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IN FOCUS

Ambient air pollution and adverse birth outcomes: A review of underlying mechanisms

Julia C. Fussell[1,2] | Eric Jauniaux[3] | Rachel B. Smith[1,2,4] | Graham J. Burton[5]

[1]MRC Centre for Environment and Health, School of Public Health, Imperial College London, London, UK

[2]National Institute for Health and Care Research Health Protection Research Unit in Environmental Exposures and Health, Imperial College London, London, UK

[3]EGA Institute for Women's Health, Faculty of Population Health Sciences, University College London, London, UK

[4]Mohn Centre for Children's Health and Wellbeing, School of Public Health, Imperial College London, London, UK

[5]Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, UK

Correspondence
Julia C. Fussell, National Institute for Health Research Health Protection Research Unit in Environmental Exposures and Health, School of Public Health, Imperial College London, London W12 0BZ, UK.
Email: julia.fussell@imperial.ac.uk

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Abstract

Epidemiological data provide varying degrees of evidence for associations between prenatal exposure to ambient air pollutants and adverse birth outcomes (suboptimal measures of fetal growth, preterm birth and stillbirth). To assess further certainty of effects, this review examines the experimental literature base to identify mechanisms by which air pollution (particulate matter, nitrogen dioxide and ozone) could cause adverse effects on the developing fetus. It likely that this environmental insult impacts multiple biological pathways important for sustaining a healthy pregnancy, depending upon the composition of the pollutant mixture and the exposure window owing to changes in physiologic maturity of the placenta, its circulations and the fetus as pregnancy ensues. The current body of evidence indicates that the placenta is a target tissue, impacted by a variety of critical processes including nitrosative/oxidative stress, inflammation, endocrine disruption, epigenetic changes, as well as vascular dysregulation of the maternal-fetal unit. All of the above can disturb placental function and, as a consequence, could contribute to compromised fetal growth as well increasing the risk of stillbirth. Furthermore, given that there is often an increased inflammatory response associated with preterm labour, inflammation is a plausible mechanism mediating the effects of air pollution on premature delivery. In the light of increased urbanisation and an ever-changing climate, both of which increase ambient air pollution and negatively affect vulnerable populations such as pregnant individuals, it is hoped that the collective evidence may contribute to decisions taken to strengthen air quality policies, reductions in exposure to air pollution and subsequent improvements in the health of those not yet born.

KEYWORDS
adverse birth outcomes, ambient air pollution, endocrine disruption, epigenetic changes, inflammation, mechanisms, oxidative stress, placenta

1 | INTRODUCTION

Air pollution has been defined by the World Health Organization (WHO) as the contamination of the indoor or outdoor environment by any chemical, physical or biological agent that modifies the natural characteristics of the atmosphere.[1] Findings from epidemiological and toxicological research have also confirmed that this heterogeneous mix of gases and particulate matter (PM) modifies public health.[2] A convincing body of evidence exists linking exposure to ambient air pollutants and cardiorespiratory disease.[3–6] Data from an increasing number of studies also suggest this environmental threat contributes to a broader number of health effects including diabetes,[7] suboptimal cognitive development,[8] cognitive decline[9] and adverse birth outcomes including preterm delivery,[10] low birthweight (LBW)[11] and stillbirth.[12] Most of these complications have also been associated with maternal

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exposure to tobacco smoke and are likely to be triggered by similar mechanisms, i.e. inflammation and oxidative stress.[13–16] It is also likely that air pollutants can induce similar placental epigenetic alterations, such as maternal smoking,[17–19] highlighting the possible long-term effects of in utero exposure on the susceptibility to childhood and adult diseases. This review stems from a larger ongoing piece of work being undertaken by the UK Government's Committee on the Medical Effects of Air Pollutants on adverse birth outcomes.[20] After a brief overview of the epidemiological evidence base, it summarises, through the discussion of studies that have produced results of special interest, our current understanding of the mechanisms activated in placental tissue through which exposure to particulate matter, nitrogen dioxide and ozone (i.e. the modern day air pollutants that are most abundant in today's urban environments and which are widely studied for their health impact) may contribute to adverse birth outcomes.

Key clinical points

- Epidemiological data provide varying degrees of evidence for associations between prenatal exposure to ambient air pollutants and adverse birth outcomes (suboptimal measures of fetal growth, preterm birth and stillbirth).
- Human studies show associations between concentrations of particulate and gaseous air pollution and increased placental vascular resistance to blood flow in the uterine circulation.
- Experimental evidence suggests exposure to air pollution during pregnancy may be associated with oxidative stress, inflammation and epigenetic alterations in placental tissue and/or maternal/cord blood as well as perturbations in the maternal fetal thyroid gland.
- In vitro work suggests PM can induce activation of stress pathways seen in the placenta in cases of FGR.

Future research

- Increased precision in quantifying (indoor and outdoor) air pollution exposure among pregnant individuals by employing reliable, low-cost portable devices/sensors and controlling the data for maternal tobacco smoke exposure by measuring cotinine levels in blood or urine.
- Use of multi-pollutant models to evaluate possible additive/synergistic effects of an overall mix of pollutants/identify independent effects of specific pollutants.
- Studies that investigate whether there is a critical exposure window during gestation for an effect of air pollution on birth outcomes.
- Greater research into mechanisms underlying the effects of ambient gaseous pollutants on adverse birth outcomes.
- More studies that link exposure to air pollutants and mechanistic endpoints with an adverse birth outcome and sex of the fetus.
- Continued use of cross-omic techniques to facilitate the identification of interacting genes/pathways that may underlie molecular mechanisms.

2 | EPIDEMIOLOGICAL EVIDENCE OF THE EFFECTS OF AIR POLLUTION ON ADVERSE BIRTH OUTCOMES

The epidemiological literature base of studies, systematic reviews and meta-analyses investigating associations between maternal exposure to air pollutants and birth outcomes is rapidly expanding. It is also characterised by inconsistency (i.e. reporting positive and null associations) in the collective evidence. The most recent authoritative reports by professional bodies on ambient pollutants are the U.S. Environmental Protection Agency Integrated Science Assessments (ISAs).[21–23] The ISA for PM concluded that many studies provide evidence for a positive association between exposure to particulate matter <2.5 microm in diameter ($PM_{2.5}$) and fetal growth and PTB.[21] The results of a recent large meta-analysis of ambient $PM_{2.5}$ during entire pregnancy and adverse birth outcomes build upon these conclusions, reporting summary estimates of 22 g lower birthweight (95% uncertainty intervals [UI] 12–32; estimates from 44 studies), 11% higher risk of low birthweight (LBW; 1.11, 95% UI 1.07–1.16; 40 studies) and 12% higher risk of PTB (1.12, 95% UI 1.06–1.19; 40 studies), each per 10 microg/m^3 increase in ambient $PM_{2.5}$.[24] It is noteworthy that in another meta-analysis, negative associations between a change in grams (β) of term birthweight and ambient $PM_{2.5}$ across the entire pregnancy were observed at concentrations <10 microg/m^3 (the WHO air quality guideline value).[25] The pooled estimates per 10 microg/m^3 increment in $PM_{2.5}$ were β = −15.58 g; 95% CI −25.38 to −5.79) in the low $PM_{2.5}$ exposure subgroup (<10 microg/m^3; 6 studies) and β = −16.58 g (95% CI −20.35 to −12.81) in the high $PM_{2.5}$ exposure subgroup (≥10 microg/m^3; 20 studies).

The ISA for NOx reports that there is largely consistent evidence to support an association between exposure to NO_2 and fetal growth restriction (FGR) but inconsistent results from studies that examined birthweight outcomes and PTB.[22] A recent meta-analysis did not find an association between entire pregnancy NO_2 exposure and PTB (relative risk [RR] 1.010, 95% CI 0.990–1.030, per 10 microg/m^3 NO_2, 20 studies) reflecting inconsistency in the direction of associations observed in underlying studies.[26] The same meta-analysis reported an inverse association

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for first trimester NO_2 (RR 0.972, 95% CI 0.950–0.994, per 10 microg/m^3 NO_2; 21 studies), a null finding for second trimester NO_2 (RR 1.002, 95% CI 0.970–1.034 per 10 microg/m^3 $NO_{2;}$ 18 studies) and a positive association for third trimester NO_2 exposure and PTB (RR 1.066, 95% CI 1.031–1.102 per 10 microg/m^3 NO_2; 15 studies). The ISA for O_3 concludes that while there is some evidence for the effects of O_3 on fetal growth (especially for continuous term birthweight), findings were more consistent for an elevated risk of PTB with ozone exposure during early to mid-pregnancy.[23] A recent meta-analysis focusing on early pregnancy exposures is supportive of the latter.[27] The pooled odds ratio (OR, 95% CI) for a 10 ppb increase in ozone exposure was 1.06 (1.03–1.10) in trimester 1 (17 studies) and 1.05 (1.02–1.08) in trimester 2 (15 studies).

