RESEARCH PAPER

Toxicology of Maternal PFAS Exposure in Gestational Diabetes Mellitus: Mechanistic Links to Endocrine and Metabolic Dysregulation

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Abstract

Gestational Diabetes Mellitus (GDM): It is a pregnancy-related metabolic disorder that is characterized by the impairment of glucose regulation and insulin sensitivities. Although well-established traditional risk factors such as maternal age, body weight, dietary habits, and genetic backgrounds are well understood, there has been growing interest in identifying the significance of exposure to "environmental" factors that influence the development of associated metabolic states of pregnancies. Among these "environmental" factors are the per- and polyfluoroalkyl substances (PFAS), which are colloquially known as "forever chemicals". These are manufactured fluorinated chemicals that are widely used as industrial chemicals, consumer products, food packaging chemicals, cosmetic chemicals, and water treatment chemicals. Because of these chemicals' stability and non-biodegradable properties, they tend to persist in the environment and bioaccumulate within biological systems such as the maternal bloodstream, placenta, and umbilical cord-blood samples of pregnant women. A lot of evidence suggests that exposure to PFAS is known to affect the regulation of endocrine systems and the function of pancreatic β-cell activity, lipid metabolism pathways, oxidative stress responses, and inflammation. Moreover, its impact on insulin resistance development and glucose intolerance states is known to potentially contribute to the development of GDM. Aligning these biological principles are the longitudinal and case-controlled studies that found associations between higher exposure levels of these maternal PFAS chemicals such as PFOS, PFOA, PFHxS, and PFNA and the development of GDM and impaired glucose tolerance.

Keywords: PFAS; Gestational Diabetes Mellitus; Pregnancy Metabolism; Perfluoroalkyl Substances; Metabolic Dysfunction.

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1.Introduction

Gestational diabetes mellitus (GDM) is the prevalent metabolic complication of pregnancy, especially due to the progressive insulin resistance and glucose intolerance generally occurring in the second to third trimester of gestation(Kim et al. 2002). There is a substantial increase in the prevalence of GDM worldwide, and in cases of inappropriate diagnosis and management of the disease, it results in serious short- and long-term complications, including preeclampsia, fetal macrosomia, neonatal hypoglycemia, and increased lifetime predisposition of the mother as well as the offspring to type 2 diabetes mellitus(Bellamy et al. 2009). Even though established predisposing factors, including obesity, genetic predisposition, older maternal age, and other environmental factors, play a crucial role in the development of GDM, recent findings emphasize the role of the environment as another indispensable factor(Zhang et al. 2016).

Within the broader category of environmental factors, endocrine-disrupting chemicals (EDCs) are one of the increasing numbers of chemicals that exhibit persistence in the environment in addition to their capacity to interfere with physiological processes of hormone regulation and metabolism in animals and humans(Gore et al. 2015b). The per- and polyfluoroalkyl substances (PFAS) are one of the most recognized synthetic EDCs with widespread applications in various products such as food packaging, firefighting foam, non-stick pans, waterproof textiles, and personal hygiene products(Lau et al. 2007). The high resilience of PFAS in the environment, with their strong carbon and fluorine bonds, makes them persistent in nature and therefore qualify them to be referred to as "forever chemicals"(Kannan et al. 2004). Consequently, their increasing persistence in the environment makes them accumulate in various environmental samples such as soil, water, and food chains, culminating in their absorption in high quantities in the bloodstream in humans, which remains there for about several years(Olsen et al. 2007). The high prevalence of PFAS in a proportion of expectant mothers in various parts of the world has attracted health-related concerns(Grandjean and Clapp 2015a).

The accumulation of experimental and epidemiological evidence suggests a potential role of PFAS as metabolic disruptors because of interference with the endocrine pathways mediated by insulin regulation and the inflammatory pathways(Heindel and Blumberg 2019). The proposed mechanisms of action involve activation of peroxisome proliferator-activated receptors (PPARs), thyroid-related homeostasis pathways, modulation of oxidative stress levels, and the absence of normal placental function(Chen et al. 2025b). Due to the convergent mechanisms of action and the associated pathological pathways of GDM onset, a potential cause-and-effect relationship has been proposed. Several observational studies have demonstrated a positive correlation between higher exposure levels of maternal PFAS and the development of impaired glucose tolerance and gestational diabetes mellitus(Xu et al. 2020).

