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Impact of Environmental Contaminants on Female Reproductive Health: A Molecular Insight

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Abstract

Background: Exposure to a multitude of chemical contaminants in the environment, such as heavy metals, pesticides, polychlorinated biphenyls, bacterial endotoxins, and plasticizers, poses a significant threat to the female reproductive system. These chemicals have the capacity to disrupt normal cellular processes by indirectly imitating or obstructing the action of natural hormones, thereby hindering reproductive physiology. The ever-increasing threat of environmental toxicity underscores the need to highlight the potential role of chemical exposures in causing adverse female reproductive outcomes. **Objectives:** To effectively minimise these risks, it is important to gain a thorough understanding of how environmental toxins impact female reproductive health. This includes identifying specific biomarkers that can accurately assess exposure levels and predict reproductive outcomes. This encompasses the assessment of various contaminants in human samples and their correlation with reproductive health hazards, appraisal of hormonal levels and inflammatory markers, estimation of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), Body Mass Index (BMI), lipid profile, *etc*. Improving our knowledge of how these environmental toxins affect ovarian function enables us to take proactive measures to reduce exposure and improve overall female reproductive health. **Conclusion:** Various environmental pollutants, such as heavy metals, bacterial endotoxins, plasticizers, and pesticides, can have detrimental effects on the reproductive health of women through ovarian dysfunction and hormonal imbalance. It is crucial to raise awareness about the potential risks of exposure to these harmful substances in order to protect public health and prevent adverse reproductive outcomes. Further research is necessary to fully comprehend the molecular mechanisms underlying compromised female reproductive physiology and to develop effective therapeutic approaches.

Keywords: Environmental Contaminants, Female Sub/Infertility, Redox/Metabolic Disruption

Highlights:

- Environmental contaminants emerge to be potent reprotoxic substances.
- The presence of endotoxins, plasticizers, and heavy metals in human samples such as blood, urine, and breast milk alarmed researchers globally.
- Environmental contaminants act via various molecular pathways, resulting in various reproductive dysfunctions.
- Besides endocrine-disrupting properties, environmental contaminants act as metabolic disruptors affecting energy homeostasis.
- Modern lifestyle (food habits, sedentary work habits, artificial lights) emerges to augment the negative effects of contaminants on female reproductive health.

1. Introduction

The constant growth of industrialisation has resulted in the daily discharge of a diverse spectrum of chemicals into the environment. Numerous epidemiological studies have shown convincing evidence that intentional and unintentional interaction with such substances can pose risks to human health, including cancer, cardiovascular events, respiratory disorders, and infertility. There has been a significant increase in human infertility worldwide. Studies based on animal models demonstrated the adverse impacts of environmental pollutants on female reproductive organs, especially

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the ovary and uterus[1,2]. The World Health Organisation (WHO) predicted a 17.5% lifetime occurrence of infertility worldwide in 2022, i.e. affecting one out of every six people at some point in their lives. Several factors contribute to the increasing infertility rate, which involves exposure to heavy metals and other environmental pollutants, Persistent Organic Pollutants (POPs), plasticizers, microbial infections, and varying lifestyle disorders[3,4]. Ovulatory disorder, which is seen as the prevalent primary cause of female infertility, is the most prevalent feature observed in female infertility[5]. Many disorders of the female reproductive system, such as Primary Ovarian Insufficiency (POI), oophoritis, and Premature Ovarian Failure (POF), are known to result directly from exposure to environmental pollutants. Thus, it is very important to extensively research them in order to raise awareness and ameliorate their harmful impact[6].

2. Environmental Toxicants

Environmental toxicants comprise a group of chemical and biological substances that pose a threat to human health. They are often called Endocrine-Disrupting Chemicals (EDCs), which include heavy metals, pesticides, cigarette smoke, pharmaceuticals, *etc*. They can affect humans, especially women, through sources like pollution, food, cosmetics, and industrial goods. These pervasive toxic substances have been identified as significant risk factors for various female pathogenesis, contributing to infertility, reproductive disorders, and adverse pregnancy outcomes. Given these concerns, it is imperative to study the impact of environmental contaminants on female reproductive physiology.

3. Heavy Metals

Exposure to heavy metals can disrupt the subtle equilibrium governing signalling pathways and gene expression, which is vital for ovarian functions. Heavy metals such as arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg) are toxic even in trace amounts and detrimentally influence the female reproductive system to disrupt embryogenesis[7]. Further, the presence of various heavy metals in human samples is reported[8,9].

