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Environmental Exposure during Pregnancy: Influence on Prenatal Development and Early Life: A Comprehensive Review

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Abstract
Preconception and prenatal exposure to environmental contaminants may affect future health. Pregnancy and early life are critical sensitive windows of susceptibility. The aim of this review was to summarize current evidence on the toxic effects of environment exposure during pregnancy, the neonatal period, and childhood. Alcohol use is related to foetal

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alcohol spectrum disorders, foetal alcohol syndrome being its most extreme form. Smoking is associated with placental abnormalities, preterm birth, stillbirth, or impaired growth and development, as well as with intellectual impairment, obesity, and cardiovascular diseases later in life. Negative birth outcomes have been linked to the use of drugs of abuse. Pregnant and lactating women are exposed to endocrine-disrupting chemicals and heavy metals present in foodstuffs, which may alter hormones in the body. Prenatal exposure to these compounds has been associated with pre-eclampsia and intrauterine growth restriction, preterm birth, and thyroid function. Metals can accumulate in the placenta, causing foetal growth restriction. Evidence on the effects of air pollutants on pregnancy is constantly growing, for example, preterm birth, foetal growth restriction, increased uterine vascular resistance, impaired placental vascularization, increased gestational diabetes, and reduced telomere length. The advantages of breastfeeding outweigh any risks from contaminants. However, it is important to assess health outcomes of toxic exposures via breastfeeding. Initial studies suggest an association between pre-eclampsia and environmental noise, particularly with early-onset pre-eclampsia. There is rising evidence of the negative effects of environmental contaminants following exposure during pregnancy and breastfeeding, which should be considered a major public health issue.

Introduction

Environmental, lifestyle, and personal factors are considered health determinants with the capacity to influence diseases, quality of life, and mortality. Recent scientific evidence suggests that preconception and prenatal exposure to toxic environmental agents may have a critical and lasting effect on future health and disease susceptibility [1–3]. This programming hypothesis was introduced by David Barker in 1990 who found an association between growth retardation, low birth weight, and premature birth, and hypertension, coronary heart disease, and non-insulin-dependent diabetes in adulthood. Given that development continues after birth, Woodruff et al. [3] described sensitive windows occurring in the periconceptional period (before, during, and shortly after fertilization) and during pregnancy but also throughout infancy, childhood, and puberty (Fig. 1) [4].

Relationship between environmental pollution and abortion has been demonstrated for exposure to magnetic fields and tobacco. In addition, more recent studies suggest that exposure to air pollutants such as particulate matter or cooking smoke may also be associated with higher risk of abortion. However, exposure to carbon monoxide showed inconsistent results, and no clear evidence was found for other pollutants like heavy metals or organochlorine compounds [5].

The placenta is a barrier between mother and foetus. It regulates the delivery of nutrients, removes waste products, and protects the foetus from potentially noxious substances [6]. However, most classes of environmental pollutants can reach the foetal environment and accumulate in the placenta and foetus. In these cases, foetal exposure is greater than maternal exposure.

The World Health Organization warns that an estimated 12.6 million people die each year as a result of living in unhealthy environments [7]. Scientific societies such as the International Federation of Gynaecology and Obstetrics work to raise awareness on this fact, in an effort to minimize the exposure to toxins that negatively influence the health of mothers and their newborns [8].

The aim of this review was to examine published studies on the effects of environmental exposure during pregnancy and the consequences on early life. Environmental contaminants included in this review are substances of abuse (alcohol, tobacco, and drugs of abuse), air pollution, chemicals, heavy metals, and noise. A search for English written articles was performed using the MEDLINE/PubMed/Cochrane databases. Papers published between 2000 and April 2020 were selected. Combinations of the following terms were used for the search: environmental exposure, pregnancy exposure, alcohol, tobacco, drugs of abuse, maternal food, endocrine disruptors, toxic metals, air pollution, noise, and breastfeeding. Studies of interest were identified, and their methodology and key results examined. Review team members screened titles and abstracts and selected articles that seemed pertinent to the topic. Moreover, publications were also analysed based on the type of study, type of environmental exposure, number of cases, and possible biases. This is a narrative review, given the high heterogeneity of results on pregnancy exposure in the literature.

