

THE ROLE OF ENDOTHELIAL DYSFUNCTION IN THE PATHOGENESIS OF PREGNANCY-RELATED PATHOLOGICAL CONDITIONS: A REVIEW

Elena Curakova Ristovska¹, Magdalena Genadieva-Dimitrova¹, Beti Todorovska¹,
Vladimir Milivojevic², Ivan Rankovic³, Igor Samardziski⁴, Maja Bojadzioska⁵

¹ University Clinic for Gastroenterohepatology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, RN Macedonia

² Section for Internal Medicine, Medcompass Alliance, School of Medicine, Belgrade University, Belgrade, Serbia

³ Section for Internal Medicine, Medcompass Alliance, Belgrade, Serbia

⁴ University Clinic for Gynecology and Obstetrics, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, RN Macedonia

⁵ University Clinic for Rheumatology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, RN Macedonia

Corresponding author: Elena Curakova Ristovska, MD, PhD, Assistant Professor, Doctor, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Mother Teresa 17, Skopje 1000, Macedonia, phone + 38970991144, e-mail address: elenacurakova@yahoo.com

ABSTRACT

In the recent decades, endothelial dysfunction (ED) has been recognized as a significant contributing factor in the pathogenesis of many pathological conditions. In interaction with atherosclerosis, hypercholesterolemia, and hypertension, ED plays a crucial role in the pathogenesis of coronary artery disease, chronic renal disease, and microvascular complications in diabetes mellitus. Although ED plays a significant role in the pathogenesis of several pregnancy-related disorders such as preeclampsia, HELLP syndrome, fetal growth restriction, and gestational diabetes mellitus, the exact pathogenetic mechanisms are still a matter of debate. The increased prevalence of these entities in patients with preexisting vascular diseases highlights the essential pathological role of the preexisting ED in these patients. The abnormal uteroplacental circulation and the release of soluble factors from the ischemic placenta into the maternal bloodstream are the main causes of the maternal ED underlying the characteristic preeclamptic phenotype. Besides the increased risk for maternal and fetal poor outcomes, the preexisting ED also increases the risk of development of future cardiovascular diseases in these patients. This study aimed to look deeper into the role of ED in the pathogenesis of several pregnancy-related hypertensive and liver diseases. Hopefully, it could contribute to improvement of the awareness, knowledge, and management of these conditions and also to the reduction of the adverse outcomes and additional long-term cardiovascular complications.

Keywords: Endothelial dysfunction, hypertensive disorders of pregnancy, gestational hypertension, preeclampsia, HELLP Syndrome, acute fatty liver of pregnancy

INTRODUCTION

In the past, the endothelial monolayer was considered mainly a mechanical barrier between the blood and the blood vessel wall. However, recent evidence indicates that the single layer of continuous endothelium lining arteries, veins and lymphatics is in fact an active biologic interface between the blood and potentially thrombogenic

ic subendothelial tissues. It is now clear that the endothelial cells (ECs) have an important role in providing many functions and that the endothelial dysfunction (ED) is significantly involved in the pathogenesis of many pathological conditions in the body. The wider concept of the endothelial

cell function made ED a very intriguing topic in the recent decades.

1.1. Endothelial cell function in normal vascular homeostasis

It is estimated that the adult human body contains about 1×10^{12} ECs that line all vessels in the body forming a distributed dynamic interface [1]. The vascular ECs secrete many cytokines in an endocrine, paracrine, or autocrine way and provide the homeostasis in the microcirculation [2]. The most important function of the endothelium is to regulate the vasomotor tone, vascular permeability, cellular and nutrient trafficking, hemostatic balance, immunity, interaction with the circulating blood cells, cellular proliferation, angiogenesis and survival [3,4].

1.1.1 Regulation of the vascular tone: One of the most important endothelial cell functions is the regulation of the vascular tone of the blood vessels, i.e., maintaining the vessel in a relatively dilated state and providing an optimal organ perfusion and oxygen tissue supply. The regulation of the vascular tone is provided by the capacity of the ECs for balanced release of vasoactive substances as well as by their capacity to properly respond to the circulating vasoactive mediators. The most important vasodilatory mediators released by the ECs are nitric oxide (NO), prostacyclin adenosine and endothelium-derived hyperpolarizing factor (EDHF) [5]. Being synthesized by the endothelial NO synthase (eNOS), NO is the most important and the strongest endothelium-derived relaxing factor. NO diffuses into the vascular smooth muscle cells and activates guanylate cyclase, which leads to cyclic guanosine monophosphate-mediated vasodilatation [3]. The endothelium has the capacity to respond to various physical stimuli, but it seems that the shear stress is the most important stimulus for vessels dilatation, the so-called flow-mediated dilation (FMD). In addition, a variety of agonists, including acetylcholine, histamine, thrombin, adenosine diphosphate, bradykinin, norepinephrine, vascular endothelial growth factor (VEGF), and serotonin can increase the synthesis and release of NO [6]. These mediators stimulate vasorelaxation on intact endothelium, and vasoconstriction when the endothelium is removed or perturbed [7]. Although NO is mainly recognized as an essential vasodilator molecule, it has been also confirmed that NO provides several other functions important for the maintenance of the vascular

homeostasis. By inhibition of platelet adhesion and aggregation, NO plays a role in modulation of the prothrombotic potential of the ECs, inhibits the monocyte and macrophage endothelial adhesion, reduces the vascular smooth muscle migration and growth and reduces the endotoxin- and cytokine-induced expression of tissue factor (TF) [7]. Prostacyclin is the second important mediator involved in the regulation of the vascular tone. It is derived via the cyclooxygenase pathway and acts by a hyperpolarization of vascular smooth muscle cells. The ECs have the ability to mediate the maintenance of the vasodilator tone via this different, NO-independent pathway that becomes involved in terms of reduced NO bioavailability [8]. It is estimated that prostacyclin has a modest, more limited role in the maintenance of vasodilator tone than NO [9]. In addition to ECs important ability to release vasodilator mediators, they also have the capacity to release vasoconstrictive mediators. The most important vasoconstrictors are endothelin-1, thromboxane A₂ (TXA₂), norepinephrine, leukotriene, angiotensin II and platelet-activating factor (PAF) [10]. Among all, endothelin-1 is the most potent vasoconstrictor and it is considered an important vasoconstrictive mediator, especially in the pathogenesis of conditions mediated and developed by predominantly increased vascular resistance.

1.1.2 Vascular permeability: One of the functions of the endothelial layer is to provide a continuous and compact semipermeable barrier that provides the vascular integrity and prevents an extravasation of circulating elements. The competent barrier function is provided by several molecules such as Glycocalyx, the endothelial junction proteins [vascular endothelial cadherin (VE-cadherin)], vascular endothelial protein tyrosine phosphatase, Src-homology phosphatase 2 (SHP2)], and Annexin A2. The ECs are covered by the endothelial glycocalyx (EG), a major proteoglycan-containing constituent which maintains the tissue integrity, contributes to cell signaling, prevents leukocyte and platelet adhesion and provides antithrombotic activity [11]. VE-cadherin and Annexin A2 maintain close inter-endothelial junctions and contribute to the preserved endothelial integrity [7]. The most important factors that affect the interaction with the EC surface, which have the capacity to stimulate extravasation of circulating elements and tissue edema and to impair the endothelial barrier function, are tumor necrosis factor-alpha (TNF-alpha), thrombin and Angiopoietin 2 (ANGPT2) [12].

1.1.3 Antiadhesive function: It is well known that one of the most important functions of the ECs in a steady, non-inflamed state is to inhibit the leukocyte adhesion and to maintain an anti-adhesive surface [13]. The antiadhesion is provided by Endomucin, a membrane-bound glycoprotein expressed by the ECs in the post-capillary venules that enables the neutrophils adhesion to the Intercellular Adhesion Molecule-1 (ICAM-1). Several membrane proteins, such as vascular cell adhesion molecule-1 (VCAM-1), ICAM-1 and E-selection, are biomarkers that reflect the ECs activation [14]. Endothelial activation increases the expression of adhesion molecules on the cell surface, promotes interaction between the ECs and circulating leukocytes and migration of adherent monocytes [15]. By that, the endothelial activation mediates the inflammatory process.