3.1 Detrimental Outcomes of Heavy Metal Exposure

Cadmium (Cd) is a heavy metal endocrine disruptor that can affect ovarian function to reduce the number and quality of oocytes. Cd exposure interferes with spindle assembly, chromosomal alignment, and actin cap development, leading to reduced fertility in female mice[10]. Further, in the oocytes, exposure to Cd increases Reactive Oxygen Species (ROS) levels and apoptosis, resulting in abnormal mitochondrial distribution and DNA damage, delayed meiosis, and affects histone modifications, thus resulting in oocyte dysplasia and failure of embryonic development[11]. Arsenic (As) and its compounds can also negatively impact oocyte and embryonic development through mitochondrial damage, decreased ATP content, and increased ROS levels[12]. It also interferes with DNA methylation and histone modifications, affecting meiotic processes in oocytes. Chronic arsenic exposure in parental generations can cause genotoxicity and global DNA methylation changes, leading to reproductive defects in offspring[13].

Exposure to lead (Pb) can lower live birth rates in women undergoing assisted reproductive treatments[14]. Pb exposure leads to reduced oocyte viability and development, histopathological changes in oocytes, and decreased antioxidant enzymes (catalase, glutathione peroxidase, superoxide dismutase, and glutathione-S-transferase) activities while increasing lipid peroxidation levels. Further, oxidative stress is induced by Pb exposure through Nrf2/Keap1 pathway activation, ultimately disrupting oocyte development[15]. Additionally, in women undergoing *in vitro* Fertilisation (IVF), mercury (Hg) exposure is noticeably correlated with increased biochemical pregnancy and decreased live birth rates[14].

3.2 Bacterial Endotoxin (Lipopolysaccharide; LPS)

Women are frequently infected with microorganisms, some of which are asymptomatic, yet have a substantial impact on embryonic development. These infections in the female reproductive tract can cause a variety of inflammatory diseases and compromise ovarian function. Lipopolysaccharide (LPS), a component of the outer membrane of gram-negative bacteria, is inflammatory and generates oxidative stress, and activates inflammatory processes by increasing the levels of ROS and pro-inflammatory cytokines[16]. LPS causes an inflammatory response by activating toll-like receptor 4 (TLR4), which in turn causes the production of proinflammatory cytokines like TNFα, IL-2, and IL-6 and via the transcription factor nuclear factor kappa B (NFκB) and the enzyme COX-2 (18,19). Its prevalence in the female reproductive tract is associated with obesity and a fat-rich diet[16-18].

3.3 Detrimental Outcomes of LPS Exposure

Previous research has shown that LPS alters the hypothalamic-pituitary-ovarian (HPO) axis, resulting in lower levels of estradiol and progesterone[19]. Further, LPS-induced NFκB activation can also block estrogen signaling by decreasing the expression of the CYP19A1 (aromatase) gene[20,21]. It has been demonstrated that LPS affects SIRT-1 and Mitogen-Activated Protein Kinase (MAPK) signaling pathways, particularly Erk1/2, which are important for controlling inflammatory signals and essential ovarian processes such as granulosa cell proliferation and oocyte maturation[20,22,23].

LPS exposure causes inflammation in a variety of tissues, including the brain, ovary, and testes[20,24,25]. Although inflammation can aid in bacterial clearance, excessive LPS levels can cause tissue damage, multi-organ malfunction, and even death. The inflammation caused by LPS-induced endotoxemia is thought to be a key modulator of insulin resistance, hyperinsulinemia, and dysglycemia[26]. Patients with Type 2 diabetes and obesity have been found to have high plasma LPS concentrations, which suggests that insulin resistance may be exacerbated by LPS-induced metabolic abnormalities[27]. Interestingly, LPS exposure can also alter the PI3K/Akt and IR/GLUT-4 signalling pathways in the ovary, thus lowering glucose absorption[19].

4. Plasticizers

Health and reproductive well-being face significant risks from Endocrine Disruptors (EDCs) that are capable of interfering with normal cellular processes such as differentiation, apoptosis, intracellular communication, and mitochondrial functions. Plasticizers like bisphenols and phthalates are especially worrisome due to their widespread presence in consumer goods, leading to exposure starting even before birth and persisting throughout one's lifetime. Research indicates that these chemicals can have effects that extend across generations, posing a major public health issue for the reproductive health of both present and future generations[28].

