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Gestational diabetes and foetoplacental vascular dysfunction

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Abstract

Gestational diabetes mellitus (GDM) shows a deficiency in the metabolism of D-glucose and other nutrients, thereby negatively affecting the foetoplacental vascular endothelium. Maternal hyperglycaemia and hyperinsulinemia play an important role in the aetiology of GDM. A combination of these and other factors predisposes women to developing GDM with pre-pregnancy normal weight, *viz.* classic GDM. However, women with GDM and prepregnancy obesity (gestational diabetes, GDty) or overweight (GDMow) show a different metabolic status than women with classic GDM. GDty and GDMow are associated with altered L-arginine/nitric oxide and insulin/adenosine axis signalling in the human foetoplacental microvascular and macrovascular endothelium. These alterations differ from those observed in classic GDM. Here, we have reviewed the consequences of GDty and GDMow in the modulation of foetoplacental endothelial cell function, highlighting studies describing the modulation of intracellular pH homeostasis and the potential implications of NO generation and adenosine signalling in GDty-associated foetal vascular insulin resistance. Moreover, with an increase in the rate of obesity in women of childbearing

age worldwide, the prevalence of GDty is expected to increase in the next decades. Therefore, we emphasize that women with GDty and GDM_{ow} should be characterized with a different metabolic state from that of women with classic GDM to develop a more specific therapeutic approach for protecting the mother and foetus.

KEYWORDS

adenosine, diabetes, diabetes, intracellular pH, obesity, placenta

1 | INTRODUCTION

Human foetal development and growth is sum of multiple physiological factors that play crucial roles, including the mother and father, placenta, foetus and environment. Alterations in the natural physiological adaptations ensuring the normal growth and development of the foetus lead to the development of adult metabolic disorders, including overweight and obesity, diabetes mellitus, hypertension and cancer.¹⁻⁸

An increasing prevalence of type 2 diabetes mellitus (T2DM) has been reported worldwide.⁹⁻¹¹ Moreover, T2DM together with obesity^{11,12} lead to a metabolic condition called diabetes.^{12,13} Patients with diabetes show vascular dysfunction and a higher risk of developing cardiovascular disease.¹⁴ Currently, pregnant women with T2DM or type 1 diabetes mellitus (T1DM) with either pre-pregnancy normal weight (body mass index (BMI) 18.5-24.9 kg (m²)⁻¹), overweight (BMI 25-29.9 kg (m²)⁻¹) or obesity (BMI ≥30 kg (m²)⁻¹)¹⁵ are categorized as having pre-gestational diabetes.¹⁶ These women usually show abnormal D-glucose tolerance during pregnancy.¹¹⁻¹⁴ However, women with pre-gestational normoglycaemia without T1DM or T2DM may also show abnormal D-glucose tolerance during pregnancy. This abnormality is frequently diagnosed at the end of the second or beginning of the third trimester of pregnancy, and it leads to metabolic disturbances during pregnancy; this condition is commonly referred to as gestational diabetes mellitus (GDM).¹⁶

GDM has profound effects on the intra-uterine environment, modulating the metabolic rate in the mother and foetus.^{8,17-19} Pregnant women are diagnosed with GDM independent of their pre-pregnancy nutritional status. Thus, the group of women with GDM is heterogeneous, although most of the studies conducted with these patients have considered them as a single group. Recent literature has shown that pre-pregnancy BMI in the range of normal weight is associated with a low risk of developing metabolic diseases, and BMI ≥25 kg (m²)⁻¹ (ie overweight and obesity) is associated with development of the disease both in youth and adults.²⁰ Therefore, women with GDM and normal pre-pregnancy weight (GDM_{nw}) may show metabolic disturbances

different from those with GDM with pre-pregnancy overweight (GDM_{ow}) or obesity (GDM_{ob}) and develop altered D-glucose metabolism during pregnancy.

Women with pre-pregnancy obesity are at a high risk of developing D-glucose intolerance during pregnancy.^{21,22} Moreover, these women, without T1DM or T2DM, but with GDM, show multifactorial metabolic alterations such as obesity and abnormal D-glucose tolerance. This type of metabolic alteration has been recently referred to as 'gestational diabetes' (GDty), highlighting the possibility that this group may represent a subtype of women with GDM.^{19,23} GDty is a condition comprising metabolic alterations found during maternal obesity (high amount of adipose tissue, high leptin, low adiponectin and increased inflammatory markers) together with the hallmarks of GDM (Figure 1). However, there are no reports addressing whether GDty may be considered a new clinical entity in human pregnancy.

GDty, a condition with an altered maternal and newborn outcome, is different from that observed in pregnant women with either pre-gestational maternal obesity or supraphysiological gestational weight gain.²³ The signalling mechanisms in the human foetoplacental vasculature are not defined because of a lack of studies on the placenta of patients with GDty. However, because of increase in the prevalence of obesity in women of reproductive age and the elevated prevalence of GDM in women with pre-gestational obesity,^{11,24-26} a higher risk for developing GDty is expected in the future. Additionally, GDM and GDty may alter the trans-placental transfer of nutrients from the mother to growing foetus. Changes in this physiological process may lead to abnormal growth and development of the foetus and potential alterations in the health of new-born, young and adult. The foetoplacental vasculature plays a key role in regulating the transfer of D-glucose from the mother to foetus, which is required for energetic metabolism.²² This also modulates the trans-placental transport of molecules regulating the foetoplacental vascular function. The molecules involved in the trans-placental transport include the cationic amino acid L-arginine, which is a substrate for the synthesis of nitric oxide (NO)²³ via various members of the human cationic amino acid transporter (hCATs) family, and the endogenous

