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ABSTRACT

A balanced communication between the mother, placenta and foetus is crucial to reach a successful pregnancy. Several windows of exposure to environmental toxins are present during pregnancy. When the women metabolic status is affected by a disease or environmental toxin, the foetus is impacted and may result in altered development and growth. Gestational diabetes mellitus (GDM) is a disease of pregnancy characterised by abnormal glucose metabolism affecting the mother and foetus. This disease of pregnancy associates with postnatal consequences for the child and the mother. The whole endogenous and exogenous environmental factors is defined as the exposome. Endogenous insults conform to the *endo*-exposome, and disruptors contained in the immediate environment are the *ecto*-exposome. Some components of the *endo*-exposome, such as Selenium, vitamins D and B_{12}, adenosine, and a high-fat diet, and *ecto*-exposome, such as the heavy metals Arsenic, Mercury, Lead and Copper, and per- and polyfluoroakyl substances, result in adverse pregnancies, including an elevated risk of GDM or gestational diabesity. The impact of the exposome on the human placenta's vascular physiology and function in GDM and gestational diabesity is reviewed.

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1. Introduction

Pregnancy is a physiological process in which the mother and foetus are in continuous communication to secure the physiologically correct progress of the gestation. When this synchronised interaction between the mother and foetus is disrupted, different diseases of pregnancy can occur. Various disruptors present in the environment can cause abnormal foetus growth and development. The harmful effect of these disruptors associates with molecular signatures imprinted in the newborn and the mother, thereby becoming the base of future diseases in adulthood and future pregnancies (Cornejo et al., 2021; Hill, 2021; Kupper and Huppertz, 2021; Lucock, 2021).

The internal and external environmental factors that delineate human health differently but complement the effects mediated by genetic background are known as the exposome (Wild, 2005, 2012). Significant advances have been made unveiling the mechanisms behind abnormal foetal growth and development in human pregnancy, showing more detailed diversity of insults leads to metabolic disturbances (Hill, 2021; Kupper and Huppertz, 2021; Lucock, 2021). The exposure to these environmental insults can be chronic (from months up to several years) or acute (minutes to few hours). Various endogenous insults impact the foetus by indirect exposure to molecules generated from metabolic alterations in the mother, i.e. the *endo*-exposome. Foetal exposure to *endo*-exposome maybe for the whole pregnancy period due to pre-existing maternal diseases such as type 1 (T1DM) or 2 (T2DM) diabetes mellitus, obesity, hypertension, or cancer. Foetal exposure to *endo*-exposome also happens in short periods (minutes, hours, few days), including occasional alcohol drinking or smoking, non-diagnosed maternal hyperglycaemia peaks, or more extensive periods (months) in women with gestational diabetes mellitus (GDM), pre-eclampsia, and other diseases of pregnancy. Disruptors are also part of our immediate environment (e.g. drinking water, processed and ultra-processed food, air, cosmetics, etc.), deteriorating human health status, i.e. the *ecto*-exposome.

The impact of the exposome on metabolic and physiologic pathways in pregnant women, on the intrauterine environment, foetal development, and newborn early life conditions is not fully understood. The exposome includes pluripotent *noxa* resulting in compromised mother and father's health status. For example, there is growing evidence that exposome can lead to overweight (body mass index, BMI, $\geq$25–29.9 kg/m^2), obesity (BMI $\geq$30 kg/m^2), increase in drug use and addiction risk and mental health disorders (Volk et al., 2020), among other yet undefined alterations (Hill, 2021; Kupper and Huppertz, 2021; Lucock, 2021). These *noxa* may also be present in pregnancy derived from internal sources during foetal growth and development, including hypoxia, increased generation of reactive species, hyperglycaemia, hyperinsulinemia, higher plasma adenosine level, abnormal placenta development, inefficient foetal circulation, reduced levels of micronutrients (e.g. Selenium, vitamin D) and mitochondrial oxidative phosphorylation (Sobrevia et al., 2020).

Since the prevalence of obesity and diabetes mellitus over the past decades in women of childbearing age worldwide increased (up to 35%) (Hutchesson et al., 2020; Ministerio Nacional de Salud del Gobierno de Chile (MINSAL) 2017; World Health Organization (WHO), 2021a,b), the prevalence of maternal obesity and other pregnancy pathologies will likely continue to increase in the years ahead. Early events during foetal life contribute to the developmental origin of diseases. For instance, pre-pregnancy maternal obesity and GDM are associated with young and adult-onset obesity and T2DM in the offspring. Furthermore, women with pre-pregnancy obesity have an increased risk to develop GDM (Yong et al., 2020), a condition referred to as gestational diabesity (Cabalín et al., 2019; Cornejo et al., 2021; Pardo and Sobrevia, 2018), and summarise a metabolic state that is different from obesity or GDM alone. Recent reports from the United Nations WHO (WHO, 2018) highlight the importance of the health status of the future mother and the harmful role of environmental pollution on foetal, newborn and children health. Thus, proper antenatal screening could help to improve the management and outcome of the current pregnancy and optimise life-long health and wellbeing for both mother and offspring.

This review emphasises the impact of the *ecto*-exposome and *endo*-exposome elements in the vascular physiology and function of the human placenta, highlighting the role of disruptors causing placental endothelial dysfunction in GDM and gestational diabesity.

2. Gestational diabetes mellitus and gestational diabesity

GDM is diabetes first diagnosed during pregnancy, generally by the end of the 2nd and beginning of the 3rd trimester of pregnancy (American Diabetes Association (ADA), 2020). GDM associates with insulin resistance, hyperglycaemia, and maternal-foetal hyperinsulinemia (ADA, 2020; Doupis, 2017; Johns et al., 2018; McIntyre et al., 2019; Mirghani Dirar & Saravanan et al., 2020). This disease of pregnancy results in D-glucose intolerance and dysfunction of the feto-placental vasculature (Colomiere et al., 2009; Haas, 2014; Sobrevia et al., 2015). GDM-associated vascular dysfunction has harmful consequences for foetal development and growth in addition to perinatal complications, including neonatal hypoglycaemia, neurological disorders, and macrosomia (Anderson et al., 2005; Ethridge et al., 2014; Koning et al., 2016; Madsen et al., 2021; McIntyre et al., 2019; Nold and Georgieff, 2004; Saravanan et al., 2020; Sendag et al., 2001).

The combination of maternal hyperinsulinemia and hyperglycaemia leads to higher protein and fat reserves in the foetus resulting in newborn macrosomia (Kc et al., 2015). At a cellular level, GDM associates with a higher capacity to synthesise nitric oxide (NO) and uptake of the semi-essential amino acid L-arginine, which is metabolised by the endothelial NO synthase (eNOS) to form NO and L-citrulline, i.e. the endothelial L-arginine/NO signalling pathway, in the human fetoplacental microvascular and macrovascular endothelium (Sobrevia et al., 2011). Human umbilical vein endothelial cells (HUVECs) collected at birth from GDM pregnancies show a higher endothelial L-arginine/NO pathway activity. This phenomenon results from the activation of adenosine receptors due to an increased extracellular concentration of the endogenous nucleoside adenosine, i.e. the ALANO signalling pathway (Adenosine/L-Arginine/Nitric Oxide) (San Martín and Sobrevia, 2006). Higher eNOS activity and NO level in the fetoplacental tissue due to activation of the ALANO signalling pathway could damage the fetoplacental endothelial function in GDM (Di Fulvio et al., 2014; San Martín and Sobrevia, 2006; Wu et al., 2018). Thus, a physiological concentration of extracellular adenosine is required for the proper function of the human foetoplacental endothelium in normal pregnancies. Interestingly, the above-described GDM-associated alterations were characterised in primary cultures of freshly isolated HUVECs from newborns with normal glycaemia (from 4.5 to 5 mmol/L) in the whole umbilical blood (Salomón et al., 2012; Vásquez et al., 2004; Westermeier et al., 2011).

Furthermore, women with GDM whose glycaemia was controlled by diet, oral hypoglycaemic drugs or in more severe cases, showed normalisation of their glycaemia soon after the initiation of treatment until delivery. Therefore, the GDM-altered ALANO signalling pathway may result from early exposure to hyperglycaemia in the uterus or as a response to other condition(s) than hyperglycaemia, or both. In addition, GDM was reported to associate with a marked increase in the nitrate plus nitrite concentration, index of NO level, in the amniotic fluid collected early (~18 weeks of gestation) but not late (~35 weeks of gestation) in pregnancy (Von Mandach et al., 2003). Thus, early foetal exposure in pregnancy to hyperglycaemia events in GDM may increase foetal NO generation.

