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CURRENT TOPIC

The Role of Environmental Toxins in Infertility: Insights From Cutting-Edge Research

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Abstract

Environmental toxins are increasingly recognised for their detrimental effects on human fertility. Substances such as bisphenol A, pesticides, tobacco smoke, heavy metals, microplastics and electromagnetic fields (EMF) have been linked to concerns regarding both male and female infertility. This review examines the roles of these chemicals in infertility, focusing on recent research findings. It encompasses numerous studies that investigate the impact of environmental agents and occupational exposures on fertility. Key areas of discussion include the effects of bisphenol A, pesticides and tobacco smoke, as well as the mechanisms by which nanoparticles (NPs) and heavy metals, such as lead (Pb) and cadmium (Cd), influence fertility systems. Moreover, the review analyses the impacts of microplastics and contemporary lifestyle habits on fertility rates, alongside the effects of EMF exposure from devices such as cell phones. Recent studies underscore the pervasive influence of environmental contaminants on reproductive health. Occupational exposures and modern pollutants, including microplastics and EMFs, heighten the risk of infertility. The uncertain long-term consequences of these toxins, particularly in conjunction with genetic predispositions, pose significant concerns. Environmental toxins represent a considerable threat to fertility, necessitating stronger regulatory measures and further investigation into mitigation strategies. Future research should prioritise understanding the cumulative impact of these toxins on human reproduction.

Key words: Infertility; Environment; Hazardous substances; Male; Female; Reproduction; Fertility; Health equity.

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Introduction

Fertility is a global concern, marked by the significant issue of infertility. Millions of individuals worldwide experience infertility, which many societies perceive as an "unexpected life transition," with "childlessness" regarded as an undesirable social role. However, direct comparisons across various studies are challenging due to differing definitions and time frames used to estimate infertility rates.[1] The meanings and etiological factors associated with infertility vary by region and are influenced by physical and social contexts, resulting in a lack of a universally accepted definition of "inability to conceive."

The World Health Organization (WHO) defines infertility as a disorder of the reproductive system in which women are unable to conceive following regular, unprotected sexual intercourse

for a duration of one year or longer (ICMART, WHO).[2] Conversely, demographers define infertility as the inability of women of reproductive age (15–49 years) to conceive after five or more years of exposure to potential pregnancy.[3] Sperm abnormalities and unspecified factors contribute to the remaining causes of infertility, where male factors account for slightly more than half of all cases.

Research indicates that infertility can arise from one or both partners; however, women are often disproportionately blamed, particularly in developing countries where the issue is frequently perceived as solely affecting women. Infertility presently affects 8–12 % of couples globally, making it a significant clinical issue.[4] Primary infertility rates—defined as cases without a history of pregnancy—range from 3 % to over 30 %. At least 80 million couples worldwide suffer from involuntary infertility, with secondary infertility rates—those relating to couples with a previous pregnancy—being twice the rates of primary infertility.[5]

Environmental and genetic factors, including lifestyle choices, stress, delayed parenthood and obesity, are considered fundamental predictors of infertility. In 18 African nations, infertility accounts for approximately 60 % of the variability in total fertility rates. One study suggests that fertility declines by one birth for every 10 percentage points increase in the proportion of women aged 45 to 49 years without young children.

Environmental agents influencing infertility

Endocrine-disrupting chemicals (EDCs) are environmental compounds that modulate the function of the endocrine system, resulting in detrimental health effects in living organisms and their offspring.[6] Environmental pollutants have diverse impacts on male fertility. EDCs can disrupt endocrine functions at various hormone receptors, with both anti-androgenic and oestrogenic activities capable of altering normal male physiology.

Xenoestrogens include polychlorinated biphenyls (PCBs), bisphenol A (BPA), parabens, polybrominated diphenyl ethers (PBDEs), alkylphenols, phthalates, UV filters and certain pesticides, such as dichlorodiphenyltrichloroethane (DDT) and its metabolites.[7] Chemicals exhibiting anti-androgenic effects include phthalates, PBDEs, p,p'-dichloro-diphenyl-dichloroethylene (p,p'-DDE) and poly- and perfluoroalkyl substances (PFASs).