FIGURE 1 Gestational diabetes mellitus and gestational diabetes. Women with pre-pregnancy body mass index (BMI) in the range of normal weight, overweight, and obesity could get pregnant (Pregnancy). Pregnant women from the three different groups could be diagnosed with gestational diabetes mellitus (GDM). This diagnosis may occur in women with pre-pregnancy normal weight (Classical GDM) or in women with pre-pregnancy obesity (Gestational diabetes or GDty). Women with either classical GDM or GDty show placenta endothelial dysfunction (*Fetoplacental endothelial dysfunction*). The functional characteristics associated with endothelial dysfunction in both groups are more severe (double arrows) in GDty than in classical GDM, where a less drastic effect (single arrow) is seen. The insulin response of the foetoplacental vasculature and GDM-increased nitric oxide (NO) generation is reduced (↓). However, a higher (↑) intracellular alkalization, pro-inflammatory response, and expression and associated signalling of A_{2B} adenosine receptors are found in both groups. Women with overweight could also be diagnosed with GDM, and they are not studied as a different group from those with pre-pregnancy normal weight or obesity. Therefore, the GDM-associated potential metabolic abnormalities in this group of women are still *undefined*. Whether GDM in women with overweight leads to foetoplacental endothelial dysfunction is still unclear (?). Dotted red arrows show that most studies have been done in placentas isolated from women with pre-pregnancy normal weight and pre-pregnancy obesity, ie all samples considered with similar characteristics. The same applies to placentas from women with pre-pregnancy overweight and with pre-pregnancy obesity

nucleoside adenosine via the human equilibrative nucleoside transporter (hENTs) family.^{19,23}

At the cellular level, GDty is associated with metabolic alterations, including endoplasmic reticulum stress increasing the protein abundance of inositol-requiring enzyme 1 α (IRE1 α) and binding immunoglobulin protein (BiP) and the mRNA level of spliced X-box binding protein 1 (XBP1) in the adipose tissue²⁷ and skeletal muscle.²⁸ Another study showed that the intrinsic mechanisms by which GDty alters outcomes in new-born are similar in twin and singleton pregnancies.²⁹ Interestingly, these are the only few reports with clearly defined groups

of pregnant, lean or obese women who developed GDM despite receiving treatment with controlled diet, oral hypoglycaemic drugs or insulin therapy during pregnancy. Moreover, most of the studies reporting experimental and clinical findings suggestive of foetoplacental vascular dysfunction are conducted in women with GDM, regardless of whether they have pre-pregnancy normal weight, overweight or obesity (ie all women in the “GDM” group), or have a mix of GDM + T1DM³⁰ or T2DM.²¹ Thus, the potential involvement of the diverse factors analysed in these reports suggest a combination of metabolic disturbances, rather than GDM, overweight or obesity individually.

Preliminary studies with the human umbilical vein endothelial cells (HUVECs) isolated from women with GDty showed alterations in the regulation of intracellular pH (pHi), possibly because of altered function of the Na⁺/H⁺ exchanger (NHEs), which is the most active membrane transporter involved in pHi regulation in the foetoplacental endothelium,^{31,32} than with cells from women, with pre-pregnancy BMI in the range for a normal weight, who developed GDM.³³ It was recently reported that HUVECs from GDty and GDMow pregnancies show higher NO generation than HUVECs from GDM pregnancies.³⁴ Additionally, a differential response to insulin is observed in HUVECs from these three groups.^{35,36} Thus, functional alterations in the foetoplacental endothelium from women with GDty, and perhaps GDMow, are different from those from women with GDM. In this review, we summarize the general understanding of the functional and metabolic alterations in the human foetoplacental vasculature in GDty pregnancies, highlighting its potential differences with that from GDM pregnancies.

2 | PLACENTAL DYSFUNCTION MECHANISMS IN GDM and GDty

2.1 | Membrane transporters and receptors

Several mechanisms are involved in maintaining proper placental function to secure foetal development and growth. Of these, plasma membrane transporters^{32,37-43} and receptors^{19,23,34,37-40,44,45} co-expressed in the human placenta play a key role. The expression and activity of membrane transporters for cationic amino acids, nucleosides and H⁺, and plasma membrane receptors for adenosine and insulin are altered in the human foetoplacental macrovascular endothelium, such as HUVECs, and microvascular endothelium, such as human placental microvascular endothelial cells (hPMECs). Alterations in the activity of these membrane transporters and expression and activity of receptors lead to endothelial and vascular dysfunction associated with GDM pregnancies.^{19,23,46}

2.1.1 | Cationic amino acid, nucleoside and H⁺ transporters

Cationic amino acid transporters (CATs)

It is known that the uptake of cationic amino acids is mediated by different membrane transport systems in most of the mammalian cells.^{41,47} The various transport systems involved in the uptake of these amino acids are the CATs family of membrane transporters, which are composed of at least five protein members, viz. CAT-1, CAT-2A, CAT-2B,

CAT-3 and CAT-4.^{42,48} The CATs family is the main group of proteins expressed in the HUVECs and hPMECs.^{41,47} In HUVECs, the uptake of L-arginine is mainly mediated by the human CAT-1 (hCAT-1) (approximately 80% of total transport) and hCAT-2B (approximately 20% of total transport).⁴⁹ The uptake of L-arginine via hCAT-1 and hCAT-2B shows kinetic parameters with apparent Michaelis constant (K_m), ie L-arginine concentration at which the uptake rate is half of its maximal value (V_{max}), in the range of 50-400 $\mu\text{mol L}^{-1}$ in HUVECs.^{39,40,49,50} As L-arginine uptake via hCAT-1 and hCAT-2A/B is linked to a higher activity of the endothelial NO synthase (eNOS) in HUVECs,^{49,51-53} alterations in the expression and activity of these membrane transporters may lead to abnormal vascular function in diseases during pregnancy, including GDM and other metabolic conditions such as obesity.

