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The role of specific nutrients and pollutants with endocrine activity on fertility in women

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Table of Contents

ABSTRACT 5

RIASSUNTO 6

INTRODUCTION 7

1. Hormonal regulation of fertility 7

1.1 Prevalence of infertility due to endocrine disruptors (epidemiology) 7

1.2 Female reproductive system 8

1.3 Link between endocrine disruptors and fertility in women 11

2. Environmental pollution and its effect on fertility 13

2.1 Different types of heavy metals (Pb, Hg, Zn, Ni) and EDCs (such as BPA, phthalates, arsenic) 15

Table 1 19

2.2 Heavy metals and EDCs mechanism of toxicity in the women reproductive system 20

2.3 Link between heavy metals and infertility 23

3. Air pollution effect on fertility 26

3.1 Sprayed pesticides and their consumption through the diet 27

3.2 Smoking habits (benzene exposure through tobacco smoke) 29

3.3 EDCs enter food chain via contamination of soil and water 30

3.4 Effects of personal Care products as EDCs on female reproductive system 32

4. Obesogens and fertility 32

4.1 what are obesogens and what is their prevalence in the food chain 33

4.2 Maternal nutrients excess and fetal overgrowth 35

4.3 How obesogens affect functioning of endocrine system 36

5. How can a nutritionist influence (triggering or helping) recovering from hormonal imbalances due to EDC and obesogens. 37

6. Prevention of the exposure to endocrine disrupting chemicals through diet 38

6.1 Nutrition effect on endocrine disrupting chemicals through diet 39

6.2 What foods are high in EDC and how to avoid them in diet 42

6.3 How to construct and design a diet plan that maintains hormonal and reproductive health 46

7. Conclusion 53

BIBLIOGRAPHY 55

ABSTRACT

Endocrine disruptors are one of the sources of greater concern, considering that it is an issue that has evolved with the growth of society. The food business uses numerous chemicals that enter the food chain and have an immediate negative impact on human health.
Endocrinological disruptors has the ability to impede typical hormonal function, metabolism, and biosynthesis, potentially resulting in a deviation from the standard hormonal equilibrium.
The purpose of this review is to shed light on the significance of nutrition and dietary management for human reproductive health by examining the effects of particular nutrients and pollutants with endocrine activity on women's fertility.
Certain endocrine disruptors are strongly linked to conditions like polycystic ovary syndrome, endometriosis, irregular menstrual cycles, and disruptions in processes like steroidogenesis and ovarian follicle growth, which are positively correlated with female infertility.
This implies that reproductive function is invariably harmed by any pollution that alters hormonal homeostasis or the reproductive system. It is no longer possible to ignore the significant social and economic ramifications of this decline.
Exposure to heavy metals is a risk factor for infertility that can harm both male and female reproductive systems. Ovulatory dysfunction, male factor infertility, and tubal illness are the main causes of infertility. However, unfavorable lifestyle choices and external circumstances can reduce fertility. More specifically, harmful environmental conditions (such as exposure to heavy metals) can harm both men's and women's reproductive systems.
Moreover, pregnant women altered metabolic pathways were discussed, with a focus on various food and lifestyle therapies.

RIASSUNTO

Gli interferenti endocrini rappresentano una delle fonti di maggiore preoccupazione, considerando che si tratta di un problema che si è evoluto con la crescita della società. L'industria alimentare utilizza numerose sostanze chimiche che entrano nella catena alimentare e hanno un impatto negativo immediato sulla salute umana. Gli interferenti endocrinologici hanno la capacità di impedire la normale funzione ormonale, il metabolismo e la biosintesi, con conseguente potenziale deviazione dall'equilibrio ormonale standard. Lo scopo di questa revisione è quello di far luce sul significato della nutrizione e della gestione dietetica per la salute riproduttiva umana esaminando gli effetti di particolari nutrienti e inquinanti con attività endocrina sulla fertilità delle donne.

Alcuni interferenti endocrini sono fortemente legati a condizioni come la sindrome dell'ovaio policistico, l'endometriosi, i cicli mestruali irregolari e le interruzioni di processi come la steroidogenesi e la crescita del follicolo ovarico, che sono positivamente correlati all'infertilità femminile.

Ciò implica che la funzione riproduttiva è invariabilmente danneggiata da qualsiasi inquinamento che alteri l'omeostasi ormonale o il sistema riproduttivo. Non è più possibile ignorare le significative conseguenze sociali ed economiche di questo declino.

L'esposizione ai metalli pesanti è un fattore di rischio per l'infertilità che può danneggiare il sistema riproduttivo sia maschile che femminile. La disfunzione ovulatoria, l'infertilità maschile e la malattia tubarica sono le principali cause di infertilità. Tuttavia, scelte di stile di vita sfavorevoli e circostanze esterne possono ridurre la fertilità. Più specificamente, condizioni ambientali dannose (come l'esposizione ai metalli pesanti) possono danneggiare il sistema riproduttivo sia degli uomini che delle donne.

Inoltre, sono stati discussi i percorsi metabolici alterati delle donne in gravidanza, con particolare attenzione alle varie terapie alimentari e allo stile di vita.

INTRODUCTION

1. Hormonal regulation of fertility

1.1 Prevalence of infertility due to endocrine disruptors (epidemiology)

According to the World Health Organisation, infertility is a public health issue affecting around 48 million couples and 186 million people globally. Endocrine disruptors are one of the most concerning causes, as they are an issue that has progressed alongside societal progress. The food business uses several chemicals, which enter the food chain and have a direct impact on human health. Endocrine disruptors can interfere with normal hormonal activity, metabolism, and biosynthesis, causing a shift in hormonal homeostasis. Some of these endocrine disruptors are substantially connected with disorders that are positively correlated with female infertility, such as polycystic ovarian syndrome, endometriosis, irregular menstrual cycle, as well as abnormalities in processes such as steroidogenesis and development of the ovarian follicles[1].

The World Health Organization (WHO) defines infertility as "a disease of the male or female reproductive system described as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse". It has a significant influence on the population because couples may endure sadness, worry, anguish, low self-esteem, and feelings of shame and blame during the process. The scientific community agrees on the definition of endocrine disruptors: "an endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, its progeny, or (sub)populations.". In 2018, the European Chemical Agency and the European Food Safety Authority (EFSA) produced a guidance sheet for identifying endocrine disruptors.

Endocrine disruptors, also known as endocrine active substances, endocrine disrupting chemicals, or endocrine disruptive compounds, are chemicals that can interfere with normal hormonal action, resulting in negative health repercussions for an organism and/or future generations. These irregular actions can have a wide range of negative health consequences because they disrupt natural hormone systems and the maintenance of the body's normal hormonal route[1.]

Endocrine disruptive chemicals, which can be found in agriculture, industry, pharmaceuticals, or the food chain, contain a wide variety of exogenous chemicals, including synthetic substances, that can influence hormone synthesis, metabolism, and function.
Endocrine disruptors have received a great deal of attention from the scientific community in recent years. A large number of laboratory and human research have been published on the various substances that cause this hazardous endocrine action. The health impacts of these chemicals have increased unitedly with their publication, demonstrating that they can cause a variety of disorders. When the hormonal imbalance is not precise, health complications can arise due to these changes in the number of hormones generated by the glands. A lot of things can affect this balance, and endocrine disruptors, as the name shows, are one of the prime responsible[1].

The endocrine system plays an important role in many physiological systems because it is in charge of hormonal communication, which is dependent on the production and release of hormones from numerous glands in the bloodstream to coordinate various functions in our bodies by carrying messages. Hormones are required for numerous processes, including metabolism, development and growth, and reproductive functions[1].

1.2 Female reproductive system

The process of human reproduction has historically piqued curiosity. Hippocrates wrote one of the earliest scientific accounts of it in the fifth century BC, proposing that the union of a

woman's menstrual flow and a man's ejaculate would give rise to new creatures. After more than two millennia, we now understand that reproduction is the result of a complicated series of biological processes, in which the union of spermatozoa and oocytes, the gametes, is a key component[2].

Gametes begin as certain cells give up on their somatic lineage to develop into primordial germ cells (PGC), which are essential for reproduction. The ovary in female humans serves as a crucial anatomical foundation for PGC development over the course of their evolution. Follicle genesis, a series of cellular changes required for maturation and preparation for a second wave of structural and functional modifications inherent to the ovarian cycle, which in turn culminates with the crucial event in female fertility: ovulation, begins once they have matured into primordial follicles, a stage reached before birth and once the subject has reached puberty. Together, these mechanisms enable reproduction and the creation of new life[2,3].

In reality, hormonal, metabolic-energetic, genetic-epigenetic, and intra- and extraovarian variables all play complex roles in female reproductive physiology, coordinating the progressive development of the female gamete. Any of these component disruptions can result in infertility, a worrying worldwide health issue for women that presently affects 48.5 million females between the ages of 20 and 44. Furthermore, changes in the physiology of female reproduction frequently have effects on other organ systems, as demonstrated by the well-known case of polycystic ovarian syndrome. In addition to the effects on women's bodies and minds, these changes could have an indirect effect on the future health of their progeny. This review attempts to characterize the physiological and molecular processes associated with female fertility because of its significant influence on female health and the health of their offspring. Throughout a female's life, the ovary undergoes a variety of anatomical and functional changes in order to give reproductive potential[1,2,3].

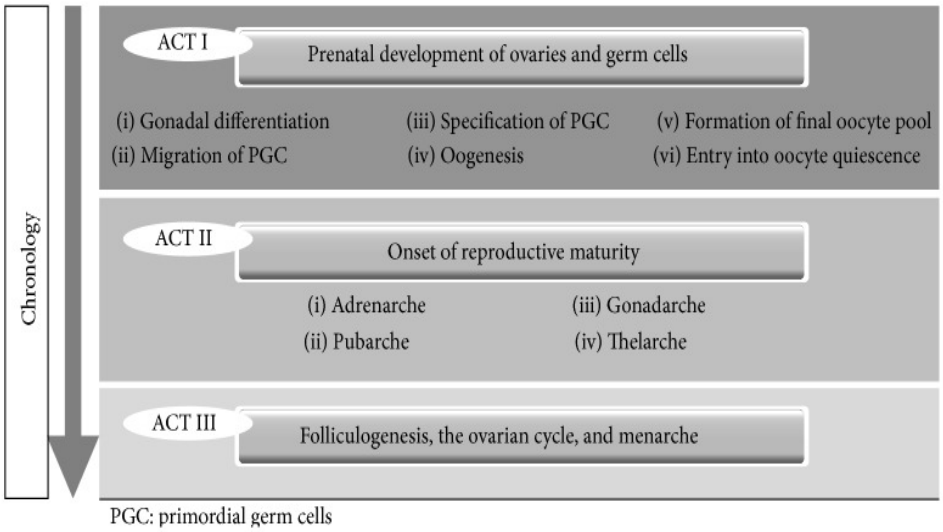

Figure 1. key events in the physiological life cycle of a woman's ability to reproduce.. Figure from "Rojas J, Chávez-Castillo M, Olivar LC, Calvo M, Mejías J, Rojas M, Morillo J, Bermúdez V. Physiologic Course of Female Reproductive Function: A Molecular Look into the Prologue of Life. J Pregnancy. 2015;2015:715735. doi: 10.1155/2015/715735. Epub 2015 Dec 1. PMID: 26697222; PMCID: PMC4678088."[2]

A chronological summary of the main events in this timeline is provided in Figure 1. Numerous endocrine signals regulate these activities, as evidenced by the wide variations in blood concentrations of mediators such as sex hormone, gonadotropin, and others across different life stages[2]. This sequence can be schematized into three elemental parts, or "acts," similar to a theatrical play: (1) the setup, which includes the ovary's development in utero, its embryonic origin, and infantile quiescence; (2) the buildup, which includes the ovarian and adrenal reactivation during puberty as well as the neuroendocrine cues that initiate sexual maturation; and (3) the climax, which includes the molecular mechanisms involved in folliculogenesis and the normal ovarian cycle. The development of female reproduction after ovulation is largely dependent on the occurrence of fecundation[2]. In fact, in the event that it is absent, the corpus luteum will quickly deteriorate, causing the ovarian cycle to restart and monthly bleeding to commence. However, the decidual reaction, an increase in endometrial secretion, and stromal edema will occur in the event that an appropriately implanted zygote is present in the endometrium. These changes facilitate healthy syncytiotrophoblast development, which in turn enables hCG secretion to sustain the corpus luteum. This is only one of the several endocrine changes that are a natural part of pregnancy. This bifurcation is periodically caused by the ovarian

cycle under healthy circumstances and lasts until menopause, which is the natural end of the ovaries' principal function, folliculogenesis and the ovarian cycle. Because the follicular phases are shorter and the follicles are smaller, the early stages of this transition have shorter cycles. The main cause of this occurrence seems to be a decrease in the synthesis of AMH and inhibin B, which increases the release of FSH and, consequently, the synthesis of estrogen. As a result, this would enable the LH surge to be triggered earlier. Along with changes to the neural networks that modulate the release of GnRH, there is also a reduction in pulse frequency and altered secretion patterns of both GnRH and the latter. Complementing decreased signaling by AMH and inhibin B, proapoptotic gene expression in oocytes drives faster follicular reserve depletion until eventually it is exhausted. In this case, the levels of circulating estradiol significantly decrease because only extraovarian sources—namely, adipose tissue—remain active providers of this hormone. Reduced estrogen levels cause a wide variety of multisystemic physiologic alterations. Menopause, the "curtain call" of female reproductive activity, is in fact a well-known risk factor for osteoporosis and cardiovascular disease, among many other conditions. Since these disruptions have an impact on global female health outside the reproductive domain, a deeper comprehension of the molecular mechanisms underlying female fertility is necessary to better control the various disruptions that may arise within its intricate regulatory networks[2,3].

