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REVIEW

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Effect of Environmental Contaminants on Female Reproductive Health: A Narrative Review

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Abstract: This narrative review explores the intricate relationship between some abundant environmental contaminants and the female reproductive system. Environmental toxicants have demonstrated significant adverse effects on female reproductive health. For instance pesticides are consistently associated with early pregnancy loss, heightened leukemia risk, intrauterine growth restriction, poor brain development, and congenital abnormalities. These contaminants can disrupt hormonal balance critical for reproductive function, exacerbating unexplained infertility in 15–30% of couples. Environmental contamination, encompassing chemical, biological, and physical constituents, exerts adverse effects on ecosystems and human health, with infertility emerging as a less recognized consequence. Various factors, including heavy metals (e.g., cadmium and lead), air pollutants, pesticides, and endocrine disruptors, uniquely impact female reproductive health. Heavy metals act as endocrine disruptors, leading to hormonal imbalances and menstrual irregularities. Simultaneously, air pollution is correlated with adverse fetal outcomes, emphasizing its relevance in the context of reproductive health. This narrative review underscores the multifaceted adverse effects of some relevant environmental contaminants on female reproductive health and the need for a comprehensive approach to mitigate these impacts and protect women's reproductive well-being.
Keywords: Reproductive Health; Environmental Contaminants; Female Fertility; Pesticides and Pregnancy; Heavy Metals and Menstrual Health

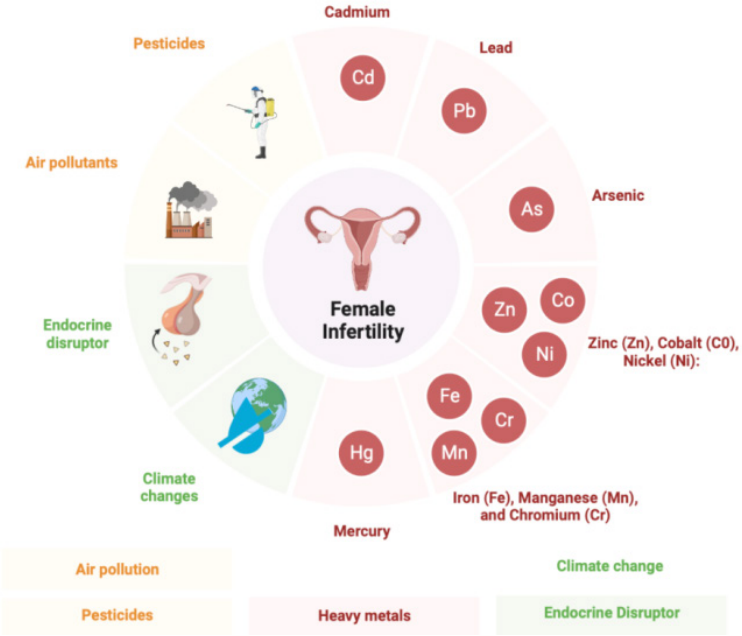

Fig: Environmental Factors Affecting Female Fertility

1. Introduction:

1.1. Changing Reproductive Health Trends

The contemporary era places significant emphasis on human reproductive health, encompassing physical, emotional, mental, and social well-being in the context of sexuality. Developed nations are witnessing a notable trend of delayed motherhood, exemplified by the mean age of women at the birth of their first child in the European Union, which reached 29.4 years in 2019 [1]. This shift contributes to a decline in total fertility rates across Europe, with various countries experiencing varying degrees of reduction. As a consequence, there has been a discernible increase in involuntary childlessness, affecting a quarter of couples globally by 2012. The landscape of infertility, defined as the inability to achieve pregnancy after 12 months of regular unprotected sexual intercourse, has undergone significant changes. Assisted reproductive technologies (ARTs), particularly in vitro fertilization (IVF), have gained widespread use, resulting in the birth of over 9 million IVF children globally [2]. Despite their increasing role in overall birth rates, ARTs only partially address the decline in fertility rates in developed countries. Notably, the risk of infertility escalates with age, particularly for females. Fertility starts to decline at 30, accelerates in the mid-30s, and renders the majority of women infertile by age 45, primarily due to age-related factors such as reduced oocyte quantity and quality, increasing the risk of embryo aneuploidies [3]. A comprehensive review by Levine *et al*. covering 1973 to 2011, involving 42,935 men, revealed a consistent decline in sperm concentration (SC) and total sperm count (TSC), with unselected Western men experiencing a 52.4% drop in mean SC and a 59.3% decline in mean TSC. The meta-regression models confirmed a persistent reduction at -0.70 million/ml/year (uncorrected) and -0.64 million/ml/year (adjusted). This significant decline in sperm counts has noteworthy public health implications, particularly for men in North America, Europe, Australia, and New Zealand, necessitating further research to understand the causes and potential consequences. In addition to age-related factors, infertility is influenced by various issues, including ovulation disorders, tubal disease, endometriosis, uterine abnormalities, and reduced ovarian reserve in females, as well as varicocele, obstructive disorders, and testicle insufficiency in males [4].

Poor environmental quality has enduring socioeconomic repercussions as it exposes individuals to numerous environmental pollutants, potentially compounding health issues due to unknown synergistic effects [5]. Infertility is among the profound and underappreciated adverse consequences. "Inability to conceive after 12 months of regular and unprotected

sexual intercourse" characterizes it [5, 6], affecting 50% of women and 10% to 15% of couples aged 20 to 45 [5, 7]. Female infertility stems from various causes, such as endocrine disorders, advanced age, and reproductive system illnesses, with 15% to 30% of cases remaining unresolved [5, 7]. Recent years have seen increasing female infertility due to delayed pregnancies, unhealthy lifestyles, cancer diagnoses, and exposure to environmental stressors [8]. Mechanistic and epidemiological evidence suggests that environmental contaminants impact placental function, fetal development, and potentially human fertility [9, 10]. These pollutants can disrupt endocrine function and initiate cascading events that compromise the reproductive system's integrity, even when it is physiologically sound [9, 10].

