OPINION PAPER

UDC 577.346 doi: https://doi.org/10.15407/ubj95.03.005

COMMON MECHANISMS OF PLACENTAL DYSFUNCTION IN PREECLAMPSIA, GESTATIONAL DIABETES, AND COVID-19 IN PREGNANT WOMEN

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Received: 13 June 2023; **Revised:** 10 July 2023; **Accepted:** 10 July 2023

Background: COVID-19 infection, preeclampsia and gestational diabetes mellitus in pregnancy cause similar changes in the placenta and influence development of the fetus between conception and birth in gestation. Proper uterine and placental vascularization is essential for normal fetal development. The transplacental exchange is regulated and maintained by the placental endothelium. During placental implantation, the trophoblast differentiates into two distinct layers, the inner cytotrophoblast and outer syncytiotrophoblast, which are key elements of the human placental barrier. Proinflammatory cytokines exacerbate ischemic events and create an upward spiral of an inflammatory reaction in the placenta. Placental pathology in gestational COVID-19 shows desquamation and damage of trophoblast and chronic histiocytic intervillositis. Similar lesions also occur in gestational diabetes mellitus and preeclampsia. Common ground: The systemic inflammatory response of the mother, the increased inflammation in the placenta and cytokine production by placental trophoblasts should be monitored throughout pregnancy. Placental angiogenesis can be evaluated by serum vascular endothelial growth factor, Annexin A2, placental growth factor or sclerostin. Tissue

damage can be assessed by measuring levels of serum lactate dehydrogenase and myeloperoxidase. Blood flow can be monitored with three-dimensional Doppler and pathological changes can be documented with paraffin-embedded tissue sections stained with hematoxylin and eosin, and electron microscope images as well as immunohistochemistry tests for vascular endothelial growth factor, placental growth factor, sclerostin and Annexin A2. Opinion: The damage of maternal and fetal vascular perfusion (villitis and fibrin deposition) is a common mechanism of gestational diseases. The placenta lesions liberate anti-endothelial factors that lead to anti-angiogenic conditions and are the common mechanism of maternal placental vascular malperfusion in gestational diseases.

K e y w o r d s: pregnancy, placenta, inflammation, vascularization, dysfunction, pathology.

Authors reviewed placental vascular development during pregnancy in gestational COVID-19 (GCD), preeclampsia (PE) and gestational diabetes mellitus (GDM). Appropriate uterine and placental vascularization is essential for the normal fetal development. During the placenta implantation, the trophoblast differentiates into two distinct layers – inner cytotrophoblasts and outer syncytiotrophoblasts – which are key elements of the human placental barrier. In placenta lesions during pregnancy, the systemic inflammatory response of the mother induces platelet activation, proinflammatory cytokine production induces pathophysiological changes that occur at the maternal-fetal interface. The proinflammatory cytokines exacerbate ischemic events and create an upward spiral of inflammatory reaction in the placenta activating cytokine production in the placental trophoblast. The pathology in placenta lesions shows inflammation, desquamation and damage of trophoblast and placental hypoplasia in GCD, PE and GDM. These disorders in pregnancy could trigger commonalities in lesions during gestation including unusual or reduced blood flow – or malperfusion – in the placental maternal vasculature, increased intramural fibrin deposition, stromal-vascular karyorrhexis and chronic villitis.

The authors concluded that different gestational diseases have a common mechanism with similar placenta lesions. The pathological changes in the placenta during pregnancy may result in the inability of the placenta to perform its normal function, which could cause placental insufficiency, induced fetal inflammatory response, vascular thrombosis, stillbirth, fetal growth restriction or delay of neurosensorial development.

The reviewed literature revealed that metabolism of the placenta adapts to maternal physiological changes, adjusting its responses to nutrients and endocrine regulations. This adaptability optimizes hormone synthesis, diversifying available sources for energy production, angiogenesis, immune activation and tolerance, and pregnancy outcomes [1,2]. The oxygen- and nutrient-rich blood is carried from the placenta to the fetus via the umbilical vein, while deoxygenated blood and waste products transport from the fetus to the placenta by two arteries.

