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Published in:
Biochimica et Biophysica Acta - General Subjects

DOI:
10.1016/j.bbagen.2022.130282

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Rudge, M. V. C., Alves, F. C. B., Hallur, R. L. S., Oliveira, R. G., Vega, S., Reyes, D. R. A., Floriano, J. F., Prudencio, C. B., Garcia, G. A., Reis, F. V. D. S., Emanueli, C., Fuentes, G., Cornejo, M., Toledo, F., Valenzuela-Hinrichsen, A., Guerra, C., Grismaldo, A., Valero, P., Barbosa, A. M. P., & Sobrevia, L. (2023). Consequences of the exposome to gestational diabetes mellitus. *Biochimica et Biophysica Acta - General Subjects*, *1867*(2), Article 130282. Advance online publication. https://doi.org/10.1016/j.bbagen.2022.130282

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BBA - General Subjects 1867 (2023) 130282

Contents lists available at ScienceDirect

BBA - General Subjects

journal homepage: www.elsevier.com/locate/bbagen

Consequences of the exposome to gestational diabetes mellitus

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ARTICLE INFO

Keywords:
exposome
gestational diabetes
biomarkers
environmental exposures
endogenous exposomes

ABSTRACT

The exposome is the cumulative measure of environmental influences and associated biological responses throughout the lifespan, including those from the environment, diet, behaviour, and endogenous processes. The exposome concept and the 2030 Agenda for the Sustainable Development Goals (SDGs) from the United Nations are the basis for understanding the aetiology and consequences of non-communicable diseases, including gestational diabetes mellitus (GDM). Pregnancy may be developed in an environment with adverse factors part of the immediate internal medium for fetus development and the external medium to which the pregnant woman is exposed. The placenta is the interface between maternal and fetal compartments and acts as a protective barrier or easing agent to transfer exposome from mother to fetus. Under and over-nutrition in utero, exposure to adverse environmental pollutants such as heavy metals, endocrine-disrupting chemicals, pesticides, drugs, pharmaceuticals, lifestyle, air pollutants, and tobacco smoke plays a determinant role in the development of GDM. This phenomenon is worsened by metabolic stress postnatally, such as obesity which increases the risk of GDM and other diseases. Clinical risk factors for GDM development include its aetiology. It is proposed that knowledge-based interventions to change the potential interdependent *ecto*-exposome and *endo*-exposome could avoid the occurrence and consequences of GDM.

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https://doi.org/10.1016/j.bbagen.2022.130282
Received 9 August 2022; Received in revised form 14 October 2022; Accepted 16 November 2022
Available online 24 November 2022
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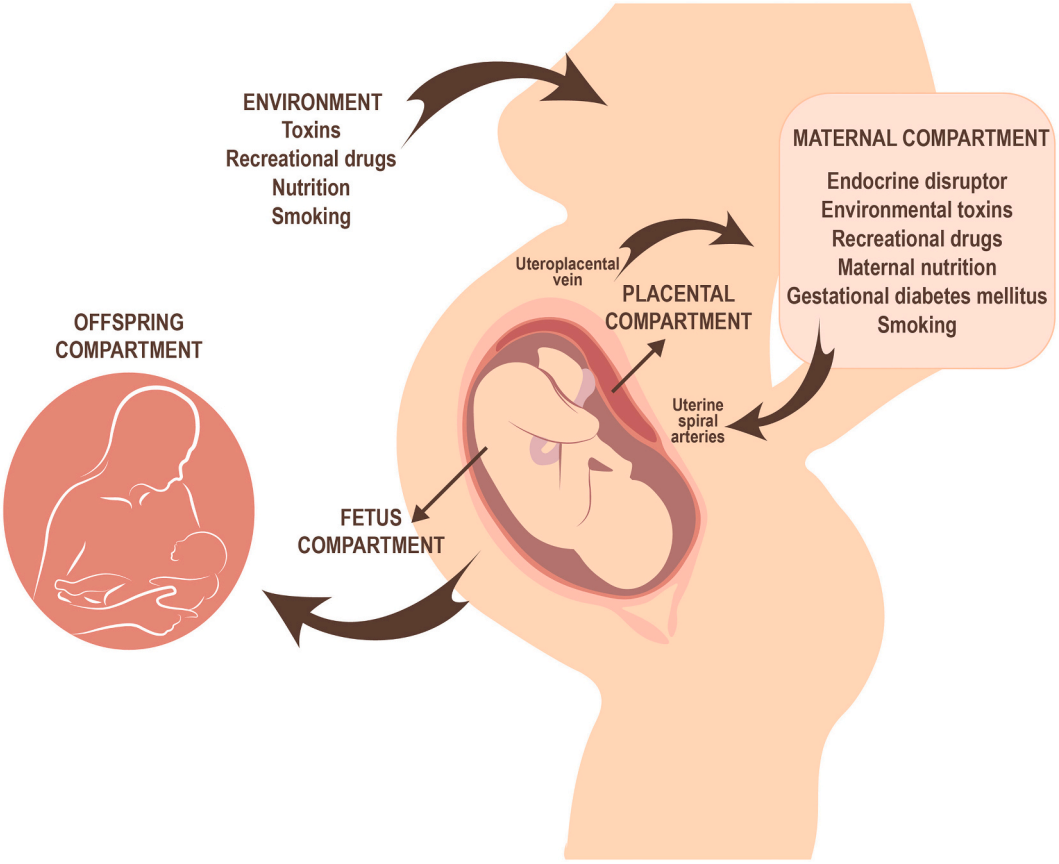

Fig. 1. Factors altering the different biological compartments in pregnancy. Pregnant women are exposed to a series of factors that are part of the environment that modify the maternal environment's normal homeostasis (Maternal Compartment) due to different noxa. An altered maternal compartment will change the feto-placental unit function (Placental Compartment), altering the blood perfusion to this organ and the fetus via the uteroplacental vein and the uterine spiral artery. The fetus (Fetus Compartment) is impacted by the altered equilibrium in the immediate maternal and placental compartments. Changes in the fetus compartment might result in modifications of the neonate (Offspring Compartment), which may increase the risk of developing diseases in the young and adults.

1. Introduction

Gestational diabetes mellitus (GDM) is one of the most common medical conditions associated with pregnancy and is defined as glucose intolerance first diagnosed during pregnancy [5]. GDM arises when maternal insulin levels are insufficient to meet the increased metabolic demands of the mother and fetus in pregnancy. GDM affects 14-18% of pregnant women globally, with a prevalence increasing by 10-100% over the past 20 years [5,28,69,145,162]. Worryingly, more increase in the prevalence of GDM soon is expected as a result of recent changes to GDM diagnostic criteria and the regular rising in obesity rates worldwide [27,28,69,145,150,162].

GDM is a pathology considered an intermediate stage triggered and kept by the exposure of pregnant women to a wide variety of external and internal sources, including chemical and biological agents, radiation, nutritional, or psychosocial, from conception and onwards throughout life leading to young and adult metabolic diseases including type 2 diabetes mellitus (T2DM). "The 2030 Agenda for Sustainable Development Goals (SDGs)" proposed by the United Nations General Assembly in 2015 [148] and the impact of the exposome —internal and external environmental factors delineating human health complementing their genetic background [149,160,161]— on GDM development provide the link for a conceptual model (Figure 1).

