*Review*

# ENVIRONMENTAL CONTAMINANT EXPOSURES DURING PREGNANCY INFLUENCE PRENATAL AND EARLY-LIFE: A COMPREHENSIVE REVIEW

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Short Title: Influence of environmental contaminants exposure in pregnancy

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## Abstract

Preconceptional and prenatal exposure to environmental toxics may have an effect on an individual future health, being pregnancy and early life critical and sensitive windows of susceptibility.

The aim of this review is to summarize the current evidence on the toxic effects of environment exposure during pregnancy, neonatal and childhood.

Alcohol use is related to Fetal Alcohol Spectrum Disorders (FASD) being Fetal Alcohol Syndrome (FAS) its most extreme form. Smoking is associated with placental abnormalities, preterm birth, increased risk of abortion, stillbirth or impaired growth and development, as well as to intellectual impairment, obesity and cardiovascular diseases later in life. Negative birth outcomes have been linked to drugs of abuse.

Pregnant and lactating women should be aware of the risks of chemicals acting as Endocrine Disruptor Compounds (EDCs) and heavy metals vehiculized by food intake and with deleterious effects on pregnancy and development. EDCs can work by altering body hormones and function, and its major evidence of effects on prenatal exposure has been found for preeclampsia and intrauterine growth restriction, preterm birth and thyroid function. Metals can accumulate in the placenta causing fetal growth restriction.

Evidence of air pollution effects over pregnancy is constantly growing. It has been related to preterm birth, with worrying evidence that synergies between its components enhance their adverse effects; fetal growth restriction; increased uterine vascular resistance and impaired vascularization of the placenta; increased gestational diabetes and reduced telomeres length.

Initial studies suggest association between preeclampsia and environmental noise, particularly early onset preeclampsia.

EDCs, heavy metals and air pollution are believed to have negative effects on the placenta, with consequential reduction in fetal growth, increased preterm birth, thyroid function disorders and neural tube defects.

Physical activity during pregnancy is believed to have psychological benefits and has also been associated with shorter and less complicated labour, lower incidence of gestational diabetes, preterm birth, large for gestational age new-borns and hypertensive disorders.

The advantages of breast-feeding outweigh any risks from contaminants. However, it is important to assess health outcomes of toxic exposures via breastfeeding that could have deleterious consequences for new-born infants.

In conclusion, there is rising evidence of the negative effects of environmental exposure during pregnancy and breastfeeding and should be considered a major public health issue in the early future.

## 1. Introduction

Environment, lifestyle and personal factors are considered to be health determinants with the capacity to influence disease, quality of life and mortality.

Environmental contaminants include those apparently under control, like food or abuse substances such as alcohol and tobacco. However, we must not forget about air pollution, chemicals, water contamination and radiation, often depending on governmental and industry policies.

We live surrounded by pollutants and objects with chemical components, but we don't always have information about security exposure limits or the synergic effects of their combinations, thus representing a major public health concern(1,2).

Scientific evidence over the past years has raised concern that preconceptional and prenatal exposure to toxic environmental agents may have a critical and lasting effect on future health and susceptibility to disease(2–4). Given that development continues after birth, critical and sensitive windows occur periconceptually (before, during and shortly after fertilization of the egg) and during pregnancy, but also during infancy, childhood and puberty(4) [Fig.1].

We must not forget that most classes of environmental pollutants can cross into the fetal environment. Some of them are xenobiotic and can accumulate in the placenta and foetus resulting in an even higher fetal than maternal exposure and damage.

The World Health Organization (WHO) warns that an estimated 12.6 million people die every year as a consequence of an unhealthy environment(5). Scientific societies such as the International Federation of Gynaecology and Obstetrics (FIGO) work to raise awareness of this fact and prevent exposure to toxins that negatively influence the health of mothers and their new-borns(6)