1.2. Environmental Threats to Female Reproductive Health

Environmental chemical impacts are intrinsically linked to various disorders affecting the female reproductive system, including polycystic ovarian syndrome, aneuploidy, and placental abnormalities [11-13]. Pregnant women exposed to air pollution face a heightened risk of developing a range of abnormalities, notably those affecting the brain, heart, and lungs [11]. Air pollution significantly disrupts the normal developmental processes of the fetal brain and is associated with various central nervous system diseases [11, 13]. Particulate matter 2.5 (PM2.5) exposure during pregnancy leads to reduced expression of Syndecan-1 (SYN1) and brain-derived neurotrophic factor (BDNF), both of which are critical for healthy fetal brain development [11, 14]. Additionally, exposure to hazardous substances during pregnancy impairs fetal lung development, increasing the susceptibility to respiratory illnesses like asthma [11, 16]. Breton et al.'s studies have identified a correlation between prenatal exposure to PM2.5 and PM10 and an increase in carotid arterial stiffness [17]. Contrary to popular belief, exposed mothers have a higher likelihood of giving birth to low-weight babies [18].

The process of female reproduction encompasses multiple phases, from ovum formation to fetal nourishment and pregnancy maintenance, spanning from intrauterine development to the culmination of the reproductive lifespan. Various impediments may hinder each of these stages, starting from oocyte development, fertilization, embryo passage, implantation, and the subsequent embryonic development to full-term pregnancy. Environmental contamination poses a substantial challenge to human reproduction, detrimentally affecting both male and female fertility [19, 20]. Environmental pollution, stemming from its deleterious biological, chemical, and physical attributes, exerts adverse consequences on the entire ecosystem, encompassing air, water, soil, and food [19, 20]. The pervasive impact of industrialization worldwide contributes to this environmental pollution that transcends national boundaries. Mitigating pollution entails complex and costly measures. Subsequently, individuals face an array of health disorders due to exposure to diverse toxicants in an unhealthy environment, including the heightened risk of infertility, recurrent miscarriages, and reproductive failures [19]. Female infertility can result from several causes, with ovulatory dysfunction playing a pivotal role. Environmental stressors and toxins influence ovulatory function, culminating in unsuccessful fertilization, follicular atresia, miscarriages, and failed implantation [21-25]. Some environmental contaminants, represented in air, water, soil, commercial products, food, and household dust, perpetuate the contamination cycle. Research conducted in the United States revealed the presence of measurable quantities of various chemicals, such as phthalates and pesticides like dich lorodiphenyldichloroethylene, dichlorodiphenyltrichl oroethane, and hexachlorobenzene in 99% to 100% of pregnant women [19, 26, 27]. Early embryos and gametes are particularly vulnerable to stress, and environmental toxins underlie numerous adult disorders, including coronary artery disease and type-2 diabetes [28]. Some theories propose that the prenatal environment directly impacts chronic adult disorders [29-31].

2. Environmental Pollutants:

Environmental pollutants possessing ova-toxic properties exert detrimental effects on female reproductive capacity, significantly impeding the intricate processes of female reproduction. By disrupting the essential physiological mechanisms necessary for successful conception and pregnancy through their toxic influence on ova (eggs), these pollutants play a critical role in hindering female

reproductive health [32, 33]. A thorough understanding of the impact of these environmental toxins on female fertility is paramount for the development of strategies aimed at mitigating their adverse effects and safeguarding the reproductive health of women [32, 33]. Moreover, the role of oxidative stress and excessive free radical generation in negatively affecting reproductive processes cannot be overlooked [34, 35].

Environmental pollution, stemming from human activities such as urbanization, industrialization, mining, and exploration, has become a critical global issue, impacting the air, water, and land. It stands as a significant cause of human morbidity and mortality, with recent analyses estimating that environmental pollution may contribute to approximately 9 million deaths worldwide annually [36]. Numerous environmental pollutants identified over the last decades pose potential risks for various acute and chronic diseases in humans. Despite individual assessments of pathogenic effects, the simultaneous and cumulative action of pollutants, considering the multitude of exposure sources, is a considerable concern. The impact of pollutants on human fertility is believed to vary based on the age of the exposed individual, with early exposure potentially resulting in greater reproductive damage. However, adults are not immune to adverse effects and as the intensity of exposure increases, so does the severity of the damage [37].

The mechanisms through which pollutants interact with reproductive health can be categorized into three classes:

1. Endocrine-Disrupting Chemicals (EDCs): These are exogenous chemicals or mixtures that interfere with hormone action, with effects ranging from transitory to permanent based on the time of exposure. Notably, polycyclic aromatic hydrocarbons (PAHs) and heavy metals in particulate matter, especially from diesel exhaust, act as EDCs. They can influence ovarian reserve by affecting receptors like the aryl hydrocarbon receptor (AhR) and estrogen receptors (ERs). Diesel exhaust particles, for example, contain substances with estrogenic, antiestrogenic, and antiandrogenic activities, influencing gonadal steroidogenesis and gametogenesis [38]. Endocrine-disrupting chemicals (EDCs), such as bisphenol A (BPA) and phthalates, interfere with hormonal actions, exhibiting estrogenic, anti-estrogenic, androgenic, and anti-androgenic effects. These xeno-estrogens impact female reproductive hormones and receptors, potentially affecting menstrual cycles, fertility, and conditions like polycystic ovary syndrome (PCOS) and endometriosis. Studies associate urinary phthalate metabolites with reduced oocyte yield and fertilization rates in in vitro fertilization (IVF). EDCs have also been implicated in early puberty onset, with environmental pollutants like BPA and phthalates possibly influencing sex steroid receptors. In conditions like PCOS, studies reveal associations between EDCs, infertility parameters, and reduced ovarian reserve. Endometriosis shows varied associations, with studies reporting links between higher EDC levels and the disease [39]. In utero exposure to EDCs, like BPA and phthalates, has been linked to altered obstetric outcomes, including changes in birth weight and gestational length. Overall, the impact of EDCs on female reproductive health involves complex interactions through multiple pathways, necessitating further research to understand their mechanisms fully Street [40].

