Chapter

GDM-Induced Vascular Injury and Its Relationship with Fetal Metabolic Impairment

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Abstract

Cardiovascular diseases are a significant health problem worldwide. To date, there is a lack of awareness that perinatal factors can predispose to CVD before birth. Gestational diabetes mellitus is an increasingly prevalent disease associated with poor fetal outcomes and CVD in the offspring. Evidence from the last decades suggests that GDM causes endothelial dysfunction and impairs nutrient transfer across the placenta to the fetus. These pathological features are associated with altered vascular and trophoblastic homeostasis in the placenta, predisposing the offspring to vascular injury, altered metabolic condition, and future CVD. This chapter focuses its discussion on the to-date understanding of GDM fetoplacental vascular and nutrient transfer impairment that causes, along with the latest advances, limitations, and questions that remain unresolved in this field.

Keywords: gestational diabetes mellitus, cardiovascular diseases, pregnancy, hyperglycemia, endothelial cells

1. Introduction

Almost one of every three adults worldwide dies because of cardiovascular diseases (CVD), making them the most prevalent cause of morbidity and mortality [1]. Several factors increase the risk of suffering a CVD. They can divide into two groups: modifiable and non-modifiable [2]. The former are those factors that can be controlled and modified by behavior, such as physical activity and diet, while the latter ones cannot be changed, like age and genetics. Environmental factors include air pollution and exposure to heavy metals, such as arsenic or lead, and the WHO recognizes them as important CVD risk factors. They could be considered "modifiable"; however, considering that most of the population affected by environmental pollution live in medium to low-income countries, their modification might be complex. An excellent review on this topic was published elsewhere [3]. The apparition of pathological conditions during pregnancy such as pre-eclampsia [4], maternal supraphysiological hypercholesterolemia (MSPH) [5], or gestational diabetes mellitus (GDM) [6] alters the fetal environment and is associated with an increase an increased risk of CVD in the offspring. They might be considered "between" modifiable and non-modifiable: In the gestational state, controlling the disease might prevent the fetal vascular impairment; however, after birth, there is a lack of evidence regarding treatments for improving their outcome and might be

considered a non-modifiable factor. Most of the published research focuses on the repercussions of maternal health after suffering pregnancy disease [7, 8]. Still, their effects on the cardiovascular health of the fetus have been less described.

Over the last decades, the evidence associating pregnancy diseases and fetal outcomes has grown. Regarding MSPH, the apparition of fatty streaks on tunica intima of large arteries at fetal stages [9], probably related to alterations in nutrient transfer through the placenta [10], increases the risk of future cardiovascular events. Sadly, this condition is frequently underdiagnosed [11], and for a solid understanding of its prognosis more studies are needed. Preeclampsia is a relatively common complication of pregnancy [12]. It is associated with a slight but sustained increase in diastolic and systolic pressure on the offspring that seems to maintain for life [13, 14]. Preeclampsia also is related to Intrauterine Growth Restriction [15], which, in turn, is associated with an impaired vascular and metabolic condition [16], predisposing the offspring to worst cardiovascular outcomes. Finally, GDM is a more common disease with global prevalence between 6 and 7% (Europe and United States) and 9 and 13% (South and Central America, Asia, Africa) [17]. The prevalence over the last decades has been increasing in most countries [18–21]; this might relate to the increase in maternal body mass index and the age of a pregnancy [18]. In terms of fetal cardiovascular impairment, a recent meta-analysis found that the offspring whose gestation was affected by GDM present higher basal glucose and systolic pressure [6]. In another large study, GDM pregnancies increased the prevalence of early-onset CVD by almost 30% in the offspring [22]. This worldwide statistical information urges researchers and clinicians to study the repercussions of GDM-complicated pregnancies further. Even more, an association between GDM and preeclampsia has been recently described [23, 24]. This relation can be explained at a systemic level by the increase in the age at which women become pregnant and the augment in body mass index told before; besides, both are related to damage on endothelial cells (EC), impairing vascular homeostasis [23]. Finally, between GDM and MSPH, a relation was recently suggested [25, 26], where EC in the placental vasculature and trophoblasts might have a crucial role; however, there is a considerable lack of evidence in this regard. At this point seems fair to suggest that EC is essential for the pathological development of the three conditions mentioned above. We will explore the GDM-induced vascular and trophoblastic injury and how it can probably impair fetal vascular health in the following pages.

1.1 Gestational diabetes mellitus pathophysiology

GDM is the apparition of spontaneous hyperglycemia in pregnancy without the previous diagnosis of a condition whose main feature is insulin resistance (IR) [27]. This definition is consistent with the evidence that GDM pathophysiology differs from pregnancies of women with prior diabetes in multiple aspects [28] as discussed later.

