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Preeclampsia and Inflammation: Inflammation Biomarkers

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SUMMARY

Pre-eclampsia (PE) is an important cause of maternal and perinatal mortality affecting 3% to 5% of pregnant women. The aetiology of the disease is unknown but recent studies have revealed that this disorder appears to originate in placenta and is characterised by widespread maternal endothelial dysfunction. Hypoperfusion, hypoxia, and ischemia, the chief factors in the pathogenesis of preeclampsia, lead to the release of many inflammatory factors by the placenta into the maternal circulation. These factors cause maternal endothelial dysfunction and subsequent systemic signs and symptoms of pre-eclampsia. Several inflammatory biomarkers such as CRP , transforming growth factor –b, tumor necrosis factor –a , interferon-g ,leptin, free radicals, changes in lymphocyte population in blood, IL-10 and others cytokines are associated with PE . As PE is an important cause of maternal and perinatal mortality in the world, in future studies it will be important to determine whether these markers play a causal role in the process in order to have a better prognosis, diagnosis and understanding to this disorder. The aim of this manuscript is to study the relation between preeclampsia and inflammation as well as the literature on the inflammation marker of PE.

INTRODUCTION

Preeclampsia (PE) is an important cause of maternal and perinatal mortality affecting 3% to 5% of pregnant women [1]. The problem is particularly important in developing countries in where the incidence of hypertensive disorders of pregnancy is higher and maternal mortality rates are 20 times higher than those reported in developed countries [2].

Clinically, arises in the second half of pregnancy and it is defined as the de novo onset of hypertension (arterial pressure exceeding 140/90 mmHg on 2 occasion, at least 6 hours apart) and proteinuria (>300 mg/dl/24h or a dipstick of >= 2+) after 20 weeks of gestation, in a previously normotensine women [3]. Often it is associated with the development of cardiovascular disease, obesity, renal damage and diabetes in adults [4,5].

A number of risk factors increase the risk of developing PE (Table 1). Among the risk factors for the development of PE, obesity insulin resistance and hyperlipidemia stimulate inflammatory cytokine release and oxidative stress, leading to endothelial dysfunction (ED). Although the aetiology of PE is still unknown, the common pathophysiological denominator of all the associated causes is the endothelial dysfunction [6].Factors which cause endothelial dysfunction are poor placental vascular remodelling and placental ischemia, oxidative stress, excessive inflammation, imbalance in antigenic factors and the loss of endogenous protective regulators.

Although the origins of preeclampsia remain unclear, a major cause is the failure to develop an adequate blood supply to the placenta, leading to placental oxidative stress. This results in the excess release of placental factors, such as the soluble fms-like tyrosine kinase-1 (sFlt-1) and the soluble receptor for vascular endothelial growth factor (VEGF), into the maternal circulation, where they trigger an inflammatory response and endothelial dysfunction. Alternatively, preeclampsia can be developed in the presence of a normal placenta in women that are susceptible to systemic inflammation, such as women with chronic cardiovascular disease or diabetes. While clinical management of preeclampsia does not currently include anti-inflammatory agents, current research is focusing on ways to reduce inflammation and oxidative stress.

Table 1: Risk factors for preeclampsia

Chronic hypertensionChronic kidney disease
Autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
Type 1 or type 2 diabetes
Uncontrolled hyperthyroidism
Heritable thrombophilias
Polycystic ovary syndrome
Obesity / insulin resistance
Age older than 40 years and younger than 20 years
Preeclampsia in a previous pregnancy
Maternal preterm birth
Maternal low birth weight
Embryo donation
Pregnancies after oocyte donation, donor insemination (Reproductive technologies)
Limited sperm exposure
primipaternity
Partner who fathered preeclamptic pregnancy with another woman

Family history of Preeclampsia (mother or sister)
Family history of cardiovascular disease
Multifetal gestation
Maternal infections
Pregnancy-related risk factors in the first trimester
Chromosomal abnormality (triploidy, trisomy 13)
Smoking(reduced risk)
Gestational trophoblastic disease
New partner
Pregnancy interval of more than 10 years
First pregnancy

PATHOGENESIS OF PREECLAMPSIA

The placenta is a crucial factor in the pathogenesis of preeclampsia and while the presence of the placenta is essential to the development of the disease, the fetus is not. The pathophysiological process that underlies PE has been proposed to occur in two stages. The first stage is a reduced placental perfusion which lead to placental ischemia and hypoxia; this followed by the second stage, consisting of classical manifestations of widespread endothelial dysfunction, hypertension, proteinuria and edema [7].

