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Atmospheric pollutants and their impact on murine and human reproduction

Contaminantes atmosféricos y su incidencia sobre la reproducción en murinos y humanos

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Abstract

Atmospheric pollution is caused by the presence or combination of physical, chemical, or biological pollutants in the air. In recent years, the most studied pollutant is particulate matter (PM), a varied mixture of solid and liquid particles. PM also carry highly toxic components from cigarette smoke combustion, with different microscopic sizes present in the atmosphere that can be inhaled and cause serious health problems due to toxicity at the cellular level and consequences at the inflammatory level. Currently, exposure to PM is associated with alterations in processes of reproduction in mammals, affecting gamete and embryo viability. The objective of this review is to describe the effects of atmospheric pollutants on reproductive processes and the possible mechanisms of action, both cellular and molecular, which are of interest in human and animal health sciences. Studies show a cause and effect relationship between exposure to pollutants and gamete quality, with pollutants causing DNA damage, epigenetic modifications, an increase in oxidative stress and alterations in morphology. Likewise, effects in the prenatal and postnatal period are reported, such as premature births, low birth weight and spontaneous abortion. The results of this review show that atmospheric pollutants negatively influence reproductive processes in some mammals, as they can alter the mechanisms of oxidative regulation and regulation of gene expression in gametes, leading to cell toxicity and potential alterations in genomic stability.

Keywords: embryos, spermatozoa, particulate matter, oocytes, spermatozoa, oocytes

Resumen

La contaminación atmosférica se da por la presencia o combinación de contaminantes físicos, químicos o biológicos en el aire. En los últimos años, el más estudiado es el material particulado (PM), una mezcla variada de partículas sólidas y líquidas, que, además, transporta elevados componentes tóxicos provenientes de la combustión del humo del cigarrillo, con diferentes tamaños microscópicos presentes en la atmósfera, las cuales pueden inhalarse y provocar graves problemas de salud debido a la toxicidad a nivel celular y consecuencias a nivel inflamatorio. Actualmente, la exposición al PM se ha asociado con alteraciones en los procesos reproductivos en mamíferos, afectando la viabilidad de gametos y embriones. El objetivo de esta revisión fue describir los efectos de los contaminantes atmosféricos en el ámbito reproductivo y los posibles mecanismos de acción tanto celulares como moleculares, los cuales son de interés en las ciencias de la salud humana y animal. Los estudios evidencian una relación de causa-efecto entre la exposición a los contaminantes y la calidad de los gametos, generando daños del ADN, modificaciones epigenéticas, aumento de estrés oxidativo y alteraciones morfológicas. Asimismo, se reportan efectos en el periodo prenatal y postnatal, como nacimientos prematuros, neonatos con bajo peso y abortos espontáneos. Los resultados de revisión evidencian que los contaminantes atmosféricos influyen negativamente en el proceso reproductivo

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de algunos mamíferos, debido a que pueden alterar los mecanismos de regulación oxidativa y regulación en la expresión génica en los gametos, lo que conlleva a toxicidad celular y potenciales alteraciones en la estabilidad genómica.

Palabras clave: embriones, espermatozoides, material particulado, ovocitos

INTRODUCTION

As a result of the economic and industrial growth of large urban centers during the last century, there has been a considerable increase in the emissions of atmospheric pollutants, generating a worldwide problem in air quality (D'Amato et al., 2010). These factors can be influenced by meteorological parameters intervening in the behavior of air pollutants such as temperature, humidity, precipitation and wind speed (Elminir, 2005).

Air pollution is related to decreased life expectancy and increased morbidity rates in human populations, especially due to respiratory and cardiovascular diseases (Dastoorpoor et al., 2018; Díez et al., 1999). *In vitro* and *in vivo* studies suggest that air pollutants have a genotoxic effect, promote oxidative stress, and act as endocrine disruptors (Conforti et al., 2018).