Additionally, dioxins and polycyclic aromatic hydrocarbons can activate the aryl hydrocarbon receptor (AhR), which is significant in the male reproductive system. Certain EDCs can also interfere with androgen biosynthesis and the functioning of the hypothalamic-pituitary-testicular axis, leading to reduced testosterone levels and compromised spermatogenesis. For example, some pyrethroids can diminish testosterone production, while PCBs can inhibit aromatase enzymes and oestrogen sulfotransferase activity. Moreover, PFASs have been associated with increased oestrogen levels and decreased serum testosterone levels.[8]

Bisphenol A

Bisphenol A (BPA), scientifically known as 4,4'-isopropylidene-diphenol (or 2,2-bis(4-hydroxylphenyl)), is a crystalline chemical substance widely utilised as a monomer in the manufacturing of plastic products, including phenolic and epoxy resins, polycarbonate, polyesters and polyacrylate. Over the past 60 years, BPA has frequently been employed as an adjuvant and/or antioxidant in the production and processing of polyvinyl chloride (PVC), cosmetics and as a plastic softener.[9]

BPA is found in various everyday products, such as plastic dinnerware, cooking utensils, dental sealants and fillings, electronics (including refrigeration systems, hair dryers and smartphones) and thermal paper, among others. Approximately 12 % of BPA is metabolised in the liver through glucuronidation, in which BPA rapidly binds to glucuronic acid *via* the enzyme uridine diphosphate glucuronosyltransferase (UGT) to form BPA glucuronide (BPA-G).[1] This metabolic process enhances the water solubility of BPA, resulting in faster excretion in urine, with an elimination half-life of 5.4 to 6.4 h.

However, the potential for BPA bioaccumulation in the liver associated with oral exposure remains a topic of debate. In contrast to food exposure, nearly all BPA absorbed through transdermal contact bypasses hepatic processing, leading to an increased concentration of the unconjugated form (free BPA) in the bloodstream. This raises

significant concerns regarding the physiological effects of transdermal BPA exposure on human health.[10]

Pesticides

Pesticides are primarily utilised in agricultural practices to enhance crop yield, although alternative uses include personal gardens, treatment of domestic animals with dewormers and even in the management of infectious diseases. Human exposure to pesticides can occur through various channels, including occupational handling during production, transportation, delivery and application, as well as through residential proximity to treated areas.[11]

Given that exposure to pesticides may contribute to various health issues, it is important to investigate the causes of pesticide-induced foetal harm and their effects on male fertility.[12] In addition to directly harming spermatozoa, chemical fertilisers can disrupt the function of Sertoli and Leydig cells and interfere with the endocrine system at multiple stages of hormone regulation, including hormone production, release, storage, transport, clearance, receptor recognition, binding, thyroid function and central nervous system activity. These processes are elucidated in relation to both *in vivo* and *in vitro* findings regarding pesticide exposure.[13]

Oxidative stress, which alters the efficacy of an individual's antioxidant defence system, can have detrimental effects on female reproductive physiology. This protective response can be compromised by various toxicants, particularly pesticides, leading to a range of lifestyle-related respiratory illnesses. Reproductive disorders, such as impaired follicle formation, follicular atresia, implantation defects, spontaneous abortions, endometriosis and various foetal and birth defects, have been linked to imbalances in the antioxidant system due to oxidative stress induced by pesticide toxicity. Consequently, this imbalance directly impacts reproductive processes and conception rates. As such, the exploration of oxidative stress caused by chemical agents warrants further investigation into its potential effects on female fertility.[14]

Tobacco smoke

Smoking is a well-established modifiable risk factor for several major pregnancy complications and constitutes a public health issue that jeopardises maternal and foetal health.[15] Notable complications associated with smoking during pregnancy include preterm premature rupture of membranes, intrauterine growth restriction, placental abruption, placenta previa, preterm birth and perinatal mortality, among others. In addition to these recognised hazards during pregnancy, smoking also has significant adverse effects on fertility and reproductive health.[16]

Infertility due to occupational exposures

The relationship between infertility and occupational exposure remains largely unexplored, with a notable lack of methodological analyses even in industrialised nations. While many professions have established occupational health procedures that include screening for reproductive status, infertility clinics have emerged as a significant source of insights into this issue, as they actively investigate the causes of infertility to enhance the effectiveness of assisted reproductive technologies (ART). Furthermore, lifestyle factors such as smoking and alcohol consumption may significantly obscure or interact with the effects of various compounds prevalent in occupational environments. Over the past few decades, numerous classes of compounds have been identified as potentially associated with male infertility. Table 1 illustrates the effects of environmental toxin exposure on the human reproductive system.