The fetus depends on the blood supply from the mother flowing into placental blood spaces via maternal spiral which are the terminal branches of radial arteries that run from the uterus through the deciduas. In normal pregnancies, extravillous trophoblast of fetal origin invades the uterine spiral arteries of the deciduas and myometrium. These invasive throphoblasts replace the endothelial layer of the maternal spiral arteries, transforming them from small high-resistance vessel into large-caliber vessels and thus the increased blood supply needed by the fetus and placenta is accommodated. On the other hand, in PE this transformation is incomplete. Cytotrophoblast invasion of the spiral arteries is limited to the superficial deciduas and does not reach the myometrium resulting in narrow blood vessels which are unable to transport adequate blood to the placenta [8]. In order to compensate the blood flow deficiency, the mother develops hypertension to increase the blood flow, usually at the end of the second or third trimester of gestation [9].

In normal placental development, the cytotrophoblasts in order to promote adequate placental invasion alter their adhesion molecule expression from those that are characteristic of epithelial cells to those characteristic of endothelial cells; this process is referred to as pseudovasculogenesis or vascular mimicry [10,11]. Trophoblasts obtained from patients with preclamptic pregnancies do not show this switching of cell-surface molecule. This leads to abnormal placentation followed by ischemia and the release of soluble factors [12].

Normal pregnancy requires proper placental oxygenation. ROS (reactive oxygen species)

derived from these high fluxes of oxygen are implicated and required for replication, proliferation and cell maturation, embryo development and pregnancy maintenance [13]. In PE due to defective trophoblast invasion, intermittency of arterial blood flow occurs, resulting in periods of ischemia/reperfusion, creating a hypoxic environment which favors oxidative stress, consequent oxidative damage and inflammation [11].

Over the course of pregnancy, the poor and shallow placentation is associated with some complications, such as placental infarcts, abruption of the placenta, intrauterine fetal death in the second trimester of pregnancy, preeclampsia with or without intrauterine growth restriction, intrauterine growth restriction of the fetus and preterm labor or premature ruptures of the membranes [15].

Hypoperfusion followed by hypoxia is also a result of abnormal placental development. Hypoperfusion becomes more pronounced as the pregnancy progresses because the growing uterus and fetus need enhanced blood flow into the vessels; the abnormal vasculature is insufficient for delivering enough blood and oxygen [16,17].

Hypoperfusion, hypoxia, and ischemia which are the chief factors in the pathogenesis of preeclampsia lead to the release of many factors by the placenta into the maternal circulation. These factors cause maternal endothelial dysfunction and subsequent systemic signs and symptoms of preeclampsia.

SYSTEMIC ENDOTHELIAL DYSFUNCTION- MICROPARTICLES (MPS)

There is strong evidence that the placenta of preeclamptic women releases factors into the maternal blood stream which may cause endothelial dysfunction and clinical manifestations of preeclampsia. A relevant outcome of the placenta damage is the shedding of trophoblast cells and trophoblast microparticles (MPS) into the maternal circulation. MPs can originate from different types of cells. Most commonly they originate from platelets (identified by the presence of surface antigens: CD41a, CD42b, CD62P), but also from endothelial cells (CD 144, CD62E, CD31), leukocytes (CD45, CD8, CD4, CD14), and erythrocytes (CD235a) [18]. Recently, Germain et al. have reported circulating microparticles derived from syncytiotrophoblasts, best known as syncytiotrophoblast microparticles [19].

The diffused maternal endothelial dysfunction manifested as increased levels of components of the endothelial extracellular matrix, increased vascular permeability, enhanced vascular resistance, endotheliosis of renal glomerulae, raised plasma levels of fibronectin and von Willebrand factor and platelet aggregation. All of these can be contributed to trophosblast microparticles [20]. MPs are released into the circulation under conditions of cell stress or damage. There has been some evidence of increased levels of platelet, endothelial, and leukocyte MPs in conditions related to endothelial dysfunction and this may reflect the degree of the endothelial dysfunction [21-23].

