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PREECLAMPSIA (VD GAROVIC, SECTION EDITOR)

The Role of Interleukin-10 in the Pathophysiology of Preeclampsia

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Abstract

Purpose of Review The pathophysiology of preeclampsia is complex and not entirely understood. A key feature in preeclampsia development is an immunological imbalance that shifts the maternal immune response from one of tolerance towards one promoting chronic inflammation and endothelial dysfunction. As a key regulator of immunity, IL-10 not only has immunomodulatory activity, but also directly benefits vasculature and promotes successful cellular interactions at the maternal-fetal interface. Here we focus on the mechanisms by which the dysregulation of IL-10 may contribute to the pathophysiology of preeclampsia.

Recent Findings Dysregulation of IL-10 has been demonstrated in various animal models of preeclampsia. Decreased IL-10 production in both placenta and peripheral blood mononuclear cells has been reported in human studies, but with inconsistent results.

Summary The significance of IL-10 in preeclampsia has shifted from a key biomarker to one with therapeutic potential. As such, a better understanding of the role of this cytokine in the pathophysiology of preeclampsia is of paramount importance.

Keywords Interleukin 10 · Regulatory T cells · Preeclampsia · Hypertension · Vascular activity · Cytokines · Inflammation

Introduction

Preeclampsia (PE) is a pregnancy-specific disorder typically characterized by elevated blood pressure and proteinuria in the second half of pregnancy. The American College of Obstetrics and Gynecology (ACOG) defines PE as new onset hypertension (systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg), with either proteinuria (> 300 mg/24 h) or organ dysfunction after 20 weeks of gestation [1]. It affects 5–8% of all pregnancies and is a major cause of maternal and fetal morbidity and mortality [2].

PE can be classified based on gestational age as early-onset (symptoms starting prior to 34 gestational weeks) or late-onset (symptoms starting at or after 34 gestational weeks) [3]. Early-onset PE is usually of placental origin and is commonly associated with abnormal utero-placental perfusion, a greater prevalence of placental lesions consistent with maternal underperfusion [4], low birth weight/preterm births, and fetal growth restriction [5]. Late-onset PE tends to be milder in severity and is considered to be related to preexisting maternal conditions, such as diabetes, obesity, and chronic kidney disease [6–8].

This article is part of the Topical Collection on *Preeclampsia*

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Role of IL-10 and Evidence of Its Dysregulation in Preeclampsia

Overview of Pathophysiology of Preeclampsia

The proposed pathophysiological mechanisms pertinent to PE are illustrated in Fig. 1. It involves two pathways resulting in two distinct clinical presentations, both of which converge on a common pathway of endothelial dysfunction, hypertension, proteinuria, and end organ damage.

One of the pathways involves abnormal placentation resulting in placental ischemia and inflammation, along with the release of anti-angiogenic, pro-inflammatory, and other substances into the maternal circulation, leading to endothelial dysfunction [6, 9]. Abnormal placentation is

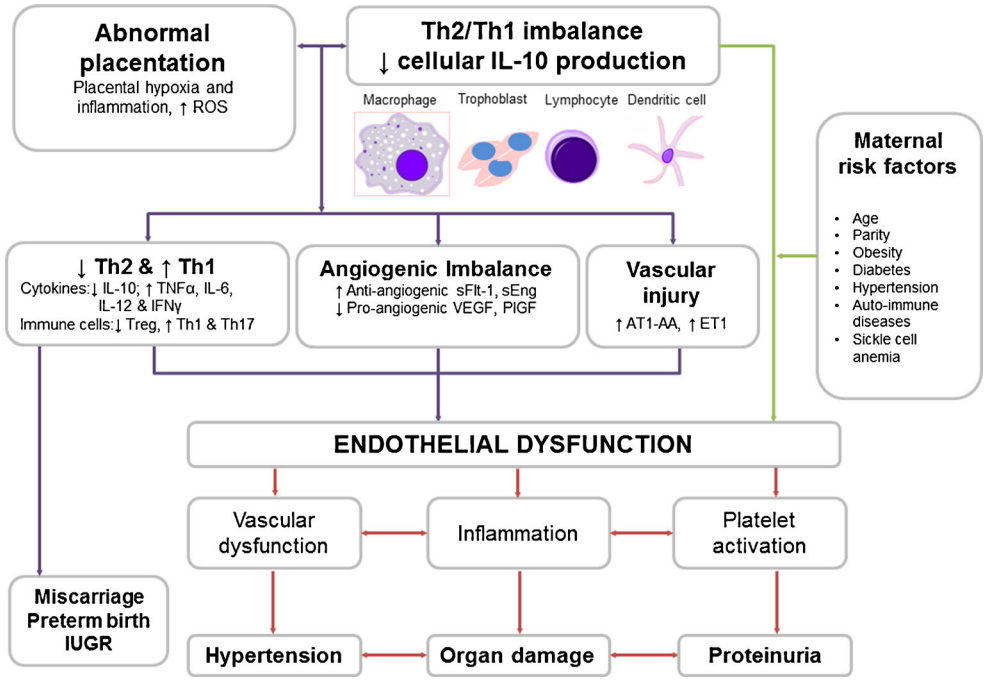

Fig. 1 The role of immune system dysregulation in the pathophysiology of preeclampsia. In the placental pathway, immune dysregulation may cause abnormal placentation with an early stop in trophoblast invasion of maternal blood vessels, or it may be that abnormal placentation and placental hypoxia cause immune imbalance, with low levels of IL-10 and a decrease in anti-inflammatory and increases in pro-inflammatory and anti-angiogenic activities. Abnormal placentation, placental hypoxia and inflammation will result in release of various active substances into the maternal circulation causing vascular dysfunction, inflammation, and thrombotic propensity, ultimately leading to preeclampsia symptoms. On the other side, maternal preexisting conditions that cause endothelial dysfunction, coupled with pro-inflammatory immune system imbalance, lead to systemic maternal cell activation resulting in hypertension, proteinuria, and/or organ dysfunction seen in preeclampsia. Abbreviations: downwards arrow decreased, upwards arrow increased, AT1-AA angiotensin II type I receptor agonistic autoantibodies, VEGF vascular endothelial growth factor, sFlt-1 soluble fms-like tyrosine kinase-1, sEng soluble endoglin, PlGF placental growth factor, Tregs regulatory T cells, IL interleukin, TNF-α tumor necrosis factor alpha, ROS reactive oxygen species, ET-1 endothelin-1, IFN-γ interferon gamma, Th1 T helper type 1, Th2 T helper type 2, Th17 T helper type 17

a consequence of shallow trophoblast invasion of the maternal spiral arteries with subsequent insufficient arterial remodeling. This results in inadequate delivery of oxygen and nutrients to the placenta and fetus. The primary event responsible for this is still unclear. One possibility is that an inappropriate maternal immunologic reaction to the allogenic fetus, with the attendant lack of the expected shift towards the Th2 phenotype, leads to a predominance of the Th1 phenotype, resulting in insufficient trophoblast invasion [10]. Alternatively, it is possible that abnormal trophoblast invasion and placental hypoxia may also play a role in this shift, as evidenced by the release of anti-angiogenic and other bioactive molecules into the maternal circulation under hypoxic conditions [11]. In a reduced uterine perfusion pressure (RUPP) model of PE, placental ischemia was associated with decreased levels of IL-10 and concurrent increases in angiotensin II type I receptor agonistic autoantibodies (AT1-AA) and endothelial cell dysfunction [12••].

An exaggerated Th1 response negatively affects the developing fetus and may cause miscarriage, preterm birth, or various forms of fetal growth restriction [13]. Furthermore, this response may exacerbate placental inflammation, with the release of reactive oxygen species (ROS), and pro-inflammatory cytokines such as TNF-α and IL-6, as well as activation of cytotoxic T cells. The Th2 cellular response is consequently further suppressed along with a decrease in the number of regulatory T cells (Tregs) and, hence, IL-10 levels. Placental tissue damaged by hypoxia or inflammation releases anti-angiogenic/vaso-active factors such as soluble fms-like tyrosine kinase-1 (sFLT-1 or sVEGFR) and soluble endoglin (sEng), stimulating AT1-AA and endothelin-1 (ET1) production, while secreting lower levels of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) [14].

The second proposed pathway relates to preexisting conditions in the mother, such as obesity, infection, autoimmune disease, hypertension, diabetes, sickle cell anemia, extremes in maternal age, and adverse obstetric history. Such conditions can induce endothelial dysfunction, creating an immune imbalance between pro- and anti-inflammatory factors, release of free radicals, vascular damage, and further endothelial cell

dysfunction. This combination eventually presents with symptoms of preeclampsia [15].

Th2/Th1 Imbalance

A critical event in the pathophysiology of PE is an abnormal maternal immune response. The main immune system regulator is the $CD4^+$ T helper cell that ultimately orchestrates other cells associated with the immune response. These cells are mainly composed of two distinct primary phenotypes, Th1 and Th2. The Th1 phenotype is characterized by the secretion of pro-inflammatory cytokines such as TNF-α, IL-6, IL-8, IL-1, and IFN-γ; the stimulation of effector cytotoxic T cells; and the inhibition of both the Th2 response and humoral immunity. The Th2 response, mediated by the Treg subpopulation of T cells, is characterized by the production of anti-inflammatory cytokines, namely IL-4, IL-5, IL-10, IL-35, and TGF-β; the inhibition of cellular cytotoxic T cells; the inhibition of Th1 response; and a shift towards humoral immunity [16]. These opposing effects of the pro-inflammatory Th1 and anti-inflammatory Th2 phenotypes allow for proper homeostasis and control of inflammation.

Normal pregnancy is characterized by a shift towards Th2 relative to Th1 immunity; this is commonly referred to as "Th2 polarization" (Fig. 2) [17, 18]. The heightened Th2 relative to the Th1 response during pregnancy corresponds with critical placentation events. Normal pregnancy, for instance, is associated with proliferation and increased numbers of Tregs, the highest levels of which are seen during the second trimester, with decreasing levels after pregnancy [19]. Tregs act to suppress Th1 and Th17 responses [20, 21] and also secrete IL-10 [22], ensuring a Th2 predominant state. This shift is believed to protect the developing fetus from the maternal immune system to ensure a state of controlled inflammation essential for a successful pregnancy. One of the key cytokines in the Th2 response is IL-10. IL-10 levels are increased during a normal pregnancy and remain elevated until delivery [23]. Serum levels of IL-10 may be hormonally regulated and correlate well with levels of progesterone and 17-β-estradiol. IL-10 may be involved in the maintenance of pregnancy by stimulating progesterone secretion from the corpus luteum [24, 25].