2. Gestational Diabetes Mellitus in the light of PFAS exposure

2.1 Overview of Gestational Diabetes Mellitus

GDM is a pregnancy-specific disorder characterized by abnormal glucose regulation that is first recognized during gestation. The condition most frequently manifests during the second or third trimester of gestation, at a time of maximal physiological insulin resistance(Kim et al. 2002; Bellamy et al. 2009). The global prevalence of GDM has increased markedly in recent decades-a trend attributed to rising rates of sedentary lifestyles, obesity, delayed maternal age at conception, and a growing burden of metabolic disorders(American Diabetes Association Professional Practice Committee et al. 2025; Zhang et al. 2016). Several factors related to mothers increase susceptibility to GDM, including advanced maternal age, a family history of diabetes, excessive weight gain during pregnancy, previous GDM, polycystic ovarian syndrome, and pre-existing metabolic abnormalities(Zhang et al. 2016).

In normal pregnancy, placental hormones stimulate insulin resistance to facilitate the supply of glucose to the growing fetus(Hotamisligil 2006; Kim et al. 2002). It exerts its effect on maternal peripheral tissues-skeletal muscle, liver, and adipose tissue-by reducing the sensitivity to insulin. When pancreatic β-cells fail to compensate through increased insulin secretion, maternal hyperglycaemia results, leading to the onset of GDM(Kim et al. 2002; Bellamy et al. 2009). This metabolic perturbation affects not only pregnancy outcome but also contributes to a long-term risk of health complications(Bellamy et al. 2009; American Diabetes Association Professional Practice Committee et al. 2025), including type 2 diabetes mellitus, metabolic syndrome, and cardiovascular disease in both the mother and the offspring.

2.2 Overview of Per- and Polyfluoroalkyl Substances (PFAS)

PFAS are a large family of man-made chemicals with very stable molecular structures that make it impossible for them to degrade easily in the environment(Lau et al. 2007; Grandjean and Clapp 2015b). These chemical compounds have found many applications in various products related to industry and consumers, including stain-resistant textiles, firefighting foams, food contact materials, non-stick cookware, waterproof coatings, and cosmetic products. Their great persistence is basically linked to very strong C-F bonds, which hardly allow the chemicals to undergo any breakdown through natural chemical, thermal, and biological processes(Lau et al. 2007).

Unlike most POPs, PFAS do not preferentially partition to adipose tissue. Instead, they bind extensively to serum proteins and distribute among soft tissues with high affinities for liver and kidneys(Olsen et al. 2007; Gaillard et al. 2025). The extensive persistence of PFAS in the human body due to their long biological half-lives allows them to remain in the human body many years even after exposure has stopped(Olsen et al. 2007). The concern about PFAS exposure has gained much attention as biomonitoring studies have all identified detectable concentrations of these chemicals in the blood of populations worldwide. PFAS have been classified as endocrine-disrupting chemicals based on evidence showing their ability to interfere with the signalling of steroid hormones, metabolic regulation, and intracellular cell signalling pathways(Gore et al. 2015b; Ehrlich et al. 2023).

2.3 PFAS Exposure During Pregnancy

Pregnancy is a critical window of susceptibility to chemical exposure because of dynamic physiological changes affecting toxicokinetics and because of the hypersensitivity of the developing fetus(Heindel and Blumberg 2019). PFAS have been consistently detected in maternal serum, placental tissue, amniotic fluid, and umbilical cord blood, confirming their ability for transplacental transfer from mother to fetus(Kannan et al. 2004; Xu et al. 2020). The efficiency of placental transfer is highly dependent on the chemical structure of individual PFAS and the mechanisms involved in maternal–fetal transport(Ehrlich et al. 2023). Nonetheless, fetal exposure seems to be widespread, even in populations without known sources of industrial contamination. Besides prenatal, postnatal exposure can also occur via breastfeeding since PFAS have been detected in human breast milk(Lau et al. 2007; Gaillard et al. 2025). While the concentrations in milk are usually low compared with maternal serum, long duration of breastfeeding may result in substantial early-life exposure. The levels of PFAS in the mothers vary based on a variety of influences, including geographical location, environment, diet, socioeconomic status, and previous regulation(Kannan et al. 2004; Dobrzyńska et al. 2025). The reason the levels of some PFAS can impact the mother before the pregnancy even occurs is because they have a long lifetime, meaning that the

earlier the exposure, the greater the influence on the levels(Jensen et al. 2025).

