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Fetoplacental endothelial dysfunction in gestational diabetes mellitus and maternal obesity: A potential threat for programming cardiovascular disease

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ABSTRACT

Gestational diabetes mellitus (GDM) and maternal obesity (MO) increase the risk of adverse fetal outcomes, and the incidence of cardiovascular disease later in life. Extensive research has been conducted to elucidate the underlying mechanisms by which GDM and MO program the offspring to disease. This review focuses on the role of fetoplacental endothelial dysfunction in programming the offspring for cardiovascular disease in GDM and MO pregnancies. We discuss how pre-existing maternal health conditions can lead to vascular dysfunction in the fetoplacental unit and the fetus. We also examine the role of fetoplacental endothelial dysfunction in impairing fetal cardiovascular system development and the involvement of nitric oxide and hydrogen sulfide in mediating fetoplacental vascular dysfunction. Furthermore, we suggest that the L-Arginine-Nitric Oxide and the Adenosine-L-Arginine-Nitric Oxide (ALANO) signaling pathways are pertinent targets for research. Despite significant progress in this area, there are still knowledge gaps that need to be addressed in future research.

1. Introduction

Obesity among women of childbearing age has been increasing worldwide at an alarming rate. Maternal obesity (MO) is one of the most common obstetric conditions and a significant risk factor for pregnancy-related disorders [1]. During pregnancy, obese women present a 2.4-fold increased risk of developing gestational diabetes mellitus (GDM) when compared to lean women [2]. Gestational diabesity (GDy) refers to the coexistence of GDM and pre-pregnancy obesity. Regrettably, most studies report GDM regardless of pre-pregnancy body-mass index [3]. Nevertheless, evidence suggests that both GDM and MO predispose the offspring to an increased risk of adverse cardiometabolic phenotypes in a sex-specific way, increasing the risk for cardiovascular disease (CVD) development [4,5]. Clinical research has suggested that neonates born either to GDM or MO-portraying mothers have an increased risk for adverse clinical outcomes [6,7], including increased birth weight,

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macrosomia, and neonatal hyperglycemia [8–12]. In older offspring, MO-associated complications include increased adiposity, adverse fat distribution, higher blood pressure, adverse lipid profile, and insulin resistance, presenting a 3-fold risk of developing obesity [13]. Likewise, GDM-offspring are at a greater risk to develop diabetes, metabolic syndrome, higher blood pressure, and obesity than lean mothers' offspring [14–16]. Thus, it has become fundamental to acknowledge that, before and during pregnancy, maternal nutrition and maternal health status are key determinants of offspring health.

Over the past few years, the incidence rates of CVD among young adults (18–45 years) have risen abruptly due to high-fat diet consumption, tobacco use, and increased blood pressure [17], as confirmed by the incidence of stroke in 10 % of this population. Indeed, MO, GDM, and GDy might also contribute to these numbers of registered premature deaths caused by CVD. Therefore, it is imperative to understand the underlying mechanisms of MO, GDM, and GDy and how these maternal conditions may impact cardiovascular system development in the offspring.

In this comprehensive review, we aim to address the current knowledge gap surrounding GDy by focusing on the effects of GDM and MO on fetoplacental function, given the limited number of available studies on GDy. Our investigation primarily delves into the dysregulation of key factors including epigenetics, inflammation, and vascular and metabolic function. Furthermore, we highlight the potential implications of fetoplacental endothelial dysfunction on fetal cardiovascular system development, while proposing potential underlying mechanisms. We extensively reviewed the studies available on the PUBMED database involving GDM/MO-induced fetoplacental vascular dysfunction (i.e, epigenetics remodeling, inflammation markers, NO and H_2S signaling, mitochondrial dysfunction, the **A**denosine-**L**-**A**rginine-**N**itric **O**xide (ALANO) pathway) and CVD programming in the offspring by MO and GDM (i.e., cardiac epigenetics remodeling, NO and H_2S signaling, cardiac mitochondrial dysfunction, endothelial cell and cardiovascular system development, and endothelial cell-cardiomyocyte interaction). The ultimate objective was to enhance understanding and provide valuable insights into the complex interactions between GDM, MO, fetoplacental function, and programming for cardiovascular disease.

2. Programming of cardiovascular disease by adverse intrauterine environment: Insights into the underlying mechanisms

The developmental programming concept states that an adverse intrauterine environment leads to structural and epigenetic fetal adaptations that could endure over the life course, predisposing to the development of non-communicable diseases later in life [6]. Different studies have explored maternal disease-induced epigenetic remodeling, mitochondrial dysfunction, oxidative stress, and impaired vascular function and nutrient transport in the fetoplacental unit as potential molecular mechanisms behind early life programming of CVD [6,18].

2.1. Epigenetic changes in the fetoplacental vascularization in response to gestational diabetes mellitus and maternal obesity

Maternal diet can have a significant impact on offspring's epigenetics. Epigenetics remodeling encompasses alterations in DNA methylation, non-coding RNAs (such as micro RNAs (miRNAs) and long non-coding RNAs (lncRNAs)), and histone modifications [19]. DNA methylation profile is passed on to daughter cells and thus, in addition to the possibility of regulating the instantaneous gene expression, has the potential to modulate gene expression in the long-term. For instance, studies of the long-term outcome of the Dutch famine during World War II have demonstrated decreased insulin tolerance [20] and long-term epigenetic alterations in adult offspring [21] that have been exposed to maternal food deficiency in utero, highlighting the importance of studying the fetoplacental epigenome to understand the relation between maternal diet/metabolism, epigenetic changes in the offspring and the resulting outcome on long-term health. The fetoplacental unit is a crucial interface between maternal and fetal circulatory systems, providing essential nutrients and oxygen to support fetal growth and development. Alterations in fetoplacental vascular and endothelial function can significantly impact fetal development and may have long-lasting consequences on the health of the offspring [19]. In this section, we explore how an adverse intrauterine environment induced by maternal conditions can remodel epigenetic mechanisms, potentially leading to fetoplacental endothelial dysfunction.

