BBA - Molecular Basis of Disease 1866 (2020) 165414

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

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

Endothelial dysfunction in pregnancy metabolic disorders☆

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ARTICLE INFO

Keywords:
Transporters
Receptors
Endothelial dysfunction
Metabolic disorders
Pregnancy

ABSTRACT

In recent years, the vascular endothelium has gained attention as a key player in the initiation and development of pregnancy disorders.

Endothelium acts as an endocrine organ that preserves the homeostatic balance by responding to changes in metabolic status. However, in metabolic disorders, endothelial cells adopt a dysfunctional function, losing their normal responsiveness.

During pregnancy, several metabolic changes occur, in which endothelial function decisively participates. Similarly, when pregnancy metabolic disorders occur, endothelial dysfunction plays a key role in pathogenesis.

This review outlines the main findings regarding endothelial dysfunction in three main metabolic pathological conditions observed during pregnancy: gestational diabetes, hypertensive disorders, and obesity and hyperlipidemia. Organ, histological and cellular characteristics were thoroughly described. Also, we focused in discussing the underlying molecular mechanisms involved in the cellular signaling pathways that mediate responses in these pathological conditions.

1. Introduction

Endothelium is an extensive cell monolayer that covers the inner wall of blood vessels in acting as an interface between blood and tissues [1]. It is composed by endothelial cells, which are bound by specific cell to cell adhesion proteins mediated by transmembrane proteins including tight junctions, tight junctional adhesion molecules, adherence junctions (Cadherins) and other molecules such as PECAM (Platelet endothelial cell adhesion molecule-1) [1]. These adhesion molecules promote a semipermeable sealing that allows endothelium to act as a necessary anatomic and functional interface between blood and other tissues [2,3].

The normal physiological functions of endothelium in relation to blood vessels are as follows: i.- to aid the blood in transporting nutrients, water and oxygen to the organs and to remove waste molecules and carbon dioxide; ii.- to induce vasocontraction and vasorelaxation to maintain normal blood pressure, and iii.- to avoid coagulation, thus maintaining blood in liquid phase by regulating hemostasis [2,4]. These normal functions of the endothelium are regulated by endocrine and nervous system mechanisms and by several metabolites that communicate its cellular signaling via cell membrane proteins and receptors [2,3]. The external signals are transmitted into intracellular signaling, thereby eliciting intracellular genomic and non-genomic actions. However, when endothelial dysfunction occurs, normal blood vessel function is altered, thereby promoting abnormal organ function [2–4].

During pregnancy, several endocrine functions must be adapted to the exceptional conditions of pregnancy, and consequently, all other systems will change, including the circulatory system [5,6]. However, such adaptation generates several metabolic changes affecting directly the function and metabolism of the endothelium [5,6]. The

☆ This article is part of a Special Issue entitled: Membrane Transporters and Receptors in Pregnancy Metabolic Complications edited by Luis Sobrevia.

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https://doi.org/10.1016/j.bbadis.2019.02.009
Received 6 October 2018; Received in revised form 3 February 2019; Accepted 5 February 2019
Available online 19 February 2019
0925-4439/

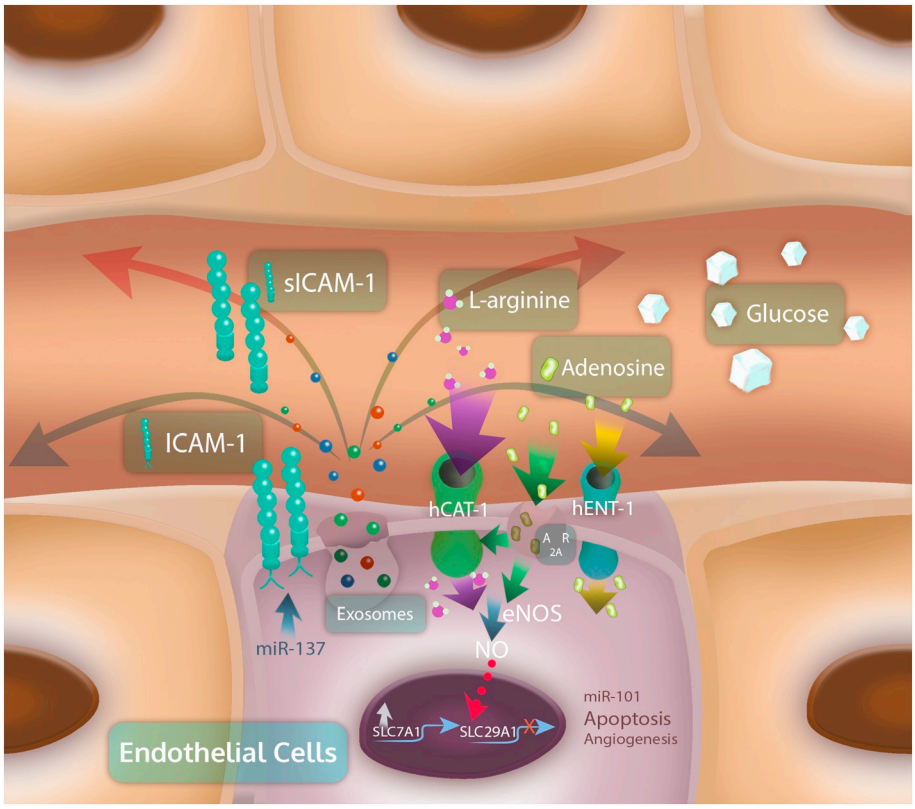

Fig. 1. Maternal hyperglycemia provokes feto-placental endothelial dysfunction.
High maternal glucose levels increase glycemia in the feto-placental vascular circulation. In turn, fetal endothelial cells, such HUVECs, that have been exposed to high glucose levels show a decreased capacity to transport adenosine, leading to its extracellular accumulation and thereby increasing adenosine bioavailability and binding to A2A adenosine receptors ($A_{2A}R$). A2AR activation results in increased L-Arginine transport via hCAT-1 and increased NO synthesis by eNOS. NO downregulates transcriptional expression of the SLC29A1 gene, resulting in a reduction in the adenosine transporter hENT-1, thus consolidating extracellular adenosine accumulation. Furthermore, increased circulating glucose levels provoke a pro-inflammatory environment that triggers the expression of ICAM-1, in part via miR-137, which increases leucocyte adhesion to endothelial cells, in parallel with increased soluble (s)ICAM-1 levels. Moreover, GDM endothelial cells produce increased exosomes in amounts that can affect (in autocrine-paracrine fashion) endothelial cells, resulting in the spreading and maintenance of feto-placental endothelial dysfunction. In addition, the increase of miR-101 increases the apoptosis of GDM endothelial cells and reduces their angiogenic capacity. Black arrows and red dotted arrows indicate induction and inhibition, respectively.

endothelium plays a key role in the pathogenesis of the pregnancy-associated metabolic disorders. It is affected by the metabolic disorders by losing its permeability control capacity, and has also been demonstrated that mediators of inflammation convert the endothelial cells into activated fibroblasts [7,8].

This review shows the main findings on endothelial dysfunction in three main metabolic pathological conditions. First, we focused on gestational diabetes because evidence shows that endothelial dysfunction is closely related to this condition during pregnancy. Furthermore, we reviewed hypertensive disorders associated with pregnancy, such as preeclampsia and hypertension. Endothelial dysfunction is a common pathogenic mechanism in the development of both preeclampsia and hypertension during pregnancy. Finally, we studied the highly associated syndromes of obesity and hyperlipidemia during pregnancy, because these metabolic disorders mainly causes elevated levels of circulating lipids in fetal-maternal micro- and macrovasculature. In all cases, we examined organ features, pathohistological changes and cellular characteristics and the underlying molecular mechanisms.