The joint analysis among GDM with long-term risk of T2DM development in mother and offspring associated with the current exposome concept [149] is a crucial opportunity to implement measures to improve global health inside the non-communicable diseases (NCDs). The 2030 Agenda for SDGs, whose main aim is reducing premature mortality from NCDs by one third by 2030 consists of 17 SDGs addressing social, economic, and environmental determinants of health and 169 associated targets focused on five themes, *viz*, people, planet, peace, prosperity, and partnership. This agenda proposes a 15-year plan of action and requires strong commitment at all levels and societal change on a large scale [35].

Several years before the 2030 Agenda for SDGs the exposome concept was coined by Christopher Wild [160,161] creating a conceptual framework and the tools to analyse the complex interactions between environment and health [78,149]. This definition was expanded for "the cumulative measure of environmental influences and associated biological responses throughout the lifespan including from the environment, diet, behaviour and endogenous processes". The exposome can be viewed as the environmental equivalent of the genome as it is an all-encompassing view of the exposures throughout life [104]. Considering human health together with The 2030 Agenda for SDGs the current exposome concept emerges as the basis to understand NCDs and to prospectively plan new strategies for their treatment.

Human pregnancy is a physiological condition that may develop in a friendly and healthy environment due to an exposome that is just what was required for a normal pregnancy trajectory. However, pregnancy may also develop in an environment containing adverse factors that form the immediate, internal medium for the fetus development and the external medium for the mother and growing fetus. Thus, a careful analysis of the exposome in pregnancy might be useful for a better understanding on how multiple and cumulative environmental exposures leads to the onset of chronic diseases, progression, and outcomes at critical life stages and across generations [147]. It is well established

that pregnancy is a period in women's life where she and their babies are susceptible to long-term NCDs development referred to as a 'window of opportunity' for exposome analysis and the establishment of new therapeutic strategies [6]. This review focuses on the events associated with the exposome involved in the development of GDM and the long-term maternal and newborn health condition.

2. The exposome

Throughout their entire lives, humans have been, are, and will be challenge to a wide variety of factors that change the course of a normal biological development and health condition, especially during the intrauterine and early postnatal life. These factors may come from external environmental exposures (i.e. the *ecto*-exposome) and endogenous processes (i.e. the *endo*-exposome) as recently proposed [87,149], both impacting the individual's phenotype [34]. Even though the group of factors in the ecto-exposome and endo-exposome are not entirely independent, external variables highly influence endogenous processes, including food quality contributing to obesity or bis-phenol consumption linked to plastics use or animal husbandry. The increase in NCDs, including obesity, infertility, autism, and cancers, has been associated with exposure to industrial chemicals contained in the contaminated air and water, diet, pesticides, pharmaceutical drugs, and personal care and hygiene products, and others [176]. Epidemiological studies suggest that exposure to environmental pollutants, such as endocrine-disrupting chemicals (EDCs) and bisphenol A, even at low concentrations in the body, may contribute, for instance, to diabetogenesis [105]. In the response to external stimuli, various physiological processes are triggered in the human body (e.g. lipid peroxidation, infections, oxidative stress), which in parallel with other natural biological processes result in the generation and regulation of internal factors associated with the development of variety of diseases. Hence, events arising from the organism itself, i.e. endogenously, are to be considered as part of the exposome [87,107,149].

Pregnancy causes important transformations in the woman's body. Linked to endogenous physiological changes, exposure to exogenous contaminants may aggravate pregnant women's health risks, altering foetal development and susceptibility to diseases throughout life. [153]. The exposome itself might be considered neither detrimental nor advantageous, i.e. neutral, but it could become a threat to the fetus and infant development and health because of their physiological immaturity, opportunistic and differential exposures, and a longer lifetime over which disease, started during pregnancy and in early life, can develop. The gestational period is a state where the fetus is impacted by several exposure windows to environmental factors that may lead to epigenetic alterations in the foetal genome [12,29]. These alterations are critical resulting in the programming of the fetus to develop diseases in adulthood, i.e. the developmental origins of health and disease [2,11,36,106].

Foetal programming is associated with critical prenatal periods where the hormonal and nutritional milieu changes altering the expression of the foetal genome leading to long-lasting effects. Programming regards with structural and functional modifications including a reset of the hormonal feedback [20]. A well described factor leading to foetal programming is maternal obesity or overweight either before or during pregnancy [20]. In this case the neonate shows higher risk of developing diabetes mellitus, obesity, and other diseases [36,106]. In addition, the mother also shows higher risk of experiencing complications in future pregnancies such as GDM and labour complications [93,102,106,117].

3. Exposome and risk of GDM

Several studies report the risk of air pollution on the prevalence of GDM in pregnant women [109,153]. A meta-analysis by Zhang and colleagues showed that exposure to air pollution in particular exposure to sulphur dioxide increased the risks of GDM [170]. Also, exposure to ozone gas increased the risks of GDM [170]. Some of the pollutants increasing the risk of GDM include fine particulates from coal mines which could also impair the D-glucose metabolism [103,166]. One reason for the increased risk of GDM is an oxidative stress-dependent abnormal D-glucose metabolism [111,138]. Studies in rats exposed to particulate matter show higher risk of altered blood D-glucose level and expression of pancreatic GLUT2 [166]. In this phenomenon, an increased production of interleukin-6 was found and proposed to alter pancreas function [166].

Some of the air pollutants cross the placenta and have been extracted from the umbilical cord [95,96,143,170]. The pollutants found in the umbilical cord include lead, carbon monoxide, and sulphur dioxide [170]. Thus, exposure to air pollutants impact the foetus. Indeed, an increased risk of insulin resistance in infants born to mothers with GDM that were exposed to environmental pollutants is reported [95].

Table 1
Effect of heavy metals in the pregnant woman, fetoplacental unit, and neonate in gestational diabetes mellitus

Agents	Tissue	Main effect or finding	References
Pregnant woman			
Vanadium	Blood	Higher concentrations in GDM compared with normal pregnancies	[19]
Cadmium	Blood	Higher risk of GDM	[94,109]
Manganese	Urine	Higher concentrations associated with lower post-prandial blood glucose level	[91]
Manganese	Blood	Higher Mn-SOD and lower 8-OHdG concentrations	[140]
Arsenic	Urine	Higher risk of GDM	[8]
Arsenic	Nail clippings	Higher risk of GDM	[45]
Arsenic	Urine	Higher risk of GDM	[45]
Arsenic	Blood	Endocrine disruption Abnormal D-glucose metabolism Higher risk of hypertension in pregnancy	[13,38,44,120]
Lead	Blood	Higher risk of GDM	[140,157]
Mercury	Blood	Higher prevalence of GDM	[115]
Fetoplacental unit			
Lead, Cobalt, Arsenic, Selenium, Mercury	Placenta and cord blood	Found in high concentrations in these fetal tissue	[129]
Vanadium	Placenta	Found in the placenta Enhances insulin receptor binding	[39,109]
Arsenic	HUVECs	Higher NHE1 activity Intracellular alkalization Higher eNOS-mediated NO synthesis Higher system y^+L transport activity	[177]
Methyl mercury	Fetal circulation	Altered fetal development	[26,58]
Neonate			
Arsenic	Meconium	Higher risk of GDM High risk of T2DM in children	[8,134,138]
Arsenic	Maternal blood	Higher fetal, neonatal, and post-neonatal lethality	[70]
Mercury	Maternal blood	Lower birth weight	[82]

eNOS, endothelial nitric oxide synthase; GDM, gestational diabetes mellitus; HUVECs, human umbilical vein endothelial cells; Mn-SOD, Manganese-superoxide dismutase; NHE1, sodium/proton exchanger 1; NO, nitric oxide; y+L, transport activity y+L type; T2DM, type 2 diabetes mellitus. 8-OHdG, 8-oxo-7,8-dihydroguanosine (8-OHdG).

