or environmental factors that trigger the release of stress hormones, such as cortisol and adrenaline [21]. These hormones can interfere with the normal functioning of the hypothalamic-pituitary-ovarian axis, which regulates the production and release of reproductive hormones [21]. This can lead to hormonal imbalances, menstrual irregularities, ovulatory dysfunction, poor egg quality, and reduced fertility. Stress can also affect the implantation process and the early development of the embryo by causing inflammation, oxidative stress, immune dysregulation, and epigenetic changes in the endometrium [21,22]. These effects can increase the risk of implantation failure, miscarriage, preterm birth, and low birth weight. Therefore, women who are trying to conceive or have a healthy pregnancy should try to reduce their stress levels by adopting coping strategies, such as relaxation techniques, exercise, social support, and counseling.

Occupational and environmental exposures

Workplace chemicals are substances that are used or produced in various industries and occupations. Some of these chemicals can act as EDCs, interfering with the normal hormone levels and functions in the female body. EDCs can affect the ovarian function, menstrual cycle, ovulation, and egg quality, as well as increase the risk of infertility, miscarriage, and pregnancy complications [10]. Pollutants can cause oxidative stress, inflammation, endocrine disruption, DNA damage, and epigenetic changes in the female reproductive system [10,17]. These effects can lead to reduced ovarian reserve, poor oocyte quality, implantation failure, miscarriage, and preterm birth [17].

Impact of Environmental Exposures on Assisted Reproductive Technologies (ART)

ART is a medical procedure that helps couples achieve pregnancy when natural conception is difficult or impossible. The most common form of ART is in vitro fertilization (IVF). However, the success rate of IVF is not very high and depends on various factors, such as the age, health, and genetic background of the couple, as well as the quality of the gametes and embryos. In addition to these factors, environmental exposures can also affect the outcome of IVF in various ways.

Influence of environmental factors on IVF success rates

Environmental factors, such as chemicals, pollutants, and radiation, can negatively affect both male and female fertility and reproductive health. These factors can impair the function and development of the reproductive organs, such as the ovaries, testes, uterus, and fallopian tubes, and affect the quantity, quality, and function of the gametes and embryos [7]. Moreover, exposure to radiation can damage the reproductive tissue and the gametes and cause ovarian failure, premature ovarian insufficiency, infertility, and an increased risk of genetic abnormalities in the offspring. These effects can reduce the chances of conception and pregnancy with IVF [7].

Consideration of environmental exposures during fertility treatments

Environmental exposures can also affect the outcome of IVF during fertility treatments. For example, exposure to EDCs can alter the response to ovarian stimulation drugs and affect the number and quality of oocytes retrieved for IVF [23]. Exposure to air pollutants can affect embryo development and quality in vitro and increase the risk of embryotoxicity. Exposure to radiation can affect the viability and implantation potential of the embryos transferred into the uterus. Therefore, it is important to consider the environmental exposures of the couple undergoing IVF and take preventive measures to reduce their exposure [7,23].

Epigenetic Mechanisms and Transgenerational Effects

Epigenetics involves the modification of DNA or histones by adding or removing chemical groups, such as methyl, acetyl, or phosphate. These modifications can alter the accessibility and activity of genes, resulting in changes in gene expression. Epigenetics is important for fertility because it can regulate the processes of gametogenesis, fertilization, implantation, placentation, and embryogenesis. Epigenetic changes can also affect the health and well-being of the offspring by influencing their growth, metabolism, behavior, and susceptibility to diseases [24]. Environmental exposures, such as chemicals, pollutants, radiation, nutrition, stress, and lifestyle factors, can induce epigenetic changes in the reproductive system and the gametes. These changes can occur during critical periods of development, such as prenatal, perinatal, or pubertal stages, when the epigenome is more sensitive and dynamic [24,25]. Environmental exposures can affect the epigenetic machinery by altering the levels or activities of enzymes, cofactors, or substrates that are involved in epigenetic modifications. Environmental exposures can also affect epigenetic patterns by inducing oxidative stress, inflammation, endocrine disruption, DNA damage, or chromatin remodeling [24,25].