Compelling evidence has shown that not only maternal food restriction, but also oversupply in case of MO impairs epigenetics mechanisms in the fetoplacental unit [22–24]. Ten-eleven translocases (TETs), which regulate overall DNA demethylation in CpG islands, are decreased in the human placenta of obese and GDM-portraying women [25], potentially leading to increased DNA methylation which will affect gene expression [25]. Epigenetic changes of GDM and MO are likely to affect also the fetoplacental vascular system. For instance, pre-pregnancy BMI correlates with increased methylation of placental EGF-like domain multiple 7 (*EGFL7*) [26], a gene that has been proposed to be involved in the angiogenesis of human endothelial colony-forming cells (ECFCs) [27]. Furthermore, in umbilical cord blood, increased gestational weight gain (GWG) positively correlates with the methylation of insulin-like growth factor binding protein 1 (*IGFBP-1)* [28], which has been suggested to play a protective role in the senescence of endothelial cells in vitro [29]. The migration of vascular endothelial cells and angiogenesis are, in part, controlled by miRNA-210 [30], which expression levels positively correlate with MO in placentas carrying female fetuses, suggesting a potentially relevant role in mediating a sex-specific response to MO in endothelial function [31,32]. Similarly to MO, GDM also induces epigenetic alterations in the fetoplacental unit [33]. GDM increases overall DNA methylation in the placenta and in umbilical cord blood [34]. Among other mechanisms, this increased global DNA methylation in the umbilical cord blood could be due to reduced levels of TET2, and of 5-hydroxymethylcytosine, a product of TETs' enzymatic action in GDM umbilical veins in the fetal side [35]. Moreover, GDM exerts epigenetic alterations directly in endothelial cells of the fetoplacental vasculature [36]. Fetoplacental endothelial cells isolated after GDM pregnancies reveal altered transcriptome and DNA methylation profiles, and the differentially methylated and expressed genes are particularly clustered in the functional pathways ‘cell morphology’ and ‘cellular movement’ [37]. In fact, GDM-exposed fetoplacental endothelial cells revealed a different actin filament organization and barrier function [37]. Moreover, fetal ECFCs isolated from cord blood after GDM pregnancies revealed impaired function with reduced proliferation and altered methylation and expression of placenta-specific-8 (*PLC8*) [38]. In human umbilical vein endothelial cells (HUVECs) isolated from GDM pregnancies, several miRNAs [39], including miRNA-101 have been found to exhibit altered expression [39]. Notably, miRNA-101 targets the enhancer of zester-homolog-2 (EZH2), a histone methyltransferase [40]. The dysregulation of miRNA-101-mediated EZH2 repression is believed to have significant implications for the migration and sprouting properties of primary endothelial cell cultures [41], highlighting the crucial role of GDM-induced histone modifications in fetoplacental endothelial cells' function [41]. Moreover, epigenetics mechanisms are known to play a pivotal role in the phenomenon known as “hyperglycemic memory”. This concept suggests that when cells are exposed to adverse stimuli, such as a hyperglycemic environment, cells may retain a memory of the exposure even after returning to normal conditions, resulting in persistent derangements of cellular function [42]. Specifically, in fetoplacental and aortic endothelial cells, hyperglycemic memory is associated with various alterations, including changes in DNA methylation [43], histone methylation [44], and miRNA expression profiles [42]. This phenomenon, observed both in vitro and potentially in utero, may explain the imprinting of fetoplacental vascular and cardiovascular

dysfunction and underscores the critical role of epigenetics remodeling in GDM/MO-induced fetoplacental vascular dysfunction [42]. In addition, the fetoplacental unit may portray protective mechanisms against GDM-induced endothelial dysfunction [45]. Cell-adhesion molecules, including the intracellular adhesion molecule 1 (ICAM-1), aid the migration of activated leukocytes to inflammatory sites and act as markers of endothelial dysfunction [46]. GDM fetoplacental endothelial cells present decreased expression levels of ICAM-1, possibly due to increased levels of the ICAM-1-targeting miRNAs, such as miRNA-222, and miRNA-221 [45]. The miRNA-mediated reduced protein expression levels of ICAM-1 may act as an endothelial compensatory mechanism of the fetoplacental endothelium to counteract inflammatory signals in the GDM intrauterine environment [45].

Furthermore, there is evidence of sex-specific epigenetic dysregulation in GDM and MO associated with fetoplacental dysfunction. Notably, a study examining the impact of GDM on miRNA expression in human fetoplacental endothelial cells discovered that miRNAs are differently expressed according to fetal sex. Specifically, the influence of GDM on miRNA expression was more pronounced in the female fetoplacental endothelial cells compared to male cells, as evidenced by a greater number of miRNAs affected by GDM [47].

The causes of GDM/MO-induced epigenetic changes may be manifold, but glucose levels may play a particular role: even in the healthy, non-diabetic range, maternal blood glucose during pregnancy (in the course of the oral glucose tolerance test (oGTT)) affects DNA methylation in the placenta, and the function of ECFCs in the cord blood, both at the time of birth. The correlation of placental DNA methylation profiles with maternal glucose levels after oGTT revealed an association of several DNA methylation sites [48]. Moreover, colony outgrowth of umbilical cord blood-derived ECFCs negatively correlated with maternal fasting blood glucose at oGTT [49]. Notably, both studies excluded women with GDM or other forms of diabetes. Thus, a subtle hyperglycemic intrauterine environment, occurring in GDM and MO, is likely to induce epigenetic modifications which contribute to the fetoplacental alterations observed in these conditions.

2.2. Evidence of gestational diabetes mellitus and maternal obesity-induced impaired epigenetics in the offspring's heart

Clinical evidence reveals altered fetal cardiac morphology in GDM offspring, i.e., increased atrial and ventricular diameter, increased left ventricular myocardial performance index, left ventricular hypertrophy from mid-gestation throughout late infancy, increased aortic stiffness in late infancy, increased interventricular septal thickness, and increased epicardial fat thickness [50–54] and in MO offspring, i.e., decreased global strain rate of both ventricles, thicker fetal interventricular septum, longitudinal systolic strain rate, and increased risk of congenital heart disease in comparison to lean pregnancies [55–57]. In spite of this, the impact of GDM and MO-induced dysfunction on fetal organs, more specifically the heart, remains to be fully understood.

In this section, we discuss the potential impact of GDM and MO in offspring's cardiac epigenetics, with a special focus on miRNA expression levels, ranging from fetal stages until adulthood. Important to note that the transient nature of the fetoplacental unit allows a wide range of studies to be performed using human subjects. This is not the case for research on offspring's heart molecular mechanisms. Thus, in this section, most of the mentioned studies use murine and non-human primate models.

Epigenetics plays a vital role in fetal heart development, through the regulation of several signaling pathways, and are crucial in postnatal heart function. Studies involving MO-induced cardiac epigenetic alterations have shown differentially methylated regions across several genes in 17-week-old female mice offspring [58] and altered histone modification in neonatal rat offspring [59]. In parallel, GDM induced a global increase in DNA methylation in 6-week-old rat offspring's cardiomyocytes, leading to Akt/sirtuin-1 signaling down-regulation and consequent autophagy progression, being associated with an ischemic heart disease phenotype in the offspring [60].