2. Induction of Oxidative Stress: Reactive oxygen species (ROS) play a crucial role in regulating oocyte growth, meiosis, and ovulation in the ovary. The balance between ROS and antioxidants is vital for proper follicular development, with increased steroid production and estradiol secretion influencing their dynamic equilibrium. ROS serve as signaling molecules during ovulation, inducing apoptosis in granulosa cells and facilitating follicular rupture. In the in vitro setting, maintaining an optimal ROS balance is essential for successful outcomes in oocyte maturation, fertilization, and subsequent embryo implantation during assisted reproductive techniques. Monitoring ROS concentration in follicular fluid emerges as a potential marker for predicting in vitro fertilization and embryo transfer outcomes, underscoring the significance of managing oxidative stress in reproductive contexts [41]. This oxidative stress is associated with reproductive disorders like endometriosis, polycystic ovarian syndrome (PCOS), and unexplained infertility, along with complications during pregnancy such as hypertension, spontaneous miscarriage, intrauterine growth restriction, and recurrent pregnancy loss (RPL) [34]. Pollutants such as nitrogen oxide (NO_2), ozone (O_3), and particulate matter containing heavy metals and PAHs induce oxidative stress, contributing

to adverse effects on ovarian function [42]. Groundwater contamination with tetrachloroethylene (TCE) and perchloroethylene (PCE) further amplifies these risks, significantly increasing the chances of spontaneous miscarriage among women [43, 44]. The presence of these chlorinated solvents compounds ROS-related oxidative stress, emphasizing the crucial need to address groundwater contamination for environmental preservation and safeguarding women's reproductive well-being.

3. Modifications of DNA: Environmental pollutants can create alterations in the DNA chain, forming DNA adducts that lead to modifications in gene expression. Exposure to pollutants may also cause epigenetic modifications in the three-dimensional DNA structure, influencing DNA methylation. If these modifications affect the germ line, they could result in nonmodifiable mutations transmitted to offspring. Understanding these mechanisms is crucial in comprehending the intricate relationship between environmental pollutants and reproductive [45].

Pollution arises from diverse environmental factors, giving rise to various health consequences. These factors fall into several key categories:

2.1. Heavy Metals

Heavy metals are a group of metals characterized by their high density compared to water. This inherent property is a result of their atomic structure and composition, leading to increased mass per unit volume. The weightiness of heavy metals gives rise to unique chemical and physical attributes, with profound consequences for their behavior in diverse environmental and biological systems [46, 47]. Trace elements also encompass heavy metals, often present in trace amounts (ranging from parts per billion to less than 10 parts per million) within various environmental matrices [47, 48]. These heavy metals accumulate in soil, water, and food systems, ultimately entering the human body through food and water consumption [19]. Environmental contamination by heavy metals has raised concerns for ecological sustainability and global public health, with the recognition that not all heavy metals are detrimental, as some are essential in trace quantities (e.g., chromium, copper, zinc, and manganese), while others, like mercury, lead, and cadmium, have no metabolic role and are toxic at any level [19]. Human activities, including mining, smelting, industrial processes, and product use, contribute to metal pollution, posing risks to human health [49–52].

The impact of heavy metals on reproductive health differs between men and women, with females experiencing a more pronounced effect due to the finite, non-renewable pool of germ cells in the ovaries, which depletes rapidly [53, 54]. These detrimental effects manifest throughout a woman's reproductive lifespan, influencing fetal development, adolescence, and maturity. Long-term exposure to specific heavy metals, such as nickel (Ni) and cadmium (Cd), can function as endocrine disruptors, disrupting the production and function of endogenous hormones and their receptors. This disruption can lead to fetal abnormalities, steroidogenic dysfunction, and embryotoxicity [55]. Additionally, an elevated concentration of heavy metals induces oxidative stress, disturbing the normal functioning of gamete hormones and resulting in the generation of reactive oxygen species (ROS) [56]. Heavy metal exposure during pregnancy can lead to the release of reactive oxygen species (ROS) and oxidative stress, potentially culminating in premature delivery [56]. While the placenta serves as both a barrier to pollutants and a vital conduit for nutrient transfer between the mother and fetus, it is not impermeable to harmful substances. Non-essential metals may pass through this barrier due to their charge and size, potentially putting the fetus at risk [6, 57, 58]. Some research investigations have suggested that elevated levels of heavy metals in the placenta could harm fetal growth and development, leading to the recognition of the placenta as an indicator of prenatal exposure to hazardous metals [59-62]. This underscores the importance of monitoring and understanding the effects of heavy metal exposure during pregnancy on both maternal and fetal health.