5. Bisphenols

Bisphenols such as BPA, BPS, BPF, and BPAF are commonly used in the lining of canned foods and beverages, as well as in the packaging of baby food, baby feeding bottles, dental implants, and sales receipts[29]. Bisphenols are found in canned soft drinks, plastic-bottled water, and household water tanks, and have been frequently reported in human urine, blood, and milk[30-32].

5.1 Detrimental Outcomes of Bisphenol Exposure

Bisphenols have gained widespread recognition as prominent EDCs that exert significant effects on the nervous, endocrine, metabolic, and reproductive systems. Bisphenols negatively impact the HPO axis, affecting the reproductive health of women. Exposure to bisphenols decreases hypothalamic GnRH mRNA expression, LH, FSH, and gonadal steroids like E2 and P4 levels, as well as ovarian aromatase expressions[33-35]. Among the several bisphenols, bisphenol A (BPA), bisphenol S (BPS), and bisphenol F (BPF) exhibit estrogenic, antiestrogenic, and antiandrogenic properties by competing with 17-*βestradiol* due to their structural similarities[36].

Initially considered a "safer alternative" to BPA, BPS has emerged as a prominent EDC, and its persistent presence in various sources, including food, water, and human samples (blood, urine, and breast milk), indicates that BPS is more environmentally resistant than BPA, thus posing greater harm to human health[32,37,38]. BPS may pose greater risks to the reproductive system than BPA and other bisphenol analogues. BPS exposure induces oxidative stress through the generation of Malondialdehyde (MDA) and TNFα; while reducing Superoxide Dismutase (SOD) and catalase activities and concomitantly downregulating SIRT-1 and Nrf2 protein expression in the ovary[35]. In addition, BPS impairs human granulosa and theca cell steroidogenesis *in vitro*[39]. Further, BPS exposure can lead to chromosomal misalignments and hinder proper spindle assembly development in bovine oocytes[40]. Moreover, BPS downregulates connexin-43 expression, impacting female fertility, and chronic exposure induces oxidative stress and inflammation, leading to reduced cell proliferation and increased apoptosis[35].

6. Phthalates

Phthalates include chemical compounds widely used in various consumer products such as plastics, cosmetics and personal care products. Di(2-ethylhexyl) phthalate (DEHP) is the most common phthalate, with an annual domestic production of over 300 million pounds. Dibutyl

Phthalate (DBP) and Diethyl Phthalate (DEP) are also produced in significant quantities and are commonly found in consumer products. In addition to these, mono (2-ethylhexyl) phthalate (MEHP), Monoethyl Phthalate (MEP), and Monobutyl Phthalate (MBP), which are metabolites of DEHP, DEP, and DBP, have been identified in the ovaries obtained from women of childbearing age[41]. Phthalate metabolites have also been detected in urine, serum, breast milk, and amniotic fluids, thereby emphasising the potential human exposure to EDCs[42,43].

6.1 Detrimental Outcomes of Phthalate Exposure

Phthalates, especially DEHP and MEHP, can disrupt different stages of folliculogenesis, *i.e.*, primordial, primary, pre-antral, and antral follicles and luteal cells, causing ovarian toxicity[28]. Studies show that exposure to MEHP can increase oocyte oxidative stress, which can lead to reduced viability, possibly through altered mitochondrial respiratory protein (Nd1) levels and increased SOD1 mRNA expression. Exposure to MEHP also disrupts lipid/cholesterol synthesis by affecting the mRNA levels of liver X receptor (LXRα) and Sterol Regulatory Element-Binding Protein (SREBP). In addition, this exposure promotes mRNA levels of the proapoptotic gene Bcl-2-associated X (BAX) while decreasing mRNA levels of the apoptotic gene Bcl2 in the ovary[41,44].