During a healthy pregnancy, the peripheral insulin sensitivity variates: In the early gestation increases to promote the fill up the glycogen and adipose stores [29], later it declines [30], increasing maternal systemic and placental glycemia. This reduction of insulin sensitivity (i.e., IR) occurs due to the pregnancy variation of systemic and placental hormones (for example, leptin, cortisol, estrogen, progesterone) [31] and is matched with a 2-fold increase in insulin secretion from pancreatic β-cells [32]. Late gestational hyperglycemia favors the transport of glucose to the fetus; however, it depletes the glycogen reservoirs and induces the use of fatty acids as fuel [33]. In GDM, maternal insulin sensitivity almost halves [34], implying two consequences: less accumulation of glycogen in both muscle and liver in the early pregnancy and faster use of them during late pregnancy. Furthermore, once the

glycogen stores deplete, the use of fatty acids to obtain energy is more pronounced than in physiological pregnancy, leading to hypertriglyceridemia (HTG) (**Figure 1**).

Nonetheless, the reader is invited to reflect that a broad spectrum of clinical conditions related to the variable peripheral state of IR can exist [35, 36]. Finally, HTG and hyperglycemia alter placental vasculature [37] and fetal metabolic homeostasis [22, 38]. These features will be the focus of the following sections.

1.2 Gestational diabetes mellitus diagnose

Even when most of the pathophysiological features are known, reaching a diagnostic criterion for GDM has been troublesome. Huhn et al. [39] recently published a review of this topic. To date, one of the most widely accepted definitions is from the International Association of Diabetes and Pregnancy Study Group (IADPSG) [40]. The American Diabetes Association (ADA) agreed with IADPSG; however, first, they suggested a more flexible criterion than IADPS [41]. **Table 1** summarizes both.

The main difference between IADPS and ADA criteria is that the former considers that only one of the mentioned values needs to be altered to diagnose GDM. At the same time, ADA suggests that at least two of them must be present to diagnose GDM [41]. This slight discrepancy seems to be clinically significant: IADPS diagnostic of GDM increases two-fold [42] or three-fold [43] compared to

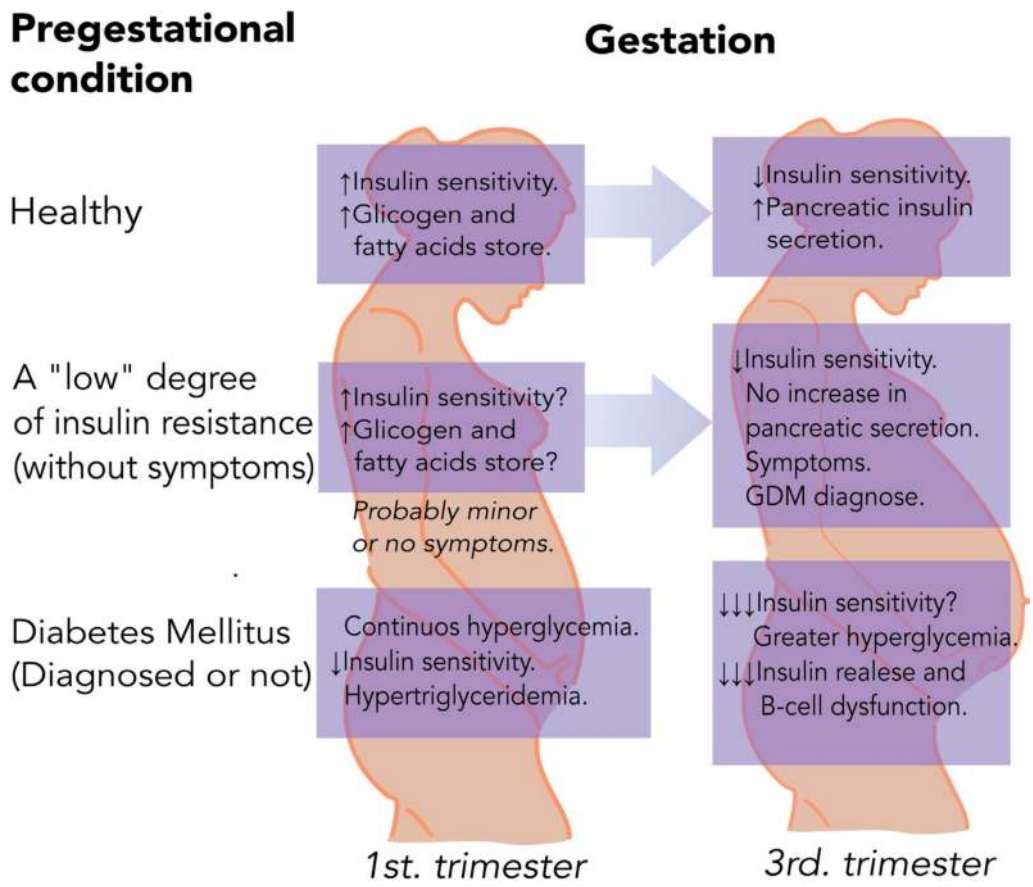

Figure 1.
Metabolic differences between first and third trimester in healthy pregnancies, with a low degree of IR and previously diagnosed Diabetes mellitus. Previous low degree of insulin resistance increases the risk of developing GDM in the third trimester; however, since it courses without significant symptoms, previous IR repercussions are not usually assessed. PGDM alters the placenta's formation in the first trimester, leading to more significant complications on the mother and the fetus in the third trimester.