2.1.1. Cadmium

Cadmium, a toxic heavy metal, poses a significant public health concern as it appears to have no beneficial effects on the human biological system and profoundly impacts female reproduction [63-65]. Cadmium interferes with steroidogenesis in the placenta and ovaries, hindering the production and release of female sex hormones, thereby significantly affecting normal reproduction [65, 66]. Both the endocrine hormone system and the neurological system regulate the

menstrual cycle in a monthly rhythm. Cadmium has the potential to damage nerve cells, resulting in menstrual irregularities that disrupt the production and release of female reproductive hormones [65-67]. In regions heavily polluted with cadmium, married women exhibit a higher prevalence of infertility, while unmarried women experience significantly more dysmenorrhea and irregular menstrual periods [68, 69]. Cadmium can accumulate in human endometrial tissue, with higher levels observed in women with a history of smoking [70, 71]. Residues of cadmium in breast milk can be passed on to future generations, increasing the risk of premature delivery and low birth weight in infants born to cadmium-exposed mothers [69, 72]. Maternal cadmium exposure is also associated with spontaneous miscarriage and low birth weight in humans [73-76]. Sources of cadmium exposure include dust, cigarette vapor, and smoke inhalation. Cadmium impedes the production of progesterone by reducing the production of steroidogenesis enzymes such as 3-hydroxysteroid dehydrogenase (3-HSD) and P450 [77]. Moreover, cadmium has been found to activate the estrogen receptor by binding to the hormone-binding region of the receptor, leading to menstrual irregularities, delayed menarche, pregnancy loss, hormonal imbalances, low birth weights, and preterm births [78, 79]. The impact of cadmium on female reproductive health highlights the need for stringent measures to mitigate exposure and protect women's reproductive well-being.

2.1.2. Lead

Blood lead levels are categorized into four groups: low (less than 4 μg/dL), moderate (between 5 and 9 μg/dL), intermediate (between 10 and 14 μg/dL), and high (between 15 and 20 μg/dL). Levels exceeding these limits are considered serious [6]. The impact of lead toxicity on human development remains a subject of debate, and no connection has been established between lead toxicity and spontaneous abortion, according to several studies [80, 81]. Lead can enter the human body through drinking water, food, dust, ambient air, and soil, affecting both the female and male reproductive systems. Workplace lead exposure has been linked to spontaneous abortions, infertility, neonatal and fetal deaths, and reproductive effects [82, 83]. Environmental lead exposure has also been associated with various health issues, including alterations in endocrine function, growth, and organ systems, as well as effects on fertility and pregnancy outcomes [69]. Higher lead levels have been linked to an increased risk of spontaneous miscarriages, even at low to moderate exposure levels [69, 84, 85]. Lead levels in the endometrium were found to be higher in women with a history of smoking [70, 71]. Research supports the hypothesis that fetal ovarian maturation is crucial for adult fertility, with females born to smokers during pregnancy experiencing decreased fertility [6, 86]. Some studies suggest that lead's teratogenic activity may increase the likelihood of spontaneous miscarriages [87, 88], particularly among women who were exposed to lead toxicity during childhood [6, 85, 89]. However, there is no clear evidence to establish a direct link between lead-exposed pregnant women and spontaneous abortion [6, 80, 81, 85].

Moreover, increased calcium requirements during pregnancy may lead to bone demineralization and the co-mobilization of stored lead (Pb) and calcium (Ca), potentially becoming a major source of fetal poisoning [6, 80, 90]. Mercury, with a blood level estimated at around 8 μg/L by the World Health Organization (WHO), can reach up to 200 μg/L with excessive fish consumption [91]. The three primary industries exposing individuals to mercury are mining, coal combustion, and the chemical sector. Despite limited research on female fertility, mercury can affect both male and female fertility [68]. Mercury crosses the placenta and disrupts estrogen's normal activity, resulting in congenital abnormalities, spontaneous miscarriages, and preterm newborns [92]. Exposure to elemental mercury increases the likelihood of irregular menstrual cycles but not the risk of miscarriages [70, 93]. Additionally, endometriosis, PCOS, dysmenorrhea, premenstrual syndrome, breast issues, amenorrhea, and improper breastfeeding have been associated with mercury exposure [5, 94]. Some studies have reported atypical menstrual cycles in women exposed to higher levels of mercury vapor at work [82, 95]. Mercury-containing compounds may also affect pregnancy outcomes, with lower birth weight associated with metal levels in the mother's blood and the baby's hair [96]. Some claims have been made that certain dental practitioners have reduced fertility due to exposure to inorganic mercury compounds and mercury vapor [83, 97].

2.1.3. Arsenic

The impact of arsenic (As) on the female reproductive system remains unclear due to limited research in this area [82]. Arsenic exposure typically occurs when individuals consume contaminated food and water. It has been suggested that arsenic exposure may lead to delayed menarche [70, 98]. Aschengrau *et al*. investigated the association between spontaneous miscarriages and community drinking water quality [72]. Arsenic may impair the female reproductive system by affecting certain steroidogenesis regulatory enzymes, such as 17-hydroxysteroid dehydrogenase (17-HSD) and 3-hydroxysteroid dehydrogenase (3-HSD) [99–104]. This impairment can lead to a reduction in the production of gonadotropins like FSH, LH, and estradiol [99–105]. Studies have shown that arsenic-exposed groups have significantly higher rates of preterm birth (PTB), stillbirth, and spontaneous miscarriages [70, 105]. Research conducted by Ahmed *et al*. suggests that arsenic exposure during pregnancy can damage immunological function and increase oxidative stress and inflammation in the placenta, potentially affecting the health of both the fetus and the infant [105]. Additionally, some environmental contaminants elevate arsenic content in the placentas during pregnancy, increasing the risk of oxidative damage. Statistically, the group exposed to arsenic has shown the highest incidence of stillbirth [82]. Further research is needed to fully understand the impact of arsenic on the female reproductive system.