The epidemiological evidence base for ambient air pollution and stillbirth remains limited. Conclusions in the ISAs included the presence of generally positive associations for $PM_{2.5}$[21] and inconsistent findings for O_3.[23] A recent meta-analysis also reported positive associations with risk of stillbirth for entire pregnancy $PM_{2.5}$ (OR 1.10, 95% CI 1.07–1.13; 7 studies), third trimester $PM_{2.5}$ (OR 1.09, 95% CI 1.01–1.18; 5 studies), and first trimester O_3 (OR 1.03, 95% CI 1.00–1.05; 6 studies), each per 10 microg/m^3 increment, but no associations for NO_2.[12] The effects of traffic-related air pollutants, which dominate exposures in urban environments where the majority of people live, work and commute, on adverse birth outcomes (term LBW, small for gestational age [SGA], term birthweight, PTB) have also undergone a recent evaluation by the Health Effects Institute.[28] For traffic-related $PM_{2.5}$, the meta-analytical summary relative risks per 5 microg/m^3 increment were 1.11 (95% CI 1.03–1.20) for term LBW, 1.09 (1.04–1.14) for SGA and a mean difference in term birthweight of –17.3 (–33.2 to –1.5) g. In contrast to the findings for ambient $PM_{2.5}$ in general, the summary estimate for traffic-related $PM_{2.5}$ and PTB was null (RR 0.99, 95% CI 0.90–1.09), likely reflecting compositional differences in the particulate mix. Apart from an association between NO_X and term low birthweight (RR 1.02, 95% CI 1.01–1.03, per 20 microg/m^3 increment), results for traffic-related NO_2, NO_X or elemental carbon in relation to risk of term LBW, continuous birthweight at term, SGA or PTB were largely null.

3 | GENERAL MECHANISMS OF TOXICITY OF AIR POLLUTANTS

A succession of events involving gaseous and particulate pollutant-induced pulmonary and systemic oxidative stress and inflammation, mediated via redox sensitive signalling pathways, are considered integrative biological pathways underlying the harmful effects of ambient pollution on the cardiorespiratory system.[29,30] An excessive oxidative challenge, as opposed to the degree that is essential in physiological redox signalling and for steady-state maintenance of stress response systems, creates an imbalance between the generation of reactive oxygen species (ROS) and antioxidant protection in favour of the former, causing excessive oxidative damage.[31] Reactive nitrogen species (RNS) also exist and when overproduced or under-eliminated can create damage via nitrosative stress. Biomolecules that are targeted by ROS/RNS include DNA, proteins, lipids and carbohydrates, giving rise to DNA mutations, lipid peroxidation and protein oxidations, respectively. This can lead to appreciable impairment of cellular function and, in the worst case, to cell death, organ dysfunction and disease.[31]

Pollutants that make up the ambient pollutant mix are free radicals (e.g. NO_2) or have the ability to drive oxidative reactions (e.g. PM, O_3). Once inhaled, O_3 and NO_2 react with proteins and lipids present in the lung lining fluid compartment to produce secondary oxidant species.[32] This means that cellular responses to concentrations of gaseous pollutants that overcome endogenous antioxidant defences are not the result of a direct reaction of the pollutant with epithelial cell surface components but are instead mediated via a cascade of secondary, free radical-derived products. Several more complicated and inter-related pathways exist by which inhaled PM can generate oxidative stress at the air-lung interface. These include an ability of the particle surface per se to elicit oxidative stress and the carriage of direct redox catalysts (e.g. transition metals, quinones) or compounds (e.g. polycyclic aromatic hydrocarbons [PAHs]) that can be metabolised to reactive electrophiles in vivo.[33]

On reaching the lung surface, secondary oxidation products arising from gaseous and particulate pollutants, initiate (via the activation of transcription factors) cytokine and chemokine generation, adhesion molecule expression and tight junction modification. These responses lead to the influx of activated inflammatory cells from the vasculature into the lung, which generates a second wave of pulmonary oxidative stress accompanied by systemic inflammation and oxidative imbalances. The latter, plus the translocation of ultrafine and nanosize particles and/or particle constituents (organic compounds, metals) across the alveolar membrane into the general circulation, paves the way for toxicity within the vasculature and at organ sites distant from the lung, including the placenta.[34]

4 | MECHANISMS UNDERLYING ADVERSE BIRTH OUTCOMES

The convincing evidence that air pollution-induced oxidative stress and inflammation play critically important roles in cardiorespiratory diseases, including maternal cardiovascular health,[35] suggests that the epidemiological associations observed between poor air quality and adverse birth outcomes could be mediated, in part, by these key pathways. Air pollution, however, likely impacts multiple biological

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mechanisms important for sustaining a healthy pregnancy, depending upon the composition of the pollutant mixture, and the exposure window owing to changes in physiologic maturity of the placenta, circulations and fetus as pregnancy ensues.

4.1 | Human studies

The experimental research summarised below originates from human pregnancy cohort studies that have assessed, for example, relevant biomarkers in biological samples (i.e. maternal blood and urine, placental tissue, cord blood) collected during pregnancy and at birth. These studies are vital to further our understanding, owing to specific inadequacies (e.g. fundamental differences in gestational sac structure, placentation, circulations, fetal/placental weight ratios, organogenesis phases and gestational length) of animal models. Table S1 provides details those studies linking maternal exposure to ambient air pollutants to a given mechanistic endpoint and an adverse birth outcome and Table 1 provides a top-level summary of the mechanistic changes that have been observed.

4.1.1 | Effect on the placental circulations

The oxidative and inflammatory properties of air pollution are linked to many pathophysiological changes in the cardiovascular system that ultimately increase cardiovascular morbidity and mortality. These include prominent effects on the vasculature leading to endothelial dysfunction and arterial vasoconstriction,[36] both of which are associated with PTB and abnormal fetal growth.[37]

Studies have investigated placental vascularisation and function in relation to air pollution exposure and have reported contradictory effects on placental vascular resistance to blood flow in the uterine circulation.[38–43] Two of these studies, using maternal personal exposure, found that higher NO_2 exposure[40,43] is associated with a lower mean artery pulsatility index (PI). Conversely, other studies reported that maternal exposure to NO_2 is associated with an increased uterine resistance index (RI)[39] and increased incidence of bilateral uterine notching.[42] Similarly, Ouidir et al.[41] observed an increased resistance index of the left uterine artery associated with exposure to NO_2 as well as $PM_{2.5}$.

4.1.2 | Oxidative stress

Human placentation is characterised by the migration of placental trophoblastic cells into the uterine wall, transforming the maternal arteries into low-velocity, high-conductance vessels and controlling the entry of oxygenated maternal blood to the placenta.[44,45] Disruption of this process is associated with hyperoxia or fluctuating levels of oxygen inside the placenta – disturbances found in common pregnancy complications such as miscarriage, pre-eclampsia and FGR.[46,47] Oxygen free radicals are an inevitable by-product of aerobic metabolism and some degree of placental oxidative stress likely occurs at the end of the first trimester,[48] regulating formation of the placental membranes.[49] Placental malperfusion generates chronically high levels of oxidative stress causing indiscriminate damage to biomolecules and disruption of signalling pathways. These have immediate consequences for the outcome of a pregnancy, but also predispose the offspring to metabolic, cardiovascular and neuropsychiatric disorders and certain cancers in adult life due to structural and epigenetic changes in organ systems.[50]

Exacerbation by maternal exposure to air pollution of the heightened oxidative state during a standard pregnancy may overcome mechanisms that minimise the deleterious effects of ROS production. Several approaches have been undertaken to investigate an exacerbation of oxidative stress in response to ambient air pollution exposure during gestation and whether such an effect has the potential to have an adverse effect on birth outcomes. These include studies on biomarkers of nitrosative/oxidative stress, oxidative potential

TABLE 1 Changes observed in human mechanistic studies in association with increased concentrations of ambient pollutants.

Mechanism	Studied changes	Result (in placenta and/or maternal/cord blood)
Oxidative stress	Oxidative DNA damage/tyrosine nitration	Increased with $PM_{2.5}$/PM_{10}[51–54] Increased with NO_2[53]
	mtDNA content	Decreased with $PM_{2.5}$/PM_{10}[56–58] Decreased with NO_2[59]
Inflammation	Intrauterine inflammation	Increased with $PM_{2.5}$[79]
	Biomarkers (CRP, IL-1β, IL-6 & TNF-α)	Increased with $PM_{2.5}$/PM_{10}[77,78,80,87] Increased with NO_2[78] Increased with O_3[77,80]
Epigenetic alterations	Global DNA methylation	Decreased with $PM_{0.1}$/$PM_{2.5}$/PM_{10}/traffic[97–100] Decreased with NO_2[101] Decreased with O_3[101]
	DNA methylation of HSD11B2	Increased with $PM_{2.5}$[98]
	DNA methylation of H19	Decreased with $PM_{2.5}$[104] Increased with NO_2[104]

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(OP; the capacity of particles to directly cause damaging oxidative reactions) of ambient pollution and genetic susceptibility due to polymorphisms in antioxidant genes.