While a normal pregnancy exhibits a heightened Th2 immune response, PE is associated with an immune system imbalance driven predominantly by a Th1-mediated response [26, 27, 28••]. Multiple studies have reported a shift towards the Th1 phenotype expressed by different PE cell types, such as uterine and circulating natural killer cells [27], placental [29], and fetal-derived macrophages [30], uterine decidual T-lymphocytes [31], and peripheral blood mononuclear cells (PBMCs) [32•, 33]. These cells have decreased secretion of IL-10 and increased secretion of pro-inflammatory cytokines. Saski et al. reported that

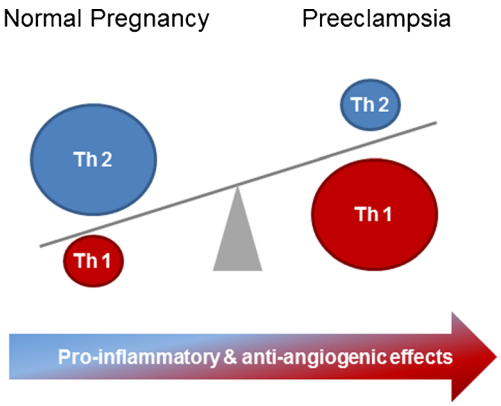

Fig. 2 Immune system helper T cell regulatory response in preeclampsia compared to normal pregnancy. Normal pregnancy is a state of increased immune tolerance characterized by predominance of the regulatory Th2 response, with increased IL-10 cellular production and tightly controlled inflammation. In preeclampsia, suppressed Th2 and increased Th1 responses cause pro-inflammatory and anti-angiogenic milieu at both the placental and maternal systemic levels, resulting in widespread maternal endothelial cell dysfunction and preeclampsia symptoms. Abbreviations: Th1 Thelper 1, Th2 Thelper type 2

circulating as well as placental levels of regulatory T-lymphocyte subsets are decreased in PE, further demonstrating an abnormal Th1 shift [34].

The Role of IL-10

As a key immunosuppressive cytokine, IL-10 is secreted primarily by Th2 cells, macrophages, natural killer cells, granulocytes, dendritic cells, and by B cells stimulated by auto-antigens. Additionally, stimulation of Toll-Like Receptors (TLR) 4 and 9 by their respective ligands, along with vitamin D3 receptor stimulation, enhanced IL-10 production [35, 36]. Mesenchymal stem cells have also been shown to secrete IL-10 [37]. Interestingly, the expression of this cytokine and its cognate receptor has been reported in a number of cell types in the decidua including, trophoblasts, stromal cells, macrophages, and uterine natural killer cells [38].

IL-10 has three major beneficial roles in normal pregnancy as one of the key cytokines in the Th2 cellular response: promoting successful placentation, controlling inflammation, and regulating vascular function. The relative deficiency of IL-10 contributes to the development of PE through these pathways.

Role of IL-10 in Placentation and Maintenance of Pregnancy

IL-10 has important roles in trophoblast invasion, differentiation, and proliferation by regulating vascular activity and endovascular interactions at the maternal-fetal interface. Placental levels of IL-10 are influenced in a gestational-dependent manner, with the highest values found in early pregnancy followed by a stepwise decrease leading up to term

[23]. IL-10 modulates the maternal reaction to paternal antigens in the fetus and promotes fetal allograft tolerance by inducing human leukocyte antigen G (HLA-G) expression and inhibiting lysis by maternal NK cells [39]. However, IL-10 is not essential for fetal survival or placental viability. IL-10-deficient mice, for instance, exhibit altered fetal growth, but otherwise have normal pregnancies [40]. Furthermore, inhibiting IL-10 during the second half of pregnancy in mice resulted in fetal growth restriction, but did not affect the duration of gestation or fetal outcome, illustrating the critical but non-essential role of IL-10 in fetal growth [41]. IL-10 promotes the maintenance of pregnancy as demonstrated by a mouse model of preterm birth in which the administration of human adipose-derived mesenchymal stem cells prevented premature delivery by increasing serum levels of IL-10 [42]. There is evidence of an association between lower IL-10 levels caused by IL-10 gene promoter polymorphisms with preterm births and recurrent pregnancy loss [43].

The mechanism(s) by which IL-10 affects trophoblast invasion is still not clear. It has been shown, however, that IL-10 increases trophoblast resistance to Fas-mediated apoptosis [39] and regulates the activities of both matrix metalloproteinases [44] and serine proteases [45] in various cells. Resistance to apoptosis may not only prevent fetal rejection, but also act to promote trophoblast invasion and adequate vascular perfusion.

Multiple investigators have demonstrated decreased placental levels of IL-10 in PE using a variety of methods. Researchers have shown that placental explants [46] and cultured placental trophoblasts [47] secrete less IL-10 in response to hypoxia. This is consistent with studies demonstrating decreased IL-10 levels in placentas from PE patients [48, 49]. Decidual T lymphocytes, in a similar manner, produce less IL-10 in PE compared to those of normotensive patients [31]. This consistent finding of decreased placental IL-10 levels across studies provides strong evidence that reduced IL-10 levels in the placenta are a characteristic hallmark of PE.

Role of IL-10 in Modulation of the Inflammatory Response

The maternal innate immune system can be activated through TLR3 stimulation by pathogens or necrotic debris, leading to activation of the adaptive immune system with a Th1 predominance, as is observed in PE [50•]. Stimulation of TLR3 in IL-10-deficient mice with polyinosine-polycytidylic acid (Poly I:C), a ds-RNA receptor agonist, resulted in an exaggerated PE-like phenotype compared to their wild type counterparts [50•]. Uncontrolled inflammation occurs at the placental level and in the maternal vasculature, with the potential to expand to other maternal organs.

IL-10 works to suppress inflammation and the cellular immune response while promoting a humoral immune response. The anti-inflammatory effect(s) of IL-10 is achieved through binding of IκBα which inhibits the release and translocation of NFκB [35, 49, 51], an important regulator of cytokine secretion. By inhibiting NFκB binding, IL-10 prevents the synthesis and secretion of various cytokines, such as TNF-α, IL-1β, IL-6, IL-8, IL-12, and *granulocyte-macrophage colony-stimulating factor* (*GM-CSF*). Pro-inflammatory cytokines stimulate the differentiation and activation of inflammatory cells in both the innate and the adaptive arms of the immune system. IL-10 also reverses the downregulation of suppressor of cytokine synthesis-3 (SOCS3), a negative regulator of the JAK-STAT signaling pathway of cytokine synthesis in PBMCs and neutrophils [52–54]. This may be an additional mechanism which promotes the pro-inflammatory phenotype of mononuclear cells observed in PE patients.

IL-10, in addition to inhibiting pro-inflammatory cytokine production, also reduces inflammation by stimulating Treg differentiation and proliferation, with subsequent increased secretion of anti-inflammatory cytokines (IL-4, IL-5, IL-10, and TGF-β). IL-10 promotes Treg population growth by stimulating the expression of the transcription factor, Forkhead box protein 3 (Foxp3) in $CD4^+$ T cells [55]. Decreased percentages of Tregs in both the peripheral blood and placenta have been reported in women with PE [56, 57], as well as in animal models of PE [58]. The induction of endogenous Tregs by a super agonistic CD28 monoclonal antibody (mAB) suppressed inflammation, lowered circulating levels of vasoactive factors, reduced hypertension, and increased IL-10 levels in the RUPP model of PE [59••]. Administration of Tregs from a normal pregnancy into pregnant rats in the RUPP model of PE, similarly, resulted in reduced blood pressure and decreased levels of the inflammatory mediators, IL-17, TNF-α, and AT1-AA, all of which have been shown to increase blood pressure during pregnancy. Interestingly, IL-10 levels were not significantly different between groups [60]. Intraperitoneal administration of IL-10 was associated with an increased number of Tregs and resulted in milder PE symptoms in pregnancies complicated by placental ischemia in rats [12••].

As IL-10 favors a Th2 phenotype over that of Th1, a deficiency of IL-10 leads to a predominantly Th1/Th17 response [56]. This Th1 response tends to further inhibit Th2 activity and increase activated $CD4^+$ Th1 cells, which themselves secrete pro-inflammatory cytokines, increase cytotoxic $CD8^+$ cells, contribute to humoral immunity dysfunction with autoantibody production, and activate cells of the innate immune system. Adoptive transfer of activated $CD4^+$ T cells obtained from RUPP pregnant rats caused PE-like features in normal pregnant rats, characterized by decreased IL-10 levels, increased AT1-AA, and elevated ET-1 and ROS levels [61]. Similarly, adoptive transfer of activated Th1-like splenocytes into pregnant BALB/c mice resulted in PE-like symptoms [62]. Stimulation of B cells with activated Th1 cells, along

with decreased influence of Tregs, may be responsible for AT1-AA production. Infusion of agonistic AT1-AA causes hypertension with a concurrent decrease in IL-10 and elevations in TNF-α in pregnant mice and rats [63, 64••]. Conversely, B cell depletion in RUPP rats was associated with a decrease in blood pressure [65]. These findings suggest that reduced IL-10 culminates in a Th1 predominant state, leading to many of the characteristic PE symptoms.

This immune system imbalance may result in release of pro-inflammatory cytokines and in immune cell type signatures that lead to immune activity against the fetus and to vascular dysfunction. Studies have reported decreased circulating IL-10 levels and increased TNF-α and IL-6 levels in PE [66, 67]. While the data regarding circulating levels of IL-10 have yielded discordant results, decreased secretion of IL-10 and increased secretion of pro-inflammatory cytokines were reported more consistently in activated PBMCs [33, 68, 69].