1.1.4 Hemostasis: There are many complex mechanisms mediated by the ECs function that are involved in providing the hemostatic balance in the body. The complex function of the competent ECs has the ability to provide balance between the prothrombotic and antithrombotic and also between fibrinolytic and antifibrinolytic state. The vascular ECs play a role in all three important components of the hemostasis: the vessels, the blood platelets and the plasma clotting and fibrinolysis [5]. Under physiological conditions, by production of adenosine, NO and prostacyclin, and by removal of Adenosine diphosphate (ADP), the endothelium prevents platelet adhesion and activation [5]. Regarding the coagulation process, by blocking the tissue factor pathway inhibitor, activation of protein C via thrombomodulin and activation of antithrombin III, it inhibits the process of thrombin formation [5]. Also, the ECs inhibit the fibrin deposition [5]. The balance in the fibrinolytic system is provided through the balanced synthesis and release of the two proteins, the tissue plasminogen activator (TPA) and the plasminogen activator inhibitor-1 (PAI-1). Hence, in terms of hemostasis, the quiescent ECs normally display a vasodilatory, thromboresistant, anti-adhesive and anticoagulant phenotype [9]. Activated ECs have the ability to stimulate all phases of the hemostatic process. They promote platelet adhesion and aggregation, decrease synthesis of thrombomodulin (TM), TPA and heparan sulfate, increase expression of TF and PAI-1, generate the procoagulant microparticles, recruit circulatory monocytes and neutrophils capable of initiating or amplifying coagulation [16]. The von-Wille-

brand factor (vWF), a largely endothelium-derived glycoprotein released into the circulation by activated endothelial cells and megakaryocytes is considered an indicator of ED [17]. The vWF plays an important role in vascular hemostasis, including promotion of platelet adhesion to the endothelium and stabilization of Factor VIII [17].

1.2 Endothelial cell activation

The term “endothelial cell activation” is a broad term indicating a change in the ECs function as a response to continuous exposure to several different physical and chemical stimuli [18]. The term was initially based on the observation that cultured ECs demonstrated increased leukocyte adhesion following exposure to inflammatory mediators [7]. It is well known that normal endothelium is highly responsive to alterations in the local extracellular milieu and as a response to a different type of stress, the ECs go through functional alteration leading to imbalance in the production of vasoactive mediators [19]. Hence, contrary to the quiescent ECs, the activated ECs have vasoconstrictive, pro-adhesive, and procoagulant properties [7]. The most frequent causes of mild and transient common environmental stresses that can activate the ECs are the shear stress, proteolytic activity, soluble mediators, cell contacts or small changes in oxygenation, temperature or pH [7]. ECs activation is not necessarily linked to a disease and it can occur as a response to a transient bacteremia, minor trauma, or some host-derived products [e.g., complement, cytokines, chemokines, serine proteases, fibrin, activated platelets and leukocytes, elevated glucose, reactive oxygen species (ROS), hypoxia-induced factors, or hemodynamic changes] [20]. Also, activation of one type of ECs may not meet the definition of ECs activation at another site. For example, some ECs express certain molecules constitutively, whereas ECs in other sites express the same molecule only when activated. ECs activation is not an all-or-nothing response. The ECs activation can occur in one specific environment by activating local defense mechanisms such as local vasoconstriction, leukocyte adhesion and migration, vascular permeability or programmed cell death [21]. However, when the host endothelial response becomes generalized, a dysregulated, severe inflammatory response occurs that could lead towards systemic inflammatory response syndrome and/or consecutive multiple organ dysfunction.

1.3 Endothelial dysfunction

When the ECs are repetitively or continuously exposed to different physical or chemical stimuli, the EC function becomes seriously disturbed, and this condition is known as ED [22]. ED as an entity refers to ECs structural changes, loss of integrity and hyper-adhesiveness of the vascular lining toward platelets leading to impaired balance in the production of vasoconstrictors and vasodilators, pro-atherogenic and antiatherogenic, promoting and inhibiting growth factors and pro-coagulant and anti-coagulant factors [7,22-24]. All the above contributes to impaired or excessive angiogenesis, decreased barrier function, and increased inflammation activation [1]. The literature data suggests that not only the extent of injury, but also the ECs repair capacity is important for the maintenance of the endothelial integrity. The repair mechanisms are represented by the ability of the ECs to replicate locally and to replace the lost and damaged cells. Moreover, it seems that recruitment of the circulating endothelial progenitor cells that originate from the bone marrow is an alternative mechanism for endothelial repairment and maintenance [25]. Hence, the balance between the exposure to risk factors and the capacity for repair determines the endothelial phenotype and behavior [26]. Severely affected endothelium not only becomes dysfunctional, but it may also lose the integrity, and endothelial particles of activated or apoptotic cells and whole endothelial cells could be detached into the circulation [27].

1.4 Indicators of endothelial dysfunction

The presence of ED can be estimated in several ways, such as by measurement of some direct products of ECs that are released when the endothelium is activated (NO derived products, inflammatory cytokines, adhesion molecules, regulators of thrombosis), or by measurement of some markers of endothelial damage and repair [9]. The most frequently measured products in the circulation are E-selectin, VCAM-1, ICAM-1, P-selectin, TPA, PAI-1 and vWF [1,14,19] as well as the detached particles from the activated or apoptotic ECs [27]. The circulating endothelial progenitor cells can provide information by the expression of characteristic surface markers. The measurement of circulating endothelial cells and circulating endothelial progenitor cell levels provides a novel and exciting means to follow the determinants of endothelial injury and repair [9].

1.5 Endothelial dysfunction in the pathogenesis of organ-specific vascular diseases

The scientific interest related to ED originates from the evidence that ED has been involved in the pathogenesis of many pathological conditions such as atherosclerosis, hypercholesterolemia, hypertension, coronary artery disease, microvascular complication of diabetes, liver cirrhosis, chronic renal disease (CRD) [28, 29]. ED has been shown to precede the development of clinically detectable atherosclerotic plaques in coronary arteries [28], and it is considered a pivotal event in the development of microvascular complications in diabetes mellitus [29]. ED has also been related to CRD [3], but the exact sequence of events is not fully understood [30]. In liver disease, it is known that ED impairs the endothelium-dependent relaxation in the liver microcirculation and contributes to increased hepatic vascular resistance, leading to portal hypertension (PH). Also, there is strong evidence regarding the important involvement of ED in the pathogenesis of most of the pregnancy-related conditions such as gestational hypertension, preeclampsia, HELLP syndrome, fetal growth restriction (FGR) and gestational diabetes mellitus (DGM). Moreover, the presence of ED-mediated pregnancy complication has been strongly related to an increased risk of future ED-mediated conditions such as arterial hypertension, cardiovascular and cerebrovascular diseases [31].

ENDOTHELIAL DYSFUNCTION IN PREGNANCY

2.1 The physiology of normal pregnancy

Pregnancy is a physiological state associated with many complex hemodynamic, metabolic and humoral disturbances [32]. In normal pregnancy there is an increased production and responsiveness to vasodilators, and decreased sensitivity to vasoconstrictive hormones [33]. Consequently, due to the increased vasodilatory tone and decreased maternal vascular resistance, normal pregnancy is associated with decreased blood pressure and increased sympathetic activation, maternal blood volume, cardiac output, and blood flow to the kidneys and uteroplacental unit [34]. Due to the stimulation of the renin-angiotensin-aldosterone system, and non-osmotic

vasopressin release, there is also a fluid retention [35]. Regarding hemostatic abnormalities, due to sequestration of blood cells in the intervillous space, there is a natural decline in platelet count throughout the gestation [36], increased leucocyte concentration and increased TX2-induced platelet aggregation [37]. Pregnancy is accompanied by insulin resistance, mediated primarily by placental secretion of diabetogenic hormones including growth hormone, corticotropin-releasing hormone, placental lactogen (chorionic somatomammotropin), prolactin, and progesterone [38]. Hormonal changes during normal pregnancy are associated with a physiological decrease in the oxidation of long- and medium-chain fatty acids, resulting in an increased maternal serum level of fatty acids over the course of gestation [39]. Most disturbances develop due to the normal physiological process in response to the fetus development. However, in some cases, as a result of some products of the placental unit and also due to the complex interaction between the mother and the fetus, some specific pregnancy-related disorders can develop.

2.2 Endothelial dysfunction in pregnancy

ECs usually react to physiological disturbances and they adapt their function in line with the transitory changes in the environment. Considering their rich functional capacity, the ECs are able to resist and compensate many different disturbances. However, in terms of continuous and repetitive ECs stimulation, a more remarkable structural and functional impairments can occur. The important function of the endothelial layer has been well established in physiological but also in many pathological conditions. Considering the fact that normal pregnancy is associated with many complex abnormalities of different nature, it is expected that the ECs function, and pregnancy-related ED would be of great importance in the pathogenesis of several pregnancy-related conditions. During pregnancy, the ECs go through many changes in the structure, integrity and function and, consequently they have been related to numerous gestational complications, such as preeclampsia, FGR and GDM [3].