1.3 Link between endocrine disruptors and fertility in women

A vital component of reproduction are hormones. These include the androgens (testosterone) secreted by men and women, as well as the sex hormones estrogen and pituitary secreted by women[3].

EDCs either obstruct the pathways that these hormones take to bind to their receptors or they mimic hormonal activity to fool a hormone receptor into responding. In any case, EDCs disrupt the hormonal systems' regular operation. Chemicals known to cause endocrine disruption are widely present and can affect both people and animals[3]. Female reproduction is a crucial process that is affected by exposure to endocrine disrupting substances and is controlled by hormones. Endocrine disrupting chemicals have the potential to cause subfertility, infertility, anomalies in

the menstrual cycle and estrous cycle, anovulation, and early reproductive senescence in females. Many endocrine disrupting substances can cause problems in fertility in both people and animals by acting as endocrine disruptors in adult females. EDCs are substances that interfere with an animal's endocrine system by either imitating or inhibiting endocrine functions. More specifically, EDCs can obstruct hormone metabolism, steroidogenesis, and receptor binding. In a variety of animals, including humans, EDCs have been demonstrated to impair female reproduction (Figure 2)[3].

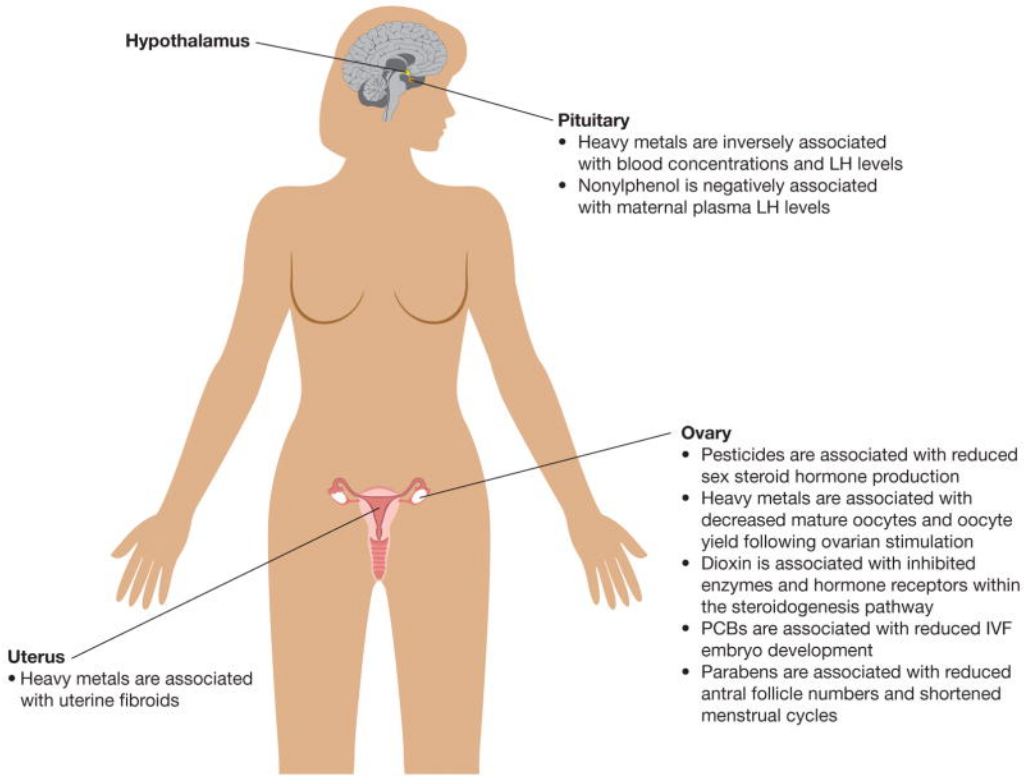

Figure 2. An overview of the relationships between adult women's reproductive organs and exposure to pesticides, heavy metals, 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin), polychlorinated bisphenols, and parabens. Figure from "Rattan S, Zhou C, Chiang C, Mahalingam S, Brehm E, Flaws JA. Exposure to endocrine disruptors during adulthood: consequences for female fertility. J Endocrinol. 2017 Jun;233(3):R109-R129. doi: 10.1530/JOE-17-0023. Epub 2017 Mar 29. PMID: 28356401; PMCID: PMC5479690[3]."

According to experimental evidence, adult EDC exposure resulted in a variety of consequences, including aberrant estrous cycles, a decline in pregnancy rates, a decrease in pup survival, and an earlier beginning of reproductive senescence[3]. To gain a better understanding of reproductive diseases caused by the environment, it is necessary to comprehend the mechanisms of action of

EDCs on the fertility of adult females. While some research claim that aryl hydrocarbon receptors, estrogen receptors, and peroxisome proliferator-activated receptor activation processes are how EDCs cause toxicity, they have not looked at other possible routes[3].

To some extent, the unfavourable effects of EDCs are not surprising. For example, many pest-control agents intended to affect pest reproductive systems also harm human reproductive systems because human reproductive processes are comparable to those of other species[3].

2. Environmental pollution and its effect on fertility

An accurate image of our globe reveals that it is badly contaminated throughout. Farm fertiliser, manure runoff, sewage, and industrial discharges damage coastal regions and oceans, and enormous islands of discarded plastic float around, posing a threat to marine life. According to recent study, human infertility is on the rise. Although several theories have been proposed to explain the rising infertility rate, environmental toxins could be key causal factors[2].

Environmental endocrine disruptors (EEDs) are substances that impair the physiological function of the endocrine system in humans and wildlife. They can affect the endocrine system by targeting different levels of the hypothalamic-pituitary-thyroid/gonad/adrenal axes, inhibiting or stimulating hormone production, or changing the way hormones travel through the body. The effects can range from hormone receptors to hormone synthesis or metabolism, so the EEDs can have negative health implications on humans[4]. Chemical pollutants are ubiquitous in our environment, and human exposure is almost unavoidable. Heavy metals and organic compounds that can be taken up and accumulated in crop plants pollute terrestrial ecosystems, while untreated industrial discharges affect water tables severely. As a result, our ecosystem and biodiversity suffer significantly, and degenerative or man-made diseases become more common. In this regard, it has been established that environmental contamination reduces fertility in all mammalian species. Females suffer the most since the amount of germ cells in the ovary remains constant during fetal life and is not renewable. This means that any contaminant that affects hormonal homeostasis and/or the reproductive machinery will inevitably reduce reproductive performance. This deterioration will have serious social and economic

ramifications that cannot be neglected. The influence of environmental pollutants has been thoroughly explored in recent years, with numerous articles demonstrating how such compounds harm human health[1].

Environmental contaminants can permanently impair male reproductive capacity, although their negative effects can be mitigated by the presence of spermatogonial stem cells (0.03% of total germ cells) in the seminiferous tubules, which are sufficient for male fertility throughout his life. In the mammalian ovary, however, the oocyte pool is fixed at birth, and the lack of stem cells makes replacement difficult. From menarche to menopause, women produce only about 400 potentially fertile oocytes because follicular degeneration (atresia) occurs throughout fetal and adult life, lowering the number of ovarian follicles by more than 99.9%. Some researchers argue that female fertility is not fixed after all, because their findings confirm the presence of stem cells in mature ovaries. Wagner et al. used single-cell transcriptome and cell-surface marker profiling to confirm the absence of ovarian stem cells in human ovarian cortices, although others found the results unsatisfactory[5]. This is a perplexing problem with no easy solution. Whatever their differing perspectives, all researchers agree that the creation of fertile oocytes is a lengthy and complex process that relies on strict coordination between the follicle's germinal and somatic compartments, as well as the coordinated interplay of multiple hormones. If this orchestration fails, there is no way to get pregnant[5].

EEDs may have an influence on the female reproductive system in terms of disorders such as irregular menstrual cycles, premature puberty, polycystic ovary syndrome, and primary ovarian failure. Uterine fibroids (leiomyomas), which affect 25% to 50% of all women, are the most frequent female tumours. Obesity, unopposed estrogen signalling, and age throughout the premenopausal years and at menarche have been linked to an increased risk of developing uterine fibroids. Furthermore, studies have found that exposure to EEDs can increase the occurrence of fibroids in humans. Shen et al. recruited 600 patients with uterine leiomyoma and 600 patients with non-uterine leiomyoma or healthy volunteers and discovered that exposure to plastic products, cosmetics, and other chemicals that most likely contain EEDs may be a risk factor for uterine leiomyoma[2].

Other negative effects of EEDs in females include increased endometrial development and an increased risk of breast cancer[1,5].

2.1 Different types of heavy metals (Pb, Hg, Zn, Ni) and EDCs (such as BPA, phthalates, arsenic)

Heavy Metals (HMs) pose a severe health risk due to their buildup in soil, water, and the food chain, as well as their resistance to decompose under natural conditions. Not all metals are inherently harmful. Copper, chromium, manganese, and zinc are required at very low quantities but hazardous at greater ones, but cadmium (Cd), mercury (Hg), and lead (Pb) have no metabolic roles and are toxic at all doses. The most common source of quantifiable human exposure to HMs is the use of contaminated drinking water, which frequently contains arsenic, Cd, nickel (Ni), Hg, chromium (Cr), zinc (Zn), and lead. Furthermore, sea and river contamination leads to the accumulation of HMs in many fish. Although fish consumption is recommended due to its high content of omega-3 polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), some concern has been raised about the presence of high levels of MeHg in fish at higher trophic levels, such as walleye, pike, swordfish, tuna, and shark, due to Hg bioaccumulation and biomagnification[1]. People that consume these fish species on a regular basis are thought to be at a higher risk for health problems. Cigarette smoking, occupational exposure to numerous industrial processes that use these metals, rechargeable Ni-Cd batteries, jewellery, solders, colour pigments, and alloys are also significant sources of HMs [1] . Lead's toxicity and effects on reproductive performance have been hypothesised since ancient times. The first data on unfavourable pregnancy consequences were published in France in 1860. Lead levels in blood are divided into four categories: normal (<4 µg/dL), mild (5-9 µg/dL), moderate (10-14 µg/dL), and high (15-20 µg/dL). Any amount that exceeds these limits is classified as serious[1] .Cadmium builds up in the body over time, gradually increasing after years of exposure. Saliva has an acceptable threshold limit of 0.55 µg/L for humans.

This metal can be found in both rechargeable Ni-Cd batteries and fiber-rich meals (such as potatoes, vegetables, cereals, and spinach). However, the most common ways of Cd exposure are inhalation of fumes and dust, as well as active/passive cigarette smoke. Female smokers had

greater Cd contents than nonsmokers (median, 1.3 vs. 0.32 µg Cd/L). Even though Cd retention affects both sexes, it is typically higher in women than in males[1]. This differential is due to the higher gastrointestinal uptake of this HM produced by iron shortage, which is typical in women of reproductive age, particularly during pregnancy[1].