Environmental Exposure during Pregnancy

Exposure to toxic environmental agents during pregnancy has an effect on perinatal outcomes as well as on health during infancy and childhood. Different toxic substances have been studied to assess their impact on pregnancy, the neonatal period, and the child's early life.

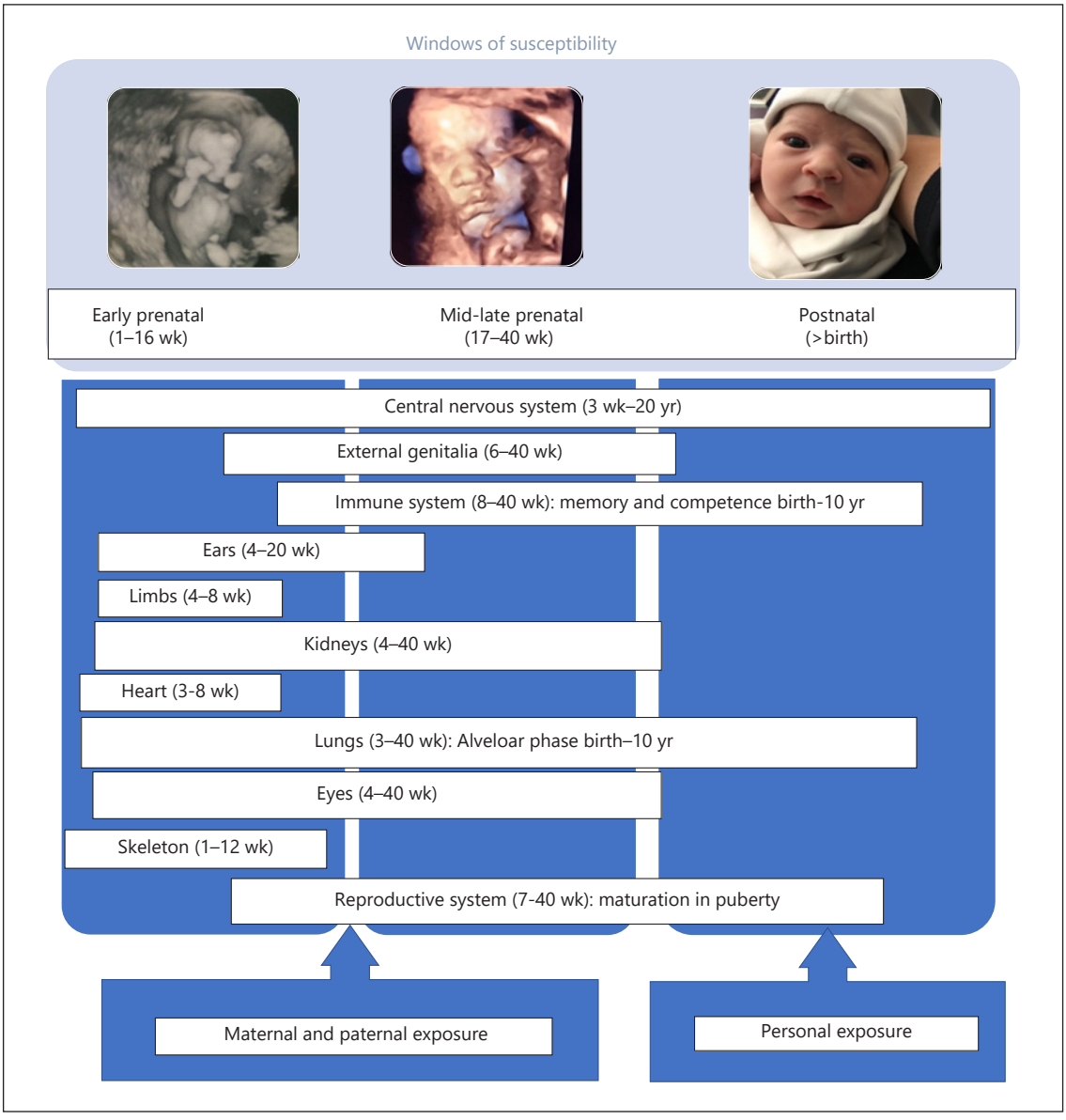

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Fig. 1. Human organogenesis and windows of susceptibility: prenatal and postnatal exposure. Modified from the World Health Organization "State of the science of endocrine-disrupting chemicals – 2012." Summary for Decision-Makers [4].