In order to analyze the relation between ED and pregnancy-related pathological conditions, in September 2022 we performed a systematic search on PubMed®/MEDLINE database by using the following MESH terms: “pregnancy”, “liver disease”, “fetal growth restriction”, “gesta-

tional diabetes mellitus”, “hypertensive disorders of pregnancy”, “gestational hypertension”, “preeclampsia”, “eclampsia”, “HELLP syndrome”, “acute fatty liver of pregnancy,” with a data filter on (AND) “endothelial dysfunction”. The selected studies were additionally analyzed according to the year of publication, study design and the topic relevance. Data from a selected number of studies most relevant for the evaluated topic were additionally summarized and analyzed for the needs of this article.

The focus of this article were the pregnancy-related pathological conditions in which the ED has been proven to play a significant role in the pathogenesis of the entities. Hence, we analyzed the ED in the pathogenesis of FGR, GDM, preeclampsia, eclampsia, HELLP syndrome and acute fatty liver of pregnancy (AFLP). The pregnancy-related entities in which the ED does not play a central role in the pathogenesis such as Hyperemesis gravidarum or Intrahepatic cholestasis of pregnancy were not in the scope of this article. Also, we analyzed the pathogenetic mechanisms and the presentation of the hepatic involvement within these conditions.

2.2.1 Endothelial dysfunction: Impaired process of placentation

Many human and animal studies have been performed in order to clarify the complex and multifactorial pathogenesis of the ED-mediated pregnancy related disorders. In this context, the so-called two-stage theory has explained the most important aspects of the pathogenesis of these mechanisms and the role of ED [40]. The literature data suggest that ED occurs in the vasculature of the placental and maternal systemic circulation. The first stage refers to the impaired placentation process, while the second stage refers to the consecutive maternal systemic ED. Within the abnormal placentation, there are two well-defined related, but separate processes that predispose to abnormalities in the maternal circulation: the abnormal spiral artery remodeling and the impaired trophoblast invasion. It has been proven that these two distinct, but related processes are underlying the hypertensive disorders of pregnancy and FGR [41,42]. During the normal placentation process, the cytotrophoblast cells of the developing placenta migrate through the decidua and through a part of the myometrium and invade both the endothelium and high-

ly muscular tunica media of the maternal spiral arteries. Thus, these vessels transform from small muscular arterioles to large low resistance vessels, enabling large blood flow capacity for providing an optimal nutrient and oxygen exchange between the mother and the fetus [43]. In parallel with this, the process of trophoblast differentiation also occurs. Normally, the invading trophoblasts transform their adhesion molecule expression from those characteristic of epithelial cells (integrin $\alpha 6/\beta 1$, $\alpha v/\beta 5$, and E-cadherin) to that characteristic for endothelial cells (integrin $\alpha 1/\beta 1$, $\alpha v/\beta 3$, and VE-cadherin) [44]. Contrary to the normal placentation process, in preeclampsia, cytotrophoblast cells infiltrate the decidual portion of the spiral arteries but fail to penetrate the myometrial segment [45]. Consequently, instead of development of large, tortuous vascular channels, the spiral arteries remain narrow, resulting in placental hypoperfusion. Also, in patients with preeclampsia, the process of differentiation of trophoblast does not occur, and instead of transformation from epithelial to endothelial phenotype, the invading trophoblasts continue to express adhesion molecules characteristic for the epithelial cells [46]. Although these two abnormal processes occur separately, still, it is considered that the impaired invasion of the trophoblast into the spiral arteries could be partly caused by the process of defective trophoblast differentiation [47]. Both processes lead to consecutive placental hypoperfusion, hypoxia and ischemia [45]. The ischemic placenta produces a variety of factors that cause the ED in the maternal circulation responsible for the abnormalities in the second stage of the abnormal preeclamptic pathogenesis.

2.2.2 Systemic endothelial dysfunction

The second stage of the two-stage theory explains the maternal systemic abnormalities and multiorgan dysfunction caused by the factors secreted by the ischemic placenta [48]. The hypertensive disorders of pregnancy are associated with widespread systemic ED in different vascular beds affecting the function of different vital organs and systems in the body. The localized ED could develop in the liver, kidneys, brain, or heart, and is considered a major contributor to end-organ damage by itself [49].

2.3 Endothelial dysfunction in fetal growth restriction

The most common obstetric definition of FGR is an estimated weight below the 10th percentile for gestational age in the second half of pregnancy [50]. FGR can occur solely, or it can develop in parallel with hypertensive disease in pregnancy, mainly with preeclampsia. The etiology of FGR is related to multiple maternal, fetal and placental factors. As in most pregnancy-related disorders, it has been considered that the initial triggering factor for the development of the condition originates from the hypoxic placenta [51], or in other words, FGR develops as a consequence of ED in the placental vasculature. The impairment in the placentation process seems to be similar to that occurring in preeclampsia. The impaired vascular remodeling and decreased vascular volume impair the ability of the placental ECs to properly respond to vasodilatory impulses. The impaired placental blood flow and fetal oxygen supply on one hand, and the progressive development of an oxidative stress environment on the other, lead to a consecutive reduction in the fetal growth [52].

Many investigations analyzed the impaired placentation in FGR in terms of differentiating this process among normotensive patients with FGR and patients with preeclampsia and FGR. In other words, they tried to define the role of placental vasoconstriction and oxidative stress in the pathogenesis of FGR. The results have indicated that oxidative stress is present in both groups [53], but it seems that it is induced by different mechanisms. Despite the dominant role of fms-like tyrosine kinase-1 (Flt-1) in the process of preeclampsia, the oxidative stress in normotensive FGR is induced by different, Flt-1-independent signaling. In these patients, a significantly higher values of endoglin have been measured, a factor that inhibits the process of angiogenesis. Endoglin was found to be significantly increased in women with normotensive FGR between the first and second trimesters [3]. According to the literature, FGR without preeclampsia is usually not associated with a significant elevation of serum markers of endothelial injury like sVCAM-1 or hyaluronan, which are increased in cases of preeclampsia with or without FGR [3].

Regarding outcomes, it has been confirmed that FGR is associated with increased fetal and neonatal morbidity and mortality, and that neonates with FGR have an increased risk of future development of atherosclerosis, hypertension, coronary artery disease and CKD [30].

2.4 Endothelial dysfunction in gestational diabetes mellitus

GDM is a pregnancy-related disorder defined as glucose intolerance with onset or first recognition during pregnancy [54] and it affects about 3%–25% of the pregnancies worldwide [55]. GDM seems to be associated with several other conditions, such as hypertensive disorders of pregnancy (gestational hypertension and preeclampsia), large-for-gestational-age newborn, birth trauma to mother or newborn, operative delivery, polyhydramnios, perinatal mortality, fetal/neonatal hypertrophic cardiomyopathy, neonatal respiratory problems and metabolic complications (hypoglycemia, hyperbilirubinemia, hypocalcemia, polycythemia) [56]. The risk factors associated with developing GDM are older maternal age, high body mass index, previous personal history of impaired glucose tolerance, GDM in previous pregnancy, significant weight gain in early adulthood or between pregnancies, excessive gestational weight gain during the first 18 to 24 weeks of pregnancy, family history of diabetes, polycystic ovary syndrome [38,57].

Considering the similar involvement of the pathophysiological impairment in GDM and in type II diabetes mellitus, GDM is considered a prediabetic state. The shared mechanisms in both conditions are the presence of insulin resistance (IR), hyperglycemia, biochemical abnormalities, and hyperlipidemia [58]. Normal pregnancy is physiologically related to some level of insulin resistance that can increase as the pregnancy advances. However, the IR that develops in normal, healthy pregnancy does not usually cause additional significant disturbances. The classical view suggests that GDM is a consequence of the increased demand for glucose during pregnancy, the IR and the relative insufficiency of insulin secretion [59]. Basically, it is a state of imbalance between the pancreatic insulin release and the IR associated with the pregnant state, and it represents the pancreatic inability to overcome the IR. [38].

It has been speculated that the increased insulin concentration has the capacity to induce

expression of some proteins in the placenta that are involved in the regulation of angiogenesis and could be later involved in progression of the ED-mediated disturbances. There are several membrane proteins that are considered to be related to the ED in these patients such as VCAM-1, ICAM-1, E-selectin, PAI-1 [14]. VCAM-1 and ICAM-1 belong to the immunoglobulin superfamily [1]. Endothelial activation increases the expression of the adhesion molecules and promotes the attachment and migration of adherent monocytes, what precedes the endothelial damage [15]. However, there are also studies that did not discover significant differences in the VCAM-1 and ICAM-1 concentrations in maternal blood when comparing GDM patients and controls [60].