The prevalence of T2DM has also increased worldwide (WHO, 2021a). This phenomenon may result from an unhealthy lifestyle, among which are sedentary lifestyle, unhealthy eating habits (Farag and Gaballa, 2011; Zimmet et al., 2001), and genetic susceptibility (Farag and Gaballa, 2011; Ling & Groop et al., 2009; Sladek et al., 2007;

Zeggini et al., 2008). The joint effect of obesity and T2DM causing an altered metabolic state in humans is named diabesity (Daly, 1994; Desoye and van Poppel, 2015; Farag and Gaballa, 2011; Ng et al., 2021; Schmidt and Duncan, 2003; Wild et al., 2004). Diabesity associates with a higher prevalence of metabolic syndrome (Farag and Gaballa, 2011; Zimmet et al., 2001), a condition that defines a group of risk factors that occur together and raises the risk for heart disease and stroke (Grundy et al., 2004; Reisinger et al., 2021; Simmons et al., 2010). Worryingly, an increasing number of women (*i*) enter pregnancy being overweight or obese, and (*ii*) develop supraphysiological gestational weight gain ending pregnancy with obesity and a high risk of weight retention after pregnancy. It is reported that maternal pre-pregnancy T2DM and obesity have independent contributions to obstetric outcomes (Simmons, 2011). Therefore, the effect of diabetes mellitus superimposed with obesity is expected to be potentially more pronounced than the effect of each condition separately (Blickstein et al., 2017).

A considerable proportion of women with pre-pregnancy overweight or obesity without T2DM or T1DM will develop GDM (Blickstein et al., 2017; Brown et al., 2017; Cabalín et al., 2019; Cornejo et al., 2021; Desoye and van Poppel, 2015; Subiabre et al., 2018). The pathophysiological origin of GDM and obesity is referred to as having insulin resistance and insulin deficiency (Verma and Hussain, 2017). Both metabolic alterations affect the development of the foetus. Women with gestational diabesity show metabolic alterations different from women with pre-pregnancy normal weight (BMI $\geq$18.5–24.9 kg/m^2) that develop GDM, i.e. classic or lean GDM (Cabalín et al., 2019; Cornejo et al., 2021). Furthermore, gestational diabesity affects the foetus differently from the lean GDM and even from women with pre-pregnancy overweight that develop GDM (Cornejo et al., 2021). Consequently, the metabolic alterations in pregnant women with gestational diabesity and their newborns may associate with differential response of the foetoplacental vasculature and other tissues to *ecto*-exposome or *endo*-exposome with women that develop the lean GDM.

3. Endogenous exposome in GDM

A wide variety of environmental components to which pregnant women are exposed could harm the women and foetus' health. In contrast, several endogenous and exogenous factors and conditions may also protect pregnant women and foetus against GDM and other diseases of pregnancy. These conditions range from a healthy lifestyle, including diet, to supplementation with micronutrients such as Selenium (Se) and vitamin D, required for a healthy pregnancy and foetal growth and development. In addition, a physiological level of endogenous metabolites such as adenosine and triglycerides are also necessary to maintain optimal cellular responses. When these conditions are altered or deficient before or during pregnancy, it may result in abnormal metabolic function in both women and foetus (Fig. 1). Unfortunately, excess food intake and the massive worldwide spread of unbalanced nutrient intake due to a diet preference for high energy and low nutrient foods are increasingly common and challenge women and foetal health.

The worldwide prevalence of overweight and obesity increased in the last 20 years from around 50% in the 1990s to 60–70% in the 2010s (Popkin et al., 2020). In line with this, unfortunately, worldwide GDM prevalence also increased between 2005 and 2018, reaching country-specific prevalence, with a mean range varying between 6 and 16% of the total pregnant women (McIntyre et al., 2019). Recent reports show that obesity in women of their childbearing age has also increased over the last decade (Hutchesson et al., 2020; MINSAL 2017; WHO, 2021a,b). This phenomenon is a critical determinant predicting a substantial increase in women with gestational diabesity (Cornejo et al., 2021). Obesity, overweight, and other internal factors involved either in the aetiology or in protecting against GDM affect the function of the fetoplacental unit. When the intensity and frequency of these internal factors are altered, i.e. the *endo*-exposome, the result is a higher risk of adverse pregnancy outcome (Hill, 2021; Kupper and Huppertz, 2021; Varshavsky et al., 2020).

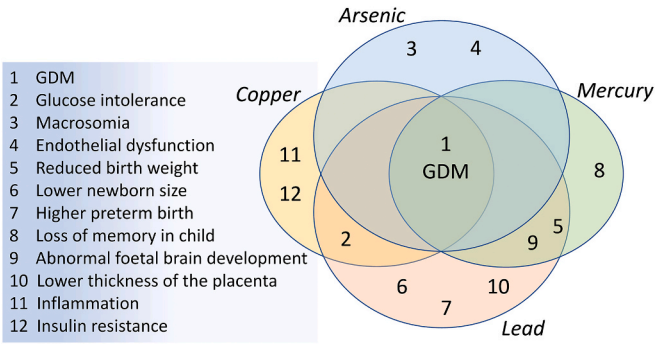

Fig. 1. *endo*-exposome in gestational diabetes mellitus. Normal Selenium and vitamin D levels and a low-fat diet are critical elements in the *endo*-exposome that protect pregnant women against developing gestational diabetes mellitus (GDM) (*Reduced risk of GDM*). Normal Selenium levels reduce (⇩) the expression of proinflammatory molecules, alleviating (⇩) inflammation. This trace element and a normal vitamin D level also reduce (⇩) oxidative stress by restricting the generation and biological actions of signalling molecules, including reactive oxygen species (ROS). Other metabolic conditions favoured by normal levels or biological action of Selenium, vitamin D or a low-fat diet include increasing (⇧) the expression and activity of glucose transporter 1 (GLUT1) and restoring insulinemia, two phenomena reducing hyperglycaemia and insulin resistance. In addition, a low-fat diet reduces the level of free fatty acids and normalises fasting glycaemia in women with GDM restoring mitochondrial respiration and D-glucose metabolism.

3.1. Selenium (Se)

Selenium is a trace element, nonmetal micronutrient with biological effects similar to As effects (Sun et al., 2014). The plasma level of Se is lower in women with GDM compared with the level measured in pregnant women with a normal pregnancy (~70 mg/dL) (Hofstee et al., 2021; Moshfeghy et al., 2020; Navarro et al., 1996; Onat et al., 2021). Se has an anti-inflammatory effect inhibiting NF-κB, toll-like receptors, and 38 kDa mitogen-activated protein kinases (p38^{mapk}) pathways in several cell types, including HUVECs (Feng et al., 2021; Zheng et al., 2008) (Fig. 1). Thus, a lower Se level in GDM is a phenomenon involved in this disease' inflammatory condition (Cabalín et al., 2019; Madsen et al., 2021; McIntyre et al., 2019; Saravanan et al., 2020).

A study performed in Arak, Iran, in women with GDM showed that a dose of 200 μg/day Se taken between 24 and 28 weeks of gestation improved glycaemic control markers and oxidative stress (Asemi et al., 2015). However, these results were achieved in only 32 patients. Furthermore, the short intervention with Se did not change the maternal HOMA β-cell function, lipid profile, plasma NO level, or total antioxidant capacity. Thus, the Se effects were limited and did not reflect a better general health condition. Furthermore, since the study included pregnant women with pre-pregnancy normal and overweight, the reported findings may be confounded by different (prior) metabolic disorders (Cornejo et al., 2021).

The beneficial effect of Se in reducing glycaemia may also result from upregulation of the glucose transporters 1 (GLUT1), as reported in lymphocytes from women with GDM (Karamali et al., 2020). This finding agrees with a previous report in this cell type from patients with polycystic ovary syndrome (Zadeh Modarres et al., 2018). Thus, the Se effect on GLUT1 expression is not restricted to GDM. Se-increased GLUT1 expression is a critical cell response since it may reduce hyperglycaemia in GDM and other diseases. Unfortunately, no studies address the Se treatment of women with GDM on GLUT1 transport activity in the fetoplacental vasculature. HUVECs from normal pregnancies treated with high extracellular D-glucose (25 mmol/L), advanced glycation end products (AGEs), and an elevated level of insulin show increased expression of cyclooxygenase 2, P-selectin, VCAM-1, and ICAM-1

(Zheng et al., 2008). Since the effect of high D-glucose, AGEs, and insulin were reversed by Se, this trace element may protect HUVECs from the harmful impact of a GDM-like environment (Zheng et al., 2008). The high extracellular D-glucose and insulin effect in this cell type was paralleled by increased activity of $p38^{mapk}$ (Li et al., 2011). Thus, a role for $p38^{mapk}$ activation in the protective effect of Se was proposed. However, these findings may reflect endothelial dysfunction due to long-term exposure (72 h for D-glucose, 6 h for AGEs, 24 h for insulin) and high level of insulin (100 nmol/L) compared with the plasma insulin in the human umbilical vein (~30 nmol/L) (Salomón et al., 2012).

3.2. Vitamin D

Vitamin D is a fat-soluble vitamin whose plasma concentration in pregnant women correlates with the umbilical cord blood level at birth (Wang et al., 2021a). Thus, it is an essential vitamin whose concentration in pregnant women with a normal pregnancy (>20 ng/L, measured as serum 25-hydroxyvitamin D, 25(OH)D) secures the health status of the newborn (Liu et al., 2020) (Fig. 1). However, women with GDM pregnancy show a lower level of vitamin D than women with normal pregnancies (Palacios et al., 2019; Zhang et al., 2008). Interestingly, vitamin D deficiency is also seen in pregnant women with pre-pregnancy obesity (Charnley et al., 2021), a phenomenon that may determine a lower level of this micronutrient in women with gestational diabesity (Cornejo et al., 2021). Therefore, the primary approach to reducing the risk of developing GDM, thus avoiding the GDM harmful effects in the foetoplacental unit and the newborn, is supplementing these women with vitamin D. The suggested vitamin D supplementation enough to obtain an adequate level of 25(OH)D varies in a wide range going 200–1600 IU/day (5–25 μg/day) in different studies. Interestingly, the output of studies where the interventions included supplementing women with GDM with vitamin D plus calcium has been not conclusive (Palacios et al., 2019).