The World Health Organization (WHO) estimates that the average total blood Hg concentration for the general population is around 8 µg/L. However, heavy fish consumption can result in blood concentrations of up to 200 µg/L. The primary sources of mercury exposure are coal combustion, mining, and the chemical sector. Microorganisms and bacteria can convert Hg into very toxic forms such as MeHg and EtHg. These transformed forms can accumulate in freshwaters, ecosystems, and food chains, with fish being the primary source of Hg exposure for humans and other living organisms[1.]

Elevated Zinc concentrations can produce embryogenesis defects, as well as teratogenic and fatal effects, whereas nutritional inadequacies in the maternal diet can affect offspring growth. Normal Zn levels in the blood range from 70-120 µg/dL, while values below 70 µg/dL indicate zinc deficiency. Maternal zinc deficiency may have a deleterious effect on offspring, either acutely during pregnancy or throughout their lives, by increasing their susceptibility to diseases as adults[1].

Cobalt is an important oligoelement that is present in Vitamin B12. It is required at low quantities in humans for the creation of new red blood cells but is harmful at high ones. The daily consumption ranges between 1.7 and 100 µg. Co mostly accumulates in the liver and kidneys, with total body levels averaging around 1.5 mg[1].

Chemical substances such as Bisphenol A (BPA) and phthalates are commonly found in everyday consumer products and have long been identified as EDs. Phthalates are a wide family of compounds that can be classed as short-chain or long-chain based on their molecular weight. They are primarily used as plasticizers in polyvinyl chloride (PVC) products and are produced via an esterification process using various phthalic anhydride substituents. Furthermore, REACH (Registration, Evaluation, Authorization, and Restriction of Chemical Substances) has classified

some phthalates (particularly dibenzyl phthalate (DBzP), diethyl hexyl phthalate (DEHP), and dimethyl phthalate (DMPH) as highly toxic substances based on animal reproduction studies.

BPA, a major monomer used in the manufacturing of epoxy resins and the most common types of polycarbonates, is harmful to reproductive health. It is mostly employed in plastic materials, and its derivatives have been on the market for more than a half-century due to its nearly unbreakable properties. However, because these molecules do not form stable and irreversible interactions with the materials in which they are embedded, they can leak out of the plastic matrices and migrate into food or drink, particularly if they are lipophilic, a process increased by heat. As a result, human exposure to these toxicants is mostly through the consumption of polluted water and food.

PAHs are lipophilic compounds with lengthy half-lives, such as polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), and other brominated flame retardants. PBDEs are now often employed in carpet backing, furniture, and other consumer products that we use on a daily basis [4]. It can also be ingested, however contact with house dust is the most common source of exposure. Fortunately, the use of PBDEs has already been restricted or is being phased out in numerous nations[4]. PCBs are commonly utilized as transformers, hydraulic fluids, and additives in paints and other building products[5]. PCB exposure from building materials is conceivable, although long-term exposure to PCBs is predominantly through diet. BFRs and other flame retardants are found in a variety of products, including electronics, fabrics, computers, foam furniture, and so on. Because BFRs are not bonded to the products and can be easily discharged into the environment, they are regarded potential endocrine disruptors. Despite the fact that they have been prohibited in many countries, BFRs are still regarded a pollutant since they remain in the environment for a longer amount of time due to their longer half-life[4].

PAEs can be employed as solubilizing or stabilizing agents, as well as plasticizers to make plastics more flexible; they can be found in a wide range of products. Because of its extensive use, phthalate metabolites can be detected in the urine of almost everyone. High molecular weight phthalates are found in flexible PVC, which is extensively used in food packaging, home

furnishings, and other materials. Low molecular weight phthalates are present in personal care items, dietary supplements, and other consumer goods. Unfortunately, infants have been exposed to phthalates at excessive levels as a result of phthalate-containing medical equipment or personal care products. Several phthalates have been shown to have a deleterious effect on reproductive development and a variety of other endpoints in rodents at high dosages. In human research, phthalates have been linked to aberrant sex steroid and thyroid hormone levels, insulin resistance, low sperm quality, and obesity, as well as type 2 diabetes in human populations [4].

Pesticides include insecticides, fungicides, herbicides, and rodenticides. Insecticides have received the most human research, with the most frequent types being organophosphates, organochlorines, pyrethroids, and carbamates. DDT, a pyrethroid, was once widely used as a pesticide in agriculture, households, and public spaces, but it was outlawed a few years ago due to its harmful nature. However, the chemical is still being used in several nations. Organophosphorus pesticides (OPs) are the most widely used pesticides, and chlorpyrifos is a notable example. After the 1940s, the insecticide was viewed as a safe alternative to arsenic-based pesticides and was used in both domestic and agricultural settings to control pests such as cockroaches, flies, mosquitoes, and termites[4]. However, studies have confirmed that the compound is highly toxic because it has a significant effect on nervous systems. Some of the most commonly used organochlorine pesticides (OCPs) were banned in industrialized nations in the 1970s due to reports of their negative effects on humans, but DDT is still used in some developing countries as an effective method against vector-borne illnesses[4]. Pesticides are typically designed to be highly sensitive to the reproductive and neural systems of organisms, but due to their similarity to human physiological function, these chemicals can also harm the normal human body, resulting in neurovirulence, particularly in acute high-dose situations. DDT has been shown to interfere with the thyroid, insulin, reproductive, and neuroendocrine systems, making it a prime candidate for endocrine disruption[4].

Other developing EEDs include triclosan, parabens, perchlorate, and fluorinated organic compounds, such as perfluorooctane sulfonate (PFOS). According to some researchers, many of these new chemicals may be linked to endocrine outcomes in both animals and humans.

EEDs can be ingested by humans, or they can be found in the environment. Table 1 summarizes some common EEDs and their applications. Because of the varied mechanisms of EEDs in the human body, it is extremely difficult to establish a relationship between EEDs based just on structural aspects (Figure 1 shows some of the most prevalent EED structures). Actually, occasionally the metabolites of EEDs are more dangerous than the substance itself [4].

Table 1

Lists some common EEDs and their uses

Common EEDs	Uses in our daily life
Polybrominated diphenyl ethers (PBDEs)	Carpet backing, furniture, dietary sources
Polychlorinated biphenyls (PCBs)	Transformer, hydraulic fluids, additives, building materials, diet (meat, higher trophic level fish etc.)
Brominated flame retardants (BFRs)	Electronics, textiles, computers, foam furniture
DDT, chlorpyrifos, atrazine, glyphosate	Pesticides
Bisphenol A (BPA)	Polycarbonate-plastic based containers, thermal paper, epoxy based lining of canned food, certain construction materials
Phthalates	Plastics, food packaging, home furnishings, personal care products, dietary supplements, medical equipment
Lead	Smelting, mining, refining, leaded petrol (gasoline), lead-acid batteries, paints, jewellery, children's products
Triclosan	Antibacterials
Perfluorochemicals	Textiles and clothing

EEDs, environmental endocrine disruptors.

Table 1. **1** Structures of some common EEDs. EEDs, environmental endocrine disruptors. Table from Li X, Gao Y, Wang J, Ji G, Lu Y, Yang D, Shen H, Dong Q, Pan L, Xiao H, Zhu B. Exposure to environmental endocrine disruptors and human health. J Public Health Emerg 2017;1:8." [4]

2.2 Heavy metals and EDCs mechanism of toxicity in the women reproductive system

In addition to their well-known ability to cause cardiovascular, renal, and neurological damage, as well as raise the risk of cancer and diabetes, HMs have sparked growing interest in the potential negative consequences on human reproduction in recent decades. Although HMs can impact fertility in both sexes, females are more vulnerable because to the fixed and non-renewable pool of germ cells in the ovary. Females can experience negative impacts at several times of their reproductive lives, including foetal life, puberty, and maturity . Data show that HMs can alter gene expression via modifying epigenetic processes and non-coding RNAs, particularly microRNAs. Furthermore, chronic exposure causes steroidogenic dysfunction, fetal malformations, and embryotoxicity because several heavy metals (HMs), including as Cd and Ni, behave as endocrine disruptors (EDs), modifying hormone synthesis and receptor activity. HMs have also been shown to increase oxidative stress (OS), influencing a variety of physiological processes involved in hormonal balance, germ cell and embryo quality. All of these unfavorable effects may eventually lead to infertility. It has been demonstrated that involuntary exposure to HMs during pregnancy is directly associated to premature birth caused by an excess of reactive oxygen species[1]. The placenta acts as an interface between maternal and fetal circulation, facilitating nutrient delivery and acting as a barrier to hazardous chemicals. However, the human placenta does not prevent the passage of all harmful elements, and non-essential metals can pass over this barrier due to their size and charge, which are comparable to those of necessary metals, posing a risk to the human fetus. Some researchers have also looked into the relationship between heavy metal concentrations in the placenta and fetal growth and development, which could lead to serious fetal harm. As a result, the placenta has been identified as a marker of fetal exposure to hazardous metals[1].

The effects of the most widely distributed HMs on female reproductive are described here.

In humans, the maternal effects of lead toxicity remain unclear. While it has been reported that females who were lead intoxicated as children have a significantly higher rate of spontaneous abortion, with a clear dose-response relationship with blood lead levels, other studies have found no significant correlation between pregnant women who were lead intoxicated and those who spontaneously aborted. However, in these situations, there was no history of lead exposure in childhood, whereas women who had been poisoned with lead during childhood had a considerably greater proportion of spontaneous abortions or stillbirths[1].

This differential is due to the higher gastrointestinal uptake of this HM produced by iron shortage, which is typical in women of reproductive age, particularly during pregnancy. Following menopause, blood Cd concentrations gradually become comparable to those of males, owing to lower gastrointestinal Cd absorption associated with improved iron status. Thus, maintaining an appropriate level of iron in women is critical for preventing/reducing Cd absorption. In vitro, Cd concentrations as low as 5 μM can inhibit Protein biosynthesis by reducing the expression of steroidogenesis enzymes, including P450 cholesterol side-chain cleavage (P450scc) and 3β-hydroxysteroid dehydrogenase (3β-HSD) in placental cells. Furthermore, Cd has been found to activate the estrogen receptor by attaching to its hormone-binding domain. These findings may explain the subsequent delays in puberty/menarche, loss of pregnancy, menstrual abnormalities, hormonal impairments, premature births, and low birth weights. Cd may alter steroidogenesis by interference with DNA-binding Zn-finger motifs via Cd-Zn exchange, as well as a role as an ED capable of mimicking or inhibiting the activities of endogenous E2 (serum estradiol)[1].

Mercury can affect both male and female fertility, however research on female fertility is once again limited. It has been demonstrated that Hg impacts E2 levels and function, and that it can pass the placental membrane, resulting in spontaneous miscarriages, premature deliveries, and congenital abnormalities. Furthermore, Hg exposure has been linked to conditions like PCOS, endometriosis, premenstrual syndrome, dysmenorrhea, amenorrhea, breast problems, and improper breastfeeding[1].

Maternal zinc deficiency may have a deleterious effect on offspring, either acutely during pregnancy or throughout their lives, by increasing their susceptibility to diseases as adults.

Suboptimal zinc consumption in humans has been linked to increased premature births, low birthweights, and congenital abnormalities, all of which are potential acute impacts of zinc insufficiency. Furthermore, Zn shortage can significantly affect egg maturation, cumulus expansion, and ovulation, as meiotic arrest and cumulus expansion are two critical Zn-dependent ovarian processes[1].

Co mimics hypoxic conditions by stabilizing hypoxia-inducible factor (HIF), which activates multiple responsive target genes involved in angiogenesis and apoptosis/cell proliferation, encouraging cancer progression. Continuous exposure of female mice to an average daily dose of 8-16 rad decreased reproductive efficiency, resulting in fewer offspring per litter, while in female mice exposed to 11.4 mg of Co/m3 daily for 13 weeks, the length of the estrous cycle was significantly increased. In humans, Co causes menstruation irregularities, abnormal sexual behaviors, infertility, a delayed onset of puberty, a shorter pregnancy, breastfeeding issues, and an altered menopause[1].

In female rats, a 5-day dose of 40 mg/kg body weight NiSO4 prevented ovulation and eliminated P4 synthesis in response to LH. Furthermore, treatment at 40 mg/kg has been shown to disrupt menstrual cycles, reduce embryo implantation, and increase embryo resorption[1].