Biomarker studies have shown associations between ambient concentrations of PM and NO_2 and markers of nitrosative (3-nitrotyrosine [3-NT]) and oxidative (8-oxo-7,8-dihydro-2′-deoxyguanosine [8-OHdG]) stress in the placenta and/or maternal/cord blood[51–54] (Table 1). 3-NT is the stable product of tyrosine nitration with the reactive oxygen species peroxynitrite and while nitration of placental proteins is evident in standard pregnancies, the presence of nitrosative stress has also been linked with diminished placental vascular reactivity,[55] which could in turn compromise placental function and thus fetal development and growth.

A number of studies have also observed significant associations between increased concentrations of PM[56–58] and NO_2[59] during pregnancy and decreased placental/cord blood mtDNA content (Table 1), indicative of mitophagy and mitochondrial death.[60] By regulating energy, placental mitochondria are essential to the proper formation and functioning of the organ and a healthy pregnancy.[61] Mitochondria are the major intracellular source and primary target of ROS and, compared with nuclear DNA, mtDNA is more sensitive to oxidative stress due a lack of protective chromatin structure, histones and introns and less efficient repair mechanisms.[62,63] Oxidative stress therefore has the potential to have an adverse effect on placental mitochondria and in doing so impairs the ability of the placenta to support the growing fetus through energy-dependent processes such as active transport and hormone secretion. Estimates from one study indicated that a 10 microg/m^3 increment in average NO_2 exposure during pregnancy was associated with a 4.9% decrease in placental mtDNA content and a 48-g decrease in birthweight[59] (Table S1). However, other studies examining links between air pollution concentrations, markers of oxidative stress and an adverse birth outcome do not provide evidence that an increased oxidative burden with increased exposure during pregnancy is associated with preterm or negative indices of fetal growth.[52–54] Studies that have sought to evaluate the involvement of oxidative stress by examining whether the OP of $PM_{2.5}$ modifies the relation between $PM_{2.5}$ mass concentrations/exposures and adverse birth outcomes have reported mixed results, possibly indicative of different assays employed and birth outcomes evaluated[64,65] (Table S1). Studies focusing on gene–environment interactions in pregnant women suggest an interaction between exposure to air pollution during pregnancy and genetic polymorphisms in antioxidant genes that results in an increased risk of preterm delivery[66,67] (Table S1).

4.1.3 | Inflammation

Maternal inflammatory responses are modified to establish and maintain a viable pregnancy. Although the second trimester is a predominantly anti-inflammatory state, elevated inflammatory signals take place during implantation,[68] placentation[69] and in preparation for delivery.[70,71] It is possible therefore that the proinflammatory effects of air pollutants could disturb these delicate balances and in doing so elicit adverse birth outcomes. In this regard, PTB is generally regarded as a syndrome resulting from multiple causes including inflammation[72] through the early activation of cytokines such as interleukin (IL)-1β and tumour necrosis factor-α (TNF-α), which are otherwise part of the body's normal preparatory step for term deliveries.[73,74] Furthermore, inflammation may affect placental growth, development and function, which in turn can lead to FGR,[75] and cytokines can cross the placental barrier and interfere with fetal development.[76]

Studies investigating whether air pollution impacts the maternal-fetal inflammatory response, measuring intrauterine inflammation or biomarkers in maternal blood in early/mid-pregnancy and/or cord blood, have reported associations with ambient concentrations of PM[77–80] and O_3[77,80] (Table 1). Although concentrations of NO_2 have not been associated with a maternal inflammatory response, associations with higher cord blood CRP concentrations have been reported[77,78] (Table 1). Only one of these studies extended their analysis to look for associations between the maternal (but not cord blood) inflammatory biomarkers and birth outcomes[80] (Table S1). No associations were observed for birthweight, but elevated levels of maternal CRP were associated with modestly older gestational age at birth. As a result of the inflammatory response to pregnancy, maternal CRP levels increase slightly during standard pregnancies, generally peaking during the third trimester.[81,82] However, a greater increase in CRP levels has been reported in women whose pregnancies are complicated by FGR and preterm delivery.[83–85] Furthermore, elevated CRP levels in cord blood have been found in SGA neonates.[86]

$PM_{2.5}$ exposure in the first trimester or around mid-gestation is associated with an increase in maternal serum IL-1β, IL-6 and TNF-α.[87] PM_{10} exposure has also been positively associated with serum cytokines IL-6 but inversely associated with cervico-vaginal cytokine TNF-α.[88]

4.1.4 | Epigenetic alterations

High DNA synthesis rates and extensive epigenetic remodelling (e.g. methylation, demethylation and re-methylation) during embryogenesis[89,90] suggest that the fetal epigenome is a link between early life exposure to environmental factors and both adverse birth outcomes and later life events.[91–93] Epigenetic regulation of genes is also crucial in placental growth and functioning.[94] Modification, during a susceptible time window, of expression of genes involved in key placental cellular processes has the potential to contribute to abnormal placental and/or fetal development. Indeed, alterations in placental DNA methylation patterns and microRNA

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expression have been reported in association with fetal growth and adverse maternal exposures such as alcohol and tobacco smoke.[95,96]

Studies exploring whether prenatal exposure to air pollution is associated with epigenetic modifications and adverse birth outcomes have primarily focused on global DNA methylation or differential gene-specific methylation in placental tissue or maternal/cord blood at birth. Those that have examined global methylation or DNA methylation within LINE-1 repetitive elements (frequently used as surrogate markers for global methylation) have observed a lower degree of methylation in association with exposure to PM[97–99] and living close to a major roadway[100] (Table 1). Decreased DNA methylation has also been observed in the few studies that looked at associations with NO_2 and O_3.[101]

The finding of a lower degree of placental global DNA methylation in association with exposure to ambient PM in early pregnancy,[99] including the critical stages of implantation, is of interest considering that disturbance of maintenance DNA methylation in placental tissue is associated with abnormal embryonic development in the mouse model.[102] Moreover, LINE-1 down-regulation can induce an inflammatory response, potentially explaining the negative correlations that have been reported with PTB.[103] Studies focusing on locus-specific methylation (and importantly genes relevant to placental/fetal development) have found that prenatal exposure to particulate or gaseous pollutants is associated with altered DNA methylation of *HSD11B2* (glucocorticoid metabolism)[98] and *H19* (fetal growth)[104] (Table 1). The negative associations between LEP methylation status in the placenta and both $PM_{2.5}$ exposure and placental NTp, suggest that oxidative/nitrosative stress might contribute to associations between $PM_{2.5}$ and placental epigenetic events. Indeed, one mechanism by which air pollution exposure is thought to modify DNA methylation involves the reaction of ROS and RNS with DNA with subsequent strand breaks, base modification, and inter-strand and intra-strand crosslinks. Global hypomethylation ensues, owing to the inability of DNA methyltransferases to recognise the damaged DNA.[17]

However, little evidence exists that these epigenetic changes may be an underlying mechanism by which air pollution may adversely affect birth outcomes. The majority of studies have not extended their analysis to look at a mediating effect of disrupted DNA methylation patterns on the relation between air pollution exposure during pregnancy and adverse birth outcomes or have found no significant associations between an epigenetic modification and an adverse birth outcome (Table S1). Cai et al.,[98] however, reported that associations of PM_{10} exposure during early pregnancy with DNA methylation were more evident in FGR newborns than in normal newborns, and Vos et al.[105] reported a significant association between mitochondrial DNA methylation and birthweight.

4.1.5 | Endocrine disruption

A steady balance of thyroid hormones regulates metabolism and stimulates differentiation and growth of the fetus. During the first trimester the fetus depends on a maternal supply of thyroid hormones until the thyroid gland becomes fully functional at around 10–12 weeks of gestation.[106] Maternal hyper- and hypothyroidism are associated with increased risk of a LBW[107,108] and studies also suggest that fetal thyroid function is instrumental in regulating fetal growth.[109,110] A number of studies have suggested that the maternal[111–114] and fetal[111,115,116] thyroid glands may be susceptible to prenatal PM exposures. Findings from Janssen et al.[111] highlight the potential influence of $PM_{2.5}$ exposure on fetal thyroid function and fetal growth. Ambient $PM_{2.5}$ concentrations were inversely associated with cord blood thyroid stimulating hormone (TSH) and free thyroxine (FT4) concentrations and the free thyroxine/free triiodothyronine ratio (FT4/FT3) ratio and were positively associated with FT3 levels. Although neither FT3 nor TSH levels in maternal or cord blood were associated with birthweight, an 11% decrease in cord blood FT4 was associated with a 56-g decrease in mean birthweight (Table S1). Shields et al.[110] reported that in healthy pregnancies, placental weight was positively associated with cord blood FT4 levels and posited that thyroid hormones could influence fetal growth indirectly by affecting placental growth. These researchers also reported that lower FT4 levels in cord blood were associated with a lower birthweight. A role for oxidative stress in the disruption of thyroid function by PM is supported by findings of increased ROS concentrations in goitrous thyroid glands.[117]

An effect of maternal exposure to PM_{10} and NO_2 on placental development and function is supported by one study reporting associations with lower concentrations of placental growth factor (PlGF) and higher concentrations of soluble fms-like tyrosine kinase 1 (sFlt) in umbilical cord blood[42] (Table S1). Whereas PlGF is important for placental development and angiogenesis, sFlt-1 binds to this protein and thereby inhibits its activity.[118] The findings of van den Hooven et al.[42,78] are consistent with an anti-angiogenic state. PM_{10} and NO_2 exposures were not associated with placenta to birthweight ratio but were associated with lower placenta weight.