Previous research has established an association between cardiac miRNA expression levels and CVD [61]. Similarly, studies report GDM/MO-induced epigenetic dysregulation in fetal and neonatal hearts. In baboons, GDM alters miRNAs that target genes involved in cardiac hypertrophy, myocardial infarction, and cardiomyopathy in third-trimester fetuses [61]. Likewise, for 77-day-old rats (young adults), MO was associated with the downregulation of miRNAs that participate in cardiogenesis, hypertrophy, fibrosis, cell survival, and metabolism (i.e., lipid transport, mitochondrial respiratory chain complexes, etc.) [62]. Notably, a subset of these downregulated miRNAs, including miRNA-21-5p, regulates transforming growth factor-β (TGF-β)-mediated signaling pathways for cardiac hypertrophy and fibrosis [62]. Interestingly, TGF-β stimulates endothelial-to-mesenchymal transition (EndMT) in cardiac endothelial cells (CECs), which occurs essentially during fetal heart valve development [63] but, in a postnatal stage, can induce cardiac fibrosis [64]. Although unclear, the higher expression of TGF-β receptors by MO-induced downregulation of miRNAs may also lead to EndMT stimulation in adult and mature CECs, ultimately inducing cardiac fibrosis. Whether MO induces similar patterns of miRNA expression during fetal development is yet unknown. However, children aged between 3 and 11 years present a higher incidence of cardiac valve problems and heart defects when exposed to GDM in utero [65]. In fact, these subjects tend to present miRNA-21-5p dysregulation in their peripheral blood, along with altered levels of other miRNAs that are involved in CVD development [65]. The relationship between dysregulated miRNAs, TGF-β signaling, EndMT impairment, and valve defects is unclear, however, it arises as an interesting approach to be applied in further studies both in MO and GDM.

2.3. Gestational diabetes mellitus and maternal obesity-induced endothelial dysfunction in the maternal-fetal interface

2.3.1. The role of endothelial cells in the maternal-fetal interface for fetal development

The fetoplacental unit is a key element that supports fetal growth, providing the growing fetus with the necessary metabolic substrates through adequate blood flow, which is associated with fetoplacental vascularity [66]. Fetal weight has been widely associated with blood flow in the fetoplacental unit [66]. Fetoplacental blood flow is, in part, regulated by the endothelium, which lines the vessels, supporting its structure and continuous growth throughout gestation [67]. The development of the vascular system is dependent on two different processes involving endothelial cells: angiogenesis and vasculogenesis [68]. Endothelial cell (EC) dysfunction has been implicated in several pregnancy-related disorders, including GDM and MO. The next sections will explore the potential impact of GDM/MO on endothelial dysfunction in the fetoplacental unit, along with the discussion of potential mechanisms that may be contributing to GDM/MO-induced fetoplacental endothelial dysfunction, highlighting the role of nitric oxide (NO) and hydrogen sulfide (H_2S).

2.3.2. Inflammation-mediated endothelial dysfunction in the fetoplacental unit under gestational diabetes mellitus and maternal obesity

In non-human primates, it has been proposed that MO decreases blood flow velocity in the intervillous space and delayed blood flow transfer through the maternal spiral arteries when compared with lean pregnancies [69]. This feature has been proposed for human individuals along with reduced placental vascularity [70].

Maternal obesity has been associated with a general chronic low-grade inflammatory state [71], representing a set of threats to the homeostasis of the endothelium. Interleukin-6 (IL-6) can cross the placenta and induce senescence in placental ECs in a dose-dependent manner [72]. Indeed, in MO-female mice, placental endothelial cell markers are decreased and associated with increased levels of IL-6 in the maternal

serum [72]. Another study highlighted the potential interference of inflammation on fetoplacental endothelial cells' homeostasis suggesting that, in humans, MO-associated endothelial dysfunction results from increased production of pro-inflammatory cytokines (by T-helper cells 2), indicated by IL-6 levels [73]. In the umbilical cord blood of GDM pregnancies, the levels of leptin and tumor necrosis factor α (TNF-α) are increased [74,75].

Similar to MO, a GDM fetoplacental unit is characterized by chronic low-grade inflammation. Umbilical cord blood-derived from GDM pregnancies present increased levels of C-reactive protein and TNF-α [76]. Recent studies suggest endothelial inflammation: HUVECs isolated after GDM pregnancies revealed increased leukocyte adhesion on the HUVECs monolayer in vitro [77]. In line with this finding, GDM-exposed HUVECs show increased protein expression levels of vascular adhesion molecule 1 (VCAM-1) and ICAM-1 under pro-inflammatory conditions, i.e., upon TNF-α treatment [78]. This picture of increased endothelial inflammation is also matched by the fact that fetoplacental endothelial cells isolated after GDM pregnancies have altered barrier function [79]. Additionally, differences in angiogenesis in the placenta and fetus after GDM pregnancy have been shown: placental villi are more vascularized with increased capillary branching [80], and increased vascularization has also been identified in the iris of GDM-exposed neonates [81].

Particularly, exosomes have been suggested to play a role in inflammation-mediated endothelial dysfunction in the fetoplacental unit [82]. Exosomes are nanovesicles that transport proteins, bio-active lipids, mRNA, and non-coding RNAs (including miRNAs). Regarding MO, exosome concentrations in maternal plasma have been positively correlated with maternal BMI and have been recently suggested to contribute to endothelial dysfunction through the stimulation of the release of pro-inflammatory cytokines in MO pregnancies, including IL-6 and TNF-α [83].

Also, in GDM, exosomes have been suggested to be involved in endothelial dysfunction in GDM-fetoplacental unit [82]. Similar to MO, GDM is associated with increased levels of exosomes in the maternal circulation. In addition, exosomes promote the release of pro-inflammatory cytokines, such as IL-6 and TNF-α from HUVECs and modulate their inflammatory response in GDM pregnancies [82]. In addition, the role of exosomes in the maintenance of the GDM phenotype of HUVECs through the modulation of the L-Arginine/NO signaling pathway (in detail, section 2.3.6.) has been demonstrated [84].

Although the above-mentioned data is promising, the relationship between maternal serum and fetoplacental inflammation markers needs to be established. Currently, there is no evidence to suggest that the maternal inflammatory state directly leads to a fetoplacental/fetal inflammatory state, and the idea that cytokine production levels reflect an inflammatory state is still actively debated in the literature. Nevertheless, the role of both GDM and MO-induced maternal inflammatory state is undeniably a factor that could impair fetoplacental endothelial function. Exosomes may also play a mechanistic role in contributing to fetoplacental endothelial dysfunction [84].

2.3.3. Impaired nitric oxide signaling in fetoplacental endothelial cells under gestational diabetes mellitus and maternal obesity

Nitric oxide concentration is an excellent indicator of endothelial homeostasis due to NO's angiogenic, vasodilative, and metabolic regulation properties [85]. NO is a gasotransmitter and a free radical with a strong oxidative capacity [86]. It is transported by cationic amino-acid transporter (CAT-1). In the endothelium, NO is a co-product of the conversion of L-Arginine into L-Citrulline by endothelial nitric oxide synthase (eNOS) [87]. NO is also a key element for endothelial function homeostasis maintenance, through the activation of soluble guanylyl cyclase (sGC) [86]. The activity of the enzyme eNOS is regulated by Ca^{2+} levels and calmodulin, along with other co-factors, such as tetrahydrobiopterin (BH_4), nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FAD), and flavin mononucleotide (FMN). Several vascular-associated disorders are linked with decreased NO bioavailability. As reviewed by Leita et al., the role of NO has been thoroughly described in the pathophysiology of pregnancy-related disorders [88].

