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Association of Cytokines in Preeclampsia: Review Article

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ABSTRACT

Background: Preeclampsia (PE) is an important, common, and dangerous complication of pregnancy that causes maternal and perinatal illness and is responsible for a high proportion of maternal and infant deaths. PE is associated with increased blood pressure and proteinuria, with a whole host of other potentially serious complications in the mother and fetus. The maternal syndrome in PE is primarily that of generalized dysfunction of the maternal endothelium, and this generalized endothelial dysfunction appears to be part of an exaggerated systemic inflammatory response that involves maternal leukocytes and proinflammatory cytokines.

Objective: This review aimed to study the role of cytokines in preeclampsia.

Methods: The databases were searched for articles published in English in 3 data bases: PubMed, Google scholar and science direct. Also, Boolean operators (and, or, not) had been used such as cytokines and preeclampsia OR cytokines and pregnancy and in peer-reviewed articles between June 1991 and April 2021.

Conclusion: Cytokines can be used as biomarkers for the prediction and better clinical management of preeclampsia in the initial stages. The balanced ratio of pro- and anti-inflammatory cytokines is essential to regulate the maternal inflammation system throughout pregnancy.

Keywords: Cytokines, Preeclampsia, Pregnancy.

INTRODUCTION

Substantial evidence has accrued over the years supporting roles for cytokines in the pathogenesis of preeclampsia (PE) at the early placental stage and in the later systemic stage as well. Cytokines play critical, essential roles in signaling between cells of the immune system, with a prolific range of regulatory activities including the recruitment, activation, stimulation, killing, and suppression of immune and non-immune cells. Interestingly, research in the last two decades has shown that cytokines are also involved in several events in pregnancy such as ovulation, implantation, placentation, and parturition **(1).**

Cytokines like granulocyte-macrophage colony-stimulating factor (GM-CSF), colony-stimulating factor-1, IL-3, and IL-10 contribute to the success of pregnancy, while cytokines such as TNF-α and IFN-γ have been shown to have harmful effects on pregnancy. IL-2, TNF-α, and IFN-γ are characteristic of T helper 1 (Th1)-type immunity and induce several cell-mediated cytotoxic and inflammatory reactions. Th2-type cells, on the other hand, secrete the Th2 cytokines IL-4, IL-5, IL-6, and IL-10 are associated with help for humeral immunity. Th2-type immunity is associated with a normal pregnancy, whereas a strong Th1 reactivity is associated with pregnancy complications such as recurrent spontaneous miscarriage, preterm delivery, and premature rupture of fetal membranes. In addition, 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, which are proinflammatory. Increased levels of such proinflammatory cytokines are associated with pregnancy complications such as preterm delivery and intrauterine growth retardation **(2).**

PE: An Inflammatory State:

Preeclampsia is associated with chronic immune activation that results in elevated levels of inflammatory cytokines released by proinflammatory helper T-cell subsets. The proinflammatory cytokines tumor necrosis factor α (TNF-α), interleukin (IL) 6, and IL-17 are typically secreted by activated TH1 and TH17 cells to instigate a cytotoxic and inflammatory immune response to foreign pathogens or injury. During PE, these cytokines are significantly increased in the maternal circulation and the placenta, resulting in chronic systemic and local placental inflammation, which contributes to the pathophysiologic complications that manifest during PE **(3).**

The increased TNF-α and IL-6 in the vasculature contribute to increased endothelial expression of adhesion molecules and permeability, resulting in endothelial dysfunction during PE. Expression of adhesion molecules in the vasculature promotes leukocyte rolling and extravasation, leading to increased endothelial permeability. Studies have demonstrated that TNF-α signaling results in endothelial cell activation, decreased nitric oxide synthase (NOS) messenger RNA (mRNA), and increased production of preproendothelin 1 (PPE-1) mRNA. Decreased nitric oxide (NO) bioavailability results in a loss of vasodilator ability of endothelial cells and leads to endothelial dysfunction and the development of hypertension and IUGR in PE. Preproendothelin 1 is the precursor to the potent vasoconstrictor endothelin 1 (ET-1), which has been shown to be increased in the circulation of preeclamptic women. Furthermore, PPE-1 mRNA expression is increased in the endothelial cells of women with PE compared to women with normal pregnancies. Interleukin 6 has also been shown to

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mediate the mRNA expression of PPE-1 and play a role in stimulating endothelial permeability [4, 5].