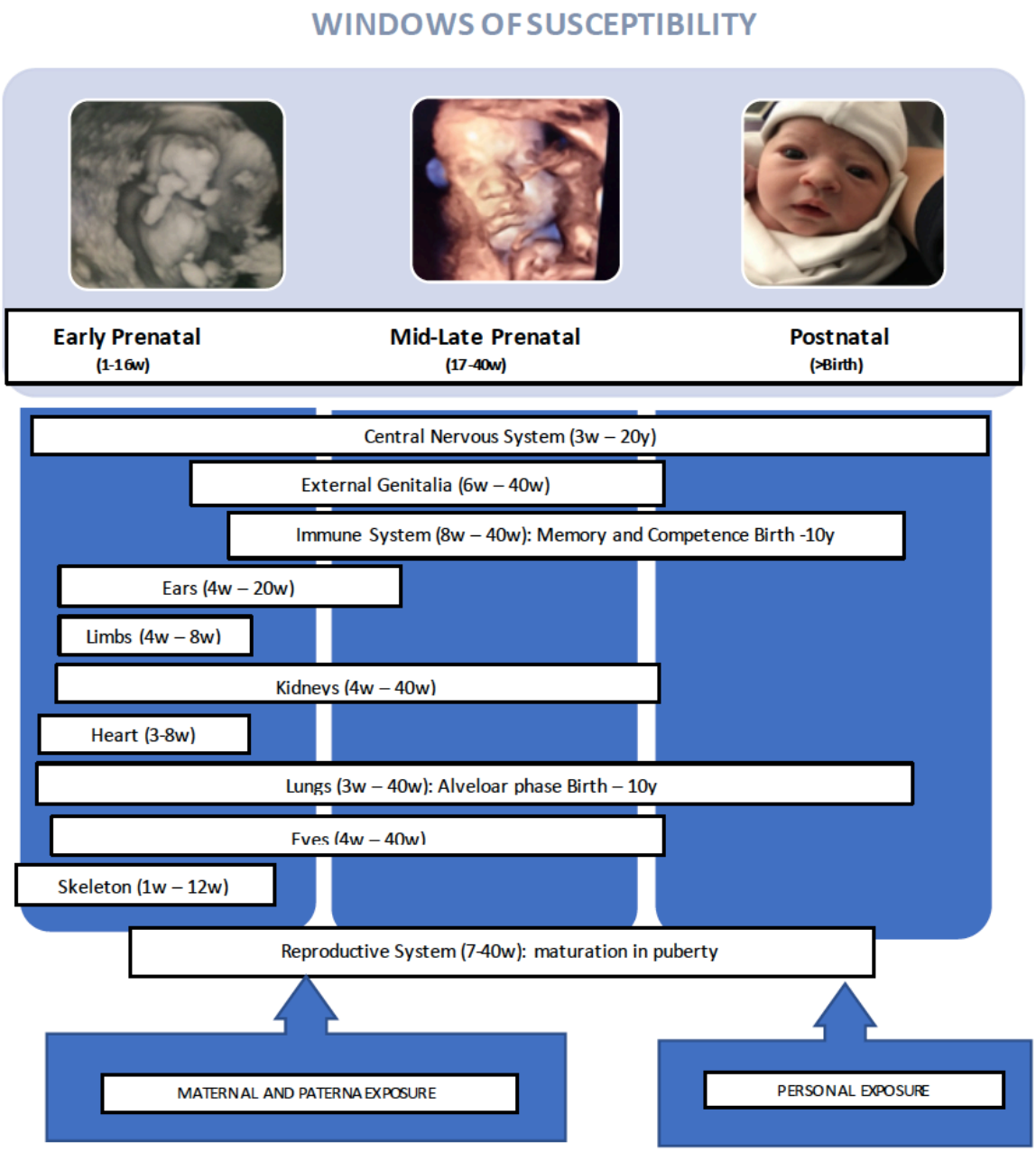


Figure 1: Human organogenesis and windows of susceptibility: prenatal and postnatal exposure. Modified from WHO State of the Science of EDCs 2012. Summary for Decision-Makers(7)

## 2. Environmental exposures in pregnancy

Pregnancy exposure to toxic environmental agents has an influence on perinatal outcomes but also on infancy and childhood health [Table 1].

