European Journal of Medical and Health Sciences
www.ejmed.org

Molecular Development of Placenta and Its Relationship with Preeclampsia and Fetal Growth Restriction

I Wayan Artana Putra

ABSTRACT

Preeclampsia (PE) is the leading causes of maternal death worldwide as well as a significant cause of fetal morbidity and mortality, including fetal growth restriction (FGR). The concept that PE and FGR shared a common etiology is widely accepted, i.e., the maladaptive response to the impaired placentation. Normal placentation is the result of dynamic integration of cell proliferation, differentiation, and migration, in which trophoblast cells play a crucial role. Impaired trophoblast invasion into the maternal decidua leads to a decrease in uteroplacental blood flow and changes in intervillous hemodynamic. The dynamic interaction of these process with maladaptive decidual immune response, impaired cytokines and angiogenic factors regulation, and oxidative stress will lead into the clinical manifestation of PE and/or FGR.

Keywords: Fetal growth restriction, placental development, preeclampsia.

Submitted : May 10, 2022

Published : August 31, 2022

ISSN: 2593-8339

DOI: 10.24018/ejmed.2022.4.4.1361

I. W. Artana Putra*
Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine Udayana University, Sanglah General Hospital, Denpasar, Bali, Indonesia.
(e-mail: artanatra@gmail.com)

****Corresponding Author***

I. Introduction

Preeclampsia (PE) is a specific pregnancy-related pathology that potentially harms both the mother and her fetus. It is one of the leading causes of maternal death worldwide as well as a significant cause of fetal morbidity and mortality. PE affects an estimated 4.6% of pregnancies globally [1]. PE can induce fetal growth restriction (FGR), premature labor, low birth weight, fetal and neonatal death. Women with PE are four times more likely to experience FGR than those without PE. On the other hand, FGR can have short-term impact, i.e. a 6-10 times higher risk of fetal mortality, as well as long-term impacts, i.e. hypertension, stroke, diabetes, cancer in adult life [2].

The exact etiology of PE is not known, and many clinicians called it “the disease of theory". Several theories exist regarding the causes of PE, i.e., immune maladaptation theory, inflammation, endothelial dysfunction, oxidative stress, and imbalance in renin-angiotensin system. Meanwhile, the causes of FGR are attributed to maternal, fetal, or placental factors. The concept that PE and FGR shared a common etiology is widely accepted and has been proven in several studies [3]-[5].

Fetal growth and development and placental structure and function result from the dynamic integration of cell proliferation, differentiation, and migration. The main aspect of normal placentation is the invasion of the extravillous trophoblast (EVT) and transformation of the decidual and spiral arteries of the uterus. In the early stage of fetal development, there are various stages of trophoblast differentiation which, if disturbed, can induce the development PE or FGR. In both PE and FGR, decreased uteroplacental blood flow and changes in intervillous hemodynamic result from the insufficient remodeling of spiral arteries by the trophoblast [6], [7]. The absence of optimal uteroplacental blood flow through impaired spiral arteries remodeling results in placental hypoxia, reoxygenation, oxidative stress. However, FGR can coexist with PE. Both conditions are generally thought to result from the defective remodeling of the spiral arteries [7].

In this review, we will discuss the molecular mechanisms underlying the development of placenta and their association to PE and FGR.

II. Placental Development in PE and FGR

The placenta is a unique organ that regulates fetal growth and maternal conditions during pregnancy. Its role as a feto-maternal mediator ends immediately after delivery. The human placenta is broadly divided into three histologic layers, i.e. the basal plate (maternal surface) and anchoring villi (the most distal extension of the main villous trunk) which interacts directly with the maternal endometrium; 2. terminal villous units where active gas and nutrient exchange occurs; and 3. the chorionic plate (fetal surface) and the villi rods which consist of dense connective tissue containing the larger fetal vessels. The amnion and chorion cover the chorionic plate, and the umbilical cord collects the chorionic artery and vein on the chorionic plate [8]. The basic structure of the placenta is formed during the first half of pregnancy. During normal placentation, trophoblast invasion occurs into the uterine spiral arteries. In particular, the multinucleated

syncytiotrophoblast, which forms the epithelial layer of the villi, is one part of the trophoblast that is in direct contact with maternal blood. Furthermore, extravillous mononuclear cytotrophoblasts (EVT) form an interface network in the uterine wall called the decidua [9].