3. Physiological Susceptibility to PFAS during Pregnancy, Mother

3.1 Placental Transfer and Maternal-Fetal Exposure

Although the placenta is involved in the facilitation of nutrient transfer and development, this is not a purpose attributed to the impermeable to environmental chemicals(Donato et al. 2008). The PFAS molecules are able to pass through the placental barrier by passive means and protein-mediated transport(Yu et al. 2019). Structural similarity with the fatty acids enables the interaction between PFAS and the placental transport proteins, thus enabling fetal exposure at critical stages of development(Mayilswami et al. 2025). Quantifiable concentrations of showing fetal uptake prenatally prove the acquisition of the fetus prenatally and suggest possible effects on child development, metabolism, and hormonal dynamics(Alonso et al. 2012).

PFAS are known to travel through the mother's bloodstream and accumulate in organs that are associated with metabolic and/or endocrine functions such endocrine regulations(Wu et al. 2022; Gonçalves et al. 2020). The changes in the body resulting from pregnancy include increased blood volume, lipid metabolism, and variations in hormones(Aloizou et al. 2020; Li and Kannan 2020). These factors may influence PFAS storage, mobilization, and redistribution. Because of the strong binding of PFAS along with albumin, the maternal serum functions as a reservoir to provide a constant exposure to the human organs and the developing baby(Heindel and Blumberg 2019; Grandjean and Clapp 2015b).

3.2 Physiological Changes Affecting PFAS

Pregnancy influences the rate of renal filtration, the output of the heart, and the perfusion of the tissues, which affect toxicokinetic processes(Aloizou et al. 2020). PFAS are metabolically persistent, meaning that PFAS do not break down effectively in primarily eliminated via renal excretion; hence, physiological renal variations are pertinent to chemical accumulation(Mayilswami et al. 2025; Dobrzyńska et al. 2025). These hormonal disturbances during pregnancy may further interact with PFAS via changes in the receptor activity, metabolic response, and tissue uptake. These changes: and establish conditions whereby exposure to PFAS could result in a higher level of metabolism than in nonpregnant people(James et al. 2006; Gore et al. 2015b).

4. Biological Mechanisms Linking PFAS to Gestational Diabetes Mellitus

4.1 Glucose Homeostasis and Insulin

Under normal physiological circumstances, the blood glucose level is kept within a tight range by a finely orchestrated process involving the synthesis and release of insulin by pancreatic β cells, the binding of insulin to its receptor, the triggering of intracellular insulin signaling pathways, and the translocation of glucose transporters that facilitate glucose uptake by peripheral tissues. During pregnancy, this complex tightly regulated process is adaptively altered, and a state of physiological insulin resistance is induced, which preferentially directs the availability of glucose to the fetus. These changes are mainly mediated by the action of placental hormones that, by themselves, are opposed by an increase in β-cell mass and insulin production, thus maintaining normal euglycemia(Kim et al. 2002; Hotamisligil 2006; Retnakaran and Shah 2009).

Recent findings also reveal that the (disruption by perfluorooctanic acids) and polyfluorooctanic acids) exposure may alter, in a negative way, the finely orchestrated compensation mechanism. In fact, it has been demonstrated that these substances can disrupt insulin receptor activation and subsequent signaling, with a prevalent effect on tissues sensitive to insulin, like skeletal muscle and fat, in which glucose uptake is a key determinant of the whole-body insulin sensitivity. The impairment of these mechanisms can alter glucose transporters translocation and reduce glucose uptake, causing an increase in circulating glucose concentration(Birru et al. 2021; Lind et al. 2014; Margolis and Sant 2021). This will increase the resistance to glucose, which will require an increase in insulin secretion by the pancreatic β cell(Fenton et al. 2020).