4.1.6 | Insights from metabolomic research

Metabolomic research is being increasingly used in maternal-fetal medicine to identify biological changes associated with fetal growth.[119] Examples include the analysis of maternal plasma and urine to identify metabolites predictive of small for gestational age babies and a PTB.[120–122] For studies investigating metabolic changes in response to environmental exposures, analysis of amniotic fluid, the placenta and cord blood would be particularly relevant as the sample

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contains the essential nutrients, hormones and immunological factors as well as potentially harmful xenobiotic metabolites to which the developing fetus is directly exposed. The use of metabolomics to identify altered biological pathways in the fetus in response to prenatal exposure to air pollution is a recent area of research.[123–125] It is noteworthy, however, that among the metabolomic features and pathways identified to date, are oxidative stress and inflammation, i.e. mechanisms already implicated using more traditional approaches.[124] A study by Laine et al.[125] assessing the effects of prenatal exposure to mixtures of air pollutants ($PM_{2.5}$, PM_{10}, NO_2, NO_x, ultrafine particles and OP of $PM_{2.5}$) on birthweight in a pooled birth cohort assessed mechanistic interactions between metabolomic signatures and targeted inflammatory proteins in cord blood pooled (Table S1). Exposure to three different mixture pollutant models was found to be negatively associated with birthweight. For example, increased concentrations of a $PM_{2.5}$, PM_{10} and NO_2 mix was estimated to result in an approximate 96-g decrease in birthweight. This relation was found to be mediated by inflammatory proteins (IL-17 and epidermal growth factor) and 665 metabolomic features, including several involved in fetal development and growth.

4.2 | Animal studies

While recognising that animal studies are less useful for understanding the underlying effects of air pollution on adverse birth outcomes in humans (e.g. owing to distinct differences in human and rodent placentas), experimental studies do have value, given that so much of the human mechanistic data is associative. Well-characterised exposures and the capacity for invasive procedures are strengths of animal inhalation experiments that facilitate the demonstration of biological plausibility for effects through various biological mechanisms. Studies in rodents investigating effects of maternal exposure to diesel exhaust (DE) or DE particles (≥300 microg PM/m^3 before and/or during gestation) have reported several effects on placentation including decreased vascularisation and perfusion,[126] injury in association with increased embryo resorption[127] and a reduction in cells responsible for structural integrity.[128] Pregestational and gestational exposure of mice to ambient air ($PM_{2.5}$: 27.5 microg/m^3; NO_2: 101 microg/m^3; CO: 1.81 microg/m^3; SO_2: 6.66 ppm) in exposure chambers placed in a location with high traffic density resulted in decreased fetal weights and changes in functional morphology of the placenta[129] and umbilical cord.[130] Exposure of rats before (5 times per week for 3 weeks) and/or during pregnancy (for 14 days) to concentrated $PM_{2.5}$ (600 microg/m^3 for 60 minutes) lowers placental concentrations of the angiogenic factors (vascular endothelial growth factor and its receptor fetal liver kinase 1).[131] A number of these changes were accompanied by an inflammatory response and oxidative stress.[127,128,130,132,133] Ozone exposure (0.4 or 0.8 ppm 4 h/day during implantation) led to changes in uterine arterial resistance and a lower offspring weight.[134,135]

4.3 | In vitro studies

A number of in vitro studies have been performed to explore mechanistic insights into how air pollution may affect placental structure and function. Most of these have been based on HTR-8/SVneo cells, a widely used first-trimester trophoblast cell line; this, however, has been shown to be a mix of trophoblast and mesenchymal cells.[136] Caution should therefore be exercised when extrapolating results based on these cells to the placenta. Nonetheless, culture of HTR-8/SVneo cells with either $PM_{2.5}$ or PM_{10} collected at sites of urban traffic showed uptake of particles into perinuclear endosomes within 30 minutes of exposure[137] and the mitochondria by 24 hours in association with vacuolation of organelles, dilation of endoplasmic reticulum cisternae and chromatin aggregation within the nucleus.[138] High doses of urban $PM_{2.5}$ or PM_{10} (5000 ng/mL) caused increased secretion of IL-6 and reduced secretion of human chorionic gonadotropin by 48 hours, whereas release of progesterone was either increased or not affected.[137,138] Proteomic analysis revealed 29 differentially expressed proteins consistent with the pattern observed in cases of FGR. Cell number was decreased after 7 days, due to increased cell death.[138] Overall, the findings suggest PM induced activation of stress pathways seen in the placenta in cases of FGR.[139] These results are consistent with findings of cytotoxicity and reduced proliferation of HTR-8/SVneo cells following exposure to $PM_{2.5}$, with cell cycle arrest at the G2/M phase.[140] In addition, a reduced mitochondrial membrane potential consistent with induction of apoptosis was demonstrated. Importantly for placentation, the invasive potential of the cells was significantly reduced due to increased expression of the migration inhibitors TIMP1 and TIMP2. Deficient, shallow trophoblast invasion is a unifying feature of many complications of pregnancy.[141]

5 | CONCLUSIONS

Epidemiological data provide varying degrees of evidence, albeit inconsistent at times, of associations between concentrations of ambient air pollutants during pregnancy and adverse birth outcomes. Overall, the effects of air pollution may represent a milder version of what has been reported for active maternal smoking, which is strongly linked to premature delivery and FGR.[13] Within this context, one of the main biases of large epidemiological studies is the lack of accurate data on both maternal active and passive smoking. Exposure to ambient air pollution and tobacco smoke during pregnancy is likely to have a cumulative effect on the incidence of PTB and SGA.

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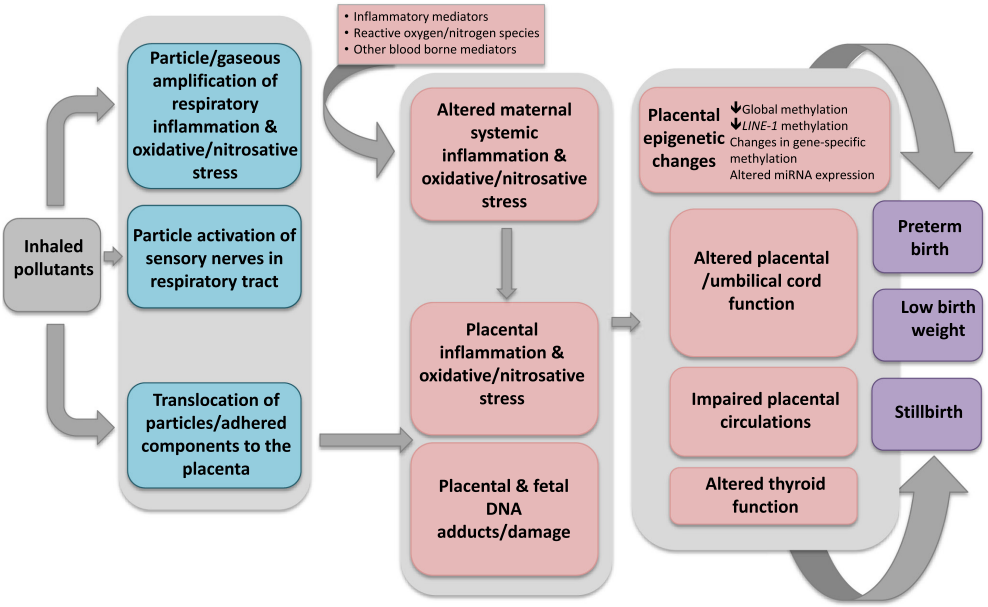

FIGURE 1 Experimental evidence indicates that the placenta is a target tissue following maternal exposure to ambient air pollutants during pregnancy. Progression of effects from left to right: grey = exposure; blue = initial effect; pink = intermediate effects; purple = clinical effect.

