Immune-Endocrine Alterations During Preeclampsia

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Abstract: Preeclampsia is a pregnancy-related disorder exclusive to human beings, and represents a public health problem worldwide whose etiology is still unknown. As diverse studies have reported, an understanding of the onset and course of this disorder depends on the knowledge about the interaction between the physiological systems of the organism, such as the immune, vascular and endocrine systems. Recently, in Mexican women with preeclampsia we genotyped the family of KIR genes and studied the phenotype of NK cells in peripheral blood and the decidua. Moreover, we are characterizing the proteins, such as HIF-1α and two of its more frequent genetic polymorphisms, as well as the pathways of their activation which participate in placental hypoxia The aim of the current study is to review the most recent contributions regarding the participation of the immune and vascular system during the development of preeclampsia, and the immunoendocrine alterations which result of them.

Keyworks: NK cells, KIR receptors, preeclampsia, angiogenesis, endometrium.

INTRODUCTION

Since the experiments conducted by Calzoari in 1898, which described the changes observed in the thymus of castrated animals, the evidence about the interaction between the endocrine and immunological systems has been accumulating and resulting in an ever greater consolidation of knowledge [1]. One of the principal challenges of immunologists as well as reproduction specialists is to understand these systems and their interactions during pregnancy, since a profound understanding of all the relevant factors is urgently needed. Strict control of complex factors involved in diverse processes, such as steroid hormones, immune system cells, Natural Killer (NK) cells [2-4], signaling molecules (e.g., cytokines and chemokines) [5, 6], growth factors, angiogenic factors, hypoxia factors [7], neurotrophins [8], among others (Fig. **1**), is essential for the healthy acceptance of the fetus (including embryo implantation) and maintenance of a normal pregnancy based on an adequate development and vascularization of the placenta.

Any alteration in the immunoendocrine networks lead to reproductive disorders that include recurrent spontaneous abortions, infertility and preeclampsia (PE) [9]. The latter is a worldwide public health problem, one of main causes of maternal death, and one of the most complex obstetric complications, both for medical practice and research. Although the etiology of preeclampsia is yet to be fully elucidated, various hypotheses incorporating angiogenic, genetic, immunological and endocrinal factors have stemmed from diverse clinical and molecular studies [10]. The complex interrelation of these factors accounts for the wide range of such hypotheses.

The aim of the present study is to describe the principal aspects related to immunoendocrine regulation during pregnancy and their implications for PE. We broach the principal hypothesis of the etiology of PE as well as the immunoendocrine factors of the endometrium, emphasizing the characterization and function of decidual NK cells (dNK) as well as angiogenic factors in the early stages of gestation.

IMMUNOENDOCRINE ASPECTS OF THE ENDOMETRIUM

The endometrium is a tissue that presents cyclical morphological changes, implicating processes of differentiation, proliferation, apoptosis, angiogenesis, vascularization, and recruitment of leukocytes [1]. From the endocrinological point of view, the majority of these processes have been widely studied. For instance, it is well known that during the development of the follicle, the maturation of the oocyte and ovulation, the female reproductive system is under the influence of hormones secreted by the pituitary (FSH and LH) and by the follicle (estradiol and progesterone) [11]. Yet in spite of the general recognition that these processes are accompanied by inflammatory mechanisms, such as the recruitment of lymphocytes, degradation of the extracellular matrix, and changes in the expression of various immune molecules (chemokines, integrins and adhesion molecules), such mechanisms have not been fully studied [12, 13].