The trophoblast invasion causes changes in the spiral arteries in the form of damage to the muscle layer, elastic layer, and nerve tissue found in the spiral artery walls and the replacement of endothelial cells with trophoblast cells. This interaction aims to induce the transformation of maternal vessels into vessels with high capacitance and low resistance that can provide adequate supply oxygen and nutrients for the placenta and the developing fetus [10]. The trophoblast cells lining the spiral arteries exhibit endothelial cell-like characteristics, adopt an endothelial phenotype, and express adhesion molecules classically found on the surface of endothelial cells [11]. This occurs through the differentiation of trophoblast cells during the invasion. This process is called pseudovasculogenesis or epithelial-endothelial transformation [12]. If trophoblast cell invasion occurs normally, by the end of the second trimester the spiral arteries will be lined only by trophoblast cells. The endothelial cells are no longer found in the endometrium and superficial myometrium. This remodeling of the spiral arteries results in the spiral arteries having a larger diameter and lower resistance, thus allowing for increased blood supply to the developing fetus.

Angiogenesis and vasculogenesis play an important role in the development of the placenta. Adequate angiogenesis and vasculogenesis will support uteroplacental flow so that the supply of oxygen and nutrients to the fetus can be adequately fulfilled. Vascular growth is critical in increasing fetoplacental flow during pregnancy. The increase in total diffused oxygen is proportional to fetal weight, making fetal well-being highly dependent on maternal (uteroplacental) and fetal (fetoplacental) blood flow systems, and efficient transplacental exchange between these two systems. The growth process of the placental vascular system consists of three stages, i.e. vasculogenesis, branching angiogenesis and non-branching or vascular transformation. Vasculogenesis is the de novo formation of new blood vessels, while angiogenesis is the formation of new capillaries or branching of existing blood vessels [7].

An imbalance between angiogenic and anti-angiogenic factors is closely related to the pathophysiology of PE and FGR [13]. During angiogenesis, differentiation of cytotrophoblast cells forms a column of cells ending in the superficial part of the endometrium, followed by interstitial invasion into the decidua basalis and endovascular invasion into the spiral arteries. During pregnancy, trophoblast cells cause remodeling of the spiral arteries through pseudovasculogenesis [7]. In early pregnancy (<6 weeks gestation), the spiral arteries have high resistance and low capacity. However, the invasion of endovascular cytotrophoblast causes smooth muscle cell breakdown. It causes remodeling of the spiral arteries, thereby reducing the resistance and increasing the flow capacity of the spiral arteries. Poor vascular development leads to intrauterine embryo death, and insufficient angiogenesis is also associated with PE and FGR. Although the exact cause of the abnormal vascularization is unknown, it is related to a deficiency of angiogenic growth factors. VEGF is one of the angiogenic growth factors that decreased in PE and FGR [14].

III. Immunological Processes of Placental Implantation and Its Association with PE and FGR

The greatest contact area between maternal and fetal immunocompetent T cells is on the surface of the trophoblast villi. Placental trophoblast cells play a crucial role in maintaining immunotolerance to the fetus. During implantation, EVT emerges from the tips of the villi and invades the decidua, creating a boundary between the mother and the fetus or the maternal-fetal interface. The decidua has a large population of maternal immune cells that interact extensively with fetal-derived trophoblasts. Nearly 40% of decidual cells are leukocytes [15]. EVT avoids the detection of maternal immune cells while promoting immune tolerance by expressing a set of significant molecules—unique major histocompatibility complex (MHC). There are two classes of MHC I, i.e. classical and non-classical. The classic class I MHC molecules, consisting of Human Leukocyte Antigen (HLA)-A, HLA-B, and HLA-C, are ubiquitous polymorphic proteins dedicated to peptide presentation to cytotoxic T cells. These class of MHCs can present many antigens, including foreign antigens. If cells express these foreign antigens, they will be attacked by cytotoxic T lymphocytes (CTL). Non-classical MHC I are not polymorphic and expresses "zero antigen" by all three known classes, i.e. HLA-E, HLA-F, and HLA-G. This HLA is soluble and expressed on the entire surface of the villous trophoblast (villous and extravillous trophoblast). Unlike most cells, EVT does not express HLA-A and HLA-B but expresses only HLA-C and non-classical MHC molecules HLA-E and HLA-G, which are non-polymorphic [16].