However, PFAS exposure can at the same time affect the susceptibility of pancreatic β cells in a manner that reduces their responsiveness to elevated demands for insulin. It has been shown that PFAS can impact the function of β cells in relation to insulin gene expression, mitochondrial function, and cellular stress responses, leading to decreased secretion of insulin. However, if this impaired insulin secretion occurs at the same time as PFAS-induced insulin resistance in the periphery, it could further challenge the buffering abilities of the maternal metabolic milieu in pregnancy, which is known to have increased susceptibility to insulin resistance(Omoike et al. 2021; Bonato et al. 2020; Heindel and Blumberg 2019).

Apart from their impact on insulin signaling and the function of beta cells, there are also the general effects on the body by the PFAS as hormonal disruptors. These compounds have been found to interfere with the production, transport, binding, or action of hormonal signaling molecules such as estrogen, thyroid hormones, and cortisol. Owing to the pivotal role such hormones play in the regulation of glucose or lipid metabolism and the close coordination involved during the gestation period, any disturbance on the part of the hormonal disruptor may have a profound effect on the metabolism of the affected women(Ehrlich et al. 2023; Grandjean and Clapp 2015a).

Moreover, PFAS can impact the endocrine and transport function of the placenta, which plays a crucial role in regulating the transfer of nutrients from mother to fetus. Indeed, the placenta has been described as a metabolic sensor that senses the nutritional environment in the mother and translates the information into growth requirements for the fetus based on the regulation of hormone secretion and nutrient transporters. Any impairment caused by PFAS in the regulation of hormones or nutrient transporters may lead to abnormal signaling between the mother and the fetus. Further impairment in glucose regulation in the mothers may occur. Collectively, these linked mechanisms, such as disturbed insulin receptor function, decreased peripheral glucose uptake, β-cell adaptability, endocrine homeostasis, and placental dysfunctions, provide a biologically valid and coherent whole that constitutes a link between PFAS exposure and metabolic susceptibility related to pregnancy. These linked mechanisms, combined with the biologically valid concept of pregnancy-related insulin resistance, add credence to metabolic PFAS exposures and susceptibility to GDM related to pregnancy. An integrative mechanism, linking PFAS exposure, pregnancy, and metabolic dysfunction, therefore highlights health relevance related to exposure to environmental health-related chemicals that affect pregnancy metabolic health(Kang et al. 2021; Starling et al. 2020; Jensen et al. 2025; Peterson et al. 2023).

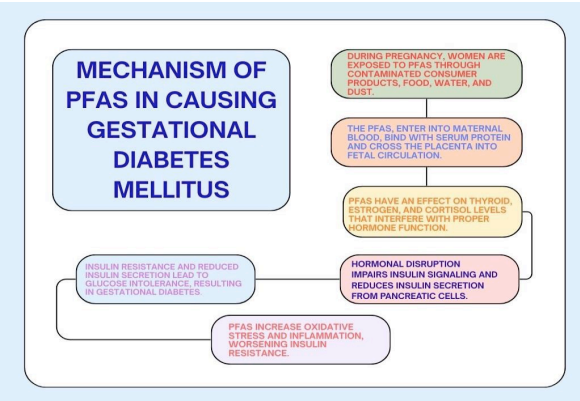

Fig. 1. Biological mechanisms linking per-and polyfluoroalkyl substance (PFAS) exposure to gestational diabetes mellitus (GDM).

4.2 Oxidative Stress and Inflammation

Reactive oxygen species (ROS) production and low-level chronic inflammation have long been confirmed as crucial factors in the development of insulin resistance and related metabolism disorders(Hotamisligil 2006; Heindel and Blumberg 2019). Recent studies presently show an increased association between the impact of per- and polyfluoroalkyl substances (PFAS) and enhanced oxidative stress levels, caused not only by the stimulation of excessive ROS production but also by the weakening of the body's own antioxidant defense system(Bonato et al. 2020; Omoike et al. 2021). This increased level of the redox system produces an unfavourable cellular environment for the regulation of metabolism. Simultaneously, enhanced levels of specific pro-inflammatory cytokines also have been observed in relation to the impact of PFAS on the body(Siwakoti et al. 2024; Taibl et al. 2022).