The direct action of steroid hormones has been confirmed in isolated lymphocytes of peripheral blood, whose response seems to be sexually dimorphic [14]. This same proposal is held by the Morales-Montor group, which utilizes a murine model of infection and observes that the immune response is different in male and female animals, possibly due to the dimorphic expression of receptors for steroid sex hormones

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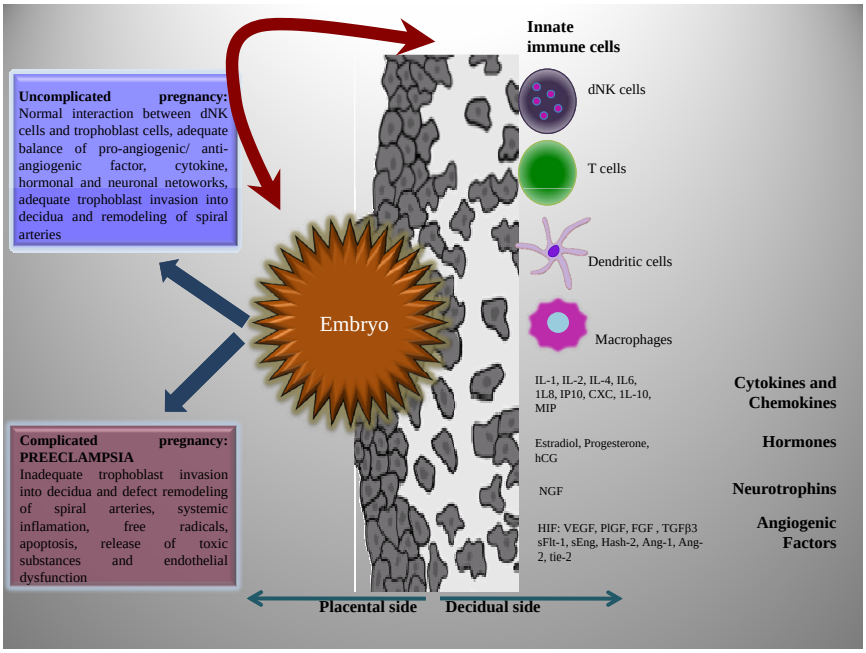

Fig. (1). Cross-talk between the embryo and the another involves the interaction between endocrine and immune systems.

in leukocytes [15, 16]. The implications of this proposal have profound repercussions not only on the current knowledge of the immune response against pathogenic agents and autoimmune diseases.

Whereas receptors for estrogens (alpha and beta) and progesterone have been identified on lymphocytes [14], only those for beta estrogen receptors have been found on decidual NK cells [17]. In the latter case the function of the beta estrogen could also be mediated by steroid sex hormones in an indirect manner, as evidenced by the fact that the stromal cell cultured from the endometrial tissue induces a great quantity of IL-15 when stimulated with progesterone, and that this cytokine is essential for the differentiation of NK cells [18]. The cell lines of NK cells (NK-92 and YT) express the receptor for prolactin and respond to *in vitro* stimulation by this hormone. Prolactin has synergic activity with IL-15, increasing the proliferation and cytotoxicity of NK cells [19].

During the menstrual cycle, the type and quantity of leukocytes that arrive to the endometrium vary depending on the phase of the cycle. During the proliferative phase principally T lymphocytes, macrophages, NK cells and dendritic cells have been detected. In the secretory phase, T lymphocytes diminish, dendritic cells remain constant, neutrophils appear and NK cells are abundant [20-22]. B lymphocytes are practically absent from this tissue during the entire cycle [23]. The functions performed by T lymphocytes, macrophages and neutrophils are directly related to the destruction of the corpus luteum [24]. The role of NK cells is not completely known, but it is thought that they are involved in decidualization [25].

During pregnancy the amount of leukocytes detected in the decidua (a new functional layer of the endometrium during pregnancy) differ from those described during the menstrual cycle. In the stage of embryonic implantation and the first weeks of pregnancy, NK cells constitute the greatest percentage of leukocytes present (70%). The function of these cells has recently been recognized such as the production of cytokines, chemokines and angiogenic factors, which contributes to the formation of the placenta and the vascular changes in the endometrium [26-28]. Although some authors report that this cellular population disappears at the end of pregnancy, recent data from our lab show an important quantity of NK cells in the decidua of women at the end of their pregnancy (data submitted to be publish).