2.1.4. Zinc (Zn)

The threshold for zinc deficiency is established at levels below 10 and 106 g/dL, while the typical range for blood zinc levels falls between 70 and 120 g/dL [106]. Maternal dietary inadequacies can influence fetal development, whereas elevated zinc concentrations can result in aberrant embryogenesis with potentially lethal and teratogenic outcomes [10, 108]. Zinc deficiency during pregnancy is associated with adverse effects including low birth weight, preterm birth, and congenital abnormalities, along with increased susceptibility to infections in adults [6, 19, 102]. Zinc plays a pivotal role in two essential ovarian processes: cumulus development and meiotic arrest, both of which may be compromised by a deficiency in zinc [5, 24]. Dietary zinc deficiency during pregnancy has been linked to developmental issues, emphasizing the significance of adequate zinc intake during this period. Moreover, it's noteworthy to mention that data indicates a high prevalence of mild to severe zinc deficiency in many underprivileged nations [107]. This underscores the importance of addressing zinc deficiency in maternal diets, particularly in regions with limited resources, to enhance maternal and fetal health. Further research and interventions are essential to mitigate the impact of zinc deficiency during pregnancy.

2.1.5. Cobalt

Cobalt (Co) holds significance in several physiological processes, particularly within the context of female reproduction [108]. While it plays a vital role in various biochemical pathways, its significance is notable, yet it's important to highlight that excessive cobalt levels can be detrimental [110]. The recommended daily intake of cobalt ranges from 1.7 to 100 µg, and fluctuations beyond this range can lead to physiological imbalances with implications for female reproductive health [19, 83]. Elevated cobalt content in the body has been linked to conditions such as lactation issues, menstrual irregularities, and menopausal complications [19, 83]. These phenomena underscore the delicate balance required for optimal female reproductive health and emphasize the intricate interplay of trace elements like cobalt. A comprehensive understanding of the role and impact of cobalt in female reproduction is crucial, both to address potential health issues arising from cobalt imbalances and to further explore its significance in this context.

2.1.6. Nickel (Ni)

The impact of nickel (Ni) exposure on the female reproductive system remains an area where comprehensive exploration, both in experimental and clinical settings, is warranted. Existing investigations have not extensively delved into this subject. While there is some evidence pointing towards human carcinogenicity and embryotoxicity associated with nickel exposure, these assertions lack robust support in the scientific literature [111]. Animal studies involving $NiSO_4$ have shown a range of adverse effects on female reproductive physiology. These effects include inhibition of progesterone synthesis, disruption of ovulation, decreased embryo implantation, menstrual cycle irregularities, and increased embryo resorption [112]. However, translating

these findings to human reproductive health requires further investigation, as interspecies variations in response to nickel exposure may exist. Comprehensive clinical research is needed to bridge this gap in knowledge and provide a more nuanced understanding of the potential effects of nickel exposure on female reproductive function while considering relevant dose-response relationships and exposure scenarios.

2.1.7. Iron (Fe)

Iron deficiency anemia, a condition associated with elevated global rates of mortality and morbidity, represents a significant health risk for women of reproductive age [111–113]. Notably, prior research has revealed that an excessive intake of iron during pregnancy can also yield adverse consequences [114]. Iron insufficiency and maternal anemia have been linked to an increased likelihood of preterm birth and low birth weight, with associated poorer iron status indicators potentially exacerbated by menstrual blood loss [111, 115–117]. Historically, pregnant Korean women have faced a relatively higher risk of iron deficiency, with a prevalence rate of approximately 20% [118]. Recent concerns have emerged regarding the excessive use of iron supplements by pregnant Korean women, often without proper consideration of their dietary iron intake or existing iron status [119]. Studies reveal that 30% to 40% of Korean women of reproductive age use nutritional supplements, with a significant 47.3% doing so without professional guidance or a prescription [120]. This emphasizes the need for informed and monitored iron supplementation during pregnancy to mitigate potential risks to both maternal and fetal health.

2.1.8. Manganese

Manganese, classified as a trace element, is essential for promoting healthy cellular function, growth, and development. However, excessive exposure to this element can yield detrimental effects on the reproductive system. While the majority of studies have primarily focused on the toxicological effects of Mn^{2+} in males, limited research has explored its impact on females [121]. Research by Eum *et al*. has indicated a correlation between elevated maternal manganese exposure and decreased birth rates [122]. Notably, environments with a heightened risk of occupational Mn^{2+} exposure include mines and factories involved in the production of dry batteries [82]. This underscores the importance of continued research into the potential reproductive health risks posed by excessive manganese exposure, particularly among women, as well as the need for stringent workplace safety measures in industries associated with increased manganese levels.

2.1.9. Chromium

The potential adverse effects of chromium on female human reproductive health have not been comprehensively studied [82]. However, research conducted by Yang *et al*. suggests that women exposed to high levels of chromium may have an increased risk of experiencing spontaneous miscarriages [123]. Additionally, elevated chromium exposure during pregnancy, especially among female offspring, has been associated with a heightened risk of giving birth to low-birth-weight infants [124]. Interestingly, there was no observed increase in the occurrence of spontaneous miscarriages among pregnant women whose husbands worked in the iron sector. Currently, further investigation is required to gain a more comprehensive understanding of how chromium affects the female reproductive system.

2.2. Air Pollutants

Air pollution consists of a complex mixture of gases, particulate matter, and volatile organic compounds originating from various sources such as industrial emissions, transportation, and natural processes [11]. It poses significant health risks, including respiratory diseases, cardiovascular issues, and impacts on reproductive health. The presence of air pollutants in the environment can have a detrimental effect on female fertility, as evidenced by studies linking air pollution to reproductive disorders and pregnancy complications [11, 14, 16]. Air pollution stands as a significant peril to global public health [125]. The act of breathing and obtaining essential oxygen via air inhalation underscores the indispensability of atmospheric air for human existence. Yet, the presence of contaminants in the air diminishes life expectancy. In fact, air pollution is responsible for an alarming 13% to 22% of global mortality [19]. Furthermore, it accelerates the aging of the reproductive system in females by reducing ovarian reserve [19, 21, 22]. Air pollution encompasses various constituents, with the primary culprits falling into four major categories:

carbon monoxide (CO), nitrate oxide (NO_2), gaseous pollutants such as sulfur dioxide (SO_2), organic compounds like dioxins and organic solvents, heavy metals like copper and lead, and particulate matter of various sizes, including PM2.5-10, PM10, and PM2.5 [22, 126]. Exposure to toxins due to air pollution leads to infertility and miscarriages in women, primarily attributed to defective oocytes during the pre- and periconceptional periods. It also disrupts gametogenesis and impairs reproductive health [19, 21, 22]. Of significant concern is the continuous scrutiny of how air pollutants affect female fertility, with emerging evidence suggesting their role in the etiology of female infertility [22, 127]. Research indicates that exposure to ozone and particulate matter with a diameter of 2.5 micrometers during the first trimester of pregnancy elevates the risk of gestational hypertension, preeclampsia, and premature delivery [19, 128]. Certain air pollutants, such as lead, copper, and diesel exhaust, may potentially disrupt the female endocrine system and consequently alter fertility [129]. High concentrations of carbon monoxide (CO), particulate matter (PMs), sulfur dioxide (SO_2), ozone (O_3), and NO_2 have been linked to significantly increased odds of stillbirth and abortion [130].

The repercussions of ambient air pollution, notably its impact on fetal growth and low birth weight, have garnered extensive research attention over recent decades [131]. Studies have also unveiled a negative correlation between air pollution levels and anti-Müllerian hormone (AMH) levels, a crucial marker of ovarian reserve, with women in highly polluted areas exhibiting lower AMH levels [132]. Moreover, women living within 200 meters or less from major roadways and high-traffic areas exhibit reduced fertility rates [133]. Notably, cigarette smoke, which contains benzene, has been found to accelerate menopause by three to four years, elevate baseline follicle-stimulating hormone (FSH) levels, and induce follicular depletion [126, 133]. Greater exposure to nitrogen dioxide (NO_2) and particulate matter with a diameter of 10 micrometers or less has been associated with reduced likelihood of women becoming pregnant [134].

2.3. Pesticides

Pesticides are chemical substances used to control pests in agriculture, and their residues can affect food and water sources. Prenatal exposure to certain pesticides like dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), and chlordane has been associated with adverse reproductive outcomes, including an increased risk of infertility, miscarriages, and developmental abnormalities [135].

The impact of organochlorine pesticides on human health, particularly reproductive health, varies depending on factors such as duration, dosage, and mode of exposure [67]. Thakur *et al*. reported a higher incidence of adverse pregnancy outcomes, including preterm births, spontaneous abortions, and other complications, in areas characterized by elevated levels of pesticide and heavy metal contamination [67, 136]. Exposure to pesticides has been associated with various reproductive problems in women, encompassing reduced fertility, spontaneous abortions, stillbirths, low birth weight, premature delivery, ovarian disorders, developmental anomalies, and disruptions in hormone regulation [137]. Evidence suggests a potential link between pesticide exposure and ovarian dysfunction [135]. Furthermore, Farr *et al*. demonstrated a connection between pesticide exposure and menstrual cycle alterations, including longer menstrual cycles and an increased likelihood of missed periods in women who used pesticides compared to those who did not [138]. Contrarily, Arbuckle *et al*. found that pesticide combinations, specifically herbicides and fungicides, were associated with a fourfold increase in the likelihood of spontaneous miscarriages when compared to women exposed solely to fungicides [139, 140].

Women engaged in agriculture or exposed to pesticides exhibited a higher prevalence of infertility [141], and multiple studies support an association between agricultural work or pesticide exposure and an increased risk of spontaneous miscarriages [142]. Finnish researchers conducted a comprehensive study revealing that exposure to pesticides during the first trimester of pregnancy substantially raised the risk of cleft palates and cleft lips in offspring [143. 144]. Reproductive diseases have been linked to pesticides and some other environmental contaminants [145]. Despite the belief that human exposure to dichlorodiphenyltrichloroethane (DDT) is not typically harmful, long-term exposure to DDT has been shown to have detrimental effects on reproduction [146].

2.4. Endocrine Disruptors

Endocrine disruptors are currently being produced in greater quantities, and their effects on the reproductive system are subjects of significant concern. These substances interfere with the release, synthesis, action, transport, binding, or elimination of the body's endogenous hormones, which govern crucial processes like reproduction, maintenance, behavior, and development [10]. The disruption of endocrine functions can have profound impacts on the reproductive system, leading to disturbances such as altered ovarian cycles, fluctuating hormone levels, and reduced fertility [147]. Evidence points to the potential for endocrine-disrupting chemicals, such as polychlorinated biphenyls (PCBs) and certain pesticides, to disrupt hormonal balance and increase the risk of infertility. These endocrine disruptors diminish the efficacy of endogenous hormones, which can contribute to birth abnormalities, malignancies, and other reproductive ailments [148].

Various factors, including dietary habits, ethnicity, stress, and more recently, exposure to endocrine disruptors, can influence early puberty in females [149]. Chemical exposures, including benzene and polychlorinated biphenyls (PCBs), have a detrimental impact on the menstrual cycle. Women with the highest levels of polychlorinated biphenyls (PCBs) face a substantial 50% reduction in their likelihood of becoming pregnant, and if they do conceive, they have an increased risk of miscarriage. Exposure to polychlorinated biphenyls (PCBs) has long been associated with a heightened risk of abortion and potential reproductive issues. Furthermore, research has shown that the presence of polychlorinated biphenyls (PCBs) in various reproductive tissues, such as follicular fluid (FF), the uterus, placenta, amniotic fluid, and the ovaries, can significantly impact female reproduction [150].