The role of IL-10 deficiency during pregnancy has been analyzed in various animal models. Inhibition of IL-10 by a recombinant mAB resulted in PE features in pregnant baboons [70•]. PE-like symptoms were induced in IL-10-deficient mice in several ways, including stimulation of TLR3 with poly I:C [50•], exposure to hypoxic environmental conditions [71], and injection of sera from women with severe PE, the latter representing a blueprint of the preeclampsia secretory milieu [72•]. IL-10-deficient mice thus represent a good in vivo system for the study of PE because IL-10 deficiency predisposes them to an exaggerated pro-inflammatory response, as well as to impaired angiogenesis during pregnancy. Supplementation with recombinant IL-10 (rIL-10) improved the symptoms associated with PE in RUPP rats [12••], desoxycorticosterone acetate (DOCA)-induced pregnant rats [73], and a poly I:C-induced IL-10 knock out (KO) model of PE [50•]. As IL-10 deficiency contributes to chronic inflammation that instigates many of the components of PE pathology, IL-10 is considered a potential therapeutic target. New treatment options focused on increasing levels of IL-10 have been investigated in animal models of PE [74–76].

It is important to emphasize the extent and degree of inflammation in the pathophysiology in PE. While normal pregnancy is viewed as a state of controlled inflammation, which in some measure is beneficial for appropriate placentation, PE is marked by an exaggerated inflammatory response, with a relative deficiency of anti-inflammatory compared to pro-inflammatory activity.

Role of IL-10 in Vascular Function

In addition to the indirect effects of IL-10 on vascular function through the inhibition of secretion of pro-inflammatory cytokines, decrease in inflammation, and prevention oxidative stress caused by inflammation, IL-10 also directly influences the vasculature. Evidence in support of this has been provided by IL-10 knockout mice which are prone to hypertension and the development of vascular dysfunction without any additional inflammatory stimuli.

IL-10 also acts to directly modulate endothelial nitric oxide synthase (eNOS) activity by preventing eNOS uncoupling, which results in increases in nitric oxide (NO) levels [77]. IL-10 increases the production of NO from human saphenous vein endothelial cells in a dose-dependent manner. This effect can be blocked by the use of nitric oxide synthase inhibitor, NG-nitro-l-arginine methyl ester (L-NAME), as well as an antibody against IL-10 [78]. Interleukin-10 KO mice have impaired endothelium-dependent vascular relaxation of isolated carotid arteries and increased levels of superoxide anion [79, 80].

Inflammation upregulates the protein expression of inducible NOS (iNOS), leading to high levels of NO. Nitric oxide, in the presence of a pro-oxidative environment, reacts with superoxide to form the potent oxidant, peroxynitrite, which subsequently nitrates tyrosine residues on proteins. This sequence of events results in reduced bioavailability of NO. IL-10 is known to prevent ROS generation by regulating the activities of NOX1, NOX2, and p22,^{phox} important subunits of the NADPH oxidase complex and superoxide anion production [81, 82]. IL-10 deficiency is associated with increased NOX activity, which leads to increased generation of ROS. Taken together, IL10 deficiency leads to inflammatory-based iNOS upregulation, ROS formation, and eNOS downregulation. The net result is decreased bioavailability of NO and consequent impairment of endothelium-dependent vascular relaxation.

The aforementioned oxidative environment, particularly that due to peroxynitrite production, also leads to a heightened state of vasoconstriction mediated by the upregulation of COX2, which increases thromboxane A2 levels in the vasculature. Young, but not old, IL-10 KO mice have increased expressions of iNOS and COX2 in their aortas compared to age-matched WT controls [83]. Both of these inducible enzymes are regulated by NFκB [84]. One of the known actions of IL-10 is inhibition of NFκB activity. Ultimately, both increased vasoconstriction and impaired vascular relaxation in the setting of IL-10 deficiency result in hypertension.

It appears that IL-10 acts as a direct antagonist of TNF-α and ET-1 activities, both of which act to inhibit expression of eNOS [85]. IL-10 inhibited ET-1-mediated vascular dysfunction in rodent blood vessels [85]. Administration of IL-10 to DOCA/saline-treated (PDS) rats decreased plasma levels of ET-1 which led to a consequent fall in their blood pressures [73]. TNF-α has been shown to impair endothelium-dependent vascular relaxation and enhance vasoconstriction in isolated aortas of pregnant rats [86, 87]. Furthermore, infusion of TNF-α into IL-10 KO mice impaired acetylcholine-induced relaxation compared to that seen in the saline-infused IL-10 KO mice. The same effect was not observed in WT

mice infused with TNF-α. The impaired relaxation was significantly reversed with the co-administration of IL-10 in the TNF-α-treated mice, suggesting that IL-10 inhibits the actions of TNF-α [77]. Similarly, treatment of primates with an anti-IL-10 mAB caused increased resting mean arterial pressure (MAP) suggesting impaired vasodilatation. The MAP-elevating effect of the anti-IL-10 mAB was not observed with co-administration of anti-TNF-α. This implies that the blood pressure effect of anti-IL-10 mAB may be mediated via TNF-α [70•]. IL-10 additionally is able to inhibit angiotensin II-mediated oxidative vascular stress, both in vivo and in vitro, thereby preventing the negative effects of AT1-AA [88]. Based upon these findings, it is evident that IL-10 exerts multiple beneficial effects on the vasculature, and its relative deficiency might trigger the sequence of impaired relaxation, increased vasoconstriction, and inflammation in the blood vessel wall causing endothelial dysfunction and symptoms of PE.

Historical Perspective

IL-10 initially was viewed as a potential predictive marker of PE. However, prior studies assessing circulating IL-10 levels have reported inconsistent results. Some studies have reported increased levels [89–91], while others have indicated decreased levels [66, 67, 92], and still other non-significant differences in IL-10 levels between PE and normotensive patients [28••, 93]. Since IL-10, as a cytokine, is predicted to have paracrine and autocrine effects, its placental and decidual secretion has also been evaluated. Most of the studies have reported decreased placental levels of IL-10, both in vivo and in vitro [48, 94]. A few, however, have reported elevated levels [90], whereas others have indicated no difference [95]. Previous in vitro studies measuring IL-10 production in placental explants or in cultures of trophoblasts have found reduced placental/trophoblast secretion of IL-10 under hypoxic conditions [46, 96, 97]. Furthermore, Makris et al. failed to show a correlation between serum IL-10 levels and either placental IL-10 mRNA or positive villous staining for IL-10 [98]. These conflicting findings relate to the variability in both experimental design and techniques of IL-10 determination among the studies and will be addressed in the ensuing discussion.

Many authors have evaluated IL-10 gene promoter polymorphisms as potential genetic links to PE. The three main IL-10 polymorphisms associated with PE are IL-10-1082 G/A, IL-10-592 A/C, and IL-10-819 T/C, all three of which have been associated with decreased IL-10 production. Although many recent studies have shown positive correlations of these polymorphisms with PE [99–102], the overall results have been inconsistent. Zhang et al., in a recent meta-analysis of 13 individual studies, concluded that there was insufficient evidence of a significant association between IL-10-1082 G/A or IL-10-819 T/C polymorphisms [103] and PE. Lee et al. [104], in a separate meta-analysis of 1082 G/A, 819 C/T, and 592 polymorphisms, concluded that these polymorphisms are unlikely to influence susceptibility to PE. Researchers have gained valuable insight into the indispensable role of IL-10 in PE pathophysiology with the development of PE animal models. IL-10-deficient mice, consequently, have been used as the basis for several PE models, namely those induced with sera from PE patients [72•], hypoxia [71], and poly I:C [50•]. Dysregulation of IL-10 has also been shown in other animal models of PE, including the RUPP [12••, 59••], NOS inhibition (L-NAME) [74, 105], and lipopolysaccharide-induced [75, 106] rat models, as well as the BPH/5 mouse model of PE [58].

Recent scientific interest in IL-10 has been related primarily to investigating whether IL-10 can be utilized as a therapeutic modality, either directly [12••, 107••] or through IL-10 upregulation using different methods, such as the upregulation of Tregs [59••], administration of human umbilical cord-derived mesenchymal stem cells (HU-MSCs) [64••, 75, 106], or dietary micronutrient and omega-3 supplementation [74].

Human Studies

Recent studies evaluating the role of IL-10 in PE are presented in Table 1. Researchers continue to investigate the significance of cytokine profiles in PE. Ferghuson et al. conducted a large cohort study assessing the levels of inflammatory and oxidative stress markers at various times during pregnancy. The individual levels of IL-10 were not significantly different between preeclampsia and normotensive patients. However, when the cytokine patterns were examined together, they showed a distinct pattern across gestation. The authors concluded that the early second trimester appears to be the optimal time point for measurement of these markers. This time point coincides with important events at the level of the placenta [28••]. The results of both Tangeras et al. and Taylor et al. were consistent with those of the Ferghuson study. However, studies continue to provide inconclusive data, with some showing increased [117] and others showing decreased [66, 118] IL-10 levels. The variability of outcomes and inconsistencies of the data were likely influenced by significant discrepancies in study design, including different patient ethnicities, IL-10 detection methods, various PE phenotypes, and the gestational ages at which the samples were obtained. Furthermore, IL-10 has a short plasma half-life, which may contribute to these outcomes. Other major sources of IL-10 may contribute to its circulating levels. This, in turn,