| CONTAMINANT | CHEMICALS COMPOUNDS | ADVERSE HEALTH OUTCOMES |
|---|---|---|
| **Alcohol** | | Fetal Alcohol Spectrum Disorders (FASD), growth restriction, behavioural problems |
| **Cannabis, cocaine, heroin and methamphetamine** | | Fetal loss, preterm birth, small-for-gestational age, birth defects, behavioral problems |
| **Air pollutants** | CO, NO, NO2 , SO2 , O3 | Preterm Birth and small-for-gestational-age infants<br>Autism spectrum disorder<br>Increased risk of sudden infant death<br>blood pressure<br>Type 1 diabetes |
| **Polycyclic aromatic hydrocarbons (PAHS)** | Coal or fossil fuel, forest fires, waste incineration | Preterm Birth and Small-for-gestational-age infants<br>Asthma and allergic disease |
| **Particulate matters** | Toxics with aerodynamic diameter (PM10-PM2.5) | Preterm Birth and lower birth weight.<br>Asthma |
| **Persistent organic compounds** | Organochlorine Compounds<br>Polychlorobiphenyls (PCBs)<br>Perfluoroalkylaed substances | Lower birth weight.<br>Small-for-gestational-age infants<br>Adverse neurodevelopmental outcome<br>Attention deficit hyperactivity disorder<br>Autism spectrum disorder<br>Congenital anomalies<br>Asthma and allergic disease<br>Increased risk of sudden infant death<br>blood pressure<br>Leukemia |
| **Not persistent organic compounds** | Phthalates, Phenols, and Parabens | Behavioral problems<br>Attention deficit hyperactivity disorder<br>Congenital anomalies |
| **Tobacco smoke** | Nicotine, CO, aniline, methanol, hydrogen sulfide, arsenic, lead, cadmium. | Preterm Birth<br>Small-for-gestational-age infants<br>Adverse neurodevelopmental outcome<br>Attention deficit hyperactivity disorder<br>Asthma and allergic disease<br>Increased risk of sudden infant death<br>Congenital anomalies<br>Leukemia |
| **Toxic Metals** | Lead, cadmium, mercury, arsenic | Small-for-gestational-age infants<br>Adverse neurodevelopmental outcome |

Table 1: Environmental contaminant exposure during pregnancy and adverse health outcomes

## 2.1. Toxic effect of prenatal exposure to substance use

Different toxic substances have been studied to assess their effects on pregnancy, neonatal and early life.

### *2.1.1. Alcohol*

In our society, there is a high prevalence of alcohol consumption during pregnancy. The RCOG (Royal College of Obstetricians and Gynaecologists) has reported that 29% of British pregnant women drinks alcohol(8). Studies in Barcelona reveal, through the use of biological matrices, a 45% mild-moderate social consumption(9,10).

Alcohol consumption during pregnancy may lead to adverse effects on fetal development described within the Fetal Alcohol Spectrum Disorders (FASD)(11). Currently, there is no definition of a safe amount and consumption period during pregnancy, implying it should be avoided. FASD affect up to 1% of world's paediatric population and its most extreme form is defined as Fetal Alcohol Syndrome (FAS)(11–13). Its clinical features can be broadly divided into: morphological malformations, especially

craniofacial features (midfacial hypoplasia, wide spaced eyes and a smooth philtrum); growth restriction and central nervous system impairment, resulting in motor, cognitive, learning and behavioural disorders(13,14).

During fetal development, alcohol affects multiple metabolic pathways, partly through the alteration of DNA methyltransferase activities, which shapes the global epigenetic pattern of the developing foetus(15,16). Consequently, the expression of key genes is deregulated(17–20), affecting organogenesis especially of the fetal brain(21). Moreover, ethanol metabolism generates high amounts of reactive oxygen species (ROS), promoting oxidative stress and inhibiting endogenous antioxidant mechanisms(22). The increase of ROS alters both protein structures and mitochondrial respiration: which finally induces cellular apoptosis(23).

Prenatal Ethanol Exposed (PEE) detection is focused on the use of alcohol consumption questionnaires and biomarkers in biological matrices. Determination of fatty acid ethyl esters (FAEEs) or ethyl-glucuronide (EtG) in meconium and maternal hair is the best procedure to identify PEE new-borns(10,24,25).

### *2.1.2. Tobacco*

The global prevalence of smoking during pregnancy is high: according to a national survey conducted in the United States, in 2012, 15,9% of pregnant women smoke cigarettes. Similar patterns of use have been observed in Europe(26).