The DALI vitamin D trial study aimed to determine whether vitamin D supplementation (1600 IU/day) reduced GDM risk (Corcoy et al., 2020). The results showed that intervention of pregnant women increased the serum 25(OH)D concentration achieving vitamin D sufficiency (defined as serum ≥50 nmol/L 25(OH)D). However, although significant, only a tiny reduction in the fasting plasma glucose was achieved in women with GDM at 35–37 weeks of gestation. Maternal insulin resistance and gestational weight gain were, however, not improved. The DALI study was done in a large cohort in which a relatively minor number of pregnant women developed GDM (79 patients), and all patients were with BMI ≥29 kg/m^2. The potential lack of beneficial effects of vitamin D supplementation may result from women with pre-pregnancy overweight/obesity. The latter conditions could potentially limit the biological actions of this vitamin as it is unclear whether overweight and obesity are metabolic disturbances counteracting or simply reducing the efficiency of vitamin D to reduce the risk of GDM.

Administration of a high, single dose of vitamin D (300,000 IU) in the form of cholecalciferol (vitamin D3) improved the status of its metabolic product 25(OH)D3 together with increasing the level of parathyroid hormone and calcium in pregnant women with GDM (Hosseinzadeh--Shamsi-Anar et al., 2012). These findings suggest that a single intramuscular administration of a high dose of vitamin D3 may improve women's health status with GDM. However, whether these improvements were affected by the nutritional status of the studied group of women with GDM is uncertain since it included a mix of women with BMI in the range of normal weight, overweight and obesity compared with untreated women. Interestingly, endothelial colony-forming cells —adult endothelial progenitor cells that regenerate endothelial cells— isolated from GDM pregnancies showed reduced capacity to migrate and form tubes *in vitro* (Gui et al., 2015). This phenomenon was restored by incubation with vitamin D. Thus, vitamin D treatment of women with GDM may reduce the GDM-associated deleterious effect on the foetoplacental vascular endothelial function.

Interestingly, vitamin D associates with the activation of vitamin D receptors increasing the NO level in HUVECs (Molinari et al., 2011; Uberti et al., 2014; Wu et al., 2021). Vitamin D also restored the H_2O_2-induced oxidative stress and reversed the oxidative stress-reduced mitochondrial activity in this cell type (Uberti et al., 2014). Thus, a reduced level of vitamin D or altered activation of vitamin D receptor in patients with GDM may increase the generation of reactive oxygen species (ROS), including the superoxide anion ($O_2^{\bullet-}$). The $O_2^{\bullet-}$ reacts with NO to form peroxynitrite ($ONOO^-$), reducing its bioavailability and limiting most biological actions of this gas (Mahdi et al., 2021). This cellular mechanism may be crucial since NO blocks the mitochondrial complex IV-cytochrome *c* oxidase, reducing the generation of ATP in foetoplacental cells (Brown and Cooper, 1994; Sobrevia et al., 2020). However, despite the elevated ROS generation and reduced activation of eNOS by vitamin D, HUVECs from GDM show higher eNOS activity, leading to higher amounts of bioactive NO before the $O_2^{\bullet-}$ scavenge it. In physiological conditions, vitamin D receptors activation is adequate, and the $O_2^{\bullet-}$ generation is lower or absent, resulting in higher NO generation and half-life, respectively. This phenomenon may result in tonic inhibition of mitochondrial respiration in foetoplacental vascular cells in normal pregnancies. Therefore, it is feasible that an inadequate response of HUVECs to vitamin D due to altered activation of vitamin D receptors and the overgeneration of $O_2^{\bullet-}$ in GDM reduced the NO bioavailability to restore mitochondrial respiration. Since HUVECs from GDM show increased eNOS activity, a reduced eNOS activation due to deficient vitamin D effect and the increased NO scavenging by $O_2^{\bullet-}$ may not be enough to limit the NO-mediated inhibition of cytochrome *c* oxidase (Sobrevia et al., 2020).

Other studies show that incubation of HUVECs with vitamin D blocked the leptin-increased $O_2^{\bullet-}$ generation and induced the expression of crucial anti-oxidative stress molecules, including superoxide dismutase 2 and glutathione peroxidase (Teixeira et al., 2017). In addition, vitamin D reduces the mitochondrial-generated ROS in HUVECs exposed to environmental toxins such as cooking oil fumes-derived $PM_{2.5}$ (COFs-derived PM2.5) (Ding et al., 2020). Thus, supplementing patients with vitamin D may increase the level and bioavailability of NO due to greater activation of vitamin D receptors and reduced oxidative stress. However, the consequence of an increased NO level due to supplementation with vitamin D may also include reduced oxidative respiration in the fetoplacental endothelium.

Calcitriol causes intracellular alkalisation (Jenis et al., 1993). Since an alkaline pHi increases the activity of eNOS in HUVECs (Fleming et al., 1994; Ramírez et al., 2018), vitamin D supplementation may also activate this enzyme' activity contributing to the increase of NO level and its inhibitory effect on mitochondrial respiration in this cell type. A recent study shows that incubating HUVECs from normal pregnancies with 33 mmol/L D-glucose increases ROS production and decreases the NO level in HUVECs (Wu et al., 2021). Vitamin D reversed the D-glucose–induced oxidative stress by upregulating the nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2), an anti-oxidative stress protein (Ma, 2013) requiring activation of vitamin D receptors in HUVECs (Wu et al., 2021). Thus, hyperglycaemia-associated diseases cause alterations in cell metabolism due to oxidative stress.

3.3. Vitamin B

Vitamin B is a group of water-soluble vitamins involved in various cell requirements acting as cofactors for several enzymes involved in DNA synthesis and sugars, fatty acids and amino acids metabolism. Vitamin B complex includes at least eight types of vitamin B, *viz*, B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_5 (pantothenic acid), B_6 (pyridoxamine), B_7 (biotin), B_9 (folic acid), B_{12} (cobalamins).

Vitamin B_{12} plays a role in maintaining an adequate foetal growth and maternal metabolic state in normal pregnancies. Once vitamin B_{12} in the food reaches the gastrointestinal system, it forms a complex with

haptocorrin (R-protein), which is included in the saliva. The gastric fluid gets to the duodenum, where it binds to the gastric parietal cells-released intrinsic factor (IF). The vitamin B–IF complex is absorbed in the terminal ileum after linked to the IF receptor and delivered to the bloodstream (Sukumar and Saravanan, 2019). Vitamin B_{12} deficiency associates with an abnormal nutritional status, drug abuse, and gastrointestinal diseases. These conditions may cause any of the steps of vitamin B_{12} absorption to be altered with the subsequent consequences in health.

Pregnancy and lactation are in high demand of vitamin B_{12} due to the foetus growth and infant nourishment. The level of vitamin B_{12} is critical in diseases of pregnancy, including GDM. It is reported that vitamin B_{12} deficiency (<150 pmol/L in pregnant women) (Sukumar and Saravanan, 2019) increases the risk of developing GDM (Kouroglou et al., 2019; Lai et al., 2018; Radzicka et al., 2019). The significant alterations resulting from reduced vitamin B_{12} are increased fasting serum glucose and triglycerides but a reduced concentration of high- and low-density lipoproteins (Radzicka et al., 2019). In the Pune Maternal Nutrition Study (India), pregnant women showed vitamin B_{12} deficiency with higher total homocysteine and oxidative stress (Yajnik et al., 2008). Accumulation of homocysteine may result from its reduced conversion to methionine due to a lower activity or content of vitamin B_{12}, a reaction that uses folic acid as a cofactor (Dell'Edera et al., 2013). Vitamin B_{12} also reduces the level of methylmalonic acid, an index of oxidative stress, by acting as a cofactor to convert methylmalonyl-CoA to succinyl-CoA. Abnormalities in these reactions result in the abnormal metabolic status of the mother and foetus. The Pune study showed higher maternal erythrocytes folate content, which, together with vitamin B_{12} deficiency, predicted insulin resistance in the neonate and at six years old children. A recent report reported that vitamin B_{12} deficiency might also result in a moderately higher risk of GDM and low birth weight (Behere et al., 2021).

Interestingly, among the factors leading to vitamin B_{12} deficiency is the use of the hypoglycaemic drug metformin, which restricts the absorption of vitamin B_{12} in non-pregnant subjects with diabetes mellitus (Aroda et al., 2016). Women diagnosed with GDM are advised a controlled diet and change in lifestyle, often together with been metformin aiming to reduce the maternal glycaemia to physiological levels. Women with GDM that took metformin showed a reduced total concentration of vitamin B_{12} (Gatford et al., 2013). However, the level of holotranscobalamin, the functional form of vitamin B_{12} (Sukumar and Saravanan, 2019), appears to be unaltered in the patients treated with this drug compared with those treated with placebo (Gatford et al., 2013). Thus, metformin may have reduced the absorption, perhaps via a lower binding of vitamin B_{12} to haptocorrin. Still, it seems not to alter the functionality of vitamin B_{12} in pregnant women with GDM.