Interestingly, L-arginine uptake via hCAT-1 and eNOS activity is increased in response to activation of adenosine receptors by adenosine in HUVECs^{40,54} and hPMECs.³⁷ The adenosine-increased L-arginine uptake and eNOS activity associated with accumulation of extracellular adenosine in these cell types from GDM pregnancies.^{37,38} Thus, the role of adenosine as a modulator of the L-arginine/NO signalling pathway in the foetoplacental endothelium has been proposed.^{37,40,54}

Nucleoside transporters

In a majority of mammalian cells, such as the HUVECs and hPMECs, the endogenous nucleoside adenosine is removed from the extracellular medium by two different families of membrane transporters, viz. the human equilibrative nucleoside transporters (hENTs) and concentrative nucleoside transporters (hCNTs).^{55,56} The hCNTs form 1 (hCNT1), 2 (hCNT2) and 3 (hCNT3) are encoded by *SLC28*. hCNT activity is concentrative, obligatory inward transport and Na⁺-dependent with a nucleoside:Na⁺ stoichiometry of 1:1 (hCNT1 and hCNT2) or 1:2 (hCNT3). Intriguingly, hCNT activity has not been detected in HUVECs or hPMECs in vitro.⁵⁶ The hENTs form a family of four proteins encoded by *SLC29*, viz. hENT1, hENT2, hENT3 and hENT4. The uptake of adenosine in HUVECs and hPMECs is mediated by hENT1 and hENT2.^{37,38,40} Interestingly, a reduced hENT1 and hENT2 transport activity may lead to extracellular accumulation of adenosine in these cell types as they do not express ecto-nucleosidases to degrade adenosine at the external face of the plasma membrane.⁴⁵ Accumulation of adenosine in the extracellular space leads to higher hCAT-1-mediated L-arginine transport and eNOS activity involving activation of adenosine receptors, a signalling mechanism referred to as ALANO (Adenosine, L-Arginine, Nitric Oxide) signalling pathway in these cell types from GDM pregnancies.^{40,54} Thus, alterations in the expression and activity of these proteins in the foetoplacental microvascular and macrovascular

endothelium may lead to abnormal vascular function in GDM and other diseases of pregnancy.

Na⁺/H⁺ exchangers (NHEs)

NHEs protein family comprises 11 members, of which NHE1 is the most studied member in human pregnancy. The NHE1 protein has 12 transmembrane domains with six extracellular and five intracellular loops.⁵⁷ NHE1 shows a cytosolic region with a C-terminal domain containing recognition sites for various signalling molecules, including p44/42^{mapk}, protein kinases C, A and B/Akt, p90 ribosomal S6 protein kinase, Rho-associated kinase and the proto-oncogene tyrosine-protein kinase, that act on several serine (Ser77, Ser703, Ser722, Ser725, Ser728 and Ser770) and threonine (Thr717) residues.^{58,59} Under a physiological pHi, NHE1 is a monomer at the plasma membrane; however, at low pHi (ie acidic) or after stimulation of cells with growth factors, NHE1 dimerises, increasing its affinity to H⁺.⁶⁰ NHE1 is highly efficient in maintaining pHi because of H⁺ efflux.⁵⁷ pHi is a critical mechanism amongst the other factors that alter cell metabolism and function.^{61,62} The involvement of pHi is supported by the fact that pHi is regulated by several transporters and buffering systems functioning in the body. Moreover, the involvement of hNHE1 and other hNHEs in regulating pHi is also described in the context of foetoplacental unit participating in pregnancy.^{31,32}

2.1.2 | Adenosine and insulin receptors

Adenosine receptors

Adenosine receptors belong to P1 family of purinergic receptors comprising four subtypes—A₁AR (A₁AR), A_{2A}AR (A_{2A}AR), A_{2B}AR (A_{2B}AR) and A₃AR (A₃AR)—which belong to the superfamily G-protein-coupled receptors.⁶³ A₁AR, A_{2A}AR and A_{2B}AR are relatively high affinity requiring nanomolar concentrations of adenosine, while A₃AR is low affinity requiring micromolar concentrations of adenosine.^{45,63,64} Activation of adenosine receptors leads to a variety of physiological responses and these receptors are involved in pathophysiological regulation.^{44,65,66} They modulate the systemic circulation, including the foetoplacental circulation, among many other biological actions.^{45,65} The HUVECs and hPMECs express all four adenosine receptor subtypes with A₁AR being less expressed than other subtypes.^{44,67} However, A_{2A}AR plays a role in the modulation of L-arginine/NO signalling pathway in these cell types from GDM^{37,40,54} or pre-eclampsia.^{44,67} Moreover, A₁AR is possibly required for insulin reversal of the GDM-activated transport of L-arginine mediated by activity of hCAT-1 in HUVECs from GDM pregnancies.⁶⁸ Additionally, A_{2B}AR may also be involved in the regulation of beneficial actions of insulin in HUVECs from pre-eclampsia,⁴⁴ complementing

the potential key role of this adenosine receptor subtype in reversing the GDty-associated alterations in endothelial cell function.¹⁹

Insulin receptors

Insulin hormone has a variety of biological actions that are mediated by insulin receptors A (IR-A) and B (IR-B).³⁸ IR-A and IR-B are derived from alternative splicing of exon 11 of the human insulin receptor gene. IR-A lacks 12 amino acids at the C-terminus of the α -subunit, while IR-B has complete sequence.^{69,70} This leads to functional differences between the two insulin receptors. For instance, a faster insulin association/dissociation dynamic has been reported for IR-A than that for IR-B.^{71,72} Additionally, IR-A has a higher affinity for insulin-like growth factor 2 (half-maximal inhibitory concentration, IC₅₀ approximately 3 nmol L⁻¹) than IR-B in insulin-like growth factor 1 receptor-null (R⁻) mouse embryonic fibroblast cells expressing IR-A (R⁻/IR-A).⁷³ Activation of IR-A by insulin leads to preferential activation of growth factor receptor-bound protein 42/44 and 42-kDa mitogen-activated protein kinase (p44/42^{mapk}) signalling, which is also referred to as the mitogenic effect of insulin.^{74,75} In contrast, activation of IR-B mediates insulin signalling via phosphatidylinositol 3-kinase/protein kinase B/Akt, which is referred to as the metabolic effect of insulin.^{74,75}

IR-A and IR-B play differential roles in the modulation of foetoplacental vascular and endothelial function, including the L-arginine/NO signalling pathway, and adenosine transporters and receptors, as described in HUVECs and hPMECs from GDM pregnancies. Therefore, the interaction of these membrane transporters and receptors is crucial in GDM_{nw}, GDM_{ow} and GDty, and it is expected to differ depending on the metabolic status of the mother and foetus.