Smoking during gestation is associated with pregnancy complications such as severe preeclampsia, placental abruption, placenta previa, preterm birth, increased risk of abortion, stillbirth or impaired growth and development among many others(27–30), and with long term consequences such as intellectual impairment later in life, leukaemia or asthma and allergic disease(29,31–36). Lean body mass of babies from non-smoker mothers seems to be more affected than fat mass(37), and during the first years of life, children from smoking mothers show complete catch-up growth(38). Based on the programming effect(39), maternal smoking during pregnancy might determine children's weight status, blood pressure or cardiovascular diseases in the medium-long term future. Although underlying mechanisms are not clear, longitudinal studies sustain that children from smoker-mothers have a higher risk of developing obesity over time(40,41). There is also a causal association between maternal exposure to cigarette smoke and the risk of orofacial clefts, congenital heart disease, neural tube defects and gastrointestinal malformations(42–44).

Thus, the deleterious effect of tobacco during pregnancy is well defined. However, due to its thousands of biologically active and toxic compounds, it is difficult to determine the causative agent of these adverse events. The anorexigenic effect of nicotine and its blood flow restriction to the placenta, the carbon monoxide exposure involving tissue hypoxia and the effect on DNA methylation are some of the most studied mechanisms(28,45).

### *2.1.3. Drugs of abuse*

Prenatal substance abuse has increased noticeably among pregnant women, but the prevalence is still underestimated. In 2017, the American National Survey on Drug Use and Health (NSDUH) assessed that 194,000 pregnant women, aged from 15 to 44 years, had used illegal drugs in the past month(46,47). Hair testing is the most sensitive and specific analysis to detect the concentration of chronic drug exposure(48).

Negative birth outcomes have been linked to drugs of abuse, although the clear influence of each substance is unknown because of the confounding effects of coexisting substances. Moreover, addicted women often experience inadequate prenatal care, malnutrition, chronic illness and poverty, which exacerbate the impairment of fetal development(26).

The principal consequences of opioid exposure in pregnancy are postnatal growth delay, microcephaly, neurobehavioral disabilities and sudden infant death syndrome(49,50). Maternal opiate use increases the risk of neonatal abstinence syndrome (NAS)(50), which comprises a wide range of symptoms, including irritability, poor feeding, tremors, hypertonia, vomiting, loose stools, seizures, and respiratory distress.

Cannabis, cocaine, heroin and methamphetamine are the most consumed substances and can cause fetal loss, preterm birth, small-for-gestational age, birth defects and admission to the neonatal intensive care unit(51). Cocaine and methamphetamine have been linked to premature rupture of membranes and placental abruption, preeclampsia and gestational hypertension(52–55). In addition, all types of drugs induce epigenetic changes in brain morphology, synaptic plasticity and behaviour(56). Prenatal drugs use has been associated with microcephaly and adverse consequences for the growth of fetal and adolescent brains(57), leading to lack of attention, reduced executive functioning skills and disabilities in learning and memory, with consequent poorer academic attainment and more behavioural problems(58–60).

## 2.2. The effect of maternal food intake

Pregnant and lactating women should be aware of the risks of heavy metals and other food toxic compounds(61). These chemicals act as Endocrine Disruptor Compounds (EDCs) with deleterious effects on pregnancy and development commented later on.

Highly toxic chemicals such as mercury, lead, arsenic, cadmium and chromium are elements that can be vehiculized in foods and accumulated in the body(62) [Table 2]. They can be found in the environment by means of voluntary application (plaguicides) and involuntary migration (from food containers and plastic utensils), and then introduced in the food chain. In fact, food and specially those aliments from animal origin with a high fat content are considered to be the main source of exposure to many pollutants for the majority of the population(63).