PE: Impaired immunoregulation:

In addition to an increase in proinflammatory T cells and inflammatory cytokines, it has been suggested that PE is characterized by a decrease in Tregs and IL-10, the anti-inflammatory cytokine produced by Tregs. A number of clinical studies have investigated the status of Tregs in the circulation of normal pregnant versus preeclamptic women. The majority of studies have consistently observed a decrease in Tregs (CD4+/FoxP3+ or CD4+/CD25+/FoxP3+) in preeclamptic women compared to normal pregnant women. However, there are a few studies that report no significant change in Tregs between women with normal pregnancies and those with PE [6].

The inconsistencies of the data presented in these studies could be affected by the use of less specific markers to identify Tregs (CD4/CD25 only or CD4/CTLA4). Some of these studies that reported no changes in total Tregs in preeclamptic women did, however, report alterations in Treg subsets. Larger studies with more standardized protocols across institutions will be necessary to conclusively determine Treg status in PE [7].

However, given the high consistency of studies reporting decreased Tregs or at least reduced regulatory function in PE, a role for decreased Tregs in contributing to PE pathophysiology remains worthy of consideration. Regulatory T cells have been shown to be decreased in the periphery and decidua of women with PE, and the decrease in Tregs is directly proportional to PE severity. Several studies report a significant decrease in Tregs in patients with severe, early-onset PE compared to patients with mild late-onset PE. Studies have also shown that decreases in decidual Tregs result in increased apoptosis in trophoblast cells and shallow invasion of trophoblasts into the deciduas. This suggests the direct involvement of Tregs in spiral artery remodeling and the initial phenomenon resulting in the development of PE [8, 9].

Interleukin 10 is a Treg-associated anti-inflammatory cytokine responsible for stimulating the differentiation of Tregs from naïve T cells. Interleukin 10 is important during pregnancy because of its ability to inhibit secretion of TH1 inflammatory cytokines and thus provide an important counterbalance for controlled inflammation at the fetal-maternal interface. Pro-inflammatory cytokines such as interferon γ (IFN-γ), IL-2, and TNF-α are down regulated by IL-6 [10].

Cytokines in the Placenta:

Cytokines are produced by cells of normal placentas and by leukocytes infiltrating the placenta, and receptors for cytokines are also expressed in the placenta. Thus, both sources and targets of cytokines are present in the placenta. Proinflammatory cytokines are produced by placental trophoblast and also by macrophages and stromal cells of the placenta. The anti-inflammatory cytokines IL-4 and IL-10 are also secreted by placental tissues. Cytokines have been shown to play beneficial roles in several normal physiologic processes in the placenta that include trophoblast invasion and differentiation and placental proliferation and angiogenesis. Widespread up regulation of cytokines in preeclamptic placentas, including proinflammatory cytokines like TNF-α and their receptors, have been shown in DNA microarray studies [11].

The expression and secretion of TNF-α and IL-1 are elevated in the placentas of preeclamptic women. Hypoxia-re oxygenation due to intermittent perfusion of the placenta has been shown to induce the production of TNF-α and IL-1. **Benyo and colleagues** [12] demonstrated increased production of the proinflammatory cytokines TNF-α and IL-1 by the normal human placenta under conditions of low oxygen tension. Considering that placental hypoxia occurs in PE, this could well explain the elevated production of these two cytokines. High local production of TNF-α may have significant effects, including increased trophoblastic apoptosis resulting in enhanced syncytial shedding and impaired placental function. Elevated levels of other proinflammatory cytokines, i.e. IL-2 and IL-18, have also been shown in preeclamptic placentas. 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 in PE are proposed to cause Th1 dominance [13].