Alcohol

Alcohol consumption is highly prevalent during pregnancy in our society. According to the Royal College of Obstetricians and Gynaecologists, 29% of British pregnant women drink alcohol [9], while studies in Barcelona (Spain) reveal, through biological matrices, a 45% mild-moderate social consumption in the study population [10, 11].

Alcohol consumption during pregnancy may cause a range of adverse effects to the foetus (foetal alcohol spectrum disorders [FASDs]) [12]. To date, a safe level of alcohol consumption during pregnancy, or consumption period, has not been determined, and the use of alcohol should thus be avoided. FASDs affect up to 1% of the paediatric population [12–14]. Broadly, the following clinical features are commonly seen in foetal alcohol syndrome: (1) morphological malformations, particularly craniofacial features (midface hypoplasia, wide-spaced eyes, and a smooth philtrum); (2) growth restriction; and (3) cen-

tral nervous system impairment, resulting in motor, cognitive, learning, and behavioural disorders [14, 15].

Alcohol affects multiple metabolic pathways during foetal development, partly through the alteration of DNA methyltransferase activities (Dnmt) (Dnmt1, Dnmt2, Dnmt3a, and Dnmt3b) that shape the global epigenetic pattern of the developing foetus [16–18]. Consequently, the expression of key genes is deregulated, for example, insulin-like growth factors 1 and 2 [19–21], glial fibrillary acidic protein in astrocytes [22], and serine/threonine protein kinase *GSK3β,* which regulates the neurogenesis regulators *NeuN* and doublecortin (*DCX*) and neuronal survival [23]. Moreover, ethanol metabolism increases the production of reactive oxygen species, reducing the capacity of the endogenous antioxidant mechanisms [24], which promotes oxidative stress and neuroinflammatory processes [25]. The increase in reactive oxygen species alters protein structures and mitochondrial respiration, leading to cellular apoptosis [26].

Tobacco

Global prevalence of smoking during pregnancy is high. A national survey conducted in the USA in 2012 revealed that 15.9% of pregnant women smoked cigarettes [27]. Similar patterns were observed in Europe in 2011 and Australia in 2014 [27].

Smoking during gestation is positively associated with a range of poor foetal outcomes, for example, increased risk of abortion or impaired development and growth [28] as well as with long-term consequences such as intellectual impairment later in life [29]. Lean body mass of babies of non-smoking mothers seems to be more affected than fat mass [30], and during the first year of life, children of smoking mothers show complete catch-up growth [31]. There is also a causal relationship between maternal exposure to smoke and the risk of orofacial cleft, congenital heart disease, neural tube defects, and gastrointestinal malformations [32–34]. Pregnancy complications such as pre-eclampsia have also been linked to smoking. Over the last years, a number of studies have reported negative associations between smoking and pre-eclampsia. A recent case-control nested study [35] carried out in Iceland found that this paradox was due to selection bias of the previous studies and absence of crucial confounders in the analyses. Based on a *programming effect* [36], maternal smoking during pregnancy may determine the child's medium- to long-term future weight status, blood pressure, or cardiovascular diseases. Although the underlying mechanisms remain unclear, longitudinal studies sustain that children of smoking mothers have a higher risk of developing obesity over time [37, 38].