VCAM-1 mainly plays a role in the leukocyte-endothelial cell signal transduction, that is in the interaction between ECs and lymphocytes, monocytes, eosinophils, and basophils [1]. It is also involved in the process of angiogenesis and endothelial injury [61]. VCAM-1 is expressed when the EC is activated, hence, it is a biomarker of ED. Regarding the relation between VCAM-1 and GDM, studies have confirmed significantly higher VCAM-1 expression in the placental tissue and higher serum VCAM-1 values in GDM patients than in healthy pregnant women, [1, 62], and also a decreased VCAM-1 levels in the group of women with GDM three years after pregnancy [63]. It seems that high expression of VCAM-1 in GDM patients may damage placental vascular endothelial and trophoblast cells, causing placental dysfunction, fetal ischemia, hypoxia and risk of stillbirth [64]. ICAM-1 vascular expression is rare under normal physiological conditions. ICAM-1 binds to lymphocyte function-associated antigen 1 (LFA-1) and interacts with the circulating leukocytes. Some pathological factors such as hyperglycemia and AGEs induce endothelial expression of ICAM-1 and production of soluble ICAM-1 [65]. Although there are contradictory findings, most studies have confirmed an increased ICAM-1 expression in decidual endothelial cells collected from women with GDM and increased soluble ICAM-1 levels in patients with GDM [66], indicating important role of ED in the pathogenesis of GDM. Asymmetric dimethylarginine (ADMA), which acts as an inhibitor of eNOS, induces oxidative stress and causes low-grade inflammation and a consecutive vascular endothelial dysfunction [67]. ADMA has been investigated as a potential marker of ED in GDM. There are numerous contradictory results of ADMA measurements

presented in many studies [68]. However, some studies have confirmed that patients with GDM have significantly higher plasma ADMA levels and significantly lower NOS and NO levels than healthy pregnant women [69]. Hence, it is considered that the injury of ADMA to vascular ECs further promotes the occurrence and development of GDM [70]. PAI-1 is a globular protein which coupled with TPA balances the fibrinolytic process. Under inflammatory conditions, PAI-1 is abundantly released from the vascular ECs [71]. Studies show abnormally elevated values of PAI-1 in GDM patients that are closely associated with the IR [72]. Hence, it is considered that PAI-1 is an important factor involved in the onset of GDM.

The causes for development and progression of IR are multiple and complex. The previous research show that the main additional factor that causes expression of significant IR is the development of placental ED. The injured ECs in the affected patients contribute to the worsening of the IR and potential development of GDM. It is believed that the main mechanism underlying the GDM is the development of endothelial damage caused by two main factors: chronic low-grade inflammation and hyperglycemia [73]. The increased concentration of inflammatory factors can make the body less sensitive to insulin and worsens the physiological pregnancy-related IR, eventually leading to a persistent increase hyperglycemia in pregnant women [74]. Later, by non-enzymatic glycosylation of proteins, lipids and nucleic acids the hyperglycemia causes formation of advanced glycation products (AGEs) [75], which are considered to promote endothelial oxidative stress and inflammation, and additionally lead to vascular injury [76]. As a result of these abnormalities, an increased generation of ROS occurs providing additional support to the ED in GDM [77]. AGEs also cause eNOS enzyme inactivation, resulting in a decrease NO concentration, reduced NO-mediated vasodilation and hypertension [78].

Regarding long-term outcomes, it is noteworthy that patients with GDM are at increased risk of future development of type 2 diabetes, metabolic syndrome, cardiovascular disease and even type 1 diabetes [79-83]. More importantly, the risks appear to be particularly higher in patients with both GDM and a hypertensive disorder of pregnancy [84].

HYPERTENSIVE DISORDERS IN PREGNANCY

The hypertensive disorders of pregnancy (HDP) are very important pathological topic in the obstetric pathology. The mild forms are in general well controlled and leave no significant maternal or fetal consequences. However, pregnancies associated with severe gestational hypertension (GH) are related to increased risk of both, maternal and perinatal morbidity [85-87]. The data confirm that in these pregnancies there is a significantly higher rate of preterm delivery, small-for-gestational-age infants, and placental abruption. Moreover, it has been established that the HDP are associated with development of hypertension and other related disorders later in life, such as cardiovascular disease, hyperlipidemia, CKD, diabetes mellitus. When discussing the HDP, all entities could be classified in four major categories [88].

3.1. Chronic hypertension (CH): Chronic hypertension is a hypertension (stage 1: Systolic 130-139 mm Hg or diastolic 80-89 mm Hg and stage 2: Systolic at least 140 mm Hg or diastolic at least 90 mm Hg) detected before pregnancy, that was present on at least two occasions before the 20th week of gestation, or persisted longer than the 12th postpartum week [89].

3.2. Gestational hypertension (GH): Gestational hypertension is the most common hypertensive disorder in pregnancy. It occurs in 6-17% of healthy nulliparous women and in about 2-4% of multiparous women [85,86,90]. GH is defined by new onset of hypertension (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mmHg) at ≥ 20 weeks of gestation in the absence of proteinuria or new signs of end-organ dysfunction [89]. In most cases, GH resolves by the 12th postpartum week. Since 10-50% of women initially diagnosed with GH progress towards the development of preeclampsia in one to five weeks [91], GH is considered a temporary diagnosis for hypertensive pregnant women who do not meet criteria for preeclampsia or CH [89]. The risk of progression towards preeclampsia is increased in patients with gestational age less than 34 weeks at diagnosis, mean systolic blood pressure >135 mm Hg at 24-hour blood pressure monitoring,

and in patients with elevated serum uric acid level [92,93].

3.3 Preeclampsia superimposed upon chronic hypertension: In this condition, preeclampsia occurs in women with CH. It can be manifested as a worsened or resistant hypertension, or as a new onset of proteinuria, sudden increase in proteinuria, and/or as a significant new end-organ dysfunction after the 20th week of gestation in women with CH.

3.4 Preeclampsia, eclampsia, HELLP: Preeclampsia, eclampsia and HELLP Syndrome (HE) are three conditions that share several mutual underlying mechanisms and clinical phenotypes, but also each poses some specific pathogenetic disturbances and characteristics.

Despite the fact that all pregnancy disorders have their one specific characteristics, still, the presence of hypertension is a mutual and typical landmark. The development of increased vasoconstrictive tone is one of the most evident indicators of ED. The hypertension develops due to the disturbed endothelial control of the vascular tone that occurs as a consequence of several mechanisms. It is considered that one of the main reasons for the development of hypertension in pregnancy disorders is the inhibition of VEGF, a mediator that is a powerful activator of the endothelial eNOS [94]. Despite the excess input of the vasoconstrictive mediators such as angiotensin, endothelin-1, and vasopressin, it is considered that the oxidative stress increases the sensitivity to vasopressor mediators, a mechanism that additionally attributes to the development of hypertension [95]. Finally, the increased vasopressin concentration is also considered to play a role in the mechanisms of hypertension. Increased vasopressin during preeclampsia may be a compensatory hypothalamic response to the generalize hypovolemia, or perhaps, a result of another mechanism, for instance to a hypothalamic disturbance [96].

Endothelin-1 is secreted from the ECs and it is the strongest vasoconstrictor that acts through its interaction with endothelin-A (ETA) and endothelin-B (ETB) receptors [97]. Moreover, the function of endothelin-1 extends far beyond vasoconstriction and it can also induce inflammation, angiogenesis, proliferation of the vascular smooth muscle cell, and even vasodilatation, depending on the receptor subtype being activated [98]. ETA

receptors are localized into the smooth muscle cells and evoke contraction, whereas ETB receptors are localized on both the endothelial and smooth muscle vascular layers and stimulate contraction in smooth muscle and vasodilation in the endothelium [99]. Endothelin-1 also contributes to oxidative stress and increases inflammatory cytokines and CD4⁺ cells [100]. Although the exact mechanism of increased Endothelin-1 production in patients with pregnancy disorders is unknown, it could be a consequence of increased production of sFlt-1 and matrix metalloproteinases (MMPs) in ischemic, hypoxic placentas [101]. It has been reported that VEGF enhances prepro-endothelial-1 mRNA expression and induces endothelin-converting enzyme-1, which is a key enzyme in endothelin processing [102,103]. According to the literature, endothelin-1 was significantly higher in patients with preeclampsia compared to those of healthy pregnant women [104,105], and even more elevated in patients with HS [106]. Interestingly, serum endothelin was also found to be significantly higher, even in the first trimester of pregnancy, in women who later developed preeclampsia compared to those who remained normotensive [107].