Tolerance is induced by HLA-G, which is known to enter the maternal circulation and binds to leukocyte immunoglobulin-like receptors (LIR-1 and LIR-2) on uterine natural killer (NK) cells, macrophages, and T lymphocytes [17]. Communication between MHC I and leukocytes (uNK cells, macrophages, and T lymphocytes) is important for inducing and maintaining maternal tolerance during physiological pregnancy [18]. The presence of HLA-G protein in the preimplantation embryos has been reported [19]. Downregulation of HLA-G is reported to be associated with poor placentation in PE and immune cell infiltration during ascending infection [20].

The decidual lymphocyte subpopulation differs dramatically from their peripheral counterparts. The human endometrium is usually filled with T cells, macrophages, NK cells, and limited amount of B cells. However, during the late luteal phase and early pregnancy, nearly 70 to 90% of endometrial lymphocytes are believed to be uterine-specific NK (uNK) cell variants, and 10-20% are antigen-presenting cells (APCs) such as macrophages and dendritic cells. Human decidual NK cells have been shown to play an essential role in spiral artery remodeling and trophoblast invasion [21], [22]. Peripheral NK cells exhibit strong cytotoxic activity and are involved in the defense against infection and neoplasia. In contrast, uterine NK cells show limited cytotoxic activity. These unusual cells are variously called decidual granular lymphocytes (DGL), large granular lymphocytes (LGL) and

decidual NK cells. Ligands on the surface of NK cells recognize MHC Class I products which can be either inhibitory or activating [23].

The categorization of NK cell receptors is complex and differs between species. In humans, NK receptors fall into two main subcategories, i.e. immunoglobulin-like inhibitory receptors (KIRs) and lectin-like heterodimers composed of the CD94/NKG receptor complex. KIR molecules of both activating and inhibitory subtypes have been shown to recognize HLA-C locus molecules, while both CD94/NKG receptor activating and inhibitory complexes recognize HLA-E molecules. HLA-G can also interact directly with various NK receptors, with some outcomes depends on the state of cell activation [23]. The correlation existing between maternal killer cell immunoglobulin-like receptor (KIR) and HLA-C in trophoblast cells constitutes robust evidence for the genetic etiology of PE. The combinations of the two kinds of gene systems, together with the KIR genotype in the mother and the HLA-C group in her fetus, are likely to exactly decide the pregnancy outcome. The women, who have the inappropriate match of KIR/HLA-C, are likely to be prone to the augmented risk of PE [24].

In addition to HLA and NK cells, preimplantation factor (PIF), a small peptide secreted by viable embryos, may also play an important role in maternal recognition leading to semi/allogeneic embryo tolerance [25]. PIF is detected since the embryo enters the two-cell stage and is associated with embryonic development. PIF has an autotrophic effect on embryonic development, inhibited by anti-PIF antibodies. In embryos, PIF targets protein-disulfide isomerase/thioredoxin and heat shock proteins (HSPs), promoting embryonic development and protecting against maternal serum toxicity. In addition, PIF reduces the toxicity of natural killer (NK) cells. PIF promotes endometrial receptivity to support embryo implantation [26]. PIF significantly promoted invasion of human EVT isolated from first-trimester placenta. The proinvasive regulatory effect of PIF in EVT was associated with increased MMP9 activity reduced tissue inhibitor of metalloproteinase-1 (TIMP1) mRNA expression [27]. Thus, PIF is involved in pathological pregnancies characterized by insufficient or excessive trophoblast invasion.