3.4. High and low-fat diet

Exposure to a high-fat diet has been explored in the last decade using experimental animal models. However, few studies of the potential effects of exposure to a high-fat diet have been addressed in humans. The impact of an unhealthy, high-fat dietary pattern compared with a healthy, low-fat dietary pattern in a case-control study performed in 104 pregnant women with GDM from Fasa, Irak, was reported (Zareei et al., 2018). It was suggested that pregnant women taking an unhealthy, high-fat diet (v.g. including mayonnaise, soda, pizza, and sugar) showed a higher risk of developing GDM than women taking a healthy low-fat diet (v.g. Leafy green vegetables, fruits, poultry, and fish) (Fig. 1). However, since there are differences between these two diets besides the fat contribution, the results must be taken cautiously.

Furthermore, the study group in this report included pregnant women with BMI in the range of normal weight, overweight, and obesity altogether. Thus, the increased risk of developing GDM in women exposed to an unhealthy, high-fat diet may differ if these groups were analysed separately. As mentioned, several metabolic characteristics resulting in foetoplacental vascular dysfunction (Cornejo et al., 2021) or a state of inflammation are expected in women with gestational diabesity, which may be different from women with pre-pregnancy normal weight or overweight (Cabalín et al., 2019; Cornejo et al., 2021; Pardo and Sobrevia, 2018).

In a different approach, women with GDM were treated with a diet containing either lower-carbohydrate (40%)/higher-fat (45%) or higher-complex carbohydrate (60%)/lower-fat (25%) diet to check whether insulin sensitivity was improved (Hernandez et al., 2016). Women showed BMI in the range of overweight and obesity when incorporated in the study (31 weeks of gestation). Despite this confounding factor, the results showed that a reduction in the fat content in the diet associated with lower fasting blood glucose and free fatty acids suggesting better metabolic handling of D-glucose in this group of pregnant women with GDM. In addition, a reduced fat content in the diet induced an anti-inflammatory response. These women showed lower mRNA expression of a battery of proinflammatory biomarker molecules, including IL-1β and TNF-α, associated with insulin resistance in the adipose tissue. It is worth mentioning that the effects of diet intervention in women with GDM were dependent on the background diet, particularly the contribution of carbohydrate to the overall intake (García-Patterson et al., 2019; Yamamoto et al., 2018). Therefore, the beneficial effects of controlled diet intervention in women with GDM may relate to a reduction in the dietary fat diet and a change in the contribution and quality of protein and carbohydrate.

Obese women taking a high-fat diet showed placental structural changes, including abnormal placental maturity, vessel density, and vascular muscularity (Roberts et al., 2011; Sureshchandra et al., 2019). In addition, obesity and GDM are associated with inflammation and high levels of oxidative stress and lipotoxicity, leading to the activation of genes regulating insulin resistance (De Luccia et al., 2020; Saben et al., 2014; Zhang et al., 2021). Unfortunately, there is a lack of clinical studies addressing the potential underlying mechanisms of the effects of a high-fat diet in patients with GDM. A preclinical study showed that feeding mice with a high-fat diet associated with an increased expression of adenosine kinase (Xu et al., 2019b), which converts adenosine in adenosine monophosphate, reducing the level of adenosine (Silva et al., 2020). It is proposed that reducing the expression of this enzyme resulted in an anti-inflammatory and antioxidant effect requiring activation of adenosine receptors, likely due to an increase in adenosine levels. As mentioned, in the foetoplacental microvasculature and microvasculature, the extracellular concentration of adenosine increases due to reduced expression and activity of hENT1 and hENT2 in GDM (Salomón et al., 2012; Westermeier et al., 2011). Since adenosine is an anti-inflammatory nucleoside with a potential beneficial effect reversing GDM-associated endothelial dysfunction in the foetoplacental endothelium (Cabalín et al., 2019), its role in the inflammation caused by a high-fat diet is likely. Thus, lowering the fat content in a diet in pregnant women with GDM may restore insulin resistance due to a lower proinflammatory environment. This response may be crucial in getting a healthier metabolic state securing foetal growth and development in the human pregnancy.

3.5. Adenosine

Adenosine is an endogenous vasoactive nucleoside that causes dilation in most vascular beds, including the human umbilical vein (Westermeier et al., 2011). The biological effects of this nucleoside are mediated by the activation of a group of at least four different adenosine receptors, *viz*, A_1 (A_1AR), A_{2A} (A_{2A}AR), A_{2B} (A_{2B}AR), and A_3 (A_3AR) (Fredholm et al., 2011; Silva et al., 2017). These subtypes of receptors are expressed in the human foetoplacental macrovasculature and microvasculature (Salomón et al., 2012; Salsoso et al., 2015, 2021; Wyatt et al., 2002). Furthermore, it is reported that adenosine uptake mediated by hENT1 and hENT2 is reduced in HUVECs from women with GDM. Therefore, a reduced removal of this nucleoside from the

extracellular space increases its extracellular concentration leading to activation of $A_{2A}AR$ (Vásquez et al., 2004). This phenomenon activates the ALANO signalling pathway resulting in excessive NO in HUVECs from GDM (San Martín and Sobrevia, 2006). Interestingly, higher levels of As, Cadmium, and Barium interfere with the ALANO signalling pathway in women with GDM (Wu et al., 2018). Thus, the potential actions of these metals as regulators of the adenosine-mediated effects in foetoplacental endothelial cells is critical since it may exacerbate the GDM-associated abnormal adenosine signalling in the foetoplacental circulation.

Adenosine plays a role in the maternal and foetal metabolic disturbances not only in GDM pregnancies (Razak et al., 2018; Vásquez et al., 2004; Wojcik et al., 2014; Wyatt et al., 2002, 2004; Zieleniak et al., 2012) but it is also likely involved in the foetoplacental vascular dysfunction seen in gestational diabesity (Cabalín et al., 2019; Cornejo et al., 2021; Fuentes et al., 2019, 2020). In addition, adenosine is also involved in other disturbances in pregnancy, including foetuses with intrauterine growth restriction (Casanello et al., 2005; Momoi et al., 2008; Rivkees and Wendler, 2011; Yoneyama et al., 1994b) or small-for-gestational-age (Yoneyama et al., 1994a), and pre-eclampsia (Iriyama et al., 2015; Salsoso et al., 2017; von Versen-Höynck et al., 2009; Yoneyama et al., 1994a,b, 1996, 2000, 2001, 2002). Therefore, the mechanisms that regulate the extracellular concentration of this nucleoside are crucial in maintaining the foetoplacental vascular function.

Gestational diabesity also associates with elevated extracellular adenosine concentration (Cabalín et al., 2019; Cornejo et al., 2021). In this group of women, an increase in the extracellular concentration of adenosine may result in activation of the ALANO pathway via $A_{2A}AR$ activation. However, it could also result in activation of $A_{2B}AR$, reducing ROS generation and activating anti-inflammatory mechanisms by an increased generation of IL-10 and adiponectin and decreased generation of proinflammatory cytokines such as TNF-α, IL-6, and leptin (Cabalín et al., 2019). Activation of $A_{2B}AR$ also lowers NO to a physiological level which is elevated in GDM. Since $O_2^{\bullet-}$ scavenges NO, it is intriguing that the activation of this subtype of receptors reduces the bioavailability of this gas in parallel with reducing the ROS level. This contradictory response may be explained partly by the involvement of second messengers with similar biological effects to NO, such as hydrogen sulfide (H_2S).

H_2S is a gasotransmitter that acts as an antioxidant and causes vasodilation (Van Den Born et al., 2016). H_2S is generated by three different enzymes in the vascular system, of which cystathionine-γ-lyase (CSE) is preferentially expressed (Dillon et al., 2020; Xu et al., 2019a). CSE expression and activity are increased in a Nox4-dependent manner with subsequent H_2O_2 elevation in HUVECs (Mistry et al., 2016). Also, the CSE activity and expression is higher in response to NO (Wang, 2002; Dillon et al., 2020), as shown in rat aortic smooth muscle cells (Zhao et al., 2001), rat intestinal tissue (Wang et al., 2019c), and C57BL/6 mice peripheral macrophages (Zhu et al., 2010). Interestingly, experimental diabetes mellitus in animal models showing insulin resistance associated with higher expression of CSE and generation of H_2S, a phenomenon proposed as a potential vasoprotective response (Zhao et al., 2014). GDM is a metabolic alteration coursing with insulin resistance and increased eNOS activity in HUVECs and hPMECs (Sobrevia et al., 2015). Thus, increased CSE and H_2S generation may counteract the GDM-associated endothelial dysfunction (Fig. 2). The latter is a possibility not yet addressed in the literature. Interestingly, in pregnant Dahl salt-sensitive rats, a model of pre-eclampsia, the administration of high oral concentrations of the H_2S donor sodium thiosulfate reduced the arterial pressure (Terstappen et al., 2020). These findings suggest that H_2S may prolong the gestational period in this disease of pregnancy. However, sodium thiosulfate also increases proteinuria and kidney weight, which is detrimental for the foetus and the mother. Thus, H_2S may play a dual role in GDM and other diseases of pregnancy, compromising the foetoplacental vascular function.