3.1. Heavy metals

Heavy metals refer to metallic elements that are high in density and even at low concentrations are toxic. Heavy metals such as Vanadium, Cadmium, Lead, Mercury, Manganese, and Arsenic are natural earth components and can neither be destroyed nor degraded [8,22,39,40]. Heavy metals enter the human body through the ingestion of food and drink. Worryingly, Lead, Cobalt, Arsenic, Selenium, and Mercury were found in the placenta and human cord blood, suggesting that most of these toxic heavy metals cross the placental barrier [129] (Table 1). The heavy metals also alter the methylation patterns of diabetes-related genes [140]. Thus, it is crucial to assess food and water for contamination with heavy metals since they are not only linked to the development of GDM [109,113,115,120,121,128,139,149] but also with adverse pregnancy outcome [70], risks of autism, hypertension, and altered fetal growth ([13] a; [40,44,77,109,140]).

3.1.1. Vanadium

Vanadium is widely distributed owing to the increase in industrialization. It is found in food products and, therefore, contamination often occurs due to consumption of contaminated food [39]. A study conducted in rats linked water contamination with Vanadium to an increase in the risks of teratogenicity, fetotoxicity, embryo lethality and fertility in exposed mice, furthermore, the increased toxicity associated with higher risk of developing diabetes mellitus [39]. Vanadium is also found in the placenta and has been shown to enhance insulin receptor binding in this tissue in women with GDM compared to women who have not been exposed to Vanadium [39,109]. Another study conducted in China included 2416 pregnant women where the Vanadium concentrations in blood and glycaemia were measured to establish GDM status [19]. The results suggest that women with GDM had a higher Vanadium concentration than women without GDM.

Vanadium's metabolites such as vanadate ($V5^{+}$), which has an insulin like effect thereby enhancing the insulin receptors expression, could result in increased risks of developing insulin resistance [39,109]. Since $V5^{+}$ crosses the placenta, it increases the risks of birth defects and T2DM [39,109]. The mechanism of Vanadium involves reducing the pancreas β-cells function associated with lower production of insulin and hence reduced uptake of D-glucose [39]. In the presence of reactive oxygen species (ROS) the Vanadium metabolites $V5^{+}$ and vanadyl ($V4^{+}$) are formed. High concentrations of these metabolites (v.g. 2 $\mu g/m^3$) trigger oxidative stress causing pancreas cellular damage. Additionally, $V5^{+}$ and $V4^{+}$ may over activate the immune cells leading to the release of natural killer cells triggering a pro-apoptotic activity in the pancreas β-cells [39].

3.1.2. Cadmium

Pregnant women are exposed to Cadmium when they consume polluted water or stay long times in environments that have their soil contaminated with this heavy metal [140]. High concentrations of Cadmium associates with higher risk of GDM and T2DM [94,109]. In a study in 2026 pregnant Chinese women, the risk ratio for GDM was 1.04 among women with Cadmium concentrations of more than 1.36 μg/L [94]. Cadmium is also considered an EDC since binds to hormone receptors acting as agonist or antagonist leading to the modification of hormone's signalling mechanisms. The role of Cadmium exposure in T2DM development remains unclear; however, an increased oxidative stress and gluconeogenic activity is associated with the development of this disease [94,109]. Cadmium increases oxidative stress in the pancreas β-cells, causes activation of gluconeogenic enzymes such as insulin, and associate with impaired insulin secretion [94,109].

3.1.3. Manganese

Manganese is a naturally occurring agent in food such as whole grains, nuts, oysters, clams, leady vegetables, and legumes and is safe when consumed in small quantities (8-9 mg/day) [140]. Overconsumption of Manganese is not only linked to a higher risk of GDM but it is also neurotoxic [140]. This often occurs in cases where there is the inhalation of Manganese-containing dust resulting in high accumulation in the brain which can result in neurodegenerative disorders. Compared to other heavy metals, the Manganese may also be a protective factor against T2DM since individuals with these diseases show lower blood levels of Manganese compared with healthy subjects [140]. Indeed, the average Manganese concentration found in 2093 pregnant Chinese women was 13.2 μg/L, and higher urinary concentrations of manganese were significantly associated with lower post-prandial blood glucose level [91].

Manganese activates enzymes involved in cell metabolism such as the ligases, isomerases lyases, hydrolases and transferases, is involved in the metabolism of D-glucose and lipids, and 8-9 mg/day consumption is protective against metabolic illnesses like diabetes mellitus [140]. Therefore, dietary consumption of Manganese and the use of food supplemented with this metal seems needed for preventing and in deciding the management of patients with T2DM. Interestingly, in a state of high oxidative stress as seen in patients with T1DM, T2DM, and GDM, the concentration in blood of Manganese-superoxide dismutase (Mn-SOD) increases resulting in a reduced formation of 8-oxo-7,8-dihydroguanosine (8-OHdG), a molecule considered a marker of oxidative stress [140].

3.1.4. Arsenic

Arsenic contamination is reported in different types of food including seaweed and rice, and also in the drinking water in some regions worldwide [7,8,70,74,99]. Arsenic dissolved in water is found as arsenate (As^{+3}) and upon ingestion, it is metabolized in the liver, and its metabolites are excreted in the urine. In pregnant women, high urine concentrations of arsenate (>200 μg/L) are associated with a higher risk of developing GDM [8]. Farzan and colleagues conducted a study that included 1151 pregnant women where the levels of arsenic were measured in home water as well as in nail clippings and maternal urine [45]. From the whole group of women, 10.3% of them drank water with arsenic levels >10 μg/L and 1.2% of the women had GDM. Unfortunately, pregnant women exposed to an elevated level of Arsenic may result in altered pregnancy outcomes, as reported in a population of Chileans inhabitants of Antofagasta city, in the North of Chile, with a higher and long-standing miner activity [70]. Contamination of consumable water with Arsenic resulted in a severe threat since increased the rate of fetal, neonatal, and post-neonatal lethality compared with the population of Valparaíso city, in Central Chile, where the level of Arsenic in the water was almost undetectable.

Arsenic contamination also associates with higher oxidative stress and altered expression of genes involved in D-glucose modulation [8,138]. Consumption of arsenic in water or food increases its concentration in the liver and other organs involved in D-glucose metabolism such as the adipose tissues and pancreas [8,138]. These alterations result in inhibition of the D-glucose transporter 4 (GLUT4)-mediated D-glucose transport due to interference with the function of the pancreas and down regulation of the protein kinase B/Akt signalling required for GLUT4 recycling. Thus, Arsenic induced hyperglycaemia due to deficient signalling to express and maintain the activity of GLUT4 [8,138].

A higher blood level of Arsenic is also reported in women with GDM leading to endocrine disruption and abnormal metabolism of D-glucose increasing the risks of hypertension in pregnancy [13,38,44,120]. The latter occurs when there is chronic exposure to Arsenic increasing the risk of cardiovascular and peripheral diseases such as hypertension [8,138]. Arsenic is also detectable in the meconium which is the first stool produced by an infant after birth linking this heavy metal with higher rates of GDM [8,138]. Also, increased Arsenic concentration in the meconium associates with the development of T2DM in children [134]. Whether Arsenic-increased risk of T2DM associated with obesity is unknown.