Both PIF and HLA-G are secreted by living embryos and interact intimately from the early stages of embryonic development. This interaction continues, with PIF and HLA-G present in the circulation in subsequent pregnancies. PIF and HLA-G are expressed by the trophoblast, as PIF is expressed by living embryos immediately after fertilization and by trophoblasts immediately after implantation. Therefore, both ligands may play a local regulatory role in trophoblast HLA class I function. The effects of PIF can be compared to that of progesterone (P4), which is known to be a HLA-G/HLA-E regulator. PIF regulates endogenous P4 activity, and Th1/Th2 cytokine secretion has also been identified. PIF regulates the increase of several HLAs, potentiates progesterone's action, and promotes the secretion of Th1/Th2 cytokines by trophoblast cells [26]. These observation provides insight into putative mechanisms of PE and the role of PIF. PIF promotes implantation, endometrium receptivity, trophoblast invasion and increases pro-tolerance trophoblastic HLA-G expression. Furthermore, PIF protects against oxidative stress and protein misfolding, interacting with specific targets in embryo [28]. Thus, PIF is a potential target for early preventative PE intervention.

IV. The Role of Cytokines in Placental Implantation and Its Association with PE and FGR

The level of cytokine, prostaglandin, and leukocyte counts are increased in the human endometrium during implantation [29]. The level of chemokines and cytokines produced by endometrial cells increase gradually, guiding the blastocyst to the implantation site allowing its interaction with the endometrium. Trophoblast cells penetrate the epithelial and stromal cells during the invasion. Endometrial tissue is repaired and renovated by the growing placenta. In humans, implantation processes mimics local wound healing and characterized by a strong Th1 inflammatory response. High pro-inflammatory cytokines such as IL-6, LIF, IL-8, and TNFα are involved. These cytokines and chemokines recruit immune cells into the decidua and large populations of human decidual leukocytes into the implantation site [26].

The potential role of cytokines during implantation is broad, as cytokines are involved during apposition, adhesion, early and late invasion. The main cytokines involved consist of interleukin 1 (IL-1), leukaemia inhibitory factor (LIF), macrophage colony-stimulating factor (M-CSF), and immune response T helper 1 (TH1) cytokine IFN-γ, IL-2, IL-12, TNF-β and T helper 2 (TH2) immune response cytokines IL-4, 6, 10 and 13. IL-1, LIF, and M-CSF appear to exert their effects during apposition and adhesion. In contrast, TH1 and TH2 immune response cytokines can influence subsequent events in the invasion phase [30].

The predominance of TH2 found in early pregnancy is due to increased progesterone levels. In addition to increasing the secretion of TH2 cytokines, progesterone inhibits the secretion of TH1 cytokines. In particular, IL-4 and IL-6 levels are increased, while IL-2, IL-12 and IFN-γ levels are decreased. The embryo directly contributes to the TH2 dominance by secreting IL-10 and transforming growth factor (TGF-b). Women with recurrent miscarriages have impaired TH2 responses (reduced IL-4, IL-6, and IL-10) and may even exhibit TH1 predominance. Decreased expression of TGF-β and IL-10 mainly secreted by TH 2, regulatory T cells (Treg) or activated macrophages (M2), and increased expression of IL-17 cells by TH17 have been reported to participate in maternal immune rejection toward the fetus [31]. PE is associated with an exaggerated inflammatory state and predominance of TH1 and TH17 immunity [32].