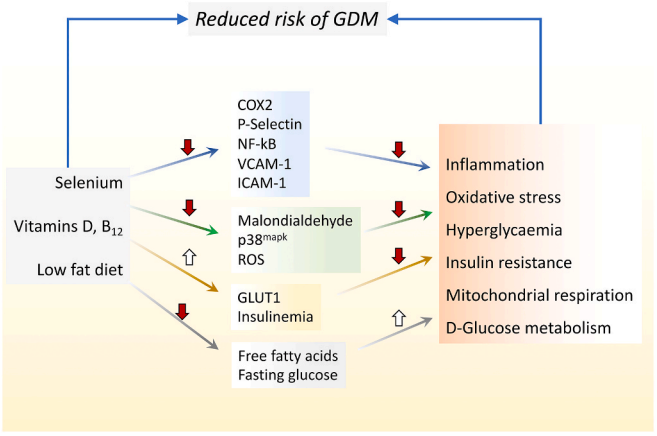

Fig. 2. Heavy metal *ecto*-exposome in gestational diabetes mellitus. The environment contains a wide variety of heavy metals in the food, air, and earth, of which *Arsenic*, *Mercury*, *Lead* and *Copper* are the most commonly found in contaminated regions. An adverse effect of these metals in pregnancy is an increased risk of developing gestational diabetes mellitus (GDM). However, several alterations in pregnancy are common (v.g. for *Mercury* and *Lead* and *Lead* and *Copper*) or unique for these metals. There are not clear reports addressing the potential effect of a combination of these metals in human pregnancy outcomes.

H_2S caused Akt activation resulting in reduced activity of the Na^+/H^+ exchanger 1 isoform (NHE1), the main NHEs isoform regulating the intracellular pH (pHi) in the foetoplacental endothelium (Ramírez et al., 2018). H2S/Akt inactivation of NHE1 result from increasing the inhibitory phosphorylation of Ser^{648} in this protein in rat ventricular myocytes (Snabaitis et al., 2008). This phenomenon results in a lower activity of NHE1, reducing the H^+ efflux ending in intracellular acidification, which is a condition that diminishes eNOS activity in HUVECs (Fleming et al., 2004; Ramírez et al., 2018). However, H_2S released from the spontaneous donor GYY4137 increases the eNOS expression and activity in HUVECs (Zhu et al., 2021). Thus, H_2S may have a dual effect on eNOS activity depending on the predominant cell signalling mechanism triggered by this gasotransmitter. Since HUVECs from GDM pregnancies show increased eNOS activity, the H_2S -associated eNOS activation signalling pathway is likely to predominate in these cells. Whether increased extracellular concentration of adenosine results in generating endothelial dysfunction via $A_{2A}AR$ activation or triggering CES/H_2S -mediated defence mechanisms via $A_{2B}AR$ receptor activation in the foetoplacental vascular endothelium is unknown (Cabalín et al., 2019; Cornejo et al., 2021).

IUGR is a condition resulting from multiple factors, of which hypoxia is a significant contributor due to reduced placental blood flow (Ducsay et al., 2018). It is proposed that adenosine via A_1AR activation may protect against IUGR since caffeine, a general antagonist of adenosine receptors (Fredholm et al., 2011), increased the risk of developing this complication of foetus growth (Rivkees and Wendler, 2011). Caffeine also decreased embryo development in CD-1 mice, likely via $A_{2A}AR$ inhibition (Momoi et al., 2008). Thus, the biological action of adenosine may also play a role in embryo development and foetus growth. Other studies show increased adenosine concentration in the umbilical vein blood in growth-retarded foetuses with hypoxia and acidosis at 31–38 weeks of gestation (Yoneyama et al., 1994a). Also, elevated plasma adenosine correlated inversely with the incidence of foetal breathing movements, partially explaining the hypoxia observed in these foetuses. Interestingly, hypoxia reduces hENT1-mediated adenosine uptake, increasing the extracellular concentration of this nucleoside in HUVECs from normal pregnancies (Casanello et al., 2005). The increased extracellular concentration of adenosine seen in IUGR and hypoxia did not activate the ALANO signalling pathway but reduced the L-arginine uptake and NO synthesis in HUVECs (Casanello et al., 2002). Thus, IUGR

may be a condition where the foetoplacental endothelium is exposed to an environment that makes this tissue react differently to those from pre-eclampsia, GDM, or gestational diabesity.

4. Heavy metals and PFAS as *ecto*-exposome

For decades, humans have been exposed to various chemicals, including phenols, parabens, and heavy metals. Arsenic (As), Mercury (Hg), Lead (Pb), Copper (Cu), and other heavy metals are found either as contaminants or as natural components in the environment (Huang et al., 2011; Marshall et al., 2007). It is also known that environmental contamination with per- and polyfluoroakyl substances (PFAS) generated in industrial activity is a reality (Al Amin et al., 2020; Birru et al., 2021; Mitro et al., 2020; Xu et al., 2020). Exposure to these environmental factors has been shown to lead to health complications in adults, in which pregnant women are a high-risk group (Gómez-Roig et al., 2021; Liu et al., 2021; Rolland et al., 2020; Soomro et al., 2019). Inhabitants of cities with high industrial activity are likely to be chronically exposed to this type of environmental chemicals either in the drinking water, polluted air, and contaminated food. These chemicals may trigger different pathologies in the mother and foetus, including an altered human foetal development and growth (Rolland et al., 2020), higher risk of obesity in young people (La Merrill and Birnbaum, 2011; Vrijheid et al., 2016, 2020), and altered responses of the immune system and abnormal nervous system function (Bellinger, 2013; Gascon et al., 2013; Vrijheid et al., 2016). Also, a higher risk of developing GDM and worsening this disease-associated alteration of the foetoplacental vascular function is reported in women exposed to As, Hg, Pd, and Cu and PFAS (Fig. 3).

4.1. Arsenic (As)

Arsenic is a natural metalloid found in several minerals, either in combination with sulfur and metals or as a pure metal in the form of crystals. The most frequent inorganic form of arsenic trioxide (ATO) is arsenite when dissolved in water. ATO increases tumour growth (Smith et al., 1992). It is contained in the drinking water for human use in geographical regions that show a higher mortality rate due to human lung and bladder cancer, v.g. Antofagasta, Chile (Marshall et al., 2007), and bladder cancer and urothelial carcinoma, v.g. Taipei, Taiwan (Huang et al., 2011).

A high risk of glucose intolerance was associated with a higher As concentration in samples of blood and hair from 532 pregnant women from the former Lead and Zinc mining area Tar Creek Superfund site in Northeastern Oklahoma, USA (Ettinger et al., 2009). The results showed that women exposed to As were at higher risk of impaired glucose tolerance at 24–28 weeks of gestation, associated with an increased risk of developing GDM (Fig. 3). The latter findings are complemented by the results described in a cohort of 1885 Canadian pregnant women showing a strong positive correlation between a higher level of As in first-trimester maternal blood samples and GDM (Shapiro et al., 2015). Furthermore, in a group of 776 Chinese women, the blood level of As was positively associated with a higher risk of developing this disease of pregnancy (Wang et al., 2019b). These results strongly suggest that As contamination of the environment is a factor that favours developing GDM in human pregnancy.

Maternal exposure to elevated levels of As in pregnancy may also cause foetal metabolic disturbances. To date, in a retrospective case-control study in a cohort of 1359 Chinese pregnant women, As was found in the neonate's meconium (Peng et al., 2015). This study showed that the concentration of As in the meconium from neonates to GDM during pregnancy (~61 ng/g meconium) was higher than the content of this metal detected in normal pregnancies (~45 ng/g meconium). Thus, As may have accumulated in the meconium after crossing the human placenta resulting ending in a more significant proportion of this metal in foetuses from GDM than in normal pregnancies (Peng et al., 2015).