Path of nanoparticles (NPs) into the reproductive system

The development of oocytes is particularly sensitive to environmental insults, especially hazardous substances.[31] Chemical effects derived from the maturation of adult germ cells may influence reproduction by reducing sperm viability, potentially leading to adverse outcomes for foetal development.[35] Direct interactions with NPs or their circulation can result in the accumulation of NPs in the testes, prostate gland and epididymis, leading to cytotoxicity. The primary targets of NPs in the male reproductive system include the epididymis, testes and seminiferous tubules, where they may disrupt sperm motility and count, consequently affecting overall fertility. Hormonal imbalances, such as those associated with polycystic ovary syndrome (PCOS), represent anoth-

Table 1: Effects of environmental toxin exposure on the human reproductive system

N	Environmental toxins	Exposure	Sex	Causes	Effects	Ref
1	Phthalates	Nail polish, deodorants, shampoos, soaps	Men; Women	Hormonal disruption, decreased oestrogen and testosterone	• Reduces sperm quality and count • Irregular ovarian function, menstruation	17
2	Bisphenol A (BPA)	Water bottle, food containers	Men; Women	Hormonal disruption, reduce oestrogen and testosterone	• Low sperm quality, sperm count and motility • Irregular menstruation cycle, polycystic ovary syndrome (PCOS)	18
3	Pesticides	Vegetables and fruits	Men; Women	Endocrine disruption	• Sperm production • Affect menstrual cycles and ovulation	19
4	Endosulfan	Vegetables and fruits	Men; Women	Interference with hormone	• Alter sperm quality, count and morphology • Impact menstrual cycle	20
5	Dichloroethylene (DDE)	Occupational, refrigerants, solvent	Men; Women	Health consequences, toxic effects on reproductive organ	• Changes sperm quality and count • Menstrual irregularities	21
6	Insecticide	Agriculture and households	Men; Women	Hormonal abnormalities influence the endocrine system	• Impacts sperm motility and morphology • Problems with the menstrual cycle	22
7	Fungicide	Use to kill the growth of fungi	Men; Women	Interfere with the normal activity of oestrogen and testosterone	• Impacts sperm count, ovarian function, embryonic development	23
8	Chlorothalonil	Used in agriculture	Men; Women	Influences reproductive hormones	• Lower sperm quality • Ovarian function	24
9	Perfluorinated (PFC)	Water and grease-resistant	Men; Women	Endocrine disruptors	• Effects on motility • Ovulation	20
10	Chromium	Water and food	Men; Women	Hormonal imbalance	• Reduced irregularities in sperm • Embryonic growth	25
11	Lead	Water and food	Men; Women	Toxic collecting in reproductive organ	• Genetic polymorphisms occurring in somatic disease	26
12	Cadmium	Water and food	Men; Women	Toxic collecting in reproductive organ	• Varicocele • Genetic variations as in somatic disease	26
13	Alcohol	Alcohol consumption	Men; Women	It influences female hormonal levels and oestrogen	• Sperm count, motility, morphology, libido and erectile function • Irregular periods	27
14	Smoking	Smoking	Men; Women	Changes oestrogen and progesterone	• Erectile dysfunction • Damage fallopian tube	28
15	Silver nanoparticles (AgNPs)	Cosmetics, water purification, textiles	Men; Women	Reactive oxygen species (ROS)	• Damage sperm cells • Damage ovarian cells and eggs	20
16	Titanium dioxide nanoparticles (TiO_2)	Skincare products, paints and coatings	Men; Women	ROS can damage cells and tissues	• Reducing sperm motility, sperm cells • Disruption of ovarian	30
17	Zinc oxide nanoparticles (ZnO)	Sunscreens, skin care products	Men; Women	Oxidative stress	• Damage sperm cells. • Impact egg quality foetus health	31

18	**Amorphous silica nanoparticles**	Cosmetics and food products	Men; Women	Oxidative stress	• Decreased sperm motility, viability, • Decreases egg quality	32
19	**X-rays**	Diagnostic radiography, CT scan	Men; Women	DNA damage, oxidative stress	• Sperm DNA damage; genetic defects in offspring	33
20	**Radiofrequency (RF) radiation**	Cell phones, Wi-Fi, broadcasting	Men; Women	DNA damage, oxidative stress	• Sperm quality, testicular temperature, • Influence on ovarian function	34

er factor influencing reproductive health; PCOS affects approximately 5–20 % of women of reproductive age.[36] Studies often measure sex hormone levels, including luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone and oestrogen.