The effects of foetal exposure to nicotine from snus (moist snuff), nicotine replacement therapies, or vaping (electronic cigarette use) are less clear [39]; for example, plasma nicotine levels when snuffing is lower in comparison to cigarette smoking, although total concentration over time is higher [39]. The amount of nicotine consumed by vaping is similar to that of cigarette smokers [40]. This is important because the prevalence of female smokers of childbearing age in Scandinavian countries (where snus is popular) is decreasing but that of snus is increasing [41]. Besides, vaping is increasing worldwide with a misperception that e-cigarettes are not as damaging as regular cigarettes during pregnancy [40]. However, similar to tobacco, once the nicotine is absorbed and reaches the maternal plasma, it affects the foetus by transfer through placenta both in snus and vaping, so the potential harmful effects are the same as in tobacco use.

Drugs of Abuse

Prenatal substance abuse has increased among pregnant women, although its prevalence is still underestimated. In 2017, the American National Survey on Drug Use and Health determined that 194,000 pregnant women had used illegal drugs in the previous month [42].

Drug misuse has been linked to negative birth outcomes, although the individual impact of each substance remains unclear because of the confounding effects with coexisting substances. Moreover, addicted women often experience inadequate prenatal care, malnutrition, chronic illness, and poverty, which may exacerbate any potential problem during foetal development [27].

Prenatal drug use has been associated with microcephaly and adverse consequences for the foetus and (later) adolescent brains [43]; changes in brain morphology and synaptic plasticity have been reported [44], leading to lack of attention, reduced executive functioning skills, and disabilities in learning and memory, and consequently poorer academic attainment and behavioural problems [45–47]. Cannabis, cocaine, heroin, and methamphetamine are the most consumed substances. Their use may cause foetal loss, preterm birth, small-for-gestational age, birth defects, and admission to the neonatal intensive care unit [48]. Cocaine and methamphetamine have been linked to premature rupture of membranes and placental abruption, pre-eclampsia, and gestational hypertension [49–52]. The main consequences of opioid exposure in pregnancy are postnatal growth delay, microcephaly, neurobehavioral disabilities, and sudden infant death syndrome [53, 54]. In addition, maternal opiate use increases the risk of neonatal abstinence syndrome [54] in-

Table 1. Toxic chemicals and main dietary sources

Toxic compound	Food presence	Toxic compound	Food presence
Mercury [59]	Fish/seafood (swordfish, sharks) Wild mushrooms Dietary supplements Non-alcoholic beverages	Cadmium [60, 61]	Cereals/grains (rice, wheat) Vegetables (roots) Meat/poultry Seafood (bivalve molluscs)
Lead [63]	Bread and rolls Tea Tap water Potatoes Fermented milk Beer-like beverages	Hexavalent chromium [62]	Drinking water Special nutritional use products Herbs, spices, condiments Sugar
Arsenic [65]	Fish/seafood Algae (hijiki) Cereals (rice grains)	Aluminium [64]	Cereals Vegetables Beverages Infant formulas

cluding irritability, poor feeding, tremors, hypertonia, vomiting, loose stools, seizures, and respiratory distress.

Drugs of abuse such as cocaine and amphetamines act by inhibiting serotonin, norepinephrine, and dopamine transporters. Cocaine- and amphetamine-related inhibition of these transporters in the placenta may increase serotonin and norepinephrine levels, which are potent vasoactive mediators in the intervillous space. This may cause uterine contraction and vasoconstriction, with subsequent premature delivery, decreased placental blood flow, and intrauterine growth retardation [55].

Prenatal Exposure to Endocrine Disruptors and Toxic Metals

Endocrine-disrupting chemicals (EDCs) are exogenous chemicals (phenols, phthalates, parabens, flame retardants, and heavy metals) that may alter the hormonal and homeostatic systems of the organism [56]. Epidemiologic studies have demonstrated that EDC exposure is nearly universal in pregnant women [2], through personal hygiene products, cosmetics, cleaning products, electronic devices, and food [2].