Other compounds that can also be present in foods are organophosphate pesticides (OPPs), polychlorinated biphenyl ethers (PBDEs)(64), acrylamide(65), perfluoroalkyl(66), as well as some mycotoxins(67) and bacteria-derived toxics(68).

| TOXIC COMPOUND | FOOD PRESENCE | TOXIC COMPOUND | FOOD PRESENCE |
|---|---|---|---|
| **Mercury** (59) | Fish/seafood (swordfish, sharks)<br>Wild mushrooms<br>Dietary supplements<br>Non-alcoholic beverages | **Cadmium** (60,61) | Cereals/grains (rice, wheat)<br>Vegetables (roots)<br>Meat/poultry<br>Seafood (bivalve molluscs) |
| **Methylmercury** | Tuna, swordfish, cod, whiting and pike. | **Hexavalent Chromium** (62) | Drinking water<br>Special nutritional use products,<br>Herbs, spices, condiments<br>Sugar |
| **Lead** (63) | Bread and rolls<br>Tea<br>Tap water<br>Potatoes<br>Fermented milk<br>Beer-like beverages | **Aluminium** (64) | Cereals<br>Vegetables<br>Beverages<br>Infant formulae |
| **Arsenic** (65) | Fish/seafood<br>Algae (hijiki)<br>Cereals (rice grains) | | |

Table 2: Toxic chemicals and main dietary sources

## 2.3. The effect of maternal physical activity

Until a few decades ago, pregnant women were discouraged from exercise. However, this was mainly due to social and cultural biases and unfounded concerns about safety for the foetus, rather than based on scientific investigation. In recent years, there has been a growing interest in the effects of physical exercise during pregnancy, so that the beneficial effects of regular physical exercise, both for the mother and the foetus, are well-established, based mostly on systematic reviews and randomized metanalysis(69–71). These physical benefits include maternal fitness and the prevention of excessive weight gain, as well as psychological benefits. Regular exercise during pregnancy has also been associated with shorter and less complicated labour, as well as the prevention of maternal-fetal diseases such as gestational diabetes, preterm birth, being born large for gestational age and a lower incidence of hypertensive disorders(72–74). Evenson et al identified, summarized and contrasted 11 clinical or public health guidelines for physical activity during pregnancy from nine countries around the world (Australia, Canada, Denmark, France, Japan, Norway, Spain, United Kingdom, United States). These clinical guidelines mostly indicated the recommendation for physical activity during pregnancy, its intensity and duration/time, as well as absolute and relative contraindications and indications for discontinuing exercise during pregnancy(75).

Pregnancy may be one of the most important times to adopt a routine of regular exercise given that lifestyle during pregnancy imprints the future health of the child.

## 2.4. Prenatal exposure to air pollution as a potential risk factor

Air pollution has a heterogeneous composition: particulate matter (PM), ozone pollution ($O_3$), carbon monoxide (CO), nitrogen oxides ($NO_2$, NOX) and sulfur dioxide ($SO_2$)(76,77). PM is a mixture of suspended particles with different chemical compositions usually classified by its size (PM10, PM2.5)(77). It has been widely studied due to its ability to trigger oxidative stress and inflammation in the lung's alveoli(78–80) and to cross the alveolar epithelium into the systemic circulation(81).

Evidence of pollution effects over pregnancy is constantly growing, and its relation with adverse perinatal outcomes such as low birth weight (<2500 g) or pregnancy-induced hypertensive disorders is being well established(78,82,83). Olsson et al. observed a positive association between NOx levels and an increased risk for pregnancy-induced hypertensive disorders (OR 1.12, 95% CI 1.06 to 1.18 per 10µg/m3 increase in the NOx level)(84). A systematic review conducted by Pedersen et al.(85), concludes that pregnancy-induced hypertensive disorders were associated with PM2.5 (OR=1.57; 95% CI, 1.26–1.96 per a 5µg/m3 increment), $NO_2$ (OR=1.20; 95% CI, 1.00–1.44 per a 10-µg/ m3 increase) and PM10, (OR=1.13; 95% CI, 1.02–1.26, per a 10-µg/m3 increase). As for fetal growth, PM2,5 exposure was negatively associated with reduced head circumference at birth and birth weight(86) while $NO_2$ was significantly linked to a shorter length at birth(86–88). $NO_x$ has been related to a decrease of abdominal circumference and femoral length and a reduce of birth weight(89).

Exposure to PM and $O_3$ has been associated to a higher risk of preterm birth (27,87,88,90). Moreover, synergies between PM2.5 and $O_3$ showed more risk (RR 3,63) than their independent effects (RR 0,99 and 1,34, respectively)(91).

PM10, NO and $O_3$ have been associated to macrosomia(92) and PM2,5 has been related in animal studies to profound metabolic effects (like glucose intolerance, decrease insulin sensitivity and altered hepatic glucose and lipid metabolism) through oxidative stress(93).