One of the most studied atmospheric pollutants is particulate matter (PM), considered a complex mixture of solid and liquid particles suspended in the air, mostly composed of elemental carbon (EC), polycyclic aromatic hydrocarbons (PAHs), sulfates, nitrates and heavy metals with high toxicity and potential carcinogenic and mutagenic effects (Ramirez et al., 2009).

According to the US EPA (US EPA, 2016), PM is classified according to size into inhalable particles with diameters of 10 μm or smaller (PM_{10}), produced by uncontrolled combustion and mostly with a basic pH, and fine inhalable particles with diameters of 2.5μm or smaller ($PM_{2.5}$) generally acidic containing derivatives from vehicular and industrial emissions, becoming more aggressive particles due to their high percentage of inhalation and penetration into the organism.

Clinical epidemiological studies in humans and in the murine model (used for its similarity to humans in biochemical and genetic processes, in addition to the economic, proliferative and adaptive advantages that they generate scientifically) (Benavides and Guénet, 2001) have shown that PM has harmful effects at the reproductive level, increasing cases of infertility and embryo damage in high atmospheric pollution countries, such as China, India and the United States (Wu et al., 2019; Wu et al., 2021; Zhou et al., 2014). These studies are a reference for Colombia, since cities such as Bogota, Medellin, Cali, Barranquilla, Cartagena, Bucaramanga and Pereira have high air pollution characteristics (Cardenas, 2017). Therefore, government entities should develop strategies to improve air quality and understand the impact PM can have on the reproductive health of the population.

The United Nations (UN) expressed concern about possible human extinction, and continued toxic pollution exposure exhibits a global threat to human rights, including reproductive health rights reflected in a diminished fertility rate (UN, 2019).

Therefore, the objective of this literature review was to analyze the effect of air pollutants, especially PM, on reproduction in mammals (murine and human), through cellular and molecular parameters that indicate gamete and embryonic quality and/or postnatal development. In addition, it is expected to contribute to the knowledge of the effects and scope of air quality problem to improve strategies for reduction, control and prevention of impacts on public health, which is an objective within the National Development Plan (NDP, 2019).

MATERIALS AND METHODS

Initially, a search was conducted for articles in research journals that follow peer-reviewed

and open access editorial processes, published in the PUBMED, ScienceDirect, SciELO, ClinicalKey, Redalyc, SpringerLink and Google Scholar databases, in the period 2011 to 2021.

Sixty-five articles were identified, with only 26 selected because of their reference to evaluating the viability of mammalian gametes and embryos exposed to PM and some of its components: $PM_{2.5}$, PM_{10}, Sulfur dioxide (SO_2), nitrogen oxides (NOx), polycyclic aromatic hydrocarbons (HAPs), heavy metals such as lead (Pb), mercury (Hg), Cadmium (Cd) and exposure to cigarette smoke containing all the above pollutants and in small fractions ($<PM_{10}$ y $<PM_{2.5}$). The remaining studies were excluded because the contaminants examined were not considered PM components.

The search was filtered by referencing biological sciences, human clinical, occupational and social medicine, using the following descriptors and their combinations in both English and Spanish: air pollution, gametes, polycyclic aromatic hydrocarbons, heavy metals and mammals (contaminación del aire, gametos, hidrocarburos aromáticos policíclicos, metales pesados y mamíferos). These terms were checked in the descriptors in Health Sciences (DeCS, https://decs.bvsalud.org/es/) and PubMed (MeSH, https://www.ncbi.nlm.nih.gov/mesh/). Subsequently, a similar analysis verifying and relating the different results was performed, as well as an evaluation of the consistency between different authors and cause-effect relationship findings. To validate the consistency of the scientific evidence, the logical connection between the results of different authors was analyzed, identifying similarities in the results of similar experiments in different populations and environments (Asia, Europe and America). Finally, the information was organized into effects of atmospheric pollution on gametes (spermatozoa and oocytes) and on embryos and postnatal consequences.