Lockwood *et al.* [14] demonstrated higher levels of IL-6 mRNA and protein in leukocyte-free decidual cells from subjects with PE. Human endometrial endothelial cells have been recently shown to be capable of phagocytizing apoptotic trophoblast and then secreting the proinflammatory cytokine IL-6. This might be one of the mechanisms that contribute to the inflammatory response seen in preeclamptic placentas. Increased production of IFN-γ, a Th1 proinflammatory cytokine, has been found in decidual lymphocytes and choriodecidual cells of placentas from preeclamptic pregnancies.

While PE is associated with increased levels of proinflammatory cytokines, it is also associated with decreased placental production of the anti-inflammatory cytokine IL-10. Considering that IL-10 is a strong suppressor of proinflammatory cytokines such as IFN-γ and TNF-α, it is suggested that the placenta responds to hypoxia in PE with insufficient IL-10 production leading to increased or uncontrolled production of pro-inflammatory cytokines. Furthermore, IL-10 has anti-apoptotic and anti-inflammatory capabilities, and it is therefore quite likely that the decreased IL-10 in the placenta is at least partly responsible for the increased apoptosis of the trophoblast seen in PE [15].

While apoptosis is actually necessary for normal placentation, excessive apoptosis or inadequate clearance of apoptotic debris may lead to increased production of proinflammatory cytokines by macrophages. In addition to proinflammatory cytokines, decidua from a murine model of PE display higher levels

of GM-CSF as well as increased numbers of both macrophages and dendritic cells when compared to control animals. Furthermore, TNF-α and IL-1 induce increased production of GM-CSF by cultured decidual cells leading to the suggestion of important roles for GM-CSF in inducing the activation of macrophages and dendritic cells in PE [16].

Cytokines in the periphery:

Levels of proinflammatory cytokines are increased in the blood and in blood leukocytes in PE. Elevated concentrations of TNF-α have been observed in the blood of women with PE. The placenta may not be the major contributor to the high TNF-α levels seen in peripheral blood, and in fact peripheral leukocytes, which are in any case in an activated state in PE may contribute significantly to the TNF-α levels in peripheral blood. Levels of soluble TNF-α receptor, a more reliable marker for TNF activity, are also increased in PE as compared to normal pregnancies. Support for a cause-and-effect association between TNF-α and PE comes from **Sibai *et al.*** [17] who showed that serum levels of TNF-R2 receptor are indeed elevated prior to overt PE suggesting a pathogenetic role for these pro inflammatory cytokines. Similarly, enhanced plasma levels of IL-1, IL-2, IL-6, IL-8, and IL-18 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 [18].

Mechanisms of action of cytokines in PE:

The pathophysiologic mechanisms underlying the initial placental changes and subsequent development of endothelial dysfunction, hypertension, proteinuria, and edema in PE have been the subject of intense investigation over the years, and these aspects are now much better understood. PE is basically a condition of generalized endothelial cell dysfunction. The disturbed endothelium results in the well-known classical features of PE – the hypertension is attributable to vasoconstriction, the proteinuria is attributable to glomerular endotheliosis, and the edema is attributable to increased vascular permeability. Generalized activation or injury of maternal vascular endothelial cells leading to micro thrombus formation and vasospasm is an important observation in PE. 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 [19].

At the level of the placenta, the cytokines IL-6 and TNF-α were shown to induce excessive or abnormal apoptotic and necrotic death of trophoblast cells. These cells were shown to induce endothelial activation when shed. Thus, cytokines appear to be involved in the early (i.e. stage 1) events of PE. The pattern of increased placental and systemic cytokines appears to be consistent with increased systemic inflammatory activation, the release of vasoconstrictor factors, endothelial dysfunction, and hypertension, which are all part of the syndrome of PE. The widespread maternal vascular endothelial dysfunction is suggested to be caused by proinflammatory cytokines and along with other mediators such as endothelin and thromboxane, are proposed to contribute to hypertension, proteinuria, and edema [20].