2. Gestational diabetes mellitus

2.1. Gestational diabetes mellitus overview

Gestational diabetes mellitus (GDM) is increasing worldwide and occurs in approximately 15% of pregnancies [9]. GDM occurs with macrosomia together with altered fetal cardiovascular and fetoplacental vasculature functions [10]. GMD is characterized by diabetes diagnosed within the second or third trimester of pregnancy that was not clearly manifested prior to gestation [11,12]. Most women experience restored glucose tolerance (to normal levels) after delivery, while GDM is associated with long-term adverse consequences for mothers and their progeny, including metabolic syndrome and increased risk for type-2 diabetes mellitus (T2DM) [9]. The 10-year risk of developing T2DM for GDM after pregnancy is ~40%; for this reason, GDM is also termed early T2DM. In both GDM and T2DM, chronic insulin resistance and inadequate pancreatic cell compensation play critical physiopathological roles [13].

In normal pregnancy, maternal circulating glucose can be delivered to the fetus via the fetoplacental circulation but is not accompanied by maternal insulin, which cannot cross the placental barrier [6,7]. Consequently, the high maternal glucose levels in GDM provoke fetal hyperglycemia and reactive fetal hyperinsulinemia, which lead to endothelial dysfunction within the fetal micro- and macrocirculation (similar to the findings observed in adult T2DM patients) [6,8]. Thus, endothelial dysfunction during pregnancy produces adverse long-term consequences for the child by increasing its susceptibility for developing T2DM and cardiovascular diseases [6,11].

It is well accepted that diabetes, beyond its classification as a metabolic disease, is also considered a vascular disease because of its effect on the macro- and microcirculation of many vascular beds [14]. For instance, endothelial dysfunction of the fetoplacental circulation is detected in GDM. Due to the lack of innervation in human placental vasculature, several metabolic mechanisms, such as production of vasoactive molecules (e.g. nitric oxide and adenosine) may lead to an acute and fast modulation of fetoplacental vascular tone [15].

2.2. Intercellular cell adhesion molecule-1 in GDM

GDM is associated with a pro-inflammatory state in both the maternal and fetal circulation, which is produced by increased levels of pro-inflammatory cytokines that are involved in endothelial activation, which is characterized by increased levels of, for instance, vascular cell adhesion molecule-1 (VCAM-1), *E*-Selectin and intercellular cell adhesion molecule-1 (ICAM-1) [16]. Moreover, the elevated expression of adhesion molecules facilitates leukocyte adhesion to the endothelium, thereby contributing further to the development of GDM-associated endothelial dysfunction [17].

ICAM-1 vascular expression is rare under normal physiological conditions, while pathogenic factors, such as hyperglycemia, activate its expression in endothelial cells, and an increase in soluble (s) ICAM-1

is also produced, reflecting endothelial cell activation and dysfunctionality [18] (Fig. 1). In this sense, pregnant women with GDM are characterized by higher concentrations of sICAM-1, and elevated ICAM-1 circulating levels may serve as a predictor of T2DM in women with a clinical history of GDM [18]. Similarly, GDM-derived human umbilical vascular endothelial cells (HUVECs) express increased levels of both ICAM-1 transcript and protein levels as consequence of alterations in fetal endothelial function due to maternal GDM [19].

Conversely, GDM human fetoplacental arterial endothelial cells (hFPAECs) are demonstrated to express reduced membrane-bounded ICAM-1 paralleled with lower sICAM-1 in cell culture supernatants [19]. This happens without changes in ICAM-1 mRNA transcript levels suggesting post-translational regulation mechanisms implications [20]. In fact, elevated levels of microRNA-221 and -222 observed in hFPAECs may cause the reduced ICAM-1 expression [20]. Although, the hFPAECs response seems to be different to those in maternal endothelium, it is not clear if this different response is compensatory or is part of the pathophysiological of ICAM-1 role in endothelium. Nevertheless, further studies are necessary to elucidate the precise impact of ICAM-1 regulation by environmental alterations in both maternal and fetal endothelium [20].

2.3. Endothelial transport alterations in gestational diabetes mellitus: adenosine-nitric oxide interplay

Several metabolic changes have been reported in GDM umbilical cord and placental endothelial cells, such as increased levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS), asymmetric (N^G, *NG*) dimethylarginine (ADMA) and nitric oxide (NO) synthesis in umbilical cord and placental endothelial cells [21]. Moreover, GDM-associated fetal vascular dysfunction provokes NO synthesis, L-arginine uptake and NO bioavailability functional dissociation in human placental endothelium [21,22].

Intriguingly, GDM provokes a reduction in the fetoplacental vascular dilation response to insulin or the endogenous vasodilator nucleoside adenosine; the molecular mechanisms include the altered expression of insulin receptors type A (IR-A) and type B (IR-B), adenosine receptors (ARs), L-arginine, adenosine transport and its transporters have been observed in macro and microvascular endothelium [23].

HUVECs are an excellent noninvasive cellular model that allows the analysis of environmental alterations to the fetal endothelium, and molecular abnormalities, such in those in the adenosine transport system, have usually been studied in GDM-derived HUVECs [24].

The GDM-reduced uptake of endogenous adenosine results in elevated extracellular concentrations, which in turn preferentially activate A_{2A} adenosine receptors ($A_{2A}R$) in the fetoplacental endothelium [25]. In consequence, GDM-derived HUVECs reduce adenosine transport, and this has been identified to occur as the result of a lower human equilibrative nucleoside transporter (hENT1) transport capacity through a reduced V^{max} rather than an altered apparent K_m, as adenosine uptake capacity efficiency remains similar to that of healthy controls; the finding can also be explained by reduced hENT-1 expression [25]. Moreover, in GDM-derived HUVECs, an approximately 50% reduction in nucleoside-binding sites has been described, which can also be explained by an increase in the rate of transporter internalization from the plasma membrane to a perinuclear location [25]. Normally, hENT-1 mediates approximately 80% of adenosine transport, while residual hENT-2 transport occurs without apparent changes in GDM [21], thus implying the importance of hENT-1 downregulation in GDM dysfunctional endothelium.

In turn, in HUVECs from normal pregnancies, adenosine transport via hENT-1 is reduced by insulin; however, this hormone increases hENT1 expression and activity to normal levels in GDM-derived HUVECs [26]. The recovery of hENT-1 expression and activity by insulin may reduce A2A-adenosine receptors activation by avoiding extracellular adenosine accumulation, which can downregulate L-arginine uptake by human cationic amino acids transporter 1 (hCAT-1) transport [23,25].

Importantly, increased NO downregulates hENT-1/*SLC29A1* gene expression by inhibiting its promoter transcriptional activity in GDM-derive HUVECs. Indeed, GDM-derived HUVECs present elevated endothelial nitric oxide synthase (eNOS) expression and activity [21] NO-dependent repressive transcription factor complexes that comprise hC/element-binding protein homologous protein 10 (CHOP)-CCAAT/enhancer-binding protein α(C/EBPα) (hCHOP-C/EBPα) interact with a specific *SLC29A1* promoter region located at -2154 to -1810 bp from transcriptional start site loaded the inhibition of hENT-1 in GDM [26]. This observation may nicely explain the increased adenosine extracellular levels found in GDM umbilical cord blood and in HUVEC culture medium compared with normal pregnancies.

Moreover, elevated extracellular adenosine levels increase ARs activation, resulting in elevated NO production, eNOS expression and substrate (L-arginine) transport by increasing human cationic amino acids transporter 1 (hCAT-1) expression, collectively known as the ALANO (Adenosine/L-arginine/Nitric Oxide) pathway [21,23]; these effects characterize GDM endothelial dysfunction (Fig. 1). In addition, HUVECs from GDM exhibit a higher number of copies of mRNA for hCAT-1, which are coded by the SLC7A1 gene, which is regulated by the Sp1 and NF-κB transcription factors [27]. Despite the increased expression of hCAT-1, increased L-arginine transport occurs because the transporter operates with higher maximal velocity due to intracellular signal pathways involved in L-arginine transport activation. For instance, PKC activators and ERK1,2 and MAPK activation increase L-arginase transport, and these intracellular signal transduction mechanisms also appear to operate in GDM-derived HUVECs [28].

Interestingly, arteries and veins in the human placenta in GDM pregnancies exhibit increased NO synthesis [29], and this is also observed in culture GDM-derived HUVECs. Although NO production seems to be increased in the fetoplacental vasculature, its bioavailability is reduced. This can be the consequence of the higher oxidative stress observed in GDM since NO reacts with ROS, thereby depleting bioactive NO from the circulation [10,30].