During the menstrual cycle there are three stages in the angiogenic processes, which: (i) repair the vascular bed during menstruation, (ii) work in synchrony with the rapid growth of the endometrium in the proliferative phase, and (iii) facilitate the growth of the arterioles in the secretory phase [29, 30]. The factors that can induce angiogenesis in the endometrium are the epidermal growth factor (EGF), the transforming growth factor α and β (TGF-α y TGF-β), the tumor necrosis factor α (TNFα), angiogenin, prostaglandin E_2 (PGE_2) and the vascular endothelium growth factor (VEGF), among others [31-33]. During the first weeks of pregnancy the angiogenic factors play a crucial role. The regulation of these factors is complex, as they depend on the cellular context and can be induced by changes in the concentration of oxygen, hormones, cytokines and phosphorilation cascades. VEGF is one of the principal inducers of angiogenesis, being essential for the normal growth of the endometrium as well as the implantation and development in the placenta. In consequence, the majority of the studies on angiogenic processes in the endometrium have focused on this factor [34-37].

1. Decidual NK Cells

NK cells comprise 10 to 15% of the lymphocytes in peripheral blood, where their phenotype is characterized by the absence of receptors for antigens and by $CD56^{+}$, $CD16^{+/-}$ surface markers [38]. NK cells can be divided in two subpopulations based on the density of the CD56 marker (bright

to heavy, or dim to medium). 90 to 95% of the circulating NK cells belong to the $CD56^{dim}$ $CD16^{+}$ phenotype and are highly cytotoxic. The remaining 5 to 10% have the $CD56^{bright}$ $CD16^{-}$ phenotype, contain less cytotoxic granules and are very efficient in the secretion of cytokines, especially IFN-γ, TNF-α and IL-6 [39, 40].

NK cells in the decidua during early gestation have been characterized. They possess a $CD56^{brigth}$ $CD16^{-}$ phenotype, are not highly cytotoxic and are very efficient in the secretion of cytokines such as INFγ, IL-10 and TGF-β. At the level of messenger RNA the presence of growth factors for the vascular beds and placenta (VEG-F and PlGF, respectively) have been detected [41, 42]. All of these elements are important in angiogenesis and the remodeling of uterine arteries during pregnancy.

Assays conducted by microarrays have compared NK cells from peripheral blood and decidual NK cells. In the latter cells some genes are found to be exclusively expressed, while others (such as those related with angiogenesis) are over expressed, suggesting that these two subpopulations of NK cells are quite distinct in the decidua [41, 43].

Jacob *et al.* (2006) recently demonstrated, through *in vitro* and *in vivo* studies, that NK cells participate in the invasion of the trophoblast, angiogenesis and the remodeling of the uterine arteries. When isolated decidual NK cells and those from peripheral blood are co-cultivate with a trophoblast cell line, only the former are capable of promoting migration, invasion and angiogenesis of these cells [28].

Another study done by Smith *et al.* (2009) suggests that NK cells participate in the uterine arterial remodeling, even independently from their interaction with trophoblast cells. That is, in the vascular remodeling phase, during which there were no trophoblast cells, the secretion of metalloproteinases by NK cells to the extracellular matrix favored the loss of vascular smooth muscle and as consequence the beginning of remodeling the vascular bed [44].

The mechanism by which decidual NK cells allow for the arrival and invasion of trophoblast cells to the decidua remains an enigma. From the immunological point of view, the trophoblast is a foreign agent that must be eliminated by the maternal immune system. Nevertheless, not only does it fail to be eliminated, on the contrary its implantation and invasion to the maternal decidua is promoted.

It has been suggested that the interaction of ligands expressed in trophoblastic cells, such as HLA-G, with NK cells receptors is responsible for the inhibition in the latter cells and their cytotoxic activity [45]. Kopcow *et al.* (2005) have demonstrated that the low cytotoxic capacity of decidual NK cells owes itself to their inability to form mature synapse activators, or to polarize the organizing centers of microtubules and granules that contain perforins facing the synapse [46].

