

REVIEW ARTICLE

The fetal exposome and pregnancy outcomes: A multi-omics perspective

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Abstract

The fetal exposome is defined as all prenatal environmental, nutritional, lifestyle, psychosocial, and endogenous exposures. These exposures alter placental function and fetal programming and are increasingly recognized as important drivers of pregnancy outcomes and lifelong offspring health. Environmental factors, such as air pollution, endocrine-disrupting chemicals, heavy metals, nutritional imbalance, infections, and psychosocial stress, induce molecular changes through oxidative stress, inflammation, endocrine disruption, mitochondrial dysfunction, and epigenetic reprogramming. The use of multi-omics technologies, such as epigenomics, transcriptomics, proteomics, metabolomics, lipidomics, and microbiomics, has emerged recently and has provided comprehensive characterization of biological pathways connecting prenatal exposures to adverse outcomes. Exposure-based molecular signatures have been identified for preterm birth, preeclampsia, gestational diabetes mellitus, fetal growth restriction, and disrupted offspring neurodevelopmental and cardiometabolic health through integrative analyses. New techniques, including single-cell sequencing, spatial transcriptomics, artificial intelligence, and systems biology, are advancing understanding of mechanisms and the discovery of biomarkers. This review aims to provide a concise overview of the state of the science on the fetal exposome, its molecular mechanisms, and associations with pregnancy outcomes from a multi-omics perspective. It also discusses current challenges, including exposure assessment, data integration, and validation, and highlights future opportunities for precision obstetrics and personalized maternal-fetal care.

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1. Introduction

The fetal exposome is the sum of all environmental factors that affect the developing fetus, including chemical, biological, nutritional, and psychosocial factors that act during “critical windows” of fetal development and interact with endogenous biological systems.¹ The exposome approach differs from traditional exposure models that focus on discrete environmental exposures as they relate to specific developmental stages or

outcomes, and it takes a systems approach to exposures, assuming that exposures are interrelated and cumulative, affecting developmental trajectories and long-term health outcomes.

Pregnancy is a special physiological period characterized by numerous metabolic, endocrine, vascular, and immunological changes in the mother that are necessary for fetal growth.² Environmental exposures, such as air pollutants, endocrine-disrupting chemicals, heavy metals, maternal nutritional imbalance, smoking, and psychosocial stress, can alter fetal development at a molecular level across multiple biological systems. These exposures are now known to be associated with adverse pregnancy outcomes, such as preterm birth, preeclampsia, gestational diabetes mellitus, fetal growth restriction, and future cardiometabolic and neurodevelopmental disorders in children.³ The placenta serves as a key mediator of maternal–fetal exchanges and an important conduit for translating environmental exposures into fetal biological responses. Recent advances in placental biology reveal that environmental toxicants can alter epigenetic regulation, transcriptomic signaling, immune pathways, and metabolic homeostasis, thereby disrupting fetal programming.⁴ These molecular disruptions can persist for a lifetime and play a role in the developmental origins of health and disease hypothesis, which posits that prenatal environments influence disease susceptibility throughout life.

The advent of multi-omics technologies has revolutionized the study of the fetal exposome by allowing integrative analyses of genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics.⁵ These methods provide a mechanistic understanding of the effects of environmental exposures on complex molecular networks (as opposed to individual molecules). For example, the Human Early-Life Exposome (HELIX) project documented unique multi-omics signatures of prenatal exposure to air pollution, tobacco smoke, and persistent organic pollutants, with coordinated changes in DNA methylation, gene expression, and metabolomic pathways, linking these changes to environmental stressors. In addition to the HELIX project, multi-omics analyses (DNA methylation, transcriptomics, metabolomics, and proteomics) have shown coordinated biological responses to prenatal exposure to air pollution, heavy metals, and endocrine-disrupting chemicals. For example, changes in methylation of inflammatory genes could alter gene expression, which in turn could affect energy metabolism and genes involved in oxidative stress. These multi-level interactions offer a mechanistic understanding of the link between environmental exposures and adverse clinical outcomes.⁶ Multi-omics

integration is typically performed using network-based methods, which explore the connections between epigenetic changes associated with exposure and downstream changes in transcription, protein levels, and metabolism. Regulation of gene expression via DNA methylation can affect protein levels and metabolite production. Integrative bioinformatics platforms can be used to identify causal pathways and key molecular hubs that contribute to disease development. Additionally, the resolution with which maternal–placental–fetal interactions can be studied is increasing due to the advancement of technology, such as single-cell sequencing, spatial transcriptomics, and artificial intelligence (AI)-assisted bioinformatics. These innovations are driving the shift toward precision obstetrics, with the potential of multi-omics biomarkers to predict and act early on adverse pregnancy outcomes.⁷ This review examines the fetal exposome using a multi-omics approach, focusing on pathways and mechanisms underlying fetal exposures, pregnancy complications, and later offspring health. The conceptual framework of the fetal exposome and maternal–placental–fetal interactions is illustrated in [Figure 1](#).

2. Components of the fetal exposome

The fetal exposome is the totality of the environment and endogenous exposures the fetus experiences during gestation. It is generally divided into the external exposome (environmental/exposome related to lifestyle) and the internal exposome (biological response to the external exposome within the maternal, placental, and fetal systems).⁵ All of these are linked and induce molecular changes that could affect fetal programming, potentially leading to poor pregnancy outcomes and long-term chronic diseases in the infant.