As abovementioned, insulin inhibits the increased L-arginine transport and NO production observed in GDM-derived HUVECs compared with the same cells from normal pregnancies [31]. Insulin affects ALANO pathways in GDM-derived endothelial cells. For instance, Insulin increases adenosine transport via hENT-1 activation, which decreases the increased adenosine extracellular levels, while also decreasing NO production by reducing eNOs expression and activity and L-arginine transport [23]. Thus, insulin seems to *in vitro* reverse GDM-associated ALANO alterations in human fetoplacental endothelium.

ADMA can also regulate endothelial function through the inhibition of both nitric oxide synthase and CATs, thereby reducing NO production. ADMA may contribute to endothelial dysfunction and generate vascular oxidative stress, which is involved in the etiopathology of vascular and organ diseases [32]. Although, Akturk et al. [22], reported that peripheral blood ADMA levels are elevated in GDM, indicating endothelial activation and consequent endothelial dysfunction, Poniedziałek-Czajkowska et al. [18] indicates that patients with GDM show significantly lower ADMA levels than healthy pregnant women. It is possible that hyperglycemia decreases ADMA levels by reducing its synthesis or by enhancing its degradation by dimethylarginine dimethylaminohydrolase [18,22]. This last observation is consistent with the increased L-arginine transport and NO synthesis in vascular endothelium. It is important to point out that some differences exist between these two studies: while Akturk et al. [22] study normal and GDM groups similar in obese status, with body mass index (BMI) 29.59 kg/m^2 and 28.66 kg/m^2 respectively, Poniedziałek-Czajkowska et al. [18] compared obese GDM (BMI 27.93 kg/m^2) with non-obese control group with BMI 22.34 kg/m^2. Although in both studies GDM show higher circulating C - reactive protein levels, as a marker of inflammatory status, higher insulin levels [22] and higher oral glucose

tolerance test values, the differences in BMI for both GDM and control groups in both studies may turn ADMA results not comparable. Therefore, a study considering both normal and obese BMI values to compare with GDM patients should be addressed to resolve the disparity between ADMA studies.

2.4. Endothelial exosomes and microRNAs influence endothelial dysfunction in GDM

Components of new molecular mechanisms, including exosomes and microRNAs (miRs), have been demonstrated to influence the GDM dysfunctional endothelium (Fig. 1).

2.4.1. Exosomes

Exosomes are nanovesicles (40–100 nm diameter) that are secreted into the extracellular environment by most cell types and contain proteins, lipids, mRNAs, miRs and noncoding RNAs, thereby representing a new type of paracrine cell-cell communication [33]. In endothelial cells, exosomes regulate such cellular functions as migration, proliferation and angiogenesis [34]. Recently, increased levels of circulating exosomes in maternal plasma of GDM have been described [35]. Interestingly, both placental and maternal GDM exosomes are increased in maternal plasma. Furthermore, HUVECs treatment with GDM-isolated exosomes increased the production of pro-inflammatory cytokines, such as GM-CSF, IL-4, IL-6, IL-8, IFN-γ, and TNF-α [35].

Moreover, GDM-derived HUVECs exosomes increased hCAT-1 expression and L-arginine endothelial transport and NO synthesis in normal pregnancy-derived HUVECs [36]. These results indicate the potential contribution of GDM exosomes as autocrine or paracrine signals to the induction and maintenance of feto-placental endothelial dysfunction [34].

2.4.2. MicroRNAs

MiRs are short and stable noncoding RNAS that finely tune gene expression and have been implicated in pathological conditions, including T2DM and diabetic-associated vascular dysfunction [37]. Dysregulation of miRs has been described in GDM, and these biomolecules may represent potential blood biomarkers for the diagnosis and monitoring of GDM evolution in pregnant women and the fetus [38]. As mentioned above, ICAM-1 is susceptible to regulation by miRs. miR-221 and -222, the expression of which is upregulated in human fetoplacental endothelial cells obtained from GDM patients, and these miRs contribute specifically to ICAM-1 downregulation since VCAM-1 and *E*-selectin are not-modified in feto-placental endothelial cells [20]. MiR-137 has been postulated as a GDM-predictive marker for glucose-induced endothelial cell dysfunction. MiR-137 is increased in the plasma of GDM women and in high-glucose (HG)-exposed HUVECs and enhances monocyte adhesion to HUVECs monolayers, accompanied by increased ICAM-1, VCAM-1, and E-selectin expression. In addition, the angiogenic potential of HUVECs is highly reduced by miR-137. These observations implicate miR-137 in the development of GDM, and the authors postulated that its peripheral blood levels in pregnancy can be useful for monitoring GDM severity [39]. Finally, GDM-derived HUVECs express elevated soluble miR-101 levels, and these miRs contribute to the increased apoptotic endothelial rate and reduced functional angiogenic capacities. These effects are partly mediated by the miR-101 inhibition of histone methyltransferase enhancer of zester homolog-2 expression (EZH2) in GDM-derived HUVECs, while ectopic EZH2 expression rescues cells from reduced migratory capacities and increased apoptotic activity. Thus, miR-101, in part by inhibiting EZH2 expression, may influence the development of endothelial dysfunction in the fetoplacental vascular system [24]. Although, miRs have been reported as part of exosomes also, it has not been studied yet whether exosomes-associated miRs may influence GDM maternal and fetal vasculature. Nevertheless, accumulating evidence supports the notion that epigenetic alterations confer molecular memory relating to gene expression in cells exposed to a diabetic milieu in vivo, which can predispose GDM pregnant women and their offspring to develop T2DM and metabolic disorders [40].

In conclusion, GDM, as a condition of carbohydrate intolerance, is associated with adverse maternal and offspring health outcomes and produces an inflammatory state that impacts both the macro- and microcirculation. Thus, GDM impairs vascular structure and function. Maternal hyperglycemia increases fetal circulating glucose levels, triggering the development of fetoplacental endothelium alterations, which are characterized by the inflammatory activation of endothelial cells and transporter changes that together result in NO synthesis deregulation. Furthermore, new actors, such as exosomes and miRs, appear to contribute to the final manifestation of endothelial dysfunction. Importantly, circulating miRs may represent potential biomarkers for early GDM diagnosis [38], but additional studies are necessary to understand the impact of the growing number of GDM-associated miRs in the vasculature pathological patterns of expression in pregnancy. Also, new potential biomarkers have been reported such sex hormone binding globulin, elevated triglycerides and reduction in HDL, inflammatory markers including TNF-α and IL-6, placental glucose transporter and epigenetic modifications are under investigation [41]. Nevertheless, several issues related to reproducibility and selectively need to be resolved before its clinical implementation.

3. Hypertensive disorders during pregnancy, preeclampsia and eclampsia

3.1. Preeclampsia and eclampsia overview

The normal fetal development depends on maternal hemodynamic and cardiovascular changes to comply with the increasing demand of oxygen and nutrients [42]. A significant increase in the maternal blood volume, is accompanied by a larger cardiac output, and vasodilation that generates a decrease in the vascular resistance and subsequently in the blood pressure [42]. Alterations in these adaptive changes may develop pregnancy hypertensive disorders that affect 5% to 8% of gestations. These pathologic conditions include chronic hypertension and four pregnancy associated disorders: preeclampsia, eclampsia, superimposed preeclampsia and gestational hypertension [43]. These disorders share the presence of hypertension but correspond to different pathological entities [43]. Gestational hypertension is the evidence of elevated blood pressure during pregnancy with no evidence of other disorders and can be transient or represent the first sign of chronic hypertension [44,45]. Preeclampsia is also characterized by proteinuria and edema, while eclampsia is defined as preeclampsia in which cerebral involvement leads to the development of seizures in the patients. Superimposed preeclampsia corresponds to the presence of preeclampsia in patients with previous chronic hypertension [43–45].