Table 1 Recent studies assessing the role of interleukin-10 in PE patients

Authors	Setting	Sample	Cases PE	Controls NT	IL-10 level in PE	Other
CIRCULATING IL-10						
Adela et al. 2017 [108]	Cross-sectional study	Serum	30	gHTN=10 PE=10 E=10	↑ eclampsia vs gHTN	IL-8 ↑, RANTES and GIP levels ↓
Ferghuson et al. 2017 [28••]	Cohort study	Plasma	50	391	NS	Predictive models of cytokine bundles (CRP, IL-1b, IL-6, IL-10, TNF-a) significant hazard ratios for IL-10 values at the 2. and 3. visits
Hao et al. 2015 [109]	Case control	Plasma	20	20	↓	
Ozkan et al 2017 [110]	Case-control	Plasma	40	40	NS	↑ IFN-γ/IL10 NS TNF-alpha/IL-10
Pinheiro et al 2015 [67]	Case control	Plasma	116 severe PE	107 NT pregnant 58 non-pregnant	↓	vs normotensive/non-pregnant
Sahin et al. 2015 [66]	Case control	Plasma	23 severe 18 mild	80	↓ in severe PE	↑IL-8
Salazar Garcia et al. 2018 [56]	cohort study	Serum	9	77	NS	PE had ↑ TNF-α/IL-10
Tangeras et al. 2015 [111]	Cohort study	Serum	19 gHTN 25 PE	504	NS	
Taylor et al. 2016 [112]	Nested case-control study	Serum	410	297	NS	
Taylor et. Al 2016 [113]	Nested case-control study	Serum	411	208	NS	
Yu et al. 2017 [57]	Cross-sectional study	Serum	46	24	NS	
PLACENTAL IL-10						
Xu et al. 2018 [94]	First-, second-, and third-trimester	Trophoblasts	12	16	↓	
Yang et al. 2017 [114]	NA	Fetal-derived macrophages (Hofbauer cells) within chorionic villi			↓	Hofbauer cells produced IL-10 at lower levels in the PE than in the normal.
Weel et al. 2016 [37]	NA	Placental homogenate	early PE =40, late PE= 80	20	↑TNF-alpha/IL-10 and sFlt-1/PlGF in early-onset PE vs late-onset PE and control groups	Th1/Th2 Imbalance in PE
Peixoto et al 2016 [115]	Third trimester	Deciduas	16 PE/E	30	↓	↓ IL-3
Ozer et al. 2016 [95]	NA	Placentas	22 severe PE 22 HELLP	22	NS	NS sFlt-1, IL-6, AT1-AA, and TNF-alfa

Table 1 (continued)

Authors	Setting	Sample	Cases PE	Controls NT	IL-10 level in PE	Other
IL-10 SECRETION FROM PBMCs						
Vianna et al. 2016 [116]	NA	PBMC culture supernatants	26	25 non-PE 7 NT	↑	↑ IL-17, TNF-α, IL-2, IL-4 NS IFN-γ
Chen et al. 2015 [32•]	Stimulation with LPS for 18h	PBMC culture supernatants	22	23	↓	↑ IL-6 and TNF-α

PBMC- Peripheral Blood Mononuclear Cells, HELLP- Hemolysis Elevated Liver Enzymes and Low platelets syndrome; NS- nonsignificant,; PIGF- Placental Growth factor; TF- tissue factor; gHTN- gestational hypertension; E- eclampsia; RANTES – regulated on activation, normal T cell expressed and secreted; GIP- glucose-dependent insulinotropic polypeptide; IFN-γ- Interferon gamma; TNF-α tumor necrosis factor alpha; sFlt -soluble fms-like tyrosine kinase-1; AT1-AA- Angiotensin II Type I Receptor Autoantibodies; IL- interleukin; CRP- C reactive protein; NS- non significant; ↓-decreased; ↑-increased, NT-normotensive, LPS-lipopolysaccharide.

may explain the lack of correlation between placental/PBMC production and systemic IL-10 levels. Increases in IL-10 levels in select PE patients may be a compensatory response secondary to the vicious circle of hyperinflammation and vascular oxidative stress. Based on the above considerations, measurement of serum IL-10 may not be a suitable early predictor of PE [119]. Considering that the relationships among pertinent interleukins more accurately represent maternal-related events in PE, emphasis should be placed on the ratios of these interleukins rather than upon individual cytokines.

Local IL-10 production, whether via the placenta or activated PBMCs, may more accurately reflect the role of IL-10 in PE. Recent studies have consistently demonstrated decreased placental IL-10 production [37, 94, 115]. Studies investigating PBMCs in PE have shown mostly reduced IL-10 secretion in both stimulated and unstimulated cells [32•, 33, 68, 120]. However, contradictory findings have also been reported, with increased IL-10 secretion along with other pro-inflammatory cytokines [116].

Animal Studies

A host of animal models have been developed to study the pathophysiology of and the possible therapeutic approaches to PE. Although there is a wide variety of animal models from which to choose, this review focused primarily on those models that emphasize IL-10 dysregulation. Kalkunte et al., in 2010, developed a serum-based murine model of PE in which sera from PE patients were administered to IL-10 KO mice. These mice developed symptoms similar to those found in PE, including placental hypoxic injury, and increased levels of sFlt-1 and sEng. The WT mice treated with the PE sera did not demonstrate the classic PE phenotype. This study also reported that the PE sera induced in vitro dysregulated cross-talk between first trimester trophoblast and human umbilical vein endothelial cells that could potentially lead to altered spiral artery remodeling [72•].

Lai et al. evaluated the important role IL-10 in a murine hypoxia-induced PE model. They showed that low oxygen levels induced more severe PE-like symptoms when associated with IL-10 deficiency. Furthermore, anti-angiogenic factors, apoptotic pathways, and placental injury were all present. Interestingly, these symptoms were reversed with IL-10 administration, emphasizing the protective role of IL-10 in hypoxia-induced PE [71].

Chatterjee et al., in 2011, demonstrated that activation of the innate immune response via TLR3 promoted the switch to the Th1 phenotype during pregnancy, resulting in increased blood pressure, endothelial dysfunction, and proteinuria. This sequence of events was found only in pregnant mice. They also showed that deficiency of IL-10, along with TLR3

Table 2 Studies investigating therapeutic interventions involving IL-10 in PE

Authors	Setting	Main findings	Conclusion/comment
Zhang et al. 2017 [64••]	HU-MSCs for the treatment of AT1-AA-induced hypertension in pregnant rats.	↓TNF-α ↑ IL-10	HU-MSCs treatment reduced AT1-AA-induced pregnancy hypertension.
Shi et al. 2017 [121••]	Randomized trial involving 683 women with PE. Treatment groups included either nifedipine+placebo or nifedipine+Vitamin D.	• ↓ The time required to manage the hypertension • ↑ The time before onset of new hypertensive crisis • ↑ IL-10 • ↓ TNF-α	Vitamin D showed promising beneficial effects supportive of oral nifedipine in the treatment of hypertension in PE patients. The possible mechanism involved the upregulation of IL-10 and the downregulation of TNF-α.
Dong et al. 2017 [105]	Effects of Simvastatin in L-NAME-induced rat model of PE were evaluated.	↓ BP	↑ VEGF, ↑ IL-10 ↓ sFlt-1, ↓TNF-α, and ↓MDA in simvastatin-treated group.
Ibrahim et al. 2017 [59••]	Treg stimulation in pregnant normotensive and RUPP-rat model of PE using superagonistic mAB CD28.	• ↓ BP • ↑circulating Tregs • ↓BP • ↓ IL-6, ↓IL-2 in serum • ↑ IL-10 and TGF-β	Beneficial effects observed in RUPP + Superagonistic mAB CD28-rats.
Kemse et al. 2016 [74]	Effects of supplementation with vitamin B-12, folate, omega-3 fatty acid, and their combination was assessed in L-NAME-induced model of PE in rats IL-10 and other cytokines measured.	• ↑ Placental mRNA levels of IL-10 • ↓ BP	Combined supplementation of folic acid, vitamin B-12 and omega-3 fatty acids improved placental levels of IL-10 mRNA and decreased blood pressure in L-NAME-induced hypertensive rats.
Wang et al. 2016 [106]	HU-MSCs administration in LPS-induced rat PE model.	• ↑IL-10 • ↓ TNFα, IL-6, IL-12, and ICAM-1	Treatment with MSC lowered blood pressure and increased fetal weight in PE rats. MSC treatment was associated with increased IL-10 levels in hypertensive pregnant rats.
Kemse et al. 2016 [122]	Effects of supplementation with vitamin B-12, folate, omega-3 fatty acid, and their combination was assessed in L-NAME-induced model of PE in rats. Placental protein levels of IL-10 and other molecules were measured.	• ↑Placental protein IL-10 and VEGF	PE induction resulted in lower IL-10 and VEGF levels compared to controls. Individual omega-3 fatty acid supplementation and combined micronutrient supplementation lessened phenotype and increased placental protein levels of IL-10 and VEGF.
Harmon et al. 2015 [12••]	I.P. infusion of IL-10 in a RUPP-rat model of PE.	• ↓ circulating $CD4^+$ T cells • ↑circulating Tregs. • ↓ BP • ↓ AT1-AA, placental ROS, and ET-1	IL-10 treatment regulated immune system response by decreasing inflammation and endothelial dysfunction.
Fu et al.2015 [75]	HU-MSCs assessed in endotoxin-induced rat model of PE.	• ↓BP, proteinuria and WBCs • ↓TNF-α and IL-1β • ↑ IL-10	Beneficial effects were associated with significantly reduced levels of pro-inflammatory and increased levels of anti-inflammatory cytokines in the endotoxin-treated rats.
Chatterjee et al. 2015 [107••]	Murine model of PE induced with I.P. injection of poly I:C. Treatment with rIL-10, rIL-4, and combination rIL-4/rIL-10 was evaluated.	• All three types of treatment ↓BP; • Only co-treatment with IL-4/IL-10 prevented proteinuria and increased incidence of fetal demise in P-PIC mice. • IL-4/IL-10 co-treatment in pregnant mice had no detrimental effects on pups.	IL-10/IL-4 treatment can normalize immune cell subsets and prevent PE induced by maternal immune system activation.

BP- blood pressure; ↓- decreased, ↑- increased; PE- preeclampsia; HU-MSCs-Human umbilical cord-derived mesenchymal stem cells; AT1-AA- Angiotensin II Type I Receptor Autoantibodies; L-NAME- Nitric oxide synthase inhibitor NG-nitro-l-arginine methyl ester; VEGF- vascular endothelial growth factor; sFlt-1- soluble fms-like tyrosine kinase-1; MDA- malondialdehyde; RUPP- reduced uterine perfusion pressure; mAB- monoclonal antibody; Tregs- regulatory T cells; IL- interleukin; TGF-β- Transforming growth factor beta; LPS- lipopolysaccharide; ICAM- Intercellular adhesion molecule; PIH- pregnancy-induced hypertension; TNF-α- tumor necrosis factor alpha; ROS- reactive oxygen species; ET-1 – Endothelin-1; MSC- mesenchymal stem cells; I.P.- intra-peritoneal; rIL-recombinant interleukin; Poly I:C- polyinosine-polycytidylic acid; P-PIC- poly I:C treated pregnant mice.

activation, worsened the PE-like phenotype and that exogenous IL-10 treatment demonstrated a protective effect [50•].