The main function of MPs is to mediate intracellular communication which leads to modifications in haemostasis, thrombosis, inflammation, and angiogenesis. In the blood stream MPs act as carrier and transport proteins (growth factors, apoptotic factors, receptors, and others) of RNA and DNA fragments from one cell to another [24].

Sargent et al demonstrated the presence of subcellular trophoblast microparticles in the plasma of normal pregnant women [25]. Studies by both Bretelle et al. and Alijotas-Reig et al. have shown that the number of endothelial and platelet MPs are increased in women with uncomplicated pregnancy compared with non-pregnant healthy women. Moreover, a higher number of these vesicles could be detected in healthy women for two months after they have delivered [26,27]. Many investigators have assessed levels of plasma endothelial MPs in pregnancies complicated by preeclampsia [28,29]. This led to the hypothesis that MPs is shed into the circulation of PE patients in higher amounts than in normal pregnancies due to oxidative stress brought about by a poor supply and hypoxia. MPs induce maternal leukocytes and endothelial cells to release proinflammatory cytokines and factors and then an inflammatory state is generated [30].

EVIDENCE OF INFLAMMATION IN PREECLAMPSIA

According to experimental and observatory studies an association between inflammation and endothelial dysfunction has been observed [31,32]. Reedman et al first proposed that preeclampsia arises as a result of an excessive maternal intravascular inflammatory response to pregnancy, which may occur because either the stimulus or the maternal response is too strong and involves both the innate and the adaptive immune system [33]. Soluble markers of neutrophil activation, released in the circulation from the degranulation of activated neutrophils, are increased in preeclamptic patients [34,35]. In PE an enhanced inflammation has been demonstrated through the uncontrolled increased activation of the complement system compared with normal pregnancy. The activation of the complement system amplifies inflammation, promotes chemotaxis of inflammatory cells and generates proteolytic fragments that enhance phagocytosis by neutrophils and monocytes [36]. Thus the etiology of preeclampsia has relation with the maladaptation of immune responses and defective trophoblast invasion.

The activation of the adaptive immune response is characterized by T helper (Th) cells which divided primarily in two subsets Th1 and Th2. In humans Th1 cells secrete inflammatory cytokines especially interferon γ (IFN-γ), tumor necrosis factor (TNF-a), IL (interleukin)-2, IL-6, IL-12 and induce cellular immunity whereas Th2 cells secrete anti-inflammatory cytokines such as IL-4, IL-5 and IL-9 and induce antibody production. IL-10 is secreted by both Th1 and Th2 [37].

Normal pregnancy is characterized by a shift towards Th2-type immunity and the inhibition of cytotoxic Th1 immune response which could be harmful to the fetus [38]. In PE there is a predominance of Th1–type immunity and a tendency for absence of Th2 . Moreover, circulating levels of proinflammatory cytokines such as IL-6, TNFa and the chemokines IL-8, IP-10 (interferong inducible protein 10) and MCP-1 (monocyte chemoattractant protein 1) are elevated in PE [39].

In contrast the same patients exhibited low spontaneous induced expression of Th2 cytokines [40]. An important decisive factor for the induction of either Th1 or Th2 pathway is the presence of certain cytokines during the initial process when antigens are recognized. IL-12 causes the predominance of Th1 cells in preeclampsia [41] while IL-4 dictates the immune response to Th2 [42] and dominates over those of IFN-γ [43].

The production of proinflammatory cytokines in PE may be stimulated by the trophoblast microparticles as these have been shown to stimulate the production of the proinlammatory cytokines IL-6, IL-8, IL-12, and IL-1b by monocytes in PE [44]. In addition to Th1 and Th2 cells, T cells may also differentiate into the distinct lineages of Treg (regulatory T cells) and Th17 (interleukin producing T cells) cells. Th17 cells secrete the proinflammatory cytokine Il-17, mediate potent tissue inflammation and are increased in PE compared to normal pregnancies [45] while Treg cells play key roles in the regulation of inflammation and are significantly lower in PE [46]. These changes are proposed to contribute to the pathophysiology of PE via the induction of unbridled inflammation and endothelial dysfunction [45].