Table 2
Effect of endocrine disrupting chemicals in the pregnant woman, fetoplacental unit, and neonate in gestational diabetes mellitus

Agents	Tissue	Main effect or finding	References
Pregnant woman			
Bisphenol A	Blood	Obesogenic action Higher risk of GDM	[42,49]
Phthalates	Blood	Obesogenic action Higher risk of GDM	[42,49]
Parabens	Placenta-derived blood EVs	Altered miRNAs profile	[174]
Triclosan	Placenta-derived blood EVs	Altered miRNAs profile	[174]
OCPs	Blood	Higher risk of GDM Impairs-glucose metabolism	[33,109,133]
PAFSs	Blood	Decreases pancreas β-cells function Higher risk of GDM	[142]
DEHPs	Blood	Higher risk of GDM when plasma level is detected at 1st and 2nd trimester of pregnancy	[76] [121]
Fetoplacental unit			
EDCs	Placenta	Altered miRNAs expression	[42]
PFASs	Placenta	Dysregulation of D-glucose metabolism	[142]
PCBs	Fetal circulation	Reduces insulin biological action	[33,159]
Neonate			
PFASs	Detected in the placenta	Higher incidence of metabolic diseases in childhood	[131,142]

EDCs, endocrine-disrupting chemicals; EVs, extracellular vesicles; DEHPs, di-(ethylhexylyl)phthalates; GDM, gestational diabetes mellitus; miRNAs, micro RNAs; OCPs, organochlorine pesticides; PCBs, polychlorinated biphenyls; PFASs, per-and polyfluoroalkyl substances.

3.1.5. Lead

Lead poisoning often occurs as a result of drinking water and food contaminated with this metal, and exposure to lead-based paint and other industry products [109,140]. Lead poisoning associates with chronic diseases including GDM [140,155] and T2DM [109,140]. In a recent report by Leff and colleagues it is shown that rodents exposed to high concentrations of Lead in the drinking water associated with higher concentrations of this metal in blood, and higher blood glucose concentration within 42 weeks [90].

Also, higher concentrations of Lead in the maternal blood (>5 mg/dL) associated with higher risk of developing GDM in women from China [157]. Other studies conducted in mice showed that exposure to Lead results in increased inflammatory reactions since this metal increased the glucose 6-phosphatase (G6pase) enzyme and hepatic phosphoenol pyruvate carboxykinase (PEPCK) levels in the liver [109,140]. Increased levels of these molecules associated with higher incidence of non-alcoholic fatty liver disease, a pathological condition that results in insulin resistance and T2DM [109,140].

3.1.6. Mercury

Exposure to Mercury increases the risk of developing T2DM [40]. Intake of Mercury occurs when consuming fish contaminated with methyl mercury (MeHg) [40]. MeHg alters the fetal development, a phenomenon due to its capacity to cross the placenta reaching the fetal circulation [26,58]. Mercury exposure also associates with the development of metabolic syndrome where subjects affected with this condition show insulin resistance [40,109].

In a study that included 1359 pregnant Chinese women, the prevalence of GDM was ~12% and they have high concentrations of Mercury in the blood [115] and the newborns were with lower birth weight [82]. Unfortunately, the mechanisms associated with the consequences of contamination with this metal in pregnancy, particularly for GDM, are still unveiled. However, folate supplementation has been associated with the detoxification of heavy metals including Mercury [82]. Folate blocks the methylation process associated with heavy metal toxicity hence preventing incidences of illnesses such as T2DM linked to folate contamination [82].

3.2. Endocrine-disrupting chemicals

Endocrine-disrupting chemicals (EDCs) are found in water, air, food, and industrial products capable of interfering with the hormonal action in the human body leading to the development of several endocrine and metabolic diseases (Table 2). EDCs include persistent organochlorine pollutants (POPs), polychlorinated biphenyls, organochlorine pesticides (OCPs), organophosphorus pesticide compounds (OPCs), plasticizers and nonyphenols, among others [57]. Some EDCs are referred to as obesogens since they have adverse effects on the insulin biological action, promote obesity, and increase the risk of developing diabetes mellitus [168]. Exposure to EDCs during pregnancy may have obesogenic properties, among of which bisphenol A (BPA) and phthalates are described [49]. These types of molecules may contribute to weight gain, insulin resistance, and pancreatic β-cell dysfunction in pregnancy playing a role in the development of pregnancy complications including GDM [42,49,149].

EDCs may have both a short- and long-term impact on the development of metabolic diseases. Endocrine disruptors act through classical nuclear receptors, such as estrogen receptors α and β and the androgen receptors [60], but also through oestrogen-related receptors and membrane-bound oestrogen receptors targeting cytosolic second messengers [105]. EDCs may dysregulate the gene expression, a phenomenon explained by their association with induction of epigenetic modifications. GDM associates with epigenetic changes in the placenta [81] including DNA methylation in term placentas, altered microRNAs (miRNAs) expression, inflammation, and endocrine disturbances in the second and third trimesters of pregnancy [54]. Thus, EDCs-associated epigenetic changes are proposed as potential biomarkers for GDM [61,81,126].

GDM characterises by causing dysregulation of the metabolism where the miRNAs play a key role [62,75]. miRNAs are a class of small non-coding RNA molecules of 18-22 nucleotides in length involved in cell proliferation and differentiation, metastasis, and apoptosis. miRNAs regulate gene expression and transcription at the post-transcriptional level interacting with the mRNA. Each miRNA can target and regulate several genes, while a single target gene can be regulated by several different miRNAs. EDCs control miRNAs expression in trophoblast cells [42]. LaRocca and colleagues reported that exposure to phenols and phthalates correlated with placental miR-142-3p, miR15a-5p, and miR-185 level [88]. These miRNAs are involved in the cellular response to insulin and insulin-like growth factor receptor mediated signalling, regulation of serine/threonine protein kinase activity, and upregulation of protein insertion into the mitochondrial membrane involved in the apoptotic signalling pathways [88].

Other studies evaluated the expression of circulating miRNAs in diabetes mellitus and their association with the regulation of β-cell mass and function and homeostasis of the immune system. The results show that miR-375 seems involved in the regulation of insulin secretion in patients with T2DM [48], while miR-96 promotes pancreas β-cell proliferation and suppresses apoptosis by the p21-activated kinase 1 in women with GDM [92]. Dysregulation of miRNAs expression has also been associated with pregnancy complications such as GDM and pre-eclampsia, and these molecules may represent a potential biomarker for early diagnosis of these diseases of pregnancy [50,62,81,86].

Expression of several of miR-146a, miR-21, miR-29a, miR-34a, miR-222, and miR-375 is altered in pancreas β cells, liver, adipose tissue and skeletal muscle from animal models of T1DM or T2DM [123,163,171]. T1DM and T2DM associate with changes in the level of miRNAs in insulin-secreting cells as well as in insulin target tissues [63]. miR-375 is highly enriched in pancreatic islets and regulates the expression of genes

involved in hormone secretion and pancreas β-cell mass expansion in response to insulin resistance [118]. Since serum miRNAs are differentially expressed in women with GDM compared with normal pregnancies, these molecules are proposed as biomarkers for GDM prediction. To date, serum levels of miR-29a, miR-222, and miR-132 were characterized in the second trimester of pregnancy in women with GDM compared with normal pregnancies [172,175]. Interestingly, prenatal exposure to EDCs leads to altered miRNAs expression in the placenta [42]. Prenatal exposure to EDCs such as parabens and triclosan is associated with an altered miRNAs profile of circulating placental-derived extracellular vesicles [174]. Since miRNAs target a diversity of cellular pathways, differential expression of miRNAs in response to EDCs during pregnancy may lead to disrupted biological processes in the fetus and mother [100].