Adverse impact on the reproductive system

NPs are absorbed through the lymphatic and circulatory systems and transported to various organs, including the reproductive system, upon entering the body. Studies in both occupational and epidemiological health, involving humans and animals, have demonstrated the potentially harmful nature of NPs. Despite the increasing use of NPs, the volume of pertinent research remains inadequate.[37] The primary route of exposure to NPs is through the respiratory system, as inhalation can facilitate their translocation to other organ systems. In the field of nanomedicine, NPs may also enter the body intravenously or through cutaneous contact.

Most notably, cytotoxic effects are often associated with metal nanoparticles and metal oxide NPs. The cytotoxicity of metal nanoparticles is primarily linked to reduced cell viability and increased production of reactive oxygen species (ROS). Nanoparticles are capable of crossing the blood-brain barrier and the blood-tumular barrier with relative ease.[38] The generation of ROS is a key mechanism underlying the antibacterial properties of nanoparticles and elevated ROS levels are strongly tied to oxidative stress (OS), which has been associated with DNA damage, cellular membrane damage, increased inflammatory activity and various pathological processes.

Reproductive toxicities related to heavy metals

The most commonly identified causes of reproductive toxicity in humans are exposure to heavy metals and metalloids. Certain metals and metalloids can exert significant negative effects on the human reproductive system. Reproductive toxicity has been documented for metals such as lead, cadmium, uranium and mercury.[39] Lead exposure, even at moderate to low levels, can influence various reproductive factors, including semen quality. The reproductive system suffers severe consequences from both environmental and industrial exposures to multiple heavy metals and metalloids. Figure 1 illustrates how heavy metals affect reproductive organs, contributing to infertility in both males and females.

Lead

Lead exposure predominantly affects female reproduction by suppressing menstruation, which diminishes fertility, delays conception and alters hormone synthesis, ultimately impacting pregnancy outcomes. It is associated with premature birth, preeclampsia, premature membrane rupture, infertility and prenatal hypertension.[1] Adverse effects on the reproductive system from low-level lead exposure are well-documented, with most effects observed in women who experience high frequencies of irregular menstruation, spontaneous abortions and threatened abortions. Lead accumulation disrupts many endocrine glands and is linked to hormonal imbalances that impair reproductive function.[37] It affects the hypothalamic-pituitary axis, thereby influencing the body's response to the stimulation of follicle-stimulating hormone (FSH), luteinising hormone, testosterone-releasing hormone and thyrotropin-releasing hormone. Figure 2 shows that lead has an impact on hormones and enzymes in both the male and female reproductive systems. Pb-induced male reproductive ste-