HUVECs isolated from GDM pregnancies present increased NO production but reduced bioavailability [78]. This can be, in part, explained by the GDM-like oxidative environment, where NO reacts with superoxide anion to form peroxynitrite, which is involved in lipid peroxidation, causing cell damage including cell membrane disruption [6]. Generally, data suggesting increased NO production in the endothelium in GDM pregnancies is consistent across the literature. In GDM umbilical cord blood, eNOS expression is increased [89]. The characterization of HUVECs isolated from GDM pregnancies also revealed increased expression and activity of eNOS [78] and, in another independent study, increased h-CAT-1 protein expression levels were detected (Fig. 1) [90].

In MO newborns, plasma nitrite levels are decreased [91]. An excessive GWG and MO seem to have the opposite effect on NO signaling as compared to GDM. Lower eNOS expression levels and activity in HUVECs isolated from abnormal GWG suggest lower fetoplacental vascular reactivity [92]. In large-for-gestational-age (LGA) newborns from obese mothers, decreased NO synthesis due to impaired eNOS activation has been suggested in the human arterial endothelial cells (HUAEC) [93]. In MO-isolated HUVECs, decreased NO levels, reduced eNOS phosphorylation in the Ser1177 residue (activation) and increased phosphorylation in the Thr495 residue (inhibition), and saturable transport of L-Arginine were demonstrated (Fig. 1) [94]. The lack of complementary data on this topic regarding MO allows some speculation regarding an impaired fetoplacental unit's endothelial function, highlighting the need to diverge more research into this topic.

Understanding the different, even paradoxical, impacts of both MO and GDM on NO signaling, especially on eNOS expression levels and activity, is important given the fact that both present very similar hyperinsulinemic, inflammatory and oxidative-characteristic environments in the fetoplacental unit. This also raises the question of whether other factors may contribute to the observed differences in NO signaling. For instance, it has been suggested that the perivascular adipose tissue is able to modulate vascularization [95]. Thus, as a hypothesis, hyperlipidemia, mostly characteristic of obesity, might contribute to the observed differences between GDM and MO on fetoplacental endothelial dysfunction [96]. Such link would reinforce the need to consider maternal BMI or fat distribution in GDM-targeted studies. Moreover, this is important given the role of NO in vascular function, which may potentially affect gestational blood pressure. Indeed, studies have shown that pregnant women portraying GDM and MO present increased rates of developing gestational hypertension/preeclampsia (defined as gestational hypertension and the presence of protein in the urine), affecting maternal circulation, and potentially, fetoplacental circulation [97–99].

2.3.4. Modulation of endothelial cells through the gasotransmitter hydrogen sulfide: Implications for health and disease

Hydrogen sulfide (H_2S) is a gasotransmitter chemically more reactive than NO [100]. Hydrogen sulfide has antioxidant, anti-apoptotic, anti-inflammatory, and vasoactive properties [100]. The production of H_2S is mediated mainly by cystathionine γ-lyase from L-Cysteine. H_2S is produced by endothelial cells, and it is considered a major endothelial-derived relaxing factor, as endothelial barrier function is regulated by H_2S [101]. Mechanistically, H_2S-NO signaling seems to function in a loop. NO induces an uptake of L-Cysteine, which is the main substrate for cystathionine γ-lyase [102], affecting H_2S production. H_2S has a dual effect on eNOS, either through the modulation of Ca^{2+} levels, activating it, or by regulating the intracellular pH [103], decreasing eNOS activity, and controlling NO levels, thus impacting endothelial function.

In HUVECs, without any associated pregnancy-related disorder, TNF-α has been suggested to transcriptionally regulate cystathionine γ-lyase gene expression in a dose-dependent way in an inverse proportion, with potential alterations in its protein expression and activity possibly