Lagarde *et al*. conducted a comprehensive study on non-monotonic dose-response (NMDR) relationships linked to endocrine disruptors, aiming to establish criteria for risk assessment. Analyzing 51 experimental studies, the research identified 82 NMDR relationships with "moderate" to "high" plausibility, emphasizing the prevalence of non-linear responses. The study proposed a decision tree for standardized analysis, applied to bisphenol A studies. Challenges in reproducibility were acknowledged, prompting the need for careful consideration of NMDR at various endpoints. The work highlights the importance of specific criteria, dose range considerations, and further research on modes of action in risk assessments. This research significantly contributes to understanding NMDR phenomena and advocates for a nuanced approach in risk assessments [151].

2.5. Climate Change

Climate change can impact reproductive health through various mechanisms, including extreme weather events, heat stress, and altered disease patterns. These effects can have indirect consequences for fertility and reproductive outcomes. The global issue of climate change poses a significant threat to human existence, with far-reaching implications for fertility rates and reproductive health, particularly among women. As women delay childbirth, fertility rates have declined, contributing to substantial social and economic consequences. Additional factors, such as obesity, pollution, and diets high in endocrine disruptors, further imperil reproductive health [152]. The primary driver of global climate change is the release of greenhouse gases (GHGs), a consequence of atmospheric warming, as reported by the Intergovernmental Panel on Climate Change (IPCC) in 2013 [153]. The IPCC projects that, atmospheric carbon dioxide (CO_2) concentrations in 2030 will range between 400 and 480 parts per million (ppm) [154]. Extreme temperatures can directly impact reproduction, while environmental changes can exert indirect effects. It is imperative to consider how rising temperatures in various regions of the world can influence pregnancy outcomes. The effects of climate change on pregnancy-related issues can lead to prenatal complications. High temperatures and air pollution are known to contribute to low birth weight and premature births. Environmental variables such as heat waves, food shortages, infectious diseases, and air pollution resulting from fossil fuel combustion can increase the risk of adverse pregnancy outcomes, including miscarriages and low birth weight [155]. Women and girls are more vulnerable to health hazards associated with climate change due to their increased exposure to natural disasters and climate-related damage. Societal and cultural constraints may further limit their ability to respond effectively to these health consequences, relative to men and boys. Additionally, climate change-

induced disasters have the potential to restrict access to and availability of maternal and reproductive healthcare services [156].

3. Specific Environmental Pollutants

3.1. Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs, common environmental pollutants from vehicular emissions and industrial processes, are linked to cancer and infertility. They interact with the pituitary–ovarian axis, causing ovarian physiology and function alterations[157].

3.2. Parabens

Used as preservatives, parabens act as endocrine disruptors, mimicking sex hormones. They impact sperm count, semen motility, and morphology in males. In females, exposure is associated with menstrual cycle irregularities and diminished ovarian reserve[158].

Perfluorooctanesulfonate (PFOS)/Perfluorooctanoate (PFOA): Widespread in everyday items, PFOS/PFOA exposure is linked to longer conception times in women and adverse effects on male reproductive health. Increased infertility likelihood is observed with higher exposure levels [159].

3.3. Bisphenol Pathophysiological Impact

Bisphenol-A (BPA), found in various products, acts as an endocrine-disrupting chemical. It affects hormone synthesis, metabolism, and function. Its impact on the female reproductive system involves stimulation of estrogen receptors and gene expression alterations. BPA contributes to female and male infertility through its impact on natural conception. Studies suggest higher BPA levels in infertile women, especially in metropolitan areas. BPA exposure during different life stages affects ovarian development, folliculogenesis, and embryo implantation [160].

The Role of Phthalates: Phthalates, used as plasticizers, are endocrine disruptors affecting both male and female reproductive systems. In males, they interfere with reproductive system development, induce testicular dysgenesis syndrome, and may lead to cancer. In females, phthalates negatively impact ovarian function, potentially causing premature ovarian failure and influencing puberty onset [161].

Kumar *et al*. have compiled a tabular summary detailing the intricate links between environmental exposures and female reproductive dysfunction(**Table 1 and 2**). The table serves as a structured resource, offering a comprehensive overview of various factors and their potential impacts on female reproductive health. This concise format provides valuable insights for researchers, healthcare professionals, and policymakers, emphasizing the significance of understanding the complex interplay between environmental influences on female reproductive processes [162]

Table 1: Metals exposure and female reproduction and pregnancy result

Exposure	Effects
	Mercury (Hg)
Dental personnel exposed to Hg	Limited evidence suggests associations with spontaneous abortions (SAb), reduced fertility, and congenital abnormalities.
Maternal exposure to Hg in pregnancy	Offspring exhibiting a 34g low birth weight (LBW) and an elevated risk of small for gestational age (SGA).
Dental staff exposed to Hg	Spontaneous abortion (SAb), preeclampsia, and the birth of SGA babies in individuals exposed to mercury (Hg) could be linked to Hg-induced oxidative stress.
Elemental Hg exposure	Higher occurrence of irregular menstrual cycles
Hg exposure	Abdominal pain, dysmenorrhoea along with abnormal menstruation
	Lead (Pb)
Men occupationally exposed to Pb	augmented danger of infertility and pregnancy postponement in wives of males occupationally exposed to Pb
Girls exposed to environmental Pb	impediment in teenage maturity and growth of girls
Prenatal higher blood Pb level	Preterm delivery, reduced head circumference, and shortened crown-heel length are associated with prenatal exposure to higher levels of lead (Pb).
Higher blood and cord Pb level	Low birth weight is observed in offspring of mothers with elevated blood lead (Pb) levels. Additionally, there is a negative association between cord Pb levels and birth length.
Pregnant women with blood Pb level $\geqslant$ 10 µg/dl	There is a three-fold higher risk of preterm birth (PTB) and a four-fold higher risk of small for gestational age (SGA) birth associated with lead (Pb) exposure in pregnant women.