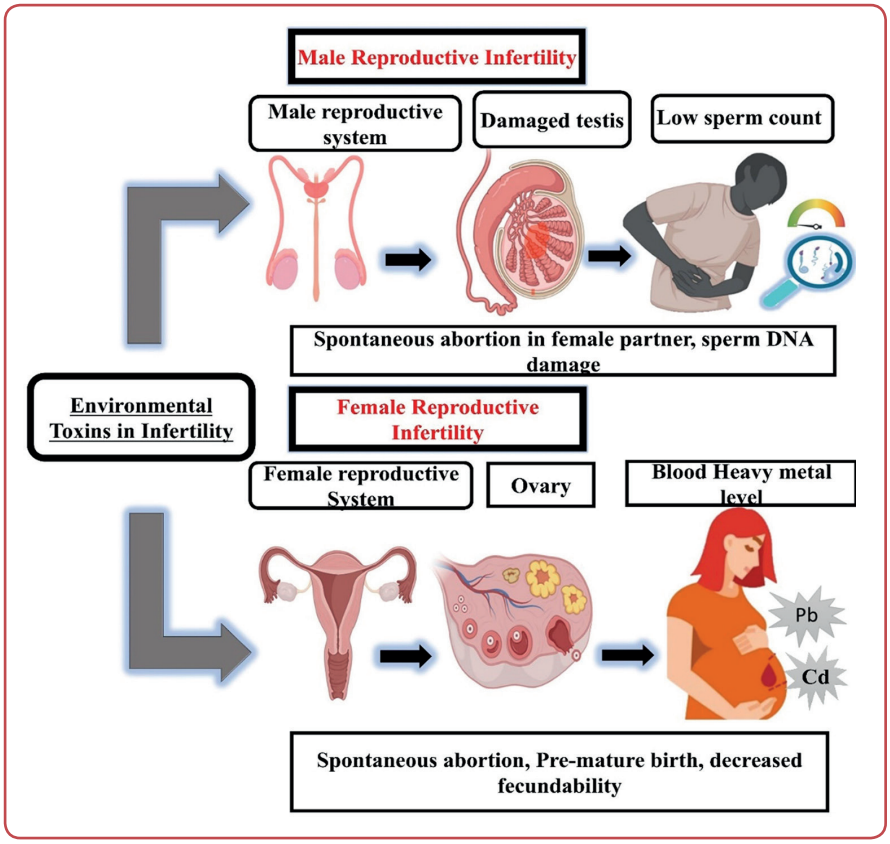

Figure 1: Heavy metals influence on reproductive organs and male and female fertility

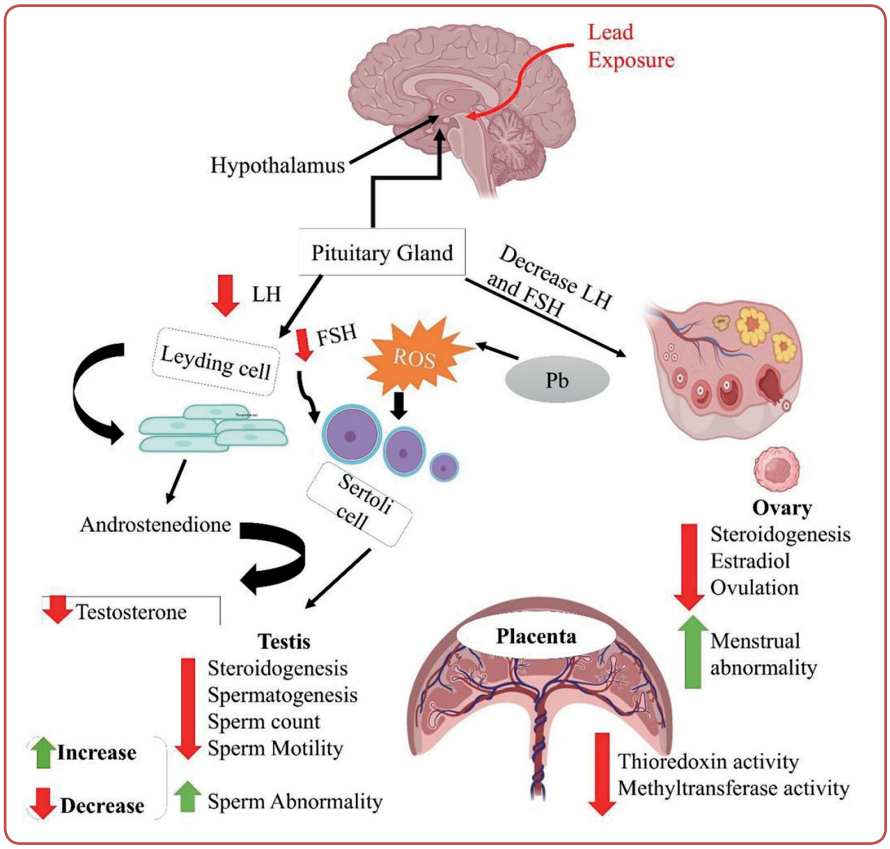

Figure 2: Impact of lead (Pb) on hormones and enzymes in both the male and female reproductive systems

LH: luteinising hormone; FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; ROS: reacive oxygen species;

rility and disruption of the blood-testis barrier (BTB). Protein carbonyl content and malondialdehyde (MDA) levels are elevated by induced oxidative stress, which leads to oligospermia.