To assess further the certainty of effects stemming from poor ambient air quality, biological plausibility can be sought by identifying the mechanisms by which exposure to air pollution could cause adverse effects on the developing fetus. Although the underlying mechanistic pathways have not yet been elucidated, the current body of experimental evidence does lend biological plausibility, indicating that the placenta is a target tissue, impacted by a variety of critical processes including nitrosative/oxidative stress, inflammation, endocrine disruption, epigenetic changes, as well as vascular dysregulation of the maternal-fetal unit. All of the above can disturb placental function and, as a consequence, could contribute to compromised fetal growth as well increasing the risk of stillbirth (Figure 1). Furthermore, given that there is an increased inflammatory response during preterm delivery, inflammation is a plausible mechanism mediating the effects of air pollution on premature labour.

Caution should be used in the interpretation of the findings from the human mechanistic studies, partly owing to the associative nature of much of the evidence as well as some notable limitations. As not all studies linked concentrations of air pollutants and a given mechanistic endpoint with a clinical outcome, the relevance of experimental findings to the epidemiological evidence may be questioned. Furthermore, while there has been an emphasis on ambient PM, effects of gaseous pollutants have been under-researched. The potential for misclassification of exposure is also high, as the majority of the epidemiological studies with a nested mechanistic component use measures of air pollution exposure generated from regional monitoring stations and modelling methods. Such studies do not allow granular measurement of changing exposure when study participants travel to different (in/outdoor) microenvironments. It is important therefore that animal studies report adverse effects on placentation and fetal weight and are supportive of a contribution by oxidative and inflammatory pathways and that in vitro work suggests pollutants can induce activation of stress pathways seen in the placenta in cases of FGR. Future studies, however, should take into account the sex of the fetus, as mounting evidence indicates that the placenta responds differentially to stress in a sex-dependent fashion.[142]

In summary, the current body of experimental evidence demonstrates that ambient air pollutants potentially affect a variety of critical processes that may underpin adverse birth outcomes caused by poor air quality during pregnancy. In doing so, they begin to add support for causality of epidemiological associations. In the light of increased urbanisation and an ever-changing climate, both of which increase ambient air pollution and negatively affect vulnerable populations such as pregnant individuals, it hoped that the collective evidence may contribute to decisions taken to broaden air quality policies, reductions in exposure to air pollution and subsequent improvements in the health of those not yet born.

AUTHOR CONTRIBUTIONS

All authors contributed to the final article.

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CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS APPROVAL

Not applicable.

PATIENT AND PUBLIC INVOLVEMENT

Our study was a literature review and did not include patients as study participants. There was no public involvement in the design or interpretation of the data of this study.

ORCID

Julia C. Fussell https://orcid.org/0000-0002-0057-6654
Eric Jauniaux https://orcid.org/0000-0003-0925-7737
Rachel B. Smith https://orcid.org/0000-0003-4000-2919
Graham J. Burton https://orcid.org/0000-0001-8677-4143

REFERENCES

1. World Health Organization (WHO). Air pollution. 2023 [cited 18 July 2023]. Available from: https://www.who.int/health-topics/air-pollution-tab=tab_1
2. Thurston GD, Kipen H, Annesi-Maesano I, Balmes J, Brook RD, Cromar K, et al. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. Eur Respir J. 2017;49(1):1600419.
3. Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. Environ Int. 2017;100:1–31.
4. Jacquemin B, Siroux V, Sanchez M, Carsin A-E, Schikowski T, Adam M, et al. Ambient air pollution and adult asthma incidence in six European cohorts (ESCAPE). Environ Health Perspect. 2015;123(6):613–21.
5. Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Effect of outdoor air pollution on asthma exacerbations in children and adults: systematic review and multilevel meta-analysis. PLoS One. 2017;12(3):e0174050.
6. Joshi SS, Miller MR, Newby DE. Air pollution and cardiovascular disease: the Paul Wood Lecture, British Cardiovascular Society 2021. Heart. 2022;108:1267–73.
7. Yang BY, Fan S, Thiering E, Seissler J, Nowak D, Dong GH, et al. Ambient air pollution and diabetes: a systematic review and meta-analysis. Environ Res. 2020;180:108817.
8. Sunyer J, Suades-Gonzalez E, Garcia-Esteban R, Rivas I, Pujol J, Alvarez-Pedrerol M, et al. Traffic-related air pollution and attention in primary school children: short-term association. Epidemiology. 2017;28(2):181–9.
9. Committee on the Medical Effects of Air Pollutants (COMEAP). Air pollution: cognitive decline and dementia. A report by the Committee on the Medical Effects of Air Pollutants; 2022.
10. Klepac P, Locatelli I, Korosec S, Kunzli N, Kukec A. Ambient air pollution and pregnancy outcomes: a comprehensive review and identification of environmental public health challenges. Environ Res. 2018;167:144–59.
11. Li C, Yang M, Zhu Z, Sun S, Zhang Q, Cao J, et al. Maternal exposure to air pollution and the risk of low birthweight: a meta-analysis of cohort studies. Environ Res. 2020;190:109970.
12. Zhang H, Zhang X, Wang Q, Xu Y, Feng Y, Yu Z, et al. Ambient air pollution and stillbirth: an updated systematic review and meta-analysis of epidemiological studies. Environ Pollut. 2021;278:116752.
13. Jauniaux E, Burton GJ. Morphological and biological effects of maternal exposure to tobacco smoke on the feto-placental unit. Early Hum Dev. 2007;83(11):699–706.
14. Aycicek A, Varma M, Ahmet K, Abdurrahim K, Erel O. Maternal active or passive smoking causes oxidative stress in placental tissue. Eur J Pediatr. 2011;170(5):645–51.
15. Mozzoni P, Iodice S, Persico N, Ferrari L, Pinelli S, Corradi M, et al. Maternal air pollution exposure during the first trimester of pregnancy and markers of inflammation and endothelial dysfunction. Environ Res. 2022;212(Pt A):113216.
16. Hoch D, Majali-Martinez A, Bankoglu EE, Stopper H, Glasner A, Desoye G, et al. Maternal smoking in the first trimester and its consequence on the early placenta. Lab Invest. 2023;103(5):100059.
17. Saenen ND, Martens DS, Neven KY, Alfano R, Bove H, Janssen BG, et al. Air pollution-induced placental alterations: an interplay of oxidative stress, epigenetics, and the aging phenotype? Clin Epigenetics. 2019;11(1):124.
18. Nakamura A, François O, Lepeule J. Epigenetic alterations of maternal tobacco smoking during pregnancy: a narrative review. Int J Environ Res Public Health. 2021;18(10):5083.
19. Everson TM, Vives-Usano M, Seyve E, Cardenas A, Lacasaña M, Craig JM, et al. Placental DNA methylation signatures of maternal smoking during pregnancy and potential impacts on fetal growth. Nat Commun. 2021;12(1):5095.
20. Committee on the Medical Effects of Air Pollutants (COMEAP). COMEAP Work Program: list of topics; 2021.
21. EPA US. Integrated Science Assessment (ISA) for particulate matter. Washington, DC: U.S. Environmental Protection Agency; 2019.
22. EPA US. Integrated Science Assessment for oxides of nitrogen – health criteria. Washington, DC: U.S. Environmental Protection Agency; 2016.
23. EPA US. Integrated Science Assessment for ozone and related photochemical oxidants. Washington, DC: U. S. Environmental Protection Agency; 2020.
24. Ghosh R, Causey K, Burkart K, Wozniak S, Cohen A, Brauer M. Ambient and household PM2.5 pollution and adverse perinatal outcomes: a meta-regression and analysis of attributable global burden for 204 countries and territories. PLoS Med. 2021;18(9):e1003718.

14710528, 2024, 5, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.17727 by Imperial College London, Wiley Online Library on [12/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