In addition, DEHP reduced mRNA levels of other factors correlated with oocyte survival and follicular development, including Lhx8, Figla, Sohlh2, and Nobox[44]. DEHP exposure further induces heritable DNA methylation changes in mouse oocytes, affecting genes such as Lhx8, Igf2r, and Peg3, which are important for early folliculogenesis. DEHP appears to accelerate primordial follicle recruitment by affecting the phosphoinositide 3-kinase (PI3K) signalling pathway that regulates follicular survival, quiescence, and recruitment. In addition, DEHP exposure increases mRNA levels of ovarian Phosphoinositide-Dependent Protein Kinase-1 (PDPK1), the mammalian target of rapamycin complex 1 (mTORc1), promoting follicular recruitment, decreasing Phosphatase and Tensin homolog (PTEN) levels and tuberosity sclerosis 1 (TSC1), which maintains follicular quiescence[45]. In addition, DEHP exposure disrupts the balance of pro- and anti-apoptotic genes, which contributes to antral-vesicular atresia[46].

7. Persistent Organic Pollutants (POPs)

POPs are a group of chemicals that, due to their resistance to environmental degradation, may accumulate within the food chain and lead to long-term exposure. Some common examples of POPs include pesticides, Polychlorinated Biphenyls (PCBs), and certain types of dioxins. These POPs have been detected in human samples such as blood, urine, and breast milk[47-52] and have been linked to several health problems, including reproductive problems, developmental disorders, immune system disorders, and even some types of cancer[53,54].

8. Pesticides

Pesticides are chemical compounds employed to manage populations of undesirable pests, which encompass a diverse array of substances, such as insecticides, fungicides, herbicides, *etc.* Based on chemical composition, the major classes of pesticides include organochlorines, organophosphates, pyrethroids, carbamates, and triazines[55]. Women are exposed to these harmful agents through sources like pollution, food, cosmetics, and various agricultural/industrial products. These widespread toxicants could potentially affect the development of oocytes and overall ovarian physiology.

8.1 Detrimental Outcomes of Pesticide Exposure

Organochloride pesticides such as Dichlorodiphenyltrichloroethane (DDT), endosulfan, and Methoxychlor (MXC) can cause an excessive rise in ROS and lipid peroxidation via decreased SOD, GPX, and catalase levels and ultimately lead to DNA damage and apoptosis through increased BAX, caspase-3 and NFκB signaling[55]. Exposure to these pesticides inhibits the expression of certain genes (StAR, P450 SCC, and epiregulin) involved in steroidogenesis and folliculogenesis[55]. Organophosphorus pesticides such as Chlorpyrifos (CPF), malathion, diazinon, and glyphosate can have similar negative effects on oocyte survival, gene regulation, mitochondrial function, and oocyte viability. These pesticides can adversely affect oocyte maturation and early embryonic development by increasing levels of ROS, causing spindle defects, mitochondrial damage, and chromosome misalignment[56]. They also damage DNA

integrity and disrupt ovarian function by altering gene expressions related to inflammation and apoptosis, such as BAX, caspase-3, TNFα, and FAS, ultimately leading to the loss of ovarian follicles. Pesticide intoxication leads to oxidative stress due to the generation of free radicals and alteration of the antioxidant defense system resulting in increased lipid peroxidation and decreased activities of SOD and catalase[7,55].

Other pesticides like pyrethroids (*e.g.*, permethrin, cypermethrin, deltamethrin), carbamates (*e.g.*, carbaryl, carbofuran, and aminocarb) and triazines (*e.g.*, atrazine) can also have negative effects on oocyte development including disruption of the cytoskeleton, apoptosis, oxidative stress, mitochondrial dysfunction and interference with meiosis leading to impaired oocyte maturation and chromosome alignment. Carbamates and triazines induce apoptosis, altering spindle morphology in oocytes. Further, pyrethroids decrease oocyte maturation rates, cause abnormal spindle morphology, and induce oxidative stress and apoptosis[7,55].

9. Polychlorinated Biphenyls (PCBs)

Until their production was banned in many countries due to concerns about their toxicity and persistence in the environment, PCBs were widely used in a variety of industrial applications, including electrical equipment and hydraulic fluids[57]. Despite these bans, PCBs are still found in the environment due to their resistance to degradation processes. Several pathways involved in hormone function can be disrupted by the estrogenic effects of PCB and binding to their receptors. There can be disruptions at the epigenetic level that ultimately affect gene expression[58].

9.1 Detrimental Outcomes of PCB Exposure

PCBs have gained recognition as endocrine disruptors due to their association with health issues such as diabetes and cardiovascular diseases and their impact on the functioning of the endocrine system, particularly the thyroid and reproductive organs. PCBs have been detected in follicular and amniotic fluid, uterus, ovary, placenta, fetal cord blood, and breast milk[53]. Currently, the mechanisms underlying PCB-induced reproductive toxicity are still under investigation. A substantial portion of research into the mechanism of PCB-induced damages to the reproductive system has been concentrated on the regulation of hormones and their receptors, the initiation of mitochondrial damage or apoptosis, and modifications to the epigenome.