3.2.1. POPs

POPs are chemicals that take long to biodegrade. POPs include per- and polyfluoroalkyl substances (PFASs), polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), and OCPs. POPs also include di-(ethylhexylyl)phthalates (DEHPs) which are used as plasticizer in polyvinyl chloride materials and organophosphorus pesticide compounds (OPCs). POPs are linked to adverse health outcomes including higher risk of immunotoxicity, cancers, autism, diabetes mellitus [43,109,131,142]. Additionally, pesticides play huge roles in the development of diseases in pregnant women, including GDM, who live in regions highly contaminated with these substances [33,109].

3.2.2. PFASs

PFASs are found in high concentrations in food, food packing materials, water, and in commercial products like lubricants, resistant coatings, and aqueous forming foams [43,131,142]. Worryingly, PFASs are also found in the human blood in ~85% of individuals [53]. The precise mechanisms underlying the impact of PFASs on cell function is unclear. However, it is reported that nuclear receptors of PFASs are fatty acids and hence interfering with the disposition of fatty acids [131,142]. In the placenta, PFASs associate with dysregulation of D-glucose metabolism [142] increasing the incidence of metabolic diseases during pregnancy and childhood [131,142].

A strong association between serum concentrations of PFASs and GDM has been reported [142]. PFASs impairs-glucose metabolism by decreasing the function of the pancreas β-cells and hence pregnant women are at higher risk of developing GDM [142]. Women showing high levels of PFASs (>30.6 mg/dL) had higher fasting and postprandial blood glucose and insulin levels [43,131,142]. Also, higher fasting blood glucose after 2 h was higher in women with elevated concentrations of PFAs compared to the other group of women [142]. Furthermore, PFASs associate with a higher risk of obesity, high serum lipid concentrations, and hypertension, conditions that play a role in the onset of GDM [13,44,101].

3.2.3. DEHPs

DEHPs are found in carpets, floors, roofs upholstery, vinyl wall covering, clothing, cable sheathing, pharmaceuticals medical devices, personal care products, off-packing materials, and children's toys [121]. A strong correlation between contaminations with phthalates and risk of insulin resistance and abdominal obesity is reported [121]. Phthalates increase the risks of T2DM associated with oxidative stress damaging the pancreas β cells reducing their functionality, exposure of pregnant women to these compounds increases the risk of developing GDM, and interfere with the biological actions of insulin [121]. It was reported that the risk of GDM increased during the first (odd ratio 2.17, 95% CI: 0.98, 4.79) and second (odd ratio 7.18, 95% CI: 0.98, 4.79) trimester of pregnancy in 350 pregnant from USA women exposures to DEHPs [76].

3.2.4. PCBs

PCBs are organochlorine compounds generated in the industry activity in the production of herbicides, insecticides, and fungicides. These pesticides have been found to contaminate the drinking water, fruits, and vegetables [113]. Pesticides contaminated food and water cross the placental barrier resulting in a child higher risk of developing T2DM [113]. PCBs and PFASs have high affinity to albumin which helps their pass through the placental barrier [33,159]. PCBs also interfere with the insulin action limiting its biological beneficial effects [33,159].

Table 3
Effect of drugs and pharmaceuticals in the pregnant woman and neonate in gestational diabetes mellitus

Agents	Time	Main effect or finding	References
Pregnant woman			
Lamivudine	In pregnancy	Adverse effects in pregnant women with HIV	[167]
Antiepileptic drugs (carbamazepine, valproic acid, phenytoin, lamotrigine, topiramate)	Before or in pregnancy	Higher risk of GDM	[110]
Valproic acid	In pregnancy	Higher risk of GDM Higher risk of T2DM	[73]
Corticosteroids	In pregnancy	Altered hypothalamic-pituitary axis Altered immune system	[59]; [135]; [151]
Testosterone	In pregnancy	Higher risk of GDM Hgher muscle D-glucose release	[119]
Marijuana (carboxyhemoglobine)	In pregnancy	Higher risk of GDM	[158]
Metformin	In pregnancy	Higher risk of GDM	[108,144]
Aripiprazole	In pregnancy	Higher risk of GDM Increases oxidative stress Reduced pancreas β-cells insulin synthesis	[14]
Neonate			
Valproic acid	In pregnancy	Induces neural tube defects in infants	[73]

GDM, gestational diabetes mellitus; T2DM, type 2 diabetes mellitus; HIV, xxxx.

3.2.5. OCPs

Several countries have tried to limit the use of pesticides by limiting the number and quantity of pesticides in food products [25]. Despite these measures, pesticides are still detectable in samples of amniotic fluid at 15-18 weeks of gestations indicating maternal exposure to these molecules [24]. The intake of OCPs in food and water increases the risk of developing GDM [24,37,133]. In a study in 11,273 pregnant USA women, 4.5% developed GDM, and the risk of GDM was higher when exposed to OCPs in pregnancy (odds ratio 2.2, 95% CI 1.5–3.3) [133].

3.2.6. OPCs

OPCs derive from phosphoric acid and are extremely poisonous pesticides that interfere with the metabolism of D-glucose increasing the incidence of T2DM [33]. OPCs form a variety of dialkyl phosphate metabolites that trigger insulin resistance [33] and increase the risk of oxidative stress limiting the pancreas β-cells function leading to altered secretion of insulin and hyperglycaemia [33]. Some of this dialkyl phosphate metabolites include diethyl phosphate (DEP), dimethyl dithiophosphate (DMDTP), dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP), and diethyl di-thiophosphate (DEDTP).