2. Angiogenic Factors

The preservation of the morphology and function of villus as well as the regulation and differentiation of trophoblasts are critical for the placentation [47, 48]. In the first 8 weeks, a pregnancy develops in an environment of hypoxia, in which trophoblasts are maintained in a proliferative state and relatively undifferentiated, with an uninvasive phenotype. From 10 to 12 weeks of gestation, the rapid increase in the concentration of oxygen promote the process of differentiation and invasion by trophoblasts [48, 49].

Under hypoxic conditions, the hypoxia inducible factor alpha (HIF-α) is activated, and this transcription factor induces angiogenic and non-angiogenic factors [34]. Angiogenic factors are indispensable for the normal development of the placenta, principally in relation to proliferation and vascularization processes and during the migration of trophoblastic cells towards the maternal region. Among the most important angiogenic factors are: VEGF, its VEGFR-1 (Flt1) and VEGFR-2 (KDR) receptors, the fibroblast growth factor (FGF), the platelet growth factor (P1GF) and angiopoyetin (ANG) [34, 50].

Studies on mice embryos demonstrate that the knockout of the VEGF gene presents an abnormal development of blood vessels and placenta formation, resulting in cardiovascular defects and causing the death of the product at day 11 of gestation. In addition, the heterozygote knockout of this gene, express low levels of VEGF leading to fetal and placental defects similar to homozygote, and causing death of the product at 11-12 days of gestation. A null mutation in the KDR receptor during pregnancy produces defects in the differentiation of the hemangioblasts, precursors of hematopoietic and angioblast cells. Embryos that lack the VEGFR-1/Flt-1 receptor develop angioblasts, but fail to form blood vessels [51-54]. In the human placenta, the union of VEGF with its Flt-1 receptor induces chemotaxis, stimulating the trophoblast invasion [55]. VEGF has also shown itself have many actions on endothelial cells such as: stimulator of the proliferation and migration, induction of an activator of the plasminogen and, an inducer of microvascular permeability [56-58]. PIGF is a weak inducer, compared to VEGF, of chemotaxis and proliferation of endothelial cells, possibly because it binds to the Flt-1 but not to the KDR receptor [59, 60].

FGF stimulates proliferation of endothelial cells as well as uterine and placenta arteries, and induces the differentiation of the embryonic germinal layers, principally of the mesoderm [61, 62]. VEGF and FGF have been associated with the regulation of placental blood flow and the production of nitric oxide (NO), a vasodilator that mediates the increase in uterine blood flow induced by estrogens [63-65].

HIF-α also can induce inhibitors of trophoblast differentiation, such as the transforming growth factor β3 (TGFβ3) and Hash-2. Consequently, during the first 8 weeks of gestation, trophoblasts remain in a relatively undifferentiated and non-proliferate state. To the extent that the gestation age progresses and the concentration of oxygen increases, the expression of HIF-α decreases, resulting in diminished levels of its target genes and the complete differentiation of the trophoblasts [66, 67].

It is commonly recognized that during pregnancy the regulation of angiogenic factors is related to the concentration of oxygen, since the main regulator of these factors, HIF-α, is regulated in this respect [68-71]. However, a normal pregnancy involves immunological and endocrine factors as well. A less explored area is the role played by hormones in the regulation of angiogenic factors, although some studies have indeed been done to establish the influence of

hormones in angiogenic processes in the endometrium [72-74].