Transgenerational effects are the transmission of epigenetic changes from one generation to another through the germline (sperm or eggs). Transgenerational effects can affect fertility and reproductive health by affecting the quantity, quality, and function of the gametes and embryos in subsequent generations. Transgenerational effects can also affect the phenotypes (traits) and diseases of the offspring in subsequent generations [24,25]. According to Zama et al. transgenerational effects of environmental exposures on fertility are: exposure to EDCs, such as BPA, can cause transgenerational effects on ovarian function, oocyte quality, and fertility in female offspring [25]. Likewise, exposure to air pollutants can cause transgenerational effects on sperm quality and fertility in male offspring [25]. Furthermore, exposure to radiation can cause transgenerational effects on genomic stability and fertility in both male and female offspring [25].

Regulatory and Public Health Implications

Environmental exposures can significantly affect human fertility and reproductive health. Therefore, it is important to have effective regulations and guidelines to protect the population from environmental hazards and to promote public awareness and education regarding fertility and the environment. There are various regulations and guidelines that aim to control or limit the sources and levels of environmental

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exposures that can affect fertility and reproductive health. Some of these regulations and guidelines are:

- The Stockholm Convention on Persistent Organic Pollutants (POPs) is an international treaty that aims to eliminate or restrict the production and use of chemicals that persevere in the environment and accumulate in the food chain, such as pesticides, industrial chemicals, and by-products [26].
- The Minamata Convention on Mercury is an international treaty that aims to protect human health and the environment from the adverse effects of mercury, a toxic metal that can impair the neurological development of fetuses and children [27].
- The World Health Organization (WHO) Air Quality Guidelines are global standards that provide recommendations for reducing the health impacts of air pollution in China [28].
- The European Union (EU) Regulation on Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) is a comprehensive framework that aims to ensure the safe use of chemicals in the EU market and to identify and regulate substances of very high concern, such as EDCs [29].

Despite the existence of various regulations and guidelines, there are still many challenges in regulating and minimizing environmental risks to fertility [30]. Some of these challenges are:

- The lack of standardized methods and criteria for measuring and assessing environmental exposures and their outcomes.
- The limited availability and quality of data on environmental exposures and fertility outcomes in different populations and regions.
- The insufficient understanding of the dose-response relationships, thresholds, windows of susceptibility, and interactions between different environmental factors and their effects on fertility.
- The inadequate consideration of the individual variability, genetic susceptibility, epigenetic modifications, and lifestyle factors that may influence the response to environmental exposures.
- The difficulty in enforcing compliance and monitoring the effectiveness of regulations and guidelines.

Public awareness and education are essential for preventing and reducing environmental risks to fertility.

Future Directions and Research Needs

There is a need to conduct further research on specific environmental factors and their mechanisms of action on fertility and ART. Some of these areas are:

- The identification and characterization of new or emerging environmental factors that may pose a threat to fertility and ART, such as nanomaterials, toxic chemicals, microplastics, electronic waste, and climate change [31-33].
- The elucidation of the molecular and cellular mechanisms by which environmental factors affect the function and development of the reproductive organs, gametes, embryos, and offspring [33].
- The evaluation of the long-term effects of environmental exposures on the reproductive health and well-being of the parents and the offspring.
- The development and validation of biomarkers, models, and tools for assessing the exposure, susceptibility, and risk of environmental factors on fertility and ART [34,35].

Environmental factors can have significant effects on fertility and ART. There is a need for more research, policy, and practice to address the gaps in knowledge, understand the mechanisms, and develop preventive strategies to protect fertility from environmental harm.

Conclusions

Environmental factors are increasingly recognized as important determinants of human fertility and reproductive health. Exposure to various chemicals, pollutants, and radiation can impair the function and development of the reproductive organs, gametes, embryos, and offspring and affect the outcome of natural conception and ART. These findings highlight the need for a call to action for interdisciplinary collaboration, policy changes, and research efforts to address the environmental influences on fertility. These actions require an overall approach that considers the complex interactions between environmental factors, genetic factors, epigenetic factors, lifestyle factors, social factors, and psychological factors that influence fertility and reproductive health. By adopting such an approach, we can better understand, prevent, and treat infertility caused by environmental exposures.

Disclosure statement

No potential conflict of interest was reported by the author.

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