RESULTS

Effect of atmospheric pollutants on the viability of gametes and embryos in murine and humans

The effect of air pollutants on reproductive alterations of gametes and embryos has become a subject of study in the last decade (Table 1). Through the review of scientific studies that evaluate the association between atmospheric pollutants, especially PM and its components, some findings related to the effects of PM components on the quality and viability of gametes in mammals and affectations during the prenatal and postnatal period are described and analyzed.

Effects on the viability of the male gametes

Several epidemiological studies around the world have been able to determine negative effects of PM pollution on sperm quality and its association with infertility, especially exposure to PAHs, which damages sperm DNA (Yang et al., 2017), generates DNA adducts and decreases sperm number (Ji et al., 2013), and decreases the number of copies of mitochondrial DNA (mtDNA) (Ling et al., 2017). Jurewicz et al. (2013) evaluated the relationship of 1-hydroxypyrene (1-OHP), a biomarker of PAH exposure, with semen quality in male smokers, finding sperm midpiece abnormalities, low semen volume and low percentage of motile sperm in patients with higher urinary 1-OHP concentrations. Additionally, the PAHs exposure biomarker 2-OHNa (2-hydroxynaphthalene) was associated with DNA damage in human spermatozoa (Han et al., 2011).

Likewise, increased sperm DNA fragmentation, as well as, reduced semen quality, have been associated with PAHs-DNA adducts (Ji et al., 2013) due to the ability of these electrophilic reactive chemicals to covalently bind to nucleophilic sites on DNA and proteins, directly or after metabolic activation, suggest−

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Table 1. Results of studies evaluating the effects of air pollutants in murine and humans

	CONTAMINANTS	EFECTS	REFERENCES
OVOCYTES In humans and murines	Cigarette smoke	Decreased ovarian reserve (reduction of primordial and primary follicles, increased follicular atresia), changes in gene expression, increased mitochondrial ROS. Increased DNA damage in granulosa cells and low proliferation, decreased oocyte size. Increased FSH levels.	Caserta et al. (2013) Paixão et al. (2012) Kilic et al. (2012) Sobinoff et al. (2013)
	Heavy metals Pb, Cd and Hg	Extracytoplasmic abnormalities in oocytes (fragile oolemma, large perivitelline space, dark cytoplasm and giant size).	Nandi et al. (2011)
	HAPS Benzo B fluoranthene Benzo A pyrene 1-OHP	Increased percentage of aneuploidy, DNA damage, reduced mitochondria, decreased oocyte maturation and fertilization, chromosomal misalignment, lack of kinetochore binding to microtubules, increased ROS and apoptosis.	Guo et al. (2020) Zhang et al. (2018)
	$PM_{2.5-}$ PM_{10}	Decrease in ovarian reserve (reduction of primordial follicles). Decrease in fertility rates and number of births.	Wu et al. (2021)
SPERMATOZOIDS In humans and murines	Cigarette smoke	Decreased sperm quality (low sperm concentration, low motility and increased abnormal morphology).	Caserta et al. (2013)
	HAPS	Affected semen quality (decreased sperm concentration, volume and motility, abnormal morphology with sperm neck abnormalities). Aneuploidy, DNA fragmentation, dysfunction and shortening of sperm telomere length, decrease in the number of mtDNA copies. Alteration in hormone levels of testosterone, estradiol, LH, prolactin, increased ROS, senescence and apoptosis of spermatogenic cells.	Han et al. (2011) Ji et al. (2013) Jurewicz et al. (2013) Radwan et al. (2018) Ling et al. (2017) Yang et al. (2017)
	Heavy metals Pb, Cd and Hg	Affected sperm quality (decreased sperm concentration and motility, abnormal morphology), decreased testosterone and luteinizing hormone, DNA integrity damage and sperm apoptosis.	Wijesekara et al. (2015) Mendiola et al. (2011)
	$PM_{2.5-}$ PM_{10}	Decreased semen quality (lower concentration, lower motility and greater abnormality in sperm morphology), aneuploidy of spermatozoa, and affectation of serum levels of LH, prolactin, estradiol and testosterone.	Zhou et al. (2014) Jurewicz et al. (2015) Wu et al. (2019) Wang and Xu. (2019)
PRENATAL AND POSTNATAL STAGE In humans and murines	Cigarette smoke	Decreased birth size and birth weight, disruption of inhibin/activin and estrogen signaling, increased estrogen exposure and dysregulation of multiple molecular pathways in the exposed human fetal ovary.	Kilic et al. (2012) Fowler et al. (2014)
	O_2 and NO_2	Verbal and motor developmental delay.	Yorifuji et al. (2016)
	Heavy metals Pb, Cd, Ni and Hg	Mercury levels in umbilical cord red blood cells associated with preterm births and low birth weight.	Wijesekara et al. (2015)
	$PM_{2.5-}$ PM_{10}	Decrease in fertility rates, premature births, reductions in birth weight, etc.	Pedersen et al. (2013) Wu et al. (2019)