2.1. External exposome

Physical, chemical, nutritional, and psychosocial exposures during pregnancy constitute the external fetal exposome. Of these, air pollution has become one of the most-studied environmental risk factors for the developing fetus. High exposure to particulate matter (PM_{2.5}), nitrogen dioxide (NO₂), and traffic-related pollutants has been linked to placental oxidative stress, inflammation, vascular disruption, and changes in fetal growth trajectories.⁸ Multi-omics investigations have also indicated that prenatal exposure to air pollution alters placental DNA methylation, lipid metabolism, and inflammatory transcriptomic pathways.⁹

Endocrine-disrupting chemicals, such as bisphenol A (BPA), phthalates, and persistent organic pollutants, are another large class of exposures. These compounds disrupt hormone signaling pathways essential to fetal development

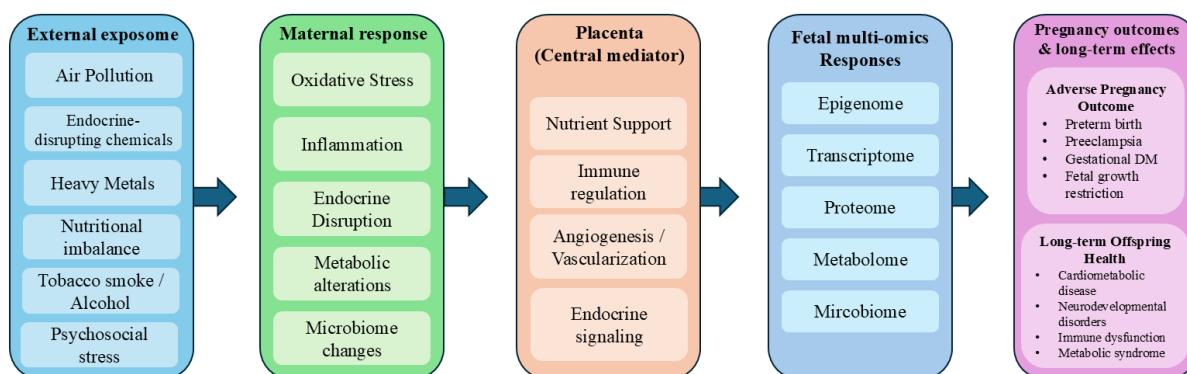


Figure 1. Overview of the fetal exposome and maternal-placental-fetal interactions
Abbreviation: DM: Diabetes mellitus

and placental function. Exposure to endocrine-disrupting chemicals during pregnancy has been associated with epigenetic dysregulation, modulation of fetal metabolic programming, and a higher risk of gestational diabetes mellitus and neurodevelopmental abnormalities.¹⁰ Other toxic elements of the prenatal exposome include lead, cadmium, mercury, and arsenic. These agents readily cross the placenta and contribute to mitochondrial dysfunction, oxidative stress, and inflammation. Recent metabolomic research suggests that alterations in lipid oxidation and amino acid metabolism pathways induced by metal exposure during pregnancy are linked to fetal growth restriction and preterm birth.¹¹

Biological exposures, especially those of the mother during the fetal period, are now known to play an important role in the fetal exposome. Placental tissue can be directly infected by viruses, including cytomegalovirus, Zika virus, rubella virus, influenza virus, and SARS-CoV-2, or viruses can trigger maternal immune activation.¹² It may be associated with intrauterine growth restriction, preterm birth, long-term neurodevelopmental diseases, congenital anomalies, and disrupted placental function. Multi-omics analyses have revealed virus-induced changes in inflammatory, immune, epigenetic, and metabolic pathways at the maternal-fetal interface.

The fetal exposome is also highly influenced by maternal lifestyle. Placental nutrient transfer and fetal immune system maturation may be affected by nutritional imbalance, smoking, alcohol, drug, and medication exposure, and psychosocial stress. In particular, maternal stress has been linked to dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and inflammatory signaling pathways, which influence fetal neurodevelopment and immune maturation.¹³

Micro- and nanoplastics are significant environmental pollutants that may pose health risks to mothers and fetuses. In recent years, plastic particles have been found in the placenta, maternal blood, and cord blood. Experimental studies have indicated that exposure to micro- and nanoplastics causes oxidative stress, inflammation, endocrine disruption, mitochondrial dysfunction, and epigenetic changes. Multi-omics studies have also uncovered metabolic, transcriptomic, and immune pathway dysregulation that may be associated with early delivery, intrauterine growth retardation, and developmental defects. While the evidence is limited at this time, the fetal exposome is a growing part of the exposome that warrants further study, particularly regarding micro- and nanoplastics.¹⁴

2.2. Internal exposome

The internal exposome encompasses biological processes resulting from external exposures, such as oxidative stress, inflammation, metabolic changes, endocrine disruption, and microbiome-derived signaling. Endogenous responses are mechanistic intermediates that connect environmental insults to adverse pregnancy outcomes. Oxidative stress is a major component of the internal exposome and occurs when the production of reactive oxygen species (ROS) exceeds antioxidant defenses.¹⁵ Exposure to environmental pollutants and toxicants increases ROS production in the placenta, leading to mitochondrial dysfunction, endothelial damage, and reduced trophoblast invasion. At the same time, chronic low-grade inflammation with increased cytokine levels (e.g., interleukin [IL]-6, tumor necrosis factor-alpha [TNF- α]) is associated with placental dysfunction and vascular changes involved in preeclampsia and preterm birth.¹⁶

There is growing evidence that the maternal microbiome is an important internal exposome factor. Pregnancy-associated changes in microbial composition may affect various aspects of immunity, nutrient metabolism, and microbial metabolite production. Dysbiosis has been associated with inflammatory activation and excessive fetal metabolic programming via the gut–placenta axis.¹⁷

Collectively, external and internal exposome factors interact to produce molecular perturbations that influence fetal programming, pregnancy outcomes, and long-term offspring health. The major fetal exposome components, their biological effects, and associated pregnancy risks are summarized in Table 1.