Pregnant and lactating women should be aware of the risks of heavy metals and other food toxic compounds [57]. Table 1 summarizes the main foods containing heavy metals. Of particular importance is the bioaccumulation of heavy metals in fish and seafood, with children having higher potential health risk than adults [58], since they are the main source of mercury, lead, arsenic, and cadmium (Cd) (Table 1). Besides the contamination of seas and oceans by humans, the resuspension of contaminated marine sediments may release sediment-bound contaminants, leading to the most toxic (dissolved) state of metals and bioaccumulation in marine waters. Recurrent tides and waves may cause release of these contaminants into different marine environments [59]. Public health agencies should provide food recommendations to help prevent exposure of the population to these toxins through food. Specifically, the Spanish Agency of Food Safety and Nutrition recommends avoiding the consumption of swordfish, tuna, shark, and pike during pregnancy and lactation and even for children under 10 years of age [60].

EDCs may alter normal hormone production or their levels, as well as mimic hormone function. The main effects of prenatal exposure to EDCs have been studied, with evidence on pre-eclampsia and intrauterine growth restriction, preterm birth, and thyroid dysfunction [61, 62].

Regarding hypertensive disorders of pregnancy, there is strong evidence between persistent exposure to certain chemicals (lead, Cd, organochlorine pesticides, and polycyclic biphenyls) and pre-eclampsia, although this association cannot always be made with low levels of exposure. On the other hand, results have been inconclusive for bisphenols, phthalates, and organophosphates [62].

Metals and metalloids accumulate in the placenta, causing a decrease in uterine blood flow, with negative impacts on foetal growth [61, 63]. It has also been described that plasticizers, such as diethylhexyl phthalate and its active metabolites and bisphenol A (BPA), induce pre-eclampsia and growth restriction [64–66]. Detrimen-

tal effects on foetal growth have also been suggested with the exposure to pesticides such as dichlorodiphenyltrichloroethane and its metabolites [67].

Organochlorine pesticides and flame retardants such as polychlorinated biphenyl ethers and tetrabromobisphenol A [68, 69] may lead to preterm birth by disturbing normal oestrogen-progesterone ratio [70]. These pollutants may also increase the risk of autism spectrum disorder [71] and disrupt thyroid function [68, 69, 72].

A growing number of studies suggest a link between congenital anomalies (cleft lip and palate, neural tube defects, and congenital heart disease) and maternal exposure to organic solvents, pesticides, and dioxins [73, 74]. Toluene embryopathy has been described after maternal inhalation of paint or glue [75]. Phthalates have antiandrogen-like effects as well as an important role in hypospadias and cryptorchidism [76]. Pesticides are considered to be a risk factor for childhood leukaemia [77]. Finally, maternal exposure to BPA increases depression rates, leads to behavioural problems, and alters the white matter in preschool children [78, 79].

Prenatal Exposure to Air Pollution as a Potential Risk Factor

Polluted air has a heterogeneous composition: particulate matter (PM), ozone pollution (O_3), carbon monoxide (CO), nitrogen oxides (NO_2 and NO_x), and sulphur dioxide (SO_2) [80, 81]. PM is a mixture of suspended particles with different chemical compositions usually classified by size (e.g., PM10 and PM2.5) [81]. It can trigger oxidative stress and inflammation in the lung's alveoli [82–84] and cross the alveolar epithelium reaching the blood stream, causing systemic problems [85].

Evidence on the effects of pollution on pregnancy is constantly growing. Its relation with adverse perinatal outcomes such as low birth weight (<2,500 g) or pregnancy-induced hypertensive disorders is well established [82, 86, 87]. Olsson et al. [88] reported a positive association between NO_x levels and increased risk for pregnancy-induced hypertensive disorders (odds ratio [OR] = 1.12; 95% confidence interval [CI], 1.06–1.18 per 10 μg/m^3 increase in the NO_x level). A systematic review conducted by Pedersen et al. [89] concludes that pregnancy-induced hypertensive disorders are associated with PM2.5 (OR = 1.57; 95% CI, 1.26–1.96 per 5 μg/m^3 increment), NO_2 (OR = 1.20; 95% CI, 1.00–1.44 per 10 μg/m^3 increase), and PM10 (OR = 1.13; 95% CI, 1.02–1.26 per 10 μg/m^3 increase). Regarding foetal growth, exposure to PM2.5 is negatively associated with reduced head circumference and weight at birth [90], while NO_2 is significantly linked to a shorter length at birth [90–92]. NO_x has also been related to a decrease of abdominal circumference and femoral length as well as reduced weight at birth [93].