Both phthalates and BPA can move in many organs and be eliminated in urine via a variety of mechanisms including hydrolysis, oxidation, and conjugation with hydrophilic molecules. Considering metabolic and excretory routes, phthalates and BPA have long been studied for their potential negative impacts on human reproduction, particularly female fertility.

In rodents, DEHP appears to influence all stages of follicle development, from PGC creation to ovulation. In fact, DEHP exposure during fetal life (10 mg/kg BW/d) causes a substantial decrease in oocyte quantity, dysregulation of meiotic development, and abnormal activation and depletion of the resting follicle pool via raising ROS levels[1].

Phthalates promote atresia in developing follicles by changing steroidogenesis and increasing OS; following the LH surge, they can impair oocyte meiotic maturation and ovulation. The deleterious impact on oocytes is most likely caused by the hyperactivation of E2-dependent genomic/non-genomic pathways in the surrounding somatic cells. DEHP can cause epigenetic alterations that

can be passed down to future generations by interacting with ERα enzymes such as acetylases, deacetylases, and methylases. These harmful effects have recently been investigated using trials in which adult female mice were chronically exposed to a mixture of phthalates and alkylphenols at environmentally relevant concentrations[1]. BPA and phthalates interfere with ovarian development, resulting in variable degrees of infertility. High urinary levels of phthalates, particularly MEHP (0.69 μg/L), have been linked to a higher risk of implantation failure in IVF women. Conversely, high BPA levels have been linked to a decrease in antral follicle count and oocyte number, potentially linked to endometriosis. Numerous animal studies have indicated that phthalates reduce testosterone production in males. In contrast, BPA binds to androgen (AR) and estrogen (ER) receptors, causing their dysregulation. Human studies are challenging, particularly due to a number of confounding factors that can cause bias in experimental design[1].

2.3 Link between heavy metals and infertility

Infertility affects around 6-15% of all couples of reproductive ages worldwide. In some poor countries, infertility rates surpass 30%. Infertility has been identified as a unique reproductive health defect that causes mental problems (such as sleeplessness, anxiety, depression, eating disorders, and addictions) and leads to divorce. According to a Chinese poll, infertile couples divorce at 2.2 times the rate of the general population. As a result, infertility has become a major medical and social issue. Nonetheless, bad lifestyle choices and environmental variables can reduce fertility. To be more specific, harmful environmental variables (such as heavy metal exposure) can harm both men and women's reproductive systems[6].

Heavy metal contamination includes mercury (Hg), lead (Pb), cadmium (Cd), chromium, and metal-like arsenic (As), which are non-essential and very harmful to humans. Acute heavy metal poisoning is quite rare. Pb and Hg values in the typical population's blood are less than 20 and 25 μg/L, respectively. When As levels in the blood approach 100 μg/L, it causes toxic effects on various tissues, including the gastrointestinal tract, neurones, and kidneys. The heavy metals listed above are commonly present in the atmosphere, food, drinking water, and cosmetics. Excessive exposure to Cd, Pb, As, and Hg in the ordinary environment may harm human

reproduction and development[6]. Cd, Pb, Hg, and As. have the following toxic effects on the reproductive endocrine system: they promote oxidative stress, reduce follicle-stimulating hormone, reduce luteinizing hormone, reduce follicular growth, promote follicular atresia, and disrupt the estrous cycle[6].

Metal pollution can reduce female fertility; however, past research has concentrated on the influence of a specific metal on fertility. We used nested case-control sets to assess the influence of metal combinations on female fertility. An inductively coupled plasma mass spectrometer (ICP-MS) measured the plasma levels of 22 metal elements in 180 women. Minimum absolute contraction and selection operator (LASSO) penalty regression were used to identify metals with the greatest influence on clinical outcome. Logistic regression was used to examine the relationship between single metals and fertility, while a Bayesian kernel function regression (BKMR) model was utilised to investigate the effect of mixed metal[7]. LASSO regression chose eight metals for further analysis: calcium (Ca), chromium (Cr), cobalt (Co), copper (Cu), zinc (Zn), rubidium (Rb), strontium (Sr), and zirconium (Zr). After controlling for variables, the logistic model revealed that Cu (Odds Ratio (OR):0.33, 95% CI: 0.13 - 0.84) and Co (OR:0.38, 95% CI: 0.15 -0.94) significantly reduced fertility, while Zn (OR: 2.96, 95% CI:1.21 - 7.50) protected fertility. Trend tests revealed that higher Cr, Cu, and Rb levels were connected with lower fertility[7]. The BKMR model revealed that Cr, Co, Cu, and Rb had a nonlinear connection with fertility drop when other metal concentrations were controlled for, implying that Cu and Cr may have an effect on fertility. Cu, Cr, Co, and Rb were found to be negatively correlated with fertility, but Zn was positively correlated. Furthermore, we discovered evidence for a Cu-Cr interaction. These findings require further validation and may reveal new processes in the future[7].

Metal exposure in the environment and workplace damages female reproductive health by altering the reproductive system at all levels of regulation and function, resulting in female infertility, menstrual disorders, spontaneous abortion, endometriosis, endometrial cancer, breast cancer, and other complications. A prior cross-sectional investigation found that blood Cd and Pb levels were positively associated with infertility in US women. Another study found that infertile women in Taiwan, China, had considerably higher blood Pb and As concentrations

than pregnant women. Pregnancy was related with a considerable decrease in Cd, Pb, and Hg. Basic and clinical research has been conducted on the negative effects of Cd, Pb, Hg, and As exposure on female infertility. Heavy metals can accumulate in human blood, urine, hair, follicles, embryos, testes, liver, kidneys, and other organs, causing harmful effects[6]. A rising amount of research demonstrates that cadmium, a non-essential heavy metal, is associated to a number of unfavourable reproductive health outcomes in women. Hormonal alterations are crucial biological signals that contribute to the development of cancer, heart disease, and other illnesses. The link between blood metal levels and hormone levels is assessed at clinically important points during the menstrual cycle. Blood cadmium levels have been linked to female reproductive hormones. Cadmium is one of the pollutants found in cigarettes that has been connected to estrogenic influences, despite the fact that smoking has been linked to anti-estrogogenic effects such as a lower risk of menopause at a younger age and endometrial cancer[8]. Cadmium levels in the placenta promote expression of the Metallothionein gene family. Metallothionein is a cysteine-rich protein that acts as a protective barrier, keeping hazardous metals from crossing the placenta. Cadmium can displace zinc in the fetus. Zinc is a trace element required for proper fetal growth and development. Metallothionein protects the developing fetus by retaining cadmium, while cadmium lowers the fetus' zinc bioavailability, impairing cellular division and differentiation. Cadmium concentrations in low-birth-weight new-borns are very high, while zinc levels are relatively low. Cadmium can also inhibit leptin hormone synthesis, raise corticosterone levels, and disrupt progesterone production in the placenta[8]. Regarding the numerous reproductive health implications, cadmium is observed as a reproductive toxin in females, with the strongest body of data linking cadmium exposure to reproductive health damage. This study focused on the risks associated with cadmium's effects on female reproductive systems, including cadmium toxicity causing variations in the steroidogenesis process, delayed puberty and menarche, pregnancy loss, menstrual cycle and reproductive hormone disorders, premature birth, and low birth weights, as well as studies on nursing babies fed cadmium-containing breast milk during lactation (Figure 3)[8].

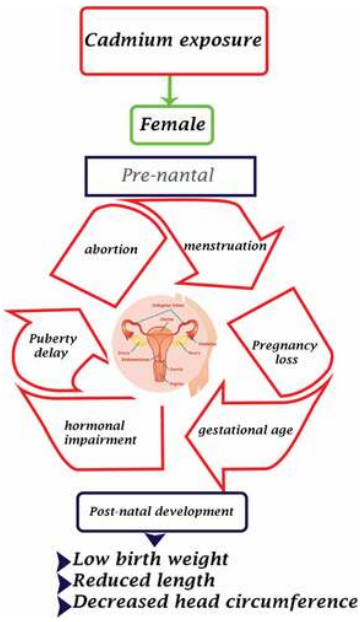

Figure 3. Describes one probable mechanism for cadmium exposure and reproductive health problems... Figure from "Ali, W., Bian, Y., Zhang, H., Qazi, I. H., Zou, H., Zhu, J., & Liu, Z. (2023). Effect of cadmium exposure during and after pregnancy of female. *Environmental Pollutants and Bioavailability*, *35*. https://doi.org/10.1080/26395940.2023.2181124"[8].

3. Air pollution effect on fertility

Every day, people in industrialised countries breathe and ingest a mixture of airborne particles and chemicals, many of which can enter the food chain through soil and water contamination. The list includes particulate matter (PM; diameters: 10, 2.5-10, and 2.5 µm), ground-level ozone (O3), benzo(a)pyrene (BaP, the main marker of polycyclic aromatic hydrocarbon (PAH) presence), polychlorinated biphenyls (PCBs), sulphur dioxide (SO2), nitrogen dioxide (NO2), carbon monoxide (CO), organic compounds (organic solvents and dioxins), and HMs, all abundantly produced by transport and industries. The majority of cases of female infertility are caused by particular illnesses such as ovulation disorders, endometriosis, chromosomal abnormalities, and male factors. There is additional evidence that air pollutants may play a role in the development of female infertility. Air pollution appears to be a health risk. For example, it has been linked to an increased risk of cancer, as well as cardiovascular and respiratory diseases in both adults and children. Furthermore, air

pollution has been connected with worse prenatal outcomes[9]. The primary causes of health-related air pollutants are anthropogenic activities, specifically transportation, industrial facilities, and fossil fuel combustion, which are especially intensive in large cities and near farms. Air pollutants are classified into four types: gaseous pollutants (sulphur dioxide [SO2], nitrate oxide [NO2], and carbon monoxide [CO]), organic compounds (organic solvents or dioxins), heavy metals (lead and copper), and particulate matter. Some air contaminants, specifically Cu, Pb, and diesel exhaust, appear to have endocrine action that may impact female fertility[9]. The principal air pollutants appear to damage both animal and human gametogenesis, resulting in reduced reproductive performance. The primary methods via which they influence the ovary include their ability to change the endocrine system, enhance oxidative stress and inflammation, and activate particular targets capable of stimulating incorrect MAPK signalling. Several reports have claimed that women living in highly industrialised areas have fewer fertile oocytes due to a significant decrease in antral follicle numbers, a lower fertility rate (number of live births per 1000 women), and a higher implantation failure rate in comparison to controls[1]. Santi et al. investigated the possibility of a relationship between increased air pollution and decreased fertility by measuring blood AMH levels[10]. This hormone is produced by ovarian somatic cells and serves as a marker of a woman's ovarian reserve, or the quantity of viable eggs her ovaries can produce. After analysing daily levels of PM2.5-10 and NO2 in the Modena area, they evaluated blood AMH levels and discovered a substantial drop in AMH among women residing in the most polluted locations. Although the association between AMH levels and the likelihood of falling pregnant naturally is still being contested, these findings support the notion that environmental variables can interfere with ovarian function[1,10].