Benyo *et al.* [12] pointed out that proinflammatory cytokines are 'notorious' for effecting changes in the endothelium in the same manner as that seen in PE. TNF-α has potent effects on endothelial and platelet function, it enhances coagulation, microvascular leakage, activation of vasoconstrictive endothelial cells, and production of antiangiogenesis factors like tissue factor. TNF-α and IL-1 cause increased production of thrombin, platelet-activating factor, and vascular cell adhesion molecule-1, increased endothelial cell permeability, and enhanced coagulation, and thus instigate inflammatory responses. TNF-α has been shown to induce the activation of endothelial cells and to cause endothelial damage. Increased concentrations of IL-8 are associated with increased activation of neutrophils, while IL-6 is known to activate endothelial cells, to induce increased permeability of endothelial cells, and to bring about systemic effects that resemble the inflammatory acute phase response. It may be pertinent to refer to another factor that appears to be involved in the pathogenesis of PE.

Zenclussen *et al.* [21] showed that the expression of the heme-degrading enzymes heme oxygenases (HO)-1 and HO-2 is reduced in PE. They suggested that low expression of HO-2 may lead to enhanced levels of free heme at the feto-maternal interface, followed by up regulation of adhesion molecules, which would then encourage the migration of inflammatory cells to the feto-maternal interface. this points to the involvement of HO in PE. HO-1 plays an important role in placental vasculature development, and a deficiency in HO-1 may contribute to pregnancy complications, such as PE. The unique combination of tissue-protective, smooth-muscle-relaxing, and angiogenesis-regulatory properties makes HO-1 a key player in the maintenance of a healthy pregnancy through a direct effect on placental structural and vascular development.

Immunomodulation for therapeutic intervention in PE:

The possibility of rational development of immunomodulatory approaches for the treatment of PE is supported by research on anti-inflammatory cytokines like IL-10 and on the suppression of proinflammatory cytokines. A negative correlation has been reported between BP and serum levels of IL-10, and this has also been demonstrated experimentally in nonhuman primates [22].

A recent elegant study by **Chatterjee *et al.*** [23] showed that TLR3 activation during murine pregnancy induced an increase in systolic BP and endothelial

function, demonstrating a connection between immune activation and symptoms of PE. TLR3 activation was shown to be associated with a proinflammatory state along with an increase in proinflammatory cytokines. Interestingly, a deficiency in IL-10 along with TLR3 activation brings about an exacerbation of PE symptoms. The addition of recombinant IL-10 prevented these symptoms, demonstrating the importance of IL-10 in this equation. These observations are significant given the well-documented anti-inflammatory properties of IL-10 and the demonstration that IL-10 deficiency is associated with PE-like symptoms. In pregnant baboons, the administration of anti-IL-10 antibody results in a significant increase in mean arterial pressure via regulation of vasodilation.

Chatterjee *et al.* [23] proposed that recombinant IL-10 may be considered for use in preventing PE. More evidence of the important role of IL-10 comes from observations that IL-10 knockout mice have mild hypertension, endothelial dysfunction, and inflammation. The possibility of manipulating cytokine production for therapeutic intervention in PE is supported by the recent study of **Keiser *et al.* [24].** This study on pregnant rats showed that progesterone inhibits TNF-α-stimulated production of endothelin-1 by endothelial cells and suggested that such immunomodulatory approach considered for PE.

CONCLUSION

Cytokines can be used as biomarkers for the prediction and better clinical management of preeclampsia in the initial stages. The balanced ratio of pro- and anti-inflammatory cytokines is essential to regulate the maternal inflammation system throughout pregnancy.

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