Subsequently the immune responses and the systemic cytokine production are likely to be predominant in the inflammatory functions which might initiate the pathology associated with preeclampsia.

NORMAL PREGNANCY

Normal pregnancy is a state of mild systemic inflammation with evidence for an acute phase reaction and activation of multiple components of the inflammatory network. A mild inflammatory response in a normal pregnancy is actually beneficial to pregnancy and when this inflammatory response becomes amplified it results in the development of PE [47].

INFLAMMATORY BIOMARKERS

During the last decades, a lot of inflammatory biochemical markers have been investigated based on pathophysiological observations of PE. In this chapter examined the most important new inflammatory biochemical markers for the prediction of PE which are responsible for placental dysfunction and inflammatory response.

CRP

CRP protein is a classical acute phase reactant discovered by Tillett and Francis at Rockefeller University in 1930 in the blood of patients with pneumonia [48]. It was crystallized in 1947 and today, over 60 years later, there is still controversy about its physiology and applications in biomedicine. CRP is a member of the pentraxin family of innate immune response proteins compromised of 5 subunits [49,50]. It is produced mainly by the liver and also by adipocytes and vascular smooth muscle cells (VSMC) in response to a rise in interleukin-6 (IL-6) and tissue necrosis factor-alpha (TNF-α) [51]. Circulating CRP values correlate closely with other markers

of inflammation, some of which show similar, though generally less significant, predictive associations [52,53].

CRP has been used routinely as a biomarker to monitor progression of disease and response to treatment in patients with inflammatory diseases [54]. Multiple epidemiological studies provide evidence that CRP can serve as an independent predictor of future cardiovascular events, including risk of hypertension, in nonpregnant populations [55].

In normal pregnancy, there is a small increase of circulating CRP, which begins in the first trimester when the long-recognized leukocytosis or pregnancy is established [56]. As pregnancy advances the systemic inflammatory response strengthens and peaks during the third trimester [57]. These changes are associated with increases in circulating CRP and inflammatory cytokines in the second half of pregnancy [58].

Maternal CRP has been positively correlated with PE in several cross-sectional and longitudinal studies of pregnancies [59,60,61] while Rebelo et al in a metaanalyses suggest that women with higher levels of CRP may have an increased risk of developing preeclampsia and this association seems to be modified by weight status (BMI) [62].

CYTOKINES AND PREECLAMPSIA

Cytokines play critical, essential roles in signaling between cells of the immune system, with a large range of regulatory activities including the recruitment, activation, stimulation, killing, and suppression of immune and nonimmune cells. Cytokines are also involved in several events in pregnancy such as ovulation, implantation, placentation, and parturition [63]. So, many cytokines are under particular interest in the pathological pregnancy outcome and especially in PE.

TRANSFORMING GROWTH FACTOR –BETA (TGF- B)

Transforming growth factor (TGF-β) is a member of the TGF superfamily which is a collection of structurally-related multifunctional cytokines. TGF-β involved in the regulation of trophoblast invasion, proliferation, and differentiation [64]. It is secreted by decidual stroma cells, macrophages and T cells and is present locally at the maternal-fetal interface. Growing evidence indicates that TGF-β1 can be involved in the pathogenesis of PE, possibly through activation of an endothelial cell pathway [65] or regulation of systemic inflammation [66]. This cytokine exerts a regulatory role by a potent negative effect on trophoblast invasiveness to matrix proteins [67].

The results of the meta-analysis of Xun Li et al support that the TGF-β1 869 T>C polymorphism is associated with the risk of PE [68]. Many studies demonstrated the involvement of TGF-β1 in the pathophysiology of PE but the results are conflicting. Some studies have found higher levels of TGF-β1 in PE especially at the third trimester compared with the control group [69-71] while in others there was no difference between PE and normotensive pregnancies [72] .Two studies measuring TGF-β1 levels during the second trimester showed that plasma TGF-β1 levels were significantly lower in the PE group (3.2 and 2.9 ng/mL) than in the normal pregnancy group (5.3

and 4.7 ng/mL) ($p<0.05$ for each study) [73,74]. One of them estimated the PE risk by calculating OR and showed that during the second trimester, women with the highest levels experienced a decreased risk of PE compared to those with the lowest quartile of level (OR = 0.2, 95% CI [0.03, 0.7]) [74].