Sulfur dioxide (SO_2), carbon monoxide (CO), nitrogen dioxide (NO_2), particulate matter PM_{10} <10 μm, particulate matter $PM_{2.5}$ <2.5 μm, polycyclic aromatic hydrocarbons (HAPs), 1-hydroxypyrene (1-OHP), lead (Pb), cadmium (Cd), selenium (Se), mercury (Hg), reactive oxygen species (ROS), luteinizing hormone (LH), mitochondrial DNA (mtDNA) and basal follicle stimulating hormone (FSH).

ing PAHs are potentially genotoxic compounds (Ewa and Danuta, 2017). Some PAH derivatives, such as benzo(a)pyrene (b[a]p), can induce oxidative stress through the production of reactive oxygen species (ROS), causing DNA damage through activation of the expression of the enzyme cytochrome P450 1A1

(CYP1A1), which is involved in the production of ROS (An et al., 2011) which is involved in the metabolic induction of PAHs producing b[a]p diol epoxides capable of producing premutagenic lesions upon reaction with DNA (Vázquez et al., 2016).

On the other hand, heavy metals, related to alterations in seminal quality parameters, have also been identified in PM. A positive association between the percentage of immotile spermatozoa and seminal plasma concentrations of lead (Pb) (30 μg/L) and cadmium (Cd) (30.9 μg/L) was found in men attending infertility clinics (Mendiola et al., 2011). In addition, another report indicated that environmental and occupational exposures to these metals are associated with poor semen quality, because seminal parameters such as progressive motility, viability and sperm morphology decreased in patients exposed to environmental contaminants (48.42%, 56.67% and 39.03%, respectively) compared to non-exposed patients (52.48%, 64.71% and 43.89%, respectively) (Wijesekara et al., 2015).

In this regard, heavy metals in natural environments are molecularly recognized, differentiated and used by organisms for their functioning. However, heavy metals cannot be differentiated when they interact with analogous ions unknown to biological systems that can use the binding sites and alter metabolism or system function (Godwin, 2001). Pb is capable of substituting for calcium and altering processes such as gene regulation, protein synthesis and energy metabolism (Garza et al., 2005). Similarly, Pb and Cd are considered endocrine disruptors during spermatogenesis, because they affect the hypothalamic-pituitary-gonadal axis, which decreases hormone secretion and increases ROS levels in testicular tissue, generating an imbalance of cellular redox state, reducing sperm quality and quantity (Lafuente, 2013; Mathur y D'Cruz, 2011).