Test	IADPSG	ADA
Fasting glucose	≥92 mg/dL	≥95 mg/dL
1-h glycemia after OGTT*	≥180 mg/dL	≥180 mg/dL
2-h glycemia after OGTT*	≥153 mg/dL	≥155 mg/dL

**OGTT: oral glucose tolerance test after a charge of 75 g of oral glucose.*
• Both entities consider that this evaluation must be performed between 24 and 28 weeks of gestation.
• The first sample must be taken after 8 h of fasting.

Table 1.
Diagnostic values for GDM.

ADA; moreover, using the IADPS criteria for diagnosis and treatment improves the adverse fetal outcomes of GDM [42, 43]. In this regard, ADA recent guidelines validated and included the IADPS criteria for GDM diagnosis [44].

1.3 Pregestational diabetes mellitus (PGDM)

Women's pregestational condition has historically complexed the study of GDM. GDM tends to appear in women with a previous degree of IR, and insufficient insulin synthesis or release from the pancreas before gravidity [40]. However, for decades, GDM was described as "any degree of glucose intolerance with onset or first recognition during pregnancy" [42, 45], regardless of the prior existence of unrecognized IR. This definition implies a severe limitation. The test for GDM is usually performed between the second and third trimester; but the screening for metabolic perturbances on women at fertile age, before pregnancy, are not actively pursued or a worldwide practice. In this regard, at the time of the GDM diagnose, there are two potential scenarios (**Figure 1**):

- GDM "de novo": the increase of IR at the third trimester will trigger the disease, leading both mother and fetus to a trimester of hyperglycemia and HTG.

- PGDM: the entire pregnancy will occur under a higher IR state, only being detected (and treated) from the third trimester and onwards.

Both conditions are clinically different. For example, birth weight over 4 kg, known as macrosomia, is associated with several fetal metabolic complications [46]. GDM is a risk factor of macrosomia; however, it has been recently suggested that PGDM might cause more severe and frequent metabolic complications, including macrosomia, in the fetus than GDM [28, 47]. A possible explanation for this might rely on more prolonged exposure to higher IR consequences, such as hyperglycemia and HTG. HTG in pregnancy on its own is associated with macrosomia [48]; besides, increased blood glucose, the primary manifestation of both GDM and PGDM, is also associated with poorer fetal outcomes [6, 49]. Both cause oxidative stress [50, 51], cytokine release, and meta-inflammation [52] in the forming placenta, impairing its ultrastructure and the nutrient transport to the fetus. Nonetheless, PGDM will expose the placental vasculature since its early formation to HTG and hyperglycemia. In the next sections, we will extensively discuss this topic.

1.4 Gestational diabetes mellitus induced vascular injury

As stated before, hyperglycemia and HTG are characteristic features of GDM and cause vascular injury on the placenta. Same as what happens on type 2 diabetes

mellitus, GDM altered glucose metabolism on placental vasculature increases the production of reactive oxygen species (ROS) leading to oxidative stress (OS) [53, 54]. OS, in turn, favors the activation of Nuclear Factor kappa Beta and other pro-inflammatory pathways [55]. In GDM, the placenta itself expresses inflammatory cytokines [56]. Inflammation and OS will further induce systemic and placental IR, reducing the entry of glucose to cells [32, 57], impairing glycogen synthesis at the muscle and liver, leading to hyperglycemia and HTG. This oxidative and inflammatory state will also induce endothelial dysfunction (ED) impairing the vascular response to tissular metabolic needs, altering nutrient transfer to the fetus, and increasing the expression of adhesion molecules. To understand better the pathophysiological features of GDM on placental blood vessels and how it impairs the fetal metabolic condition, it is necessary first to summarize the main characteristics of the human placenta.

1.4.1 Development of the placental vascular system

In this section, we will explore the main features of placental development. For an in-depth study on this topic, the reader is invited to review the recent publication done by Turco et al. [58]. In brief, after the fertilization, the zygote will course with successive divisions forming the blastocyst, which will, in turn, adhere to the endometrium and invade it. The most external epithelial layer of the blastocyst will produce various trophoblast cell types and generate the primary syncytium below the implanted embryo [59]. The outer trophoblasts cells will differentiate and fusion, creating the syncytiotrophoblasts [60], whereas the inner cells will differentiate in cytotrophoblast. The syncytiotrophoblasts invade the endometrium and give rise to lacunas, spaces filled with maternal blood that will enlarge, merge, and develop the trabecular system of the forming placenta. The structure formed by both cell types around the lacunae is the primary villi. Later, the fetal mesenchyme will penetrate the villous core forming a structure known as secondary villi. Finally, vascular capillaries will appear within the center of fetal mesenchyme, forming the tertiary villi after the third gestation week. In the following weeks, angiogenesis predominates, increasing capillary density in the villi by developing new branches from preexisting vessels. Thus, the surface area for nutrient and oxygen exchange between the mother and the fetus increase [61]. At this point, in terms of vascular development, the placenta has reached its maturity (**Figure 2**). It is important to note that there are other essential structures in placentogenesis; however, they are beyond the scope of this chapter.

1.4.2 Diabetes impact on placental vascular formation

Tertiary villi arise at half of the second trimester. The pathological difference between PGDM and GDM becomes essential at this stage: from the implantation, and onwards, PGDM will expose the trophoblastic layer to an insulin-resistant, hyperglycemic, and hypoxic environment. Exploring the detrimental effects of both conditions is complicated since it needs the interruption of the pregnancy in human studies. Nonetheless, recent data permitted insight into the alterations caused by GDM or PGDM on the early placenta.