Treg cells, generally defined as CD4+CD25+ cells expressing the transcription factor Foxp3, anti-inflammatory and immune suppression. A vital feature of the pregnancy-specific immune response is the presence of Treg cell. Treg cells are potent suppressors of Th1 and Th17 cell-mediated inflammatory and immune events. Treg cells are essential for preventing exogenous and self-antigen immune reactions through various mechanisms, including inhibition of T cell proliferation and cytokine production, suppression of B cell proliferation and antibody production, prevention of NK cell cytotoxicity and inhibition of dendritic cells and macrophage maturation and activation. Treg cells suppress via paracrine mechanism involving the production of the cytokines TGFB

and IL10 [33]. Impaired Treg activity has been associated with the development of PE [34], [35].

Dendritic cells (DC) are in the right place at the right time to promote Treg cell proliferation before implantation. The population is abundant in endometrial tissue at ovulation. A specific phenotype of dendritic cells known as 'tolerogenic dendritic cells' controls the activation and expansion of Treg cells. Uterine dendritic cells express markers suggesting a tolerogenic phenotype that will be retained by GM-CSF, IL4 and IL10 produced by uterine tissue. Trophoblast-derived IL-9 promoted the immature differentiation of CD4+ DC, and induced the secretion of Th2 cytokines, including IL4 and IL10, shifting the Th1/Th2 ratio to Th2. IL-9 secretion is decreased in PE and thus, may impair the regulation of DC activity [36].

V. Molecular Pathology of the Placenta in PE

The clinical syndrome of PE arises from systemic circulatory disturbances secondary to widespread maternal endothelial dysfunction. The observation that there is an abnormal interaction between maternal tissues, paternal, and fetal causes of PE has led to the hypothesis that this syndrome consists of two stages (two-stage disorder). The concept of a two-stage disorder in PE, which Redman and colleagues introduced, states that in the first stage, trophoblastic endovascular remodeling disorder ends with reduced placental perfusion (stage 1), resulting in factors that cause clinical manifestations of PE (stage 2) [37]. The first stage is an asymptomatic, preclinical stage, while the second stage is the clinical impact that manifest on both mother and fetus due to placental ischemia.

The early stage of PE is characterized by a hypoxic and dysfunctional placental state, which in turn causes oxidative stress to the placenta [37]. Placental hypoxia and/or ischemia accompanied by excessive oxidative stress triggers the release of placental factors into the maternal circulation, which then causes a systemic inflammatory response and endothelial dysfunction, the prominent components of PE. These factors include anti-angiogenic factors (sFlt, sEng), inflammatory mediators (TNF-a, IL-6), immune cells (neutrophils, monocytes, NK cells, T cells), and angiotensin-1 autoantibodies [38]. These molecules in the maternal circulation cause exaggerated inflammatory response and increase the oxidative environment (ROS, such as superoxide, and RNS such as peroxynitrite) in the blood vessels. This sequence of events further causes endothelial activation and dysfunction characterized by increased vasoconstriction, decreased vasodilation, and altered angiogenesis processes. This imbalance causes a systemic maternal response in increased blood pressure and vascular resistance in all organs, including the placenta. Increased constriction of the uterine or placental arteries causes a negative feedback loop, which results in an even more difficult ischemic situation in the placenta [39].

Recent data suggest that endothelial dysfunction in PE is the result of an angiogenic imbalance [40]. The syncytiotrophoblast releases many bioactive factors into the maternal circulation in a hypoxic state. One of them is a soluble receptor for vascular endothelial growth factor (sVEGFR-1) called soluble Fms-like tyrosine kinase 1 (sFlt1). These are anti-angiogenic factors that potentially bind and inactivate pro-angiogenic factors, such as VEGF in the circulation and other target tissues such as the kidneys. VEGF is a key factor in endothelial resistance, and the inactivation of these factors leads to systemic endothelial dysfunction [41].

VI. Molecular Pathology of the Placenta in FGR

FGR is caused by placental dysfunction, which result in abnormalities in the transfer of oxygen and nutrients from the placenta into the fetus, leading to fetal hypoxia and growth abnormalities [42]. It is well known that the placenta in FGR is smaller and has increased maternal and fetal vascular lesions. Maternal vascular lesions were observed in 50% of placentas in pregnancies with FGR at term, compared to only 20% in normal pregnancies, and fetal vascular lesions were observed in 11% versus 4% in normal pregnancies. Furthermore, there is an association between an abnormal umbilical artery 2D Doppler flow study and a recent 3D Doppler study that demonstrated deterioration of placental function and abnormal villous branch development, represented by high maternal and fetal placental vascular lesions [43].