25. Gong C, Wang J, Bai Z, Rich DQ, Zhang Y. Maternal exposure to ambient PM(2.5) and term birthweight: a systematic review and meta-analysis of effect estimates. Sci Total Environ. 2022;807(Pt 1):150744.
26. Ju L, Li C, Yang M, Sun S, Zhang Q, Cao J, et al. Maternal air pollution exposure increases the risk of preterm birth: evidence from the meta-analysis of cohort studies. Environ Res. 2021;202:111654.
27. Rappazzo KM, Nichols JL, Byron Rice R, Luben TJ. Ozone exposure during early pregnancy and preterm birth: a systematic review and meta-analysis. Environ Res. 2021;198:111317.
28. HEI (Health Effects Institute). Systematic review and meta-analysis of selected health effects of long-term exposure to traffic-related air pollution. Boston, MA: Health Effects Institute; 2022.
29. Kelly FJ, Fussell JC. Linking ambient particulate matter pollution effects with oxidative biology and immune responses. Ann N Y Acad Sci. 2015;1340:84–94.
30. Pourazar J, Mudway IS, Samet JM, Helleday R, Blomberg A, Wilson SJ, et al. Diesel exhaust activates redox-sensitive transcription factors and kinases in human airways. Am J Physiol Lung Cell Mol Physiol. 2005;289(5):L724–30.
31. Mudway IS, Kelly FJ, Holgate ST. Oxidative stress in air pollution research. Free Radic Biol Med. 2020;151:2–6.
32. Kelly FJ, Tetley TD. Nitrogen dioxide depletes uric acid and ascorbic but not glutathione from lung lining fluid. Biochem J. 1997;325:95–9.
33. Kelly FJ, Mudway IS. Particle-mediated extracellular oxidative stress in the lung. In: Donaldson K, Borm PJA, editors. Particle toxicity. Boca Raton, MA: CRC Press, Taylor Francis Group; 2007. p. 100.
34. Bongaerts E, Lecante LL, Bové H, Roeffaers MBJ, Ameloot M, Fowler PA, et al. Maternal exposure to ambient black carbon particles and their presence in maternal and fetal circulation and organs: an analysis of two independent population-based observational studies. Lancet Planet Health. 2022;6(10):e804–11.
35. Decrue F, Townsend R, Miller MR, Newby DE, Reynolds RM. Ambient air pollution and maternal cardiovascular health in pregnancy. Heart. 2023;109:1586–93.
36. Miller MR, Newby DE. Air pollution and cardiovascular disease: car sick. Cardiovasc Res. 2019;116:279–94.
37. Boeldt DS, Bird IM. Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. J Endocrinol. 2017;232(1):R27–44.
38. Carvalho MA, Bernardes LS, Hettfleisch K, Pastro LD, Vieira SE, Saldiva SR, et al. Associations of maternal personal exposure to air pollution on fetal weight and fetoplacental Doppler: a prospective cohort study. Reprod Toxicol. 2016;62:9–17.
39. Contreras ZA, Heck JE, Lee PC, Cui X, Hobel CJ, Janzen C, et al. Prenatal air pollution exposure, smoking, and uterine vascular resistance. Environ Epidemiol. 2018;2(3):e017.
40. Hettfleisch K, Bernardes LS, Carvalho MA, Pastro LD, Vieira SE, Saldiva SR, et al. Short-term exposure to urban air pollution and influences on placental vascularization indexes. Environ Health Perspect. 2017;125:753–9.
41. Ouidir M, Tekola-Ayele F, Canty T, Grantz KL, Sciscione A, Tong D, et al. Acute ambient air pollution exposure and placental Doppler results in the NICHD fetal growth studies – singleton cohort. Environ Res. 2021;202:111728.
42. van den Hooven EH, Pierik FH, de Kluizenaar Y, Hofman A, van Ratingen SW, Zandveld PY, et al. Air pollution exposure and markers of placental growth and function: the generation R study. Environ Health Perspect. 2012;120(12):1753–9.
43. Cahuana-Bartra MJ, Mazarico-Gallego E, Cahuana-Bartra AJ, Pascal R, Alonso-Garcia L, Targa J, et al. Maternal short-term exposure to NO(2) during pregnancy and its relationship with Doppler markers of placental function. Environ Res. 2022;214(Pt 1):113813.
44. Burton GJ, Jauniaux E. Placentation in the human and higher primates. Adv Anat Embryol Cell Biol. 2021;234:223–54.
45. Burton GJ, Jauniaux E. The human placenta: new perspectives on its formation and function during early pregnancy. Proc Biol Sci. 2023;290(1997):20230191.
46. Burton GJ, Jauniaux E. Oxidative stress. Best Pract Res Clin Obstet Gynaecol. 2011;25(3):287–99.
47. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. Am J Obstet Gynecol. 2018;218(2s):S745–61.
48. Burton GJ, Cindrova-Davies T, Yung HW, Jauniaux E. Hypoxia and reproductive health: oxygen and development of the human placenta. Reproduction. 2021;161(1):F53–65.
49. Jauniaux E, Hempstock J, Greenwold N, Burton GJ. Trophoblastic oxidative stress in relation to temporal and regional differences in maternal placental blood flow in normal and abnormal early pregnancies. Am J Pathol. 2003;162(1):115–25.
50. Burton GJ, Fowden AL, Thornburg KL. Placental origins of chronic disease. Physiol Rev. 2016;96(4):1509–65.
51. Ambroz A, Vlkova V, Rossner P Jr, Rossnerova A, Svecova V, Milcova A, et al. Impact of air pollution on oxidative DNA damage and lipid peroxidation in mothers and their newborns. Int J Hyg Environ Health. 2016;219(6):545–56.
52. Rossner P Jr, Tabashidze N, Dostal M, Novakova Z, Chvatalova I, Spatova M, et al. Genetic, biochemical, and environmental factors associated with pregnancy outcomes in newborns from The Czech Republic. Environ Health Perspect. 2011;119(2):265–71.
53. Saenen ND, Vrijens K, Janssen BG, Madhloum N, Peusens M, Gyselaers W, et al. Placental Nitrosative stress and exposure to ambient air pollution during gestation: a population study. Am J Epidemiol. 2016;184(6):442–9.
54. Grevendonk L, Janssen BG, Vanpoucke C, Lefebvre W, Hoxha M, Bollati V, et al. Mitochondrial oxidative DNA damage and exposure to particulate air pollution in mother-newborn pairs. Environ Health. 2016;15:10.
55. Myatt L. Review: reactive oxygen and nitrogen species and functional adaptation of the placenta. Placenta. 2010;31:S66–9.
56. Brunst KJ, Sanchez-Guerra M, Chiu YM, Wilson A, Coull BA, Kloog I, et al. Prenatal particulate matter exposure and mitochondrial dysfunction at the maternal-fetal interface: effect modification by maternal lifetime trauma and child sex. Environ Int. 2018;112:49–58.
57. Rosa MJ, Just AC, Guerra MS, Kloog I, Hsu HL, Brennan KJ, et al. Identifying sensitive windows for prenatal particulate air pollution exposure and mitochondrial DNA content in cord blood. Environ Int. 2017;98:198–203.
58. Janssen BG, Munters E, Pieters N, Smeets K, Cox B, Cuypers A, et al. Placental mitochondrial DNA content and particulate air pollution during in utero life. Environ Health Perspect. 2012;120(9):1346–52.
59. Clemente DB, Casas M, Vilahur N, Begiristain H, Bustamante M, Carsin AE, et al. Prenatal ambient air pollution, placental mitochondrial DNA content, and birth weight in the INMA (Spain) and ENVIRONAGE (Belgium) birth cohorts. Environ Health Perspect. 2016;124(5):659–65.
60. Chistiakov DA, Sobenin IA, Revin VV, Orekhov AN, Bobryshev YV. Mitochondrial aging and age-related dysfunction of mitochondria. Biomed Res Int. 2014;2014:238463.
61. Bartho LA, O'Callaghan JL, Fisher JJ, Cuffe JSM, Kaitu'u-Lino TJ, Hannan NJ, et al. Analysis of mitochondrial regulatory transcripts in publicly available datasets with validation in placentae from preterm, post-term and fetal growth restriction pregnancies. Placenta. 2021;112:162–71.
62. Lee HC, Wei YH. Mitochondrial role in life and death of the cell. J Biomed Sci. 2000;7(1):2–15.
63. Payne BA, Wilson IJ, Yu-Wai-Man P, Coxhead J, Deehan D, Horvath R, et al. Universal heteroplasmy of human mitochondrial DNA. Hum Mol Genet. 2013;22(2):384–90.
64. Lavigne E, Burnett RT, Stieb DM, Evans GJ, Godri Pollitt KJ, Chen H, et al. Fine particulate air pollution and adverse birth outcomes: effect modification by regional nonvolatile oxidative potential. Environ Health Perspect. 2018;126(7):077012.
65. Borlaza LJS, Uzu G, Ouidir M, Lyon-Caen S, Marsal A, Weber S, et al. Personal exposure to PM2.5 oxidative potential and its