In a multicentric European birth cohort of 1396 subjects, the Helix Project, exposure levels of $NO_2$ and PM 2,5 were inversely associated with telomer length(94)

Regarding the fetal nervous system, *in utero* exposure to PM2.5 during the first trimester was found to decrease placental transcription of brain-derived neurotrophic factor (BDNF). This factor plays an important role in fetal neurodevelopment(95). Furthermore, neuropathological changes (microglial activation, ventriculomegaly, increased size of the Corpus Callosum, reduction in hippocampal size) were found to be induced by prenatal exposure to ultrafine particles in mice(96). In addition, Guxens et al. showed cerebral cortex alterations and impairment of inhibitory control function in children exposed to fine particles during gestation. This impaired function is related to attention-deficit or hyperactivity disorder(97). According to Danish investigators, gestational exposure to air pollution may also increase the risk of autism spectrum disorder(98).

## 2.5. Prenatal exposure to endocrine disruptors and toxic metals

EDCs are exogenous chemicals (phenols, phthalates, parabens, flame retardants and heavy metals) that can alter the hormonal and homeostatic systems of the organism(99). Exposure to EDCs may occur in pregnancy by way of personal hygiene products, cosmetics, cleaning products, electronic devices and consumption of animal, plant or processed foods(2).

EDCs can work by altering normal hormonal production and levels and mimicking their function. Its main effects on prenatal exposure have been studied with major evidence on preeclampsia and intrauterine growth restriction, preterm birth and thyroid dysfunction(100,101).

When talking about hypertensive disorders of pregnancy, evidence is strongest for links between persistent chemicals (lead, cadmium, organochlorine pesticides and polycyclic biphenyls) and preeclampsia, although low-exposure levels associations are not always detectable. However, results have been inconclusive for bisphenols, phthalates and organophosphates(101).

Metals and metalloids accumulate in the placenta, causing a decrease in uterine blood flow and having a negative impact on fetal growth(100,102). It has also been described that plasticizers, like diethylhexylphthalate (DEHP) and its active metabolites, and bisphenols A (BPA) induce preeclampsia and growth restriction(103–105). The exposure to pesticides such as dichlorodiphenyltrichloroethane (DDT) and its metabolites have also been suggested to have a detrimental effect on fetal growth(106). Organochlorine pesticides may lead to preterm birth through disturbance of normal estrogen-progesterone ratio(107), might increase the risk of autism spectrum disorder(108) and with also evidence of thyroid disrupting properties(109).

Flame-retardants such as PBDE and tetrabromopisphenol A (TBBPA) have been linked to growth restriction and preterm birth, as well as impairment of the thyroid hormone function(110,111).

A growing number of studies suggest a link between congenital anomalies and maternal exposure to organic solvents, pesticides and dioxins (cleft lip and palate, neural tube defects, and congenital heart disease)(112,113). Toluene embryopathy has been described after maternal inhalation of paint or glue(114). Phthalates have antiandrogenic-like properties and have a great role in hypospadias and cryptorchidie(115). Pesticides are considered to be a risk factor for childhood leukaemia(116). Finally, maternal exposure to BPA increases rates of depression, behavioural problems and alterations in white matter in preschool aged children(117,118).

## 2.6. Prenatal noise stress

Noise pollution is a major environmental health concern. It is estimated that 113 million people in Europe are exposed to excessive environmental noise levels according to the European Environmental Noise Directive (2002/49/EC), majorly from road traffic noise. The implication of environmental noise on several health disorders is already recognized(119,120).

Exposure to noise has been associated with cardiovascular effects, like hypertension, stroke and myocardial infarction in many studies(120), with high-quality evidence for the association between road traffic noise and incidence of ischemic heart disease(121). The suggested biological pathways indicate that repeated exposure to noise causes stress responses, as well as sleep disturbance, leading to endocrine and sympathetic responses, which increase blood pressure, heart rate, and cardiac output through the release of catecholamines(119) and corticosteroids(122), and to oxidative-stress and immunological responses(123). These reactions persist even while asleep and can lead to chronic physiological deregulations(120). However, few studies have investigated the effect of exposure to noise in pregnant women, being preeclampsia of special interest. A recent study of 269.263 deliveries in Quebec, Canada(124), 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) preeclampsia compared to those exposed to <50 dB(A)(124).