Spiral arteries in the endometrium are invaded by trophoblasts and remodeled [62]. This remodeling turns them into a resistance vessel, favoring the fell of arterial pressure, increasing placental blood flow. This process occurs by a coordinated proliferation, differentiation, and invasion of the trophoblasts, further forming the placenta. Several growth factors, including insulin-like growth factor I (IGF-I), and II (IGF-II) among others, released from the same trophoblasts [63] and other

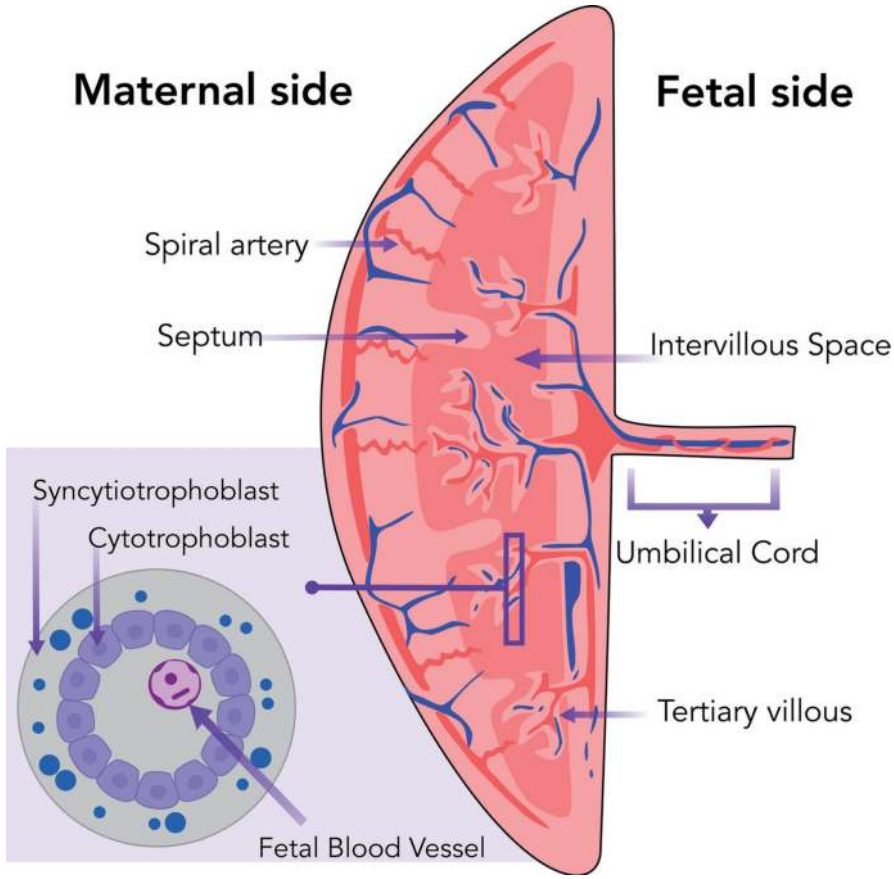

Figure 2.
The human term placenta. Maternal blood reaches the intervillous space (lacunae) through spiral arteries. Then, nutrients and oxygen cross the cytotrophoblasts from the microvillous membrane to the basal membrane and gets to the fetal blood vessels.

placental cell types, stimulate this process [64]. The placenta of GDM is heavier than healthy pregnancies, at least from the second trimester [65] and onwards [66]. This process is not fully understood; however, some findings have elucidated the role of growth factors. Placentas of IR pregnancies have an increased number of cytotrophoblasts, syncytiotrophoblasts, and EC due to a higher proliferation rate [64]. Consequently, placental vascularization in GDM is also enhanced by increased angiogenesis [67]. Differences in expression and secretion of growth factors from GDM trophoblasts themselves seem likely [68]. This increase in proliferation and angiogenesis has been shown in term placentas [68, 69]; yet, a recent study found that high IR is associated with a decrease in trophoblasts' proliferation and increased apoptosis on first-trimester placentas [70]. Another recent work suggested that hyperinsulinemia can also exert those detrimental effects [71]. Apoptosis is low in early healthy pregnancies placentas [72], progressively increasing until term [73]. On GDM, apoptosis analysis has led to conflicting results, showing a decrease [74] or an increase [75] in term placentas. Different technical approaches or the criteria used to diagnose GDM might explain these discrepancies; therefore, more detailed studies are needed. In summary, IR impairs the signaling of growth factors on vascular and trophoblast cells, diminishing the development and invasion respectively at the first trimester; however, as gestation progresses, more growth factors are secreted in a compensatory manner further increasing the size, weight, and the number of blood vessels in the placenta.