14710528, 2024, 5, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.17727 by Imperial College London, Wiley Online Library on [12/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

association to birth outcomes. J Expo Sci Environ Epidemiol. 2022;33:416–26.
66. Suh YJ, Ha EH, Park H, Kim YJ, Kim H, Hong YC. GSTM1 polymorphism along with PM10 exposure contributes to the risk of preterm delivery. Mutat Res. 2008;656(1–2):62–7.
67. Zhao N, Wu W, Feng Y, Yang F, Han T, Guo M, et al. Polymorphisms in oxidative stress, metabolic detoxification, and immune function genes, maternal exposure to ambient air pollution, and risk of preterm birth in Taiyuan, China. Environ Res. 2021;194:110659.
68. Mor G, Aldo P, Alvero AB. The unique immunological and microbial aspects of pregnancy. Nat Rev Immunol. 2017;17(8):469–82.
69. Brown MB, von Chamier M, Allam AB, Reyes L. M1/M2 macrophage polarity in normal and complicated pregnancy. Front Immunol. 2014;5:606.
70. Palm M, Axelsson O, Wernroth L, Larsson A, Basu S. Involvement of inflammation in normal pregnancy. Acta Obstet Gynecol Scand. 2013;92(5):601–5.
71. Dubicke A, Fransson E, Centini G, Andersson E, Byström B, Malmström A, et al. Pro-inflammatory and anti-inflammatory cytokines in human preterm and term cervical ripening. J Reprod Immunol. 2010;84(2):176–85.
72. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75–84.
73. Engel SA, Erichsen HC, Savitz DA, Thorp J, Chanock SJ, Olshan AF. Risk of spontaneous preterm birth is associated with common proinflammatory cytokine polymorphisms. Epidemiology. 2005;16(4):469–77.
74. Keelan JA, Blumenstein M, Helliwell RJ, Sato TA, Marvin KW, Mitchell MD. Cytokines, prostaglandins and parturition—a review. Placenta. 2003;24(Suppl A):S33–46.
75. Williams MC, O'Brien WF, Nelson RN, Spellacy WN. Histologic chorioamnionitis is associated with fetal growth restriction in term and preterm infants. Am J Obstet Gynecol. 2000;183(5):1094–9.
76. Jonakait GM. The effects of maternal inflammation on neuronal development: possible mechanisms. Int J Dev Neurosci. 2007;25(7):415–25.
77. Lee PC, Talbott EO, Roberts JM, Catov JM, Sharma RK, Ritz B. Particulate air pollution exposure and C-reactive protein during early pregnancy. Epidemiology. 2011;22(4):524–31.
78. van den Hooven EH, de Kluizenaar Y, Pierik FH, Hofman A, van Ratingen SW, Zandveld PY, et al. Chronic air pollution exposure during pregnancy and maternal and fetal C-reactive protein levels: the generation R study. Environ Health Perspect. 2012;120(5):746–51.
79. Nachman RM, Mao G, Zhang X, Hong X, Chen Z, Soria CS, et al. Intrauterine inflammation and maternal exposure to ambient PM2.5 during preconception and specific periods of pregnancy: the Boston birth cohort. Environ Health Perspect. 2016;124(10):1608–15.
80. Friedman C, Dabelea D, Thomas DSK, Peel JL, Adgate JL, Magzamen S, et al. Exposure to ambient air pollution during pregnancy and inflammatory biomarkers in maternal and umbilical cord blood: the Healthy Start study. Environ Res. 2021;197:111165.
81. Thornton CA. Immunology of pregnancy. Proc Nutr Soc. 2010;69(3):357–65.
82. von Versen-Hoeynck FM, Hubel CA, Gallaher MJ, Gammill HS, Powers RW. Plasma levels of inflammatory markers neopterin, sialic acid, and C-reactive protein in pregnancy and preeclampsia. Am J Hypertens. 2009;22(6):687–92.
83. Guven MA, Coskun A, Ertas IE, Aral M, Zencirci B, Oksuz H. Association of maternal serum CRP, IL-6, TNF-alpha, homocysteine, folic acid and vitamin B12 levels with the severity of preeclampsia and fetal birthweight. Hypertens Pregnancy. 2009;28(2):190–200.
84. Pitiphat W, Gillman MW, Joshipura KJ, Williams PL, Douglass CW, Rich-Edwards JW. Plasma C-reactive protein in early pregnancy and preterm delivery. Am J Epidemiol. 2005;162(11):1108–13.
85. Tjoa ML, van Vugt JM, Go AT, Blankenstein MA, Oudejans CB, van Wijk IJ. Elevated C-reactive protein levels during first trimester of pregnancy are indicative of preeclampsia and intrauterine growth restriction. J Reprod Immunol. 2003;59(1):29–37.
86. Trevisanuto D, Doglioni N, Altinier S, Zaninotto M, Plebani M, Zanardo V. High-sensitivity C-reactive protein in umbilical cord of small-for-gestational-age neonates. Neonatology. 2007;91(3):186–9.
87. Volk HE, Park B, Hollingue C, Jones KL, Ashwood P, Windham GC, et al. Maternal immune response and air pollution exposure during pregnancy: insights from the Early Markers for Autism (EMA) study. J Neurodev Disord. 2020;12(1):42.
88. Buxton MA, Meraz-Cruz N, Sanchez BN, Gronlund CJ, Foxman B, Vadillo-Ortega F, et al. Air pollution and inflammation: findings from concurrent repeated measures of systemic and reproductive tract cytokines during term pregnancy in Mexico City. Sci Total Environ. 2019;681:235–41.
89. Chaillet JR, Vogt TF, Beier DR, Leder P. Parental-specific methylation of an imprinted transgene is established during gametogenesis and progressively changes during embryogenesis. Cell. 1991;66(1):77–83.
90. Hochberg Z, Feil R, Constancia M, Fraga M, Junien C, Carel JC, et al. Child health, developmental plasticity, and epigenetic programming. Endocr Rev. 2011;32(2):159–224.
91. Odom LN, Taylor HS. Environmental induction of the fetal epigenome. Expert Rev Obstet Gynecol. 2010;5(6):657–64.
92. Perera F, Herbstman J. Prenatal environmental exposures, epigenetics, and disease. Reprod Toxicol. 2011;31(3):363–73.
93. Szyf M. Early life, the epigenome and human health. Acta Paediatr. 2009;98(7):1082–4.
94. Nelissen EC, van Montfoort AP, Dumoulin JC, Evers JL. Epigenetics and the placenta. Hum Reprod Update. 2011;17(3):397–417.
95. Maccani MA, Avissar-Whiting M, Banister CE, McGonnigal B, Padbury JF, Marsit CJ. Maternal cigarette smoking during pregnancy is associated with downregulation of miR-16, miR-21, and miR-146a in the placenta. Epigenetics. 2010;5(7):583–9.
96. Wilhelm-Benartzi CS, Houseman EA, Maccani MA, Poage GM, Koestler DC, Langevin SM, et al. In utero exposures, infant growth, and DNA methylation of repetitive elements and developmentally related genes in human placenta. Environ Health Perspect. 2012;120(2):296–302.
97. Liu X, Ye Y, Chen Y, Li X, Feng B, Cao G, et al. Effects of prenatal exposure to air particulate matter on the risk of preterm birth and roles of maternal and cord blood LINE-1 methylation: a birth cohort study in Guangzhou, China. Environ Int. 2019;133(Pt A):105177.
98. Cai J, Zhao Y, Liu P, Xia B, Zhu Q, Wang X, et al. Exposure to particulate air pollution during early pregnancy is associated with placental DNA methylation. Sci Total Environ. 2017;607–608:1103–8.
99. Janssen BG, Godderis L, Pieters N, Poels K, Kiciński M, Cuypers A, et al. Placental DNA hypomethylation in association with particulate air pollution in early life. Part Fibre Toxicol. 2013;10:22.
100. Kingsley SL, Eliot MN, Whitsel EA, Huang YT, Kelsey KT, Marsit CJ, et al. Maternal residential proximity to major roadways, birthweight, and placental DNA methylation. Environ Int. 2016;92–93:43–9.
101. Ladd-Acosta C, Feinberg JI, Brown SC, Lurmann FW, Croen LA, Hertz-Picciotto I, et al. Epigenetic marks of prenatal air pollution exposure found in multiple tissues relevant for child health. Environ Int. 2019;126:363–76.
102. Yin LJ, Zhang Y, Lv PP, He WH, Wu YT, Liu AX, et al. Insufficient maintenance DNA methylation is associated with abnormal embryonic development. BMC Med. 2012;10:26.
103. Burris HH, Rifas-Shiman SL, Baccarelli A, Tarantini L, Boeke CE, Kleinman K, et al. Associations of LINE-1 DNA methylation with preterm birth in a prospective cohort study. J Dev Orig Health Dis. 2012;3(3):173–81.
104. He T, Zhu J, Wang J, Ren X, Cheng G, Liu X, et al. Ambient air pollution, H19/DMR methylation in cord blood and newborn size: a pilot study in Zhengzhou City, China. Chemosphere. 2018;212:863–71.
105. Vos S, Nawrot TS, Martens DS, Byun H-M, Janssen BG. Mitochondrial DNA methylation in placental tissue: a proof of