ENDOTHELIAL DYSFUNCTION IN PREGNANCY RELATED HYPERTENSIVE AND LIVER DISEASE

4.1 Endothelial dysfunction in liver disease

One of the major characteristics of the ECs is their capacity for certain phenotypic heterogeneity. Despite the signals from the flowing blood, ECs also receive and respond to signals from surrounding cells and tissues. Therefore, the structure and behavior of the ECs significantly depend on the local environmental stimuli and their morphology, biosynthetic repertoire, and behavior depends on their localization in specific vascular bed [108,109]. ECs in different tissues and organs have a different structure [110] and also the ability to disparate different site-specific synthetic properties depending on the local environment [111]. For instance, the ECs in the central nervous system form a continuous endothelial layer provided by complex tight intercellular junctions that form the blood-brain barrier [7]. The EC in the endocrine glands and renal glomeruli pose a transcellular pore which

enables the hormone protein secretion and plasma filtration [7]. The ECs of the sinusoids of the liver, spleen, and bone marrow are “fenestrated” and display gaps between adjacent cells and the poorly formed underlying basement membrane enabling an exchange of cells or particles [7]. The sinusoidal endothelial cells (SECs) in the hepatic microcirculation have unique and distinct characteristics from any other vascular ECs. SECs pose fenestrae on the cell surface and practically lack a basement membrane. The endothelial layer is very important for selecting molecules and substances that are exchanged between the sinusoidal lumen and the space of Disse. Owing to the SECs structure, the circulating lymphocytes are able to reach the hepatocytes directly [112] which makes the hepatocytes very exposed and potentially vulnerable.

Certain morphological and functional specifics of the hepatic ECs play a crucial role in the regulation of the intrahepatic vascular tone and in the pathogenesis of portal hypertension [113,114]. It is now well known that the ED of the SEC is the initial event responsible for the development of liver injury [112]. In interaction with different stimuli such as inflammatory mediators, or alcohol, the SECs release different vasoactive mediators that diffuse into the hepatic stellate cells (HSCs) and cause their relaxation or constriction. Thus, the SEC activity regulates the blood flow in the sinusoidal microcirculation. In the contrary to the systemic ED that is mainly manifested with increased vasodilatory tone, the intrahepatic ED is characterized by increased vasoconstriction. There are few reasons for these developments. The increased generation of vasoconstrictive substances such as endothelin and TXA2 seems to play a certain role [115]. However, it is considered that the main cause for the increased vasoconstriction is the reduced bioavailability of NO in the hepatic microcirculation that makes a major contribution to the hepatic endothelial dysfunction [116]. The reduced NO bioavailability is a consequence of the balance between the reduced NO production, increased NO breakdown due to the oxidative stress and inflammation [117], and also of the reduced vasodilatory response to NO [118]. In patients with liver disease, ROS are shown to decrease the bioavailability of NO in EC by directly reacting with NO [77]. Several inflammatory mediators are considered to be involved in downregulation of the endothelial nitric oxide synthase (eNOS) activity and NO bioavailability within the hepatic

circulation, among which TNF- α , nuclear factor- κ B (NF κ B), Toll-like receptors (TLRs) and Angiotensin II seem to be the most important ones [116]. Also, in an advanced stage of liver damage, the intrahepatic vasculature seems to display increased sensitivity to vasoconstrictive mediators [119]. The increased vasocontractile tone leads towards impaired flow-mediated relaxation and increased intrahepatic vascular resistance. The abnormalities in the hepatic microcirculation are the basic mechanism responsible for the remodeling of the sinusoidal capillary bed and the development of PH. In patients with advanced liver disease, the vascular remodeling leads to a process called capillarization, indicating a defenestration of the sinusoidal endothelium and development of subendothelial basement membrane [120,121].

Opposite to the hepatic vasoconstriction, in patients with advanced liver disease, the ED in the systemic circulation increases the periphery vasodilatory tone. There are many vasodilatory factors responsible for the development of the ED in the peripheral circulation. However, the increased portal pressure in the hepatic microcirculation mediated by the NO-synthetase stimulates the systemic ED that leads to hyperactivity of the ECs in the systemic arteries and increases peripheral vasodilatation [122]. There are many factors that are assumed to increase the hyperreactivity of the systemic ECs. However, it has been confirmed that the PH by itself acts as an endothelial stress and stimulates NO production. It also increases the endothelium dependent relaxation, that is, the PH indirectly participates in the development and progression of the vasodilatation in the splanchnic circulation. These complex disturbances in the hepatic microcirculation and in the systemic circulation, and also their mutual interactions are responsible for the development of the hyperdynamic circulatory disturbances observed in patients with advanced chronic liver disease.

4.2 Endothelial dysfunction in preeclampsia

Preeclampsia is a multisystem progressive disorder specifically related to pathological pregnancy and characterized by the new onset of hypertension, proteinuria and multisystem progressive disorder. It occurs after the 20th week of gestation, but most cases occur between 34 and 37 weeks. One systematic review detected preeclampsia in 4.6% of pregnancies worldwide [123]. The most important risk factors for pre-

eclampsia are past history of preeclampsia or placental insufficiency (fetal growth restriction, abruption and stillbirth), family history of preeclampsia in a first-degree relative, preexisting hypertension, diabetes, chronic kidney disease, or some autoimmune diseases (antiphospholipid syndrome, systemic lupus erythematosus), advanced maternal age, obesity, multifetal gestation, the use of assisted reproductive technology [124-126].

The diagnostic criteria for preeclampsia are the presence of new onset of hypertension and proteinuria or the new onset of hypertension and significant end-organ dysfunction with or without proteinuria after the 20th week of gestation in a previously normotensive patient [88,127]. During pregnancy, hypertension is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg [43], while severe hypertension is defined as systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 110 mmHg [43]. In preeclampsia, proteinuria can be defined as more than 0.3 g protein in a 24-hour urine specimen, as more than 0.3 g/g by urine protein/creatinine ratio, or as more than 2+ protein (equivalent to 100 - 300 mg/dL) on a paper test strip dipped into a fresh, clean voided mid-stream urine specimen [88,128]. However, more recent guidelines consider some specific organ dysfunctions (renal impairment, liver disease, neurological or hematological complications, as well as uteroplacental dysfunction and fetal growth restriction) as diagnostic criteria in preeclampsia [32,129]. It is not clear whether GH and preeclampsia are independent diseases with a similar phenotype (hypertension) or whether GH is an early mild stage of preeclampsia. According to some epidemiological data and the significantly different recurrence rate, more evidence suggest that preeclampsia and GH are independent diseases [130,131].

In most typical cases of preeclampsia, the disease starts to manifest in the third trimester, mainly after the 34th gestational week, by gradual development of hypertension and proteinuria. In patients with atypical presentation, the onset of symptoms begins before the 20th gestational week or two days after delivery, it may present only with gestational hypertension or proteinuria alone, or predominantly with symptoms of significant end-organ dysfunction [43]. A subentity defined as "preeclampsia with severe features" (formerly severe preeclampsia) is characterized by the presence of severe hypertension and/or spe-

cific signs or symptoms of significant end-organ dysfunction such as: headache, visual abnormalities (scotomata, photophobia, blurred vision, or temporary blindness), upper abdominal, retrosternal, or epigastric pain, altered mental status (confusion, altered behavior, or new-onset dyspnea/orthopnea [132]. Patients with preeclampsia are at increased risk for life-threatening events, including placental abruption, acute kidney injury, cerebral hemorrhage, hepatic failure or rupture, pulmonary edema, stroke, cardiac failure, and progression to eclampsia [43]. The clinical spectrum of preeclampsia is composed of two main subtypes. The first one is the early-onset preeclampsia (< 34 weeks of gestation) and the second one is the late-onset preeclampsia (≥ 34 weeks of gestation). It is now considered that different pathophysiological mechanisms are mainly responsible for the two different phenotypes related to different clinical outcomes [133, 134]. Early-onset disease has been associated with more severe maternal and fetal clinical findings and worse maternal/fetal outcomes [134].