3.1 Sprayed pesticides and their consumption through the diet

Female infertility has risen in recent years. It is estimated that this disorder affects one in every seven marriages in developed countries[9]. The effects of pesticide spraying on fertility are worth noting. Furthermore, these endocrine "disruptors" have estrogenic, antiestrogenic, and antiandrogenic activity, and some may interfere with the thyroid axis

and influence metabolic problems such as insulin resistance and obesity, which are strongly linked to infertility. The rise in female infertility appears to correspond with an increase in hazardous emissions, implying that the impact of air pollution on human health may worsen in the coming years[9,12]. The most prevalent routes of entry for farmers are cutaneous and inhalation, while persons living in pesticide-treated regions might also be exposed to direct spray spread from neighbouring fields. Some pesticide action mechanisms can be explained using laboratory animals. Mancozeb is an intriguing example of a fungicide used to combat fungal plant infections. It is commonly used to protect vegetables (tomatoes and potatoes), fruit (grapevines, apples, and bananas), ginseng, ornamental plants, and golf courses. Because mancozeb is typically sprayed with aerial equipment, the general public is easily exposed through inhalation and/or consumption of contaminated food. Despite its modest acute toxicity, mancozeb reduces fertility and embryo development in female mice exposed to high dosages (500 mg/mL) during pregnancy and lactation. In vitro, low dosages of mancozeb (0.001-1 μg/mL) affect GC (Germinal Centers) morphology and mitochondrial metabolism. Other pesticides that have been sprayed have had similar effects on fertilisation[1]. Although substantial study has been undertaken to identify male infertility caused by pesticide exposure, studies on women are limited[11,13]. One possible explanation is that men are more likely to be exposed to pesticides than women since men often administer pesticides, whereas women are only exposed through re-entry activities. On the other hand, assessing fertility in women is more challenging than in men. The ovarian cycle in women has not been as thoroughly studied as spermatogenesis in males. Benzene and polychlorinated biphenyls (PCBs) are chemicals that can disrupt the menstrual cycle. Other studies have found that exposure to specific chemicals may cause ovarian dysfunction[11,13]. Farr et al. investigated the relationship between pesticide exposure and menstrual cycle features. A comparative investigation found that women who worked with pesticides had longer cycles missing periods, and intermenstrual bleeding than women who did not work with pesticides[11,14]. Some pesticides may interfere with female hormone activity and so have a harmful impact on the reproductive system. The majority of past research has focused on interference with the estrogen and/or androgen receptors, but pesticide

exposure can affect hormonal function in a variety of ways[11,14]. The formamidine insecticides, such as chlordimeform and amitraz, have been shown to inhibit norepinephrine binding to alpha 2-andrenoreceptors[11,15]. Norepinephrine is required for the preovulatory increase in pulsatile GnRH release and the following ovulatory surge of LH[11,16]. Thiram inhibits the proestrus surge of LH in female rats and causes ovulation to be delayed. Pre-ovulatory over-ripeness ovopathy (PrOO) can affect the viability and quality of an egg as well as a prospective conceptus[10,17]. In cattle, malathion exposure at the commencement of estrus reduced progesterone secretion and resulted in poor conception[11,18]. Another two investigations verified the effects of various pesticide exposures on the menstrual cycle. Serum levels of DDT and a DDT metabolite were reported to be elevated in undefined'menstrual abnormalities'[11,19]. A study found that women who used pesticides often had longer and irregular menstrual cycles and missed more periods than women who never used pesticides[11,14].

3.2 Smoking habits (benzene exposure through tobacco smoke)

Smoking is a significant concern for reproductive health in women. Tobacco smoke accounts for over half of all benzene exposure in the United States. According to a recent American Society of Reproductive Medicine research, approximately 15% of adult women in the United States smoke, yet they are typically unaware of the effects of smoking on their reproductive mechanism. More importantly, it is widely known that persons exposed to second-hand smoke face the same health hazards as smokers. A cigarette includes roughly 600 elements and, when burned, produces more than 7000 compounds, of which at least 70 are known to cause cancer: nicotine, NO2, formaldehyde, CO, HMs, tar, and benzene. Benzene, one of the compounds created by cigarette smoke, was tested in the FFs (Follicular Fluid) of women undergoing IVF, and when it was present at levels greater than 0.54 ng/mL, women showed increased baseline FSH levels as well as significant reductions in E2 (estradiol) and the number of oocytes retrieved and transferred. Smoking also causes follicular depletion, a rise in mean basal follicle FSH levels, and a 3–4-year delay in menopause. Furlong et al. discovered that cigarette smoke causes ovarian dysfunction by

altering the expression of 152 miRNAs, five of which directly influence the MAPK pathway[12]. It is worth noting that overexpression of the phosphorylated form of MAPK is common in ovarian tumours[1,12].

3.3 EDCs enter food chain via contamination of soil and water

Food contact materials (FCMs) are materials that come into touch with food and beverages during the preparation, packing, transportation, storage, cooking, or serving stages. Different types of FCMs, including as plastics, paper, glass, metal, adhesives, or printing inks, can be used alone or in combination to make food contact articles (FCAs). Phthalates are widely employed as plasticisers in the production of flexible polyvinyl chloride products. Phthalates can also be found in the atmosphere, sediments, agricultural and urban soil, wastewater, and natural bodies of water[10,20,21]. Phthalates have been proven to disrupt graafian follicle development and growth, as well as impede follicle functionality. A study found that exposure to phthalates may accelerate primordial follicle recruitment. Specifically, exposure to Di-(2-ethylhexyl) phthalate (DEHP) (20 lg-750 mg/kg/day) in vivo for 10 to 30 days promotes primary follicle recruitment through a mechanism that requires overactivation of the phosphatidylinositol 3-kinase (PI3K) pathway[10,22]. Phthalates have a negative impact on the health of follicles. DEHP (600 mg/kg) administered orally over 60 days reduces primary and secondary follicle numbers while increasing atretic follicles. This could be related to an increase in DEHP-induced apoptotic granulosa cells[10,23]. Mono-(2ethylhexyl) phthalate (MEHP) has been shown to affect follicle health by inducing oxidative stress by increasing reactive oxygen species levels and disrupting the expression and activity of the antioxidants superoxide dismutase 1 (SOD1) and glutathione peroxidase (GPX), resulting in MEHP-induced inhibition of antral follicle growth[10,24].

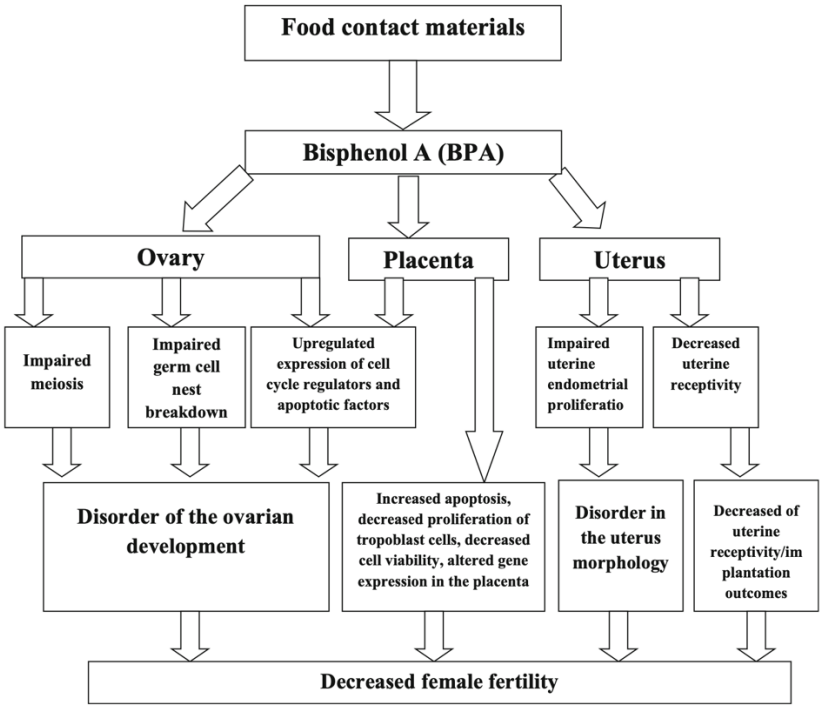

Figure 4. Proposed model of BPA as EDCs on female infertility ... Figure from "Ghosh, A., Tripathy, A. & Ghosh, D. Impact of Endocrine Disrupting Chemicals (EDCs) on Reproductive Health of Human. *Proc Zool Soc* **75**, 16–30 (2022). https://doi.org/10.1007/s12595-021-00412-3" [11]

Bisphenol A (BPA) is a high-production monomer used to make a wide range of polycarbonate polymers and resins, mostly in the food industry[11]. Polycystic ovarian syndrome (PCOS) is a relatively common endocrine condition among women of reproductive age. PCOS is distinguished by insulin resistance, hyperandrogenism, and chronic ovulation. BPA's significance as an endocrine disruptor in PCOS pathogenesis has recently been hypothesised[10,11,25]. Several studies found that premenopausal women with PCOS had greater BPA levels than women who ovulated regularly. Furthermore, BPA treatment in rats throughout gestation and in the neonatal period resulted in the development of a PCOS-like condition in adulthood[10,26]. Furthermore, BPA alters androgen metabolism in the liver by acting as a powerful ligand of sex hormone binding globulin (SHBG); hence, it can displace androgens from SHBG, resulting in higher serum free androgen levels[10,27].

3.4 Effects of personal Care products as EDCs on female reproductive system

Cosmetics are applied to the body to beautify, cleanse, or improve its appearance. Cosmetic items include dangerous ingredients that can hurt the skin. Cosmetic makers may employ both synthetic and natural ingredients, such as rose extract, cane sugar, shea butter, aloe vera, and so on, which are less expensive and safer for consumers. Perfumes, nail polish, make-up, and other skincare items remain on the skin for extended periods of time, posing significant health risks[10,28]. Other EDCs in personal health care include dibutyl phthalates, butylated hydroxytoluene (BHT), talc, parabens, polyethylene glycols (PEGs), triclosan, and formaldehyde, which all have negative effects on women's health, particularly female reproduction. The use of these drugs resulted in fewer primordial follicles and more ovarian cysts. Paraben is another EDC found in cosmetics. Higher urine paraben levels in females were closely connected to a lower antral follicle count, a shorter menstrual cycle, and a lower likelihood of becoming pregnant. According to studies, paraben exposure reduces ovarian weight, decreases the number of corpora lutea, increases the number of cystic follicles, thins the follicular epithelium, alters the estrous cycle, and lowers plasma estradiol levels[10,27]. Triclosan is an organic lipophilic chemical commonly used in lotions, toothpaste, soap, and detergent. Studies found that a high urine triclosan concentration was connected with a low rate of fertilisation and implantation, which is directly related to infertility. Formaldehyde is a hydrophilic, extensively used EDC in cosmetics. Studies also found a detrimental effect on the hormones involved for female fertility[10,29].

4. Obesogens and fertility

The cause of today's obesity pandemic is still debated. However, the simplistic notion that obesity can be explained by two factors: caloric intake and energy expenditure, is increasingly being challenged due to the lack of effectiveness in reducing obesity based just on these two variables. In this paper, we present an emerging theory that the recent rapid increase in obesity could be attributed to developmental nutrition, developmental exposure to environmental chemicals, or a combination of nutrition and environmental chemical

exposures throughout development. Indeed, animal studies have demonstrated that embryonic exposure to environmental toxins increases vulnerability to a variety of disorders, including obesity. Obesity is thus one of several disorders found to have a developmental origin[4]. We demonstrate that factors affecting fetal and neonatal growth, such as placental blood flow and nutrition transfer to fetuses, as well as components of maternal and new-born diets, might influence weight gain later in life. Furthermore, we demonstrate that embryonic exposure to endocrine disrupting substances might cause anomalies in the homeostatic regulatory systems necessary to maintain a normal body weight throughout life. Eliminating exposure to these substances and increasing nutrition throughout development have the potential to reduce obesity and related disorders[4]. Obesity issues are rapidly increasing across the globe. Lifestyle, including eating and work habits, is regarded as the key contributors to obesity; nevertheless, other data suggests that various other factors, such as chemical exposures, also have an essential role[10,30]. Obesogens are substances that cause weight gain by modifying or reprogramming important components of the endocrine system, particularly appetite, metabolism, and energy balance, which leads to obesity and associated negative health outcomes. According to research, developmental exposure can predispose an individual to weight gain and its associated health risks, such as type 2 diabetes, cardiovascular disease, altered lipid metabolism, and altered glucose sensitivity[10,31].