3. Multi-omics platforms in fetal exposome research

Because of the complex nature of the fetal exposome, integrative analytical methods are needed to identify multiple molecular changes across several layers of the biological systems. Most studies that rely on a single biomarker are unable to capture the complexity of environmental exposures and biological systems in pregnancy.¹⁸ Multi-omics technologies offer a comprehensive picture of the effects of prenatal exposures on placental function, fetal development, and pregnancy outcomes via interconnected genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microbiomic pathways.

Understanding fetal developmental programming is a key element of understanding the effects of prenatal environmental exposures, a field in which genomics and

epigenomics play a central role. Genomic approaches help detect inherited susceptibility variants, whereas epigenomics assesses environmentally induced changes in gene expression that do not involve changes in the DNA sequence.¹⁹ DNA methylation is by far the most studied epigenetic mechanism in fetal exposome studies. Prenatal exposure to pollutants, endocrine-disrupting chemicals, and maternal stress has been linked to changes in placental cord blood methylation that affect genes related to immune regulation, metabolism, angiogenesis, and neurodevelopment. The HELIX project showed that several prenatal exposures produce specific DNA methylation patterns associated with inflammatory and metabolic pathways, indicating the cumulative biological effects of environmental exposures.⁶

In addition to DNA methylation, histone modifications and non-coding RNAs (e.g., microRNAs) play major roles in fetal programming. The placental microRNAs are particularly vulnerable to adverse exposures and may regulate trophoblast differentiation, vascular remodeling, and immune signaling. The environmentally induced epigenetic changes can persist into postnatal life, thus substantiating the developmental origins of health and disease hypothesis.²⁰ Transcriptomics is also a tool for extending knowledge of the molecular changes that occur upon exposure, in this case, changes in gene expression. Transcriptional networks in the placenta, critical for oxidative stress responses, cytokine signaling, nutrient transport, mitochondrial metabolism, and angiogenesis, can be affected by environmental toxicants.²¹ Studies of

Table 1. Components of the fetal exposome and associated molecular effects

Exposome component	Representative exposures	Principal molecular effects	Associated pregnancy risks
Air pollution	PM2.5, NO ₂ , traffic pollutants	Oxidative stress, inflammation, altered DNA methylation	PTB, FGR, preeclampsia
Endocrine-disrupting chemicals	BPA, phthalates, persistent organic pollutants	Hormonal disruption, epigenetic dysregulation	GDM, neurodevelopmental abnormalities
Heavy metals	Lead, cadmium, mercury, arsenic	Mitochondrial dysfunction, oxidative stress	PTB, FGR
Maternal nutrition imbalance	Undernutrition, overnutrition	Metabolic reprogramming, altered nutrient signaling	GDM, abnormal fetal growth
Tobacco smoke	Active/passive smoking	Placental hypoxia, inflammation	PTB, low birth weight
Psychosocial stress	Anxiety, chronic stress	HPA-axis dysregulation, inflammatory activation	PTB, neurodevelopmental effects
Oxidative stress (internal exposome)	ROS accumulation	DNA damage, endothelial dysfunction	Preeclampsia, FGR
Inflammation (internal exposome)	IL-6, TNF- α activation	Placental dysfunction, vascular injury	PTB, preeclampsia
Microbiome dysbiosis	Gut–placenta axis disruption	Altered immune and metabolic signaling	GDM, inflammatory complications

Abbreviations: BPA: Bisphenol A; FGR: Fetal growth restriction; GDM: Gestational diabetes mellitus; HPA: Hypothalamic–pituitary–adrenal; IL: Interleukin; PTB: Preterm birth; ROS: Reactive oxygen species; TNF- α : Tumor necrosis factor- α .

whole-genome RNA sequences from pregnancies exposed to air pollution and heavy metals have revealed changes in inflammatory and hypoxia-related pathways. Typical transcriptomic approaches, however, tend to obscure the cellular heterogeneity of placental tissues.

Recent developments in single-cell RNA sequencing have greatly enhanced the resolution of fetal exposome studies by enabling analysis of various cell types in the placenta and at the maternal–fetal interface.²² There are clear differences in responses among trophoblasts, endothelial cells, stromal cells, and immune populations to environmental exposure when examined at the single-cell level. These analyses can be further improved by preserving tissue architecture through spatial transcriptomics and by localizing molecular changes to specific regions of the placenta. These technologies are especially useful in comprehending disorders, including preeclampsia and fetal growth restriction, in which a localized failure of the placenta plays a major role in the pathogenesis of disease.²³

Proteomics and metabolomics provide functional insights into downstream biological effects resulting from environmental exposure. Proteomic profiling can detect inflammatory mediators, angiogenic proteins, oxidative stress markers, and immune regulators that are associated with exposure that may lead to placental dysfunction and poor pregnancy outcomes.²⁴ Metabolomics, especially, has become one of the most informative tools in exposomics, as metabolites are a direct reflection of the interaction between the environment and biological systems.