Potential Therapeutic Options in PE Involving Interleukin-10

Due to a better understanding of the mechanisms underlying the pathophysiology of PE, a number of recent studies evaluating the potential therapeutic approaches towards PE have been performed (Table 2).

A recent clinical trial involving PE patients showed that vitamin D administration augmented the efficacy of anti-hypertensive drug treatment in severe PE patients. This effect was accompanied by increased IL-10 and decreased TNF-α levels in these patients [121••]. This suggests that vitamin D may enhance the effects of anti-hypertensive treatment through beneficial modulation of pro- vs anti-inflammatory cytokines in PE patients.

At least five different animal model studies have shown an advantageous role of exogenous administration of IL-10 in pregnancy-induced hypertension. Tinsley et al. demonstrated that continuous intraperitoneal administration of recombinant human IL-10 attenuated the PE-like phenotype with DOCA-induced hypertension in pregnant rats [73]. The positive effects of IL-10 treatment during gestation included normalized blood pressure, endothelial function, urinary protein excretion, number of pups per litter, as well as decreased plasma levels of ET-1 and serum levels of IFN-γ, reduced placental levels of IFN-α, and lower aortic/placental platelet-endothelial cell adhesion molecule (PECAM) expression. A similar study using rIL-10 in a poly I:C-induced mouse model of PE resulted in significantly decreased blood pressure, increased aortic relaxation, decreased PECAM expression, and diminished placental TLR3 levels [50•]. These findings were corroborated by the same group in 2015 [107••]. This latter study further demonstrated that co-treatment with rIL-4/IL-10 prevented PE-related proteinuria, as well as the increased incidence of fetal demise in Poly I:C treated pregnant mice, whereas the use of either cytokine alone had no effect on these parameters. Harmon et al. evaluated the effects of IL-10 supplementation using mini-osmotic pumps in the RUPP rat model of PE [12••]. This treatment resulted in a significant drop in blood pressure, a rise in circulating levels of IL-10 and Tregs, and an elevation in placental levels of TGF-β when compared to those seen in the RUPP controls. Furthermore, the numbers of circulating $CD4^+$ T cells, levels of TNF-α and IL-6, placental levels of ET-1 and AT1-AA, and placental oxidative stress were decreased. None of the studies reported any adverse effects of these interventions on the fetuses.

In addition to exogenous IL-10 treatment, human umbilical cord mesenchymal stem cells (Hu-MSC) also have been used as treatment in animal models of PE. Fu et al., Zhang et al., and Wang et al. all evaluated the effectiveness of MSC administration in an endotoxin/LPS/AT1-AA-induced-induced rat model of PE [64••, 75, 106]. Treatment using MSCs significantly ameliorated hypertension, proteinuria, and the numbers of white blood cells in the LPS-induced rats. This effect was also associated with decreases in pro-inflammatory TNF-α and IL-1β levels and with an increased level of anti-inflammatory IL-10 [75]. Zhang et al. assessed the effects of Hu-MSC in an AT1-AA-induced hypertension pregnant rat model and demonstrated that intravenous infusion of Hu-MSCs attenuated the hypertension in pregnant rats, with a concomitant increase in circulating IL-10 [64••].

Dong et al. reported that simvastatin treatment significantly raised VEGF and IL-10 levels while reducing sFlt-1, TNF-alpha, and malondialdehyde (MDA) levels compared to the untreated group in a L-NAME-induced rat model of PE [105]. A recent study reported that the stimulation of Tregs with a CD28 antibody reduces inflammation; downregulates ET-1, AT-AA, and ROS pathways; and lowers hypertension in the RUPP rat model of PE [59••]. These effects may be attributable in part to the observed increase in IL-10 production as a result of Treg stimulation. The study also reported an improvement in fetal weights.

Nutritional supplementation of omega-3 fatty acids, vitamin B12, and folic acid has also been shown to reduce inflammation in pregnancy-induced hypertension and to improve the symptoms of PE in an L-NAME-induced rat model of PE, accompanied by increases in both mRNA and protein levels of placental IL-10 [74, 122].

Conclusion

PE is not the result of a single causative factor or pathophysiological pathway, but rather a complex entity with multiple etiological components contributing to its development and progression. We have addressed in this review the integral role of IL-10, a critical cytokine and key regulator of the immune system, its biologic effects, and its association in the context of PE. We conclude that immune system dysregulation, particularly related to IL-10 production, may present a setting that promotes PE development and progression. Therapeutic approaches aimed at IL-10 upregulation may offer promising treatment options in the clinical management of PE.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Roberts JMAP, Bakris G, Barton JR, Bernstein IM, Druzin M, et al. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122–31. https://doi.org/10.1097/01.aog.0000437382.03963.88.
2. George EM, Granger JP. Recent insights into the pathophysiology of preeclampsia. Expert review of obstetrics & gynecology. 2010;5(5):557–66. https://doi.org/10.1586/eog.10.45.
3. von Dadelszen P, Magee LA, Roberts JM. Subclassification of Preeclampsia. Hypertens. 2003;22(2):143–8. https://doi.org/10.1081/PRG-120021060.
4. Ogge G, Chaiworapongsa T, Romero R, Hussein Y, Kusanovic JP, Yeo L, et al. Placental lesions associated with maternal underperfusion are more frequent in early-onset than in late-onset preeclampsia. J Perinat Med. 2011;39(6):641–52. https://doi.org/10.1515/JPM.2011.098.
5. Kovo M, Schreiber L, Ben-Haroush A, Gold E, Golan A, Bar J. The placental component in early-onset and late-onset preeclampsia in relation to fetal growth restriction. Prenat Diagn. 2012;32(7):632–7. https://doi.org/10.1002/pd.3872.
6. Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. Placenta. 2009;30(Suppl A):S32–7. https://doi.org/10.1016/j.placenta.2008.11.009.
7. Paruk F, Moodley J. Maternal and neonatal outcome in early- and late-onset pre-eclampsia. Seminars in neonatology : SN. 2000;5(3):197–207. https://doi.org/10.1053/siny.2000.0023.
8. Myatt L, Redman CW, Staff AC, Hansson S, Wilson ML, Laivuori H, et al. Strategy for standardization of preeclampsia research study design. Hypertension. 2014;63(6):1293–301. https://doi.org/10.1161/hypertensionaha.113.02664.
9. Roberts JM, Gammill HS. Preeclampsia: recent insights. Hypertension. 2005;46(6):1243–9. https://doi.org/10.1161/01.HYP.0000188408.49896.c5.
10. Sowmya S, Sri Manjari K, Ramaiah A, Sunitha T, Nallari P, Jyothy A, et al. Interleukin 10 gene promoter polymorphisms in women with early-onset pre-eclampsia. Clin Exp Immunol. 2014;178(2):334–41. https://doi.org/10.1111/cei.12402.
11. Gilbert JS, Ryan MJ, LaMarca BB, Sedeek M, Murphy SR, Granger JP. Pathophysiology of hypertension during preeclampsia: linking placental ischemia with endothelial dysfunction. Am J Physiol Heart Circ Physiol. 2008;294(2):H541–50. https://doi.org/10.1152/ajpheart.01113.2007.
12. •• Harmon A, Cornelius D, Amaral L, Paige A, Herse F, Ibrahim T, et al. IL-10 supplementation increases Tregs and decreases hypertension in the RUPP rat model of preeclampsia. Hypertens. 2015;34(3):291–306. https://doi.org/10.3109/10641955.2015.1032054. **This article describes the mechanisms through which IL-10 treatment in a rat model of PE decreases blood pressure.**
13. Romero R, Espinoza J, Goncalves LF, Kusanovic JP, Friel L, Hassan S. The role of inflammation and infection in preterm birth. Seminars in reproductive medicine. 2007;25(1):21–39. https://doi.org/10.1055/s-2006-956773.
14. Romero R, Nien JK, Espinoza J, Todem D, Fu W, Chung H, et al. A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate. J Matern Fetal Neonatal Med. 2008;21(1):9–23. https://doi.org/10.1080/14767050701830480.
15. Freeman DJ, McManus F, Brown EA, Cherry L, Norrie J, Ramsay JE, et al. Short- and long-term changes in plasma inflammatory markers associated with preeclampsia. Hypertension. 2004;44(5):708–14. https://doi.org/10.1161/01.HYP.0000143849.67254.ca.
16. Romagnani S. T-cell subsets (Th1 versus Th2). Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2000;85(1):9–18; quiz , 21. https://doi.org/10.1016/s1081-1206(10)62426-x.
17. Saito S, Sakai M. Th1/Th2 balance in preeclampsia. J Reprod Immunol. 2003;59(2):161–73. https://doi.org/10.1016/S0165-0378%2803%2900045-7.
18. Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? Immunology today. 1993;14(7):353–6. https://doi.org/10.1016/0167-5699(93)90235-d.
19. Quinn KH, Lacoursiere DY, Cui L, Bui J, Parast MM. The unique pathophysiology of early-onset severe preeclampsia: role of decidual T regulatory cells. J Reprod Immunol. 2011;91(1-2):76–82. https://doi.org/10.1016/j.jri.2011.05.006.
20. D'Addio F, Riella LV, Mfarrej BG, Chabtini L, Adams LT, Yeung M, et al. The link between the PDL1 costimulatory pathway and Th17 in fetomaternal tolerance. J Immunol. 2011;187(9):4530–41. https://doi.org/10.4049/jimmunol.1002031.
21. Habicht A, Dada S, Jurewicz M, Fife BT, Yagita H, Azuma M, et al. A link between PDL1 and T regulatory cells in fetomaternal tolerance. J Immunol. 2007;179(8):5211–9.
22. Alijotas-Reig J, Llurba E, Gris JM. Potentiating maternal immune tolerance in pregnancy: a new challenging role for regulatory T cells. Placenta. 2014;35(4):241–8. https://doi.org/10.1016/j.placenta.2014.02.004.
23. Hanna N, Hanna I, Hleb M, Wagner E, Dougherty J, Balkundi D, et al. Gestational age-dependent expression of IL-10 and its receptor in human placental tissues and isolated cytotrophoblasts. J Immunol. 2000;164(11):5721–8.
24. Hashii K, Fujiwara H, Yoshioka S, Kataoka N, Yamada S, Hirano T, et al. Peripheral blood mononuclear cells stimulate progesterone production by luteal cells derived from pregnant and non-pregnant women: possible involvement of interleukin-4 and interleukin-10 in corpus luteum function and differentiation. Human reproduction (Oxford, England). 1998;13(1o):2738–44.
25. Kruse N, Greif M, Moriabadi NF, Marx L, Toyka KV, Rieckmann P. Variations in cytokine mRNA expression during normal human pregnancy. Clin Exp Immunol. 2000;119(2):317–22.
26. Darmochwal-Kolarz D, Leszczynska-Gorzelak B, Rolinski J, Oleszczuk J. T helper 1- and T helper 2-type cytokine imbalance in pregnant women with pre-eclampsia. Eur J Obstet Gynecol Reprod Biol. 1999;86(2):165–70.
27. Darmochwal-Kolarz D, Rolinski J, Leszczynska-Goarzelak B, Oleszczuk J. The expressions of intracellular cytokines in the lymphocytes of preeclamptic patients. Am J Reprod Immunol. 2002;48(6):381–6.
28. •• Ferguson KK, Meeker JD, McElrath TF, Mukherjee B, Cantonwine DE. Repeated measures of inflammation and oxidative stress biomarkers in preeclamptic and normotensive pregnancies. American Journal of Obstetrics and Gynecology. 2017;216(5):527.e1–9. https://doi.org/10.1016/j.ajog.2016.12.