4.1 what are obesogens and what is their prevalence in the food chain

Recent research has shown that endocrine-disrupting substances known as "obesogens" can stimulate adipogenesis and lead to weight gain. This comprises substances that humans are exposed to on a daily basis through the usage of pesticides/herbicides, industrial and home items, plastics, detergents, flame retardants, and personal care product ingredients[30]. The growing number of overweight and obese people in the world (and the associated health and socioeconomic ramifications) has compelled experts to investigate the potential causes of this pandemic. Obesity is caused by an imbalance between energy intake and expenditure, but it is not solely due to overeating and a lack of physical activity. Excessive

body mass increase is caused by a long-term disruption in the hormonally controlled homeostasis of energy balance, which involves the metabolisms of numerous tissues and organs[31]. Appetite regulation, lipid accumulation and mobilisation from adipose storage depots, and basal metabolic rate are all influenced by hormonal factors that interact with human behaviour, genetic predisposition, and the environment[31]. The current rise in global obesity is associated with an increase in exposure to environmental pollutants. Based on this discovery, Gluckman and Hanson created the "Developmental Origins of Health and Disease" (DOHaD) model in 2004, establishing that life-long health and illness patterns are determined by interactions between genetic determinants and early-life exposure to environmental influences[32]. Later, the same researchers proposed that events during the prenatal period are crucial for metabolism and cause persistent alterations that manifest in adolescence and maturity[33]. In parallel, other studies have focused on factors occurring during the postnatal period that may lead to a propensity to obesity, establishing a link between global pollution, chemicals in the environment, and irreversible metabolic changes[34]. Baille-Hamilton was the first to propose that the current obesity epidemic is linked to an increase in environmental contamination from chemicals. She published a paper titled "Chemical Toxins: A Hypothesis to Explain the Global Obesity Epidemic" in 2002, in which she reported an association between laboratory animal weight gain and exposure to various chemical compounds (pesticides, solvents, plastics, flame retardants, and heavy metals)[34]. Other researchers have focused on endocrine-disrupting chemicals (EDCs) as the most likely culprits. Obesogens are EDCs that target metabolic "set-points" and so promote weight gain. Blumberg used the phrase to describe chemicals that disrupt the systems that control lipid homeostasis[35,36]. Obesogens were discovered to promote obesity directly, by increasing the number of fat cells and/or fat storage in existing adipocytes, and indirectly, by shifting the energy balance to favour calorie storage (by changing the basal metabolic rate to promote food storage) and affecting the hormonal control of appetite and satiety[37,38]. To date, around 20 chemical substances have been discovered as obesogens. Some are naturally occurring (for example, phytoestrogens), but the majority are manufactured chemical substances that have been intentionally or

mistakenly discharged into the environment. These chemicals may be ingested, inhaled, or absorbed via the skin[39]. Pesticides, particularly organotins like tributyltin oxide (TBT) and triphenyltin (TPT), are among the most well-documented classes of compounds with obesogenic effects[40]. Polycyclic aromatic hydrocarbons (PAHs), such as benzo[a]pyrene, are byproducts of fuel combustion[41]. Bisphenol A (BPA) is a chemical found in polycarbonate plastics, which are commonly used in products including beverage containers and food cans[42]. Polybrominated biphenyls and diphenyl ethers (PBDEs) are flame retardants[43]. Another type of obesogens is phthalates, which are phthalic acid diesters used to give plastic items flexibility and to carry fragrances in cosmetics. They can easily leach from these goods and end up in indoor air and dust[44]. Alkylphenols (derivatives of alkylphenol ethoxylates), non-ionic surfactants used in cleaning, have been linked to obesity[45]. The insecticide dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE) have also been linked to an increase in obesity[46]. Other examples of obesogens are parabens, which are found in antimicrobial compounds used to preserve food, paper, and pharmaceutical products[47]. Obesogens work by reprogramming several signalling pathways that have common endpoints in tissues critical for whole-body metabolism, resulting in increased adiposity and/or altered adipose tissue function [31].

4.2 Maternal nutrients excess and fetal overgrowth

Obesogens have also been shown to alter preadipocyte differentiation in various in vivo investigations, including those in vertebrata and invertebrata, as well as some in humans. TBT exposure in pregnant mice predisposed their offspring to have higher adipose tissue content than those who were not exposed[40]. Similar findings were reported for animals in puberty and early adulthood[48]. In turn, PBDE exposure in gestation and early childhood resulted in increased weight growth in both experimental animals and humans, and it has been linked to thyroid dysfunction and altered testosterone metabolism[49,50,51]. DEHP treatment for father or mother Drosophila melanogaster caused increased or decreased body weight in the progeny, respectively[52]. In mice, prenatal and neonatal exposure to

diethylhexyl phthalate increased the number of adipocytes and, as a result, the body weight of offspring and adult animals[53,54]. In epidemiological investigations, greater urine quantities of phthalate metabolites were associated with a larger waist circumference and body mass index (BMI)[55]. Similarly, prenatal exposure to DDT enhanced rodent adiposity in following generations, whereas epidemiological studies found that prenatal exposure to DDT and DDE increased the likelihood of human obesity[56]. In epidemiological studies, maternal BPA exposure resulted in low birth weight, which is an established risk factor for adult obesity, but urine BPA levels associated favourably with BMI and waist circumference in children and adults[57].

4.3 How obesogens affect functioning of endocrine system

Blumberg first expected TBT to activate nuclear sex steroid receptors, but instead found activation of the peroxisome proliferator-activated receptor gamma (PPARγ)[40]. PPARγ has a vital role in adipogenesis and mature adipocyte activity. Its activation causes mesenchymal stem cells (MSCs) to develop into adipocytes (rather than bone cells) and initiates lipogenesis[58]. In addition to TBT, several obesogens increase PPARγ expression or directly bind to it, activating downstream pathways that promote adipogenesis. These include, among others, DDT and its metabolite DDE, nonylphenol (NP), octylphenol (OP), BPA, di-(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), benzyl butyl phthalate (BBP), and mono-benzyl phthalate (MBzP)[59]. Obesogens may enhance the expression of genes involved in lipid storage in adipocytes, such as lipoprotein lipase and fatty-acid-binding protein 4/adipocyte protein 2 (aP2). They also alter PPARγ. These reactions occur in response to DDT, DDE, 4NP, BPA, DEHP, mono(2-ethylhexyl) phthalate (MEHP), and BBP[59]. Furthermore, BPA was discovered to alter adipose tissue metabolism via affecting the action of glucocorticoid receptors (GRs). BPA-binding GRs both directly and indirectly promote lipid accumulation and adipogenesis by raising mRNA expression and the enzymatic activity of 11beta-hydroxysteroid dehydrogenase 1 (an enzyme that converts cortisone to cortisol)[60]. Typically, stimulation of estrogen receptors (ERs) in MSCs reduces adipogenesis. Obesogens, such as DDT, NP, and BPA, can trigger ER-mediated signalling in MSCs, which promotes

adipogenesis[61]. Interestingly, some obesogens (such as TBT and alkylphenols) have been shown to affect the activity of aromatase (CYP19A1), a crucial enzyme in estrogen production that converts androgens to estrone (E1) or estradiol (E2)[62]. Phthalates can also disrupt the thyroid hormone system, which is necessary to maintain the basal metabolic rate. Phthalates have been demonstrated to have antithyroid characteristics both in vivo and in vitro[49], and epidemiological investigations have found a negative correlation between urine phthalate metabolite concentrations and thyroid hormones as well as testosterone levels[63]. Obesogens can increase adipose tissue volume by increasing adipocyte number and size. TBT, DDT, NP, OP, BPA, PCB, DEHP, MEHP, DBP, BBP, MBzP, and parabens have all been shown in vitro to induce the differentiation of MSCs into preadipocytes and then adipocytes (by the pathways mentioned above)[59,64]. Obesogens, on the other hand, can have a paracrine effect on adipogenesis by influencing the intercellular milieu of preadipocytes or MSCs. For example, by blocking leptin release and activity, PCBs might enhance adipogenesis and fatty acid storage, resulting in triglycerides[65].

5. How can a nutritionist influence (triggering or helping) recovering from hormonal imbalances due to EDC and obesogens.

Diet is the primary route of exposure to endocrine-disrupting chemicals (EDCs), with ingestion accounting for the majority of exposure globally[66]. There have also been reports of dermal absorption and inhalation exposure to EDCs. EDCs can be found in building materials and industrial items, such as flame retardants and PVC as well as in cosmetics, personal care items, anti-microbial and cleaning agents, and pesticides used in homes and industries [67,68,69].

Type 1 diabetes mellitus is caused by abnormal fetal development of pancreatic beta cells and the immune system[70]. Separately, endocrine disruptor interaction with glucose and lipid metabolism contributes to insulin resistance, type 2 diabetes mellitus, metabolic toxicity, and obesity[50,71,72,73,74]. There is a synergistic effect here because some EDCs are obesogenic, boosting weight gain, inhibiting weight loss, increasing adipose tissue volume, and resulting in EDC bioaccumulation[75]. Endocrine disruptors found in the placenta and

amniotic fluid may contribute to unfavourable obstetric outcomes such as preterm birth, gestational diabetes, pre-eclampsia, and fetal growth restriction[76]. The systematic analysis suggests that consuming organic food, avoiding plastics, and avoiding canned foods and beverages can reduce exposure to endocrine disruptors. High-quality data supports interventions such as avoiding fast food, supplementing with iodine, following a vegetarian or fatty fish diet, changing personal care products, removing dust, and adjusting fish feed. To reduce plastic use in the diet, treatments included utilising glass or stainless-steel bottles and containers, cardboard instead of plastic packaging, and avoiding plastic utensils and non-stick pans. These therapies resulted in significant decreases in EDC exposure, as evaluated by urine BPA levels or other EDC metabolites. Reduced intake of canned foods and drinks also reduces dietary exposure to EDCs. This is very important for mothers and families while preparing meals and selecting infant food. There is observational evidence that avoidance of bottle feeding and manufactured baby food can effectively minimise exposure to EDCs[77,78]. Avoiding canned and processed foods can help reduce dietary exposure to EDCs. Healthcare professionals should be aware that endocrine disruptors pose a major danger to reproductive health and prenatal development [79]. Recommendations from professional bodies may include those from the American College of Obstetricians and Gynaecologists, which focus on the environmental health history and counselling for reducing exposure[80]. Education within medical communities on this issue is critical, including the actions listed above as effective techniques for reducing exposure, as well as the incorporation of environmental health into medical training[80].

6. Prevention of the exposure to endocrine disrupting chemicals through diet

Vegetables and fruits are important parts of a healthy diet since they include the majority of minerals, vitamins, folate, and dietary fiber. The salad is made up of raw vegetables such as carrots, cucumbers, beetroot, and lettuce. According to experimental research, eating salads on a regular basis reduces the chance of developing diabetes[81]. Another study on South Asians found that a lack of vegetable consumption was connected with a higher risk

of noncommunicable diseases[82]. According to del Río-Celestino and Font (2020), eating fruits and vegetables on a daily basis may reduce the risk of life-threatening diseases like cardiovascular disease, metabolic syndromes, cancer, and neurological disorders[83]. However, when these health benefits of veggies are combined with a trace amount of Endocrine-disrupting chemicals (EDCs), the results change dramatically. Sandoval-Insausti et al. (2021) found a link between consuming traditional fruits and vegetables with pesticide residues and cancer development[84]. Salads are incomplete without carrots (Daucus carota), which are high in antioxidants such alpha- and beta-carotene, lutein, and lycopene[85]. However, when cultivated in a polluted environment high in polycyclic aromatic hydrocarbons (PAH), the same carrot is expected to induce significant endocrine disruption in adulthood [85,86]. In another new investigation, more than 24 novel endocrine disrupting (ED) compounds were tested in frequently produced fruits and vegetables using techniques such as continuous solid-phase extraction (SPE) and gas chromatography-mass spectrometry (GC-MS)[87]. Organophosphorus insecticides, phenyl phenol, alkylphenols, parabens, triclosan, and bisphenol A were among the top endocrine disrupting substances detected in vegetable and fruit samples. Cadmium, hexavalent chromium, tin, arsenic, mercury, and lead are prevalent contaminants and endocrine disruptors in the environment[88]. When heavy metal levels in food, particularly vegetables, exceed the recommended permissible level of exposure, either singly or in combination, the risk of developing gestational diabetes increases, supporting the claim that heavy metals are potential diabetogenic agents. Our laboratory's studies have demonstrated high amounts of endocrine-disrupting heavy metals in vegetables produced along the Baroda effluent channel, affecting the local subjects living along the effluent channel[89]. We observed circulatory problems in rats by simulating the exact dosage of cadmium using the empirical field value of metals contained in cereals and vegetables[90]. Thus, it is natural to suppose that EDCs in vegetables and fruits can hide the benefits of antioxidants while causing endocrine disruption[6].