The bi-layered trophoblast of villi shares a basement membrane that lines the villous core, which contains fetal blood vessels that pass through a connective tissue matrix. Although the placental function is essential at all stages of gestation, nutrient transport requires the chorioallantoic villi in general, especially the villous trophoblast, and peaks at the time the fetal weight gain triples in the third trimester of gestation. Thus, villous trophoblast apoptosis increases with pregnancy and causes villous injury that a compensatory increase in cytotrophoblast proliferation may not accompany. The imbalance between damage and repair and developmental abnormalities of the villous branches is a feature of the placenta in FGR [44].

VII. Conclusion

The main aspects of good placentation are the invasion of extravillous trophoblasts (EVT) and the transformation of the decidual portion of the uterine spiral arteries to ensure access to oxygen into the maternal circulation and nutrients for the placenta and the developing fetus. If the process of arterial remodeling is disrupted, this condition will lead to the release of necrotic and aponeurotic trophoblast fragments culminating in the maternal systemic inflammatory response. Failure of EVT invasion correlates with the incidence of PE and FGR. Increased knowledge on the molecular pathophysiology of placental development can improve the clinical management and the prognosis of PE and FGR. Hopefully, future studies will add to a deeper understanding into the pathophysiology and the role of the placental development in both PE and FGR.

References

[1] Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2013; 170(1): 1-7.