Among growth factors, IGF-I and IGF-II are potent stimulators of placental vascular growth, acting through their cognate receptor or insulin receptor. It is important to note that the insulin receptor has two isoforms: A and B. Isoform B presents a sequence of 12 amino acids in the α subunit that A does not have. This slight difference gives them different intracellular signaling and substrate affinity. Isoform A is associated with a mitogenic phenotype via mitogen-activated protein kinases (MAPK), while Isoform B induces metabolic modulation via protein kinase B (Akt). Moreover, IGF-II interaction with insulin receptor A induces cell growth and invasion, while insulin activity on the same isoform protects from apoptosis [76]. This differential action may explain the differences observed in the regulation of apoptosis and cell cycle described above. Exposure to increased insulin levels reduces the insulin receptor and IGF-I receptor's signaling via insulin response element I and downstream targets such as Akt [63]. At this point seems fair to hypothesize that IR impairs placental vascular development by altering the insulin and IGF-I receptor signaling, dysregulating proliferation, and apoptosis. This impairment might explain the high immaturity level of the villous observed in the GDM placenta [77]. Concordant with this hypothesis, human umbilical veins endothelial cells (HUVEC) increase MAPK signaling probably via isoform A of the insulin receptor in GDM [78]. Insulin exposure reestablishes the downstream signaling and membrane expression of both isoforms [78], making it an attractive therapeutic alternative; however, the effectiveness of insulin is highly dependent on the previous IR state. Indeed, obese women that develop GDM respond worse to insulin treatment than lean, diminishing the insulin receptor presence at the membrane and lesser downstream signaling [79, 80]. It is important to note that maternal obesity does not mean necessary IR; however, since most studies do not present evidence from the pregestational state, this suggestion seems fair to be made. More studies are needed taking this consideration since insulin does not seem to be always the better option. An excellent review on this matter has been published elsewhere [81].

Finally, disruption of insulin and IGF receptors signaling, observed in IR states, is related to insufficient trophoblasts invasion, pregnancy-associated hypertension, and increased pregnancy complications, including abortion [63]. In this regard, insulin signaling in the placenta seems crucial and will focus on in the next section.

1.4.3 Placental vasomotor alterations on GDM

The human placenta has no autonomic innervation, so vascular tone regulation is performed by the myogenic tone and humoral and metabolic factors. Humoral factors include norepinephrine [82], renin-angiotensin system (RAS), and vasopressin [83]. The three of them impair invasion of the trophoblast in spiral arteries and alter placental vascular homeostasis. This phenomenon has been studied in pre-eclampsia; however, in GDM, there is a lack of evidence pointing to its potential pathological role. Strikingly, GDM increases the risk of pre-eclampsia from the first trimester and onwards [84]. Indeed, GDM curses with some of the same pre-eclampsia's placental vascular complications (i.e., placental hypoxia and ED) [85]. In particular, maternal vasopressin does not seem to affect fetal blood flow [86], same as norepinephrine [87]. Nonetheless, the latter is related to a reduction in fetal oxygen delivery. This is likely to happen in pregnancies of women with prior diabetes [88] and GDM [89]: both conditions increase catecholamines plasmatic concentration in part because of hyperglycemia [90]. Moreover, norepinephrine augments IR [91, 92], and epinephrine diminishes insulin secretion from the pancreas [93]. In summary, upregulation of catecholamines in GDM negatively impacts placental vessel homeostasis; however, further studies are needed to explore this issue.

Several studies have highlighted the physiological role of the RAS system in placental development and function. A review in this regard has been recently published elsewhere [94]. In brief, the placenta presents all the components of RAS [95]. After implantation, tissular hypoxia induces syncytiotrophoblast formation, the remodeling of the spiral arteries, and angiogenesis. Angiotensin II receptor 1 (AT1R) expression is increased by hypoxia in trophoblasts and spiral arteries, augmenting the expression of angiogenic factors [96]. In healthy pregnancies, AT1R is highly expressed in the trophoblasts in the first and second trimester, declining its levels on the third [97]. However, if hypoxia persists, the expression of AT1R remains high until the end of the pregnancy [98]. As mentioned above, GDM incurs placental hypoxia, which might increase AT1R expression in trophoblasts [99], vascularity in the placenta and placental weight. AT1R expression due to GDM also increases in other vascular beds in rodent models, increasing vascular resistance and systemic arterial pressure [99]. Further, GDM increases the plasma concentration of angiotensin II (AGII), and permanent exposure to AGII induces vasoconstriction, diminishing placental blood flow and fetal oxygen delivery [100]. Also, IR in GDM may cause hyperinsulinemia, which in turn enhances the AT1R [101] and AGII [102] expression. In this regard, the relation between RAS and GDM seems to be even more complex. Higher plasma levels of soluble renin/prorenin receptor in the early pregnancy relate to an increased risk of developing GDM in late pregnancy [103]. This observation is in concordance with the fact that inhibitors of RAS, such as losartan, improve the vascular condition in human diabetes [104, 105] and rodent models of GDM [106]. Furthermore, GDM also increases the plasma concentration of aldosterone [107], an end product of RAS. Interestingly, hyperaldosteronism is associated with ED [108], which will be the subject of the following section. Nevertheless, to the best of my knowledge, this issue has not been assessed on fetoplacental vessels of GDM. Finally, increased AGII umbilical cord levels are associated with increased IR in GDM offspring [109]. Lesser perfusion of the β-cells can explain this due to vasoconstriction and a reduction of insulin sensitivity [110]. Indeed, blockade of RAS ameliorates IR [111]. Both processes converge in EC, where AGII increases ROS production, favoring oxidative stress (OS) [112]. In turn, GDM placenta incurs in OS [54], which impairs insulin signaling in multiple points and induces an inflammatory response mediated by Nuclear Factor kappa B, JNK, and p38 MAPK [113]. On the other hand, AT1R stimulation increases the apoptosis in villous explants and trophoblasts, which associates with pre-eclampsia [114], an event that might also happen in GDM; however, further studies are needed to explore this intricate process.