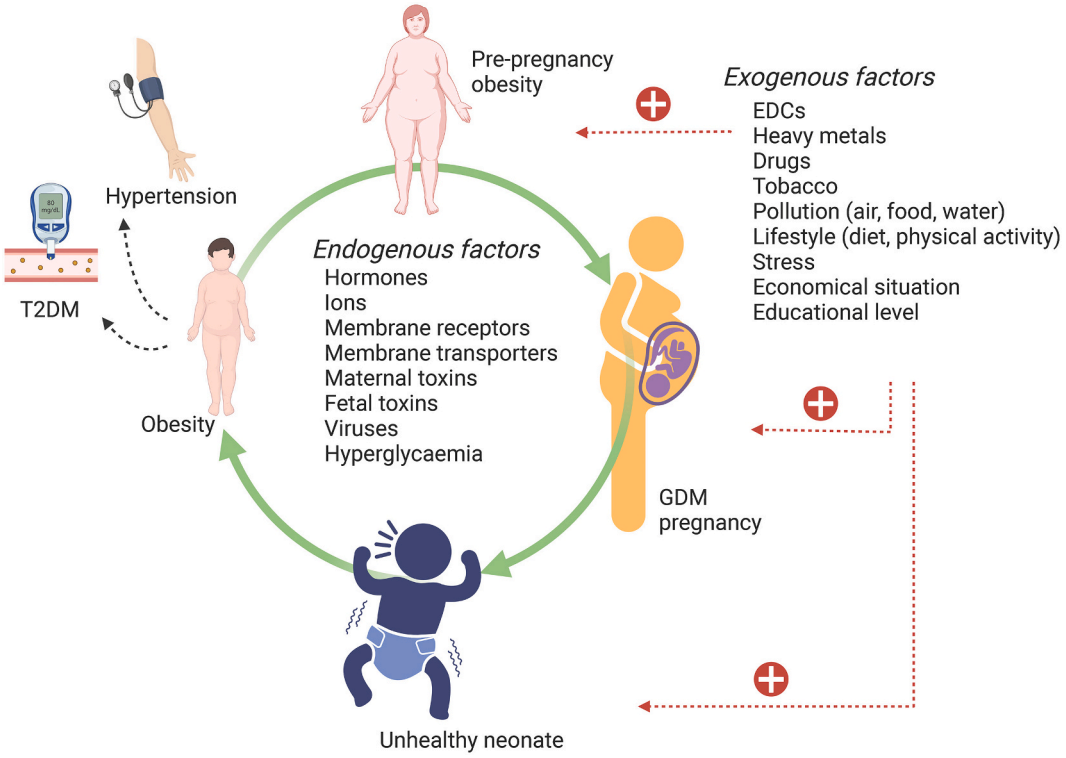

Fig. 2. Impact of the exposome in the cycle of human diseases of pregnancy. Pregnant women are exposed (+) to internal (*Endogenous factors*) and external (*Exogenous factors*) environmental factors that might result in triggering gestational diabetes mellitus (GDM pregnancy). GDM is a disease of pregnancy in which the neonate is distressed (Unhealthy neonate). GDM and an unhealthy neonate are conditions associated with child and adult obesity and a high risk of type 2 diabetes mellitus (T2DM) and hypertension. Child obesity can extend to women in the reproductive age presenting with obesity (Pre-pregnancy obesity), which is a condition increasing the risk of GDM.

3.3. Drugs and pharmaceuticals

3.3.1. Lamivudine

Lamivudine is an antiviral agent used to treat viral diseases like the human immunodeficiency virus (HIV) and hepatitis B [167]. This drug has been associated with higher risk (~8.3%) of developing GDM in pregnant women infected with HIV [167] (Table 3). Even when lamivudine seems safe to use in pregnancy, some studies show that it may have adverse effects in pregnant women and their fetuses [167].

3.3.2. Antiepileptic agents

Antiepileptic agents have also been associated with an increased risk of GDM [98]. The risk of GDM was 2.7-4.3% in a study in 590 Swedish women treated with the antiepileptic agents pregabalin. Pregabalin is an anticonvulsant whose effect is to stop seizures by reducing the abnormal brain electrical activity. Another study reported that GDM was a complication associated with the use of the antiepileptic drugs carbamazepine, valproic acid, phenytoin, lamotrigine, and topiramate in 25 Malacian women before and during pregnancy [110].

Valproic acid is another medication used to treat seizures and other psychiatric conditions linked with GDM [73]. Valproic acid is also potentially involved in diabetes-induced neural tube defects in infants [73]. The aetiology of diabetes mellitus in a patient using valproic acid is characterised by an increased immune response leading to the production of interferon-gamma (IFN-γ) which result in damaging the pancreas β-cells reducing the insulin secretion [73].

3.3.3. Corticosteroids and steroids

Exposure to corticosteroids also associates with GDM and T2DM in infants born to women treated with these molecules [59,135,151]. In a retrospective study by Greene et al. [59] 360,484 pregnant Denmark women were included aiming to show the effect of corticosteroids on T2DM. The results revealed a higher risk of developing T2DM or having elevated glycaemia among the individuals who were on corticosteroid medications. Glucocorticoids disturb insulin D-glucose homeostasis increasing the liver release of D-glucose into the blood resulting in hyperglycaemia [15,59]. Furthermore, glucocorticoids also interfere with the hypothalamic-pituitary axis as well as the immune system as part of the aetiology of GDM [59,135,151]. Changes in the hypothalamic-pituitary axis associated with higher stress leading to increased release of corticosteroids such as hydrocortisone which stimulate the muscle release of D-glucose.

Dexamethasone is a steroid-based medication used as an anti-inflammatory agent that increased the release of insulin leading to insulin resistance and altered D-glucose homeostasis [15,32]. One other steroid that increases the risk of GDM is the testosterone which results in the reprogramming of the D-glucose homeostasis by increasing the release of this hexose from the muscles hence leading to hyperglycaemia [119].

3.3.4. Marijuana

Marijuana is a psychoactive drug obtained from the *Cannabis sativa* plant. Several countries have legalized the use of marijuana for both recreational and medical purposes; however, some studies reported that marijuana results in higher risk of adverse pregnancy outcomes, including GDM [158]. The odds ratio of developing GDM while using marijuana among pregnant women is 0.87 (p-value 0.04). Marijuana's active product is delta-9-tetrahydrocannabinol (Δ-9-THC) which associates with higher production of carboxyhemoglobin, which crosses the human placenta. Carboxyhemoglobin is a compound also linked to other diseases of pregnancy apart from GDM including gestational weight gain, haemorrhage, hormonal imbalance, and increased blood pressure [158].

3.3.5. Metformin and chromium

Medications used to treat diabetes mellitus such as metformin have also been linked to higher risk of GDM [108,144]. Pregnant women with pre-pregnancy diabetes mellitus on low dose of metformin are at risk of developing hyperglycaemia during pregnancy. Lower than needed doses results in poor management of blood glucose level and hence hyperglycaemia [108]. However, metformin doses resulting in blood D-glucose control (<7.8 mmol/L) are associated with lower hyperglycaemia-adverse pregnancy outcomes [108,144]. On the other hand, Chromium is used to treat patients with T2DM improving insulin sensitivity and D-glucose metabolism [10,79].

3.3.6. Antipsychotics

There is an increased worldwide incidence of mental illnesses and hence there is a demand of using medications for treating pregnant women with this condition [41]. An example is the use of aripiprazole, an antipsychotic that crosses the placental barrier [14]. The use of aripiprazole during pregnancy is shown to increase the risk of developing GDM by ~4.7% due to increased oxidative stress which interferes with pancreas β-cells function limiting the insulin production [14].

3.4. Other exposome

3.4.1. Lifestyle

Lifestyle plays a major role in the development of GDM [85,169] (Figure 2). Lifestyle factors include over nutrition, lack of exercise, and increased stress level resulting in higher risk of GDM and obesity during pregnancy [127,165,169]. Obesity is also a risk factor for developing GDM [12,84,146,173]. Women with pre-pregnancy obesity that develop GDM are referred to as having 'gestational diabesity' [17,27,112,139]. It is shown that in women with pre-pregnancy obesity the relative risk for developing GDM is 5-times compared with women with pre-pregnancy normal weight [52].

Gestational diabesity is characterised by metabolic alterations that are different compared with women with a pre-pregnancy normal weight that develop GDM (i.e. lean GDM) or overweight [17,27,51,139,149,150]. To date, gestational diabesity associates with higher mRNA expression of A2B adenosine receptors (A2BAR) protein abundance as a potential mechanism to decrease this condition-associated inflammation [17]. The mechanisms include a reduced release of pro-inflammatory cytokines including tumour necrosis factor and interleukin-6 [164] and increased release of anti-inflammatory cytokines such as interleukin-10 [65], leading to normalizing the nitric oxide level and ROS generation.