TUMOR NECROSIS FACTOR – A (TNF- A)

Tumor necrosis factor-α (TNF-α) is an inflammatory cytokine produced by human uterine and placental cells at the early and late stages of gestation and promotes the regulation of trophoblast growth and invasion. Furthermore, TNF-α which is a Th1 type cytokine induce trophoblastic apoptosis, inhibit differentiation and invasion of trophoblast and finally, may be involved in the incomplete invasion of trophoblast to spiral arteries; pathologic processes which leads to PE [75-77]. Preeclampsia is an endothelial disorder and TNF plays a significant role in changing the balance between oxidant and antioxidant, the pattern of prostaglandin production and expression of adhesion molecules in blood vessels [78,79]. In vitro studies have shown that hypoxia/re-oxygenation of placental tissues in vitro increased the secretion of the cytokine and the activation of endothelial cells in a TNF-α-dependent manner [80].

In the last two decades a lot of studies suggested that the levels TNF-a are significantly increased in preeclamptic patients compared with health controls [81,84]. In general, these studies demonstrated that TNF-α is a potent pro-inflammatory cytokine, its primary biological activity includes inflammation and it may contribute to the abnormal placental invasion.

Also in many studies, TNF-a has been shown to elevate leptin protein levels which have been observed to be raised in preeclampsia by several research groups [85,87].

INTERFERON –GAMMA (IFN-G)

Interferon gamma (IFN-g) is a proinflammatory cytokine secreted in the uterus during early pregnancy. It is abundantly produced by uterine natural killer cells (uNK) in maternal endometrium but also by trophoblasts in some species. In normal pregnancies of mice, IFN-g plays critical roles that include initiation of endometrial vasculature remodeling, angiogenesis at implantation sites, and maintenance of the decidual (maternal) component of the placenta [88].

IFN-g concentrations are elevated in plasma, circulating leukocytes, and decidual tissue from women with preeclampsia compared with gestation stage-matched pregnant control women [89]. This has been proposed to be the key cytokine disturbance promoting vascular dysregulation and disease progression [89,90]. IFN-g decreases production of VEGF by human endometrial stromal cells [91] and contributes in complex ways to the expression of genes involved in natural killer cell recruitment, embryo and trophoblast migration, endometrial decidualization, angiogenesis, angiostasis, and anti-viral infection in human uterine microvascular endothelial cells [92]. Excessive amounts of IFN-g in conjuction with TNF-a and IL-1 can lead to apoptosis of trophoblast [93].

IL-10

Interleukin-10 (IL-10) as an anti-inflammatory cytokine is produced by some subpopulations of T lymphocytes, monocytes, macrophages, and cytotrophoblasts [94]. Production of this cytokine is considered to play an important role in maternal immune tolerance of the fetus in normal pregnancy [95]. IL-10 can be produced by both Th1 and Th2 cells, as well as non-T cells, therefore it does not fit the classical Th2 cytokine profile. It can help to establish the Th2 immune environment and inhibit the secretion of Th1-type cytokines like IL-6, TNF-α and IFN-gamma [96-98]. IL-10 might therefore play a critical role in different pregnancy disorders associated with down-regulation of inflammatory responses in the placenta. IL-10 has been reported to contribute to trophoblast invasion, corpus luteum maturation and placental angiogenesis during pregnancy [99-101]. The IL-10 down-regulation of cytokine production by Th1 cells and macrophages [101,102], is thought to be mediated in trophoblastic tissue by progesterone [103]. The physiological role of IL-10 in preeclampsia is not well understood, but it has been shown to attenuate related pregnancy disorders, such as fetal growth restriction and demise [104]. Evidence showed that the expression levels of placental and decidual IL-10 were altered in preeclampsia [105,106]. In many studies reduced production of IL-10 has been suggested to cause a proinflammatory cytokine response and thus lead to the pathogenesis of preeclampsia [107,108].On the other hand in a small number of preeclampsia cases, high levels of IL-10 have been seen both in the placenta and in peripheral blood, which might be a compensatory response to elevated levels of IFN-g, TNF-a, IL-2 and IL-12 [109,110].