Angiogenesis in the endometrium involves processes of proteolytic degradation of the extracellular matrix, proliferation and migration of endothelial cells, and the formation of capillary vessels that supply blood for the growth of the endometrium. VEGF is an important factor in the regulation of these processes, as it is known that the interaction of VEGF with its VEGF-R2 receptor induces the recruitment and proliferation of endothelial cells, while interaction with its VEGF-R1 receptor induces endothelial cells to form capillary vessels and promotes their interaction with tightly bound proteins [51, 52]. Ang-1 and tie-2 participate in the maturity of these vessels that promote the recruitment of perycites to them [75, 76]. On the other hand, Ang-2 can bind to tie-2, thus competitively inhibiting Ang-1 and causing the rupture of blood vessels. It has been speculated that this process has the aim of preventing the basal membrane from enclosing the endothelial cells, thus allowing VEGF to have access to these cells in order to induce proliferation [77, 78].

The regulation of the angiogenic factors in the endometrium is very complex. The first studies on rhesus monkeys suggested that during menstruation there is an environment of hypoxia and ischemia in the endometrium [79]. Nonetheless, studies in women that used different techniques for determining blood flow in the endometrium (xenon-133, doppler) did not show a low concentration of oxygen, which led to the questioning of former assumptions [80, 81].

It is known that steroid sex hormones play an important role in the remodeling of the endometrium during the menstrual cycle. Although the detection of receptors for steroid hormones and the discovery of their mechanism of action has been the subject of intense study in endothelial cells, there is still controversy about the expression of these receptors in endometrial endothelial tissue and their possible role in angiogenesis. On the one hand, there is evidence of an important participation of these hormones in angiogenesis [82, 83]. Studies on stromal cells *in vitro* found that estradiol and medroxiprogesterone acetate increase expression of the mRNA of VEGF, and experiments in rat uterus showed that estradiol (E_2) and progesterone also augment the expression of this factor [37, 84-87].

On the other hand, there is contradictory evidence about the location and regulation of the expression of estrogen response elements (EREs) in the promotor of the VEGF gene [88-94]. Stoner *et al*. (2000 and 2004) demonstrated that the alpha receptor for estrogens (ERα) does not interact directly with EREs on VEGF, but in fact does so with Sp1 and Sp3 transcription factors, which interact with the VEGF promoter after being induced by estradiol [95, 96].

In order to identify the transcription factors that interact with the VEGF promoter, Kazi *et al*. (2005) studied the effect of E_2 on the expression of VEGF by immunoprecipitation assays done with chromatin, finding that E_2 induces the recruitment of ERα and HIF-α to the VEGF promoter. The binding of HIF-α to the VEGF gene is transitory and is in accordance with the expression pattern of VEGF in the endometrium. ERα interacts with the VEGF promoter through the bond with Sp1 and Sp3. The binding of ERα with these factors is maintained even though the levels of the VEGF messenger diminish, which suggests that other factors are probably involved in its expression. It has also been demonstrated that the binding of HIF-1α to the VEGF promoter is necessary for the induction of the latter mediated by E_2 [97].

Other studies conducted on cell lines show that the expression of this factor increases through the influence of other hormones, growth factors and cytokines under conditions of a normal oxygen supply [98-101].

The increase in the expression of HIF-1α by diverse factors has been associated with its activation by phosphorylation. These factors stabilize HIF-1α and at the same time increase its expression levels and transcriptional activity. HIF-α can be phosphorylated by the PI3K and MAPK signaling pathways, and these can be activated by E_2 [102-104]. The angiogenic processes in the endometrium during pregnancy have still not been fully clarified and require further study.

PREECLAMPSIA

In the first trimester of pregnancy and the normal development of the placenta, great changes take place in the uterine vascular system. Extravillous trophoblast cells invade up to the first third of the myometrium in the uterine wall and interact with spiral arteries, replacing the vascular wall and causing arteries of the placenta and uterus to distend. As a consequence, the blood flow to the uterus increases, allowing for an adequate perfusion and a supply of sufficient nutrients for fetal growth [105, 106].