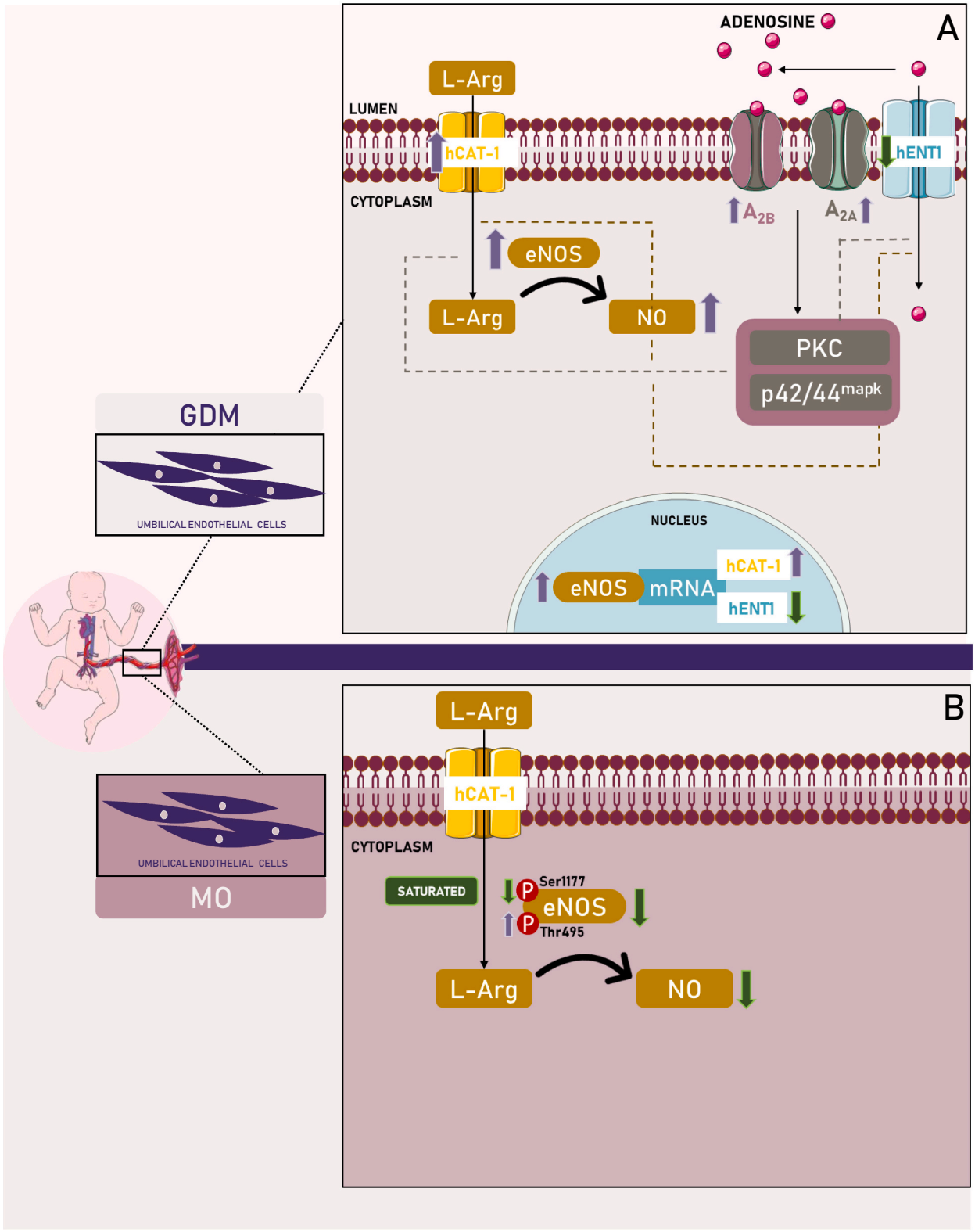

Fig. 1. Impaired mechanism involved in nitric oxide (NO) production that potentially contributes to fetoplacental vascular dysfunction in gestational diabetes mellitus (GDM) and maternal obesity (MO). (A) In GDM human umbilical vein endothelial cells (HUVECs), overexpression of nucleoside transporter (h-ENT-1) leads to extracellular accumulation of adenosine, stimulating adenosine receptors A_{2A}AR and A_{2B}AR. Additionally, GDM induces overexpression of human cationic amino acid transporter (h-CAT-1) and endothelial nitric oxide synthase (eNOS), resulting in increased nitric oxide production. These events are linked through the ALANO pathway, in which adenosine receptors regulate L-Arginine transport through protein kinase C (PKC) and mitogen-activated protein kinases (p42/44mapk), thereby regulating NO production in HUVECs. (B) In contrast, MO/abnormal gestational weight gain (GWG) HUVECs exhibit decreased NO levels, reduced eNOS phosphorylation in the Ser1177 residue (activation), increased phosphorylation in the Thr495 residue (inhibition), decreased eNOS expression levels and activity, and saturable transport of L-Arginine.

altering H_2S production [104]. As thoroughly discussed in section 2.3.2., a chronic-low grade inflammatory environment, characteristic of both GDM and MO, with markedly increased levels of TNF-α, could lead to endothelial dysfunction. Although not understood yet, it is possible that H_2S levels might play a role in the response of endothelial cells toward inflammation due to their interaction with NO.

In fact, GDM mothers present decreased H_2S levels in their plasma as well as the newborn umbilical vein blood [105]. Data regarding human MO studies are lacking. Nonetheless, in an animal mice model of MO, maternal serum plasma and the placenta present decreased H_2S concentration [106]. Either mediated by increased levels of TNF-α or other factors, H_2S depletion is characteristic of endothelial dysfunction [103]. Nonetheless, further research is needed to unravel the exact role of H_2S in GDM and MO fetoplacental endothelial dysfunction.

2.3.5. Interplay between nitric oxide, hydrogen sulfide, and mitochondrial dysfunction in fetoplacental endothelial cells under gestational diabetes mellitus and maternal obesity

Mitochondria are essential organelles for endothelial cell proliferation and migration [107]. Mitochondria are known to generate reactive oxygen species (ROS), which can be produced at abnormally high levels in pathological conditions, thereby contributing to oxidative stress and cellular damage. When an imbalance between ROS overproduction and antioxidant defenses levels is verified, the environment becomes oxidative [108]. The GDM and MO fetoplacental environments have been characterized as being oxidative [109]. The presence of oxidative stress can disrupt mitochondrial membrane potential (MMP) and damage mitochondrial DNA (mtDNA). Mitochondrial DNA is particularly susceptible to oxidative damage because it is located near the inner mitochondrial membrane, where ROS are generated (Fig. 2). Additionally, mtDNA is not protected by histones or other proteins, making it more prone to damage than nuclear DNA. Potential modifications in the mtDNA-coded genes of the mitochondrial respiratory chain (MRC), can promote MRC dysfunction, fostering electron escaping, especially through complex I and III, exacerbating ROS production [110]. These electrons may react with oxygen and produce more ROS (such as superoxide anion, hydrogen peroxide, and hydroxyl radical, Fig. 2), contributing to the oxidative microenvironment and generating a vicious cycle of ROS production and macromolecules damage [108].

In HUVECs derived from GDM pregnancies, oxidative stress is systematically described either assessed through the ratio between GSSG/GSH or MitoSox assays [111–113]. On top of these observations, GDM-isolated HUVECs present decreased MMP [111], increased protein oxidation (assessed by augmented protein carbonyl groups), DNA damage [112], and reduced glucose uptake [114] in comparison with HUVECs from lean pregnancies (Fig. 2).

The data on mitochondrial function and oxidative stress generation regarding MO-HUVECs is limited in the existing literature. Nonetheless, it is suggested that these cells present transcriptional alterations regarding mitochondrial function, especially in oxidative phosphorylation system genes (complex I, IV, and ATP synthase), being negatively correlated with maternal BMI [115]. These transcriptional alterations may impair the protein expression of MRC complexes, impacting mitochondrial function and thus potentially affecting the redox balance in MO-HUVECs (Fig. 2).

The interplay between ROS and NO production is essential to maintain endothelial function [116]. As briefly mentioned, the superoxide radical scavenges NO to form peroxynitrite (Fig. 2), resulting in membrane disruption and vascular disruption [117]. Interestingly, eNOS activity is suppressed by excessive ROS production [116]. It appears that disproportionate ROS production leads to decreased bioavailability of NO and diminished activity of eNOS, significantly reducing NO levels in the endothelium [6]. Excessive NO levels have an inhibitory effect on mitochondrial respiratory chain complex I (through S-nitrosation) and complex IV in endothelial cells [118]. Thus, GDM/MO-induced decreased NO bioavailability could contribute to impaired mitochondrial respiration and energy production and to the generation of detrimental ROS in endothelial cells.

Besides NO, H_2S is also a gasotransmitter that has been suggested to modulate endothelial cell mitochondrial function. It has been suggested that H_2S plays a protective role against oxidative species, produced by mitochondria in HUVECs [119]. Indeed, H_2S is capable of inhibiting hydrogen peroxide-mediated mitochondrial dysfunction, by increasing antioxidant defenses [119]. H_2S is a very potent reducing agent and is able to react with superoxide anion and NO, offering protection to HUVECs mitochondria against oxidative damage. Moreover, the treatment of HUVECs mitochondria with a donor of H_2S led to increased antioxidant proteins' expression levels and activity, including glutathione peroxidase and glutathione S-transferase [119], possibly due to its ability to regulate glutathione in HUVECs [120]. As discussed in the previous section (2.3.4), maternal H_2S serum plasma levels are likely reduced in both GDM and MO, potentially affecting the endothelial function in the fetoplacental unit.

While the mechanisms underlying both GDM and MO-induced mitochondrial dysfunction and oxidative stress in fetoplacental endothelial cells are not fully understood, recent studies have shown that both NO and H_2S play a critical role in the development of fetoplacental vascular dysfunction in these pregnancy-related disorders. Therefore, targeting these molecules could represent a promising therapeutic strategy to improve maternal and fetal health outcomes.