On the other hand, among the effects of PM_{10} and $PM_{2.5}$, aneuploidies in spermatozoa have been identified, such as sex chromosome disomy and disomy of 21 (Jurewicz et al., 2015). It has been suggested that these alterations are due to perturbations in the mechanisms of synapsis or recombination in the pairing region and nondisjunction of chromosome 21, including an increase in the expression of genes on chromosome 21 that alter the formation of the midpiece, on which the motility of the sperm depends (Tempest et al., 2004). Additionally, a negative association between PM exposure ($PM_{2.5-10}$) and the proportion of sperm with Y/X chromosomes has been reported in humans, indicating that the concentration of the Y chromosome is lower with respect to the X chromosome in the presence of increased PM levels. Although the toxicological mechanisms of this modification have not been established, an alteration of testicular function by these pollutants has been proposed, which would allow a higher concentration of X sperm (Radwan et al., 2018). In addition, it has been suggested that the effect of $PM_{2.5}$ on sperm motility is due to an alteration in transcription or translation factors that lead to the synthesis of proteins necessary for sperm motility (Hammoud et al., 2010).

Likewise, PM contains metals, PAHs, nitrogen dioxide (NO_2) and other pollutants, which are released by mobile sources, such as vehicles (Calogero et al., 2011). In a recent study, researchers reported DNA fragmentation, low concentration, low mobility and abnormal sperm morphology in men working in tollbooths exposed to traffic pollutants. Although the diversity of air pollutants from vehicular traffic makes it difficult to identify the individual effects, it has been related to an imbalanced generation of oxidizing agents and antioxidants at the cellular level, consequently increasing ROS levels which may attack the nucleophilic groups of deoxyribose and nitrogenous bases exposed in the DNA molecule, modifying its bases, generating breaks in the DNA and activating and inactivating suppressor genes, negatively affecting the fertility of the sperm (Zorrilla et al., 2004). This negatively affects the fertility of males. On the one hand, the high index of polyunsaturated fatty acids (PUFA) in the sperm membrane can generate damage by lipid peroxidation and the reduction of cytoplasm, which limits the number of antioxidant enzymes, triggering a cascade of degradative changes that alter the function and organization of the sperm membrane, resulting in DNA damage and proteolysis, leading to reduced sperm mobility and affecting the paternal genome (Vicenta et al., 2015).

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Finally, the results of the aforementioned studies show that exposure to PM and its components can affect sperm viability, although it is difficult to determine the effect of each pollutant particle due to its diversity and nature. However, in males, these negative impacts can be mitigated by the presence of spermatogonial stem cells helping maintain fertility throughout life due to their potential for self-renewal (Canipari et al., 2020; Gonzalez and Gonzalez, 2017).

Effects on the viability of female gametes

Oocyte maturation is a complex meiotic process, since oocytes are sensitive to exogenous toxic agents and can experience nuclear and cytoplasmic maturation dysfunction, decreasing their fertilization capacity and embryo development potential (Guo et al., 2020).

The effects of PM and its components on fertility and ovarian physiology, especially the exposure to cigarette smoke, a mixture containing more than 7000 chemicals, 69 of which are known carcinogens, including PAHs, metals, and NO_2, which cause birth defects and reproductive disorders (OMS, 2019; Estrada et al., 2016). In a study of rats exposed to cigarette smoke, a low rate of oocyte growth was observed due to damage to ovarian function, affecting follicular development, resulting in a marked reduction in granulosa cell proliferation (Paixão et al., 2012). Likewise, in rats ovaries exposed to cigarette smoke, a boost in expression of genes involved in cell proliferation and growth (Mycl1 and Stat1), genes associated with the activation of the primordial follicle (Gdnf and Cxcl12), genes involved in the maturation process of the ovarian follicle (Ihh, Cyp19a1, Cldn5) and markers of follicular atresia and early apoptosis (p53, Casp3 and Casp2) was found. Likewise, DNA damage and increased follicular atresia were evidenced due to the overregulation of the oxidative DNA damage biomarker 8-hydroxy-2-deoxyguanosine (8-oxo-dG) and increased levels of mitochondrial ROS and lipid peroxidation, which cause oxidative damage to the oolemma membrane, reducing the fertilization potential in murine oocytes (Sobinoff et al., 2013).