1.4.4 Endothelial dysfunction on GDM

ED is characterized by imbalanced vasodilation and vasoconstriction, elevated ROS, inflammation, and a deficit of nitric oxide (NO) bioavailability [115, 116]. All these phenomena occur in the GDM placenta, leading to an increased vascular tone and reduced perfusion.

Arachidonic acid is the precursor of thromboxane A2 (TXA2), a vasoconstrictor, and prostacyclin, a vasodilator. The synthesis of both can occur in EC. TXA2 acts through the TXA2 receptor (TR), present in the human umbilical vein. Besides, non-enzymatic oxidation of arachidonic acid produces isoprostanes [117], which can also interact with TR and induce constriction. GDM placentas show an increased synthesis of isoprostanes [54], probably due to the increased production of ROS. In GDM [118] and preeclampsia [119] the prostacyclin/TXA2 ratio is lower in the placenta. Interestingly, OS in trophoblasts increases the concentration of TXA2 but not prostacyclin, pointing to ROS as the responsible for this mechanism

that increases the vascular tone. Endothelium-derived hyperpolarization (EDH) is mostly unexplored in placental vessels, yet it may play a role in GDM placental vascular impairment. EDH exerts vasodilation via stimulation of the Ca^{2+}-activated K^+ channels, which hyperpolarize vascular smooth muscle cells (VSMC) [120]. It is hard to guess if GDM alters this mechanism. Preeclamptic pregnancies show a lesser EDH effect [121]; however, type 2 diabetes mellitus increases the EDH effect [122]. Further studies are needed to elucidate if EDH impairs or compensates ED in GDM.

Nitric oxide (NO) is probably the most characterized endothelium-derived vasodilator agent. Indeed, some consider that NO is the most potent vasodilator in the human placenta [123]. Due to its biological relevance, it is not surprising that its bioavailability is highly regulated. For instance, NO depends on the cellular intake of L-Arginine and the activity of the nitric oxide synthases. In EC, endothelial nitric oxide synthase (eNOS) is the primary source of NO, and cytosolic calcium, protein kinase A, and AKT favor the activity of this enzyme [124]. Insulin stimulates eNOS via AKT; besides, diabetes impairs this stimulation reducing eNOS activity, while reduction of NO induces IR, forming a vicious cycle [125]. On the other hand, NO acts on the VSMC, causing dilation via guanylyl-cyclase; however, it favors apoptosis [126] and inhibits proliferation [127] of the same cell type. VSMC apoptosis reduces the capability of resistance vessels to contract; in contrast, AGII favors proliferation via ROS activation of p38 MAPK [128]. Interestingly, a recent publication observed that GDM increases the insulin receptor isoform A and IGF 1R [129]. This gives consistency to the observations stated before: GDM enhances RAS and insulin receptor isoform A signaling in the placenta, both favoring the proliferation of VSMC; however, even when the machinery to produce NO upregulates in GDM [130], a reduction in its bioavailability is observed probably due to depletion by oxidative stress [131]. In turn, NO reduction inhibits apoptosis and further favors proliferation of VSMC, which will increase vascular tone, reduce perfusion, increasing hypoxia, and stimulate angiogenesis and even more OS. Nonetheless, even when consistent, this idea (**Figure 3**) needs further experimental support.