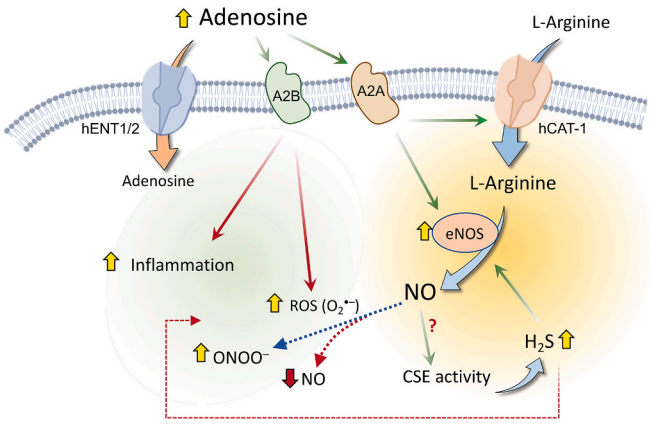

Fig. 3. Involvement of the *endo*-exposome adenosine in gestational diabetes mellitus. Gestational diabetes mellitus (GDM) associates with reduced expression and activity of the human equilibrative nucleoside transporters 1 and 2 (hENT1/2), leading to reduced adenosine uptake of the foetoplacental endothelium. The reduced adenosine uptake results in increased (⇧) adenosine concentration in the extracellular medium, favouring its broad biological actions mediated by activation (green arrows) of A_{2A} (A2A) and A_{2B} (A2B) adenosine receptors. Activation of A_{2A}AR leads to increased L-arginine uptake mediated by the human cationic amino acid transporter 1 (hCAT-1) and activation of the endothelial nitric oxide synthase (eNOS), resulting in a higher synthesis of nitric oxide (NO). The elevated level of NO may also result from higher levels of the gasotransmitter hydrogen sulfide (H_2S) generated by the cystathionine-γ-lyase (CSE). It is uncertain (?) but likely that overgeneration of NO may result in CSE activation. Furthermore, H_2S inhibits (red segmented arrow) the formation of reactive oxygen species (ROS), including superoxide anion ($O_2^{\bullet-}$), favouring a higher level of NO in GDM. The increase in the extracellular adenosine concentration leads to activation of A_{2B}AR, diminishing (red arrows) the GDM-increased ROS/$O_2^{\bullet-}$generation and inflammation. Lowering the generation of ROS/$O_2^{\bullet-}$ after A_{2B}AR activation or in response to a higher H_2S level limits the scavenge of NO by $O_2^{\bullet-}$ which decreases (⇩) the NO bioavailability together with forming peroxynitrite ($ONOO^-$). Thus, GDM-increased extracellular adenosine concentration in the human foetoplacental vascular endothelium may restore endothelial function by combining A_{2A}AR/A_{2B}AR activation in the human foetal endothelium. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Interestingly, in 96 pregnant women in the Tenerife Island, Spain, the As level in the neonate's meconium (~7 ng/g meconium) was lower than the level reported in meconium samples in normal pregnancies (Peng et al., 2015) and did not associate with risk for the neonate outcome or maternal obstetric history (Vall et al., 2012). However, the low level of As detected in these meconium samples associated with a higher infant birth weight compared with infants from pregnant women not exposed to this heavy metal. Unfortunately, the authors did not explain the latter findings. However, a higher risk of being large-for-gestational age or showing macrosomia is described in GDM pregnancies (Hartling et al., 2014; Wendland et al., 2012). Therefore, large-for-gestational-age may reflect a potential subclinical GDM associated with the presence of As in the neonate's meconium.

The WHO recommendation as a maximal concentration of ATO in the drinking water to avoid health problems in humans is ~0.05 μmol/L (~10 μg/L, ~0.01 ppm) (WHO, 2017). Interestingly, exposure of HUVECs primary cultures *in vitro* to 0.05 μmol/L ATO resulted in endothelial metabolic alterations associated with reduced maximal transport capacity (i.e. maximal velocity (V_{max})/apparent Michaelis-Menten parameter (K_m), V_{max}/K_m) for adenosine via the human equilibrative nucleoside transporters 1 (hENT1) and 2 (hENT2) (Celis et al., 2017). Also, 0.05 μmol/L ATO increased the V_{max}/K_m for L-arginine transport via the very high affinity, low-capacity transport system y^+L in this type of endothelium (Ramírez et al., 2018; San Martín and Sobrevia, 2006).

Interestingly, an ATO-associated increase in system y^+L–mediated L-arginine transport was required to increase eNOS activity in HUVECs (Ramírez et al., 2018). Previous studies reported that GDM results in higher NO generation in HUVECs (Farías et al., 2006; Vásquez et al., 2004; Westermeier et al., 2011) and human placental microvascular endothelial cells (hPMECs) (Salomón et al., 2012). GDM-increased generation of NO in HUVECs reduced the promoter activity of *SLC29A1* (for hENT1). This phenomenon resulted from activation of the C/EBP homologous protein 10 (hCHOP) —a member of the CCAAT/enhancer binding protein family that forms heterodimers with the C/EBP family of activating transcription factors (hCHOP/C-EBPα)— leading to lower expression and transport activity of hENT1 in this cell type (Farías et al., 2006; Westermeier et al., 2011). Thus, an increase in the NO synthesis may be a mechanism by which ATO reduces adenosine transport via hENT1 in HUVECs (Celis et al., 2017).

Unfortunately, it was recently reported that a considerable proportion of the population (reaching more than 230 million people over more than 108 countries), including pregnant women, are exposed to drinking water having >10 μg/L ATO (Shaji et al., 2021). To date, a cohort of 853 pregnant women in the New Hampshire Birth Cohort, USA, with a diagnosis of GDM consumed drinking water containing above the USA Environmental Protection Agency (EPA) maximum contaminant limit of 10 μg/L (Farzan et al., 2016; National Research Council (NRC), 2013). A positive association between the level of ATO in drinking water and odds of GDM was found. Interestingly, the latter study also showed an association between the higher risk of GDM and pre-pregnancy maternal obesity (Farzan et al., 2016).

Various alterations in regulatory mechanisms of cell homeostasis are associated with pre-pregnancy maternal obesity. These alterations include the triggering of endoplasmic reticulum stress (Villalobos-Labra et al., 2018), reduced hENT1-mediated membrane transport of adenosine (Pardo et al., 2015), and abnormal regulation of pHi (Fuentes et al., 2019, 2020). Therefore, contamination of drinking water with ATO may trigger different mechanisms in women with pre-pregnancy obesity than women with pre-pregnancy normal weight or mild to moderate overweight that develop GDM (Cornejo et al., 2021). The possibility that pre-pregnancy maternal obesity is a condition making this group of women more prone to develop GDM when exposed to As is supported by the findings in pregnant women in the New Hampshire Birth Cohort, USA, as described above (Farzan et al., 2016). Interestingly, the As harmful effect seems more critical in developing GDM at the 1st trimester of pregnancy rather than at the 2nd and 3rd trimester of pregnancy since the level of this metal was found to be higher early in pregnancy (Xia et al., 2018). Unfortunately, the mechanisms underlying the effect of As in GDM induction are not precise.

4.2. Mercury (Hg)

Mercury is a heavy metal that is liquid at room temperature and is found in at least two oxidant states, the Hg(I) and Hg(II), with Hg(II) being the most common oxidation state and most frequently found in nature. Hg is highly toxic and is still present in electrical and electronic devices and is also contained in some thermometers specifically for the measurement of high temperatures. Methylmercury (MeHg) is the principal constituent of organic Hg and damages foetal development since it crosses the placenta and blood-brain barrier (Clarkson and Magos, 2006; Granitzer et al., 2021). MeHg is present in high levels in seafood and some fishes. Therefore, this pollutant is found in reachable food for all population, including pregnant women and women of childbearing age. When pregnant women ingest MeHg as a contaminant in the food, it becomes a public health problem. Foetal exposure to this environmental pollutant in the uterus is a hazardous condition for the wellbeing of the foetus, the mother, and the newborn (Fig. 3). Prenatal exposure to MeHg was neurotoxic in 7-years old children causing abnormal visuospatial processing and memory (Grandjean et al., 2014). While MeHg is associated with an increased risk of obesity and T2DM in adulthood (Cho et al., 2012; Skalnaya and Demidov, 2007), there is a lack of information about this pollutant in metabolic diseases in pregnancy.

A high Hg level was detected in the red blood cells (1.04–3.7 μg/L) of three days postnatally 1442 children born to mothers from an urban low-income population in the USA (Wang et al., 2019a). The findings showed that children were at higher risk of being overweight or obese from preschool to adolescence. Interestingly, the risk of Hg-associated overweight and obesity in these children was higher when mothers were with pre-pregnancy overweight or obesity and diabetes mellitus. Thus, pre-pregnancy maternal diabesity may result in the worst possible condition for the foetus due to the increased Hg accumulation in the mother. Other studies showed a higher Hg content in maternal blood in Chinese women associated with an increased risk of developing GDM (Wang et al., 2019b) and lower birth weight (Kim et al., 2017). Unfortunately, no mechanisms were reported for these findings in GDM pregnancies.

Interestingly, an adequate maternal folate level in pregnancy (≥20.4 nmol/L) may be protective to Hg-damaging effects since pre-pregnancy maternal folate levels were negatively correlated with maternal Hg levels (Wang et al., 2019a). The mechanisms by which Hg caused these metabolic alterations is still unclear. However, an altered D-glucose and lipids metabolism due to oxidative stress and inflammation was proposed to be involved in the effect of MeHg (Chen et al., 2006; Yin et al., 2017).

4.3. Lead (Pb)

Lead is a heavy metal found in at least two oxidation states, +4 and + 2, of which the oxidation stage +2 is predominant. Pb is also found in water and elements of general use, including solders, batteries, and some types of paints. Pb crosses the human placenta and accumulates in the placenta and foetus, causing abnormal foetal brain development (Al-Saleh et al., 2011, 2014; Gundacker et al., 2016) (Fig. 3). Exposure of pregnant women to Pb positively correlate with reduced birth weight and birth size (Gundacker and Hengstschläger, 2012). In a cohort of mother-infant pairs from the National Children's Study in the USA, prenatal exposure to Pb also associates with reduced birth weight, head circumference, and gestational age (Shih et al., 2021). These findings are complemented with a higher incidence of preterm birth after exposure to Pb (Khanam et al., 2021). Since exposure to this metal resulted in reduced placental thickness (Al-Saleh et al., 2014), Pb might alter the structure and function of the placenta, restricting its capacity of delivering metabolic substrates to the growing foetus.