Cadmium

Cadmium is an environmental hazard resulting from agricultural practices and industrial operations. For non-smokers in the general population, dietary sources are the primary route of cadmium exposure. Prolonged dietary absorption of cadmium in humans is relatively modest, typically ranging from 3 % to 5 %. Exposure to cadmium occurs primarily through diet, inhalation and, to a lesser extent, through skin contact.[8] Cadmium chloride ($CdCl_2$) is a highly soluble, water-soluble form of cadmium that is readily absorbed in the gastrointestinal tract. The most common airborne form of cadmium encountered is cadmium oxide (CdO). Certain occupational groups are subject to significant cadmium exposure, including workers in battery manufacturing, mining and paint production. Inhalation leads to a rapid absorption of cadmium into the lungs and a daily smoker of 20 cigarettes can absorb approximately 1 µg of cadmium into their body.[40]

Microplastics and modern-day habits in fertility rate

Microplastics (MPs) are created when larger plastic products are broken down. Microplastics are ubiquitous in our environment; they may be found in sewage, rivers, groundwater, soil, sediments and even the air we breathe. Current polymers are very resistant to biodegradation. However, by photochemical and mechanical processes.[41] Nanoparticles are plastic particles with sizes between 1 nm and 1 µm.

Plastic pollution

Synthetic polymers, which emerged during the 19th-century industrial revolution are extensively utilised in food packaging due to their numerous advantages over alternative materials. These advantages include being lightweight, infinitely mouldable, cost-effective to produce, chemically resistant and easy to manufacture and transport.[42] The rise of plastics has also transformed medicine through the development of sterile, single-use instruments, personal protective equipment and life-saving devices. However, excessive plastic use has fostered a throwaway culture that exacerbates environmental pollution and resists degradation.

The accumulation of plastic products in the environment disrupts habitats for both humans and animals.[43] The rapidly increasing production of disposable plastic items has become one of the most pressing environmental challenges, surpassing our ability to manage their disposal. According to estimates by Hirt and colleagues, between 4.8 and 12.7 million metric tons of plastic waste enter the ocean each year, accounting for 80 % of the plastic pollution found in the world's oceans and seas. In 2018, the volume of plastic waste exceeded 359 million metric tons. Major rivers also transport plastic waste to the sea, contributing to the spread of litter as they flow downstream.[26] Once in the ocean, plastic waste can be disseminated globally. Despite having useful lifespans ranging from minutes to a few hours, many single-use plastic products can persist in the environment for hundreds of years.

Routes of exposure and adverse human fertility health

Male fertility, foetal health and the future well-being of children are defined by programmed epigenetic events that can be adversely affected by various testicular toxicants occurring throughout spermatogenesis.[44] Epigenetic modifications play a crucial role in regulating gene transcription and developmental processes, such as sperm production and germ cell differentiation. While there is currently limited research on the effects of micro/nanoplastics (MNPs) on the sperm epigenome in mammals, substantial evidence indicates that common additives found in MNPs, such as BPA and phthalates, can disrupt these critical developmental processes.

In rodent germline models, exposure to phthalates and BPA can alter gene methylation patterns, histone modifications and the expression of non-coding RNA.[45] These alterations may interfere with normal epigenetic programming during critical windows of spermatogenesis, affecting sperm development, quality and viability. In human populations, associations have been observed between reduced sperm quality and adverse reproductive outcomes with urine concentrations of phthalate and/or BPA metabolites, demonstrating differential methylation patterns

in sperm, often in promoter regions of genes linked to cellular growth and development. Furthermore, studies investigating the effects of BPA and phthalates on germ cell epigenetic markers across generations raise concerns about potential long-term implications for subsequent generations.[46]

Similar to the majority of studies examining the reproductive implications of MNPs in males, polystyrene micro/nanoplastics (PS-MNPs) are among the most frequently studied plastic particles in relation to their toxicity to female offspring. These particles have been identified in various ovarian compartments, including within developing oocytes and uterine tissue. In exposed ovaries, altered follicular dynamics have been indicated by increased numbers of atretic and cystic follicles and decreased quantities of developing and mature follicles, along with diminished ovarian weight and reduced expression of cytoskeletal proteins. Concurrently, distinct changes in reproductive hormone signalling have been observed, including lower circulating levels of anti-Müllerian hormone (AMH) and oestradiol (E2), alongside elevated levels of testosterone and FSH.