Exposure to pollutants and toxicants during pregnancy has been linked to changes in amino acid metabolism, lipid oxidation, mitochondrial function, and oxidative stress biomarkers. Exposure-specific metabolic fingerprints have been found in several metabolomic studies and are characteristic of preterm birth, gestational diabetes mellitus, and fetal growth restriction.²⁵ To assess lipid dysregulation in the placenta caused by environmental stressors, a specialized component of metabolomics, lipidomics, is increasingly used. These changes in phospholipid and fatty acid profiles could contribute to inflammation, endothelial dysfunction, and impaired placental nutrient transport.²⁶ The ability of metabolomics to respond rapidly to environmental perturbations also has great potential to discover early biomarkers and monitor pregnancy.

The maternal microbiome is also a key factor in research on the fetal exposome. Changes in the gut, vaginal, and placental microbial communities during pregnancy affect immune regulation, nutrient metabolism, and inflammatory signaling. Microbial dysbiosis may alter maternal–fetal communication via microbial metabolites

and immune mediators, as a result of environmental exposures such as diet, antibiotics, pollutants, and/or psychosocial stress.²⁷ Integrated microbiome–metabolome studies have indicated that metabolites produced by microbes (e.g., short-chain fatty acids and bile acid derivatives) may affect placental inflammation and fetal metabolic programming. Overall, these results help confirm the hypothesis of a gut–placenta axis from the mother's environment to the fetus's developmental outcomes.

Advanced computational techniques, such as multi-omics factor analysis (MOFA), similarity network fusion (SNF), weighted gene co-expression network analysis (WGCNA), Bayesian network modeling, and deep-learning architectures, are increasingly being employed to integrate heterogeneous datasets. These approaches enhance biomarker discovery, exposure classification, and prediction of adverse pregnancy outcomes. Recent advances in spatial multi-omics technologies have enabled the integration of transcriptomic, proteomic, and metabolomic data while retaining tissue architecture, enabling more precise mapping of exposure-associated molecular changes within the placenta.²⁸ At the same time, AI and machine learning algorithms are revolutionizing exposome research, connecting high-dimensional omics data with clinical and environmental data. Such computational tools could help predict adverse pregnancy outcomes at an early stage and aid in the formulation of precision obstetrics strategies based on a woman's exposure profile.

4. Mechanistic links between the fetal exposome and pregnancy outcomes

The effects of environmental exposures on fetal development are mediated by multiple interconnected molecular and cellular pathways that influence fetal programming, metabolic signaling, immune regulation, and placental homeostasis. As evidence from multi-omics studies accumulates, it is becoming clear that the fetal exposome exerts effects through interconnected pathways, causing coordinated changes across the epigenome, transcriptome, proteome, metabolome, and microbiome, leading to adverse pregnancy outcomes.²⁹ The major mechanistic pathways linking environmental exposures to placental dysfunction, molecular alterations, and adverse pregnancy outcomes are summarized in [Figure 2](#). Placental dysfunction is one of the key mechanisms whereby the fetal exposome contributes to pregnancy complications. The placenta is the primary mediator of nutrient, gas, endocrine, and immune signaling exchange between the maternal and fetal systems. Environmental contaminants,