2.2 | Hyperglycaemia

Hyperglycaemia during pregnancy is associated with an increased risk of adverse maternal, foetal and neonatal outcomes,^{16,76,77} and may occur because of either pre-pregnancy T1DM, T2DM or GDM.⁷⁶ The metabolic conditions associated with hyperglycaemia during pregnancy also contribute to health risks after birth in both mothers and babies, leading to a subsequent amplification of the pandemic of non-communicable diseases.⁹

Maternal hyperglycaemia in pregnancy leads to foetal hyperglycaemia,⁷⁸ and maternal insulin resistance shows a positive correlation with neonatal insulin resistance.⁷⁹ Thus, maternal D-glucose metabolic deficiency could determine inadequate foetal handling of this hexose (Figure 2). Increased foetal insulin resistance is one of the complications associated with foetal hyperglycaemia and GDM.^{37-39,49,50,80,81} Hyperglycaemia alters vascular function, including the

FIGURE 2 Foetoplacental endothelial dysfunction in GDMnw/ow. Short-term exposure to hyperglycaemia results in *Foetoplacental endothelial dysfunction* characterized by reduced ($\Downarrow$) expression and activity of the human equilibrative nucleoside transporters 1 and 2 (*hENT1/2*) but increased ($\Uparrow$) expression and activity of the human cationic amino acid transporters 1 and 2A (*hCAT-1/2A*), endothelial nitric oxide synthase (*eNOS*), and *A_{2A}* and *A_{2B}* adenosine receptors (*A_{2A}AR/A_{2B}AR*). Pregnant women diagnosed with gestational diabetes mellitus (GDM) experience short periods of hyperglycaemia (*Short-term hyperglycaemia*) before undergoing treatment with diet, exercise, insulin, or oral hypoglycaemic drugs. After the treatment, the patients normalized their glycaemia (*Normoglycaemia*), but the alterations in the foetoplacental endothelial function are still present. Other metabolic abnormalities (*Other factors*), including reducing the lipid metabolism and mitochondrial respiration, may also alter endothelial function in the human placenta

human foetal vasculature. Vascular endothelium is one of the main targets of hyperglycaemia, as it is the first tissue in direct contact with the blood.

It has been reported that HUVECs exposed to high concentrations of extracellular D-glucose (approximately 25 mmol L⁻¹) show increased uptake of L-arginine.^{39,49,50} Exposure to high concentrations of extracellular D-glucose increases the expression (mRNA and protein) and maximal transport capacity ($V_{\max}/K_m$) of *hCAT-1* and *2A/B* (*hCAT-2A/B*) in HUVECs.^{49,50} The effective concentration (EC₅₀) of D-glucose, approximately 12 mmol L⁻¹, leads to a half-maximal increase in the expression of *hCAT-1* and *hCAT-2A/B*. Interestingly, the elevated $V_{\max}/K_m$ for L-arginine transport via *hCAT-1* in HUVECs from GDM treated with diet remained unaltered by increasing the levels of extracellular D-glucose from 5 mmol L⁻¹ to 25 mmol L⁻¹ for 24 hours in vitro.³⁹ Thus, HUVECs from GDM pregnancies

are insensitive or conditioned to an abnormally elevated extracellular concentration of D-glucose, perhaps as a mechanism of adaptation or plasticity in an adverse environment.

Umbilical vein glycaemia values at birth in GDM pregnancies are similar or approximately 0.5 mmol L⁻¹ (~9 mg dL⁻¹) lesser than those in normal pregnancies (4–5.5 mmol L⁻¹, 72–99 mg dL⁻¹), as reported previously.^{34,38} These studies included women with GDM who received a restricted diet or were subjected to insulin therapy to control glycaemia. Even when maternal glycaemia was controlled with diet or insulin and within the range of expected values after the treatments, the metabolic alterations detected in HUVECs and hPMECs from GDM were present at birth. It has also been reported that HUVECs and hPMECs from GDM pregnancies cultured for 3–5 passages in vitro in a medium containing 5 mmol L⁻¹ D-glucose maintained GDM-associated alterations in endothelial function.^{37,38} Thus, disruption of the foetoplacental

endothelial cell function by elevated levels of extracellular D-glucose may occur because of short exposure to hyperglycaemia. However, other factors, such as lower lipid metabolism or mitochondrial respiration, can also lead to these alterations in the foetoplacental vasculature in GDM.⁸

Elevated levels of extracellular D-glucose and GDM are associated with higher NOS activity and activating phosphorylation at serine¹¹⁷⁷ of eNOS in the HUVECs,^{49,82–84} hPMECs,³⁷ and human microvascular retinal endothelial cells.⁸⁵ This phenomenon leads to increased generation of NO in these cell types. As NO may block complex IV by inhibiting activity of cytochrome *c* oxidase in the mitochondrial electron transport chain,⁸⁶ it is feasible that hyperglycaemia in GDM leads to reduced mitochondrial respiration in the foetoplacental endothelium under these conditions.⁸