Preeclampsia is characterized by a deficient development of the placenta, accompanied by a superficial endovascular invasion of the trophoblast and an inadequate remodeling of spiral arteries in the decidua and myometrium. The result is placental hypoperfusion, oxidative stress and an exacerbated inflammatory response, leading to clinical manifestations in the mother, such as hypertension, proteinuria and/or indications of multi-systemic disorders, as well as the restriction of intrauterine fetal growth [10, 107, 108]. The principal hypotheses about the etiology of preeclampsia involve neuroendocrine and immunological factors, the most accepted being the immunological hypothesis and the angiogenic hypothesis [109].

1. Immunological Factors in PE

As aforementioned, at the moment of embryonic implantation the maternal decidua is completely infiltrated by NK cells. The specific recognition of trophoblast ligands by NK cell receptors causes the interaction of these two factors. The effector functions of NK cells depend on a very fine regulation between inhibitory and activating receptors, which can belong to distinct structural families: Immunoglobulin-like receptors (KIR), type C heterodimeric receptors of lectin (CD94/NKG), immunoglobulin-like transcripts (ILT) and cytotoxic receptors of NK cells (NCR) [110].

KIR receptors recognize histocompatibility molecules of the trophoblast, specifically HLA-G and HLA-C, the latter of which is the only highly polymorphic HLA expressed in trophoblast tissue. The interaction between the HLA molecules of the trophoblast and KIR receptors of maternal endometrial NK cells inhibits the cyotoxic activity of the latter cells and modulates their production of cytokines and growth

factors, thus favoring the growth of the trophoblast, the invasion of the endometrium and vascular remodeling, which are all necessary for the normal development of the placenta [111-113].

There are at least 14 different members of the family of KIR receptors. A study conducted on Caucasian women, which compared the genotype of KIR receptors in women with normal pregnancies and those with PE, found that the presence of genotype AA (inhibitor), particularly the *KIR2DL1* gene, in women with PE, combined with the HLA-C of group 2 in their babies increased the prevalence of this disorder. The frequency of this combination was two-fold greater in women with PE, representing an almost 50% greater frequency than in women with normal pregnancies. Given that this interaction is considered to be a strong inhibitory signal for NK cells, and that the over inhibition of decidual NK cells would avoid the adequate formation of the placenta caused by the secretion of cytokines and factors of vascular remodeling, it is probably the inhibition and not the activation of NK cells that predisposes women to PE. Contrarily, the presence of activating receptors could be a protective factor [114, 115].

2. Angiogenic Factors in PE

In the trophoblast of women with PE, the over expression of HIF-α and its target proteins has been found. These are principally non-angiogenic factors: soluble fms-like tyrosine 1 (sFlt-1) and soluble endoglin (sEng). Additionally, inhibitors of trophoblast (TGFβ3) differentiation have been found. sFlt-1 is a truncated variant of the membrane receptor VEGFR1, which antagonizes VEGF and P1GF. sEng acts in the same manner through its soluble receptor for TGF-β1 [66, 116-118]. In women with PE a decrease in angiogenic factors and an increase in anti-angiogenic factors have been observed. Moreover, inhibitors of trophoblast differentiation have been found, which coincides with the phenotypes found in the placentas of these patients, characterized by an inadequate invasion due to an immature trophoblasts [119].

The imbalance between angiogenic and non-angiogenic factors has been proposed as one of the principal causes of the development of PE. Since HIF-α is the principal regulator of such factors, various work groups are studying the different pathways that could be responsible for its over expression in the placenta of women with PE [120, 121].

One of the most important and best characterized regulatory pathways of HIF-α is degradation by polyubiquitination, which depends on the concentration of oxygen [122]. The HIF protein is a heterodimeric transcription factor (HIF-α y HIF-β). The best characterized isoforms are HIF-1α y HIF-2α, whose transcriptional activity is regulated through two transactivation domains, N-TAD and C-TAD, located towards the extreme COOH-terminal [123, 124]. HIF-1α is directly regulated by a complex with ubiquitin E_3 ligase activity. This complex, formed by the von Hippel Lindau protein (pVHL), elongin C and B, Cu12, and the E_2 enzyme conjugated with ubiquitin and Rbx1, is responsible for the polyubiquitination of HIF1-α, leading to its degradation by the 26S proteasome [125].