Preeclampsia and eclampsia affect more than half a million of women every year. Preeclampsia and eclampsia are responsible of 15% of maternal deaths [46], significantly increase the risk of malformations [44], reduce birth weight [45], and are the leading causes of indicated preterm delivery [43]. Despite the normalization of the maternal vascular disturbances after birth, formerly preeclamptic women have an increased risk of cardiovascular and kidney disease later in life [47,48]. Eclampsia constitutes a severe form of preeclampsia, that can affect up to 3% of women with preeclampsia, but can also develop in women without obvious signs of preeclampsia [49]. The etiology of preeclampsia has been proposed to be multifactorial, with a demonstrated racial predisposition [50]. The genetic component in pregnancy-related hypertensive disorders is supported by the fact that first degree relatives have a fourfold higher predisposition than the general population [51]. A study in twins showed that in dizygotic twins, preeclampsia was concordant in 2 out of 61 cases, but in monozygotic twins, it was concordant in 8 out of 56 cases [52]. It was proposed then that 35% of the variance in the risk of preeclampsia is due to a maternal genetic

effect and that 20% is due to fetal genetics [53].

3.2. Etiology of preeclampsia and eclampsia: a placental disorder of immunological causes

Altered implantation of placenta has been traditionally accepted as the primary event responsible for the histological abnormalities observed in preeclampsia [7]. During normal placentation, cytotrophoblasts are attached to the basement membrane that surrounds the stromal core of chorionic villi [7]. Some of these cells fuse, forming syncytial trophoblasts that cover the villus and transport nutrients between fetal and maternal blood. At specific locations, the cytotrophoblasts break through the syncytium and form multilayered columns of cells that invade the uterus [54]. These invasive extravillous cytotrophoblasts infiltrate the spiral arteries of the endometrium and replace the maternal endothelium in the arteries of the endometrium and part of the myometrium and remodel the tunica media (the muscular-elastic layer) of these arteries, consequently increasing the width and decreasing the resistance of the spiral arteries, increasing the blood flow according to fetal demand [55]. With the infiltration of cytotrophoblasts, endothelial cells undergo apoptosis at the time that cytotrophoblasts adopt an endothelial phenotype in the spiral arteries [56].

It is largely accepted that preeclampsia is associated with the shallow infiltration of cytotrophoblast cells, which lead to a narrowing of arterioles and decreased blood flow; the consequent lack of nutrients might be the main cause of the growth alterations observed in hypertension-preeclampsia pregnancies [57]. Early histological studies demonstrated the presence of morphological differences in the spiral arteries of the placenta in patients with preeclampsia, and the diseased group showed a lack of the arteries with increased diameter compared to controls [58]. It was then suggested that the hypertension observed in preeclampsia corresponds to a compensatory mechanism that provides adequate blood supply to the developing fetus. However, later findings supported a two-stage model: In stage 1, placental ischemia is generated by the impaired development of the spiral arteries, and in stage 2, the ischemic placenta releases antiangiogenic factors into the maternal circulation, causing generalized endothelial damage [59].

Because preeclampsia occurs mainly in first pregnancies and this rate is lower in first pregnancies following a miscarriage, immunological causes and adaptation have been invoked as mechanisms of preeclampsia [60]. Furthermore, an immunological adaptation to the paternal genetic component has been proposed, since the preeclampsia rate is higher in multiparous women with multiple partners than in single-partner multiparous women [61,62]. Infectious diseases also increase the risk of preeclampsia [63]. Researchers have proposed that the Th2/Th1 switch together with high levels of inflammatory cytokines such as TNF-α and IFN-γ and increased oxidative stress can lead to an increase in the levels of FLT1, a known factor in the development of preeclampsia [64]. These findings led to the proposal of a three-stage model of development of preeclampsia, the currently most-accepted model (Fig. 2). The first stage occurs during the very early stages of development, during which a failed immunological tolerance to the embryo occurs (the first stage). This impedes normal infiltration and remodeling of the spiral arteries in the placenta (the second stage), thereby generating placental ischemia with the release of antiangiogenic factors that have detrimental consequences for the maternal endothelial functions (the third stage) (Fig. 2).

3.3. Cell interactions in the placental development as cause of preeclampsia

During the infiltration of cytotrophoblasts into the spiral arteries of the uterus, the fetal cells undergo differentiation. The cells express MMP9 to facilitate cell migration and express HLA-G, a specific trophoblastic form of HLA-I, to prevent rejection by the maternal immune system [65]. The cells exhibit decreased expression of α6β4 integrin (laminin 332 receptor) and increased expression of integrin α5β1 (fibronectin receptor) and α1β1 (collagen IV receptor). The expression of integrins αVβ3 (vitronectin receptor) and α1β1 (collagen and laminin receptors) as well as a reduction in the expression of E-cadherin play key roles in cytotrophoblast invasion (Fig. 2) [66]. Cytotrophoblasts express a normal endothelial cell cadherin pattern when they are fully localized in the intima of the blood vessels [67] In conclusion, as cytotrophoblasts differentiate, they downregulate adhesion receptors that are characteristic of epithelial cells (integrin α6β4 and E-cadherin) and upregulate receptors that are expressed by endothelial cells (α1β1, αVβ3, VE-cadherin) (Fig. 2) [68].

The abovementioned changes are needed for normal placental development. It has been demonstrated that cytotrophoblasts in preeclampsia patients have important differences from those in control patients. Cytotrophoblast cells of preeclampsia patients show lower α5 integrin and MMP9 expression than control patients, but no difference is seen for α1 integrin [69]. Using immunohistochemical analyses of biopsies of patients with preeclampsia, it was also demonstrated that cytotrophoblasts exhibit downregulated α6β4 integrin compared to that seen in normal development and do not express α1β1 integrin, which is usually upregulated in these cells [70]. Furthermore, cytotrophoblasts in preeclampsia patients fail to upregulate the extracellular matrix proteins receptors αVβ6 and αVβ3 integrin, suggesting a decreased interaction with their extracellular matrix. In the same way, these cells fail in the regulation of VE-cadherin and the leukocyte adhesion molecule receptors αVβ6 and αVβ3 integrin, suggesting a decreased interaction with their extracellular matrix. In the same way, these cells fail in the regulation of VE-cadherin and the leukocyte adhesion molecule receptors integrin α4β1 and α4β7. These observations demonstrate that the cells fail to develop the mechanisms for intercellular adhesion that are critical for the appropriate function of blood vessels [71].

3.4. Endothelial alterations in eclampsia: a consequence of decreased placental perfusion

Placental hypoperfusion is accepted as the ultimate cause of endothelial dysfunction. The hypoperfusion of placenta is due to the narrow spiral arteries caused by a shallow infiltration of trophoblasts. A major evidence of the effects of altered placental perfusion on maternal hypertension has been provided by animal models of reduced uterine perfusion pressure (RUPP) [72,73]. Despite the limitations induced by these mechanisms that usually include aortic constriction, different models of RUPP in mammals have demonstrated that the reduction in blood supply in the uterus generates an increase in the maternal blood pressure [74–76], and some of the effects revers after the normal blood supply in the uterus is restored [72]. It has been proposed then that under lack of oxygenation, placental cells release factors that affect the endothelial function in the whole maternal circulation [72].

In preeclampsia, perfusion is decreased in all maternal organs, secondarily to a generalized vasospasm generated by an increased sensitivity of the vasculature to vasopressors [77], which has been demonstrated to persist after delivery [5]. The maternal endothelial dysfunction in preeclampsia generates increased systemic resistance, thereby reducing the perfusion of all organs [8]. In order to evaluate if these alterations are due to endothelial function, studies have measured the effects of endothelium-dependent mechanisms of vasodilation such as flow-mediated vasodilation, or acetylcholine-induced vasodilation. These mechanisms are usually compared with the effects of smooth muscle vasodilators such as nitroglycerin that acts preferentially in venous smooth muscle, or sodium nitroprusside which preferentially acts in arterial smooth muscle. Through these methods it has been demonstrated that the endothelium-mediated vasodilation is altered in preeclamptic women [78]. In vivo studies have demonstrated that in large arteries, preeclamptic women experience a lower flow-mediated (endothelium-dependent) vasodilation compared with non-preeclamptic women, as measured by Doppler flow velocity pattern in