Interestingly, GDM-increased NO generation by the foetoplacental endothelium may be potentiated via activation of A_{2A} adenosine receptors by adenosine in HUVECs^{38,40} and hPMECs.³⁷ This phenomenon may occur because of increased extracellular concentration of adenosine detected in pregnant women with GDM ($\sim 0.3 \mu\text{mol L}^{-1}$ vs $\sim 0.1 \mu\text{mol L}^{-1}$ in normal pregnancies) and umbilical vein blood ($\sim 1.5 \mu\text{mol L}^{-1}$ vs $\sim 0.2 \mu\text{mol L}^{-1}$ in normal pregnancies).^{38,66} Increased plasma levels of adenosine in women with GDM and the culture medium in HUVECs and hPMECs from GDM pregnancies may occur because of a reduced V_{max}/K_m for adenosine transport via the hENT1 and hENT2.^{38,40}

HUVECs also express A_{2B} adenosine receptors (A_{2B}AR).^{44,67} A_{2B}AR are low-affinity receptors for adenosine with an EC₅₀ of approximately $24 \mu\text{mol L}^{-1}$ in mammalian cells.^{63,64} Furthermore, a nonselective agonist 5'-N-ethylcarboxamidoadenosine shows K_i of approximately 2 mmol L^{-1} .⁶⁵ As the GDM-associated increase in the extracellular concentration of adenosine reaches levels that could partially activate A_{2B}AR, these receptor subtypes may possibly modulate signalling in HUVEC and hPMEC, including NO-dependent inhibition of mitochondrial respiration.⁸ The involvement of A_{2B}AR is supported by a few studies which show that activation of the A_{2B}AR may reverse GDty-increased eNOS activity in the human foetoplacental endothelium.¹⁹ Therefore, restoring the generation of NO to physiological levels in the foetoplacental endothelium of GDty pregnancies may restore ATP generation via oxidative phosphorylation in the foetoplacental macro- and microvascular endothelium. Interestingly, no study has addressed the potential role of A_{2B}AR in the regulation of eNOS activity in the foetoplacental endothelium from pregnant women with pre-pregnancy overweight who developed GDM.

2.3 | Hyperinsulinemia

Diabetes mellitus and obesity are both causes of impaired insulin secretion and disrupt homeostasis of physiological

D-glucose in the mother. The changes associated with these abnormal metabolic conditions result in similar alterations in the foetus, leading to metabolic diseases in the offspring⁸⁷ (Figure 2). An increase in the insulin level in the umbilical cord blood or amniotic fluid is associated with an approximately 3-fold elevated risk of developing glucose intolerance, obesity and T2DM during infancy and adulthood.^{88,89} Thus, insulin plays a critical role in modulating the mechanisms involved in D-glucose metabolism in the mother, foetus, placenta and newborn.

Increased plasma levels of insulin over its physiological concentrations at fasting ($\leq 50 \mu\text{U mL}^{-1}$ or 0.3 nmol L^{-1} in a healthy adult, considering $1 \mu\text{U mL}^{-1} = 0.006 \text{ nmol L}^{-1}$) or increased insulin concentration at 2 to 3 h post meal ($\geq 100 \mu\text{U mL}^{-1}$ or 0.6 nmol L^{-1}),⁹⁰ is referred to as supra-physiological hyperinsulinemia in patients with defective modulation of internal homeostasis. Hyperinsulinemia is also observed in neonates born to mothers with GDM (neonatal insulin approximately $8 \mu\text{U mL}^{-1}$ or $0.048 \text{ nmol L}^{-1}$), but not in those born to mother with normal pregnancies (neonatal insulin $\sim 5 \mu\text{U mL}^{-1}$ or $\sim 0.03 \text{ nmol L}^{-1}$).^{34,38}

A differential effect of insulin has been reported in HUVECs isolated from a group of pregnant women comprising women with pre-pregnancy normal weight or overweight who developed GDM (hereafter referred to as GDM_{nw/ow}, BMI $18.5\text{--}29.9 \text{ kg (m}^2\text{)}^{-1}$) than in those from pregnant women with normal pre-pregnancy weight and normal pregnancy, ie non GDM (N_{nw}).⁴² HUVECs from N_{nw} exposed to 1 nmol L^{-1} insulin show increased transport of L-arginine associated with higher V_{max}/K_m with an EC₅₀ of approximately 0.2 nmol L^{-1} requiring a half-maximal time of approximately 6–8 hours in vitro.⁴⁹ Insulin reversed the increase in the transport of L-arginine observed in cells from GDM_{nw/ow} pregnancies, regardless of whether the mothers were treated with diet or insulin therapy.³⁴ As the pregnant women included in the latter study were GDM_{nw/ow}, it is not possible to determine whether the differential effect of insulin is because of GDM alone (ie women with pre-pregnancy normal weight, GDM_{nw}) or is also present in women with GDM_{ow}. Interestingly, GDM_{ow} corresponds to a group of women showing a metabolic condition—pre-pregnancy overweight and GDM—which has not been defined as a clinical entity in human pregnancy. Thus, the findings mentioned above highlight the need to conduct studies in at least three groups of pregnant women, ie GDM_{nw}, GDM_{ow} and GDty (or GDM_{ob}), separately instead of pooling them into one group.

The differential effects of insulin on HUVECs from normal pregnancies and those from GDM_{nw/ow} pregnancies may occur because of differential activation of insulin receptors, leading to various intracellular signalling mechanisms. HUVECs co-express IR-A and IR-B forms.³⁸ Interestingly, adult endothelial cells, HUVECs and hPMECs respond to insulin with marked differences depending on the preferential

expression of these subtypes of insulin receptors.³⁸ Thus, insulin sensitivity and the endothelial response to this hormone depends on expression of insulin receptor and the associated signalling pathways following their activation by insulin.