The recent investigations in the area have made a deeper insight into the role of many potential pathogenetic factors that could possibly play a role in the pathogenesis of preeclampsia. Evidence suggests that genetic, immunological, vascular and environmental factors interact and contribute to the development of preeclampsia [135]. Some epidemiological data suggest the potential role of some maternal, paternal and fetal genetic factors involved in the pathogenesis of abnormal placentation and the increased risk of development of preeclampsia-related abnormalities [136,137]. It has been confirmed that a genetic locus on chromosome 13 is responsible for the production of some of the anti-endothelial factors, a polymorphism of PAI-1 4G/5G plays a role [138], and the variants of the gene for angiotensinogen and eNOS have also been pointed as contributing genetic factors [136]. Regarding the immunologic factors, it has been established that some interaction between maternal, paternal, and fetal HLA types could contribute to the possible immunologic intolerance between the mother and the fetus. [85,138].

Abnormalities in the placenta are believed to be a critical feature of the preeclampsia syndrome. The incomplete spiral artery remodeling, placental hypoxia, oxidative damage, and shear stress from uteroplacental blood flow impose a substantial immunological burden resulting in

development of proinflammatory environment that can induce placental apoptosis or necrosis and release of circulating inflammatory markers [139]. Trophoblast differentiation during endothelial invasion involves alteration in expression of a number of different classes of molecules, such as cytokines, adhesion molecules, extracellular matrix molecules, metalloproteinases, and the class Ib major histocompatibility complex molecule, HLA-G [140]. Preeclampsia is a state of oxidative stress in which mitochondria are the major source of ROS [141]. The placental stress related to abnormal placental development promotes a proinflammatory milieu, accompanied by increased TNF α , decreased IL-10, changes in T cell ratios, and disrupted vasodilatory function [142-144].

Mammalian placentation requires extensive angiogenesis for the establishment of a suitable vascular network and for optimal fetal oxygen and nutrients supply. A variety of proangiogenic [VEGF, Placental growth factor (PlGF) and antiangiogenic factors] are produced by the developing placenta, and the balance between these factors is important for normal placental development. The VEGF represents a major proangiogenic factor. By binding to its tyrosine kinase receptors VEGFR1 and VEGFR2, VEGF stimulates the angiogenesis, vascular permeability, cell migration and proliferation, and inhibition of cell apoptosis [145]. VEGF stimulates the NO production by upregulation of eNOS expression in ECs and also by induction of prostacyclin synthesis [146]. PlGF is also a member of the VEGF family and it is important for the blood vessel development and maintenance of endothelial function [147]. Contrary to VEGF, PlGF specifically signals through VEGFR-1 binding [148].

VEGF and PlGF are the most important mediator responsible for the normal placentation process.

In patients with preeclampsia, the placenta-derived factors cause ED in different vascular beds in the maternal circulation along with many complex abnormalities. There are several mediators responsible for the development of the typical preeclamptic phenotype. Increased placental production of several antiangiogenic factors causes the systemic ED typical for preeclampsia. Consequently, there is also an increased concentration of circulating cellular fibronectin, factor VIII antigen, and thrombomodulin [149,150]. The impaired ED cell function leads to decreased pro-

duction of endothelial-derived vasodilators, such as NO and prostacyclin, increased production of vasoconstrictors, such as endothelin and TXA2 and an impaired flow-mediated and acetylcholine mediated vasodilation [151]. Several placenta-derived and circulating factors have been identified as the major cause for the maternal ED. Among them, the most important factors are Flt-1, the soluble Flt-1 (sFlt-1), and Endoglin.

According to the relevant data, increased placental expression and secretion of Flt-1 appear to play a central role in the pathogenesis of preeclampsia [152-155]. sFlt-1 is probably the most important placental factor responsible for at least some features of preeclampsia [156]. The soluble Flt-1 is (sFlt-1) produced by the placenta, macrophages, endothelial cells, and vascular smooth muscle cells [157]. sFlt-1 is a naturally occurring, circulating antagonist to VEGF and PlGF. The VEGF represents a major proangiogenic factor. VEGFA stimulates angiogenesis, vascular permeability, and cell migration by binding to its tyrosine kinase receptors VEGFR1 and VEGFR2 [144]. VEGF stimulates the NO and prostacyclin production in the ECs [146,152]. The evidence that confirms the unique ability of the placental cytotrophoblasts to enhance sFlt-1 production in vitro when oxygen availability is reduced [158] suggests that the sFlt1 production is most likely triggered by the placental ischemia [158]. After it is released into the maternal circulation, the increased concentration of sFlt-1 interacts and antagonizes the proangiogenic biologic activity of circulating VEGF and PlGF, it binds to them and hence, prevents their interaction with their endogenous receptors [159]. In fact, the main mechanism of action of sFlt-1 in preeclampsia is sequestration of VEGF. Also, the prolonged hypoxic placental environment stimulates mRNA expression of Flt-1 and the sFLT-1 peptide is released in cultured primary cytotrophoblast and syncytiotrophoblast cells [158]. By inhibition of VEGF and PlGF action, the sFlt-1 additionally impairs the placental angiogenesis, additionally stimulates mRNA expression of Flt-1 and secretion of hypoxia-induced mediators including sFlt-1. Also, it has been confirmed that through the reduction of PlGF and VEGF bioavailability, sFlt1 presents a significant cause of proteinuria, glomerular endotheliosis and hypertension in obstetric complications [160]. An increased ratio of sFlt-1:PlGF, accompanied by an increased Endoglin is most predictive of developing pre-

eclampsia and has been considered as a diagnostic tool for detecting preeclampsia [155].

The clinical features of fully-expressed preeclampsia can be explained as responses to generalized ED [161]. The maternal ED caused by the placenta-derived mediator is underlying the pathogenic mechanisms that later express as the typical preeclamptic symptoms and signs. The development of hypertension that almost defines preeclampsia is due to the increased concentration and action of endothelin-1, Angiotensin II and other vasoconstrictive hormones, including vasopressin and the inhibitory effect of Flt-1 on VEGF. The increased vascular permeability is due to the impaired endothelial barrier integrity caused by the effect of some placental factors. The main proposed underlying mechanism is the early-onset release of the HtrA serine peptidase 4 (HTRA4) derived from the ischemic placenta, which according to some research cleaves the endothelial junctional protein VE-cadherin [162]. The impaired endothelial barrier integrity enables vascular leak and emphasizes the hypovolemia, which compensatory stimulates the vasopressin secretion. The nonselective proteinuria that develops in patients with preeclampsia is a result of the impaired integrity of the glomerular filtration barrier that becomes permeable for non-selective protein excretion [163]. This is at least partly due to the deficient VEGF signaling [43]. Several mechanisms play a role in this process, such as the podocyte loss from the glomerulus, the nonselective protein excretion and the reduced tubular handling of the filtered proteins [43,164]. The presence of other symptoms and signs (coagulopathy, headache, seizures, visual symptoms, epigastric pain, and FGR) is a consequence of ED in the vasculature of target organs, such as the brain, liver, kidney, and placenta.

The hepatic affection is not uncommon in patients with preeclampsia and it could be attributed to several mechanisms. The vasospasm and the reduced hepatic blood flow lead to an increased resistance within the hepatic vascular bed. The periportal and sinusoidal fibrin deposition precipitates consecutive sinusoidal obstruction. Also, the microvesicular fat deposition probably contributes to the hepatic injury within preeclampsia [39,40]. In most severe cases, the intense liver ischemia leads to development of large hematomas, capsular tears, and intraperitoneal hemorrhage [164]. The clinical manifestations of hepatic dysfunction include right upper quadrant or epigastric pain

caused by the hepatic swelling and the stretching of Glisson's capsule, liver tenderness, elevated transaminase concentration, coagulopathy, and, in the most severe cases some of the bleeding complications.

Preeclampsia is the leading cause of maternal and perinatal morbidity and mortality in pregnancy [165]. The fetus is at an increased risk of FGR and medically or obstetrically indicated preterm birth. The relationship between preexisting vascular disease and susceptibility to developing preeclampsia may be explained by the preexisting endothelial cell damage in these patients [166]. Moreover, preeclampsia is significantly associated with increased risks of cardiovascular diseases later in life [31,167].

4.3 Endothelial dysfunction in eclampsia

Eclampsia refers to the occurrence of new-onset, generalized, tonic-clonic seizures or coma in a woman with preeclampsia (including gestational hypertension and HS) in the absence of other neurologic conditions that could account for the seizure [168]. Eclampsia is a convulsive manifestation of preeclampsia and it is one of the most severe manifestations within the heterogeneous preeclamptic phenotype. In patients not receiving antiseizure prophylaxis, an eclamptic seizure occurs in 2-3 % of patients with severe preeclampsia and in 0-0.6 % of those without severe features [169]. The exact mechanisms that cause the seizures in preeclampsia are not precisely understood. There are two concepts trying to clarify the pathogenesis of seizures in eclampsia, and both models include the role of hypertension and ED in the pathogenesis of the entity. According to the first model, the hypertension causes a breakdown of the autoregulatory system of the cerebral circulation, leading to cerebral hyper perfusion, ED and vasogenic and/or cytotoxic edema [168]. According to the second model, hypertension causes activation of the autoregulatory system, leading to vasoconstriction of cerebral vessels, hypoperfusion, localized ischemia, ED and vasogenic and/or cytotoxic edema [170]. Also, the cerebral inflammation is considered to be an additional factor that plays a role in the pathogenesis of eclampsia [171].