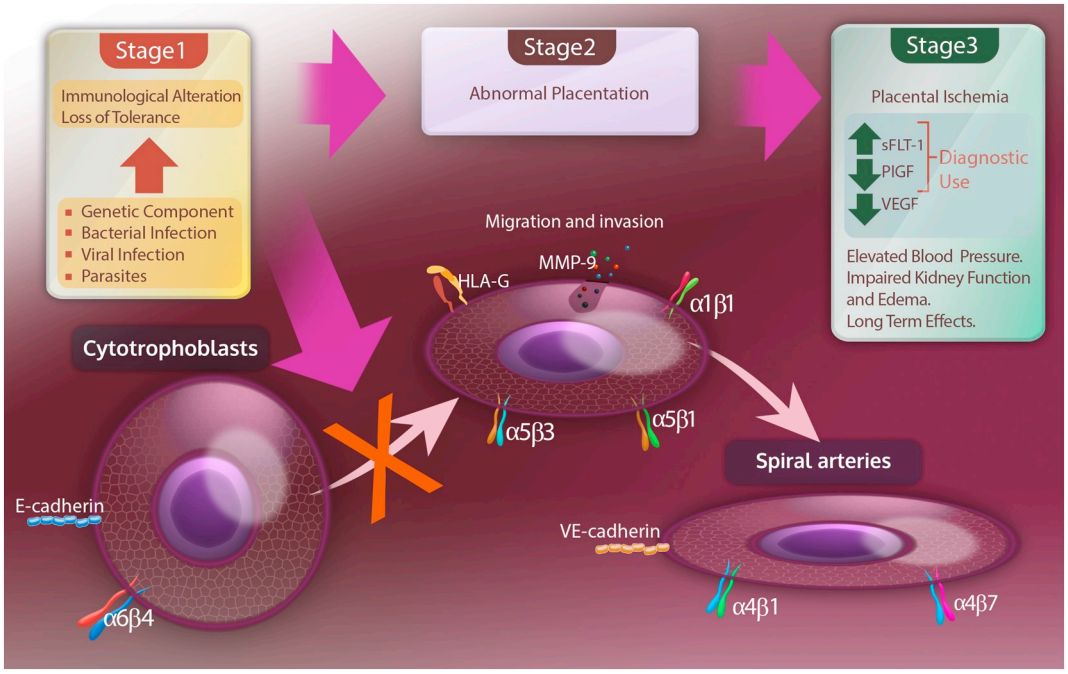

Fig. 2. Three-stage model of preeclampsia.
Stage 1, immunological disorders affect maternal tolerance to the embryo, affecting the cytotrophoblasts infiltration in the developing placenta. Stage 2, the lack of immunological tolerance affects placentation. As a consequence, exists an inhibition of the cytotrophoblast invasion of spiral arteries in the endometrium. This is observed by the inhibition of the down regulation of adhesion molecules as E-cadherin and integrin α6β4, and inhibiting the expression of proteins that allows migration such as matrix metalloprotease-9 (MMP-9), human leukocyte antigen-G (HLA-G) and the integrins α5β3, α5β1 and α1β1; this failure also prevents the final differentiation into endothelial cells of spiral arteries that express VE-cadherin, and integrins α4β1 and α4β7. Stage 3, the ischemic placenta responds with an increased secretion of the antiangiogenic soluble receptor sFLT-1, and decreased secretion of the angiogenic factors vascular endothelial growth factor (VEGF) and the placenta growth factor (PlGF), which generates endothelial alterations in tissues and organs.

brachial artery [79]. Interestingly, the microvasculature of women with preeclampsia have a higher response to endothelium-dependent vasodilation (acetylcholine) than non-preeclamptic women during pregnancy [80,81]. But there are no differences in the microvascular response to endothelium-independent vasodilators (sodium nitroprusside), demonstrating that the microvascular changes during preeclampsia have an endothelial origin [80,81]. These contradictory results in response to endothelium-mediated vasodilators in pre-eclamptic women (lower vasodilation in large arteries and increased vasodilation in microvasculature) should not be considered as compensatory effect to maintain blood pressure, since microvasculature has no capacity of overcoming changes in large vessels; indeed, the vasodilation of large arteries and microvasculature do not correlate in physiological or pathological conditions, and is accepted that respond to different mechanisms [82]. The lower flow-mediated vasodilation observed in large arteries, and increased acetylcholine induced vasodilation of microvasculature in preeclamptic women, have shown to persist after delivery, suggesting that these alterations are associated to endothelial changes that persist in absence of placental factors [80,83]. Interestingly, the administration of ascorbic acid (inhibitor of oxidative stress) increases the flow mediated vasodilation in large arteries of former preeclamptic women but not in controls, demonstrating the role of oxidative stress in mediating the endothelial dysfunction in pre-eclampsia [83,84]. This association between oxidative stress and pre-eclampsia has recently been shown to increase plasma biomarkers of inflammation and oxidative stress such as 8-isoprostane, C-reactive protein, IL-1β, IL-6 and IL-10, in preeclamptic women during pregnancy [85].

Despite this progress, the molecular mechanisms that underlie these functional alterations remain unclear. Many factors have been studied in the search for soluble factors that could explain the endothelial alteration in pre-eclampsia. To date, factors that have shown a higher association with the disease include the antiangiogenic soluble fms-like protein kinase-1 (sFLT-1) and the proangiogenic placental growth factor (PlGF) [86,87]. Gene expression analysis has demonstrated that sFLT-1 is upregulated while free VEGF and free PlGF are reduced in the placenta of preeclampsia patients [88]. In the same study, Maynard et al. demonstrated that this elevation in sFLT-1 levels decreases the angiogenesis induced by VEGF and PlGF as well as the vasodilation produced by these two factors, thereby causing proteinuria and glomerular endotheliosis. Subsequent clinical studies have demonstrated that pregnancies with poorer outcomes are associated with higher serum levels of sFLT-1 and lower levels of PLGF [89,90]. A recent study in 1055 women proposed a FLT-1/PlGF ratio of 38 as a cut-off in pregnancy monitoring for predicting preeclampsia and found mean levels of sFLT-1 of 4380 pg/mL in preeclampsia compared to 1643 pg/mL in controls; for PlGF, the corresponding values were 90 mg/mL in preeclampsia and 142 in control women [91]. An sFLT-1/PlGF ratio of 38 showed a 98.9% negative predictive value, 88.2% sensitivity, and 80% specificity. Commercial automated systems have been recently released to measure the FLT-1/PlGF ratio for research and diagnostic purposes [92].

3.5. Molecular effects on maternal endothelium

The elevated concentration of sFLT-1 and lower concentration of PlGF in preeclampsia suggests that these molecules play a role in the pathogenesis of pregnancy hypertension diseases rather than act as simple markers of dysfunction. Placental growth factor was first described in 1991 by Maglione et al. as a 149-amino acid protein sharing 53% homology with VEGF [93]. The secretion of PlGF and VEGF is induced by the activation of HIF-a after exposure to hypoxia [94]. Similar to VEGF, PlGF exists as a homodimeric glycoprotein that can bind heparin, depending on its alternative splicing [95]. PlGF binds VEGF

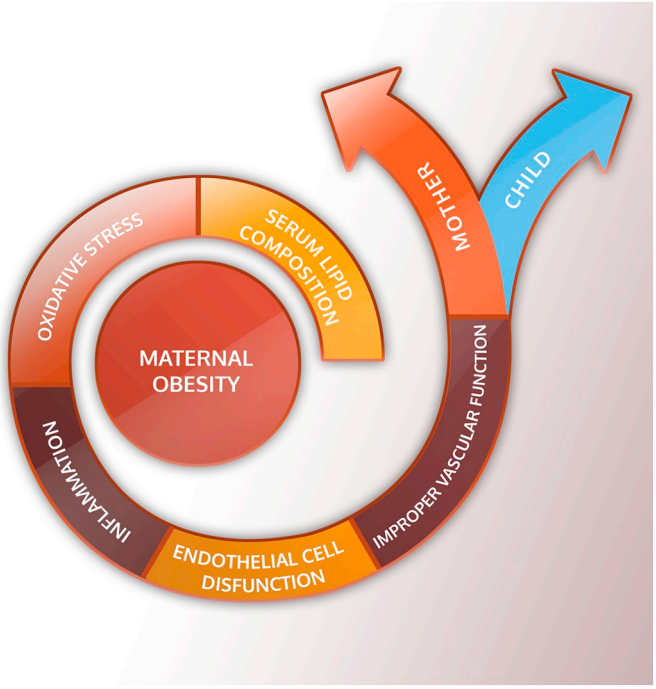

Fig. 3. Effects of maternal obesity during pregnancy
Diagram summarizing the effects of maternal obesity during pregnancy. Obesity represents a cardinal risk factor for both mother and child, which alter serum lipid composition before and during gestation. This leads to childbearing in an oxidative and pro-inflammatory environment, having a deleterious impact on endothelial and vascular physiology for both, mother and child.