[2] Bujold E, Roberge S, Lacasse Y, Bureau M, Audibert F, Marcoux S, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *Obstet Gynecol*. 2010; 116(2 Pt 1): 402-414.
[3] Spinillo A, Gardella B, Adamo L, Muscettola G, Fiandrino G, Cesari S. Pathologic placental lesions in early and late fetal growth restriction. *Acta Obstet Gynecol Scand*. 2019; 98(12): 1585-1594.
[4] Egbor M, Ansari T, Morris N, Green CJ, Sibbons PD. Morphometric placental villous and vascular abnormalities in early- and late-onset pre-eclampsia with and without fetal growth restriction. *BJOG*. 2006; 113(5): 580-589.
[5] Mayhew TM, Manwani R, Ohadike C, Wijesekara J, Baker PN. The placenta in pre-eclampsia and intrauterine growth restriction: studies on exchange surface areas, diffusion distances and villous membrane diffusive conductances. *Placenta*. 2007; 28(2-3): 233-238.
[6] Staun-Ram E, Shalev E. Human trophoblast function during the implantation process. *Reprod Biol Endocrinol*. 2005; 3: 56.
[7] Veerbeek JH, Nikkels PG, Torrance HL, Gravestejin J, Uiterweer EP, Derks JB, et al. Placental pathology in early intrauterine growth restriction associated with maternal hypertension. *Placenta*. 2014; 35(9): 696-701.
[8] Furuya M, Kurasawa K, Nagahama K, Kawachi K, Nozawa A, Takahashi T, et al. Disrupted balance of angiogenic and antiangiogenic signalings in PE. *J Pregnancy.* 2011; 2011: 123717.
[9] Varberg KM, Soares MJ. Paradigms for investigating invasive trophoblast cell development and contributions to uterine spiral artery remodeling. *Placenta*. 2021; 113: 48-56.
[10] James JL, Boss AL, Sun C, Allerkamp HH, Clark AR. From stem cells to spiral arteries: A journey through early placental development. *Placenta*. 2022; 125: 68-77.
[11] James JL, Saghian R, Perwick R, Clark AR. Trophoblast plugs: impact on utero-placental haemodynamics and spiral artery remodelling. *Hum Reprod*. 2018; 33(8): 1430-1441.
[12] Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. *Circulation*. 2011; 123(24): 2856-2869.
[13] Rana S, Burke SD, Karumanchi SA. Imbalances in circulating angiogenic factors in the pathophysiology of preeclampsia and related disorders. *Am J Obstet Gynecol*. 2022; 226(2S): S1019-S1034.
[14] Ravikumar G, Mukhopadhyay A, Mani C, Kocchar P, Crasta J, Thomas T, et al. Placental expression of angiogenesis-related genes and their receptors in IUGR pregnancies: correlation with fetoplacental and maternal parameters. *J Matern Fetal Neonatal Med*. 2019: 1-8.
[15] Fisher SJ. Why is placentation abnormal in PE? *Am J Obstet Gynecol.* 2015; 213(4 Suppl): S115-22.
[16] Xu X, Zhou Y, Wei H. Roles of HLA-G in the Maternal-Fetal Immune Microenvironment. *Front Immunol.* 2020; 11: 592010.
[17] Rapacz-Leonard A, Dąbrowska M, Janowski T. Major histocompatibility complex I mediates immunological tolerance of the trophoblast during pregnancy and may mediate rejection during parturition. *Mediators Inflamm*. 2014; 2014: 579279.
[18] Pollheimer J, Vondra S, Baltayeva J, Beristain AG, Knöfler M. Regulation of Placental Extravillous Trophoblasts by the Maternal Uterine Environment. *Front Immunol.* 2018; 9: 2597.
[19] Nilsson LL, Hviid TVF. HLA Class Ib-receptor interactions during embryo implantation and early pregnancy. *Hum Reprod Update.* 2022.
[20] Tantengco OAG, Richardson L, Lee A, Kammala A, de Castro Silva M, Shahin H, et al. Histocompatibility Antigen, Class I, G (HLA-G)'s Role during Pregnancy and Parturition: A Systematic Review of the Literature. *Life (Basel).* 2021; 11(10)
[21] Pan Y, Yang L, Chen D, Hou H, Zhang M, Chen M, et al. Decidual macrophage derived MMP3 contributes to extracellular matrix breakdown in spiral artery remodeling in early human pregnancy. *J Reprod Immunol.* 2022; 150: 103494.
[22] Liu Y, Gao S, Zhao Y, Wang H, Pan Q, Shao Q. Decidual Natural Killer Cells: A Good Nanny at the Maternal-Fetal Interface During Early Pregnancy. *Front Immunol.* 2021; 12: 663660.
[23] Díaz-Hernández I, Alecsandru D, García-Velasco JA, Dominguez F. Uterine natural killer cells: from foe to friend in reproduction. *Hum Reprod Update.* 2021; 27(4): 720-46.