4.4 Endothelial dysfunction in HELLP Syndrome

HS is a pregnancy-related entity characterized by hemolysis, elevated liver enzymes, and a low platelet count (hemolysis, elevated liver enzymes and low platelets). Since hypertension and proteinuria are present in approximately 85% of the HS cases, HS has been considered a variant of the severe form of preeclampsia. However, HS can occur in pregnant women with no hypertension or proteinuria. HS develops in 0.1 to 1% of the pregnancies overall and in 12% of pregnant women with severe preeclampsia [172]. Most cases of HS are diagnosed between 28 and 36 weeks of gestation, but symptoms may present up to 7 days postpartum [173]. Patients often complain of nausea, vomiting, malaise, headache, abdominal pain and tenderness in the right upper quadrant. In most severe cases, thrombocytopenia-related bleeding (mucosal, hematuria, petechial hemorrhages, ecchymosis) may occur [174]. Some affected patients do not have concurrent hypertension or proteinuria, and some authors consider HS a separate disorder from preeclampsia [175]. By using the Tennessee classification, in most cases the diagnosis is easily established [176]. However, the American College of Obstetricians and Gynecologists proposed diagnostic criteria for HS (LDH ≥ 600 IU/L, AST and ALT elevated more than twice the upper limit of normal and Platelet count $< 100,000$ cells/microl) [88]. Additionally, according to the severity of thrombocytopenia, the Mississippi classification subclassifies the HS in three classes [177]. During evaluation, HS should be distinguished mainly from AFPL, thrombotic thrombocytopenic purpura, pregnancy-related hemolytic-uremic syndrome, and from systemic lupus erythematosus [172].

The cause for development of HS is not fully understood and the pathogenetic mechanisms are still a matter of debate. It is known that HS develops as a result of interaction between genetic (maternal and fetal), placental, autoimmune and some environmental factors [178]. Although an isolated causative genetic abnormality has not yet been identified, it is known that multiple genetic variants are responsible for the development of HS [179]. According to the literature, the possibly involved genetic factors are the mutations in the Fas gene, the VEGF gene, the gene for coagulation factor V Leiden, the glucocorticoid receptor gene, the Toll-like receptor gene, the G1528C mutation, a locus at 12q, and a genetic defect associated with deficiency in the fetal long-chain 3-hydroxyacyl CoA dehydrogenase (LCHAD) [180].

Recent studies have pointed out the important role of placenta-derived inflammatory cytokines released from the ischemic placenta and the role of immune dysfunction in the HS pathogenesis [180]. Endoglin is important placental mediator considered to be important factor for the development of severe preeclampsia, HS and FGR [181,182]. This protein is located on the ECs, syncytiotrophoblast, and columnar cytotrophoblasts prior to uterine invasion and exists in either a proangiogenic membrane-bound form or an antiangiogenic soluble form (sEng) [181]. Endoglin serves as a receptor for the cytokines transforming growth factor-beta 1 and 3 (TGF- β 1 and TGF- β 3), which are important for placental angiogenesis, cell proliferation, differentiation and apoptosis. Despite the inhibition of the TGF- β 1 binding to receptor type II (T β RII) on the ECs, it also causes vascular damage and increases permeability. Because TGF- β cannot bind to its receptor, its circulatory concentration is increased, explaining the rise in TGF- β in preeclamptic women [183]. The TGF- β 1 rise could be also due to the phagocytosis of the necrotic trophoblasts by the ECs and the circulatory release of TGF- β 1, IL-6 and additional stimulation of placental endoglin secretion [184]. Not only that sEng is elevated, but also the endoglin concentration is higher than the concentration of sFlt1 in HS patients [185]. The soluble endoglin is also elevated in the sera of preeclamptic women two to three months before the onset of clinical signs of preeclampsia, it correlates with disease severity, and decreases after delivery [46]. Moreover, TGF- β 1 is responsible for the production of VEGF by the stellate cells in the space of Disse, and hence, it is thought that this process impairs the production of VEGF by the pericytes [185] which could explain the pronounced endothelial damage within the hepatic vascular bed.

There are few other important mediators in HS. Fas receptor (Fas) and Fas ligand (FasL) are part of the TNF receptor family and regulate the inflammatory response via activation and proliferation of CD4⁺ T lymphocytes. Expression of FasL is not detected in the liver endothelial cells, but in HS patients the liver sinusoidal endothelial cells exhibit an increased expression of Fas [186]. Exposing the liver sinusoidal endothelial cells to an increased TNF α level drives a higher expression of Fas and, thus, greater susceptibility to apoptosis. In HS, the FasL coming from the placenta binds Fas and can cause an apoptotic cell death in the liver of HS patients [187]. In patients with

HS there is also elevated concentration of sFlt-1, endothelin-1, galectin, the angiopoietins and ADMA [100,188]. As in preeclampsia, the sFlt-1 secretion is also increased in HS patients, but it seems that some other placental factors are more closely related to the complex pathogenesis of HS.

There are still many unclear and unfamiliar facts regarding HS pathogenesis. The pathogenetic mechanisms for development of HS are complex. If HS is a severe form of preeclampsia, then it is expected that there is an involvement of the same mechanisms as in preeclampsia. It is known that the physiological and pathological changes of the disease are similar to those of HDP, but the initial mechanism of its development into HS is still unclear [189]. However, there is certainly some kind of variation in the pathogenesis that stimulates intense hepatic inflammation and activation of the coagulation system. As in preeclampsia, the initial trigger for the ED in HS is assumed to be some mediators released from the placenta into the maternal blood stream that induce maternal ED. For instance, the sFlt-1 concentration is elevated in both conditions. Still, probably the release of different types of placental factor in different susceptible patients would lead to the development of different phenotype.

The abnormalities that occur in HS could be explained by several factors. Initially, it seems that specific placental factors are released from the ischemic placenta that causes maternal endothelial damage presented and manifested by production of antiangiogenic factors, exposure to TNF α , and high levels of active VWF. On the other hand, an interesting aspect of the HS pathogenesis is the involvement of the complement. It is considered that in some patients with HS, the thrombotic microangiopathy, the main landmark of this entity, is caused by complement dysregulation [172], and that the complement dysfunction could be the key mediator in the pathogenic mechanisms of HS [190]. In line with this assumption is the fact that women with mutations in complement regulatory proteins appear to be at an increased risk of severe preeclampsia [191]. The interaction between these factors leads to the development of specific inflammatory milieu that causes the microangiopathy, that is, the unexplained maternal systemic small blood vessel spasm and the red blood cells sequestration when passing through the spastic blood vessels [192]. Macroangiopathic hemolysis is the curtail abnormality in patients with HS. Later, the exposure of collagenous tissue

after endothelial cell damage leads to platelet activation, aggregation, and excessive consumption resulting in thrombocytopenia [193]. The microangiopathy is clinically most evident within the hepatic tissue. However, despite liver damage, the microangiopathy is also responsible for the renal dysfunction, hypertension, and it increases the vulnerability to an ischemic insult.

The predominant liver affection is the second characteristic of HS. Liver dysfunction that occurs in HS patients is a reflection of the pronounced microangiopathy within the hepatic sinusoids resulting in sinusoidal vasospasm and fibrin deposition. This leads to obstruction of the Disse space caused by the erythrocytes [185], increased formation of microthrombi, hepatocyte ischemia and necrosis, and ultimately liver injury [164,185]. Practically, the microangiopathy seen in HS enhances hepatocyte damage because it significantly restricts the portal blood flow [194]. The intense and diffuse microangiopathy can sometimes progress to development of large hematomas, capsular tears, or intraperitoneal hemorrhage.

The third important presentation of HS is the remarkably impaired coagulation and the tendency for development of disseminated intravascular coagulation (DIC). Although it can be often registered in preeclampsia, the presence of coagulation cascade activation seems to be more pronounced in HS patients. The main activator of the coagulation cascade in HS patients are the activated platelets, the increased levels of coagulation factors, and most importantly, the thrombotic microangiopathy and the intense intravascular hemolysis [180].