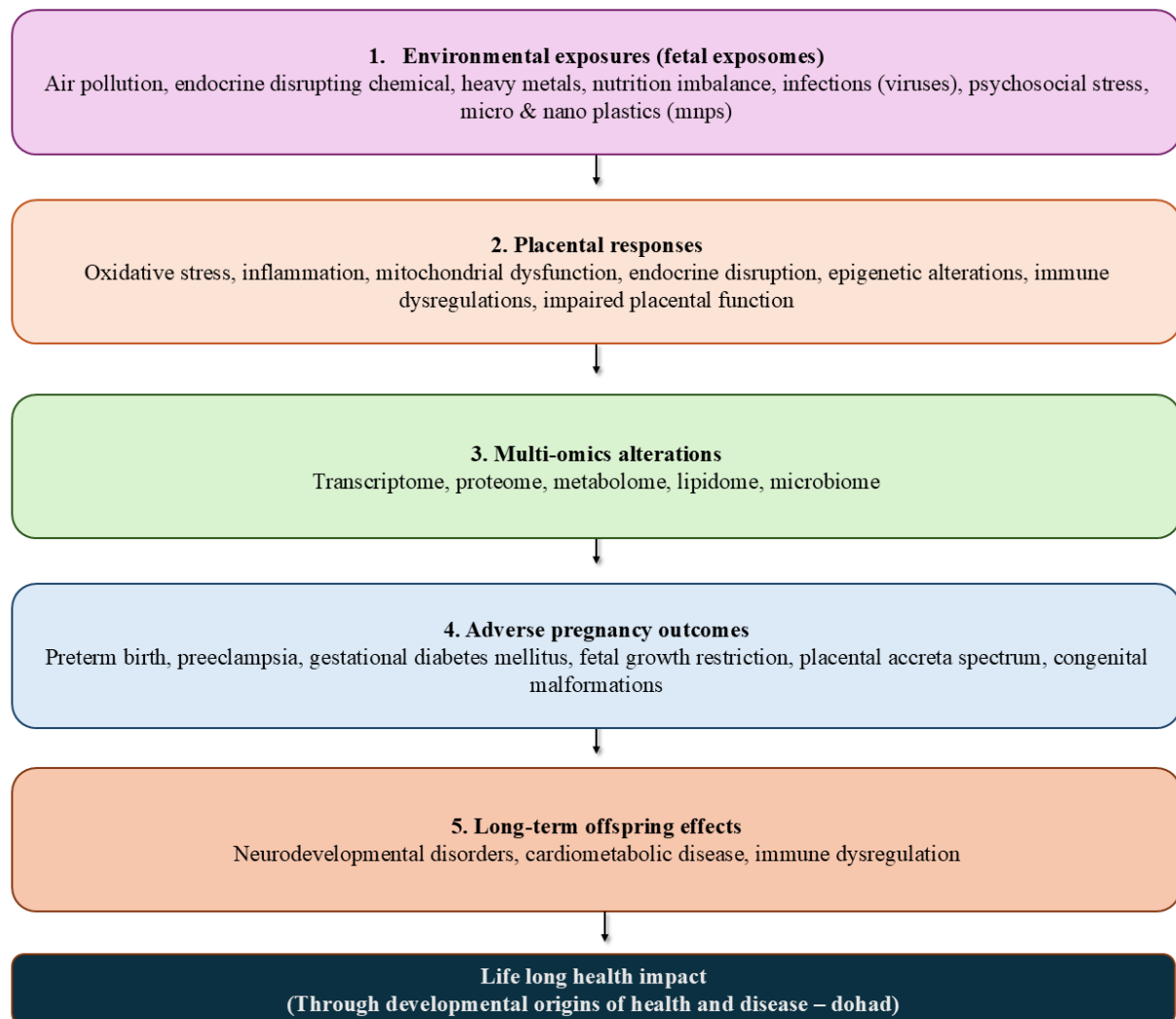


Figure 2. Mechanistic pathways linking the fetal exposome to adverse pregnancy outcomes

such as air pollutants, endocrine-disrupting chemicals, heavy metals, and tobacco-derived compounds, can disrupt placental vascularization, trophoblast invasion, and angiogenic signaling.³⁰ These changes affect the placenta's ability to provide the fetus with oxygen and nutrients, leading to hypoxic stress and underdevelopment. Placental multi-omics studies have identified pathways that are dysregulated in pregnancies with fetal growth restriction and preeclampsia, including inflammation, mitochondrial dysfunction, oxidative phosphorylation, and vascular remodeling.

Changes in nutrient transport systems and endocrine signaling are also linked to placental insufficiency.

Disruption of amino acid and glucose transporters in response to exposure can reduce their availability to the fetus, thereby influencing fetal growth trajectory and metabolic programming. Spatial transcriptomics analysis in more recent studies has also shown that environmental stressors cause region-specific alterations in the placental molecular landscape, including in trophoblast and endothelial cells involved in vascular adaptation and immune regulation.³¹ These results highlight the role of the placenta as an active bio-reporter of the prenatal environment. Oxidative stress is another major mechanism that contributes to pregnancy complications that the exposome can cause. Environmental pollutants and toxicants can increase the amount of ROS in

placental and fetal tissue to a level that exceeds the body's natural antioxidant capacity.³² High levels of ROS lead to mitochondrial dysfunction, lipid peroxidation, endothelial damage, and DNA damage. Pathological conditions such as preeclampsia, preterm delivery, and fetal growth restriction involve placental hypoxia and vascular abnormalities, emphasizing the significance of oxidative stress in these conditions.

Multi-omics studies have revealed extensive crosstalk between oxidative stress pathways and inflammatory signaling pathways. Particulate matter, heavy metals, and endocrine-disrupting chemicals have been known to activate inflammatory cytokines, such as IL-6 and TNF- α , and the nuclear factor kappa B (NF- κ B) pathway, leading to chronic low-grade inflammation at the maternal-fetal interface.³³ Chronic inflammatory activation impairs trophoblast differentiation and endothelial integrity, causing placental fibrosis and vascular damage. In addition to proteomic assays, metabolomic studies of pregnant women exposed to environmental toxicants also revealed changes in lipid oxidation products, inflammatory metabolites, and mitochondrial stress markers.¹¹

Another important mechanism that could account for the long-term biological effects of prenatal environmental exposures is epigenetic reprogramming. The epigenome is extensively remodeled during fetal development and is highly sensitive to environmental perturbations during this time. Exposures to the environment can alter DNA methylation, histone modifications, and non-coding RNA expression, thereby affecting gene expression profiles linked to immune regulation, neurodevelopment, metabolism, and endocrine signaling.³⁴ Importantly, such epigenetic changes can be transmitted across generations and have implications for lifelong susceptibility to disease, consistent with the developmental origins of health and disease hypothesis. Prenatal exposure to air pollution, maternal malnutrition, and endocrine-disrupting chemicals has been associated with epigenetic changes in offspring linked to obesity, insulin resistance, neurodevelopmental disorders, and cardiovascular disease, as shown in multi-omics studies.³⁵ Environmental conditions are potentially the most important factors affecting placental microRNAs and may regulate adaptive or maladaptive fetal responses by controlling angiogenesis, immune signaling, and metabolic pathways.