A plausible mechanism of obesity-associated GDM include epigenetic modifications resulting in DNA methylation [81,96,169]. DNA methylation has been shown to interfere with GLUT4 activity limiting D-glucose uptake causing hyperglycaemia [96,169]. Obesity by itself is also associated with mitochondrial dysfunction impairing the pancreas β-cells function leading to insulin resistance [3,165]. One of the proposed mechanisms involved in the reduced pancreas β-cells function includes increased oxidative stress [165].

Exposure to a high-fat diet also impairs D-glucose tolerance in patients with GDM. Studies in animal models show that a high-fat diet increased the risk of hyperglycaemia due to impaired pancreas β-cells function [3,21,30,68]. A high-fat diet impairs D-glucose tolerance by causing vascular dysfunction, a phenomenon reducing the functions of the endocrine function of the pancreas [3]. A high-fat diet is also linked to higher prevalence of obesity, and women with this disease show higher level of the adipocytokine leptin compared with lean women [154]. Leptin increases the plasma D-glucose level and fatty acid breakdown as a consequence of its potential c-Jun N-terminal kinases-mediated inhibition of insulin receptor substrate 1 and 2 lowering insulin sensitivity [154]. Leptin levels change according to the expression level of *ADIPOQ* (coding for adiponectin) and *RETN* (coding for resistin) and the degree to which DNA methylation affect the expression of these genes [12,71,97,146].

Another element of the lifestyle is the intensity of occupational activity. A higher occupational activity may also increase the risks of developing GDM. It is reported that individuals involved in high-intensity occupational activity including lifting and physical workload have lower risk of developing GDM [18]. However, involvement in heavy workloads, heavy lifting, and standing for longer than two hours linked with higher risk of preterm birth [18]. Interestingly, individuals who work in a research laboratory have also been shown to have elevated risk of developing GDM and T2DM due to a regular exposure to a variety sort of chemicals [64].

Because of the existing associations between lifestyle factors and GDM, non-pharmacological interventions to change dietary patterns and the inclusion of physical activity are effective in reducing the burden of GDM [31,47]. A proposed diet for the management of GDM is the use of the Mediterranean diet. When Mediterranean diet is introduced within the first trimester of pregnancy the risk of GDM was lower [9,173]. In addition, consumption of micronutrients including Selenium may restore insulin sensitivity and hence protect against GDM [116,141]. It is proposed that micronutrients such as Selenium reduce the oxidative stress and the autoimmunity linked to damage of the pancreatic β-cells [116,141]. Several studies, however, suggest that intake of micronutrients and macronutrients is important in reducing the burden of GDM and insulin resistance [9,72,116,132,141].

3.4.2. Natural polyphenols

Polyphenols increase the risk of GDM damaging the pancreas β-cells [89]. [38,66,114,116,125,152]. Phenolic compounds are contained in Lentinus edodes, a type of mushroom consumed by pregnant women in China [89]. Women who consumed these mushrooms had higher risk of developing GDM due to the develop of insulin resistance. Consumption of polyphenols associate with higher production of oxidative stress biomarkers such as glutathione, glutathione peroxidase, and catalase which have been linked to the damaging of the pancreas β-cells [89]. Other studies in animal models show that phenolic compounds cause severe hyperglycaemia and hyperinsulinemia [56,67,89,114,116,136,152,156].

Cosmetic products contain high levels of phenols, including products such as lipstick, eye shadow, day cream, cleansers, and makeup removers [91]. Pregnant women that applied cosmetic products show higher risk of GDM and other associated chronic conditions such as overweight, hypothyroidism, hyperthyroidism, anaemia, and heart, liver and kidney disease [91]. The use of cosmetic products interferes with the immune system leading to autoimmune conditions that interferes with the thyroid as well as other organs including the pancreas increasing their damage [91].

3.4.3. Air pollutants

Several studies report the risk of air pollution on the prevalence of GDM in pregnant women [109,153]. A meta-analysis by Zhang and colleagues showed that exposure to air pollution in particular exposure to sulphur dioxide increased the risks of GDM [170]. Also, exposure to ozone gas increased the risks of GDM [170]. Some of the pollutants increasing the risk of GDM include fine particulates from coal mines which could also impair the D-glucose metabolism [103,166]. One reason for the increased risk of GDM is an oxidative stress-dependent abnormal D-glucose metabolism [111,138]. Studies in rats exposed to particulate matter show higher risk of altered blood D-glucose level and expression of pancreatic GLUT2 [166]. In this phenomenon, an increased production of interleukin-6 was found and proposed to alter pancreas function [166].

Some of the air pollutants cross the placenta and have been extracted from the umbilical cord [95,96,143,170]. The pollutants found in the umbilical cord include lead, carbon monoxide, and sulphur dioxide [170]. Thus, exposure to air pollutants impact the foetus. Indeed, an increased risk of insulin resistance in infants born to mothers with GDM that were exposed to environmental pollutants is reported [95].

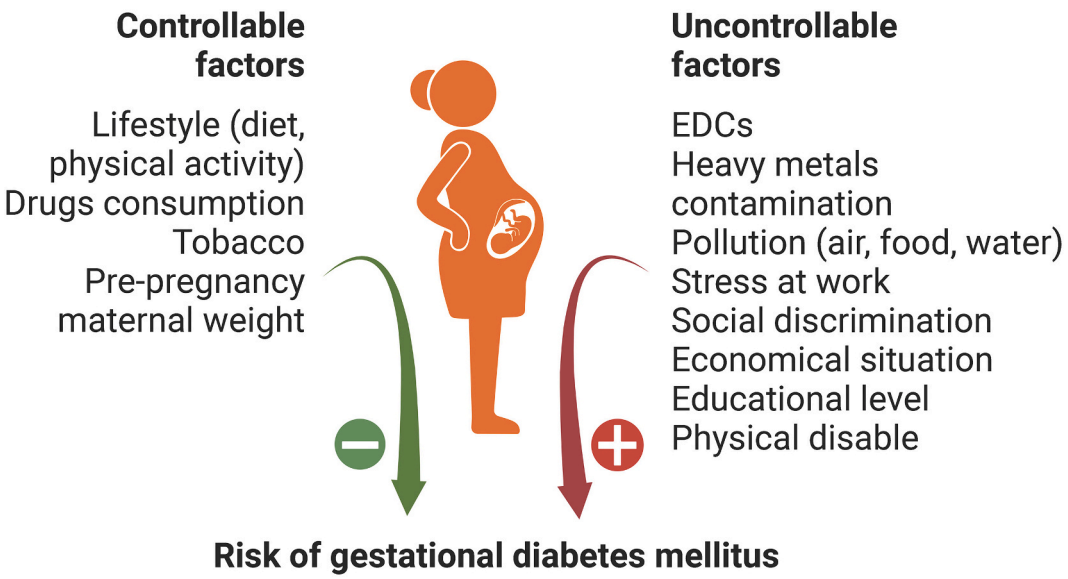

Fig. 3. Impact of the exposome in the risk of gestational diabetes mellitus. Pregnant women are exposed to a variety of environmental factors. These factors may be partially or completely under the control of the women (*Controllable factors*) or far from being controlled by the pregnant women (*Uncontrollable factors*). Depending on the equilibrium between the controllable and uncontrollable factors in pregnancy may result in lower (–) or higher (+) risk of developing gestational diabetes mellitus. EDCs, endocrine disrupting chemicals.