The chronic coexistence of oxidative stress and inflammation negatively impacts mitochondrial function and structure, contributing to inefficient metabolism and a rise in secondary ROS production(Chen et al. 2025a; Bonato et al. 2020). Mitochondrial dysfunction, in turn, impacts insulin signaling pathways by impairing critical phosphorylation steps necessary for proper activation of the insulin receptor, and consequently, glucose uptake(Lind et al. 2014; Margolis and Sant 2021). The efficacy of insulin signaling pathways becomes progressively impaired; therefore, peripheral tissues, such as skeletal muscle and adipose tissues, show resistance to insulin, a major factor in glucose intolerance in the body. These molecular changes form a cumulative, self-feeding loop of inflammation, oxidative stress, and metabolic dysfunction(Heindel and Blumberg 2019; Fenton et al. 2020).

Adipose inflammatory changes are a significant mechanism by which PFAS is related to the development of insulin resistance(Hotamisligil 2006; Omoike et al. 2021). Chronic low-grade inflammation in the adipose depot challenges the normal function of the adipocytes and leads to abnormal lipid uptake and a corresponding spill over into the circulation of free fatty acids. The high lipid levels in the circulation lead to abnormal lipid uptake by the insulin-sensitive organs such as the liver and muscle(Heindel and Blumberg 2019; Lind et al. 2014). Moreover, the inflammatory signaling in the adipose depot leads to changes in the levels of adipokine secretion, which results in low levels of factors that mediate insulin sensitivity and high levels of inflammatory mediators(Bonato et al. 2020; Margolis and Sant 2021). In pregnant women, for whom insulin sensitivity is already physiologically reduced due to increased metabolic demands the impact of pregnancy-induced insulin resistance, oxidative stress, and inflammation might critically interact with that of PFAS, providing a mechanistic background for increased glucose intolerance; Because of this, the processes mentioned above make a clear pathway with a mechanistic link for a connection to gestational diabetes mellitus, thereby proving that oxidative stress and inflammation play important roles in metabolically disrupting pregnancy due to PFAS(Xu et al. 2020; Peterson et al. 2023; Siwakoti et al. 2024).

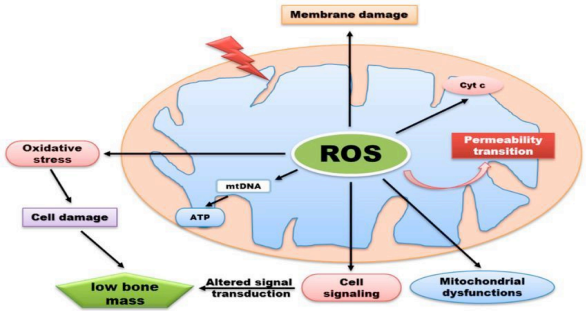

Fig. 2. Role of reactive oxygen species (ROS) in mitochondrial dysfunction and oxidative stress-mediated cellular damage.

Table 1:Proposed mechanisms through which PFAS exposure influences glucose regulation during pregnancy.

Mechanistic Category	Biological Effect
Insulin Signaling Disruption	PFAS interfere wit phosphorylation
ß-Cell Dysfunction	Reduced insulin secretion
Endocrine Disturbances	Altered estrogen hormones
Oxidative stress	Excess ROS produ tissues
Placental Dysfunction	PFAS cross placenta and alter nutrient transport
Lipid Metabolism Alteration	Increases circulatir triglycerides

5. Epidemiological Evidence Linking PFAS Exposure to Gestational Diabetes

A growing number of observational studies have increasingly supported the presence of a strong link between maternal exposure to perfluorooctanoic acid (PFOA) and other fluorinated compounds (FSAA)s and the increased risk of gestational diabetes mellitus (GDM) and glucose intolerance impairments (IGT) in pregnancy(Zhang et al. 2016; Peterson et al. 2023; Matilla-Santander et al. 2017). A variety of epidemiological studies have repeatedly identified increased blood levels of individual compounds classified under the broad category of perfluorosurfactants (PFAS)s in women with GDM compared to women with normal glucose metabolism(Xu et al. 2020; Omoike et al. 2021), supporting the potential involvement of such chemicals as a contributing factor in the altered metabolism during gestation. The potential involvement of such chemicals can also be supported by the fact that the altered metabolism caused by exposure to such chemicals has been found to have a variety of exposure-related dependencies, which has led research on the dose-response relationship for the evaluation of the existence and nature of such associations(Fenton et al. 2020; Taibl et al. 2022).