There is also growing evidence for immune-metabolic crosstalk, which plays a key role in mediating fetal exposome effects. During pregnancy, the delicate balance between maternal immune tolerance and metabolic adaptation must be maintained to support fetal development. This balance can be disrupted by environmental exposures

that simultaneously activate the immune system and induce metabolic dysfunction. A coordinated regulation of inflammatory signaling, lipid metabolism, amino acid pathways, and mitochondrial function was observed in preeclampsia, suggesting a tight interplay between immune and metabolic dysfunction.³⁶

Chronic inflammatory conditions, such as increased cytokine production, insulin resistance, and changes in lipid metabolism, can be induced by maternal obesity and pollutants such as endocrine-disrupting chemicals. Such metabolic changes can lead to endothelial dysfunction and placental inflammation, resulting in a higher risk of gestational diabetes mellitus and hypertension in pregnancy. Additionally, recent metabolomic and transcriptomic studies have shown that environmental exposures can disrupt nicotinamide metabolism, mitochondrial energetics, and redox signaling pathways associated with fetal growth and placental adaptation.³⁷

The maternal microbiome also plays a role in immune-metabolic regulation in the fetal exposome. Diet, pollutants, antibiotics, and stress can induce dysbiosis, altering microbial metabolite production, immune maturation, and inflammatory signaling. Combining microbiome and metabolome data via multi-omics analysis led to the hypothesis that microbiome-derived metabolites are linked to placental metabolic homeostasis and fetal metabolic programming, including via short-chain fatty acids.³⁸ The results provide evidence for the hypothesis that there is a gut-placenta axis through which interactions between environmental exposures and fetal development occur. Together, these mechanistic events show that the fetal exposome acts in a complex manner on the individual level, rather than as a single, discrete toxicological event. Thus, multi-omics technologies will play a key role in deciphering the complex interactions between prenatal environmental exposures, placental dysfunction, altered fetal programming, and adverse pregnancy outcomes.³⁹

5. Pregnancy outcomes associated with the fetal exposome

The fetal exposome is a significant factor in pregnancy health, affecting the health of fetuses both in the present and in their future lives. During pregnancy, environmental exposures can interfere with multiple molecular pathways involved in maintaining the normal function of the placenta, immune regulation, vascular adaptation, and metabolism.⁴⁰ Using multi-omics technologies, exposure-related epigenetic, transcriptomic, proteomic, metabolomic, and microbiomic changes associated with adverse pregnancy outcomes have been identified, greatly enhancing our understanding of these processes.

One of the most frequently mentioned effects of the fetal exposome is preterm birth. Higher risk of preterm birth has been strongly associated with prenatal exposure to air pollutants, tobacco smoke, heavy metals, and psychosocial stress.⁴¹ These exposures are mechanistically responsible for placental oxidative stress, inflammation, endothelial dysfunction, and earlier activation of pathways of parturition. Multi-omics analyses have revealed unique molecular signatures of pregnancies complicated by preterm birth, including dysregulated cytokine networks, mitochondrial dysfunction, altered lipid metabolism, and placental hypoxia-related pathways.⁴² Environmental pollutants, such as particulate matter and polycyclic aromatic hydrocarbons, may also affect trophoblast invasion and vascular remodeling, leading to reduced placental perfusion and an increased risk of premature labor.

Metabolomic profiling has also shown changes in amino acid metabolism, oxidative stress markers, and inflammatory metabolites in women at risk for preterm birth, indicating metabolic changes can occur before clinical signs of disease. Epigenetic analyses have suggested that in utero exposures cause methylation changes in genes involved with endocrine and inflammatory pathways linked to spontaneous preterm birth.⁴³ These results reinforce the concept that the fetal exposome can disrupt the function of pathways in the placenta and the immune system that are critical to normal gestation.

Preeclampsia, a hypertensive pregnancy complication, is another significant complication that is strongly linked to environmental exposures before conception. Preeclampsia involves placental insufficiency, endothelial dysfunction, and systemic maternal inflammation. Exposure to environmental toxicants, such as air pollution, endocrine-disrupting chemicals, and heavy metals, can facilitate the development of the disease by multiple mechanisms, including oxidative stress, abnormal angiogenesis, impaired mitochondrial function, and immune system dysfunction.⁴⁴ Recent multi-omics studies have shown coordinated changes in placental transcriptomic, epigenomic, and metabolomic pathways related to vascular remodeling, inflammatory signaling, and energy metabolism in preeclamptic pregnancies.

Epigenetic analyses of the placenta have also shown that environmental exposures alter the expression of DNA methylation and non-coding RNA related to trophoblast invasion and endothelial function. Spatial transcriptomics has revealed tissue-specific inflammatory and hypoxic responses in preeclamptic placentas. Changes in nicotinamide metabolism, oxidative stress pathways, and dysregulated lipids have been identified as metabolites

associated with disease severity and adverse outcomes for the mother and fetus through metabolomics and lipidomics profiling.⁴⁵ These results, taken together, provide a glimpse of the complexity of preeclampsia and the importance of applying multi-omics approaches to develop early predictive markers.

The fetal exposome plays an important role in the development of gestational diabetes mellitus. Endocrine-disrupting chemicals, obesogenic pollutants, dietary imbalance, and chronic psychosocial stress are factors that may disrupt glucose metabolism and insulin signaling during pregnancy. In multi-omics studies, changes in lipid metabolism, inflammatory pathways, amino acid composition, and the gut microbiome have been identified in pregnancies affected by gestational diabetes mellitus. Chronic low-grade inflammation and oxidative stress due to environmental factors could further contribute to insulin resistance and to the impairment of placental metabolic adaptation. Altered metabolites of branched-chain amino acids, fatty acid oxidation pathways, and oxidative stress are consistently identified in metabolomic analyses of women with gestational diabetes mellitus.⁴⁶

Lifestyle intervention is the mainstay of gestational diabetes mellitus prevention and management. Low-glycemic-index diets, adequate micronutrient intake, and appropriate proportions of macronutrients, coupled with regular moderate exercise, improve insulin sensitivity and glycemic control. Recent metabolomic studies have indicated that a tailored nutrition approach could dampen the effects of environmental exposures and enhance pregnancy outcomes.⁴⁷

Recently, gut dysbiosis in the mother has been identified as a potential source of inflammatory activation and metabolic dysfunction, driven by metabolites produced by gut microbes that affect the gut–placenta axis.⁴⁸ Integrative microbiome–metabolome analysis, therefore, provides significant insights into the interactions between environmental exposures and maternal metabolism during pregnancy.