Exposure to both PM and O_3 has been associated with a higher risk of preterm birth [91, 92, 94, 95]. Synergies between PM2.5 and O_3 showed worse outcomes (risk ratio = 3.63) than their independent effects (risk ratio = 0.99 and 1.34, respectively) [96]. Moreover, the multicentre European birth cohort HELIX study with 1,396 subjects showed that prenatal and first year of childhood exposure to NO_2 and PM2.5 were inversely associated with telomere length [97].

PM10, NO, and O_3 have been linked to macrosomia [98], and PM2.5 to profound metabolic effects (e.g., glucose intolerance, decreased insulin sensitivity, and altered hepatic glucose and lipid metabolism) through oxidative stress, in animal studies [99]. A cohort study found that in utero exposure to PM2.5 during the first trimester decreased placental transcription of the brain-derived neurotrophic factor. This factor plays an important role in foetal neurodevelopment [100].

Many placental biomolecular changes have been observed secondary to air pollution exposure, including altered proteins and gene expression, increased oxidative stress inflammation, mitochondrial dysfunction, altered DNA methylation, and hormone dysregulation [101, 102]. These pathologic features are the result of increased oxidative stress and inflammatory response in the placental cells [102, 103]. The accumulation of vesicular-bound particles triggers many dysfunctional cellular processes that lead to the expression of proteins that are similar to those seen in pre-eclampsia and intrauterine growth restriction, including the tumour necrosis factor and vascular endothelial growth factor signalling [104, 105]. In later stages of pregnancy, exposure to PM2.5 induced placental chorioamnionitis and thrombosis of placental capillaries in an animal model [82]. These changes in the placental tissue may lead to a reduction in the maternal-foetal exchange surface and the development of placental dysfunction.

Prenatal Noise

Noise pollution is a major environmental health concern. Around 113 million people in Europe are exposed to excessive environmental noise levels according to the European Environmental Noise Directive (2002/49/EC), mainly from road traffic noise. The impact of environmental noise on several health disorders is already recognized [106, 107].

Many studies have found an association between exposure to noise and cardiovascular effects, for example, hy-

pertension, stroke, and myocardial infarction [107]. Furthermore, there is high-quality evidence linking road traffic noise and incidence of ischemic heart disease [108]. Repeated exposure to noise generates stress and sleep disturbances, leading to endocrine and sympathetic responses with the consequent increase in blood pressure, heart rate, and cardiac output through the release of catecholamines [106] and corticosteroids [109], as well as oxidative stress and immunological responses [110]. These reactions to noise persist even during sleep and may cause chronic physiological deregulations [107]. Few studies have investigated the effect of noise exposure in pregnant women, with pre-eclampsia being of special interest. A recent study in Quebec, Canada, comprising 269,263 deliveries, showed that women exposed to >65 dB(A) had 1.29 times the odds of severe (95% CI, 1.09–1.54) and 1.71 times the odds of early-onset (95% CI: 1.20–2.43) pre-eclampsia compared to those exposed to <50 dB(A) [111].

A Danish prospective cohort study with 72,745 women showed that a 10-dB increase in road traffic noise was associated with increased risk (10%) of pre-eclampsia [112]. These associations were stronger for mild and early-onset pre-eclampsia but not evident for severe pre-eclampsia. The authors conclude that the effects of air pollution and noise were generally difficult to separate.

Studies evaluating exposure to noise pollution and its effect on placental development are still scarce. However, it has been hypothesized that noise, through a sustained stress reaction, may lead to excessive secretion of stress hormones, for example, cortisol, causing adverse effects on the uterus and foetus. Furthermore, stress reactions activate the sympathetic-adrenal axis and release of catecholamines, with the consequent increase in blood pressure and possibly an increase in uterine reactivity and impairment of placental function leading to foetal hypoxia [113].