Continuation Table:

Exposure	Effects
Pb exposure to women	There is a risk of spontaneous abortion (SAb), but blood lead (Pb) levels below 5 µg/dl are not identified as a risk factor for SAb.
Low to moderate Pb exposure	Risk of SAb
	Cadmium (Cd)
Women living in Cd polluted area	Exposure to cadmium (Cd) is associated with abnormal menstrual cycles, dysmenorrhea in unmarried women, and sterility in married women.
Cd exposure	Associated with preeclampsia
Maternal Cd exposure	Exposure to cadmium (Cd) during pregnancy is linked to a high risk of early delivery and low birth weight (LBW).
Low level Cd exposure	Cadmium (Cd) exposure interferes with steroid hormones and disrupts steroidogenesis, leading to alterations in sex differentiation and gametogenesis.
	Arsenic (As)
As-contaminated drinking water	Adverse effects on menarcheal age, SAb, stillbirth, and PTB; negligible risk of PTB and LBW.
As exposure during pregnancy	Reduced gestational age, lower maternal weight gain23, six-fold stillbirth risk, no link with infant mortality or SAb24; increased placental oxidative stress.
	Zinc (Zn)
Role of Zn	Essential for growth, cellular integrity, protein synthesis, nucleic acid metabolism, and beneficial for infant neurobehavioral development.
Maternal Zn deficiency	Linked to infertility, embryo/fetal death, intrauterine growth retardation, and teratogenesis.
	Mangnese (Mn)
Maternal Mn level	elevated concentration associated with LBW
Maternal and cord blood Mn	Birth weight elevated with Mn upto 4.18 µg/dl and reducted at higher levels
Mn exposure	Increased birth weight up to 3.1 µg/l Mn, reduced at higher levels.
	Chromium (Cr)
Female workers exposed to occupational Cr	augmented danger of SAb and threatened abortion
Female exposed to Cr during pregnancy	Elevated risk of PTB in male offspring and LBW in female offspring.
	Vanadium (V)
Exposure to vanadium through food, water, and polluted air.	LBW positively linked to maternal urinary Vanadium.

SAb, spontaneous abortion; LBW, lower birth weight; SGA, small gestational age; PTB, preterm birth

Table 2: Exposure to phthalates and its impact on female reproduction and pregnancy outcomes

Exposure	Effects
Exposure to Phthalates and Its Impact on Reproductive Outcomes and Children's Health	(i)Impact on LH, free testosterone, sex hormone-binding globulin, anogenital distance, and thyroid function. (ii) Elevated urinary phthalate levels observed in individuals with pubertal gynecomastia, girls experiencing thelarche, and those with precocious puberty.
Concentration of phthalates in individuals experiencing thelarche compared to control subjects.	Elevated concentrations of phthalates, including dimethyl, diethyl, dibutyl, and DEH, along with their metabolite mono-(2-ethylhexyl) phthalate, were observed in individuals experiencing thelarche.
Exposures to DEHP metabolite, MBP, and MEP during pregnancy.	Prenatal phthalate exposure linked to sex steroid hormone concentrations, but no association with infant reproductive outcomes.
Exposure to DEH and its metabolite, MEHP, in endometriosis.	Women with endometriosis exhibited elevated plasma levels of DEHP, with 92.6% having detectable levels of DEHP and MEHP in peritoneal fluid.Top of Form
Urinary levels of phthalate metabolites, including MBP, MBzP, mono(3-carboxylpropyl) phthalate, and four DEHP metabolites.Top of Form	Elevated urinary concentrations of phthalates in women who experienced preterm birth (PTB).

LH, luteinizing hormone; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; DEH, di-2-ethylhexyl; MEHP, monoethyl hexyl phthalate; DEHP, di-2-ethylhexyl phthalate

Limitation of the study and future directions: Top of Form This study acknowledges limitations and outlines future directions for research. It emphasizes the need to delve into the precise molecular and cellular mechanisms by which environmental contaminants disrupt female reproductive processes, paving the way for targeted interventions. Additionally, the study underscores the importance of investigating the long-term consequences of early-life exposure, contributing to informed policies that consider both immediate fertility and enduring reproductive health. The exploration of transgenerational effects through induced epigenetic modifications and the development of enhanced screening methods for early detection are identified as crucial areas for future inquiry. The research is positioned to actively contribute to shaping effective environmental policies and interventions, taking into account the diverse challenges faced by women globally and aiming to safeguard female fertility and overall well-being.

4. Conclusion

The female reproductive system undergoes significant impacts due to exposure to toxicants and pollutants in the environment. Various studies have demonstrated that certain chemicals, such as pesticides, as well as heavy metals can result in early pregnancy loss, infertility, and diverse reproductive disorders. Environmental contaminants have the ability to disrupt hormonal balance and interfere with the intricate processes involved in female reproduction. Notably, air pollution has been associated with abnormalities in fetal development, including those affecting the brain, heart, and lungs. Additionally, the oxidative stress induced by environmental toxins can have detrimental effects on reproductive processes. Heavy metals have been identified as endocrine disruptors that interfere with hormone production and function, leading to menstrual problems and imbalances in reproductive hormones. While the placenta serves as a protective barrier against pollutants, some metals can permeate through it and impact fetal growth and development. Specifically, cadmium has been linked to infertility, dysmenorrhea, irregular menstrual cycles, and negative pregnancy outcomes. Similarly, exposure to lead has been associated with spontaneous abortions, infertility, and alterations in reproductive function. Understanding the consequences of environmental toxins on female fertility is crucial in order to develop strategies that can mitigate their adverse effects and safeguard women's reproductive health.

5. Conflict of Interest

The authors declare no conflict of interest.

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