In regard to environmental agents such as cigarette smoke that have been associated with high ROS levels (Nicolich et al., 2013), the generation of oxidative stress due to its high chemical reactivity induces damage to molecular and biological structures, altering cellular physiological processes such as enzymatic and hormonal activities (Sierra et al., 2004). In addition, increased ROS is associated with endometriosis, a chronic inflammation related to two oxidative stress markers: 8-oxo-dG, one of the most important DNA adducts formed by hydroxyl radical attack on guanine residues, and the biomarker 8-isoprostane, involved in the peroxidation of cell membranes (Polak et al., 2013). Likewise, high ROS levels can generate oxidative damage, mtDNA degradation and alter transcription and translation processes important for inducing mitochondrial activity and Adenosine triphosphate (ATP) biosynthesis. Therefore, low ATP levels affect the proliferative activity of granulosa cells during follicular development and thus the process of folliculogenesis (Hoque et al., 2021).

On the other hand, Caserta et al. (2013) evaluated reproductive hormone levels in infertile smoking and non-smoking women, finding a lower antral follicle count (AFR) and an increase in basal follicle stimulating hormone (FSH) concentration in women smokers. In non-smoking women, no effects on these hormones were reported. FSH is a significant predictor of ovarian reserve as it is associated with the number of oocytes retrieved or available to be ovulated, which means that the fertilization process would be affected if there is a decrease in FSH (Vrontikis et al., 2010).

With respect to PAHs, they are an extensive group of pollutants that present variable toxicity due to their molecular structure (Lopez et al., 2016) and are related to infertility problems. Oocytes of mice exposed to benzo a pyrene (b[a]p), showed a higher proportion of meiotic spindle morphological alterations (disorganized), misalignment of chromosomes at the equatorial plate, increased ROS and apoptosis (Zhang et al., 2018). Chromosomal misalignment and lack of microtubule attachment to the kinetochores provide a potential route to aneuploidy, as it hinders the delivery of chromosomes to the forming daughter cells (Shomper et al., 2014).

Also, exposure to benzo(b)fluoranthene (b[b]f), has been shown to cause DNA damage, loss of trimethylation of histone H3 lysine 4 (H3K4me3), apoptosis in oocytes, decreased number of mitochondria, and increased adenosine monophosphate-activated protein kinase (AMPK) (Guo et al., 2020). Within the framework of normal oxidative processes in cellular metabolism, mitochondria is characterized as the main producer of ROS. An increase in ROS generation induces oxidative damage to various cellular components, altering the function of the respiratory chain, which leads to the accumulation of mtDNA mutations (Macedo, 2012). A decrease or alteration in mitochondrial function causes intracellular ATP levels to decrease, being detected by AMPKs (proteins that regulate energy balance) and activated to restore them upstream. However, downstream, AMPKs can phosphoactivate protein kinases such as p53, which, upon molecular binding, induce cellular apoptosis as a result of oxidative stress (Filomeni et al., 2009). On the other hand, H3K4me3 is an epigenetic maturation marker linked to active and inactive regions of the genome, involved in DNA transcription, proliferation and replication, and of great importance in embryonic stem cell differentiation and oocyte development, which means that insufficient trimethylation of H3K4 decreases genome transcription, impairing the process of oocyte maturation and embryonic development (Yu et al., 2017).

In relation to some metals such as Pb, Cd and As (arsenic), they have been studied for their relationship with female reproduction. It has been shown that patients with successful results to *in vitro* fertilization (IVF) treatments have low concentration of these metals in the follicular fluid, compared to high levels of metals in patients who failed to become pregnant (Nandi et al., 2011). These results are probably due to the fact that Cd affects epigenetic modifications by decreasing histone H3K9me3 methylation and histone H3K9ac acetylation, which are involved in the regulatory activity of gene expression and chromatin configuration (Huang et al., 2012). In addition, Cd causes DNA damage through increased 8-oxo-dG, affecting genome stability and thus oocyte nuclear maturation (Cheng et al., 2019). Likewise, As induces the increase of ROS, producing damage and low mtDNA copy number in oocytes, leading to a reduction in energy status and ATP-dependent metabolic activity (Zhang et al., 2011). Also, Pb has been shown to diminish GSH levels and generate mitochondrial dysfunction, leading to activation of the Nrf2/Keap1 oxidative stress signaling cascade, affecting embryo development and maturation of female gametes (Jiang et al., 2021). Reduced glutathione (GSH) is the main cellular defense mechanism against oxidative stress and increased ROS production and is involved in regulatory processes such as gene expression, modulation of DNA synthesis and cell proliferation (Scirè et al., 2019).