2.3.6. ALANO pathway: A mechanism for endothelial dysfunction in gestational diabetes mellitus in human umbilical vein endothelial cells

Endothelial NO production is regulated by adenosine receptors ($A_{2A}AR$; $A_{2B}AR$), through the activation of protein kinase C (PKC) and p42/44mapk that regulate L-Arginine transport and endothelial nitric oxide synthase activity, known as the ALANO pathway [121].

In HUVECs, the ALANO pathway is modulated by glucose, insulin, and adenosine. High-glucose treatment of HUVECs increased L-Arginine transport, mediated by h-CAT-1 and NO synthesis, and increased ROS production (specifically superoxide anion, hydrogen peroxide, hydroxyl radical) [122]. Insulin treatment of these cells improved D-glucose-induced effects, by decreasing h-CAT-1 expression levels, the activity of the promoter of the SLC7A1 gene (h-CAT-1), decreased NO synthesis, and decreased the activation of p42/44mapk [122]. Indeed, HUVECs isolated from normal pregnancies only treated with insulin present increased L-Arginine transport along with increased mRNA copy number of h-CAT-1 and eNOS, increased intracellular levels of Ca^{2+}, highlighting the regulatory role of insulin [94]. Interestingly, in comparison with HUVECs derived from lean pregnancies, MO-HUVECs show decreased reactivity to insulin, as shown by unaltered eNOS expression, NOS-dependent NO synthesis, or L-Arginine transport [94]. The mechanisms by which this is suggested to occur are due to reduced signaling of the IRS-1/Akt/eNOS pathway in MO-HUVECs. This may reflect an insulin-resistant phenotype in MO neonates, potentially leading to insulin-resistance-related metabolic disorders development [94]. The mechanisms by which insulin mediates the ALANO pathway are yet unknown, however, it has been suggested that insulin levels interfere with L-Arginine transporters' number in GDM fetoplacental unit [121].

Adenosine extracellular accumulation was observed in GDM-HUVECs [123]. This is thought to be due to a decreased activity of the nucleoside transporter (h-ENT-1). The treatment with h-ENT-1 inhibitor (nitrobenzylthioinosine) of HUVEC isolated from lean pregnancies resulted in eNOS, PKC, and p42/44mapk activation. This was associated with increased mRNA copy numbers of h-CAT-1, and increased eNOS activity and expression [123]. Indeed, studies have confirmed GDM-induced impairment of the ALANO pathway. This occurs through decreased activity of h-ENT-1, leading to extracellular accumulation of adenosine, overstimulation of $A_{2A}AR$ + $A_{2B}AR$ (Fig. 1) [3], and subsequently increased transport of L-Arginine and increased production of NO. This highlights that GDM induces an impairment of the ALANO pathway, becoming a relevant mechanism contributing to endothelial