As mRNA expression of IR-A is higher in HUVECs from GDM_{ow}^{34,38} or GDty³⁴ pregnancies than in cells from GDM_{nw} pregnancies, IR-A may be responsible for the effects of insulin on transport of L-arginine in HUVECs from GDM pregnancies. Differential insulin activity via IR-A-associated signalling is not restricted to insulin modulation of L-arginine transport as insulin also modulates the uptake of adenosine via hENT1 and hENT2 in HUVECs³⁸ and hPMECs³⁷ from GDM_{ow} pregnancies. Interestingly, the insulin modulation of adenosine transport in HUVECs from GDM_{ow} pregnancies is different from that in HUVECs from Nnw pregnancies.³⁵ However, whether the differential regulation of foetoplacental endothelial function by insulin via IR-A or IR-B is also a mechanism in cells from GDty pregnancies remains unknown.

2.4 | Membrane transporters

2.4.1 | Cationic amino acid transporters (CATs)

GDM alters the expression and activity of CATs in several cell types, including HUVECs and hPMECs.^{34,39,40,68} It has been reported that expression of hCAT-1 mRNA (number of copies) and protein is higher in HUVECs from GDM_{nw/ow} pregnancies than in those from Nnw pregnancies.^{34,68} Thus, GDM_{nw/ow} may lead to an increased abundance and bio-availability of hCAT-1, inducing more efficient removal of L-arginine from the extracellular medium of cells from GDM_{nw/ow} pregnancies than that from Nnw pregnancies (Figure 3). GDM_{nw/ow}-increased hCAT-1 expression and activity is supported by results showing increased $V_{\max}/K_m$ because of higher $V_{\max}$ but unaltered K_m (approximately 100 $\mu\text{mol L}^{-1}$) in HUVECs from GDM_{nw/ow} pregnancies. These observations may not be restricted to the human foetoplacental endothelium and may also apply to other cell types.^{43,91}

The higher hCAT-1 expression detected in HUVECs from GDM_{nw/ow} pregnancies may occur because of a higher transcriptional activity of the *SLC7A1* (for hCAT1) than that in cells from Nnw pregnancies.⁶⁸ Higher *SLC7A1* expression is associated with higher activity of specificity protein 1 (Sp1) transcription factor at consensus regions between -177 and -105 bp upstream of the TATA box in the *SLC7A1* promoter.^{50,68} The involvement of Sp1 in the modulation of *SLC7A1* is not exclusive to this gene as its activity at the *SLC29A1* (for hENT1) promoter consensus sequence between -815 and -801 bp from the transcription start site is

also higher in HUVECs from Nnw pregnancies exposed to 25 mmol L^{-1} D-glucose for 24 hours.⁹² Interestingly, increased Sp1 activity at the promoters of *SLC29A1* and *SLC7A1* may require activation of NOS, p44/42^{mapk} and protein kinase C to mediate insulin signalling in the human foetoplacental endothelium in GDM pregnancies. It should be noted that studies on HUVECs from GDM pregnancies have mainly focussed on mothers treated with diet and insulin therapy. However, it remains uncertain whether these gene expressions and transport activity of their transcripts are differentially altered in cells from GDM_{ow} or GDty pregnancies than those from GDM_{nw} pregnancies.

2.4.2 | Equilibrative nucleoside transporters (ENTs)

HUVECs and hPMECs express hENT1 and hENT2 which mediate extracellular adenosine uptake in cells from normal pregnancies³¹ and from GDM_{nw/ow} pregnancies.^{37,42} The hENT1/hENT2 transport activity is sufficient to maintain the extracellular adenosine concentration in HUVECs and hPMECs in vitro (approximately 200 nmol L^{-1}) at physiological extracellular pH (pHo ~7.3).^{37,42} Moreover, the adenosine concentration is well within the range of the plasma adenosine levels determined in pregnant women (200-500 nmol L^{-1}).^{93,94}

The relative $V_{\max}/K_m$ value for hENT1-mediated adenosine transport than that for hENT2-mediated transport ($^{hENT1/2}F$) is a useful parameter for interpreting the involvement of these membrane transport activities in cells from normal pregnancies and those from pathological pregnancies.⁸ It is reported that the $^{hENT1/2}F$ value is higher in HUVECs ($^{hENT1/2}F$ approximately 4-fold)⁹⁵ and human umbilical vein smooth muscle cells ($^{hENT1/2}F$ approximately 5-fold)⁹⁶ but similar ($^{hENT1/2}F$ ~1) in hPMECs³⁷ from normal pregnancies. Thus, hENT1 may be preferentially involved in maintaining the extracellular concentration of this nucleoside within a physiological range in pregnant women with normal pregnancy compared with the potential role of hENT2 in the human foetoplacental vasculature in normal pregnancies.

GDM_{nw/ow} is associated with reduced (approximately 50%) hENT1-mediated adenosine transport in HUVECs and hPMECs^{37,38} (Figure 3). However, hENT2-mediated adenosine transport in hPMECs remains unaltered by this disease during pregnancy. Thus, reduced activity of hENT1, rather than hENT2, may be a determinant of the resulting increase in levels of extracellular adenosine reported in human foetoplacental vascular endothelium in GDM_{nw/ow} pregnancies. The effect of GDM_{nw/ow} on hENTs is known, but there is no information addressing the potential differential roles of hENT1 and hENT2 in the foetoplacental endothelium and vascular function in GDty pregnancies.