The chorionic plate, the umbilical cord and the chorionic villi are the main structural elements of the human placenta. The intervillous space is filled with maternal blood that enters in this cavity via remodeled and opened maternal spiral arteries and leaves via uterine veins [3]. Binding of SARS-CoV-2 to the angiotensin-converting enzyme 2 (ACE2) and its entrance into endothelial cells play a crucial role in inflammation of the placental endothelium [4]. The upward spiral of an inflammatory reaction in the placenta is initiated and maintained by proinflammatory cytokines, which exacerbate the ischemic events that will ultimately affect fetal development [5]. The histomorphology of the placenta in patients with PE and GDM shows a significant number of capillaries in terminal villi, syncytial knots and stromal fibrosis. Failure of placental angiogenesis and pseudo-vasculogenesis during placental development have been linked to the pathogenesis of GDM and PE, and recently published papers on GCD report similar placental changes [6]. Invasion of trophoblast cells into lymphatics occurs before the trophoblast cells remodel the spiral arteries in the decidua, and it is in line with immunomodulation as an early aspect

Abbreviations: PE – preeclampsia, GDM – gestational diabetes mellitus, GCD – gestational COVID-19, ACE2 – angiotensin-converting enzyme 2, PCD – placental cytotrophoblast dysfunction, VEGF – endothelial growth factor, PGF – placental growth factor, TNF-α – tumor necrosis factor-alpha, IL – interleukin, IFN-γ – interferon-gamma, MPO – myeloperoxidase, eNOS – endothelial nitric oxide synthase, NO – nitric oxide.

of pregnancy. However, endometrial lymphatics may later lose their functional significance [7].

Several published papers featuring diseases in pregnancy (GDM, PE, GCD) indicate the driving force of placental cytotrophoblast dysfunction (PCD) is the expression of decidual chemokines, cytokines, and growth factors such as endothelial growth factor (VEGF), placental growth factor (PGF) and Annexin A2 that affect trophoblast migration and/or invasion. Decreased expression of Annexin A2 and loss of its association with VEGF leads to deficient trophoblastic invasion in PE [8]. Some of these molecules including sclerostin likely play numerous roles at the maternal-fetal interface including decidual angiogenesis, spiral artery remodeling and activation and maturation of immune cells, extravillous trophoblasts, uterine natural killer cells and decidual fibroblasts [9].

Authors believe that the vascular inflammatory disorders cause placental hypoplasia, fetal vascular thrombosis and may result in maternal vascular malperfusion and fetal vascular malperfusion that leads to possible long-term damaging effects for newborns [10]. Maternal vascular malperfusion results in trophoblast necrosis, trophoblast necrosis, increased intramural fibrin deposition, stromal-vascular karyorrhexis and chronic villitis. Histopathology, electron microscope images, and immunohistochemistry are used to quantify pro-inflammatory and ischemic effects in the placenta [6]. Therefore, the risks due to GCD, GDM and PE include miscarriage, fetal inflammatory response, stillbirth, fetal growth restriction and delay of neurosensorial development [11].

These findings highlight the importance of a combined assessment of the decidua and placenta for the understanding of pathophysiological changes occurring at the maternal-fetal interface. In clinical practice, three-dimensional power Doppler has enabled us to study the morphology of the vascular tree *in vivo* and to calculate the direct blood flow of the placenta [12, 13].

The immune status of pregnant women and consequently the newborn is altered in PE, GCD and GDM due to inflammation. Unpublished data by Vari SG et al. show the balance between proinflammatory cytokines and anti-inflammatory cytokines play a significant role in PCD. Immune activation at the maternal-fetal interface by proinflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukins (IL) such as IL-1β, IL-2, IL-6, IL-12, IL-17A) and anti-inflammatory cytokines (human interferon-gamma (IFN-γ), IL-4, IL-5, IL-8, IL-10, IL-22) are main pathogenic factor in PE, GDM and GCD. Polymorphonuclear neutrophils are activated in PE patients, and IL-32 expression is upregulated in syncytiotrophoblasts [14].

It is well proven and reported that in the coronary and peripheral circulation, oxidative stress and endothelial dysfunction have important prognostic implications. The endothelial nitric oxide synthase (eNOS) produces nitric oxide (NO) at low levels unless stimulated by bradykinin during inflammation [15]. At the same time, it is well known that NO plays a curtailing role in the intracellular antiviral defense and inhibits a broad spectrum of viruses including SARS-CoV-19 [16].