Indeed, several studies do indicate the presence of clear exposure-response gradients, where progressively increased exposures to PFAS are associated with progressively increased impairments in insulin sensitivity and glucose metabolism(Fenton et al. 2020; Siwakoti et al. 2024). Moreover, the fact that gradients do exist speaks to the issue of a casual association as opposed to a mere coincidence and therefore indicates that increases in the levels of PFAS, while not necessarily high, do carry a certain level of risk concerning the impact on metabolic issues during pregnancies(Heindel and Blumberg 2019). Moreover, a realistic scenario, as far as the nature and levels of PFAS exposures are concerned, would not include a single compound but rather a multitude of compounds that the individual might come into contact with through drinking water consumption and everyday household products. Such a scenario speaks to the issue of possible additive or synergistic effects in the impact on metabolism(Heindel and Blumberg 2019; Omoike et al. 2021). These overall trends, however, have been shown to be relatively consistent, yet there has also been divergence observed with regard to the strength and extent of positive association between pregnancy exposure to PFAS and pregnancy-related metabolic outcomes across different groups of people and research settings(Matilla-Santander et al. 2017; Peterson et al. 2023). For example, this may be attributed by different PFAS concentrations, genetic factors, and food consumption practices among individuals, among other factors which may cause discrepancies among research findings(Xu et al. 2020; Zhang et al. 2016).

There is also need for consistent research designs across research settings, which may also help account for divergent findings across research settings with regard to linkage between pregnancy exposure to PFAS and pregnancy-related metabolic outcomes among individuals taking into consideration mixture-based analysis techniques(Fenton et al. 2020; Taibl et al. 2022).

Table 2:Summary of observational studies evaluating maternal PFAS exposure and gestational diabetes-related metabolic outcomes.

Mechanistic Category	Biological Effect	Impact on Glucose Regulation
Insulin Signaling Disruption	PFAS interfere with insulin receptor phosphorylation	↓ GLUT4 translocation → ↓ glucose uptake
ß-Cell Dysfunction	Reduced insulin synthesis and secretion	Hyperglycaemia and impaired fasting glucose
Endocrine Disturbances	Altered estrogen and thyroid hormones	Increased insulin resistance in pregnancy
Oxidative stress	Excess ROS production in maternal tissues	Inflammation → impaired insulin

		sensitivity
Placental Dysfunction	PFAS cross placenta and alter nutrient transport	Fetal metabolic programming abnormalities
Lipid Metabolism Alteration	Increases circulating fatty acids & triglycerides	Worsening insulin resistance

6. Implications for Maternal and Fetal Health

Women suffering from gestational diabetes mellitus are also predisposed to an increased risk for the development of further complications related to the current pregnancy, such as gestational hypertension, adverse labour outcomes, and a greater reliance on pharmacologic therapy for the management of glycemic control. Moreover, the increased susceptibility for the development of the aforementioned (American Diabetes Association Professional Practice Committee et al. 2025) complications is indicative of an existent predisposition to a compromised, pre-pregnancy state of insulin resistance and an impaired ability to regulate blood glucose levels, which is likely to be further accentuated through environmental exposures, including the presence of environmental contaminants such as per- and polyfluoroalkyl compounds (PFAS)(Gore et al. 2015b; Heindel and Blumberg 2019). In view of the fact that PFAS compounds have been found to impair insulin and lipid metabolism-induced signalling pathways and induce a heightened state of inflammation(Fenton et al. 2020; Gore et al. 2015b), the existent predisposition through environmental exposures is likely to accentuate the pre-pregnancy predisposition and impair the ability for adequate glycemic regulation in women suffering from gestational diabetes mellitus. The accentuation in the predisposition for insulin resistance and an impaired ability for glucose tolerance not only contributes to an increased severity of the current predisposition but also predisposes for an increased risk for the development of the described complications in the mother.