receptor FLT-1 (VEGFR1) with high affinity and binds to the soluble form sFLT-1 but does not bind the most active receptor FLK1/KDR (VEGFR2). FLT-1 is a transmembrane receptor with tyrosine-kinase activity. The binding of PlGF to FLT-1 results in the transphosphorylation of FLK1/KDR. This FLT1-mediated phosphorylation enhances the downstream effects of FLK1/KDR activation by VEGF, which are produced by the activation of PLCγ [96], and PI3K/AKT [97]. The soluble form sFLT-1 is the truncated form of FLT-1 and is obtained by alternative splicing of the same mRNA such that it does not encode the transmembrane region [98]. This protein is a powerful specific inhibitor of the effects of VEGF [98]. sFLT-1 has a higher affinity for VEGF than PlGF and inhibits the angiogenic effects of VEGF and PlGF [99]. Experimental studies have demonstrated that the serum of preeclampsia patients has a lower potential for inducing angiogenesis than that of normotensive patients and that this effect results from the elevated concentration of sFLT-1 [88]. The same study also demonstrated that the elevated levels of sFLT-1 can induce hypertension and glomerular endotheliosis in a murine model. The authors then suggested that the presence of soluble FLT-1 is causative of hypertension, renal failure and proteinuria in preeclampsia [88]. Subsequent clinical studies have shown a positive correlation between the concentration of sFLT-1 and proteinuria and between sFLT-1 and cardiovascular risk, affecting both men and women [100]. Using blocking antibodies, the anti-angiogenic effect of sFLT-1 was demonstrated in the serum of patients, as was the effect of sFLT-1 in increasing the apoptotic rate in endothelial cells, thereby generating renal damage [100]; in addition, elevated levels of sFLT-1 and PlGF have been associated with pulmonary hypertension in men and women [101]. The presence of sFLT-1 does not itself affect endothelial cell function but acts by inhibiting VEGF and PlGF activity. It has also been demonstrated that sFLT-1 acts synergistically with the inflammatory effects of TGF-α, perhaps inhibiting the VEGF activation of iNOS [97]. The inhibitory effect of sFLT-1 also affects other functions of VEGF, such as leucocyte migration [102]. Taking these findings together, it seems that sFLT-1 is capable of altering endothelial function by blocking the effects of VEGF; together with a decrease in the level of PlGF, this could explain the effects on liver and kidney function that lead to proteinuria and edema. However, there is no certainty of how these molecules could generate permanent alterations in the affected women. In the murine model in which sFLT-1 is increased during gestation, blood pressure, vascular function and FLT-1 levels return to normal postpartum; for this reason, it is thought that more complex molecular interactions are responsible for the permanent changes and damage to vascular function that occur during eclampsia [103]. In humans, it has been shown that sFLT-1 decreases rapidly postpartum in late onset preeclampsia, reaching normal levels, but remains elevated in early onset preeclampsia [87].

In conclusion, preeclampsia is currently explained in a three-stage model, in which the role of the immune system is still not fully understood. The mechanisms that provoke a shallow infiltration of trophoblasts and thus generating a poor remodeling of spiral arteries are not currently known, but the subsequent decreased placental dysfunction and its association with a generalized hypertension is widely accepted. Despite many soluble factors have been associated with PE development, only sFLT-1 and PlGF are currently accepted markers of the disease.

4. Obesity and hyperlipidemia during pregnancy

4.1. Normal lipid changes in plasma maternal plasma during pregnancy

Obesity during pregnancy is a prevalent condition, and its incidence is increasing in the USA, Europe, Asia, Latin America, and Africa [104]. Obesity represents a significant risk factor for the mother by increasing the risk of developing gestational diabetes [105], gestational hypertensive disease [106], preeclampsia [105], eclampsia, thromboembolic events, and complications of anesthesia during obstetric interventions [107]. Furthermore, it represents a significant risk factor for the fetus to develop severe congenital malformations, congenital heart defects, orofacial cleft, and gastrointestinal malformations, among many others [108] (Fig. 3).

During pregnancy, it is well-known that due to the effects of estrogen, progesterone, and human placental lactogen, plasma lipid levels increase significantly [109], which is associated with hypertriglyceridemia-induced attenuated endothelium-dependent relaxation in human subjects with normal plasma low-density lipoprotein (LDL) cholesterol levels [110]. Two mechanisms have been proposed for the changed lipid profile during pregnancy. One is the estrogen-induced hepatic synthesis of very low-density lipoprotein (VLDL) triglycerides [111]. The second mechanism proposed to explain the increased TG in all circulating lipoproteins during gestation is the impaired removal of lipoprotein TG by one or both of the lipolytic enzymes, lipoprotein lipase and hepatic lipase [112].

Human pregnancy is associated with severe physiological hyperlipidemia, even during normal human gestation. Plasma high-density lipoprotein (HDL)- and LDL-cholesterol levels are increased by 50%, while TG levels increase between 2- and 4-fold [109,113]. The normal gestational increase in TG is associated with a change in the LDL profile [114,115]. It has been observed that maternal lipoproteins and triglyceride concentrations is increased over time from preconception to the third trimester of pregnancy [116]. LDL particles are the second smallest lipo-protein particles, and their principal role is to transport cholesterol to cells, where delivery is facilitated via the LDL receptor. Oxidized LDL (oxLDL) and dense LDL particles have a particularly cytotoxic effect on endothelial function [115,117]. Once oxidized, LDL is believed to have enhanced atherogenic potential, promoting foam cell formation and initiating endothelial dysfunction [118]. OxLDL is a ligand for lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) and is increased in the circulation of women with preeclampsia [115,119].

Sankaralingam et al. used plasma from women with preeclampsia to

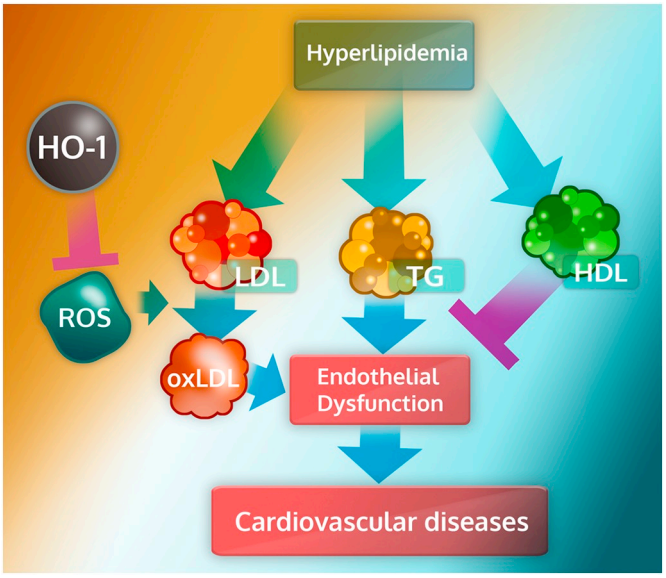

Fig. 4. Hyperlipidemia during pregnancy.
Hyperlipidemia during pregnancies is associated with increases in LDL, TG and HDL. ROS production induces oxLDL. Increased plasma levels of TG and oxLDL are usually associated with endothelial dysfunction. HO-1 inhibits the oxidation of LDL to form oxidized oxLDL. HDL can also inhibit endothelial dysfunction, decreasing the risk of cardiovascular disease. LDL: Low density lipoprotein; TG: Triglyceride; HDL: High density lipoprotein; oxLDL: Oxidized Low density lipoprotein; HO-1: heme oxygenase system-1.