These initial studies suggest that exposure to environmental noise may be associated with pre-eclampsia, particularly early-onset pre-eclampsia. Further studies are needed to confirm these findings.

Effects of Environmental Factors on the Placenta

The placenta is a highly sensitive organ to environmental contaminants with estrogenic activity, as it expresses the oestrogen receptors ERα and ERβ [114]. Although there are many publications on the in vitro effects of different EDCs on the human placenta, some controversies remain regarding the timing, dose, and duration of exposure [115]. It is important to emphasize that the effects of EDCs on human trophoblasts are dose-dependent: low doses, which are detected in humans, are more effective than high doses [76].

Ferguson et al. [116] found a positive correlation between BPA urine levels and an increase in plasma soluble vascular endothelial growth factor receptor-1 (sFlt-1) as well as an increase in the ratio of sFlt-1 to placental growth factor. This suggests altered placentation and trophoblast function related to pre-eclampsia and hypertensive disorders [117]. In vitro studies have shown that para-nonylphenol substances, used in the industry, may increase β-hCG secretion and cell apoptosis, reduce trophoblast migration and invasion, and downregulate the expression of some placental carriers like ABCG2, a key transporter for xenobiotics [118]. In addition, polybrominated diphenyl ether mixtures enhanced in vitro placental proinflammatory response to infection. This may increase the risk of infection-mediated preterm birth by lowering the threshold for bacteria to stimulate a proinflammatory response [119]. The effects of polybrominated diphenyl ether exposure on the placenta and foetus in rats during gestation varied by foetal sex. Moreover, higher concentrations of polycyclic aromatic hydrocarbons such as benzo[a]pyrene, benzo[b]fluorine, and dibenz[a,h]anthracene were found in the placenta of preterm deliveries in comparison to term deliveries [120].

Regarding heavy metals, the New Hampshire Birth Cohort Study (N = 1,159) reported an indirect relationship between placental Cd and birth weight mediated by placental weight. With every ng/g increase in placental Cd concentration, lower placental weight was seen (−7.81 g; 95% CI, −15.42, −2.48) [121]. Furthermore, the authors observed greater decrements in placental weight and efficiency associated with placental Cd concentrations, depending on placental zinc and selenium concentrations. For the placenta with concentrations below median zinc and selenium values, decrements in placental weight were −8.81 g (95% CI: −16.85, −0.76) and −13.20 g (95% CI: −20.70, −5.70), respectively. No appreciable differences were observed with other elements (arsenic, mercury, or lead) [121].

Concerning air pollution, Liu et al. [82] reported chorioamnionitis and thrombosis of placental capillaries in rats following exposure to PM2.5. These placental tissue changes cause a decrease in the maternal-foetal exchange surface as well as placental dysfunction. Human studies have demonstrated that PM-induced circulating proinflammatory cytokines may disrupt trophoblastic invasion during placenta formation [122, 123]. In a cohort study, Neven et al. [103] analysed placental DNA and found an

association between elevated placental mutation rate and prenatal exposure to PM2.5 and black carbon. The authors postulated that placental mutations may represent an early effect to air pollutant exposure in the process of carcinogenesis.

Breastfeeding: Environmental Toxins in Human Milk and Effects on Early Life

Breastfeeding is the gold standard of newborn and child nutrition for at least the first 6 months of life [124]. However, transfer to breast milk of toxic substances to which the mother has previously been exposed may occur during breastfeeding. Several comprehensive reviews conclude that breastfeeding is generally contraindicated in mothers who use illegal drugs [125], although there are little pharmacokinetic data available for lactating women [126].