Effects of radiofrequency (RF) fertility and electromagnetic fields (EMF) exposure effect on testicular organ

The World Health Organization (WHO) is actively engaged in ongoing efforts to evaluate the potential health consequences of radiofrequency electromagnetic fields (RF-EMF) on both general and working populations.[20] The WHO conducted a large-scale global survey among RF experts to prioritise the assessment of possible negative health effects associated with exposure to these fields. The survey identified six major areas of concern: reproductive effects, cognitive decline, associated symptoms, oxidative stress and heat-related consequences. To compile, evaluate and consolidate the existing body of knowledge on these issues, the WHO subsequently commissioned ten systematic reviews of observational and experimental studies.

As technology has advanced, exposure to RF-EMF from various devices has sharply increased. The testes are among the organs most susceptible to RF electromagnetic radiation (RF-EMR) due to their rapid cell division rate and high mitochondrial oxygen consumption, making testicular tissues more vulnerable to oxidative stress.[34] Significant cell proliferation can lead to replication errors that fragment DNA in sperm, while increased oxygen consumption raises the level of oxidative phosphorylation byproducts (free radicals) in the mitochondria. Furthermore, the testes are particularly sensitive to thermal effects from RF-EMR exposure, as they are less able to dissipate excess heat. Consequently, concerns have arisen regarding the impact of RF-EMR on male reproductive capabilities. Research has indicated that RF-EMR generated by Wi-Fi and mobile phones may lead to reduced testosterone levels. Various factors can influence these outcomes, affecting both the biological effects of RF-EMR and energy absorption. In numerous animal and human studies, the impact of RF-EMR appears to be correlated with the duration of smartphone usage; therefore, limiting the time spent using wireless devices is recommended.

Cell phone usage and male infertility

The widespread use of smartphones has contributed to environmental contamination by RF-EMF. The continuous increase in mobile phone usage has raised concerns regarding the impact of electromagnetic waves on male reproductive health.[15] Epidemiological studies indicate that approximately 14 % of couples worldwide experience difficulties with conception, with a significant number of these cases attributed to male infertility factors. Male infertility is known to be influenced in part by lifestyle and environmental factors and the testes may be adversely affected by radiation, temperature, or radioactivity, among other biological tissues.

Given the prevalent use of mobile phones, it is crucial to further elucidate the potential negative consequences of the resulting ambient radiation on reproductive health, particularly regarding sperm quality. Understanding how elevated testicular temperature and oxidative stress influence male fertility rates and how these variables may interact with physiological processes in the testes is essential.[47] Furthermore, the development of a financially viable, affordable and environmentally friendly strategy to address these issues is greatly needed. Current research has

not sufficiently explored the potential of certain natural reducing agents for the remediation of environmentally harmful compounds. There remains a lack of clarity in defining toxicity and its mechanistic aspects. The toxicity of environmental toxicants can vary based on specific characteristics such as concentration and exposure duration.[48]

Conclusion

Two facts are evident: human fertility is declining and we are continually exposed to environmental pollutants in our daily lives. While some studies suggest a connection between these exposures and ovulation in humans, establishing clear evidence linking common toxins to the observed decline in ovulation remains challenging. The complexities and extended timelines necessary to prove a causal relationship, along with the ethical concerns surrounding prospective studies involving human exposure, present significant obstacles—not because there is a lack of evidence that these substances can harm reproductive health.

Furthermore, although these toxins may affect semen quality, it remains unclear whether these changes lead to reduced pregnancy and childbirth rates. Until further research is conducted, exposure to these substances should be minimised and, if possible, avoided, as they can negatively impact fertility. The reproductive health of future generations is likely to be influenced by multiple factors, including the ability of governmental organisations to impose restrictions on the use of certain chemicals, establish concentration limits and gradually phase out substances that may be detrimental to reproductive health.

This approach contrasts with the current regulatory strategy, which often waits for clear evidence of harm before taking action. Instead, a proactive, preventative strategy is warranted. Emerging technologies will enable consumers to assess their exposures, increasing public awareness of potential risks and fostering advocacy for more comprehensive regulatory changes.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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