FIGURE 3 Membrane transport in the foetoplacental endothelium in GDM. Human foetoplacental endothelial cells are isolated from women with gestational diabetes mellitus (GDM) being with pre-pregnancy normal weight (GDMnw, or classical GDM), overweight (GDMow), or obesity (GDty). Most studies describe alterations in the foetoplacental endothelium function isolated from women with GDM regardless of whether they show pre-pregnancy normal weight or overweight (GDMnw/ow). Cells from GDMnw/ow (green area) show increased (↑) expression and maximal L-arginine transport activity (V_{max}/K_m) of the human cationic amino acid transporter 1 (*hCAT-1*) compared with cells from normal pregnancies (ie non-GDM and maternal pre-pregnancy normal weight). These alterations are associated with activation (↑) of cell signalling mechanisms, including increased nitric oxide synthase (*NOS*), protein kinase C (*PKC*), mitogen-activated protein kinases (*MAPK*), and the specific protein 1 transcription factor (*Sp1*) activity. Cells from GDMnw (light blue area) show reduced (↓) adenosine transport resulting from a reduced expression and V_{max}/K_m of the human equilibrative nucleoside transporters 1 and 2 (*hENT1/2*) via a mechanism involving increased *NOS* and *Sp1* activity. However, cells from GDMow (orange area) show reduced (↓) expression and V_{max}/K_m of *hENT1* but not *hENT2*, reducing the uptake of adenosine. The mechanisms involved in this phenomenon associate with higher intracellular pH (pHi) value (ΔpHi), leading to intracellular alkalization. The increase in pHi value results from higher H⁺ efflux because of the activation of the human Na⁺/H⁺ exchanger 1 (*hNHE1*) isoform. HUVECs from GDty (red area) show higher V_{max}/K_m for *hNHE1*- but lower *hENT1*-mediated transport. GDty-associated increase in the *hNHE1* activity causes intracellular alkalization less pronounced than that of cells from GDMnw or GDMow

Preliminary results comparing *hENT1*- and *hENT2*-mediated adenosine transport in HUVECs from GDMnw and GDMow pregnancies suggest that maternal overweight may lead to a differential effect on the transport activity of these equilibrative transporters.³⁵ HUVECs from GDMnw pregnancies showed adenosine transport mediated via *hENT1* and *hENT2* with $^{hENT1/2}F$ of approximately 0.8. In contrast, cells from GDMow pregnancies showed adenosine transport mediated via activity of *hENT1*, but not *hENT2*. Thus, maternal pre-pregnancy overweight in women who develop GDM may determine the differential mechanisms involving *hENT1*

activity for handling extracellular adenosine. This phenomenon may increase the extracellular concentration of this nucleoside and dysregulation of its broad biological actions in the human foetoplacental vascular endothelium in GDM pregnancies.

Preliminary evidence suggests that *hENT* activity may be modulated by pHi in HUVECs from GDMnw/ow pregnancies.³⁵ It has been shown that an alkaline pHi may inhibit *hENT1* activity. As the activity of the human Na⁺/H⁺ exchanger (*hNHE*), with a significant role played by *hNHE1*,^{31,32} regulates the pHi in HUVECs, these membrane

exchangers may also modulate the extracellular concentration of adenosine. Interestingly, the basal pHi and hNHE1-mediated pHi recovery rates ($dpHi/dt$) in HUVECs from GDty pregnancies were higher than those in cells from Nnw pregnancies, but lower than the GDM-increased basal pHi and $dpHi/dt$ detected in cells from GDMnw or GDMow pregnancies.³⁵ Thus, less severe metabolic disturbances in terms of pHi regulation may occur in HUVECs from GDty than in those from GDMnw or GDMow. Indeed, the pHi buffering capacity (β_i) in HUVECs from GDty pregnancies is higher than that in HUVECs from GDMnw or GDMow pregnancies. However, the potential mechanisms by which hNHEs act as modulators of pHi in GDty pregnancies and their possible effects on the transport of L-arginine and adenosine in the human foetoplacental endothelium are unknown.

2.4.3 | Na^+/H^+ exchangers (NHEs)

Human foetoplacental tissue expresses different NHE forms to maintain pHi homeostasis. The NHE1, NHE2 and NHE3 isoforms are located at the basolateral membrane, apical membrane and cytoplasm of the syncytiotrophoblast.⁹⁷ NHE activity is undetectable at the basolateral membrane in term human placenta syncytiotrophoblast; however, NHE1 activity appears to be predominant in the apical membrane of these cells.⁴³ Thus, the expression of hNHEs, particularly hNHE1, in the human syncytiotrophoblast may be associated with an early development of the foetus. Moreover, inhibition of hNHE1 also led to lower aquaporin-mediated water uptake by the syncytiotrophoblast.⁹⁸ Therefore, inefficient hNHE1 activity may lead to vascular dysfunction with subsequent alterations in the nutrient supply, including water, to the developing foetus.

Human placental villi express hNHE1 mRNA, whose levels are unaffected by the duration of pregnancy. However, the hNHE2 mRNA expression level increases by approximately 18-fold at term than that during the first trimester of pregnancy.⁹⁹ Thus, hNHE1 and hNHE2 can perform different and deterministic functions in regulating pHi during the final stages of pregnancy. Few reports have addressed hNHE activity in the foetoplacental unit in women with pre-pregnancy diabetes mellitus. A higher hNHE1 activity is associated with hyperglycaemia, T1DM^{100,101} and T2DM.^{102,103} The hNHE1 expression level is lower in placentae from women with T2DM than in placentae from women without this disease.¹⁰⁴ This may limit the provision of electrolytes and other nutrients to the foetus. It has also been reported that HUVECs from women with GDM regardless of maternal pre-pregnancy BMI (ie cells pooled from these different patients), showed a higher basal pHi (pHi ~7.5) than HUVECs from normal pregnancies (pHi ~7.1).^{33,35,36}

Interestingly, pooled HUVECs from women with GDM and HUVECs separated by pre-pregnancy maternal BMI from GDMnw, GDMow and GDty (or GDMob) pregnancies showed basal pHi higher than HUVECs from Nnw, Now or Nob pregnancies (Figure 3). However, HUVECs from GDty pregnancies showed a less pronounced difference in basal pHi (ie ΔpHi) than those from Nob pregnancies than with the ΔpHi detected in cells from GDMnw or GDMow pregnancies. Thus, GDty may alter the pHi in the foetoplacental macrovascular endothelium controlled by different or more efficient mechanisms than in cells from GDMnw or GDMow pregnancies. However, detailed mechanisms are still unknown and require further investigation.