Regarding $PM_{2.5}$, its increase could be related to the reduction in fertility rates. This is evidenced in a study carried out in women undergoing IVF in the United States, in which a relationship was found between $PM_{2.5}$ exposure and a lower probability of pregnancy after an IVF cycle (Legro et al., 2010). In another study, female rats exposed to $PM_{2.5}$ showed a negative regulation in genes related to mitochondrial functions belonging to complex I (Ndufa5 and Ndufa7) and complex III genes (Lyrm7 and Uqcr10) of the mitochondrial respiratory chain, which are responsible for the coding of proteins active in electron transport reactions in the mitochondrial membrane. Likewise, cell damage and increased ROS levels were found in oocytes (Guo et al., 2021). This increase in ROS production decreases the efficiency of electron transfer, increases lipid oxidation and increases oxidative stress, destabilizing protein complexes with mitochondrial functions, which seek to counteract the excess of ROS, causing breaks in mtDNA (Martinez et al., 2005). These alterations in the structural components would generate affectations in the metabolism, dysfunctionality and cell death of the female gametes (Córdova et al., 2010).

Prenatal and postnatal disorders

Exposure to PM and its components not only has a negative impact on the gametogenesis process, but also on gestation and after birth. From conception and during intrauterine growth and development, organisms receive environmental signals with the potential to cross the placental barrier and generate functional changes in adults that facilitate the development of diseases such as diabetes mellitus, obesity,

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dyslipidemia, among others (Casanello et al., 2015). These signals can mediate epigenetic changes, modifying gene expression through histone modifications, microRNA (miRNA) expression, DNA methylation and nucleosome remodeling (Esteller, 2008).

Due to the adverse effects that have been reported in various investigations, exposure to cigarette smoke is a phenomenon often studied during fetal and neonatal development. It has been found to alter ovarian development in human fetuses, as it reduces the proportion of primordial follicles and the proliferation of germ cells (Fowler et al., 2014). Cigarette smoke was also found to inhibit embryonic development and induce formation of neural tube defects in rats (Yin et al., 2021). In addition, newborn rats exposed to cigarette smoke showed increased follicular atresia, apoptosis in granulosa cells and low birth weight of offspring (Kilic et al., 2012). Substances from cigarette smoke activates the aryl hydrocarbon receptor (AhR), a cytoplasmic transcription factor involved in the adaptive response to cellular stress, which has been reported to affect cell proliferation, generate apoptosis by decreasing ATP synthesis and increasing oxidative stress (Wang and Xu, 2019). Thus, in utero exposure to cigarette smoke and other combustion products before birth influences ovarian germ cell proliferation and subsequently female reproductive function in response to AhR ligand action (Anderson et al., 2014). Additionally, in women who have had babies with neural tube defects, an increase in serum homocysteine, a sulfur amino acid metabolic product of methionine, has been found, and this is the proposed mechanism by which exposure to cigarette smoke is associated with increased frequency of neural tube defects and fetal death (Pintó, 2000; Suarez et al., 2011).