174. **This article describes a longitudinal study that examined levels of various biomarkers including IL-10 in a large patient population.**

29. Del Gobbo V, Giganti MG, Zenobi R, Villani V, Premrov MG. The immunosuppressive cytokines influence the fetal survival in patients with pregnancy-induced hypertension. Am J Reprod Immunol. 2000;44(4):214–21.
30. Yang SW, Kwon HS, Sohn IS, Hwang HS, Kim YH, Cho KJ, et al. DC-SIGN expression in Hofbauer cells may play an important role in immune tolerance in fetal chorionic villi during the development of preeclampsia. Am J Reprod Immunol. 2017;78:72. https://doi.org/10.1016/j.jri.2017.09.012.
31. Wilczynski JR, Tchorzewski H, Glowacka E, Banasik M, Lewkowicz P, Szpakowski M, et al. Cytokine secretion by decidual lymphocytes in transient hypertension of pregnancy and preeclampsia. Mediators Inflamm. 2002;11(2):105–11. https://doi.org/10.1080/09629350220131962.
32.• Chen W, Qian L, Wu F, Li M, Wang H. Significance of Toll-like Receptor 4 Signaling in Peripheral Blood Monocytes of Preeclamptic Patients. Hypertens. 2015;34(4):486–94. https://doi.org/10.3109/10641955.2015.1077860. **This article confirms decreased IL-10 secretion by peripheral blood monocytes in preeclamptic patients.**
33. Medeiros LT, Peracoli JC, Bannwart-Castro CF, Romao M, Weel IC, Golim MA, et al. Monocytes from pregnant women with preeclampsia are polarized to a M1 phenotype. Am J Reprod Immunol. 2014;72(1):5–13. https://doi.org/10.1111/aji.12222.
34. Sasaki Y, Darmochwal-Kolarz D, Suzuki D, Sakai M, Ito M, Shima T, et al. Proportion of peripheral blood and decidual CD4(+) CD25(bright) regulatory T cells in pre-eclampsia. Clin Exp Immunol. 2007;149(1):139–45. https://doi.org/10.1111/j.1365-2249.2007.03397.x.
35. Moore KW, de Waal MR, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annual review of immunology. 2001;19:683–765. https://doi.org/10.1146/annurev.immunol.19.1.683.
36. Saraiva M, O'Garra A. The regulation of IL-10 production by immune cells. Nature reviews Immunology. 2010;10(3):170–81. https://doi.org/10.1038/nri2711.
37. Weel IC, Baergen RN, Romao-Veiga M, Borges VT, Ribeiro VR, Witkin SS, et al. Association between placental lesions, cytokines and angiogenic factors in pregnant women with preeclampsia. PLoS ONE. 2016;11(6):e0157584. https://doi.org/10.1371/journal.pone.0157584.
38. LaMarca B, Cornelius DC, Harmon AC, Amaral LM, Cunningham MW, Faulkner JL, et al. Identifying immune mechanisms mediating the hypertension during preeclampsia. American Journal of Physiology - Regulatory Integrative and Comparative Physiology. 2016;311(1):R1–9. https://doi.org/10.1152/ajpregu.00052.2016.
39. Aschkenazi S, Straszewski S, Verwer KM, Foellmer H, Rutherford T, Mor G. Differential regulation and function of the Fas/Fas ligand system in human trophoblast cells. Biol Reprod. 2002;66(6):1853–61.
40. White CA, Johansson M, Roberts CT, Ramsay AJ, Robertson SA. Effect of interleukin-10 null mutation on maternal immune response and reproductive outcome in mice. Biol Reprod. 2004;70(1):123–31. https://doi.org/10.1095/biolreprod.103.018754.
41. Rijhsinghani AG, Thompson K, Tygrette L, Bhatia SK. Inhibition of interleukin-10 during pregnancy results in neonatal growth retardation. Am J Reprod Immunol. 1997;37(3):232–5.
42. Lei J, Firdaus W, Rosenzweig JM, Alrebh S, Bakhshwin A, Borbiev T, et al. Murine model: maternal administration of stem cells for prevention of prematurity. Am J Obstet Gynecol. 2015;212(5):639.e1–10. https://doi.org/10.1016/j.ajog.2014.12.032.
43. Zhang M, Xu J, Bao X, Niu W, Wang L, Du L, et al. Association between Genetic Polymorphisms in Interleukin Genes and Recurrent Pregnancy Loss - A Systematic Review and Meta-Analysis. PLoS ONE. 2017;12(1):e0169891. https://doi.org/10.1371/journal.pone.0169891.
44. Mertz PM, DeWitt DL, Stetler-Stevenson WG, Wahl LM. Interleukin 10 suppression of monocyte prostaglandin H synthase-2. Mechanism of inhibition of prostaglandin-dependent matrix metalloproteinase production. The Journal of biological chemistry. 1994;269(33):21322–9.
45. Ghildyal N, McNeil HP, Gurish MF, Austen KF, Stevens RL. Transcriptional regulation of the mucosal mast cell-specific protease gene, MMCP-2, by interleukin 10 and interleukin 3. The Journal of biological chemistry. 1992;267(12):8473–7.
46. Royle C, Lim S, Xu B, Tooher J, Ogle R, Hennessy A. Effect of hypoxia and exogenous IL-10 on the pro-inflammatory cytokine TNF-alpha and the anti-angiogenic molecule soluble Flt-1 in placental villous explants. Cytokine. 2009;47(1):56–60. https://doi.org/10.1016/j.cyto.2009.04.006.
47. Bowen RS, Gu Y, Zhang Y, Lewis DF, Wang Y. Hypoxia promotes interleukin-6 and -8 but reduces interleukin-10 production by placental trophoblast cells from preeclamptic pregnancies. J Soc Gynecol Investig. 2005;12(6):428–32. https://doi.org/10.1016/j.jsgi.2005.04.001.
48. Kamali-Sarvestani E, Kiany S, Gharesi-Fard B, Robati M. Association study of IL-10 and IFN-gamma gene polymorphisms in Iranian women with preeclampsia. J Reprod Immunol. 2006;72(1-2):118–26. https://doi.org/10.1016/j.jri.2006.04.001.
49. Hennessy A, Pilmore HL, Simmons LA, Painter DM. A deficiency of placental IL-10 in preeclampsia. J Immunol. 1999;163(6):3491–5.
50.• Chatterjee P, Chiasson VL, Kopriva SE, Young KJ, Chatterjee V, Jones KA, et al. Interleukin 10 deficiency exacerbates toll-like receptor 3-induced preeclampsia-like symptoms in mice. Hypertension. 2011;58(3):489–96. https://doi.org/10.1161/HYPERTENSIONAHA.111.172114. **This article emphasized the role of IL-10 in preeclampsia by showing an exacerbated preeclampsia-phenotype in IL-10 deficient mice**.
51. Park SH, Kim KE, Hwang HY, Kim TY. Regulatory effect of SOCS on NF-kappaB activity in murine monocytes/macrophages. DNA and cell biology. 2003;22(2):131–9. https://doi.org/10.1089/104454903321515931.
52. Starr R, Willson TA, Viney EM, Murray LJ, Rayner JR, Jenkins BJ, et al. A family of cytokine-inducible inhibitors of signalling. Nature. 1997;387(6636):917–21. https://doi.org/10.1038/43206.
53. Larsen L, Ropke C. Suppressors of cytokine signalling: SOCS. APMIS : acta pathologica, microbiologica, et immunologica Scandinavica. 2002;110(12):833–44.
54. Berlato C, Cassatella MA, Kinjyo I, Gatto L, Yoshimura A, Bazzoni F. Involvement of suppressor of cytokine signaling-3 as a mediator of the inhibitory effects of IL-10 on lipopolysaccharide-induced macrophage activation. J Immunol. 2002;168(12):6404–11.
55. Murai M, Turovskaya O, Kim G, Madan R, Karp CL, Cheroutre H, et al. Interleukin 10 acts on regulatory T cells to maintain expression of the transcription factor Foxp3 and suppressive function in mice with colitis. Nature immunology. 2009;10(11):1178–84. https://doi.org/10.1038/ni.1791.
56. Salazar Garcia MD, Mobley Y, Henson J, Davies M, Skariah A, Dambaeva S, et al. Early pregnancy immune biomarkers in peripheral blood may predict preeclampsia. J Reprod Immunol. 2018;125:25–31. https://doi.org/10.1016/j.jri.2017.10.048.
57. Yu J, Qian L, Wu F, Li M, Chen W, Wang H. Decreased frequency of peripheral blood $CD8^{+}CD25^{+}FoxP3^{+}$regulatory T cells

correlates with IL-33 levels in pre-eclampsia. Hypertens. 2017;36(2):217–25. https://doi.org/10.1080/10641955.2017.1302470.

58. Heyward CY, Sones JL, Lob HE, Yuen LC, Abbott KE, Huang W, et al. The decidua of preeclamptic-like BPH/5 mice exhibits an exaggerated inflammatory response during early pregnancy. J Reprod Immunol. 2017;120:27–33. https://doi.org/10.1016/j.jri.2017.04.002.