A Danish prospective cohort study with 72,745 women showed that a 10-dB increase in road traffic noise was associated with a 10% increase in the risk of preeclampsia(125). These associations were stronger for the mild subtypes of preeclampsia and early preeclampsia and not evident for severe preeclampsia. They concluded that the effects of air pollution and noise were generally difficult to separate.

In conclusion, these initial studies suggest that exposure to environmental noise is associated with preeclampsia, particularly early onset preeclampsia. However, more studies are needed.

## 3. Environmental effects on placenta

The placenta is a highly sensitive organ to environmental contaminants with estrogenic activity as it expresses the oestrogen receptors ERα and ERβ(126). Although there are many reports in the literature of the in vitro action of different EDCs in human placenta, some controversies remain regarding the timing, dose and duration of exposure(127). It is important to emphasize that the effects of EDCs in human trophoblasts are dose-dependent with low doses being more effective than high doses(115): This is concerning because the efficacious low doses correspond to the levels detected in the human population.

Fergusson et al.(128) found a positive association between BPA levels and an increase of 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 (PlGF), suggesting an altered placentation and trophoblast function related to preeclampsia and hypertensive disorders(129).

In vitro studies showed that para-Nonylphenol (p-NP) substances, used as plasticizer and surfactant in the manufacturing industry, could increase β-hCG secretion, cell apoptosis and reduce trophoblasts migration and invasion. Exposure to BPA and p-NP down-regulated expression of some placental carriers like ABCG2, a key transporter for xenobiotics(130).

In addition, PBDEs mixtures enhanced the 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(131). Rats exposed to PBDEs during gestation showed effects on placenta and foetus that varied by foetal sex. mRNA expression in the placenta also significantly varied by foetal sex and dose. Thus, PBDEs are impacting thyroid hormones regulation in a sex-specific manner during this critical window of development(132).

Higher concentrations of polycyclic aromatic hydrocarbons (PAHs) such as benzo[a]pyene (BP), benzo[b]fluorene (BbF) and dibenz[a,h]anthracene (DBA) were found in placenta from preterm deliveries compared with term deliveries(133).

Related to heavy metals, in the New Hampshire Birth Cohort Study (N = 1159), with every ng/g increase in the Cadmiun concentration of placenta there was lower placental weight (- 7.81 g; 95% CI: -15.42, -2.48). For placentae with below median Zinc and Selenium concentrations, 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. However, no appreciable differences were observed with other elements (arsenic, mercury and lead)(134).

As far as air pollution is concerned, circulating proinflammatory cytokines induced by PM may disrupt trophoblastic invasion during placenta formation(135,136). Likewise, PM could enter in uteroplacental circulation resulting in placenta pathological changes(137). Placenta chorioamnionitis and thrombosis of placental capillaries have been demonstrated by LiuY in a rat model after PM2.5 exposure. These changes in placenta tissue lead to reduced maternofoetal exchange surface and to placental dysfunction(78). Neven et al. analysed placental DNA and found an association between elevated placental mutation rate and prenatal exposure to PM2.5 and black carbon. They postulated that this placental mutations could represent some of the earliest effects to air pollutants exposure in the process of carcinogenesis(137).

## 4. Breastfeeding: Environmental toxins in human milk and early-life consequences

Breast feeding is the gold standard of new-born and child nutrition during at least the first 6 months of life(138). Bottle-feeding is associated to the transfer of toxic substances from recipients to milk. However, milk transfer of toxic substances to which the mother has previously been exposed, may also occur during breastfeeding. Several comprehensive reviews conclude that breastfeeding is generally contraindicated in mothers who use illegal drugs(139), although pharmacokinetic data are sparse in lactating woman(140).