Fetal growth restriction and low birth weight are critical outcomes of fetal environmental exposures. Exposure to heavy metals, air pollutants, and toxic chemicals, as well as maternal malnutrition, may disrupt the normal transport of nutrients to the fetus, vascularization, and oxygen exchange, resulting in impaired fetal growth. Placental tissue from fetal growth restriction pregnancies has been analyzed using multiple omics approaches, which have identified pathways related to angiogenesis, hypoxia, mitochondrial function, inflammatory signaling, and nutrient metabolism as being dysregulated.²³

Epigenetic changes in genes regulating growth may also contribute to abnormal fetal growth trajectories and long-term metabolic dysfunction. Placental transcriptomic analysis also shows differential gene expression associated with trophoblast development and vascular adaptation in pregnancies exposed to environmental factors and complicated by fetal growth restriction. The results support the hypothesis that placental dysfunction plays a pivotal role in the fetal exposome's effects on fetal development. In addition to immediate pregnancy complications, the fetal exposome has far-reaching implications for longer-term offspring health, with evidence emerging.¹ Epigenetic and metabolic changes that occur during pregnancy can be long-lasting and affect susceptibility to obesity, insulin resistance, cardiovascular diseases, neurodevelopmental disorders, and immune dysfunction later in life. The developmental origins of health and disease hypothesis is based on this concept.

In recent multi-omics studies, it has been shown that prenatal exposure to pollutants affects neurodevelopmental pathways, inflammatory signaling networks, and mitochondrial metabolism, which are linked to later cognitive and behavioral abnormalities.⁴⁹ Placental epigenetic changes due to exposure to toxicants have also been associated with risk for cardiometabolic disease and obesity in childhood. There is also emerging evidence that modifications in the placental secretome and extracellular vesicle communication could affect fetal metabolic programming and long-term health trajectories in offspring.⁵⁰ In summary, the fetal exposome is a source of a broad range of pregnancy conditions and outcomes, and the mechanisms by which it affects the body are interrelated. Therefore, multi-omics technologies offer a vital approach

to the discovery of mechanistic biomarkers, to enhance risk stratification, and to advance precision approaches in obstetrics focused on optimizing maternal and fetal health. Multi-omics studies have identified distinct molecular signatures linking environmental exposures with adverse pregnancy outcomes. A summary of the major pregnancy complications, associated exposures, and omics alterations is presented in [Table 2](#).

Recent reports have indicated that environmental exposures may play a role in abnormal placentation associated with placenta accreta spectrum. Exposure-induced dysregulation of trophoblast invasion, extracellular matrix remodeling, angiogenesis, and inflammatory signaling can disrupt normal decidualization and contribute to abnormal placental attachment. Multi-omics studies have identified changes in genes involved in cell adhesion, vascular remodeling, and immunity in placenta accreta spectrum tissue. In addition, chronic inflammation and oxidative stress caused by exposure to toxic chemicals from the environment can make women more vulnerable to abnormal placentation.⁵¹

Gene–environment interactions can influence fetal responses to environmental exposures through genetic susceptibility. Recent research has shown that inherited variants in pathways that regulate detoxification, oxidative stress, angiogenesis, and immune regulation can affect susceptibility to adverse pregnancy outcomes. In addition, assisted reproductive technologies have unique epigenetic and transcriptomic signatures in placental and fetal tissues. The integration of genomic information into exposome analyses could enhance understanding of personalized risk profiles and the underlying mechanisms of pregnancy complications.^{52,53}

Table 2. Multi-omics signatures associated with major pregnancy outcomes

Pregnancy outcome	Major environmental contributors	Key multi-omics alterations	Potential biomarkers
Preterm birth	Air pollution, smoking, heavy metals, stress	Inflammatory transcriptomes, mitochondrial dysfunction, altered lipid metabolism	Cytokines, oxidative stress metabolites
Preeclampsia	Air pollution, EDCs, heavy metals	Abnormal angiogenesis, oxidative stress pathways, altered DNA methylation	Angiogenic proteins, lipidomic markers
Gestational diabetes mellitus	EDCs, obesogenic pollutants, dietary imbalance	Altered amino acid metabolism, gut dysbiosis, inflammatory signaling	BCAAs, fatty acid metabolites
Fetal growth restriction	Heavy metals, air pollution, maternal malnutrition	Hypoxia signaling, mitochondrial dysfunction, impaired angiogenesis	Placental transcriptomic markers
Long-term offspring disorders	Multiple prenatal exposures	Persistent epigenetic modifications, metabolic reprogramming	DNA methylation signatures, microRNAs

Abbreviations: BCAA: Branched-chain amino acid; EDC: Endocrine-disrupting chemical.