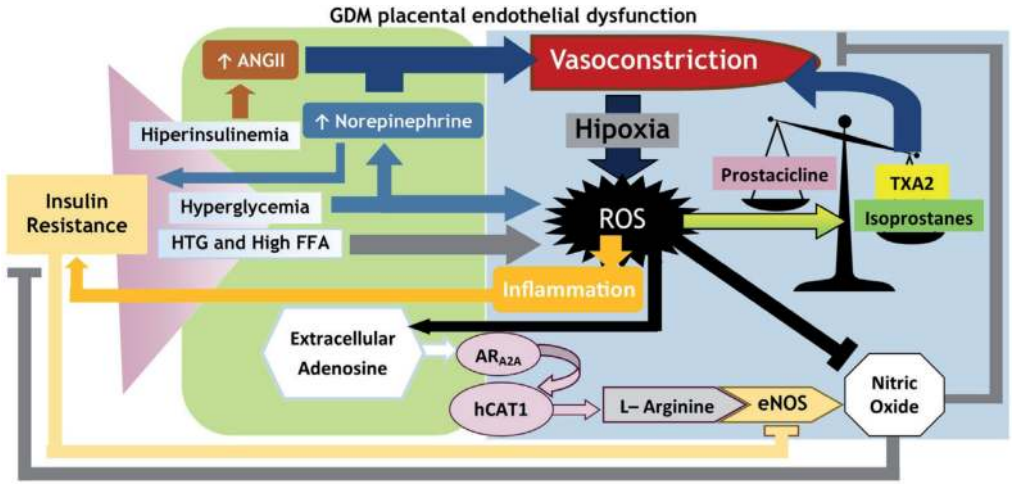

Figure 3.
Mechanisms of GDM-induced endothelial dysfunction in the human placenta. Insulin resistance, hyperinsulinemia, hyperglycemia, hypertriglyceridemia (HTG), and high plasma concentration of free fatty acids (FFA) characterize GDM. These alterations induce vasoconstriction, hypoxia, and reactive oxygen species (ROS) production. ROS, in turn, will increase thromboxane A2 (TxA2) and isoprostanes in endothelial cells, further favoring vasoconstriction. ROS also upregulates the adenosine signaling, and the adenosine/L-Arginine/nitric oxide axis will be upregulated; however, insulin resistance diminishes endothelial nitric oxide synthase (eNOS) phosphorylation and nitric oxide (NO) production. Also, ROS will interact with NO and produce peroxynitrite, reducing NO bioavailability.

L-Arginine also determines the synthesis of NO by eNOS. L-Arginine is transformed in L-citrulline for NO production by eNOS [123]; so, NO production is dependent on intracellular L-Arginine content. Cationic amino acid transporter 1 (hCAT-1) is the main responsible for the entry of L-Arginine to the cell in the human [132]. Interestingly, insulin, OS and the activation of adenosine receptor A 2A (AR_{A2A}) induce hCAT-1 expression [133]. In this regard, even when in GDM impairs insulin signaling, OS and the activation of AR_{A2A} will favor the expression of hCAT-1 and secure the L-Arginine entry. OS can also induce the activation of adenosine receptor [134]. However, the insulin effect over hCAT-1 expression and activity has been described as requiring functional AR_{A2A} in HUVEC [135]. GDM hinders adenosine transport to the cell, increasing its extracellular concentration [136, 137]. Extracellular adenosine will activate AR_{A2A}, which will induce vasodilation [133]. Interestingly, adenosine can also interact with adenosine receptor A 2B (AR_{A2B}), which is expressed in microvascular EC and induces angiogenesis [138]. The high adenosine concentration facilitates the AR_{A2B} activation and may relate to the increased vascularization and weight observed in GDM placentas. A recent work has shown that adenosine induces fetal vessels constriction; however, GDM impairs its vasoconstrictor effect [139]. Going back to the above, even when the whole adenosine/L-Arginine/NO axis raises in GDM, the lesser bioavailability of NO impedes its biological effect. Likewise, NO deficit might explain why GDM reduces the insulin vasodilatory effect [131]. In this regard, endothelial dysfunction by GDM not only affects vasodilation but vasoconstriction as well, hindering the capability of the endothelium to regulate the vascular tone.

Finally, it is crucial to note that hypoxia [140] and hyperglycemia [141] induce OS. Interestingly, hyperglycemia on its own can induce hypoxia [142]. Mitochondrial impairment is probably the most important source of ROS in GDM; an excellent review has been made elsewhere [143]. Further, a recent work described mitochondrial dysfunction in cytotrophoblast and syncytiotrophoblast from GDM pregnancies. The latter seems to be more comprised in terms of ATP generation and increases the expression of antioxidants [144]. Nonetheless, this impairment is more profound when higher grades of IR are present [113] and the pregestational condition is highly relevant [143]. Insulin can increase the production of antioxidants; however, in GDM placentas, the expression of antioxidants is increased constantly [145], making them less responsive to future oxidants insults. Finally, ROS can react non-enzymatically with NO, producing peroxynitrite, which has been shown to inhibit mitochondrial respiration and damaged mitochondria [146], making a vicious cycle for ROS production.

1.4.5 Placental altered nutrient transfer on GDM and fetal metabolic injury

Hyperglycemia and HTG are the most common metabolic alterations in GDM. Recent work evidenced that HTG in early pregnancy is related to IR, β-cell dysfunction, and hyperglycemia [147]. Umbilical cord blood analysis has demonstrated that GDM causes fetal hyperinsulinemia proportional to maternal IR [148]. Triglyceridemia remains unaltered, but LDL concentrations increase and HDL diminishes in cord blood of GDM deliveries and directly associates with macrosomia [149]. Intriguingly, triglyceridemia remains unaltered since maternal HTG is better related to macrosomia than hyperglycemia itself [150–152]. In this regard, the relationship observed between HTG and macrosomia in GDM might have two possible causes: an increase in the fetal delivery of free fatty acids (FFA) posterior to the action of lipases or the impairment of placental homeostasis due to ED. The first hypothesis does not seem likely: even when GDM curses with high FFA maternal plasma concentration [153], cord blood FFA content remains unaltered

in GDM deliveries [154]. In this regard, the second hypothesis seems more plausible. HTG is related to ED; however, a mechanistic explanation is lacking to date. A recent review was made about this topic elsewhere [155]. A probable explanation for ED lies in macrophage activation by triglyceride-rich lipoproteins like Very-Low-Density Lipoprotein (VLDL) [156]. VLDL also induces ROS production and expression of inflammation mediators such as Tumoral Necrosis Factor α (TNF-α) in EC [157]. Interestingly, TNF-α favors IR and hyperinsulinemia in GDM [32], hindering insulin-mediated vasodilation. Also, the oxidative environment induced by triglycerides may favor the NO consumption, establishing the ED. Nonetheless, further studies are needed to address this issue in GDM placentas.