Interestingly, the reduced birth weight, head circumference, and gestational age caused by prenatal exposure to Pb were seen only in female offspring (Shih et al., 2021). Thus, a sex-specific mechanism may protect the male foetus development from environmental toxic heavy metals. It is noteworthy that female placentas may show different cell signalling mechanisms regulating this organ function than male placentas. To date, female placentas showed lower NO-dependent reactivity of the umbilical vein to insulin than vessels from male placentas from women with late-onset pre-eclampsia (Salsoso et al., 2021). Also, the foetal sex was proposed to associate with a HUVECs female or male phenotype (Lorenz et al., 2015; Zhou et al., 2019). It is reported that a male foetus associates with altered maternal metabolism glucose metabolism, likely due to reduced pancreatic β-cell function and a higher risk of GDM (Retnakaran et al., 2015). A male foetus increases in ~4% the relative risk of GDM than a female foetus (Jaskolka et al., 2015). Thus, foetal sex may be a factor in the placenta and foetus's response to Pb and other heavy metal contaminants. Synergistic interaction between Pb and Hg was recently found in metal-metal interaction analyses (Shih et al., 2021). A combination of heavy metals in the environment, as it is likely to happen, to which pregnant women are exposed may increase the risk of abnormal foetus development and pregnancy outcomes. Whether a different response to these metals will

be seen in the female or male placenta is not yet addressed.

Changes in the maternal plasma concentration of Pb are also involved in GDM (Onat et al., 2021; Soomro et al., 2019; Wang et al., 2021b). An increase in Pb concentration in the mother' blood associated with a higher risk of developing GDM (Wang et al., 2019b). Interestingly, this association is less pronounced than the increased risk of GDM due to higher concentrations of Hg, yet similar to As (Pb = As < Hg effects). Thus, it is hypothesised that Pb may make pregnant women susceptible to developing GDM via mechanisms similar to As but different from Hg. Interestingly, in a group of women underweight, an increased concentration of Pb in the serum was associated with reduced mean fasting plasma glucose in the oral glucose tolerance test (Zhou et al., 2021). These findings suggest that the pre-pregnancy nutrition status may steer the pathophysiological mechanisms associated with the disruption of glucose homeostasis due to an increased Pb concentration in pregnant women. However, it is worth noting that a change in the circulating D-glucose concentrations in pregnancy may not be the only cause of the reported GDM-associated alterations in the fetoplacental vascular function. The latter idea is supported by the fact that women with GDM showed these alterations even when they reached normal glycemia after being treated with diet or insulin therapy (Cornejo et al., 2021; Sobrevia et al., 2015, 2020).

4.4. Copper (Cu)

Copper is a trace element essential for the proper function of several metabolic processes in the human body since it is a constitutive trace in a wide variety of enzymes (Festa and Thiele, 2011). The biological action of Cu depends on at least two different states, *viz*. the reduced state (Cu^{+}) with high affinity for thiol and thioether groups and the oxidised form (Cu^{2+}) with preferential actions in oxygen or imidazole nitrogen groups. This trace metal is crucial in mitochondrial oxidative respiration since three Cu ions are required for cytochrome *c* oxidase activity (complex IV of the respiratory chain) in the final step for the generation of ATP in mammalian cells (Han Du et al., 2020).

A change in the plasma concentration of Cu results in several metabolic alterations, including GDM (Li et al., 2019; Onat et al., 2021; Zhang et al., 2021) (Fig. 3). GDM associates with lower expression of mitochondrial complex II and IV in pregnant women under a controlled diet compared with women with normal pregnancies, and complex I, II, III, and IV in women under insulin therapy compared with normal pregnancies or under diet treatment (Muralimanoharan et al., 2016; Sobrevia et al., 2020). Thus, altered function of complex IV may result from altered bioactivity and bioavailability of Cu in patients with GDM.

In a group of 60 women with GDM, the plasma level of Cu (~1484 μg/L) was slightly but significantly increased (~1.1 fold) and likely associated with insulin resistance (Onat et al., 2021). In this study, the women with GDM were all overweight before pregnancy compared to normoglycaemic pregnancies, where all women showed normal weight before pregnancy. Thus, it is unclear whether the association between elevated Cu level and GDM may have resulted from overweight associated with GDM in these women. The latter is a possibility since women with gestational diabesity or with pre-pregnancy maternal overweight may show different mechanisms of metabolic adaptation due to the over imposed abnormal metabolic condition (Cornejo et al., 2021; Fuentes et al., 2019, 2020).

It was also proposed that an increased Cu level in women with GDM associates with chronic inflammation since women with GDM showed an increased monocyte/high-density lipoprotein ratio (Zhang et al., 2021). GDM may increase monocytes number in maternal blood (Angelo et al., 2018) and monocytes adhesion to HUVECs *in vitro* via a mechanism including higher expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (Zhang et al., 2021). GDM associated with a low grade of inflammation and impaired maternal immune response (De Luccia et al., 2020). However, the precise mechanisms by which Cu is involved in the increased inflammatory response in GDM pregnancies is still unveiled. However, activation of the phosphatidylinositol-3 kinase/protein kinase B/nuclear factor-κB (PI3K/Akt/NF-κB) signalling pathway may potentially be involved (Zhang et al., 2021).

Interestingly, HUVECs from GDM pregnancies showed unaltered Akt (Ser^{473}) but higher eNOS (Ser^{1177}) activator phosphorylation (Subiabre et al., 2017). Since the latter study included GDM patients with pre-pregnancy overweight, the potential role of Cu as an activator of Akt in HUVECs may depend on the pre-pregnancy nutritional status of the mother. The activator phosphorylation of Akt was higher, but the eNOS activator phosphorylation was lower in HUVECs from women with pre-pregnancy obesity (Villalobos-Labra et al., 2018). Instead, inhibitory phosphorylation at Thr^{495} in eNOS was increased, limiting the activity of this enzyme, thus reducing the NO generation and the subsequent vasodilatory response of the umbilical vein to insulin. Therefore, maternal pre-pregnancy normal weight, overweight, or obesity will delineate different metabolic conditions *per se*, resulting in different responses of foetoplacental vascular cells when these patients develop GDM. Whether these metabolic conditions associated with abnormal Cu handling by the human placenta is still unknown.

An increased maternal plasma concentration of Cu was reported associated with a higher odds ratio of GDM in 248 women with GDM from Wuhan, China (Li et al., 2019). Interestingly, this study included GDM and normal pregnancies showing a normal pre-pregnancy weight (mean BMI 20.7 and 22.2 kg/m^2 for normal and GDM, respectively). Therefore, Cu may increase the possibility of developing lean GDM ruling out the potential that overweight or obesity may affect the biological actions of an elevated level of Cu in pregnancy.

The potential mechanisms behind Cu effects in pregnancy include abnormal D-glucose metabolism. The increased maternal plasma Cu in patients with GDM was positively associated with abnormal fasting plasma glucose, 1 and 2 h post-glucose load. It is accepted that an increase in maternal glycaemia results in foetal hyperglycaemia, which causes abnormal placental endothelial function (McIntyre et al., 2019). Even when women with GDM show normal glycaemia due to a change to a healthier lifestyle, diet, hypoglycaemic drugs, or insulin therapy, they still associate with abnormal glucose homeostasis in the early stages of pregnancy. Thus, an increase in the maternal plasma concentration of Cu may worsen the capacity of maintaining an equilibrated D-glucose metabolism in the foetus and the placenta in GDM. The latter is a phenomenon beyond the mechanisms associating diverse factors with the development of GDM, such as hyperinsulinemia, hypertriglyceridemia, inflammation, and altered L-arginine/NO endothelial and ALANO signalling pathways (Madsen et al., 2021; McIntyre et al., 2019; San Martín and Sobrevia, 2006; Saravanan et al., 2020; Vásquez et al., 2004). However, it is unknown whether an increase in the maternal plasma level of Cu results in altering these mechanisms in the human placenta vasculature.

4.5. Per- and polyfluoroakyl substances (PFAS)

PFAS are synthetic organic toxic chemicals in the persistent organic pollutants (POPs) that are permanently released by industrial activity leading to contamination of the water, food, and air (Al Amin et al., 2020; Birru et al., 2021). These toxic chemicals are also present in different widespread use products, including food packaging, personal care products, and cooking pieces of equipment (Al Amin et al., 2020; Mitro et al., 2020; Xu et al., 2020). The PFAS accumulate in the body and could take years to be cleared from human tissues. To date, two fluorinated organic compounds, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) may last 6–10 years in the body (Olsen et al., 2007).

PFAS is involved in regulating glucose handling with subsequent consequences in glycaemia in pregnant women (Ehrlich et al., 2016). Several studies suggest that PFAS associate with a higher risk of GDM (Birru et al., 2021; Xu et al., 2020; Rahman et al., 2019). The

mechanisms of PFAS to increase the risk of GDM is not yet unveiled. However, a disrupted thyroid function resulting in increased thyrotropin (TSH) but reduced triiodothyronine (T3) and thyroxine (T4) leading to altered glucose homeostasis has been proposed (Birru et al., 2021). Also, exposure to 12 carbon, long-chain PFAS (known as PFDoA) may play a role in increasing the risk of GDM (Xu et al., 2020). Interestingly, women with GDM show a higher mother-*to*-foetus transplacental transfer ratio of PFAS, including PFOS, PFOA, perfluorohexanesulfonate (PFHpS), perfluorohexanoate (PFHxS), perfluoroundecanoate (PFUnDA), perfluorodecanoate (PFDA), and perfluorononanoate (PFNA) (Eryasa et al., 2019). Therefore, these metabolic disruptors reach the foetus, most likely having an impact on glucose homeostasis. GDM-associated insulin resistance leads to foetal hyperinsulinemia (umbilical cord plasma insulin: ~6 versus ~11 IU/mL in GDM versus normal pregnancies) (Westermeier et al., 2015) and a potential state of insulin resistance (Wang et al., 2013) as well as foetoplacental vasculature insulin resistance (Guzmán-Gutiérrez et al., 2016; Salomón et al., 2012; Subiabre et al., 2018; Westermeier et al., 2011, 2015). Thus, the possibility that PFAS impact the foetus involving foetal insulin resistance in GDM is likely.