3.4.4. Tobacco smoke

Cigarette smoking as well as secondary exposure to cigarette smoking associates with various diseases, including GDM [1,4,55,124]. Cigarette smoking also associates with reduced function of the pancreas β-cells impairing insulin function [55,124,137]. Smoking increases the risk of oxidative stress which interferes with the function of the pancreas β-cells reducing the release of insulin and hence increasing the insulin resistance [124,137]. In a study including 325,297 pregnant Korean women, 0.65% of the women had GDM and needed to be on insulin therapy [83]. The odds ratio for insulin requiring GDM for smokers compared to non-smokers was 1.55 for former smokers and 1.73 for women who currently smoke. Thus, smoking before pregnancy as well as smoking during pregnancy was associated with increased risk for GDM.

3.4.5. Stress level

Stress contributes to chronic hyperglycaemia in individuals with diabetes mellitus due to alterations the metabolic activity [80,122]. In response to stress various hormones such as catecholamines, cortisol, and growth hormones are released triggering increased release of D-glucose into the blood through the process of gluconeogenesis into most cells [80,122]. Stress can induce the release of growth hormones and catecholamines which reduce the uptake of D-glucose in the cells and hence result in hyperglycaemia [80,122]. Feng et al. [46] conducted a study to evaluate stress levels among pregnant women recruiting 70 women with GDM and 70 healthy women. The results established a higher concentration of stress-related hormones among women with GDM compared to the healthy women. GDM was positively related to levels of cortisol, glucagon, plasma epinephrine, and noradrenalin [46].

Increased concentrations of serum cortisol have also been linked to higher plasma D-glucose concentration [80]. Studies conducted in sheep showed that a high cortisol level linked to high serum D-glucose level even when the animals were no dietary changes or changes in the quantity of the food. Cortisol causes the body to tap into protein and fat cells through the gluconeogenesis resulting in a release of D-glucose into the blood in GDM [80,122].

3.4.6. Placental material

The placenta acts as exposome since the mother and foetus are exposed to a variety of factors including infectious agents, environmental contaminants, radiation, lifestyle-derived factors, metabolism-derived molecules, hormones, and inflammation [68,87,149]. The placenta releases a bulk of products into the foetal and maternal circulation, and this influences the physiology of both the mother and foetus [16]. The material released into the maternal circulation, for example packaged into exosomes and ectosomes [23,130], is involved in the pathophysiology of pregnancy-related disorders such as GDM [130]. The number of particles released into the maternal circulation increases with gestational age and the risk of pregnancy-related disorders in the latter trimesters of pregnancy. In some pregnancies, abnormal placental extracellular vesicles, including exosomes, are produced and these are often involved in diseases of gestation including GDM and preeclampsia [23,87,130].

4. Concluding Remarks

Human pregnancy is a complex physiological process where several mechanisms, including hormonal changes, mechanical adaptations, and psychological and social conditions, are involved in facilitating the progress of pregnancy and the fetus's development and growth for a successful birth. These changes are adaptative mechanisms leading to specific modulations of physiological processes such as increased vascular blood flow to the growing fetus, repressive maternal immune response, and increased nutrition requirements by the mother and fetus. The reaction of the fetoplacental unit to these requirements is essential. However, the response of the mother, fetoplacental unit, and fetus to adverse conditions in the internal (*endo*-exposome) and external (*ecto*-exposome) environment, considering that external environmental factors are highly influencing the internal environment, may result in diseases of pregnancy where GDM is one of high prevalence worldwide [28,145,149,162]. The adverse factors included in the exposome drastically affect the well-being of the mother, fetus, and newborn (Figure 2).

Some of the factors increasing the risk for the development of GDM include (*i*) chemical agents such as EDCs to which people may be exposed throughout life, (*ii*) heavy metals present in contaminated soils, crops and waters, (*iii*) excessive and often unnecessary use of drugs such as antidepressants, corticosteroids, steroids, hypoglycaemics, and hallucinogenic agents, (*iv*) exposure to tobacco and pollution, (*v*) lifestyle lacking a healthy diet, (*vi*) sedentary lifestyle, and (*vii*) high levels

of stress. Interestingly, some of these factors may constitute a controllable set of conditions that could result in a lower risk of GDM (Figure 3). Others are uncontrollable factors or conditions that may increase the risk of GDM. Some of the uncontrollable factors are potentially manageable by making the right public political decisions, and others are more on the social environment that may not depend on the pregnant women.

The placenta is critical in maintaining the communication between the mother and fetus by transferring metabolic substrates (v.g., D-glucose, lipids, amino acids) and clearing the fetus circulation of toxins by an efficient fetus-*to*-mother transfer of waste products derived from the highly active fetal metabolic activity. However, the several contaminants to which pregnant women may be exposed may result in the appearance of pollutants in the placenta and umbilical cord blood. These contaminants associate with a higher risk of GDM in these pregnant women and include heavy metals (v.g. Vanadium, Arsenic, Lead, others), EDCs (v.g. POPs, PFASs, others), antiviral and antiepileptic drugs, corticosteroids, and psychoactive drug including marijuana and antipsychotics. Whether the mother's exposure to adverse exposome results in placental or fetal metabolic changes leading to detrimental signalling-back to the mother to develop GMD is not yet unveiled.

Taking care of the exposure of the mother and fetus to an adverse exposome during the pre-pregnancy and gestational periods may help to reduce the risk of developing GDM and, consequently, T2DM in the long term for the maternal/fetal binomial. GDM symbolizes a window of opportunity to avoid or delay the development of T2DM and is considered an intermediate stage between various external and internal sources from conception to birth. Future cohort studies guided by omics research may rely on several exposome factors acting as biomarkers. These biomarkers, in conjunction with pre-existing risk factors such as obesity or exposure to viruses (including SARS-CoV-2 virus inducing the COVID-19 disease), can help predict the stage and onset of GDM.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Luis Sobrevia reports financial support was provided by Fondo Nacional de Desarrollo Científico y Tecnológico. Marilza Vieira Cunha Rudge reports financial support was provided by São Paulo Research Foundation (FAPESP).

Data availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by the Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) [grant number 1190316], Chile, and International Sabbaticals (LS) (University Medical Centre Groningen, University of Groningen, The Netherlands) from the Vicerectorate of Academic Affairs, Academic Development Office of the Pontificia Universidad Católica de Chile. MVCR, FCBA, RLSH, RGO, SV, DRAR, JFF, CBP, GAG, FVDSR, AMPB, and LS are supported by the Thematic Project – Diamater, from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) [grant number 16/01743-5], Brazil. MVCR holds UNIVERSAL grant and research productivity scholarship (PQ–1C) from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) [305116/2018-5]. RGO and SV were the recipient of PhD fellowships from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil. RGO holds a PhD fellowship from FAPESP [grant number 18/26305-6], Brazil. FCBA, RHLS, DRAR, JFF, and CBP hold postdoctoral fellowships from FAPESP [grant numbers 19/05710-2, 18/02979-8, 18/10661-8, 17/21783-4, and 21/10665-6], Brazil. GF and MC hold PhD fellowships from the Abel Tasman Talent program and University Medical Center Groningen (UMCG), University of Groningen, The Netherlands. GF, MC, and PV hold PhD fellowships from Agencia Nacional de Investigación y Desarrollo (ANID) [Scholarships/National Doctorate 21221950, 21222280, and 21221870] and Universidad de Talca, Chile. AF-H and CG were the recipients of Vicerectorate of Research summer and winter research grants 2023 from the Pontificia Universidad Católica de Chile.

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