14710528, 2024, 5, Downloaded from https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.17727 by Imperial College London, Wiley Online Library on [12/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

concept study by means of prenatal environmental stressors. Epigenetics. 2020;1–11:121–31.
106. Calvo RM, Jauniaux E, Gulbis B, Asunción M, Gervy C, Contempré B, et al. Fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development. J Clin Endocrinol Metab. 2002;87(4):1768–77.
107. Blazer S, Moreh-Waterman Y, Miller-Lotan R, Tamir A, Hochberg Z. Maternal hypothyroidism may affect fetal growth and neonatal thyroid function. Obstet Gynecol. 2003;102(2):232–41.
108. Millar LK, Wing DA, Leung AS, Koonings PP, Montoro MN, Mestman JH. Low birthweight and preeclampsia in pregnancies complicated by hyperthyroidism. Obstet Gynecol. 1994;84(6):946–9.
109. Medici M, Timmermans S, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VW, Hofman A, et al. Maternal thyroid hormone parameters during early pregnancy and birthweight: the generation R study. J Clin Endocrinol Metab. 2013;98(1):59–66.
110. Shields BM, Knight BA, Hill A, Hattersley AT, Vaidya B. Fetal thyroid hormone level at birth is associated with fetal growth. J Clin Endocrinol Metab. 2011;96(6):E934–8.
111. Janssen BG, Saenen ND, Roels HA, Madhloum N, Gyselaers W, Lefebvre W, et al. Fetal thyroid function, birth weight, and in utero exposure to fine particle air pollution: a birth cohort study. Environ Health Perspect. 2017;125(4):699–705.
112. Wang X, Liu C, Zhang M, Han Y, Aase H, Villanger GD, et al. Evaluation of maternal exposure to PM(2.5) and its components on maternal and neonatal thyroid function and birth weight: a cohort study. Thyroid. 2019;29(8):1147–57.
113. Ghassabian A, Pierotti L, Basterrechea M, Chatzi L, Estarlich M, Fernández-Somoano A, et al. Association of exposure to ambient air pollution with thyroid function during pregnancy. JAMA Netw Open. 2019;2(10):e1912902.
114. Ilias I, Kakoulidis I, Togias S, Stergiotis S, Michou A, Lekkou A, et al. Atmospheric pollution and thyroid function of pregnant women in Athens, Greece: a pilot study. Med Sci. 2020;8(2):19.
115. Howe CG, Eckel SP, Habre R, Girguis MS, Gao L, Lurmann FW, et al. Association of prenatal exposure to ambient and traffic-related air pollution with newborn thyroid function: findings from the Children's Health Study. JAMA Netw Open. 2018;1(5):e182172.
116. Irizar A, Txintxurreta A, Molinuevo A, Jimeno-Romero A, Anabitarte A, Álvarez JI, et al. Association between prenatal exposure to air pollutants and newborn thyroxine (T4) levels. Environ Res. 2021;197:111132.
117. Mutaku JF, Many MC, Colin I, Denef JF, van den Hove MF. Antigoitrogenic effect of combined supplementation with dl-alpha-tocopherol, ascorbic acid and beta-carotene and of dl-alpha-tocopherol alone in the rat. J Endocrinol. 1998;156(3):551–61.
118. Coolman M, Timmermans S, de Groot CJM, Russcher H, Lindemans J, Hofman A, et al. Angiogenic and fibrinolytic factors in blood during the first half of pregnancy and adverse pregnancy outcomes. J Obstet Gynecol. 2012;119(6):1190–200.
119. Govarts E, Nieuwenhuijsen M, Schoeters G, Ballester F, Bloemen K, de Boer M, et al. Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): a meta-analysis within 12 European birth cohorts. Environ Health Perspect. 2012;120(2):162–70.
120. Horgan RP, Broadhurst DI, Walsh SK, Dunn WB, Brown M, Roberts CT, et al. Metabolic profiling uncovers a phenotypic signature of small for gestational age in early pregnancy. J Proteome Res. 2011;10(8):3660–73.
121. Maitre L, Fthenou E, Athersuch T, Coen M, Toledano MB, Holmes E, et al. Urinary metabolic profiles in early pregnancy are associated with preterm birth and fetal growth restriction in the Rhea mother-child cohort study. BMC Med. 2014;12:110.
122. Maitre L, Villanueva CM, Lewis MR, Ibarluzea J, Santa-Marina L, Vrijheid M, et al. Maternal urinary metabolic signatures of fetal growth and associated clinical and environmental factors in the INMA study. BMC Med. 2016;14(1):177.
123. Robinson O, Keski-Rahkonen P, Chatzi L, Kogevinas M, Nawrot T, Pizzi C, et al. Cord blood metabolic signatures of birth weight: a population-based study. J Proteome Res. 2018;17(3):1235–47.
124. Yan Q, Liew Z, Uppal K, Cui X, Ling C, Heck JE, et al. Maternal serum metabolome and traffic-related air pollution exposure in pregnancy. Environ Int. 2019;130:104872.
125. Laine JE, Bodinier B, Robinson O, Plusquin M, Scalbert A, Keski-Rahkonen P, et al. Prenatal exposure to multiple air pollutants, mediating molecular mechanisms, and shifts in birthweight. Environ Sci Technol. 2020;54:14502–13.
126. Valentino SA, Tarrade A, Aioun J, Mourier E, Richard C, Dahirel M, et al. Maternal exposure to diluted diesel engine exhaust alters placental function and induces intergenerational effects in rabbits. Part Fibre Toxicol. 2016;13(1):39.
127. Weldy CS, Liu Y, Liggitt HD, Chin MT. In utero exposure to diesel exhaust air pollution promotes adverse intrauterine conditions, resulting in weight gain, altered blood pressure, and increased susceptibility to heart failure in adult mice. PLoS One. 2014;9(2):e88582.
128. Tosevska A, Ghosh S, Ganguly A, Cappelletti M, Kallapur SG, Pellegrini M, et al. Integrated analysis of an in vivo model of intra-nasal exposure to instilled air pollutants reveals cell-type specific responses in the placenta. Sci Rep. 2022;12(1):8438.
129. Veras MM, Damaceno-Rodrigues NR, Caldini EG, Maciel Ribeiro AA, Mayhew TM, Saldiva PH, et al. Particulate urban air pollution affects the functional morphology of mouse placenta. Biol Reprod. 2008;79(3):578–84.
130. Veras MM, Guimaraes-Silva RM, Caldini EG, Saldiva PH, Dolhnikoff M, Mayhew TM. The effects of particulate ambient air pollution on the murine umbilical cord and its vessels: a quantitative morphological and immunohistochemical study. Reprod Toxicol. 2012;34(4):598–606.
131. Soto SF, Melo JO, Marchesi GD, Lopes KL, Veras MM, Oliveira IB, et al. Exposure to fine particulate matter in the air alters placental structure and the renin-angiotensin system. PLoS One. 2017;12(8):e0183314.
132. de Melo JO, Soto SF, Katayama IA, Wenceslau CF, Pires AG, Veras MM, et al. Inhalation of fine particulate matter during pregnancy increased IL-4 cytokine levels in the fetal portion of the placenta. Toxicol Lett. 2015;232(2):475–80.
133. Fujimoto A, Tsukue N, Watanabe M, Sugawara I, Yanagisawa R, Takano H, et al. Diesel exhaust affects immunological action in the placentas of mice. Environ Toxicol. 2005;20(4):431–40.
134. Miller CN, Dye JA, Ledbetter AD, Schladweiler MC, Richards JH, Snow SJ, et al. Uterine artery flow and offspring growth in long-Evans rats following maternal exposure to ozone during implantation. Environ Health Perspect. 2017;125(12):127005.
135. Miller CN, Kodavanti UP, Stewart EJ, Schladweiler MC, Richards JH, Snow SJ, et al. Fetal growth outcomes following peri-implantation exposure of Long-Evans rats to noise and ozone differ by sex. Biol Sex Differ. 2019;10(1):54.
136. Abou-Kheir W, Barrak J, Hadadeh O, Daoud G. HTR-8/SVneo cell line contains a mixed population of cells. Placenta. 2017;50:1–7.
137. Familari M, Nääv Å, Erlandsson L, de Iongh RU, Isaxon C, Strandberg B, et al. Exposure of trophoblast cells to fine particulate matter air pollution leads to growth inhibition, inflammation and ER stress. PLoS One. 2019;14(7):e0218799.
138. Nääv Å, Erlandsson L, Isaxon C, Åsander Frostner E, Ehinger J, Sporre MK, et al. Urban PM2.5 induces cellular toxicity, hormone dysregulation, oxidative damage, inflammation, and mitochondrial interference in the HRT8 trophoblast cell line. Front Endocrinol. 2020;11:75.
139. Burton GJ, Yung HW, Cindrova-Davies T, Charnock-Jones DS. Placental endoplasmic reticulum stress and oxidative stress in the pathophysiology of unexplained intrauterine growth restriction and early onset preeclampsia. Placenta. 2009;30:S43–8.
140. Qin Z, Hou H, Fu F, Wu J, Han B, Yang W, et al. Fine particulate matter exposure induces cell cycle arrest and inhibits migration and invasion of human extravillous trophoblast, as determined by an iTRAQ-based quantitative proteomics strategy. Reprod Toxicol. 2017;74:10–22.

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141. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol. 2011;204(3):193–201.
142. Kalisch-Smith JI, Simmons DG, Dickinson H, Moritz KM. Review: sexual dimorphism in the formation, function and adaptation of the placenta. Placenta. 2017;54:10–6.

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