Finally, glucose transport in the placenta is regulated by maternal glycemia and by the expression and activity of glucose transporters (GLUT). For transportation from the mother to the fetus, glucose must go through the microvillous membrane (MVM), at the maternal side, to the basal membrane (BM) on the fetal side [158]. At least 6 GLUT transporters have been identified in the placenta: GLUT1, GLUT3, GLUT4, GLUT8, GLUT9, and GLUT12. Nonetheless, the most abundant isoforms in the placenta are GLUT1 and GLUT4. GLUT1 levels increase in syncytiotrophoblasts along with the pregnancy progression [159]. GLUT1 expresses in the MVM 3-fold than in the BM. Thus, crossing the BM is the rate-limiting step for glucose transport to fetal circulation [160]. Indeed, increased content of GLUT1 is correlated proportionally with fetal weight and macrosomia [161]. GLUT4 expression, contrarily to what was thought before [159], increases during gestation in the MVM, but only in healthy lean women [162]. In GDM, interestingly, insulin lowers mRNA of GLUT4; besides, various authors found increased GLUT1 expression [79, 163, 164]. Even more, GLUT1 upregulation is more profound in PGDM [164]. In this regard, it seems fair to suggest that GLUT 1 in the BM is critical for GDM pregnancy complications due to increased glucose transport [165]. Hyperglycemia should limit GLUT1 expression in trophoblasts and favor its movement from the membrane to the cytoplasm [166, 167]; however, in GDM, this does not seem to happen. A mechanistic study is necessary to address this issue. Finally, an increased transfer of maternal insulin to the fetus could explain hyperinsulinemia observed in the fetal cord of GDM deliveries. Nonetheless, near 1% maternal insulin crosses the placenta [168]. This could hardly cause an increase in fetal insulinemia; however, it may contribute. In this regard, the Modified Pedersen hypothesis offers a better explanation: Maternal hyperglycemia passes through the placenta to the fetus; then, from the second trimester and onwards, the fetal pancreas responds to hyperglycemia with hyperinsulinemia, further favoring glucose disposition in fat stores and the anabolic effects of insulin, resulting in macrosomia [169]. This could also explain the vascular alterations observed in the GDM offspring; however, further research for addressing this issue is needed.

2. Conclusion

GDM is a complex condition that affects both fetus and mother. Its impact on the offspring includes vascular and metabolic impairment before birth, predisposing them to early CVD. The real prevalence of GDM worldwide is unknown and might go beyond our expectations since it is mostly underdiagnosed. Moreover, the differential impact of previously diagnosed diabetes in pregnancy has begun to elucidate in the last few decades. On the other hand, the reader is invited to reflect that the pathological IR state in pregnancy is not a "black-or-white" matter but a continuous spectrum of possible conditions and fetal outcomes that needs to be assessed in every pregnancy individually. Including the assessment of HbA1c and

lipid profile test in the first trimester, evaluation might improve the diagnosis of PGDM and foresee the future GDM development.

Previous IR state and PGDM hinder syncytiotrophoblast invasion in maternal vessels and the placenta formation; however, there is still much to research and learn from this subject. After development, GDM will continuously expose the placenta to a hypoxic environment that will impair vascular function due to increased OS and inflammation. HTG, hyperglycemia, and increased FFA will favor this pro-oxidant environment, causing ED. The regulation of the vascular tone by EC will impair favoring vasoconstriction and further tissular hypoxia. The nutrient transfer to the fetus will alter on this condition, exposing it constantly to hyperglycemia. Persistent hyperglycemia will damage its blood vessels and force its β-cells to secrete insulin extensively, causing metabolic and vascular impairment that will predispose it to CVD before its birth.

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Conflict of interest

The authors declare no conflict of interest.

Nomenclature

ADA	American Diabetes Association
AGII	angiotensin II
AT1R	angiotensin II receptor 1
AR_{A2A}	adenosine receptor A 2A
AR_{A2B}	adenosine receptor A 2B
BM	basal membrane
CVD	cardiovascular diseases
EC	endothelial cells
ED	endothelial dysfunction
eNOS	endothelial nitric oxide synthase
EDH	endothelium-derived hyperpolarization
FFA	free fatty acids
GDM	gestational diabetes mellitus
HTG	hypertriglyceridemia
hCAT-1	human cationic amino acid transporter 1
HUVEC	human umbilical veins endothelial cells
IGF-I	insulin-like growth factor I
IGF-II	insulin-like growth factor II
IR	insulin resistance
IADPSG	International Association of Diabetes and Pregnancy Study Group
MSPH	maternal supraphysiological hypercholesterolemia
MVM	microvillous membrane
MAPK	mitogen-activated protein kinases
NO	nitric oxide
OS	oxidative stress

PGDM	pregestational diabetes mellitus
Akt	protein kinase B
ROS	reactive oxygen species
RAS	renin-angiotensin system
TXA2	thromboxane A2
TR	thromboxane A2 receptor
TNF-α	tumoral necrosis factor α
VSMC	vascular smooth muscle cells

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