increase the NAD(P)H oxidase-mediated superoxide and peroxynitrite production by means of LOX-1 activation in endothelial cells [120]. In addition to oxLDL, other circulating factors that are increased in preeclampsia are also able to activate LOX-1. These include anionic phospholipids, apoptotic cells, activated platelets, and bacteria [120]. Thus, LOX-1 pathway emerges as a key factor participating in endothelial dysfunction and cardiovascular diseases during pregnancy (Fig. 4). The oxLDL increases heme oxygenase system-1 (HO-1) induction in response to ROS [121]. HO-1 is a powerful anti-inflammatory and vasodilator agent that exerts a protective effect against a wide variety of pathological conditions during pregnancy [122,123]. It has been reported that HO-1 has been used in the treatment of cardiovascular diseases and hypertension [124,125] (Fig. 4). Furthermore, studies performed in pregnant mice showed an important participation for the heme oxygenases in the establishment and maintenance of pregnancy and adequate placental blood flow [126]. HO-1 pathway has a direct effect inhibiting endothelin-1 production in cultured human glomerular endothelial cells, suggesting that HO-1 could inhibit placental ischemia-mediated endothelin-1 production, playing an important role in blood pressure regulation during placental ischemia [127]. Interestingly, nuclear factor erythroid 2-related factor (Nrf2) is a transcription factor that binds sites in the human *HO-1* gene [128]. Because Nfr2 is activated in response to oxLDL [129,130], it is possible to propose that oxHDL controls HO-1 levels by means of Nfr2 activity. Congruently, Chigusa et al. observed that high oxLDL circulating levels induces HO-1 expression in woman with preeclampsia [131]. The finding of high serum HO-1 levels in maternal and cord blood in preeclampsia suggests that heme derived from free hemoglobin in plasma may threaten vascular endothelial cell integrity via the oxidative modification of LDL [132].

4.2. Blood lipid composition and endothelial dysfunction during pregnancy

Hyperlipidemia can compromise endothelial function, and this may contribute to the development of atherosclerotic vascular disease [133,134]. In complicated pregnancies, the mechanisms regulating physiological hyperlipidemia may malfunction. Abnormal lipid profiles and species may play a role in the promotion of the oxidative stress and vascular dysfunction that occur in preeclampsia [135]. When LDL particles are oxidized, they are readily taken up into macrophages via the scavenger receptor, promoting foam cell formation and the development of atherosclerotic lesions, thereby initiating vascular occlusion and endothelial dysfunction [136]. In addition, increased levels of lipid hydroperoxide in pregnancy have been associated with the development of atherosclerosis and an increased risk of cardiovascular diseases [137], especially in women with Type II diabetes [138]. Women with a history of preeclampsia have significant differences in their lipid parameters and exhibit an increased susceptibility to lipoprotein oxidation when compared with women who had a normal pregnancy one to three years after delivery [139]. Cekmen et al. found that abnormal lipid metabolism and particularly high TG, LDL and lipid peroxide concentrations and low HDL concentrations may contribute to the promotion of oxidative stress and endothelial dysfunction in preeclampsia [134]. Among those who develop preeclampsia, an additional change in the lipid metabolism is present since plasma TG levels are further increased compared to women with normal pregnancies [140]. These results are consistent with findings reported in studies of other populations. Patients with preeclampsia had lower mean serum HDL and higher mean TG concentrations than control groups in the Finnish and Peruvian populations [141,142]. Hyperlipidemia with oxidative stress resulting in lipid peroxidation may add to the promotion of vascular dysfunction, leading to pregnancy-induced hypertension [143]. In the area of cardiovascular research, there is increasing evidence that hyperlipidemia can cause endothelial dysfunction [144]. In recent years, the evaluation of lipid profiles during pregnancy have been required for the early diagnosis of cardiovascular risk factors, especially in high risk populations [145]. Elevated TG-rich lipoprotein levels constitute a substantial cardiovascular risk factor and are perhaps as important as cholesterol [146,147]. Hypertriglyceridemia is associated with attenuated endothelium-dependent relaxation in human subjects with normal plasma LDL-cholesterol levels [110]. Plasma HDL concentrations increase at 10 weeks of gestation and reach a maximum level with a 42% increased concentration at 20 weeks of gestation; levels then decline to a plateau at only 7% above early pregnancy levels by 30 weeks of gestation [110]. The postpartum decline in HDL concentration is delayed until approximately 10 weeks after delivery, and pregnancy levels are eventually reached by 20 weeks after delivery [148]. These researchers propose the existence of a new HDL in plasma that improves the feto-placental circulation. The increased serum concentrations of TG, LDL-cholesterol, and VLDL-cholesterol did not lead to endothelial dysfunction during pregnancy. In contrast, endothelial function improved in the second and third trimesters of the pregnancy, partly because of the increased concentration of HDL-cholesterol, which may inhibit the oxidation of LDL and thus protect the endothelium [149] (Fig. 4).

Interestingly, exposure of human umbilical vein endothelial cells (HUVEC) to VLDL and oxidized-VLDL particles leads to a dose-dependent decrease in the expression of endothelial NO synthase (eNOS) as well as to differences in phosphorylation at key regulatory sites, Ser1177 and Thr495. Moreover, nitrite-nitrate, ROS, and 3-nitrotyrosine accumulation showed a proportional increase that was consistent with eNOS uncoupling. This imbalance in NO and ROS metabolism promotes the modification of relevant proteins, including mitochondrial proteins that are involved in oxidative phosphorylation [150]. Thus, persistent stimulus of VLDL in an oxidative environment leads to a decrease in mitochondrial respiration, endothelial cell dysfunction and, eventually, cell death [150].

Among endothelial cell products, one class of molecules that has been suggested to play a critical role in preeclampsia is the prostanoids [151]. The major prostanoid produced by endothelial cells is prostacyclin, a powerful cardioprotective hormone that is released by the endothelium of all blood vessels. It has been observed that preeclamptic

women release less prostacyclin from endothelial cells. This effect is associated with a 3-fold increase in the cellular TG content [152]. The latter finding indicates that the lipoproteins in and lipid metabolic properties of sera from preeclamptic women are different from those of the sera of uncomplicated pregnancies [152]. Experiments performed in human cultured endothelial cells suggest that elevated levels of free fatty acids cause reduction in prostacyclin and NO production, which could result in diminished relaxation capacity [111]. The inhibition resulting from the secretion of prostacyclin might be associated with the endothelial dysfunction reflected by an increase in plasma TG.

The endothelial dysfunction in preeclampsia might originate from oxidative stress and dyslipidemia. Free radicals can be generated by many enzymatic processes. These species are extremely reactive and interact with polyunsaturated fatty acids to produce lipid peroxides with a much longer half-life [153–155]. An association of dyslipidemia and the lipid peroxidation product malondialdehyde (MDA) with severity of pregnancy-induced hypertension has been documented. This increase in MDA is strongly related to the lipid peroxidation caused by oxidative stress and is expected to affect various tissues and organ systems, including the vascular endothelium [154,156,157]. Estimation of the serum lipid profile and MDA in pregnant women during antenatal care can be useful in the early diagnosis of pregnancy-induced hypertension and the prevention of obstetric complications [143]. Oxidative stress is a major contributing factor to tissue injury, apoptosis and aging. ROS are mainly created as byproducts of normal metabolic functions such as breathing and mitochondrial energy generation. Oxidative stress might mainly affect endothelial vessels and many tissues and organs, both locally and systematically. During these processes, other molecules that play a role in vasodilatation, such as nitric oxide, are inhibited by high lipid peroxide concentrations [153,155]. Plasma lipid peroxide levels are also significantly elevated [158], whereas Vitamin E and other plasma antioxidants are decreased in preeclampsia [158–160]. Wakatsuki et al. showed that in postmenopausal women, the administration of antioxidants reduces the susceptibility of LDL to oxidative modification [161].