In the presence of oxygen, HIF-α is enzymatically hydroxylated by members of the EGLN1-3 or PHD1-3 family in an N-TAD domain, referred to as oxygen dependent degradation domain (ODDD) [126-128]. Under conditions of scarce oxygen, HIF-α is stabilized, translocated to the nucleus, and dimerized with HIF-β, forming an active complex that binds with response elements in the promoter of its target genes, allowing for its transcription [126, 127].

Rajakumar studied diverse proteins that participate in this route of degradation, looking for the probable cause of the over expression of HIF-α. Whereas no differences in the expression of pVHL were found between the placenta of women with normal pregnancies and those with PE, in the latter cases an increase was observed in hydroxylase PHD-3, which may participate in reestablishing the concentration of HIF-α [129, 130].

Currently we are studying other proteins involved in the regulation of HIF-α. The results indicate that there are differences in the expression of pVHL in women with severe PE versus those who are normotensive with mild PE. Furthermore, we have analyzed different hydroxylases that participate in this pathway and like Rajakumar have found an increase in the expression of some of the HIF-α hydroxylases (data submitted to be publish).

The expression of HIF-α could also be modified by genetic factors. Yamada *et al*. (2005) have described 35 polymorphisms of the HIF1A gene, three of which are located in coding regions S28Y, P582S and A588T [131]. Tanimoto *et al*. (2003) explained that the presence of P582S and A588T polymorphisms can increase the transcriptional activity of this gene in comparison with the common isoform [132]. Heino *et al*. (2008) studied these polymorphisms and their relation to the development of PE in a Finnish population, without finding any correlation between the presence of these variants of the HIF1A gene and the development of PE [133]. In a Mexican population we have found frequencies of these polymorphisms similar to those in other populations. Like Heino *et al*., we did not observe any significant difference in these polymorphisms between pregnant normotensive women and those with PE, suggesting that other factors associated with HIF-α probably participate in the development of this disorder.

Diverse studies have indicated that 2-metoxioestradiol (2-ME) destabilizes the formation of microtubules and inhibits HIF-α [134, 135]. 2-ME is a metabolite produced from E_2 by the catecol-O-metiltransferase (COMT) enzyme, which increases its concentration during pregnancy [136, 137]. Kanasaki *et al*. (2008) demonstrated that mice with a COMT deficiency acquire a phenotype with characteristics similar to PE. They found that the levels of COMT and 2-ME were significantly less in women with PE compared to those who were pregnant and normotensive. In this way, they managed to establish the first model of human like-PE in mice and suggested that COMT and 2-ME could be good markers in the clinical diagnosis of PE [138].

Angiogenic factors are also regulated by immunological factors. Fons *et al*. (2006) demonstrated that the soluble HLA-G1 isoform (sHLA-G1) has anti-angiogenic properties *in vitro* and *in vivo*. In a model of neovascularization in rabbit cornea they showed that sHLA-G1 can decrease angiogenesis by inhibiting FGF [139].

Angiogenic factors have a fundamental participation in the normal development of the placenta. Hence, alterations in factors that regulate angiogenesis, such as HIF-α, COMT, 2-ME and HLA-G, are probably related to the development of PE.

CONCLUSION

Owing to the complexity of the regulation of placentation, it is important to continue developing an integral analysis of the distinct pathways involved, as well as of all of the other molecular and genetic mechanisms that could participate in the etiology of PE, especially in relation to the immune and endocrine systems. Such an integral analysis of the etiology of PE based on a better understanding of all of the factors of the physiopathology of the development of the placenta in women with PE could facilitate the discovery of better treatments for affected women.

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