6.1 Nutrition effect on endocrine disrupting chemicals through diet

One of the best sources of inexpensive, high-quality protein is eggs, and daily consumption of eggs not only improves cognitive health, but available evidence has documented that regular consumption of table eggs can prevent age-related macular degeneration[91]. Contrary to the popular notion that egg cholesterol content predisposes patients to cardiovascular disease and stroke, a significant cause of concern stands ascribed to the consumption of eggs contaminated with hazardous chemicals[92]. Several endocrine disruptors such as hexachlorobenzene (HCB), polychlorinated naphthalenes (PCNs), polychlorinated-dibenzodioxins, polycyclic hydrocarbons (PAHs) have all been found in eggs from polluted sites [91,92,93]. Home-grown eggs are more nutritious than commercial eggs throughout the Asian subcontinent, particularly in the Indian subcontinent. Based on this belief, the majority of people in tribal areas raise hens for eggs and meat. However, pesticide abuse in the home garden has resulted in a significant load of endocrine disrupting pesticide residues such as hexachlorocyclohexane, aldrin, and malathion in locally deposited eggs[91].

Regular fish consumption has various benefits, one of which is that it protects cardiovascular disease. Omega-3 fatty acid, a potent antioxidant found in fish, helps to remove low-density lipoproteins by increasing the activity of the enzyme lipoprotein lipase, resulting in lower plasma triglycerides. Although the hazard score was less than one, endocrine disruptors such as dexamethasone, progesterone, and caffeine were found in fish from Malaysian water bodies[94]. In the Indian situation, 1,1-Dichloro-2,2-bis(p-chlorophenyl) ethylene (p,p'-DDE) was the most common endocrine disruptor in fish. Other EDCs discovered in Indian edible fish include polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs)[95]. Nonylphenol exposure in freshwater fish Labeo rohita induced oxidative stress and haematological changes as the toxic reaction[96]. Because humans consume fish, human exposure to EDCs from aquatic food in general, particularly fish, requires strict supervision.

The investigators discovered over 400 pesticide residues in samples of green tea, which is otherwise considered a powerful antioxidant. Several studies have found pesticide residues in tea and coffee[97,98,99]. Drinking tea that contains organochlorine pesticide residues has

been linked to increased illness vulnerability in Ethiopia [98,99,100]. A strong endocrine disruptor, phthalate, has been identified in trace amounts in commercial tea containers[101]. Most people consume at least two cups of tea every day, a pattern that persists throughout their lives. As a result, when present in beverages, endocrine-disrupting chemicals (EDCs) offer a higher risk to human health than typical cereals, vegetables, and fruits. Medicinal plants treat a wide range of ailments and are the foundation of the herbal nutraceutical sector. Translocation of heavy metals such as cadmium, arsenic, and lead, which are known to exhibit endocrine disruptive effects, antagonises the therapeutic benefits of these plants[102]. Wei et al. (2018) developed a new fluorescence approach for detecting carbamate residues in Chinese medicinal herbs. Carbamate and organophosphate insecticides are powerful endocrine disruptors that operate as antagonists by binding to the Androgen receptor (AR) [103,104]. Herbal medications are widely used around the world since they are easily accessible and have few negative effects. Herbal treatments have recently become increasingly popular in both developing and developed countries. Shaban et al. (2016) examined the impact of heavy metals and pesticide residues in herbal products. The authors believe that the soil and the quality of irrigation water are the key sources of heavy metals for these plants[84]. The inclusion of EDCs and other toxicants in herbal medicines and formulations might have serious consequences, such that instead of being treated, a subject may become ill after consuming herbal formulations contaminated with EDCs[84,105]. The gut microbiota has recently emerged as a key player in illness development[106]. In addition to influencing microbial diversity, one's daily food influences human health. Diabetes, one of the major endocrine illnesses, is connected to changes in gut microbiota[107]. Fertilisers, plastics, electronic items, and pesticides all emit endocrine disrupting chemicals (EDCs) into the environment. Exposure to EDCs is strongly linked to a higher risk of diabetes because the gut flora metabolises these EDCs, altering their toxicodynamics[108]. Pesticides, polychlorinated bisphenyls, heavy metals, bisphenol A, phthalates, and dioxins are other environmental endocrine disruptors associated to diabetes. When discussing the role of EDCs and their interaction with diet, Gálvez-Ontiveros (2020) emphasised the interrelationships between the complicated triangle of EDCs, food, and metabolic

disorders[109]. EDCs cause microbial dysbiosis, which activates xenobiotic pathways. Microbial metabolites influence the development of metabolic disorders. Based on the examples provided above, it is clear that gut microbiota and its relationship with EDCs in disease settings require greater investigation to have a better understanding of the various mechanisms involved in these interactions[109].

Not only does food cause endocrine disruption, but so does the food packaging business. Food contact materials (FCMs) include a variety of materials such as tetra packs' paper, plastics, ceramics, and metal cans. While packing extends the shelf life of food and prevents microbiological contamination, it can be harmful to endocrine health because packaging materials introduce particles into the meal. Bisphenol A, a possible endocrine disruptor of human reproduction, has been found in significant amounts in food contact materials (FCMs), particularly polycarbonate plastic containers used for hotel parcel service. The finest example in this area is microwave reheating of food-grade plastics, which leaches phthalate, an endocrine disrupting chemical[110].

6.2 What foods are high in EDC and how to avoid them in diet

During the last few decades, the production of many types of chemicals has increased significantly around the world, paralleling changes in people's lives[111,112,113]. The endocrine system is a complex network of inside body organs that produce different hormones. The primary signalling molecules travel from the circulatory system to the target. To maintain homeostasis in the human body, the endocrine system must function properly. Endogenous and exogenous factors can cause hormonal dysfunction[114,115]. The reasons of endocrine disruption have been the topic of much dispute in the scientific community. A growing corpus of research has investigated the negative impacts of endocrine-disrupting chemical pollutants (EDCs). An increasing amount of research has examined the negative impacts of endocrine-disrupting chemical pollutants (EDCs). The World Health Organisation (WHO) defines an endocrine-disrupting chemical as an exogenous substance or compound that alters the function(s) of the endocrine system, resulting in health side effects in a healthy organism, its posterity, or (sub)populations[116]. According to another definition announced

by the United States Environmental Protection Agency (US EPA), an EDC is an exogenous substance that can interfere with the synthesis, excretion, receptor binding, metabolism, transport, or removal of endogenous hormones, altering endocrine homeostatic systems[117]. EDCs have been linked to changes in reproductive function in both men and women, an increased risk of cancer, including breast cancer, changes in miRNA transcription, obesity, type 2 diabetes, neurodevelopmental delays in children, unusual growth patterns, and immune function abnormalities[118,119]. Human exposure to EDCs occurs via inhalation, food and water consumption, and direct skin contact[111,120,121,122]. It is important to note that EDCs can be transferred from mother to new-born via breast milk and from pregnant women to the developing fetus via the placenta. Furthermore, children and pregnant women are regarded the most vulnerable to EDCs[121]. The International Agency for Research on Cancer (IARC) has released the carcinogenicity status of EDCs, as seen in Table 2. [123]

An updated classification of IARC [13], Origin and Dietary exposure for EDCs.

Chemical group	Origin	Main source of Dietary exposure	Agent	IARC group	year of report
Dioxins and dibenzofurans	byproduct in manufacturing and disposal processes (Organochloride Production, paper bleaching, incineration of chloride-containing substances	Milk and milk products, Bovine adipose tissue, eggs, fish	2,3,7,8-Tetrachlorodibenzo-para-dioxin	1	2012
	Volcanic eruptions, Forest fires, Incineration of hazardous, municipal and medical wastes, Cement plants, Chlorine bleaching of paper pulp or smelting, Traffic of motor vehicles	animal fats, dairy products, cereals, vegetables, meat, fish, shellfish	2,3,4,7,8-Pentachlorodibenzofuran Text	1	2012
Biphenyls	Production, utilization, and disposal of PCB treated products, Unintentional emission from combustion processes, Re-emission of PCBs from environmental reservoirs (e.g. soil, sediment, and water)	fish, meat, dairy products, fats	Polychlorinated biphenyls, dioxin-like (PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189)	1	2016
			Polybrominated biphenyls	2A	2016
Bisphenol	polycarbonate plastics, epoxy resins	canned food	Tetrabromobisphenol A	2A	2018
			Bisphenol A diglycidyl ether	3	1999

phthalate	pesticides, detergents and plasticizers	legumes, vegetables and cereals	Di (2-ethylhexyl) phthalate	2B	2013
Cd	volcanic activity, river transport, erosion, and weathering [14], or human activities, such as cigarette smoke, waste burning, metal ore combustion, fossil fuels, old Zn/Cd sealed water pipes or industrial pollution	agricultural products, fish, shellfish,	Cadmium and cadmium compounds	1	2012
As	occurring naturally in the soil, exceedingly unleashed via volcanic activity, erosion of rocks, human activity, and forest fires, soaps, paints, dyes, metals, drugs, semi-conductors, pesticides, and fertilizers	agricultural products, especially rice	Arsenic and inorganic arsenic compounds	1	2012
Pb	food cans, water pipes, contaminated drinking water, cosmetics, batteries, paint, traditional remedies, gasoline, Pb-crystal, Pb-glazed ceramics, cigarette	agricultural products, especially rice, root vegetables, cucurbits	Lead compounds, inorganic	2A	2006

Hg	natural phenomena (such as volcanic activity and weathering of rocks), human activities (coal-fired power plants, mining processes, metal refineries, electronic waste recycling factories, and municipal solid waste incinerators), pesticides	seafood, poultry	Methylmercury compounds	2B	1993
Organochlorine pesticides	disposal of polluted wastes into landfills, sewage discharge, industrial release, agricultural runoff, disposal of empty chemical containers, leaching of pesticides from surface soil to downstream water	vegetables and fruits, dairy products, meat, and fish	4,4′-dichlorodiphenyltrichloroethane (DDT)	2A	2018
			Dieldrin	2A	2019
			Methoxychlor	3	1987
			Dicofol	3	1987
			Hexachlorocyclohexane	2B	1987
			Heptachlor	2B	2001
			Endrin	3	1987
			Chlordane	2B	2001
			Chlordecones	2B	1987
			Toxaphene (Polychlorinated camphenes)	2B	2001

Table 2. An updated classification of IARC (123), Origin and Dietary exposure for EDCs. Table from "Origin, dietary exposure, and toxicity of endocrine-disrupting food chemical contaminants: A comprehensive review", https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10395372/ [123]

6.3 How to construct and design a diet plan that maintains hormonal and reproductive health

Nutrition and lifestyle have a significant impact on human reproduction and infertility since they are required for various processes like as implantation, placental expansion, angiogenesis, and the transfer of nutrients from mother to fetus[97].

Plant-based antioxidants are abundant in fruits and vegetables. These antioxidants are said to have a variety of beneficial impacts on health. Citrus fruits, carrots, green leafy vegetables, bananas, and other foods contain antioxidant-rich substances. Antioxidants are widely recognised for their metabolic actions, which govern the course and onset of a variety of chronic diseases. A lower intake of antioxidants appears to be connected with an

increased risk of cardiovascular disease and stroke. WHO has advised a minimum dietary intake of 400-500 g per day of food rich in antioxidants to avoid diseases like hypertension, stroke, cardiovascular disease, and various other lifestyle problems. Omics (including metabolomics and nutrigenomics) have been used to report the impact of nutrients on physiological processes at the molecular level, as well as to explain how food and specific nutrients interact with genes, proteins, and metabolites to alter metabolic phenotypes and disease consequences[97]. The link between various biological processes in living beings is mostly determined by nutritional factors. Food is required for all species to extract energy and perform all necessary functions such as reproduction. Nutrients are required for all developmental stages in humans, including growth, puberty, and reproduction[97]. Nutritional factors have an important role in determining reproductive health and can either positively or negatively impact fertility in people. As a result, it is vital to understand the suitable type of food and the influence of each dietary element on the reproductive system, particularly on male and female fertility[97]. Several critical elements (minerals, carbohydrates, lipids, amino acids [AAs], and vitamins) are required for the development of reproductive cells and the generation of proteins, hormones, and secretions. Nutrigenetic processes can influence fertility when a genetic differentiation influences nutrition metabolism. Males and females require distinct nutrition for the expression of reproductive characteristics because they play diverse roles in reproduction (Figure 5)[97]. Despite sharing a genome, both sexes may benefit from regulating nutrition intake to optimise sex-specific performance. Isoflavones have a deleterious effect on men's fertility, while they improve the sexual health of menopausal women. Consumption of whole milk boosts fertility in women, whereas skimmed milk provides the same advantage in men[97].