59.•• Ibrahim T, Przybyl L, Harmon AC, Amaral LM, Faulkner JL, Cornelius DC, et al. Proliferation of endogenous regulatory T cells improve the pathophysiology associated with placental ischaemia of pregnancy. Am J Reprod Immunol. 2017;78(5):10.1111/aji.12724. **This article describes a study in which the stimulation of Tregs increased IL-10 and ameliorated PE-like symptoms in rats.**

60. Cornelius DC, Amaral LM, Harmon A, Wallace K, Thomas AJ, Campbell N, et al. An increased population of regulatory T cells improves the pathophysiology of placental ischemia in a rat model of preeclampsia. Am J Physiol Regul Integr Comp Physiol. 2015;309(8):R884–91. https://doi.org/10.1152/ajpregu.00154.2015.

61. Wallace K, Novotny S, Heath J, Moseley J, Martin JN Jr, Owens MY, et al. Hypertension in response to CD4(+) T cells from reduced uterine perfusion pregnant rats is associated with activation of the endothelin-1 system. Am J Physiol Regul Integr Comp Physiol. 2012;303(2):R144–9. https://doi.org/10.1152/ajpregu.00049.2012.

62. Zenclussen AC. A novel mouse model for preeclampsia by transferring activated th1 cells into normal pregnant mice. Methods in molecular medicine. 2006;122:401–12.

63. Zhou CC, Zhang Y, Irani RA, Zhang H, Mi T, Popek EJ, et al. Angiotensin receptor agonistic autoantibodies induce pre-eclampsia in pregnant mice. Nature medicine. 2008;14(8):855–62. https://doi.org/10.1038/nm.1856.

64.•• Zhang D, Fu L, Wang L, Lin L, Yu L, Zhang L, et al. Therapeutic benefit of mesenchymal stem cells in pregnant rats with angiotensin receptor agonistic autoantibody-induced hypertension: Implications for immunomodulation and cytoprotection. Hypertens. 2017;36(3):247–58. https://doi.org/10.1080/10641955.2017.1329429. **This article showed the beneficial correlation between mesenchymal stem cell treatment and IL-10 in a rat model of preeclampsia.**

65. LaMarca B, Wallace K, Herse F, Wallukat G, Martin JN Jr, Weimer A, et al. Hypertension in response to placental ischemia during pregnancy: role of B lymphocytes. Hypertension. 2011;57(4):865–71. https://doi.org/10.1161/HYPERTENSIONAHA.110.167569.

66. Sahin S, Ozakpinar OB, Eroglu M, Tulunay A, Ciraci E, Uras F, et al. The impact of platelet functions and inflammatory status on the severity of preeclampsia. J Matern Fetal Neonatal Med. 2015;28(6):643–8. https://doi.org/10.3109/14767058.2014.927860.

67. Pinheiro MB, Gomes KB, Ronda CR, Guimaraes GG, Freitas LG, Teixeira-Carvalho A, et al. Severe preeclampsia: association of genes polymorphisms and maternal cytokines production in Brazilian population. Cytokine. 2015;71(2):232–7. https://doi.org/10.1016/j.cyto.2014.10.021.

68. Campos-Canas J, Romo-Palafox I, Albani-Campanario M, Hernandez-Guerrero C. An imbalance in the production of proinflammatory and anti-inflammatory cytokines is observed in whole blood cultures of preeclamptic women in comparison with healthy pregnant women. Hypertens. 2014;33(2):236–49. https://doi.org/10.3109/10641955.2013.858744.

69. Jonsson Y, Matthiesen L, Berg G, Ernerudh J, Nieminen K, Ekerfelt C. Indications of an altered immune balance in preeclampsia: a decrease in in vitro secretion of IL-5 and IL-10 from blood mononuclear cells and in blood basophil counts compared with normal pregnancy. J Reprod Immunol. 2005;66(1):69–84. https://doi.org/10.1016/j.jri.2005.02.002.

70.• Orange S, Rasko JE, Thompson JF, Vaughan J, Olive E, Pedler M, et al. Interleukin-10 regulates arterial pressure in early primate pregnancy. Cytokine. 2005;29(4):176–85. https://doi.org/10.1016/j.cyto.2004.10.011. **This article demonstrated direct beneficial effects of IL-10 on vascular function in a primate-pregnancy preeclamptic model. This was one of the first studies to explore the effects of recombinant IL-10 treatment in a pregnancy-induced hypertension.**

71. Lai Z, Kalkunte S, Sharma S. A critical role of interleukin-10 in modulating hypoxia-induced preeclampsia-like disease in mice. Hypertension. 2011;57(3):505–14. https://doi.org/10.1161/HYPERTENSIONAHA.110.163329.

72.• Kalkunte S, Boij R, Norris W, Friedman J, Lai Z, Kurtis J et al. Sera from preeclampsia patients elicit symptoms of human disease in mice and provide a basis for an in vitro predictive assay. Am J Pathol. 2010;177(5):2387-2398. doi:10.2353/ajpath.2010.100475. **This study presents an important model of preeclampsia in IL-10 deficient mice induced by injection of preeclamptic patient serum.**

73. Tinsley JH, South S, Chiasson VL, Mitchell BM. Interleukin-10 reduces inflammation, endothelial dysfunction, and blood pressure in hypertensive pregnant rats. Am J Physiol Regul Integr Comp Physiol. 2010;298(3):R713–9. https://doi.org/10.1152/ajpregu.00712.2009.

74. Kemse N, Sundrani D, Kale A, Joshi S. Maternal Micronutrients, Omega-3 Fatty Acids and Gene Expression of Angiogenic and Inflammatory Markers in Pregnancy Induced Hypertension Rats. Arch Med Res. 2017;48(5):414–22. https://doi.org/10.1016/j.arcmed.2017.10.006.

75. Fu L, Liu Y, Zhang D, Xie J, Guan H, Shang T. Beneficial effect of human umbilical cord-derived mesenchymal stem cells on an endotoxin-induced rat model of preeclampsia. Experimental Ther. 2015;10(5):1851–6. https://doi.org/10.3892/etm.2015.2742.

76. Wang A, Liu Q, Zhang J, Zheng R. Berberine alleviates preeclampsia possibly by regulating the expression of interleukin-2/interleukin-10 and Bcl-2/Bax. Int J Clin Exp Med. 2015;8(9):16301–7.

77. Zemse SM, Chiao CW, Hilgers RH, Webb RC. Interleukin-10 inhibits the in vivo and in vitro adverse effects of TNF-alpha on the endothelium of murine aorta. Am J Physiol Heart Circ Physiol. 2010;299(4):H1160–7. https://doi.org/10.1152/ajpheart.00763.2009.

78. Stefano GB, Christensen VB, Tonnesen E, Liu Y, Hughes TK Jr, Bilfinger TV. Interleukin-10 stimulation of endogenous nitric oxide release from human saphenous veins diminishes immunocyte adherence. Journal of cardiovascular pharmacology. 1997;30(1):90–5.

79. Gunnett CA, Heistad DD, Berg DJ, Faraci FM. IL-10 deficiency increases superoxide and endothelial dysfunction during inflammation. Am J Physiol Heart Circ Physiol. 2000;279(4):H1555–62. https://doi.org/10.1152/ajpheart.2000.279.4.H1555.

80. Gunnett CA, Heistad DD, Faraci FM. Interleukin-10 protects nitric oxide-dependent relaxation during diabetes: role of superoxide. Diabetes. 2002;51(6):1931–7.

81. Garcia JM, Stillings SA, Leclerc JL, Phillips H, Edwards NJ, Robicsek SA, et al. Role of Interleukin-10 in Acute Brain Injuries. Frontiers in neurology. 2017;8:244. https://doi.org/10.3389/fneur.2017.00244.

82. Dammanahalli JK, Wang X, Sun Z. Genetic interleukin-10 deficiency causes vascular remodeling via the upregulation of Nox1. J Hypertens. 2011;29(11):2116–25. https://doi.org/10.1097/HJH.0b013e32834b22a0.