Preliminary studies also showed that insulin modulated the basal pHi and $dpHi/dt$ in HUVECs from GDM pregnancies, depending on the pre-pregnancy maternal BMI.³⁶ Insulin restored hNHE1-independent basal pHi in cells from GDty pregnancies, but restored hNHE1-dependent basal pHi and $dpHi/dt$ in cells from GDMow pregnancies. Thus, insulin modulates the pHi in HUVECs from GDty pregnancies in a differential manner than in those from GDMnw or GDMow pregnancies.³⁶ These findings highlight the need to consider at least these three groups of women with GDM pregnancies, according to their pre-pregnancy health status.

The hNHE activity is modulated by several molecules that have crucial effects on the human placenta. Epidermal growth factor and sphingosine-1-phosphate increase hNHE1 activity in the syncytiotrophoblast¹⁰⁵; this is associated with the anti-apoptotic effect of these molecules in these cells. Other studies have shown an increased hNHE activity in response to aldosterone in the syncytiotrophoblast from placentae with a female foetus (ie female placenta) but not in male placentae.¹⁰⁶ The aldosterone effect is possibly mediated by classical mineralocorticoid and glucocorticoid receptors.¹⁰⁶ The consequence of hNHE activation in the female placenta reduces nutrient transport during pregnancy in this organ. However, the mechanisms modulating hNHE expression and activity in GDMnw, GDMow or GDty in response to these molecules remains to be elucidated.

3 | CONCLUDING REMARKS

The physiological process of pregnancy is highly demanding in terms of energy and systemic adaptation to a new environment for both the mother and growing foetus. An increase in metabolic substrate transfer towards the foetus depends on the capacity of the placenta to adapt to the increasing energy requirement by the growing foetus. Several nutrients are required for this phenomenon, including D-glucose, amino acids, oxygen, water and ions. In diseases of pregnancy in which foetal metabolism is compromised, such as GDM,

endothelium-dependent vascular function in the foetoplacental unit is also affected.

The foetoplacental vascular endothelium plays a crucial role in controlling placental vascular tone, thereby modulating the foetal blood flow. GDM is associated with foetoplacental endothelial dysfunction characterized by up-regulation of the endothelial L-arginine/NO signalling pathway³⁴ and abnormal insulin/adenosine signalling axis.^{19,45} Hyperglycaemia-associated vascular endothelial dysfunction contributes to abnormal placental functionality in GDM.⁷⁷ Additionally, foetal hyperinsulinemia in GDM leads to dysregulation of hCAT-1-mediated transport of L-arginine and eNOS activity, possibly because of the preferential adenosine-facilitative effect of insulin via IR-A in the foetoplacental micro- and macrovascular endothelium. Other membrane transport mechanisms, including those regulating pHi, such

as NHE1, may also be functional in endothelial cells from GDM pregnancies.

Obesity and overweight are pandemics, and obesity associated with T2DM leads to diabetes. The elevated incidence of obesity in women of reproductive age will continue to increase the prevalence of maternal obesity (and overweight). GDM_{nw}, GDM_{ow} and GD_{ty} are different maternal and foetal metabolic conditions, which possibly lead to development of various diseases in new-borns, infants, and adults (Figure 4). GD_{ty} leads to changes in foetoplacental endothelial functions that are apparently less drastic or different from those influenced by GDM_{nw} or GDM_{ow}. Most of the studies on GDM include a pool of women with pre-pregnancy normal weight, overweight and obesity. However, studying these groups of women separately is crucial as it will allow experimental data to delineate

FIGURE 4 A cycle of events leading to abnormal foetoplacental vascular function in gestational diabetes mellitus. Obesity and overweight in women in their childbearing age (*Childbearing age women*) associate with pregnant women (*Mother*) developing gestational diabetes mellitus (GDM) being with pre-pregnancy normal weight (GDM_{nw}, or classical GDM), overweight (GDM_{ow}) or obesity (GD_{ty}). Studies reported in pregnant women with GDM, regardless of whether they show pre-pregnancy normal weight or overweight (GDM_{nw/ow}), GDM_{ow}, and GD_{ty} show placental dysfunction. These metabolic conditions cause inefficient transfer of essential metabolic substrates (*Altered nutrients transfer*) through the foetoplacental endothelium (*Placenta*) from the mother to the foetus (*Foetus*). The *foetoplacental endothelium* plays critical roles in this phenomenon resulting in altered *growth and development* of the foetus associated with defective cell signalling mechanisms, including the L-arginine/nitric oxide pathway and the insulin/adenosine axis. The newborn will show metabolic alterations that may result in the development of metabolic alterations in adulthood, leading to obesity and overweight

clinical outcomes in a more specific manner. Moreover, a comprehensive integration of specific maternal conditions affecting foetal phenotypes at birth and throughout their life cycle can be achieved.

When maternal overweight and obesity coexist with GDM, the concept of GDty as a different metabolic entity emerges, which differs from the classic GDM, wherein all women, including those with normal weight and those with obesity, are considered together regardless of pre-pregnancy BMI. Additionally, the coexistence of maternal pre-pregnancy overweight and GDM may configure another, although undefined, metabolic entity. As the foetoplacental vascular endothelium is the main target of blood metabolites, it has been proposed that GDty (and GDM_{nw} or GDM_{ow}) will affect this tissue differently than classic GDM. Therefore, patients with pre-pregnancy obesity who develop GDM should be grouped under a specific metabolic category to facilitate a more specific therapeutic approach.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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