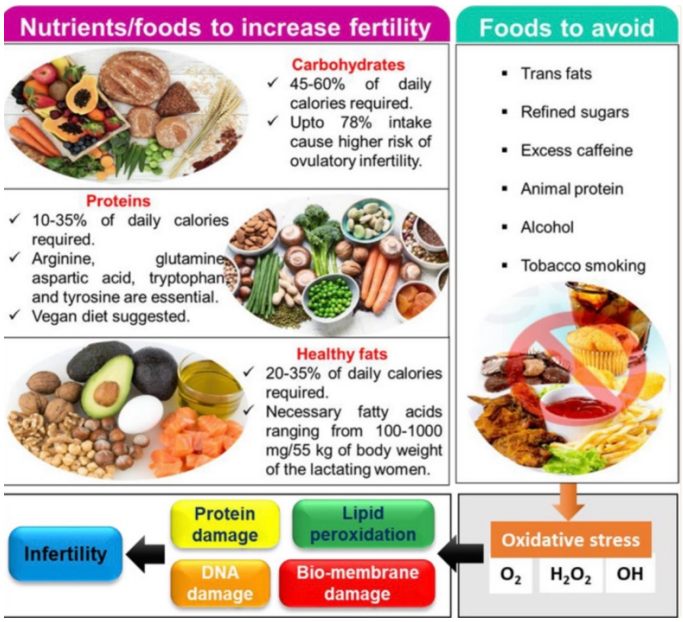

Figure 5. Essential foods (nutrients) to enhance the fertility in women. Carbohydrates, proteins, and healthy fats are macronutrients that are necessary for pregnant or lactating women. Few foods, which include animal proteins and transfats, should be avoided, as they cause infertility by different factors that induce production of reactive oxygen species... Figure from "Ma X, Wu L, Wang Y, Han S, El-Dalatony MM, Feng F, Tao Z, Yu L, Wang Y. Diet and human reproductive system: Insight of omics approaches. Food Sci Nutr. 2022 Mar 21;10(5):1368-1384. doi: 10.1002/fsn3.2708. PMID: 35592285; PMCID: PMC9094499[97]."

The treatment and improvement of fertility in couples has been investigated using a daily tablet from certified goods such as Fertility Support, FertiliWhey, and OvaBoost. The use of researched nutrients in commercial products would give a full number of proteins and all-important amino acids, help to control blood sugar levels, and maintain a healthy weight for natural reproductive support. They improve the quality, motility, volume, morphology, function, and count of sperm in men. In addition, they improve polycystic ovarian syndrome (PCOS), cycle and/or hormone abnormalities, and egg quality in women[97]. The patented blend of Vitex agnus-castus (Vitex) extract, active folate, and Lepidium meyenii (Maca) extract is available in daily tablets or as a gel capsule with minerals, vitamins, oligo-elements, and omega-3 fatty acids (DHA and EPA). These ingestible supplements and nutrients were used to aid and prepare the female body for conception, as well as to improve women's health during and after pregnancy[97].

Sugar consumption is significant because it contributes to daily caloric intake, and when consumed in excess, it can lead to the development of chronic disorders such as obesity and

type 2 diabetes (T2D), both of which have detrimental effects on fertility. Consumption of sugar-sweetened cookies and beverages had the opposite effect on sperm progressive motility, increasing the chance of azoospermia. In diabetics, there is a clear link between female infertility and decreased insulin sensitivity[97]. PCOS in women of reproductive age confirms that the quantity and quality of carbs in diet will influence reproductive health functions[124].

As a nutrient, protein provides amino acids, which are required for critical activities and energy production. Each protein contains a unique sequence of amino acids. There are 20 amino acids; ten of them (nonessential amino acids) can be synthesised sufficiently by the body to meet its needs, while the remaining ten (essential amino acids) must be supplied through diet. Functional amino acids, including arginine, glutamine, aspartic acid, sulfur-containing AAs, tryptophan, and tyrosine, aid in fertility and reproduction. During pregnancy, particular AAs are required for specific processes (implantation, placental expansion, angiogenesis, and nutrient transfer from the mother to the fetus)[97]. Research suggests that high-protein diets can impact female fertility by delaying estrous cycles after calving, decreasing fertility, and lengthening the time between calving and conception[124]. Animal protein consumption has garnered attention in the context of fertility, mostly due to its potential to contain high levels of environmental pollutants, which could harm reproductive health (Figure 3)[97]. Thus, it is possible to conclude that consuming protein from vegetable sources rather than animal sources reduces the likelihood of ovulatory infertility greatly. The kind and amount of protein in the diet have been shown to influence insulin sensitivity, which stimulates ovulatory activity[97]. The protein content increased menstrual regularity and lowered circulating androgens without affecting reproductive function[125].

Dietary fat has many vital functions within the body. Its physiological roles include acting as an energy source, insulating organs, and playing an essential part in the formation of hormones, cell membranes, and tissue membranes[97]. New nutritional compositions containing essential fatty acids (EFAs) (linoleic acid, linolenic acid, arachidonic acid, docosahexaenoic acid, eicosapentaenoic acid, omega-3 fatty acids, and omega-6 fatty acids) were studied to improve neurological development of the embryo, fetus, and child, to provide nutritional support for women before and during lactation, and to improve gestational length and birth weight. The

essential fatty acids should range from 100 to 1000 mg/55 kg of body weight for a pregnant or breastfeeding woman[97]. Omega-6 fatty acids can negatively impact fertility by causing mild inflammation, atherosclerosis, endothelial dysfunction, and oxidative stress[97]. Fats play an important role in women's reproductive health, with the kind of fats having a substantial impact on fertility. Omega-3 (n-3) and polyunsaturated fatty acids (PUFAs) are necessary for female fertility as they produce substrates for implantation and pregnancy maintenance. They also participate in oocyte maturation and embryo development. TFAs (Trans Fatty Acids) had a deleterious effect on fertility by promoting insulin resistance, which altered ovarian function and resulted in ovulatory infertility. Consuming a diet high in PUFAs and omega-3 fatty acids yet low in TFAs can boost fertility. More research is needed to determine how saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), and omega-6 polyunsaturated fatty acids (PUFAs) affect female fertility. Fast food, snacks, and processed meat are key sources of dangerous fatty acids in the diet[97].

The Mediterranean diet (MD) is the most extensively researched dietary pattern worldwide. For almost 60 years, several research have examined its relationship with human health, finding its therapeutic features. The MD diet is seen as necessary for fertility. A specific diet comprises a high intake of nutritious grains, fruits and vegetables, olive oil, and nuts, all of which have the ability to boost fertility in both men and women. MD has various claimed advantages, including antioxidant, anti-inflammatory, and lipid-reducing properties[126]. In fact, this diet is recommended to help avoid cardiovascular disease, type 2 diabetes, and neurodegenerative illnesses. MD intake improves semen quality, but more research is needed to understand whether it contributes to a higher risk of favourable pregnancy outcomes[127].

Mediterranean dietary products beneficial for fertility in women and men

Mediterranean dietary products	Active substances	Benefits for women and men	References
Fresh fish	Polyunsaturated fatty acid (PUFA), omega-3 Fat-soluble vitamins A, D, E, and K	Women: lower the risk of obesity Men: sources of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in the diet and associated with improvement in the quality of semen	Afeiche et al. (2014)
Eggs	Folate and B6	Women: increase both progesterone and estrogen levels, which regulate menstrual cycles and ovulation Men: support both the semen quality and semen count. They can also increase their levels of testosterone, which boosts libido	Salas-Huetos, James et al. (2019)
Vegetables and fruit	Antioxidants, folic acid, fiber, minerals	Women and men: vegetables and fruits provide the basis for prohealthy nutrition models, which are associated with the improvement of semen quality and fertility	Ricci et al. (2018)
Nuts, seeds	Essential fatty acids (EFAs), fiber, tocopherols, phytosterols, polyphenols, minerals	Women: rich source of protein, minerals, and fatty acids which help to improve ovulation Men: it is important to choose nuts and	Salas-Huetos et al. (2018)

		Men: it is important to choose nuts and unroasted and unsalted seeds. The use of nuts in the diet may have a beneficial effect on the quality of sperm	
Whole-grain products	Fiber, zinc, magnesium	Women: increase the thickness of endometrial lining, which supports the implantation of an embryo Men: improve semen quality	Salas-Huetos et al. (2017)
Lean dairy	Calcium, a wholesome protein	Women and men: dairy contains protein and other nutrients known to support fertility like zinc, choline, selenium, vitamin A, and vitamin D. Vitamin A is essential for reproduction in both.	Salas-Huetos James, et al. (2019)
Olive oil, rapeseed oil	PUFA, alpha-linolenic acid, vitamin E, polyphenols	Women: improve the structure of reproductive cells Men: increase the level of testosterone and enhance fertility	Giahi et al. (2016)

Table 3. Mediterranean dietary products beneficial for fertility in women and men. Table from "Ma X, Wu L, Wang Y, Han S, El-Dalatony MM, Feng F, Tao Z, Yu L, Wang Y. Diet and human reproductive system: Insight of omics approaches. Food Sci Nutr. 2022 Mar 21;10(5):1368-1384. doi: 10.1002/fsn3.2708. PMID: 35592285; PMCID: PMC9094499".
For references, number of articles used in table 3 are 128, 126, 129, 126, 126, 126, 130 respectively.

Cigarette smoke contains known reproductive poisons that affect both males and women. Despite the link between tobacco use and negative effects on overall health and reproductive characteristics, smoking is nonetheless widespread over the world. Tobacco smoke is mostly composed of nicotine and its metabolite, cotinine, which causes significant harm to germ cells. Smoking at an early age can lead to infertility, menopause, premature ovarian failure, and spontaneous abortion. Furthermore, smoking during pregnancy thickens the villous membrane, reducing absorption of nutrients that permeate through the placenta. Pregnant smokers face a considerable nutritional risk as a result of their poor diet and inadequate vitamin intake. Smoking causes oxidative stress in the testes, influences spermatogenesis and steroidogenesis, and has a deleterious impact on sperm quality[97].

Drinking too much alcohol has a negative impact on human health, including an increased risk of several malignancies, heart failure, stroke, and death. Alcohol intake during pregnancy has a

deleterious impact on various fetal organ systems, resulting in low fertility in both men and women, significant pregnancy problems, and bad fetal development. Alcohol poisoning lowers sperm quality and impairs the hypothalamic-pituitary-testicular axis. Furthermore, it reduces female fertility by perhaps affecting the hypothalamus, which reduces luteinizing hormone release and anovulation. The teratogenic effects of such alcohol (particularly on embryo and fetus development) have led to general advice for women to avoid drinking[97].

Caffeine can be found naturally in tea, coffee, chocolate, energy drinks, and cola-based soft beverages. Caffeine use still has an uncertain impact on human reproduction. Some research suggests that caffeine use has no influence on male fertility characteristics. However, drinking more than 6 cups of coffee per day has been linked to lower fertility in couples[97]. Oluwole et al. (2016) determined that using 300 mg of caffeine per day is safe[131].

7. Conclusion

Over the last two decades, there has been an increased awareness of endocrine disrupting substances and their potential negative consequences on human health. This is seen as a serious health issue worldwide, along with infertility. According to WHO data, around 48 million couples and 186 million individuals worldwide are now experiencing infertility[5]. The endocrine system is complex, and one of the most difficult barriers to understanding the various mechanisms underlying these toxic compounds is the question of whether or not exposure can cause reproductive system failures[5]. Despite the numerous health risks, the use of EDCs is becoming more common in today's culture. However, the long-term effects on human and animal health, as well as the management of these threats, remain unknown. More research data is needed to provide a remedy for this problem[10]. Addressing the impact of EDCs and reducing chemical exposure is an urgent priority. Individual initiatives can help decrease exposure while government and regulatory organisations develop policy solutions. While human studies are still in their early stages, there are effective nutritional therapies that may mitigate the negative effects of EDCs. Avoiding

plastic containers, bottles, and packaging, as well as canned foods, has been demonstrated to drastically minimise endocrine disruptor exposure. Consuming fresh and organic food, as well as preventing dust accumulation in the home, can help reduce exposure[97].

Finally, the complex interaction between nutrition and hormonal balance has a significant impact on women's endocrine and reproductive health[19].

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