These metabolic disorders in the mother directly affect the uterine environment, where glucose, hormones, and inflammation in the mother are intricately related to placental function. Abnormal placental function due to metabolic and chemical stressors may impact the fetal transfer of glucose, lipids, and oxygen to the developing fetus. Therefore, offspring born to metabolic stressed mothers, who are also diabetic, may show variations in their fetal growth patterns, resulting in variations in birth weight and body composition(Fenton et al. 2020) Fetal metabolic disorders may affect neonatal metabolic function, predisposing them to problems like hypoglycemia and respiratory distress in early life(Zhang et al. 2016).

Beyond neonatal outcomes, the intersection of hyperglycemic states among women and exposure to PFAS can have a profound, lifelong impact upon fetal metabolic programming. It is possible that a lifelong exposure to an improperly regulated state of glucose as well as improperly regulated levels of endocrine-disrupting chemicals during critical developmental periods can provoke a profound shift across gene expression(Fenton et al. 2020), sensitivity, as well as responsiveness to insulin through mechanisms such as epigenetics and inflammation of the placenta. These events in early life can provoke a lifelong vulnerability to obesity, as well as type 2 diabetes, with increased risk factors of these diseases apparent across life(Bellamy et al. 2009), suggesting that this complex pathway remains thoroughly governed by developmental events across gestational metabolic derangements as well as properly addressed environmental chemical exposure as a confluence of treatments post-GDM diagnosis.

Conclusion

Per- and polyfluoroalkyl substances (PFASs) have begun to receive increasing attention globally as a concern for environment and public health due to their chemical resilience, widespread distribution in the environment, and biological interactiveness(Kannan et al. 2004; Lau et al. 2007; Grandjean and Clapp 2015b). As research into the effects of PFASs continues to accumulate over time, there appears to be an increasing wealth of evidence that indicates maternal pregnancy and exposure to PFASs can impact her metabolic changes, potentially resulting in an increased risk of gestational diabetes mellitus (GDM)(Xu et al. 2020; Matilla-Santander et al. 2017). Such a link has already begun to find rationale through various biological mechanisms, including but not limited to, disrupting insulin signalling, lipid metabolism, increasing oxidative stress, and endocrine effects, that could potentially lead to an imbalance of glucose regulation(Gore et al. 2015b; Fenton et al. 2020; Heindel and Blumberg 2019). These mechanisms already remain potentially volatile due to the natural, increased metabolic needs of pregnancy, in addition to increasing insulin resistance that is needed for fetal development(Kim et al. 2002).

In this sensitive metabolic context, an additional burden of PFAS can potentially exceed the body's compensatory capacities, hence increasing the vulnerability to glucose intolerance and GDM(Fenton et al. 2020). Although the observed epidemiological evidence had not been absolutely consistent in all studies and populations, there has consistently been an association revealed between impaired glucose regulation and pregnant women with greater body burdens of PFAS(Xu et al. 2020; Matilla-Santander et al. 2017). Apparently, variations in observed

relationships may lie in the differing PFAS chemicals evaluated, the level of exposure, duration of exposure, co-exposure with more complex chemical mixtures, and individual population factors still not well understood, including genetic potential, individual dietary practices, societal socioeconomics, and country-specific environmental regulation(Zhang et al. 2016; Ehrlich et al. 2023). As knowledge about metabolic consequences linked to PFAS continues to develop, the role of environmental exposure evaluation within maternal healthcare and prenatal risk assessment is becoming increasingly relevant(Heindel and Blumberg 2019). Improving public awareness campaigns, development and adoption of stronger and more unified regulations, and incorporation of environmental risk factors into clinical screening models could potentially improve detection rates for at-risk populations. The challenge of mitigating metabolic effects and outcomes linked to exposure to PFAS is going to require interdisciplinary knowledge collaboration among areas such as toxicology, endocrinology, and epidemiology(Gore et al. 2015b). In light of this evidence, there is clearly sufficient reason to recognize exposure to PFAS as a credible and emerging environmental risk factor for GDM with downstream effects also potentially manifesting for both mother and child(Xu et al. 2020; Bellamy et al. 2009).

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