4.3. High fat intake leads to obesity and altered blood lipid composition during pregnancy

Similarly, in a mouse model with obesity induced by a high-fat diet (HFD) or a “Western-style diet” (high in calories and saturated fats), the metabolic profiling of pregnant mouse plasma revealed significant changes in the levels of multiple amino acid metabolites, thereby revealing a significant increase in lysine catabolites and a significant decrease in acetylated lysine, glycine, and several glycine metabolites; this likely reflects an impaired utilization of carbohydrates, especially when insulin resistance is present, thus promoting the oxidation of amino acids as an alternative energy source as they enter the citric acid cycle at different points [162]. Analogously, significant changes in the levels of biochemicals involved in fatty acid metabolism in maternal plasma were revealed. In particular, long-chain fatty acids, polyunsaturated fatty acids, and ω-6 fatty acids were significantly increased in HFD dams. The increases in glycerophospholipids and sphingomyelin species together with decreases in carnitine and its metabolic precursor, deoxycarnitine, that were detected in the plasma of the obese dams suggest that significant alterations in β-oxidation had occurred [162]. Analogously, a recent study found that maternal obesity (pregestational body mass index (BMI) > 30) is accompanied by a change in serum lipid composition [163]. Obese patients exhibit a characteristic pattern involving significant increases in concentration of several low-density lipoproteins (LDL) subclasses (e.g., the concentration of medium, large, and very large LDL particles; total and free cholesterol and cholesterol esters in very large VLDL particles; the concentration of chylomicrons; and the concentration of phospholipids in VLDL particles) and significant decreases in the concentration of free cholesterol in intermediate-density lipoproteins and several high-density lipoproteins subclasses (i.e., total cholesterol and cholesterol esters in high-density lipoprotein particles, as well as polyunsaturated fatty acids) [163].

4.4. Obesity during pregnancy leads to redox imbalance and inflammation

Recent observations indicate that maternal obesity has a substantial impact on the inflammatory state of the mother at both the placental and systemic levels (Fig. 3). Evidence from in vitro studies reveals that treatment of HUVEC with palmitate (a long-chain fatty acid) increases intracellular ROS production and decreases cell proliferation [164]. Moreover, treatment of HUVEC with *trans* fatty acids (which are present in fast foods, bakery products, packaged snacks, and margarines [165]), results in an increase in the expression of proteins that are involved in pathways related to the biosynthesis of amino acids, the synthesis and degradation of ketone bodies, cysteine and methionine metabolism, fatty acid degradation, and several others [166]. This shift in lipid composition in sera obtained from obese female subjects is accompanied by a significant increase in the levels of inflammation-related proteins [167]. In particular, C-reactive protein and GlycA (a complex NMR signal reflecting the abundance of *N*-acetyl sugar groups on glycoproteins) were found to be significantly increased in obese pregnant women (pregestational BMI > 30) [163,168]. In addition, IL-6, C-reactive protein, CCL22, IL-8, and CCL4 as well as the frequency of circulating CD4+ T-cells and their response to stimulation were found to be increased in pregravid obese mothers [169]. Similarly, visceral adipose tissue-resident and recruited macrophage subsets show upregulated CD11c, CD163, and CD206 expression in obese pregnant women (pregestational BMI > 30) [170]. Moreover, uterine NK activity is imbalanced in decidua obtained from obese pregnant women (pregestational BMI > 30). Specifically, cell degranulation is significantly increased, NK-receptor phenotype is modified, and TNFα production is potentiated [171]. This effect has been identified not only in human patients but also in animal subjects. Observations in pregnant Japanese macaques show that maternal obesity (induced by an HFD) stimulates a significant increase in pro-inflammatory mediators (i.e., IL-12, IL-1β, MIP-1a, GM-CSF, ICAM-1, IFN-γ, and TNF-α) [172]. Observations in obese pregnant swines show that increased levels of fatty acid metabolites in obese pregnant subjects stimulate placental lipotoxicity, inflammation, and oxidative stress [173]. Proteins related to lipid metabolic processes (e.g., fatty acid synthase, lipoprotein lipase, and Fatty Acid Transport Protein 2) and immune and inflammatory responses (e.g., TLR4, IL-6, and IL-1β) were significantly upregulated in the placenta of obese sows. Areas of the villous stroma with increased fatty acid deposits were significantly enriched in lipid regulation-related proteins and accumulated macrophages. Moreover, proteomic analyses corroborated by RT-PCR and Western blot analyses revealed that proinflammatory cytokines IL-6, IL-8, IL-18, and TNFα; receptors TLR2 and TLR4; and inflammation signaling pathway proteins JNK and NF-κB exhibited upregulated mRNA and protein expressions in the placenta in the obese group. Interestingly, placental samples exhibited a reduced antioxidant capacity, as measured by a total antioxidant capacity analysis [173].

As mentioned above, HFD and inflammation affect redox homeostasis (Fig. 3). The assessment of antioxidant status reveals that placental homogenates from obese pregnant women (pregestational BMI > 30) have decreased antioxidant activity, as measured by catalase activity. Moreover, and consistent with results obtained by Magnifico et al. [150], protein carbonyl formation is significantly increased in mitochondrial extracts obtained from obese-women placenta (an indirect indicator of increased ROS levels). Nitric oxide generation and mitochondrial nitrative stress are also significantly increased in the placenta of obese pregnant women (pregestational BMI > 30) [174]. Furthermore, maternal obesity has profound effects on antioxidant metabolizing enzymes. In a rat model, glutathione peroxidase was significantly increased, while glutathione reductase activity was significantly reduced, when compared to control rats [175].

4.5. Obesity during pregnancy and its consequences to vascular function

This impaired inflammatory and oxidative environment result in endothelial dysfunction and improper vascular function (Fig. 3). As observed in animal studies, maternal obesity induces a significant decrease in total maternal-side placental blood flow and in-flow velocity of blood flow to the placenta, while transit time through the spiral arteries is significantly increased with respect to lean control subjects [172]. Similarly, exposure to an HFD determines a decrease in placental microvessel density, being lower in the placenta associated with male offspring than in that associated with female placenta throughout gestation [162]. Moreover, an increase in dietary fat may lead to pathways inhibiting angiogenesis and result in endothelial dysfunction by abolishing vascular endothelial growth factor or insulin-stimulated endothelial nitric oxide synthase activation and subsequent nitric oxide production from endothelial cells [176]. Interestingly, some of these parameters may be restored to levels close to control subjects only by reversing the HFD to a control diet just prior to the pregnancy [172].

In conclusion, evidence from studies performed in vitro, in vivo, and in human subjects, is univocal pointing obesity as a threat to pregnancy. Causal chain may be originated by an imbalanced diet leading to obesity, in turn leading to inflammation and oxidative stress, which represents a dangerous baseline for pregnancy, increasing the risk of vascular endothelial complications and impaired nutrient exchange. Thus, to reduce the burden of these disorders, public policies regarding obesity and healthy lifestyles during childbearing ages should be strengthened.

5. Conclusions

During pregnancy, a number of changes take place in response to the high metabolic demand from organ and tissues. For this reason, pregnancy is a vulnerable condition in which to acquire and develop pathophysiological disorders. In this context, the pathological conditions described in this review cause severe detrimental effects in the vascular relationship among the mother, placenta and fetus, generating changes in the endothelium at the cellular and molecular levels. Unfortunately, despite basic and clinical research, advances in understanding and effective treatments for pregnancy disorders compromising endothelium physiology are far from satisfactory. For this reason, it is necessary further basic and clinical research to reach a good understanding in the role played by endothelial cells during pregnancy disorders and to develop more effective therapies.

Funding

This work was supported by research grants from Fondo Nacional de Desarrollo Científico y Tecnológico - Fondecyt 1161288 (FS), 21171566 (SG), 11170840 (CE), and 1161646 (CCV). Millennium Institute on Immunology and Immunotherapy P09-016-F (FS, CCV). Comisión Nacional de Investigación Científica y Tecnológica – CONICYT 21171566 (SG). Ministry of Education, Science and Technological Development of the Republic of Serbia grants 175024 and 175053 (JFS). Programa de Cooperación Científica ECOS-CONICYT C16S02 (CCV). BASAL Grant CEDENNA FB0807 (CCV).

Transparency document

The Transparency document associated this article can be found, in online version.

Acknowledgments

The authors would like to thank the graphic design and illustrations of http://estudiokbza.cl

Conflict of interest statement

The authors declare no conflicts of interest.

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