Myeloperoxidase (MPO)-derived oxidants also contribute to tissue damage during inflammation leading to PCD. Throughout the progression of cardiovascular disease, MPO-catalyzed reactions are attributed to pro-atherogenic biological activities in different phases of the atherosclerotic process that includes initiation, propagation, and acute complication [17].

Common ground

From our perspective, the placental cytotrophoblasts convert from an epithelial to an endothelial phenotype during normal fetal development in PE, GDM and GCD. The changes in vasculogenesis throughout fetal development could lead to pseudovasculogenesis and PCD [18, 19]. During COVID-19 infection, changes in physiological features result from the harmful amplification loop between inflammation and tissue damage and induced dysregulation of neutrophil extracellular traps formation [20, 21].

The maternal platelet count decreases gradually during pregnancy from the first, to second and to third trimester. It is our understanding that in PE and GDM, the maternal platelets promote endovascular trophoblast infiltration and thus cause pathological changes in the placenta [22]. In GCD, several factors accelerate platelet aggregation and microvascular thrombosis in the placenta. Platelets are activated by proinflammatory cytokines that induce their binding to placental cytotrophoblasts [18]. PCD stimulates the production of placental IL-32 and proinflammatory cytokines in gravid women trigger a coagulation cascade. The endothelial dysfunction in the maternal vasculature leads to thrombin generation, platelet activation and consumption. The syn-

cytiotrophoblast layer damage within the placental intervillous space can activate maternal platelets and induce the formation of the fibrin-type fibrinoid [22] that has been found in the placenta of women with GCD [23]. On the other hand, decreased urokinase-type plasminogen activator and increased plasminogen activator inhibitor-1 will suppress the removal of fibrin depositions by fibrinolysis [24]. The histopathology of abnormal uterine perfusion during pregnancy in GCD, GDM and PE shows numerous pathological changes. In the literature, we found accelerated villous maturation, increased perivillous, intervillous fibrin deposition, decidual vasculopathy, villous infarction and intervillous thrombosis.

Opinion

The leading cause of changes in the placenta is inflammation that is characterized by immunoglobulins, C-reactive protein, interleukins and cytokines TNF-α and IFN-γ, as well as decidual cytokine IL-32. Inflammation induces tissue damage that can be measured by lactate dehydrogenase and oxidative stress that can be monitored by eNOS and MPO. Factors that accelerate platelet aggregation and microvascular thrombosis in the placenta during GCD, PE and GDM should be explored. Analysis of platelet count, the release of adenosine diphosphate during collagen- or thrombin-induced platelet aggregation and platelet-derived cytokines in pregnant women could predict thrombotic complications and placental disorders. The pro-angiogenic effects on the fetoplacental circulation supports trophoblast growth, and thus placental angiogenesis shall be monitored by measuring serum VEGF, Annexin A2, and PGF. Also, it is required to investigate umbilical cord plasma sclerostin as a predictor of placental and newborn weight. The evaluation of the vascular tree morphology and placental blood flow with three-dimensional power Doppler will help to establish a protocol for monitoring pregnant women with comorbidities such as pregnancy-induced hypertension, GDM and GCD. Histopathologic changes shall be documented in the placenta using electron microscope images, and/or formalin-fixed, paraffin-embedded tissue sections stained with hematoxylin and eosin, also using immunohistochemistry involving antibodies for VEGF, sclerostin, PGF and Annexin A2. The selected markers could be evaluated using enzyme-linked immunosorbent assays to monitor changes in blood serum, and monoclonal antibodies could be used for immunohistochemistry.

The associations of placental changes in pregnant women with GCD, PE and GDM should be investigated during gestation to find a solid fundament for the selection of biomarkers in these complex pregnancy disorders.

Acknowledgment. This study was supported by the Regional Cooperation for Health, Science and Technology Association (RECOOP HST Association) and the participating Cedars-Sinai Medical Center, RECOOP Research Centers (CRRC).

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

Funding. This research was supported by the Regional Cooperation for Health, Science and Technology Association (RECOOP HST Association) RECOOP Grant # 028 COVID-19 disease and comorbidities during pregnancy.