Interestingly, perfluorobutane sulfonate (PFBS) is a pollutant synthesised in replacing the PFOS since its shorter half-life in human tissues (~1 month). However, PFBS was recently shown to increase trophoblast invasion (Du et al., 2021). PFBS increased trophoblast invasion via a mechanism involving the higher generation of NO by the inducible NOS isoform in response to activation of $p44/42^{mapk}$ and increased level of matrix metalloproteinase 9 (Du et al., 2021). Since GDM associates with a higher generation of NO via eNOS and activation of eNOS due to increased $p44/42^{mapk}$ in HUVECs (Subiabre et al., 2017), is it possible that PFAS disrupts foetoplacental NO signalling favouring the development of GDM-associated vascular endothelial dysfunction. The latter is supported by the findings showing the exposure of the JEG3 cell line —a trophoblast lineage derived from human placental choriocarcinoma— to PFAS associated with changes in the mRNA expression of several genes. Genes dysregulated by PAFS are involved in critical placental functions. These functions include syncytialisation, inflammation, membrane transport, invasion/mesenchymal transition, and the apoptosis-related genes BAD and BAX (Bangma et al., 2020).

PFAS is also reported to be obesogenic (Ding et al., 2021). Pre-pregnancy obesity associates with a higher risk of gestational diabesity (Cornejo et al., 2021). Also, PFAS reduced the mRNA expression of placental membrane transporters associated with GDM, such as *SLC19A2* encoding for the thiamine carrier 1 and insulin resistance such as *SLC30A1* encoding for Zinc transporters (Bangma et al., 2020; Norouzi et al., 2017). Thus, pre-pregnancy and pregnancy exposure to PFAS will potentially increase the risk of gestational diabesity and perhaps GDM in women with pre-pregnancy overweight, with the subsequent harmful consequences to the development of the foetus.

5. Concluding remarks

The prevalence and risk of developing GDM are increased in women exposed to heavy metals contained in an immediate adverse environment, i.e. the *ecto*-exposome. Similarly, the exposure of the growing foetus to an intrauterine environment with altered balance in the concentration and bioavailability of endogenous molecules, i.e. the *endo*-exposome, causes modifications in the function of the foetoplacental vasculature in GDM pregnancies. Thus, the presence of harmful components of the *ecto*-exposome and *endo*-exposome result in abnormal foetus growth and development with potential consequences in the mother and infant health. Many regions worldwide are highly industrialised, overpopulated, and deforested, among other misconceived conditions, showing a critical imbalance between the macro-ecosystem and micro-ecosystem with a nowadays corroborated harmful effect on 'global warming', flora and fauna, and human health. A higher environmental concentration of As, Pb, Hg, Cu, PAFS, and others, increases the exposure of pregnant women to these heavy metals, resulting in adverse maternal and newborn outcomes. Worryingly, an increase in the content of these heavy metals in the environment accumulates in the human placenta, increasing the risk of developing GDM (Fig. 4).

The placenta allows communication between the mother and foetus by transferring metabolic substrates and toxins to keep the growing foetus in a safe intrauterine environment. Together with or as a consequence of an increased concentration of heavy metals in the placenta, a lack of the regulation of the anti-inflammatory and proinflammatory mechanisms (Zhang et al., 2021), the effectiveness of the pro-oxidant and antioxidant defence mechanisms (Asemi et al., 2015; Ding et al., 2020), and the modulation of crucial signalling pathways such as the endothelial L-arginine/NO signalling (Di Fulvio et al., 2014; Sobrevia et al., 2011), ALANO signalling (San Martín and Sobrevia, 2006; Vásquez et al., 2004; Wu et al., 2018), and insulin/adenosine axis (Silva et al., 2017), is seen in the foetoplacental vasculature.

Alterations in the concentration and activity of molecules of the *endo*-exposome are also determinant for the placenta and foetus in normal and pathological pregnancies. The biological actions of micronutrients and endogenous vasoactive molecules are critical to protecting the fetoplacental vascular function keeping a proper environment for a healthy pregnancy, protecting against GDM. However, an altered bioavailability of these molecules, including Se, vitamin D, and adenosine, result in a higher risk of developing GDM with negative consequences to the newborn and maternal outcome. It is worrying that a concurrent harmful effect of the *ecto*-exposome and altered *endo*-exposome may result in more drastic consequences than their effect individually. Thus, women of childbearing age and pregnant women must

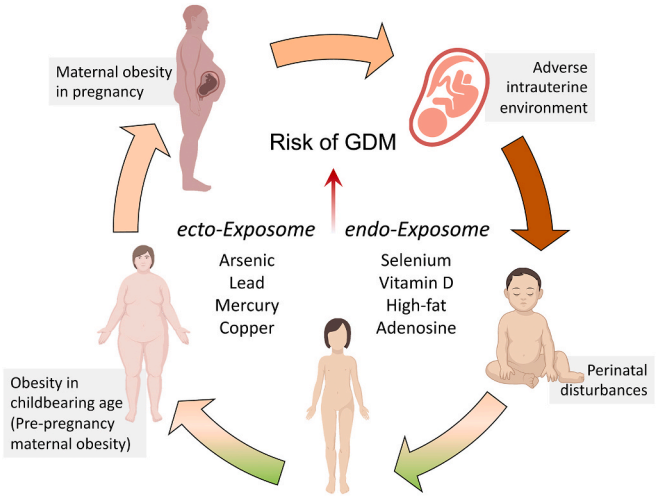

Fig. 4. Risk of gestational diabetes mellitus due to *ecto*-exposome and *endo*-exposome. The ecto-exposome and endo-exposome interact to increase the risk of developing gestational diabetes mellitus (*Risk of GDM*). Elements of the *ecto*-exposome (Arsenic, Lead, Mercury, Copper) are contained in the contaminated external environment and increase the risk of GDM. Also, a decreased or increased concentration or biological actions of elements of the *endo*-exposome (Selenium, vitamin D, low-fat, adenosine) may increase the risk of GDM. The mix of the *ecto*-exposome and *endo*-exposome triggers cell and systemic mechanisms affecting the newborn's health status, conforming to programming to develop young and adult diseases that associate with GDM. Obesity in childbearing age women, i.e. pre-pregnancy maternal obesity, is one of these affections leading to pregnant women that enter pregnancy with obesity maintaining this abnormal metabolic condition in the whole pregnancy period. This group of women develop GDM, a condition referred to as gestational diabesity (Cabalín et al., 2019; Cornejo et al., 2021), generating an adverse intrauterine environment altering foetus growth and development. Because of this cycle, newborns present with perinatal metabolic disturbances that are not evident in the newborn's health status but are manifested soon after birth at childbearing age.

avoid exposure to contaminated environments to reduce the potentially harmful impact causing programming of adult diseases in the new generations, thus, increasing the risk of an unhealthy future pregnancy of the mother.

It is worth mentioning that since a different metabolic condition is expected in women with pre-pregnancy normal weight from those with overweight and obesity (Sobrevia et al., 2020; Cornejo et al., 2021), the consequences of exposing these women before and during pregnancy to harmful *ecto*-exposome and *endo*-exposome may result in a differential impact on the fetoplacental vasculature function. Therefore, we reinforce the concept of being aware of the possibility that women with classic GDM (i.e. GDM and normal pre-pregnancy weight), GMD in women with pre-pregnancy overweight, and gestational diabesity may react differently to these conditions with potentially different effects on the health of the foetus, newborn, infant, child, and adult.

5.1. A final thought

In the constant search for biomarkers effective in predicting and therefore preventing the risk of GDM and other diseases of pregnancy, several endogenous molecules and changes in their bioavailability and functional effects have been proposed. It is worth mentioning that identifying those biomarkers may help focus on the underlying insulin sensitivity rather than the development of hyperglycaemia. Some of the mechanisms might include a reduced vitamin D level, increased adenosine concentration, and increased inflammation and oxidative stress biomarkers. Estimation of the degree of changes in the maternal plasma levels of heavy metals before the women get pregnant will predict a higher risk of developing GDM and this disease-associated detrimental effects on the foetoplacental vascular function. Unfortunately, most heavy metals will last in the human body for decades, and future generations will suffer the consequences of our past and present lack of action. Therefore, preventing heavy metals poisoning by reducing these toxins in essential foods, including drinking water, vegetables, seeds, fish, and others, is an action urgently needed from those who make public health policies. A reduction in the severity and prevalence of GDM by lowering the prevalence of pre-pregnancy maternal obesity and overweight is one goal. However, there is only a modest expectation of the ability to change if the harmful *ecto*-exposome is still present worldwide.

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Declaration of competing interest

The authors confirm that there are no conflicts of interest.

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