OTHER CYTOKINES

Several other cytokine have been identified in the immunopathological cascade of PE. As PE is a condition of generalized endothelial cell dysfunction, the disturbed endothelium results in the well-known classical features of PE. So the hypertension being the result of vasoconstriction, the proteinuria being the result of glomerular endotheliosis and the edema being the result of increased vascular permeability [111]. Also an important observation in PE is that the generalized activation or injury of maternal vascular endothelial cells leading to microthrombus formation and vasospasm [112]. Given the powerful effects of cytokines on endothelial cells, the increased tendency for maternal blood cells to produce inflammatory cytokines in PE is significant. Maternal proinflammatory cytokines are likely to be the most important effectors of these effects [113,114].

In addition to being classified as Th1 and Th2 cytokines, cytokines can also be classified as pro- and anti-inflammatory. Cytokines such as IL-1, IL-2, IL-8, TNF-α, and IFN-γ are proinflammatory, and increased levels of such proinflammatory cytokines are associated with pregnancy complications such as preterm delivery [115] and intrauterine growth retardation [116]. In conjunction with the overexpression and secretion of TNF-a in placenta and in plasma, an enhanced IL-1 [117,118] has been reported in PE women as hypoxia –reoxygenation, due to intermittent perfusion of the placenta, has been shown to induce the production of TNF-α and

IL-1 [119]. In addition, increased production of TNF-a and IL-1 have been observed in normal placenta under conditions of low hypoxia as it occurs in PE [120].

Elevated levels of the proinflammatory cytokine IL-18 have also been shown in preeclamptic placentas [121]. IL-18 is a proinflammatory cytokine which, in the presence of IL-12, tips the balance of immune reactivity towards a Th1 phenotype. High levels of IL-18 along with high levels of IL-12 [122] in PE are proposed to cause Th1 dominance [123].

In addition, enhanced plasma levels of IL-1 [124], IL-2 [125], IL-6 [126,127], IL-8, and IL-18 [128] have been reported in preeclamptic women. Elevations of IL-6 and IL-8 have also been shown in the amniotic fluid of preeclamptic patients; in fact, elevated levels of IL-6 have been shown to be associated with the onset of PE.

In contrast to the generally increased levels of proinflammatory cytokines, the blood levels of some anti-inflammatory cytokines such as IL-4 [129,130] and IL-10 [131] are reduced in patients with PE.

LEPTIN

Leptin is a peptide hormone of 16 kDa molecular weight comprising 167 amino acids. The major source of leptin is the adipose tissue, but it can also be produced by other organs, including the placenta [132]. This anti-obesity hormone decreases food intake and increases energy expenditure, thereby reducing body weight and adiposity [132]. Leptin has been implicated in the control of the reproductive function, including embryonic development and implantation [133]. Leptin can also be considered as a pro-inflammatory cytokine that belongs to the type I cytokine superfamily and has structural similarity with interleukin-6 [134]. Increasing evidence suggests that leptin is involved in the regulation of innate and adaptive immune responses and inflammation [135]. Maternal serum leptin levels have been reported to increase during the course of a normal pregnancy with a peak at around 20-30 weeks of gestation and to decrease rapidly after birth [136,137,138]. According to evidences, there is a further increase in complicated pregnancies, such as gestational diabetes mellitus, preeclampsia and intrauterine growth restriction [139-141].