[24] Yang X, Yang Y, Yuan Y, Liu L, Meng T. The Roles of Uterine Natural Killer (NK) Cells and KIR/HLA-C Combination in the Development of PE: A Systematic Review. *Biomed Res Int.* 2020; 2020: 4808072.
[25] Santos ED, Moindjie H, Sérazin V, Arnould L, Rodrigues Y, Fathallah K, et al. Preimplantation factor modulates trophoblastic invasion throughout the decidualization of human endometrial stromal cells. *Reprod Biol Endocrinol* 2021; 9(1): 96.
[26] Hakam MS, Miranda-Sayago JM, Hayrabedyan S, Todorova K, Spencer PS, Jabeen A, et al. Preimplantation Factor (PIF) Promotes HLA-G, -E, -F, -C Expression in JEG-3 Choriocarcinoma Cells and Endogenous Progesterone Activity. *Cell Physiol Biochem.* 2017; 43(6): 2277-96.
[27] Moindjie H, Santos ED, Loeuillet L, Gronier H, de Mazancourt P, Barnea ER, et al. Preimplantation factor (PIF) promotes human trophoblast invasion. *Biol Reprod.* 2014; 91(5): 118.
[28] Barnea ER, Vialard F, Moindjie H, Ornaghi S, Dieudonne MN, Paidas MJ. PreImplantation Factor (PIF*) endogenously prevents PE: Promotes trophoblast invasion and reduces oxidative stress. *J Reprod Immunol.* 2016; 114: 58-64.
[29] Lv J, Shan X, Yang H, Wen Y, Zhang X, Chen H, et al. Single Cell Proteomics Profiling Reveals That Embryo-Secreted TNF-α Plays a Critical Role During Embryo Implantation to the Endometrium. *Reprod Sci.* 2022.
[30] Kim SM, Kim JS. A Review of Mechanisms of Implantation. *Dev Reprod.* 2017; 21(4): 351-59.
[31] Wang WJ, Zhang H, Chen ZQ, Zhang W, Liu X-M, Fang J-Y, et al. Endometrial TGF-β, IL-10, IL-17 and autophagy are dysregulated in women with recurrent implantation failure with chronic endometritis. *Reprod Biol Endocrinol.* 2019; 17(1): 2.
[32] Göhner C, Plösch T, Faas MM. Immune-modulatory effects of syncytiotrophoblast extracellular vesicles in pregnancy and PE. *Placenta.* 2017; 60 Suppl 1: S41-s51.
[33] Granne I, Shen M, Rodriguez-Caro H, Chadha G, O'Donnell E, Brosens JJ, et al. Characterisation of peri-implantation endometrial Treg and identification of an altered phenotype in recurrent pregnancy loss. *Mucosal Immunol.* 2022; 15(1): 120-29.
[34] Jafri S, Ormiston ML. Immune regulation of systemic hypertension, pulmonary arterial hypertension, and PE: shared disease mechanisms and translational opportunities. *Am J Physiol Regul Integr Comp Physiol.* 2017; 313(6): R693-r705.
[35] Steinborn A, Schmitt E, Kisielewicz A, Rechenberg S, Seissler N, Mahnke K, et al. Pregnancy-associated diseases are characterized by the composition of the systemic regulatory T cell (Treg) pool with distinct subsets of Tregs. *Clin Exp Immunol.* 2012; 167(1): 84-98.
[36] Sun Y, Wu S, Zhou Q, Li X. Trophoblast-derived interleukin 9 mediates immune cell conversion and contributes to maternal-fetal tolerance. *J Reprod Immunol.* 2021; 148: 103379.
[37] Redman CWG, Staff AC, Roberts JM. Syncytiotrophoblast stress in PE: the convergence point for multiple pathways. *Am J Obstet Gynecol.* 2022; 226(2s): S907-s27.
[38] Jung E, Romero R, Yeo L, Gomez-Lopez N, Chaemsaithong P, Jaovisidha A, et al. The etiology of PE. *Am J Obstet Gynecol.* 2022; 226(2s): S844-s66.
[39] Gyselaers W. Hemodynamic pathways of gestational hypertension and PE. *Am J Obstet Gynecol.* 2022; 226(2s): S988-s1005.
[40] Margioula-Siarkou G, Margioula-Siarkou C, Petousis S, Margaritis K, Vavoulidis E, Gullo G, et al. The role of endoglin and its soluble form in pathogenesis of PE. *Mol Cell Biochem.* 2022; 477(2): 479-91.
[41] Redman CW, Staff AC. PE, biomarkers, syncytiotrophoblast stress, and placental capacity. *Am J Obstet Gynecol.* 2015; 213(4 Suppl): S9.e1, S9-11.
[42] Kingdom JC, Audette MC, Hobson SR, Windrim RC, Morgen E. A placenta clinic approach to the diagnosis and management of fetal growth restriction. *Am J Obstet Gynecol*. 2018; 218(2s): S803-s17.
[43] Aviram R, Kidron D. Placental aetiologies of foetal growth restriction: clinical and pathological differences. *Early Hum Dev.* 2010; 86(1): 59-63.
[44] Novac MV, Niculescu M, Manolea MM, Dijamarescu AL, Illiescu DG, Novac MB, et al. Placental findings in pregnancies complicated with IUGR-histopathological and immunohistochemical analysis. *Rom J Morphol Embryol.* 2018; 59(3): 715-20.