Regarding outcomes, patients with severe preeclampsia complicated with HS have significantly worse adverse pregnancy outcomes in comparison to women with preeclampsia without HS [189]. The maternal outcomes are generally good, although, serious complications such as DIC, placental abruption, acute kidney injury, and less frequently subcapsular liver hematoma, hepatic rupture, pulmonary edema, and retinal detachment can occur [172]. Regarding the infant outcomes, the prognosis is mainly related to the gestational age at onset, gestational age at delivery and birth weight [189].

4.5. Endothelial dysfunction in acute fatty liver of pregnancy

AFLP is a rare obstetric emergency characterized by maternal liver dysfunction as a result of microvesicular fatty infiltration of the hepatocytes. It typically presents between the 30th and the 38th gestational week and it is the most common cause of acute liver failure in pregnancy. Potential risk factors for AFLP include past AFLP, preeclampsia or HS, multiple gestation, fetal long-chain 3-hydroxyacyl CoA dehydrogenase deficiency, male fetal sex, low body mass index, nulliparity [195,196]. Despite the nonspecific symptoms, the development of manifestations of acute liver failure presented with jaundice, encephalopathy, coagulopathy and/or hypoglycemia is the typical landmark of the entity [197]. Multisystem involvement, including acute kidney injury, encephalopathy, coagulopathy, pancreatitis, pulmonary edema, and/or adult respiratory distress syndrome, strengthens the diagnosis of AFLP [197]. Many AFLP patients have hypertension, with or without proteinuria. Coexisting HS occurs in 20%, and 20% to 40% of patients are also diagnosed with preeclampsia [198].

Although the pathogenesis of AFLP is not fully understood, still some important mechanisms have been clarified. The literature data suggest that in most cases, AFLP occurs due to a dysfunction in the mitochondrial fatty acid oxidation metabolism. The dysfunction may occur in the maternal, in the fetal, or in the mitochondrial function of both. There are two enzymes involved in mitochondrial fatty acid oxidation, and mutations in these enzymes are thought to be closely associated with AFLP: mitochondrial trifunctional protein and its alpha subunit LCHAD [199]. Being diagnosed in 20% of AFLP patients, the presence of fetal LCHAD deficiency is the most frequent cause for AFLP [200] and G1528C mutation is the most commonly related mutation associated with LCHAD deficiency [200]. Due to the fetoplacental growth and development, the concentration of free fatty acids increases during normal pregnancy, particularly in the advanced gestation. Considering the increased metabolism, in case of defective maternal-fetal fatty acid metabolism, intermediate products would accumulate in the maternal blood and hepatocytes inducing a liver injury [200]. However, one of the breakthroughs in the pathogenesis of AFLP has been the discovery of fetal fatty acid oxidation disorders linked to acute fatty liver in the mother [201] and that AFLP is even more related to the fetal LCHAD deficiency. Earlier reports demonstrated that mothers of neonates with LCHAD deficiency have a 79%

chance of developing AFLP or HS [200,201]. In fetuses homozygous for LCHAD deficiency, the fetoplacental unit cannot perform the fatty acid oxygenation properly, so the intermediate products of fatty acid metabolism increase and enter the maternal circulation [202]. Since the mother is a heterozygous for LCHAD deficiency, her ability for fatty acid oxidation is also diminished, and consequently, long-chain metabolites accumulate in the maternal blood and hepatocytes, resulting in toxic effects. The cytotoxic effect of the elevated concentration of free fatty acids and the increased reactive oxidative and nitrosative stress, activate the proinflammatory pathway and induce apoptosis [39,203]. Hence, in this setting, the unoxidized fatty acids are transferred to the mother through the placenta, rather than accumulating in the fetus, representing a threat for the maternal liver function.

In the contrary to preeclampsia and HS, the ED does not have a central role in the pathogenesis of AFLP. However, it seems the ED could probably emphasize some aspects of the pathogenesis of this entity. According to the literature, one of the hallmark findings in patients with AFLP is the presence of multiorgan fatty infiltration. Not only in the liver, but there is also an increased fatty infiltration in the kidneys, pancreas, and also in the placenta [204]. The increased amount of fatty acid in the placenta stimulates the development of hypoxic placental dysfunction and consecutive impaired fetal oxygen supply. It is assumed that the hypoxic placenta could precipitate the development of consecutive ED. Since acute liver failure of any cause is closely related to coagulopathy due to decreased production of procoagulant and also anticoagulant factors, a balanced coagulopathy development secondary to the liver dysfunction accompanies AFLP. It is usually presented by impaired primary hemostasis, decreased production of fibrinogen, reduced levels of antifibrinolytic pathway components, and upregulation of TPG, all of which promote hyperfibrinolysis and DIC [205]. It is considered that the coexisting ED contributes to development of consumption coagulopathy with enhanced fibrinolysis and increased vascular permeability [206].

Although AFLP was associated with high mortality, the rates have significantly decreased over the past several decades [195,196]. AFLP is associated with an increased risk of perinatal mortality and morbidity mainly due to maternal decompensation and/or preterm birth [196,196].

CONCLUSION

ED is increasingly recognized as a complex and important entity that plays a crucial role in the pathogenesis of many important conditions. The interaction between the numerous hemodynamic, hormonal, metabolic and immunological pregnancy disorders, and the ED in specific vascular beds is crucial for the development of many abnormalities within the pregnancy-related hypertensive and hepatic diseases. The more focused insight into the different aspects of ED in the specific pathophysiological settings gives the opportunity for application of more effective, specific target therapies which could also contribute to the reduction of the fetal and maternal poor outcomes.

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Резиме**УЛОГАТА НА ЕНДОТЕЛНАТА ДИСФУНКЦИЈА ВО ПАТОГЕНЕЗАТА НА ПАТОЛОШКИ СОСТОЈБИ ПОВРЗАНИ СО БРЕМЕНОСТА: ПРЕГЛЕД**

Елена Цуракова Ристовска¹, Магдалена Генадиева-Димитрова¹, Бети Тодоровска¹, Владимир Миливојевиќ², Иван Ранковиќ³, Игор Самарџиски⁴, Маја Бојациоска⁵

¹ Универзитетска клиника за гастроентерохепатологија, Медицински факултет, Универзитет „Св. Кирил и Методиј“ во Скопје, Скопје, РС Македонија

² Оддел за интерна медицина, Медкомпас Алијанса, Медицински факултет, Универзитет во Белград, Белград, Србија

³ Оддел за интерна медицина, Медкомпас Алијанса, Белград, Србија

⁴ Универзитетска клиника за гинекологија и акушерство, Медицински факултет, Универзитет „Св. Кирил и Методиј“ во Скопје, Скопје, РС Македонија

⁵ Универзитетска клиника за ревматологија, Медицински факултет, СУниверзитет „Св. Кирил и Методиј“ во Скопје, Скопје, РС Македонија

Во последните децении ендотелната дисфункција (ЕД) е препознаена како значаен фактор што учествува во патогенезата на многу патолошки состојби. Во интеракција со атеросклерозата, хиперхолестеролемијата и хипертензијата, ЕД игра клучна улога во патогенезата на коронарната артериска болест, хроничната бубрежна болест и микроваскуларните компликации кај дијабетес мелитус. Иако ЕД игра значајна улога во патогенезата на неколку нарушувања поврзани со бременоста, какви што се прееклампсијата, синдромот HELLP, феталната рестрикција во растот и гестацискиот дијабетес мелитус, точните патогенетски механизми сè уште се предмет на дебата. Зголемената преваленца на овие ентитети кај пациенти со постојни васкуларни заболувања ја нагласува суштинската патолошка улога на претходно постојната ЕД кај овие пациенти. Абнормалната утероплацентарна циркулација и ослободувањето солубилни фактори од исхемијната плацента во мајчиниот крвоток се главните причини за ЕД кај мајката, што лежи во основата на карактеристичниот преекламптичен фенотип. Покрај зголемениот ризик за лоши исходи кај мајката и кај фетусот, постојната ЕД, исто така, го зголемува и ризикот од развој на идни кардиоваскуларни заболувања кај овие пациенти. Оваа студија имаше цел да погледне подлабоко во улогата на ЕД во патогенезата на неколку хипертензивни заболувања и заболувања на црниот дроб поврзани со бременоста. Тоа би можело да придонесе за подобрување на свеста, на знаењето и на управувањето со овие состојби, а исто така, и за намалување на негативните исходи и дополнителни долгорочни кардиоваскуларни компликации.

Клучни зборови: ендотелијална дисфункција, хипертензивни нарушувања на бременоста, гестациска хипертензија, прееклампсија, HELLP синдром, акутен мастен црн дроб во бременост