6. Current challenges and limitations

While the development of exposomics and multi-omics technologies has made significant progress, some challenges remain that hinder the translation of fetal exposome research into clinical practice. The accurate assessment of prenatal environmental exposures is one of the main challenges. Exposome components are highly dynamic, whereas static genetic factors are not. Precise monitoring of maternal exposure over time is challenging because of exposure variability, driven by factors such as diet, lifestyle, environment, and physiological adaptation.⁵⁴ Another challenge is the heterogeneity and high dimensionality of multi-omics data. There is a need for sophisticated tools for integrating epigenomic, transcriptomic, proteomic, metabolomic, and microbiomic data and for developing robust bioinformatics pipelines. Variations in sample collection, sequencing platforms, analytical workflows, and statistical modeling of data may negatively affect reproducibility and make cross-study comparisons challenging.⁵⁵ In addition, most existing studies have small sample sizes, which limit statistical power and decrease the generalizability of the results to ethnically and geographically diverse groups.

In addition to spatial variability, temporal variability poses a major challenge in pregnancy studies. While molecular signatures can vary significantly across gestational stages, many studies rely on single-time-point sampling, which fails to account for the dynamic changes in biological systems during fetal development. However, longitudinal cohort studies are needed to establish causal relationships between environmental exposures and pregnancy outcomes, but they are costly, time-consuming, and logistically challenging to sustain.¹⁸ Another limitation is the biological interpretation of omics results. Multi-omics techniques produce vast amounts of molecular data, but it is difficult to determine which mechanisms are primary and which are secondary responses. Exposure-associated biomarkers detected in one population may not be reproducible in other independent populations because of differences in environmental conditions, genetic makeup, and socio-economic status.

Further challenges to fetal exposome studies have been raised from an ethical and practical standpoint. Access to placental and fetal tissue is limited, and multiple biological samplings throughout pregnancy may raise ethical concerns. Furthermore, long-term follow-up of offspring health outcomes is difficult due to participant attrition, data standardization, and resource allocation.⁵⁶ Fetal exposome studies have limitations, but with ongoing progress in longitudinal exposure monitoring, AI-driven bioinformatics, and standardized multi-omics approaches,

their accuracy and translatability are likely to improve.

7. Future perspectives and clinical translation

Combining exposomics with other omics technologies may drastically shift prenatal medicine and precision obstetrics. Future studies can be directed toward creating detailed exposure profiles along the pregnancy developmental trajectory that incorporate environmental monitoring, along with genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microbiomic data at various time points of pregnancy. These integrative strategies could help clarify the long-term effects of dynamic prenatal exposures on placental biology and fetal programming.⁵⁷

Additionally, the clinical application of fetal exposome studies is anticipated to improve with advances in AI and machine learning. High-dimensional omics data can be integrated using AI to identify predictive biomarkers that may detect pregnancy complications prior to their clinical manifestations.⁷ These technologies may contribute to early intervention of disorders such as preeclampsia, gestational diabetes mellitus, and preterm birth through individualized risk prediction models, thereby optimizing management of maternal health.

In addition to molecular markers, prenatal ultrasonography is still an important clinical tool for early detection of structural fetal abnormalities. Using ultrasound phenotyping in combination with multi-omics and exposome profiles could further improve the ability to predict risks and help detect congenital malformations and placental problems at an earlier stage.^{51,58}

Resolution of maternal-placental-fetal interactions is further enhanced by emerging technologies, such as spatial transcriptomics, single-cell multi-omics, and extracellular vesicle profiling.⁵⁹ Such innovations could help researchers identify new biomarkers in maternal blood and placental molecules without having to extract them from tissues. Further, integrating exposome science, personalized nutrition, and environmental risk-reduction strategies into microbiome-based therapies could help develop preventive prenatal care and improve future health outcomes for children.⁶⁰ The implementation of fetal exposome studies in clinical practice can support precision obstetrics by enabling tailored prevention, early diagnosis, and therapeutic intervention during pregnancy.

More work is needed in the future to identify clinically relevant biomarker panels from complex multi-omics data. If a small number of highly predictive biomarkers can be identified, they could be used to develop rapid, inexpensive screening assays useful for routine prenatal care and population-level implementation.

Functional validation remains a critical step in translating multi-omics discoveries into biological understanding. Placental organoids, trophoblast cell cultures, and placenta-on-a-chip platforms provide physiologically relevant experimental systems for validating exposure-associated molecular pathways and investigating causal mechanisms underlying adverse pregnancy outcomes.⁵⁹

8. Conclusion

The fetal exposome is a novel concept that integrates the multiple molecular and biological interactions through which environmental exposures shape fetal development during pregnancy, and it is recognized as a key factor in pregnancy health. Multi-omics technologies have made tremendous strides in understanding the impact of environmental stressors on placental function, immune regulation, metabolic pathways, and fetal programming that confer risk for adverse pregnancy outcomes. The interconnections among the mechanisms underlying preterm birth, preeclampsia, gestational diabetes mellitus, and fetal growth restriction have been discovered through integrative analyses across epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics.

The placenta has become a major player in the exposome, connecting maternal environmental exposures to fetal biological responses, highlighting its relevance for exposome research and biomarker discovery. In addition, emerging evidence suggests that prenatal environmental exposures contribute to offspring susceptibility to cardiometabolic, neurodevelopmental, and immune-related disorders later in life. While a number of challenges with exposure assessment, data integration, and longitudinal validation remain, advances in spatial multi-omics, AI, and precision medicine have been advancing and accelerating the translation of fetal exposome research into clinical obstetrics. In conclusion, incorporating exposomics into prenatal care could lead to better early risk identification, preventive measures, and tailored maternal–fetal care.

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Conflict of interest

The authors declare no competing interests.

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