Smoking and alcohol consumption should be avoided during breastfeeding. Alcohol interferes with the milk ejection reflex and may reduce milk production. Human milk alcohol levels generally parallel maternal blood alcohol levels. Some authors suggest limiting alcohol intake to the equivalent of 8 ounces of wine or 2 beers [125]. However, others hold that alcohol consumption during pregnancy and breastfeeding should be totally avoided since no specific amount has been proven to be safe [11, 127]. Nicotine and other compounds can be passed to the infant through breast milk, increasing the incidence of respiratory allergy in infants and the risk of sudden infant death syndrome risk [128].

Polycyclic aromatic hydrocarbons and heavy metals are among the most studied contaminants [129]. Polycyclic aromatic hydrocarbons are lipophilic compounds and are stored in maternal body fat, released into breast milk with the onset of lactation, and passed directly to the child. However, limited evidence exists on significant toxicity associated with this mode of transmission. On the other hand, the presence of heavy metals such as arsenic, lead, Cd, and mercury in milk stimulates or supresses important immune modulators and may indirectly affect the child's health, for example, allergy development, disorders of the endocrine system, and even neurodevelopmental delay [130]. Lactating mothers are a high-risk population to mercury exposure and may transfer significant quantities to their babies [131].

The endocrine disruptor BPA has also been widely studied. A temporary tolerable daily intake of 4 μg/kg bw/day for oral exposure to BPA has been established [132]. Interestingly, while BPA content in mature milk reflects recent ingestion, its presence in the colostrum reflects intake in the second half of pregnancy [133]. The place of residence of the mother and use of personal care products showed significant association with BPA concentration [134].

In addition, human milk contains conjugated and unconjugated paraben forms, exposing the mother, foetus, and neonate during windows of heightened vulnerability for endocrine disruptors [135]. In a Spanish study, the detection frequency ranges of parabens in breast milk were 41–60 and 61–89% for unconjugated and total (unconjugated + conjugated) parabens, respectively. Estimated daily intake of parabens by newborns through human milk (median = 0.014 μg/kg bw/day) was several orders of magnitude lower than the 1–10 mg/kg bw/day acceptable daily intake established by the European Food Safety Authority [132, 136]. In a recent study, Sanchis et al. [137] found high urinary concentrations of methylparaben (MP), ethylparaben, and BPA in lactating mothers although estimated exposures were lower than the reference values for risk assessment. The use of personal care products was associated with higher urinary levels of MP and propylparaben. MP was also associated with the consumption of packaged and bakery products [137]. All these chemicals may affect infant gut microbial function [138]; increase the risk of hyperkinetic disorder [139]; and cause toxicity to the liver and kidney, cancer, reproductive and respiratory disorders [132, 140], or changes in thyroid and growth hormones with potential neurodevelopmental sequelae [132, 141].

Conclusions

Exposure to environmental contaminants is a health determinant that may lead to the development of diseases, which could be life-threatening, and affect quality of life. Although exposure may be deleterious to any person, pregnancy and early life exposure are critical windows of susceptibility, with lasting effects on future health and susceptibility to disease [1–3].

The use of alcohol, tobacco, and/or drugs of abuse by pregnant women is linked to harmful effects for the newborn and later in life, including FASD and other negative pregnancy and birth outcomes. EDCs and heavy metals present in food or the environment are related to pre-eclampsia, foetal growth restriction, preterm birth, and thyroid dysfunction. Air pollution may lead to preterm birth, foetal growth restriction, effects on pregnancy vascularization, increased gestational diabetes, and reduced telomere length. Association between pre-eclampsia and

environmental noise is rising. Breastfeeding is recommended; however, mothers should be warned about the risk of exposure for their newborns via breast milk.

Healthcare professionals (e.g., physicians) should have sound knowledge on harmful exposures, be able to counsel their patients on their risk, and provide advice on the precautions they should take to minimize them, especially during pregnancy and breastfeeding. Protection from governments should be strengthened through actions limiting environmental exposure to substances known to have deleterious effects. The design of a global public health policy in the early future is the best way to translate evidence into action.

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Conflict of Interest Statement

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Author Contributions

All authors contributed to manuscript preparation. M.D.G.-R. and R.P. had primary responsibility for the final content. All authors have read and approved the final version of the manuscript.

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