On the other hand, the exposure of pregnant women to heavy metals such as Hg and Pb was related to premature births and low birth weights, as these metals are transferred from the mother to the fetus, generating high perinatal metabolic abnormalities (Chen et al., 2014). Pb has been negatively associated with the expression of the collagen type I Alpha 2 (COL1A2) gene, because it decreases its methylation, compromising human reproduction (Hanna et al., 2012). COL1A2 encodes the 2 chains of type I collagen, a structural fibrillar protein present in the chorio-amniotic membranes and cervix. Alterations in the expression of the maternal collagen I gene lead to cervical insufficiency due to premature degradation of membranes before delivery (Romero et al., 2010). Similarly, Hg exposure in utero can affect the epigenome by hypermethylating relevant CpG regions (cytosine- and guanine-rich areas of the genome) that have the potential to influence infant neurodevelopment (Rebelo and Caldas, 2016).

As for elevated levels of carbon monoxide (CO), $PM_{2.5}$, PM_{10} and NO_2 produced by high traffic density, they have also been studied for their relationship with premature births, low birth weight infants (Pedersen et al., 2013) and delays in the process of acquiring verbal skills in children exposed to PM (Yorifuji et al., 2016). In a study conducted in the United States with women exposed to $PM_{2.5}$ during gestational periods, it was found that out of 53,094 neonates, 4543 were born prematurely (8.56%), which associated the exposure of mothers with alterations in fetal development (Zhu et al., 2019). Another study found that exposure of rats to fine ammonium sulfate particles (a constituent of PM) during the gestational period increased the stillbirth rate, lessening the number and weight of the offspring, altering organogenesis of the offspring with metabolic dysfunctions and generating alterations in some organs (heart, small intestine, brain and lungs, among others); in adults, an increase in the concentrations of glucose, non-esterified fatty acids and hepatic lipids was found (Wu et al., 2019).

On the other hand, elevated tryptophan concentrations are linked to impairments of fetal brain development, because in response to maternal inflammation in the placenta, tryptophan provides immunosuppressive protection for the fetus through indolamine 2,3-dioxygenase and tryptophan hydroxylase 1 (TPH1; the initial enzyme of the serotonin pathway) and, as a consequence, increases serotonin (5-HT) levels which may affect important developmental processes in the fetal brain that are normally modulated by 5-HT in early pregnancy (Goeden et al., 2016). PM and its components induce TLR2/4 receptor-dependent inflammatory activation and lipid oxidation, leading to metabolic

dysfunction and weight gain (Wei et al., 2016). In addition, metabolic alterations caused by exposure to environmental pollutants have been explained by alterations in the gene expression profile permanently or temporarily due to chemical modifications in chromatin, histone modifications or DNA methylation (Rogers, 2019). The thrifty phenotype hypothesis relates epigenetic mechanisms involved in prenatal development and birth defects, suggesting that fetuses adapt to an intrauterine environment with nutrient limitation in order to survive, causing some systems to develop more than others, altering the growth and function of tissues, which generates vulnerability during exposure to subsequent environmental agents that involve a positive energy balance, leading to risks of developing obesity, hyperlipidemia and hypertension, if they have an excess of nutrients in their adult life (Simmons, 2005).

In conclusion, PM negatively affects the formation of gametes (oocytes and spermatozoa), due to the increase of reactive oxygen species that lead to oxidative stress, altering signaling pathways important for proper cellular functioning, inducing DNA damage, epigenetic modifications, hormonal alterations and cell death, which have been related to reproductive viability, morphology and quality of gametes.

The direct effects of air pollution on embryonic development include an increase in low birth weights, spontaneous abortions and premature births, because the increase in free radicals alters the balance between these molecules and the antioxidant defense system, leading to alterations in the expression of genes necessary for the formation of molecules involved in cellular processes, damaging biomolecules and thus altering the metabolism and embryonic development. This generates a reduction in fertility rates in fertile women and in those who have resorted to IVF techniques.

Finally, this article provides reference elements that contribute to the understanding of the effects and scope generated by PM air pollution on the reproductive health of the exposed population, since it allows us to understand some molecular and biological mechanisms that induce the effect of atmospheric pollutants on reproductive capacity and efficiency.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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