Ethical committee approval. The protocol and research materials were reviewed and approved by the Local Ethics Committee at I. Horbachevsky Ternopil National Medical University, Ukraine No 61 from November 13, 2020, and the Faculty of Medicine, University of Szeged, Approval number 101/2018-SZTE, issue date April 10, 2018.

Authors' information. The author is a member of the Regional Cooperation for Health, Science and Technology (RECOOP HST) Association led by Cedars-Sinai Medical Center and formed in 2006 as a consortium and transformed into an association in 2012. RECOOP HST includes 17 universities and academic organizations from seven countries in Central and Eastern Europe (Croatia, Czech Republic, Hungary, Poland, Romania, Slovakia, and Ukraine) and USA. According to its mission statement: "The RECOOP HST Association explores and enhances LOCAL scientific outputs of the partner organizations, creates critical mass of scientifically sound innovative research at REGIONAL level and exploits the research outcomes at GLOBAL level to improve the prevention and treatment of major public health problems." ™

Authors' contributions. Sandor G. Vari, MD, conceived, wrote, reviewed, and edited the manuscript. Oksana Shevchuk and Alla Boychuk performed study design and data acquisition. Solomiia Kramar, Zoia Nebesna, Yuliia Yakymchuk, Lesya Kobylinska, Volodymyr Chernyshenko, Daria Korolova and Andrea Gaspar-Suranyi, Abel Tamas Al-

torjay performed data acquisition, interpretation and Robert Gaspar performed data interpretation and manuscript editing. All authors read and approved the final version of the manuscript.

Consent for publication. The undersigned authors gave consent for the publication of identifiable details to be published.

ЗАГАЛЬНІ МЕХАНІЗМИ РОЗВИТКУ ПЛАЦЕНТАРНОЇ ДИСФУНКЦІЇ ПРИ ПРЕЕКЛАМПСІЇ, ГЕСТАЦІЙНОМУ ДІАБЕТІ ТА COVID-19 У ВАГІТНИХ ЖІНОК

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Коронавірусна інфекція, прееклампсія та гестаційний цукровий діабет під час вагітності спричинюють подібні зміни у плаценті та впливають на розвиток плода від зачаття до пологів і народження дитини. Відповідне кровопостачання матки та плаценти є необхідною умовою для нормального розвитку плода. Трансплацентарний обмін регулюється та підтримується через функціонування плацентарного ендотелію. Під час формування плаценти трофобласт диференціюється у два окремих шари: внутрішній цитотрофобласт та зовнішній синтиціотрофобласт, які є ключовими елементами фето-плацентарного бар'єру у людини. Прозапальні цитокіни посилюють ішемічні прояви та запускають каскад процесу запалення у плаценті. У разі COVID-19 під час вагітності у плаценті спостерігається десквамація і пошкодження трофобласта та хронічний гістіоцитарний інтервільозит. Подібні зміни також розвиваються при гестаційному діабету та прееклампсії. Під час вагітності потрібно моніторити показники системної запальної відповіді організму жінки, запальні процеси у плаценті та продукцію цитокінів плацентарним трофобластом. Процеси ангіогенезу у плаценті можна оцінити за вмістом у сироватці крові васкулярного ендотеліального фактора росту, аннексину А2 та плацентарного фактора росту або склеростину. Маркерами ушкодження тканин слугують лактатдегідрогеназа та мієлопероксидаза. Стан кровотоку можна оцінити за допомогою тривимірної допплерографії, а структурні зміни – за допомогою гістологічних досліджень, електронної мікроскопії, а також імуногістохімічних досліджень з використанням васкулярного ендотеліального фактора росту, аннексину А2 та плацентарного фактора росту або склеростину. Порушення судинної перфузії матері і плода (вітіліт та накопичення фібрину) – це типовий механізм у патогенезі гестаційних хвороб. Ушкодження плаценти вивільняє анти-ендотеліальні фактори, що призводить до порушення ангіогенезу та розвитку плацентарно-васкулярної мальперфузії при захворюваннях, пов'язаних із вагітністю.

Ключові слова: вагітність, плацентарне запалення, васкуляризація, дисфункція, патологія.

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