Research indicates that PCBs have significant negative effects on reproductive functions. These compounds disrupt the reproductive axis by interfering with GnRH release from the hypothalamus, impacting LH and FSH production[7]. Female mice exposed to Aroclor-1254, a specific PCB, exhibited fewer follicles, disrupted oocyte development, and increased granulosa cell apoptosis, potentially causing POF. Aroclor-1254 can also impair mouse oocyte maturation *in vitro* by disrupting the normal movement of γ-tubulin and Aurora-A kinase, needed for spindle assembly. Further, Aroclor-1254 resulted in an increase in DNA damage in cumulus cells[59]. Additionally, various PCBs decrease LH-stimulated progesterone secretion in luteal cells as well as testosterone secretion by theca cells while simultaneously disrupting the aromatisation process in granulosa cells[60]. Exposure to low levels of PCBs during late fetal development can also have significant consequences on the maturation and physiology of two generations of female offspring, with implications for reproductive health and fertility[61].

10. Dioxins

Dioxins are a type of environmental toxicant generated from the incineration process of various industrial waste products. Dioxins encompass a vast range of chemicals such as 2,3,7,8-tetrachlordibenzo-p-dioxin (TCDD), dibenzo-p-dioxins, furans, naphthalene and azo/azoxybenzenes. Among them, TCDD is the most potent and toxic dioxin that acts through the aryl hydrocarbon receptor (AhR), which is expressed in various tissues, including the ovary. Because of their ubiquitous presence, dioxins and dioxin-like compounds pose a great health hazard and negatively impact female reproductive physiology[62].

10.1 Detrimental Outcomes of Dioxin Exposure

Dioxins, as potent EDCs, are known to affect ovarian functions at various levels. TCDD has been shown to negatively affect the HPO axis, resulting in altered LH and FSH secretion from the pituitary. This, in turn, resulted in reduced estradiol synthesis and altered expression

of various steroidogenic markers such as CYP11A1, CYP19A1 (aromatase), ER, and AhR in ovarian tissue[63,64]. AhR has the ability to interact with several important signalling pathways in the body, including NFκB and Nrf2 activation pathways, which lead to the inhibition of estrogenic activities and the upregulation of inflammatory cytokines. Additionally, AhR induces the formation of ROS and triggers the activation of various antioxidant enzymes, ultimately contributing to oxidative stress and tissue damage[65]. TCDD can also impede ovulation by declining the expressions of Cdk2 and cyclin D2 and thus reducing the number of granulosa cells in the S-phase of the cell cycle, establishing the ovary as a key target of TCDD actions[66].

Further, TCDD is also able to exert transgenerational effects due to its lipophilicity, which allows it to