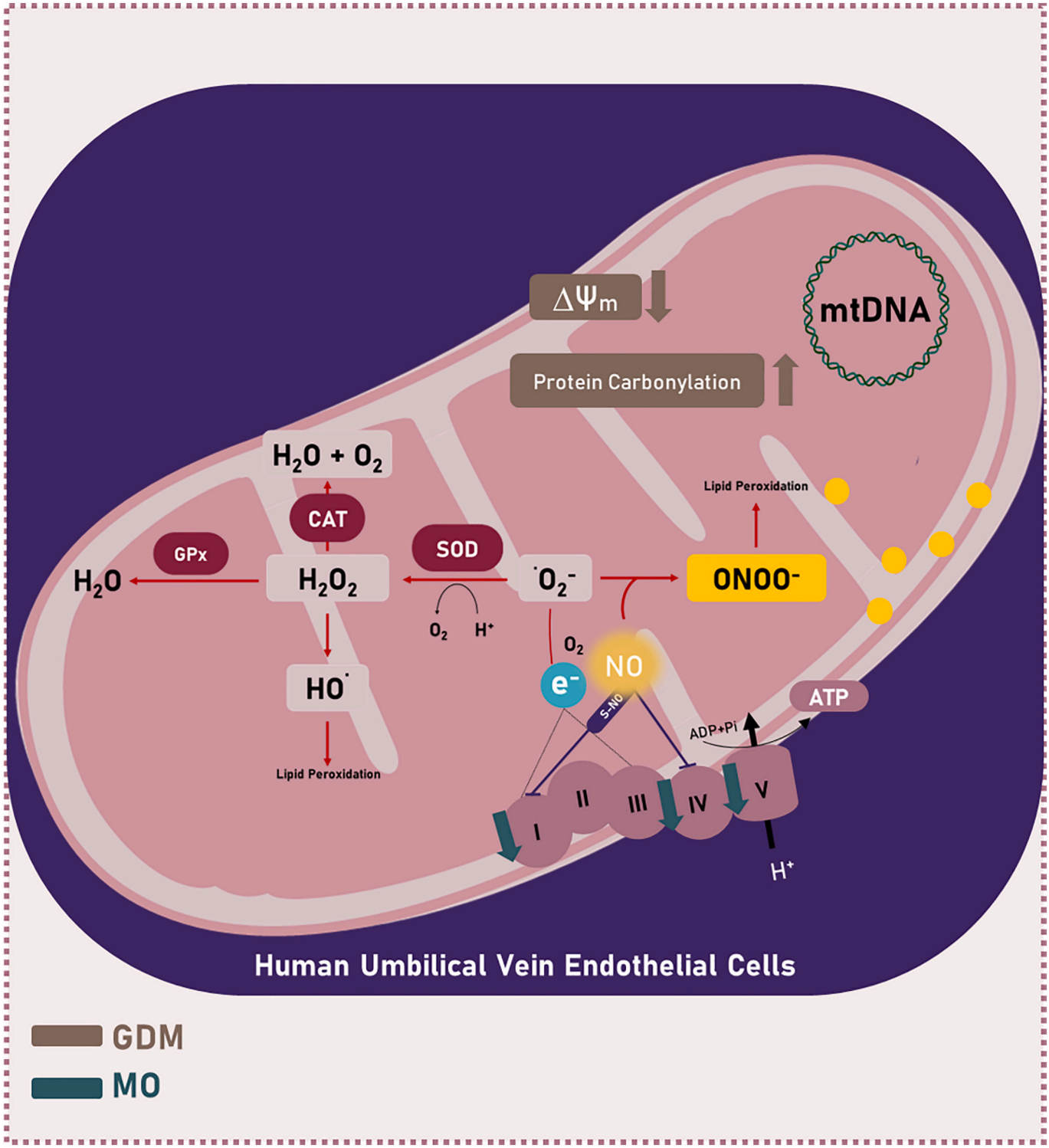

Fig. 2. The interplay between oxidative and nitrosative species and effects in the mitochondria from human umbilical vein endothelial cells (HUVECs) in maternal obesity (MO) and gestational diabetes mellitus (GDM) pregnancies. Nitric oxide inhibits mitochondrial respiratory chain complex I through S-Nitrosation (S-NO) and complex IV, altering mitochondrial respiration and ATP production and potentially, mitochondrial function. In MO (green dotted arrows), HUVECs present transcriptional alterations of genes related to mitochondrial oxidative phosphorylation system complexes I, IV, and ATP synthase, being negatively correlated with maternal body mass index. In GDM (brown arrows), HUVECs present decreased mitochondrial membrane potential, increased protein carbonylation (oxidation), and evidence of oxidative stress. An oxidative environment has been described for MO and GDM HUVECs. Typically, increased electron escaping from complexes I and III react with oxygen to form enhanced levels of superoxide anion ($^{\cdot}O_2^-$). Superoxide dismutase (SOD) transforms $^{\cdot}O_2^-$ into hydrogen peroxide (H_2O_2), which is either broken down into water and oxygen by catalase (CAT) or converted into the hydroxyl radical ($HO^{\cdot}$). Hydrogen peroxide is transformed into water by glutathione peroxidase (GPx). When an imbalance between reactive oxygen species production and antioxidant capacity is verified, oxidative stress occurs. Nitrosative stress occurs when superoxide anion reacts with nitric oxide originating increased peroxynitrite ($ONOO^-$) levels, promoting enhanced lipid peroxidation (yellow dots). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dysfunction in GDM fetoplacental unit [3].

While the activity and expression of eNOS in MO differ from GDM, the modulation of the ALANO pathway in MO remains to be fully elucidated. Further evaluation of this mechanism is needed in other endothelial types, such as cardiac endothelium, to determine its impact on cardiovascular system development.

2.4. Programming of cardiovascular disease by endothelial dysfunction associated with gestational diabetes mellitus and maternal obesity

Endothelial dysfunction, characterized by impaired endothelial NO production and increased oxidative stress, plays a major role in the development of CVD. The endothelium is responsible for regulating the vascular tone of the cardiovascular system and for regulating the elasticity of the blood vessels [124]. If endothelial dysfunction is induced by pregnancy-related disorders, such as GDM and MO in the fetoplacental unit, it could potentially affect the development of the fetal cardiovascular system. This could lead to long-term programming effects and increase the risk of CVD in the offspring later in life, emphasizing the need to understand the mechanisms and consequences of endothelial dysfunction in these maternal conditions.

2.4.1. The role of endothelial cells in fetal heart development

The endocardium is constituted by a continual inner layer of endothelial cells [125]. These cells eventually go through the EndMT process, potentiating cardiac valve and septa development [126]. For this process to occur, vascular endothelial growth factor (VEGF) is repressed by the nuclear factor of activated T-cells (NFAT) and TGF-β is activated [126]. After this, VEGF is upregulated, repressing the EndMT process once the cardiac cushions have been formed.

Interestingly, in a study of systematic mapping of the transcriptomic landscape of the human fetal heart, ECs were identified as one of the main cell types in the heart, which present several sub-types and vary according to different microenvironments [127]. Cardiac ECs mainly expressed CD31, VE-cadherin, and, interestingly, receptor 2 of VEGF (VEGFR-2), which has been proposed to be essential in the EndMT process [128]. Highlighting the importance of ECs for the developing heart, a study in transgenic mice showed that the depletion of the platelet-derived growth factor gene, which is dependent on ECs, impairs cardiac development, resulting in a thinner myocardial wall, dilation of the chamber, and septal defects [129], suggesting that ECs are essential for cardiomyocytes physiological and structural maturation.

2.4.2. Cardiovascular endothelium-cardiomyocytes crosstalk: Implications for cardiovascular disease development

Endothelial cells are in numbers three times more abundant than cardiomyocytes in the adult cardiovascular system, play a crucial role in fetal heart development, and regulate cardiac performance in postnatal life [126]. In the prenatal stage, ECs are essential for fetal heart development, and during postnatal life, ECs become essential for adequate cardiac performance [126]. The main function of cardiac ECs is the release of factors that regulate cardiac contraction, i.e., ventricular relaxation [126]. The production of NO, the main factor regulating this process, occurs in ECs. The stimulation of sGC by NO increases the production of cGMP, activating protein kinase G (PKG) (cGMP-PKG mediated troponin I phosphorylation), decreasing intracellular calcium levels, inducing vasodilation (Fig. 3) [6]. In resemblance to the effects of NO on mitochondria in endothelial cells (section 2.3.5), NO also regulates myocardial mitochondrial respiration and ATP production (Fig. 3) [118]. In canine freshly isolated cardiac left ventricle myocardial muscle segments, the depletion of NO released from microvascular endothelium led to decreased myocardial mitochondrial respiration [130]. Moreover, ECs also play a key role in controlling cardiomyocyte metabolism [131]. On the one hand, ECs act as 'gate-keepers' of free fatty-acid uptake in cardiomyocytes, by facilitating the release of free fatty acids in the bloodstream through the action of heparanase [132]. On the other hand, it has been suggested that NO has the capability to modulate substrate utilization by the heart to obtain energy. In canines, the inhibition of