83. Sikka G, Miller KL, Steppan J, Pandey D, Jung SM, Fraser CD 3rd, et al. Interleukin 10 knockout frail mice develop cardiac and vascular dysfunction with increased age. Experimental gerontology. 2013;48(2):128–35. https://doi.org/10.1016/j.exger.2012.11.001.
84. Baeuerle PA, Baltimore D. NF-kappa B: ten years after. Cell. 1996;87(1):13–20.
85. Zemse SM, Hilgers RH, Simkins GB, Rudic RD, Webb RC. Restoration of endothelin-1-induced impairment in endothelium-dependent relaxation by interleukin-10 in murine aortic rings. Canadian journal of physiology and pharmacology. 2008;86(8):557–65. https://doi.org/10.1139/y08-049.
86. Giardina JB, Green GM, Cockrell KL, Granger JP, Khalil RA. TNF-alpha enhances contraction and inhibits endothelial NO-cGMP relaxation in systemic vessels of pregnant rats. Am J Physiol Regul Integr Comp Physiol. 2002;283(1):R130–43. https://doi.org/10.1152/ajpregu.00704.2001.
87. Davis JR, Giardina JB, Green GM, Alexander BT, Granger JP, Khalil RA. Reduced endothelial NO-cGMP vascular relaxation pathway during TNF-alpha-induced hypertension in pregnant rats. Am J Physiol Regul Integr Comp Physiol. 2002;282(2):R390–9. https://doi.org/10.1152/ajpregu.00270.2001.
88. Didion SP, Kinzenbaw DA, Schrader LI, Chu Y, Faraci FM. Endogenous interleukin-10 inhibits angiotensin II-induced vascular dysfunction. Hypertension. 2009;54(3):619–24. https://doi.org/10.1161/hypertensionaha.109.137158.
89. Arriaga-Pizano L, Jimenez-Zamudio L, Vadillo-Ortega F, Martinez-Flores A, Herrerias-Canedo T, Hernandez-Guerrero C. The predominant Th1 cytokine profile in maternal plasma of pre-eclamptic women is not reflected in the choriodecidual and fetal compartments. J Soc Gynecol Investig. 2005;12(5):335–42. https://doi.org/10.1016/j.jsgi.2005.02.005.
90. Benian A, Madazli R, Aksu F, Uzun H, Aydin S. Plasma and placental levels of interleukin-10, transforming growth factor-beta1, and epithelial-cadherin in preeclampsia. Obstet Gynecol. 2002;100(2):327–31.
91. Szarka A, Rigo J Jr, Lazar L, Beko G, Molvarec A. Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension array. BMC Immunol. 2010;11:59. https://doi.org/10.1186/1471-2172-11-59.
92. Sharma A, Satyam A, Sharma JB. Leptin, IL-10 and inflammatory markers (TNF-alpha, IL-6 and IL-8) in pre-eclamptic, normotensive pregnant and healthy non-pregnant women. Am J Reprod Immunol. 2007;58(1):21–30. https://doi.org/10.1111/j.1600-0897.2007.00486.x.
93. Mosimann B, Wagner M, Poon LCY, Bansal AS, Nicolaides KH. Maternal serum cytokines at 30-33weeks in the prediction of pre-eclampsia. Prenatal Diagnosis. 2013;33(9):823–30. https://doi.org/10.1002/pd.4129.
94. Xu J, Gu Y, Sun J, Zhu H, Lewis DF, Wang Y. Reduced CD200 expression is associated with altered Th1/Th2 cytokine production in placental trophoblasts from preeclampsia. Am J Reprod Immunol. 2018;79(1). doi:https://doi.org/10.1111/aji.12763.
95. Ozer DP, Dolgun ZN, Inan C, Sayin NC. The evaluation of placental apoptosis in severe preeclampsia with auto-antibodies and pro-inflammatory cytokines. Journal of the Turkish German Gynecology Association. 2016;17:S51.
96. Darby MM, Wallace K, Cornelius D, Chatman KT, Mosely JN, Martin JN, et al. Vitamin D Supplementation Suppresses Hypoxia-Stimulated Placental Cytokine Secretion, Hypertension and CD4⁺ T Cell Stimulation in Response to Placental Ischemia. Med J Obstet Gynecol. 2013;1(2):23.
97. Rein DT, Breidenbach M, Honscheid B, Friebe-Hoffmann U, Engel H, Gohring UJ, et al. Preeclamptic women are deficient of interleukin-10 as assessed by cytokine release of trophoblast cells in vitro. Cytokine. 2003;23(4-5):119–25.
98. Makris A, Xu B, Yu B, Thornton C, Hennessy A. Placental deficiency of interleukin-10 (IL-10) in preeclampsia and its relationship to an IL10 promoter polymorphism. Placenta. 2006;27(4-5):445–51. https://doi.org/10.1016/j.placenta.2005.05.003.
99. Fan DM, Wang Y, Liu XL, Zhang A, Xu Q. Polymorphisms in interleukin-6 and interleukin-10 may be associated with risk of preeclampsia. Genetics and Molecular Research. 2017;16(1):gmr16018588. https://doi.org/10.4238/gmr16018588.
100. Zhou L, Cheng L, He Y, Gu Y, Wang Y, Wang C. Association of gene polymorphisms of FV, FII, MTHFR, SERPINE1, CTLA4, IL10, and TNFalpha with pre-eclampsia in Chinese women. Inflamm Res. 2016;65(9):717–24. https://doi.org/10.1007/s00011-016-0953-y.
101. Song L, Zhong M. Association between Interleukin-10 gene polymorphisms and risk of early-onset preeclampsia. Int J Clin Exp Pathol. 2015;8(9):11659–64.
102. Liu QY, Gao FY, Liu XR, Li J, Ji M, Dong J, et al. Investigations into the association between polymorphisms in the interleukin-10 gene and risk of early-onset preeclampsia. Genet Mol Res. 2015;14(4):19323–8. https://doi.org/10.4238/2015.December.29.42.
103. Zhang G, Zhao J, Yi J, Luan Y, Wang Q. Association Between Gene Polymorphisms on Chromosome 1 and Susceptibility to Pre-Eclampsia: An Updated Meta-Analysis. Med Sci Monit. 2016;22:2202–14.
104. Lee YH, Kim JH, Song GG. Meta-analysis of associations between interleukin-10 polymorphisms and susceptibility to pre-eclampsia. Eur J Obstet Gynecol Reprod Biol. 2014;182:202–7. https://doi.org/10.1016/j.ejogrb.2014.09.030.
105. Dong X, Shi D. Simvastatin Alleviates Pathology in a Rat Model of Preeclampsia Involving ERK/MAPK Pathway. Reprod Sci. 2017;24(7):1053–61. https://doi.org/10.1177/1933719116678693.
106. Wang LL, Yu Y, Guan HB, Qiao C. Effect of Human Umbilical Cord Mesenchymal Stem Cell Transplantation in a Rat Model of Preeclampsia. Reprod Sci. 2016;23(8):1058–70. https://doi.org/10.1177/1933719116630417.
107.•• Chatterjee P, Chiasson VL, Seerangan G, Tobin RP, Kopriva SE, Newell-Rogers MK, et al. Cotreatment with interleukin 4 and interleukin 10 modulates immune cells and prevents hypertension in pregnant mice. Am J Hypertens. 2015;28(1):135–42. https://doi.org/10.1093/ajh/hpu100. **This article evaluates treatment with recombinant IL-10 in a mouse model of preeclampsia**.
108. Adela R, Borkar RM, Mishra N, Bhandi MM, Vishwakarma G, Varma BA, et al. Lower Serum Vitamin D Metabolite Levels in Relation to Circulating Cytokines/Chemokines and Metabolic Hormones in Pregnant Women with Hypertensive Disorders. Front. 2017;8:273. https://doi.org/10.3389/fimmu.2017.00273.
109. Hao H, He M, Li J, Zhou Y, Dang J, Li F, et al. Upregulation of the Tim-3/Gal-9 pathway and correlation with the development of preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2015;194:85–91. https://doi.org/10.1016/j.ejogrb.2015.08.022.
110. Ozkan ZS, Deveci D, Akpolat N, Simsek M, Ilhan F, Yavuzkir S, et al. Are there any differences between the distribution of placental bed leukocyte subtypes of preeclamptic and healty pregnants? Journal of the Turkish German Gynecology Association. 2016;17:S169.
111. Tangeras LH, Austdal M, Skrastad RB, Salvesen KA, Austgulen R, Bathen TF, et al. Distinct First Trimester Cytokine Profiles for Gestational Hypertension and Preeclampsia. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015;35(11):2478–85. https://doi.org/10.1161/ATVBAHA.115.305817.
112. Taylor BD, Tang G, Ness RB, Olsen J, Hougaard DM, Skogstrand K, et al. Mid-pregnancy circulating immune biomarkers in women

with preeclampsia and normotensive controls. Pregnancy Hypertens. 2016;6(1):72–8. https://doi.org/10.1016/j.preghy.2015.11.002.

113. Taylor BD, Ness RB, Klebanoff MA, Zoh R, Bass D, Hougaard DM, et al. First and second trimester immune biomarkers in pre-eclamptic and normotensive women. Pregnancy Hypertens. 2016;6(4):388–93. https://doi.org/10.1016/j.preghy.2016.09.002.
114. Yang SW, Cho EH, Choi SY, Lee YK, Park JH, Kim MK, et al. DC-SIGN expression in Hofbauer cells may play an important role in immune tolerance in fetal chorionic villi during the development of preeclampsia. J Reprod Immunol. 2017;124:30–7. https://doi.org/10.1016/j.jri.2017.09.012.
115. Peixoto AB, Araujo Junior E, Ribeiro JU, Rodrigues DB, Castro EC, Caldas TM, et al. Evaluation of inflammatory mediators in the deciduas of pregnant women with pre-eclampsia/eclampsia. J Matern Fetal Neonatal Med. 2016;29(1):75–9. https://doi.org/10.3109/14767058.2014.987117.
116. Vianna P, Mondadori AG, Bauer ME, Dornfeld D, Chies JA. HLA-G and CD8+ regulatory T cells in the inflammatory environment of pre-eclampsia. Reproduction. 2016;152(6):741–51. https://doi.org/10.1530/REP-15-0608.
117. Molvarec A, Szarka A, Walentin S, Beko G, Karadi I, Prohaszka Z, et al. Serum heat shock protein 70 levels in relation to circulating cytokines, chemokines, adhesion molecules and angiogenic factors in women with preeclampsia. Clin Chim Acta. 2011;412(21-22):1957–62. https://doi.org/10.1016/j.cca.2011.06.042.
118. Ribeiro VR, Romao-Veiga M, Romagnoli GG, Matias ML, Nunes PR, Borges VTM, et al. Association between cytokine profile and transcription factors produced by T-cell subsets in early- and late-onset pre-eclampsia. Immunology. 2017;152(1):163–73. https://doi.org/10.1111/imm.12757.
119. Mansouri R, Akbari F, Vodjgani M, Mahboudi F, Kalantar F, Mirahmadian M. Serum cytokines profiles in Iranian patients with preeclampsia. Iran J Immunol. 2007;4(3):179-85. doi:https://dx.doi.org/IJIv4i3A7.
120. Cristofalo R, Bannwart-Castro CF, Magalhaes CG, Borges VT, Peracoli JC, Witkin SS, et al. Silibinin attenuates oxidative metabolism and cytokine production by monocytes from preeclamptic women. Free Radic Res. 2013;47(4):268–75. https://doi.org/10.3109/10715762.2013.765951.
121.•• Shi DD, Wang Y, Guo JJ, Zhou L, Wang N. Vitamin D Enhances Efficacy of Oral Nifedipine in Treating Preeclampsia with Severe Features: A Double Blinded, Placebo-Controlled and Randomized Clinical Trial. Front Pharmacol. 2017;8:865. https://doi.org/10.3389/fphar.2017.00865. **This article is a randomized controlled study of the beneficial effects of D vitamin supplementation on the cytokine profile and IL-10 in preeclamptic patients.**
122. Kemse NG, Kale AA, Joshi SR. Supplementation of maternal omega-3 fatty acids to pregnancy induced hypertension Wistar rats improves IL10 and VEGF levels. Prostaglandins Leukot Essent Fatty Acids. 2016;104:25–32. https://doi.org/10.1016/j.plefa.2015.11.003.