Smoking and alcohol consumption should be avoided during the breastfeeding period. Alcohol interferes with the milk ejection reflex, which may reduce milk production. Human milk alcohol levels generally parallel maternal blood alcohol levels. Studies evaluating infant effects of maternal alcohol consumption have been mixed, with some mild effects seen in infant sleep patterns, amount of milk consumed during

breastfeeding sessions and early psychomotor development. Some authors suggest limiting alcohol intake to the equivalent of 8 ounces of wine or two beer is recommended(139). However, others state that alcohol consumption during both pregnancy and breastfeeding should be totally avoided since there is not a proven safe consumption dose(10,47). Nicotine and other compounds are known to be milk-transferred to the infant causing increases in the incidence of respiratory allergy in infants and in Sudden Infant Death Syndrome (SIDS) risks(141).

Infants are exposed trough breastfeeding to a mixture of environmental chemicals. Lactating mothers are among the high-risk population to mercury exposure because they may suffer the consequences of mercury themselves, but also they may transfer significant quantities of mercury to their babies(142).

BPA has also been widely studied: The temporary tolerability daily intake (t-TDI) of 4 μg/kg. $bw^{-1}$ $day^{-1}$ for oral exposure to BPA has been established(143). In lactating mothers, BPA is rapidly introduced into the breast causing an elevation of BPA content in the milk within hours. Only the unconjugated BPA present in the milk is active, consequently its determination is more suitable for the assessment of BPA risk in breastfed infants(144). Interestingly, while BPA content in mature milk reflects recent ingestion, its content in colostrum reflects ingestion in the second half of pregnancy(145). The place of residence of the mother and the use of personal care products showed significant association with BPA concentration(146).

Human milk contains conjugated and un-conjugated parabens and provides the exposure of the mother, the foetus, and the neonate in a period of high vulnerability to the endocrine disruptors(147). 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. The frequency of use of some cosmetic products and human milk protein levels were the main predictors of parabens in milk. The new-borns estimated daily intake of parabens 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 as established by European Food Safety Authority (EFSA)(143,148). In a recent study, Sanchis et al found high urinary concentrations of Methylparaben (MP), Ethylparaben (EP) and BPA in lactating mothers although estimated exposures was lower than the reference values for risk assessment. The use of personal care products was associated with higher urinary levels of MP and Propylparaben (PP). MP was also associated with the consumption of packaged and bakery products(149).

All these chemicals may influence infant gut microbial function(150), increase risk of hyperkinetic disorder(151), toxicity to the liver and kidney, cancer, reproductive and respiratory disorders (143,152) or changes in thyroid and growth hormones that may have effects on neurodevelopment(143,153).

When mother's milk is not available or is insufficient, pasteurized donor milk is recommended. The use of illegal drugs, alcohol and tobacco is an exclusion criterion for accepting a nursing mother as a milk donor. Escuder et al. found that donors do not use illegal drugs during either the donation period or the

months leading up to it, they are occasionally exposed to tobacco smoke and almost all of them consume caffeine(154).

Although most scientific evidence indicate that the advantages of breast-feeding outweigh any risks from contaminants exposure to these toxics can have deleterious consequences especially for a vulnerable population such as lactating women and breastfed new-born infants. Special caution with preterm infants should be posed.

## 5. Conclusions

Environment exposure is considered to be a health determinant with the capacity to influence disease, quality of life and mortality. Although this exposure can be deleterious for any person, pregnancy and early life exposure have been demonstrated to be critical windows of susceptibility, with a lasting effect on future health and susceptibility to disease(2–4).

The use of alcohol, tobacco and drugs of abuse has been linked to a serious of deleterious effects in the new-born and later in life, including FASD and other negative pregnancy and birth outcomes. EDCs and heavy metals vehiculized by food intake or present in the environment are related to preeclampsia, foetal growth restriction, preterm birth and thyroid misfunction. Air pollution has been linked to preterm birth, foetal growth restriction, effects on pregnancy vascularization, increased gestational diabetes and reduced telomeres length. Association between preeclampsia and environmental noise is rising. On the contrary, physical activity during pregnancy is believed to have remarkable benefits and therefore should be recommended during pregnancy. Breastfeeding should be recommended; however, mothers should be aware of toxic exposures via breastfeeding that could have consequences for new-born infants.

Therefore, doctors should have knowledge of harmful exposures to be able to counsel patients on the risk and advise them with precautions to minimize exposure, especially during pregnancy and breastfeeding. Governmental protection should be strengthened, by limiting environmental exposure to substances with evidence of a deleterious effect. However, only with a global public health policy in the early future could all this evidence be translated into action.

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