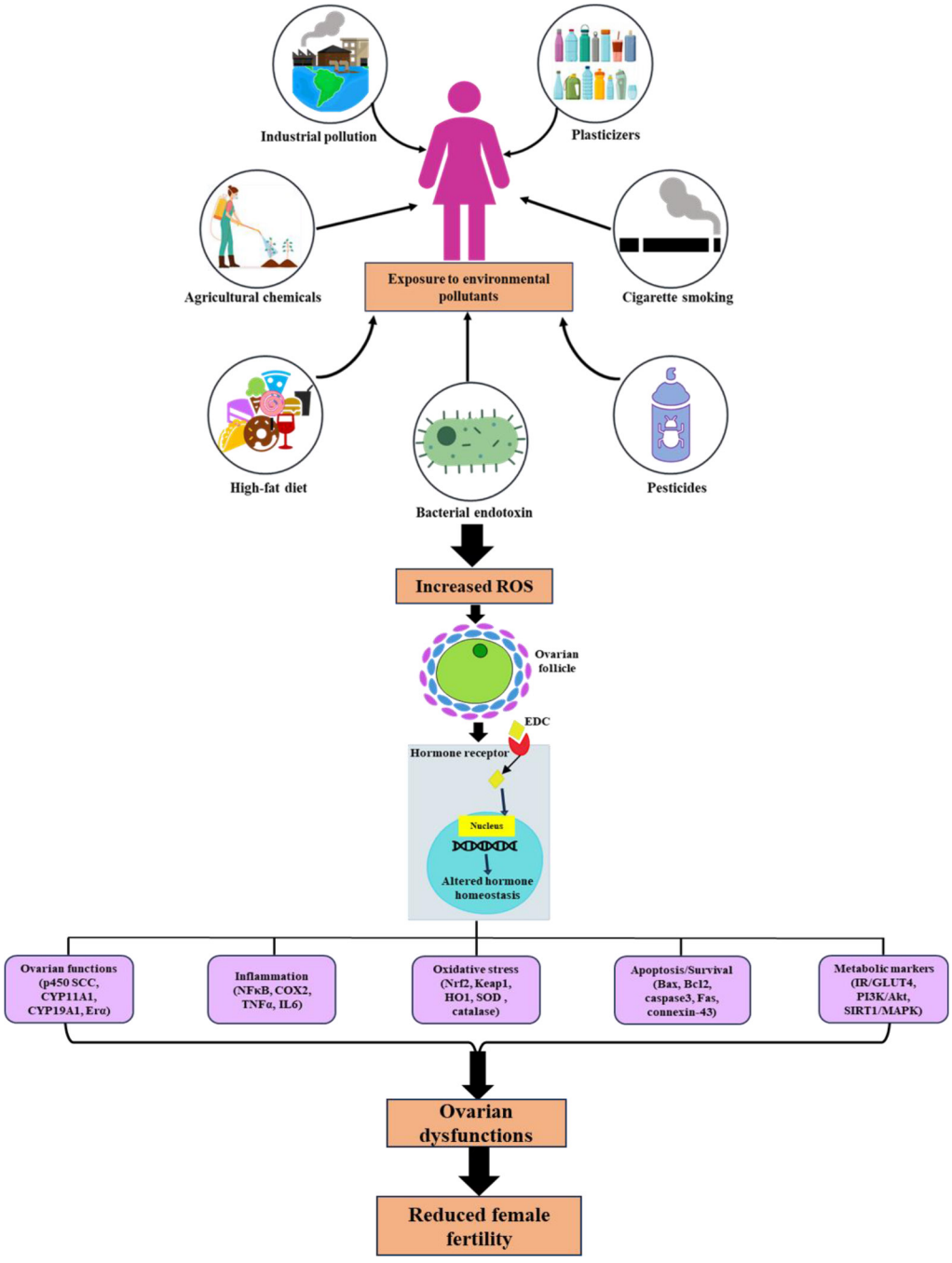


Figure 1. Depicting the impact of various environmental contaminants on female reproductive health.

accumulate and later transmit to subsequent generations via the placenta[64]. Maternal TCDD exposure diminishes gonadotropin (LH and FSH) levels, increases serum AMH concentration and the apoptosis rate of granulosa cells along with the number of ovarian follicular pools in the subsequent generations, which may lead to the development of POI or PCOS in later life[67]. Moreover, TCDD exposure in utero also alters the number of primordial and secondary follicles as well as corpora lutea. Additionally, maternal exposure to TCDD stimulates impairment in ovarian follicle formation and altered Igf2/H19 mRNA expressions, ultimately affecting steroid hormone secretion and estrous cyclicity in the next generations[68,69].

11. Conclusion

Environmental contaminants, such as heavy metals, bacterial endotoxins, plasticizers, pesticides, *etc*., can affect female reproductive health by inducing ovarian dysfunction and hormonal abnormalities. Raising awareness about the potential dangers of toxicant exposure is crucial to promote public health and prevent negative outcomes in reproduction. To effectively minimise these risks, it is essential to comprehend the ways environmental toxicants affect reproductive health, which includes identifying biomarkers for accurate exposure assessment and predicting reproductive outcomes. Advancing our understanding of how environmental toxins impact reproduction allows us to take proactive steps to reduce exposure and enhance overall reproductive outcomes. Successful prevention and intervention strategies may involve regulating industrial practices or new treatments for infertility or miscarriages to reduce exposure and fertility damage. When it comes to reducing exposure to environmental toxins, foods and supplements with antioxidant properties may be beneficial for safeguarding oocyte development. Further research is needed to fully understand the underlying molecular mechanisms of the actions of compromised female reproductive physiology to develop effective therapeutic strategies (Figure 1).

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