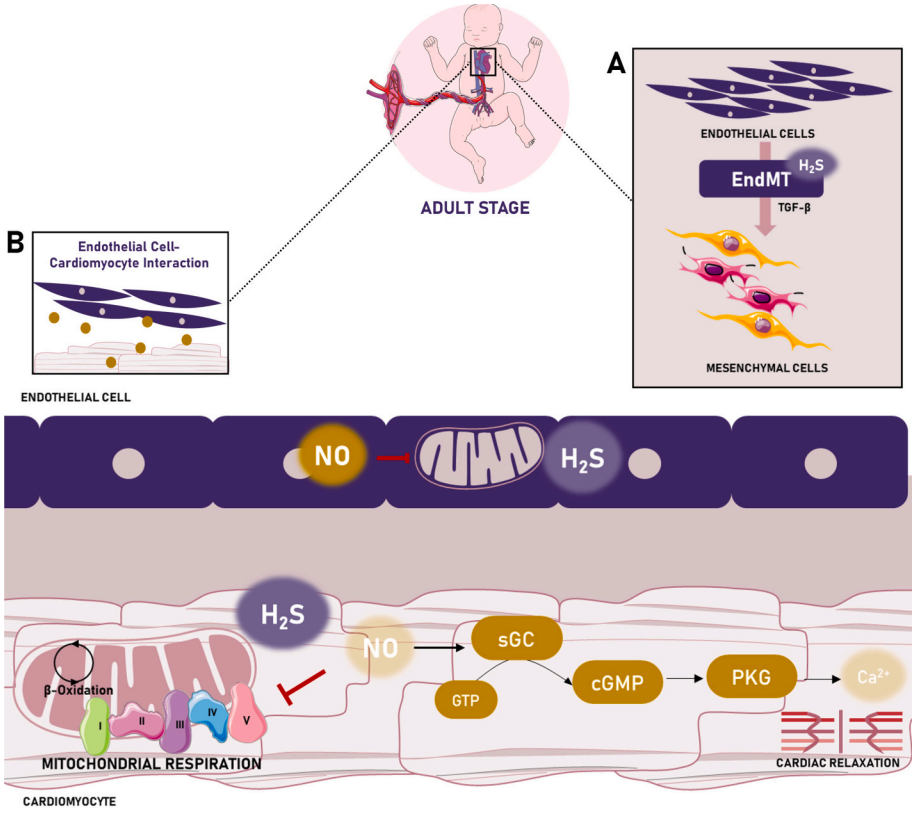

Fig. 3. Endothelial cell-cardiomyocyte interaction in the adult cardiovascular system. (A) During fetal development, endothelial-to-mesenchymal transition (EndMT) is regulated by TGF-β and H_2S, and is critical for cardiac valve formation. However, in adults, EndMT activation has been associated with fibrosis development. Epigenetic studies have shown that microRNAs targeting TGF-β, such as miRNA-21-5p, are downregulated in the cardiac tissues of adult rats born to mothers with obesity (MO) and in the peripheral blood of young offspring of mothers with gestational diabetes mellitus (GDM), suggesting that both MO and GDM may impair EndMT in adulthood. However, it is unclear whether these pregnancy disorders also affect EndMT during fetal development. (B) H_2S is produced by both cardiac endothelial cells (CECs) and cardiomyocytes, and CECs release nitric oxide (NO) to cardiomyocytes. Within cardiomyocytes, NO plays a crucial role in mitochondrial function, cardiac fatty-acid uptake, and substrate utilization. In mitochondria, NO inhibits complex I and complex IV, altering the mitochondrial respiratory rate. NO also plays an essential role in cardiac relaxation by activating soluble guanylyl-cyclase (sGC) and increasing the production of guanosine 3',5'-cyclic monophosphate (GMP), which stimulates protein kinase G (PKG) and reduces Ca^{2+} levels, resulting in cardiac relaxation.

NOS caused a metabolic shift in substrate preference, from fatty acids to lactate and glucose [133]. This process was shown to be reversible through the administration of a NO donor [133]. Thus, it seems that endothelium-released NO plays an essential role in cardiac physiology and metabolism. It seems important to discuss the impact of maternal eNOS depletion on the fetus/offspring. Mice offspring born to eNOS knockout dams and thus, partly lacking eNOS developed hypertension, highlighting the essential role of NO signaling in cardiac homeostasis [134].

Growing evidence suggests that H_2S is involved in cardioprotective mechanisms. The synthesis of H_2S occurs both in endothelial cells and in cardiomyocytes [135]. The role of H_2S in regulating endothelial function has already been discussed in section 2.3.4. In the heart, research on the role of H_2S has grown exponentially. H_2S deficiency is thought to contribute to several cardiac diseases, especially hypertension. In an intimate relationship with NO, H_2S induces a dose-dependent relaxation of the thoracoabdominal aorta in rats [136]. This is thought to be due to H_2S ability to downregulate L-Arginine/NO pathway. In an animal mice model of cystathionine γ-lyase deficiency, the development of hypertension occurs within 8 weeks of birth. The administration of H_2S in cystathionine γ-lyase -deficient mice reduced systolic blood pressure, highlighting H_2S cardioprotective role [137]. Importantly, H_2S has been suggested to modulate EndMT transition (Fig. 3), through the attenuation of EndMT-induced endoplasmic reticulum stress in HUVECs, protecting the heart against a possible cardiac fibrosis development [138]. Thus, the decreased H_2S levels in cardiac-associated pathologies could induce an increased rate of EndMT, promoting the development of cardiac fibrosis in the adult heart. This opens the discussion of whether H_2S also plays an important role in EndMT in early life. Further studies are required in order to fully understand the relationship between H_2S levels and EndMT transition in pre-and post-natal life.

In a closing remark, both NO and H_2S seem to play an important role in mediating the intercellular communication between cardiomyocytes and cardiac endothelial cells. In the context of pregnancy-related disorders, it is likely that the levels of both of these gasotransmitters are decreased in the maternal serum plasma, therefore affecting the levels in the fetoplacental unit, with possible repercussions in the development of the cardiovascular system in the fetus.

2.4.3. Role of the ALANO pathway in the cardiomyocytes: Implications for cardiac function and disease

The discussion in the sections above emphasizes the crucial role of NO signaling and the ALANO pathway in endothelial function/dysfunction in the fetoplacental unit, particularly in HUVECs. The contribution of endothelial cells to fetal heart development and the intercellular communication between cardiac ECs and cardiomyocytes in the adult cardiovascular system highlights the importance of unraveling novel crosstalk mechanisms between endothelial cells and cardiomyocytes that may contribute to fetal programming of CVD of pregnancy-related disorders, such as MO and GDM. To this extent, whether adenosine receptors regulate NO signaling in the cardiomyocytes remains unknown. Nevertheless, the expression of both adenosine receptors A_{2A}AR and A_{2B}AR in ovine and murine fetal hearts and eNOS in adult mammalian hearts has been confirmed [139–142]. In rat adult cardiomyocytes, it has been shown that adenosine regulates NO synthesis and protects against H_2O_2-induced cardiac mitochondrial oxidative damage [143,144]. Whether adenosine-NO regulation occurs through PKC and p42/p44mapk signaling needs to be established to further determine the ALANO pathway in cardiomyocytes. Collectively, these findings make it reasonable to propose that GDM/MO-induced vascular dysfunction in the fetoplacental unit through the ALANO pathway in adult offspring's cardiac endothelial cells and cardiomyocytes result in impaired cardiac relaxation and mitochondrial function increasing the risk for CVD development later in life.

3. Final remarks

Pregnancy-related disorders have been identified as risk factors for the subsequent increased risk of CVD development in the offspring later in life. Through a comprehensive analysis of the research findings, we postulate that GDM/MO induce significant epigenetic remodeling processes, including increased DNA methylation, alterations in histone modifications, and changes in miRNA expression profiles. These epigenetic modifications have an impact on the functionality of fetoplacental endothelial cells, and influence offspring's cardiac function. Moreover, we highlight that GDM/MO may induce fetoplacental endothelial dysfunction through NO and H_2S signaling leading to impaired fetal cardiovascular system development and predisposing the offspring to an increased risk of CVD later in life. The ALANO pathway may play a pivotal role in this response, through NO signaling regulation, which has been implicated in fetoplacental endothelial dysfunction and in intercellular communication between adult cardiac endothelial cells and cardiomyocytes. Our review highlights the current understanding of the ALANO pathway and points this pathway as a potential mechanism acting in cardiomyocytes, contributing to GDM/MO-induced CVD development in the offspring, while also identifying research gaps that require further exploration. In the future, it is crucial to delve deeper into understanding whether GDy disrupts the mechanisms discussed in this review, such as epigenetics remodeling, inflammation, NO and H_2S signaling, within the fetoplacental units. Additionally, it is essential to elucidate the specific mechanisms by which GDy may impair the development of the fetal cardiovascular system. This line of investigation will shed light in the effects of concurrent metabolic dysregulation caused by GDM and pre-gestational obesity, which remain understudied in the literature. By acquiring this knowledge, more targeted and specialized neonatal care will be possible, addressing the unique challenges posed by GDy and its impact on offspring's health.

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Informed consent statement

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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