FREE RADICALS

Reactive oxygen species, in particular superoxide anions, are other important mediators of inflammation in the pathogenesis of PE. Lipid peroxidation, which involves conversion of unsaturated fatty acids to lipid hydroperoxides, is a process that occurs normally at low levels in all cells and tissues. This process can be initiated by free radicals which are unstable molecules [142]. Low concentrations of lipid peroxides are essential and may act endogenously as intracellular messengers [143].The organism normally has anti-oxidative mechanisms that limit this process but under certain circumstances, the protective mechanisms can be overwhelmed, leading to elevated steady-state tissue concentrations of lipid peroxides. Antioxidants (vitamine

E, ascorbic acid, glutathione peroxidase, superoxide catalase/mutase, and caeruloplasmin) are produced by many cells, also trophoblast and leucocytes, as part of cellular homeostasis and ageing or to protect them from free radicals. An imbalance between the pro-oxidants and the anti-oxidants has been defined as "oxidative stress" [144] and is observed in PE.

During normal human pregnancy, serum lipid peroxidation products are elevated but are counterbalanced by an increased activity of the Anti-oxidant system [145,146]. According to studies it is suggested that preeclampsia is associated with increased circulating free radicals and lipid peroxides while placental antioxidant protective mechanisms are decreased compared to normal pregnancy [147,148]. This indicates that the placenta may be the source for this imbalance in pro-oxidant/anti-oxidant activity. This imbalance is capable of evoking systemic endothelial activation, including platelet consumption, altered thromboxane/prostacyclin ratio, increased TNF-a production and promotion of the coagulation cascade [149].

LYPHOCYTE POPULATION IN BLOOD

The maternal-fetal interface is full of immune cells which cross-talk with hormonal, endocrine, and angiogenic regulators to program a normal pregnancy outcome. PE is also characterized by systemic changes in the distribution of lymphocyte population in peripheral blood. Among immune cell types, one CD4+ lymphocyte subset that may be involved in the pathophysiology of preeclampsia is the CD4+CD25+FoxP3+ Treg (FoxP3 is a Treg (regulatory T cells) transcription factor [150]. CD4+CD25+FoxP3+ Treg function is reduced in preeclampsia, which may be related to the presence of inflammatory conditions [151]. The CD4+/CD25+/Foxp3+, play an important role in protecting the fetus by dampening harmful inflammatory immuneresponses at the maternal-fetal interface. It has been shown in humans that Treg numbers increase very early in pregnancy, peak during the early second trimester and then begin to decline until they reach pre-pregnancy levels [152]. Tregs have also been shown to be crucial in immune tolerance of the fetus in the mouse pregnancy model [153] and also follow a gestational age-dependent presence in the uterus. In addition to Tregs, CD4+ Th17 (IL-17-producing T cells) may participate in preeclampsia. Preeclamptic patients have a lower ratio of Tregs: Th17 cells [154].

CD19+CD5+ B cells are important contributors to the pathophysiology of preeclampsia and have rendered preeclampsia as a syndrome with autoimmune characteristics. This concept is also supported by the presence of autoantibodies against adrenoreceptors in patients with severe preeclampsia [155].

Matthiesen and al have been noticed a significant increased level of the proportion of suppressor/inducer T-cell population (CD4+CD45RA+) while the memory and helper/inducer T-cells (CD4+CD45RO+ and CD4+CD29+) significantly decreased during normal pregnancy compared to nonpregnant controls. In addition, in PE they have been noticed increased levels of activated/memory cells CD4+CD45RO+ and CD4+CD29+ and decreased levels of naïve /

suppressor cells (CD4+cd45RA+). The interpretation is that antigens have activated the T cells observed in PE [156].

CONCLUSION

PE is a multisystem disorder based on the cascade immunological events originating from the ischemic placenta. Until now there is no predictive marker of preeclampsia. The identification of first trimester inflammation markers will contribute to a better understanding of the pathophysiology of PE and will give us a clinically validated screening procedure for a better management of this disorder. In addition the early identification of high-risk cases will offer the opportunity for prophylactic therapy, thus improving the perinatal outcome.

Recently published data suggest that studies on metabolomics, proteomics, fetal free DNA/RNA and other new techniques which aim to generate new predictive markers of PE, are promising prognostic tools of PE. PE is a multifactorial disorder. Therefore there is a need for large scale multicenter studies including women with different demographic characteristic and different risk of developing the syndrome in order to have a significant predictive model for a routine use in clinical settings. The goal for future studies will be to identify the best combination of markers that would result in optimal screening prediction for PE.

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