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Key Points:

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Preeclampsia (PE), new-onset hypertension during pregnancy, affects up to 10% of pregnancies worldwide. Despite being the leading cause of maternal and fetal morbidity and mortality, there is no cure for PE beyond the delivery of the fetal-placental unit. Although the exact pathogenesis of PE is unclear, there is a strong correlation between chronic immune activation, intrauterine growth restriction, uterine artery resistance, dysregulation of the renin angiotensin system which contributes to renal dysfunction, and the resulting hypertension during pregnancy. The genesis of PE is thought to begin with insufficient trophoblast invasion leading to reduced spiral artery remodeling resulting in decreased placental perfusion thereby causing placental ischemia. The ischemic placenta releases factors that shower the endothelium and contribute to peripheral vasoconstriction and chronic immune activation and oxidative stress. Studies have shown imbalances in pro-inflammatory and anti-inflammatory cell types in women with PE and in animal models utilized to examine mediators of a PE phenotype during pregnancy. T cells, B cells, and natural killer cells have all emerged as potential mediators contributing to the production of vasoactive factors, renal and endothelial dysfunction, mitochondrial dysfunction, and hypertension during pregnancy. The chronic immune activation seen in PE leads to a higher risk for other diseases such as cardiovascular disease, chronic kidney disease, dementia during their postpartum period, and PE during a subsequent pregnancy. The purpose of this review is to highlight studies demonstrating the role that different lymphoid cell populations in the pathophysiology of PE. Moreover, we will discuss treatments focused on restoring immune balance or targeting specific immune mediators that may be potential strategies to improve maternal and fetal outcomes associated with PE.

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The Role of Different Lymphoid Cell Populations in Preeclampsia Pathophysiology

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Abstract

Preeclampsia (PE), new-onset hypertension during pregnancy, affects up to 10% of pregnancies worldwide. Despite being the leading cause of maternal and fetal morbidity and mortality, there is no cure for PE beyond the delivery of the fetal-placental unit. Although the exact pathogenesis of PE is unclear, there is a strong correlation between chronic immune activation, intrauterine growth restriction, uterine artery resistance, dysregulation of the renin angiotensin system which contributes to renal dysfunction, and the resulting hypertension during pregnancy. The genesis of PE is thought to begin with insufficient trophoblast invasion leading to reduced spiral artery remodeling resulting in decreased placental perfusion thereby causing placental ischemia. The ischemic placenta releases factors that shower the endothelium and contribute to peripheral vasoconstriction and chronic immune activation and oxidative stress. Studies have shown imbalances in pro-inflammatory and anti-inflammatory cell types in women with PE and in animal models utilized to examine mediators of a PE phenotype during pregnancy. T cells, B cells, and natural killer cells have all emerged as potential mediators contributing to the production of vasoactive factors, renal and endothelial dysfunction, mitochondrial dysfunction, and hypertension during pregnancy. The chronic immune activation seen in PE leads to a higher risk for other diseases such as cardiovascular disease, chronic kidney disease, dementia during their postpartum period, and PE during a subsequent pregnancy. The purpose of this review is to highlight studies demonstrating the role that different lymphoid cell populations play in the pathophysiology of PE. Moreover, we will discuss treatments focused on restoring immune balance or targeting specific immune mediators that may be potential strategies to improve maternal and fetal outcomes associated with PE.
**Introduction**

Preeclampsia (PE) is a hypertensive disorder during pregnancy affecting 3-5% of pregnancies in the United States and up to 10% of pregnancies worldwide [1-3]. Major characteristics of PE include new-onset hypertension after the 20th week of gestation, multi-organ system dysfunction, fetal growth restriction, endothelial dysfunction, and chronic immune activation [1, 3]. PE typically worsens as the pregnancy progresses, and delivery of the fetal-placental unit remains the only known treatment. The current standard of care involves treating symptoms of PE with antihypertensive drugs such as hydralazine and labetalol, magnesium sulfate to reduce risk of seizures and strokes, and steroids for fetal lung development in order to sustain the pregnancy as long as possible, which is critical for fetal development.

The specific mechanisms that contribute to the development of PE are still being better defined, but the current belief is that insufficient trophoblast invasion leads to spiral artery remodeling, compromised blood flow to the fetal-placental unit, and a deficiency of oxygen and nutrient delivery to the placenta and fetus. This results in intrauterine growth restriction and placental ischemia which appears to be a stimulus for anti-angiogenic factors and inflammatory mediators [4-6]. In normal pregnancies, trophoblast invasion and spiral artery remodeling rely on maternal immune regulation for adequate vascular transformation [7, 8]. Due to inadequate vascular remodeling, women with PE have elevated uterine artery resistance which contributes to activation of the maternal endothelium, chronic inflammation and oxidative stress systemically [9-11]. Women with normal pregnancies experience increased plasma volume that peaks near gestational week 32, continuing until delivery and a natural upregulation of renin-angiotensin-aldosterone system (RAAS) components such as Angiotensin II (Ang II) which is counterbalanced by the vasodilator Angiotensin 1-7[12-14] (Figure 1). Increased Angiotensin 1-
7 and increased endothelial nitric oxide production due to estrogen and progesterone may account for increased resistance or decreased sensitivity to Ang II allowing for blood pressure to remain lower in non-pregnant women [15-17]. In contrast, women with PE have significantly increased sensitivity to Ang II and decreased plasma volumes, the degree of which correlates with the severity of the disease [18]. Gallery et al. [19] demonstrated that this decreased plasma volume occurs several weeks prior to elevated blood pressure as well as other symptoms of PE. In addition to the decreased plasma volume, PE women have reduced glomerular filtration rate (GFR) and increased renal vascular resistance (RVR) [20]. PE is associated with glomerular capillary endotheliosis, characterized by swollen glomerular cells and capillary occlusion [21, 22]. Often times this reverses after delivery[22], however, PE is associated with increased risk for the development of end-stage kidney disease [23, 24]. Interestingly, in contrast to normal pregnancy, PE women have a downregulation of many components of the RAAS which likely contributes to variations in plasma volume load, renal function and the lack of blood pressure regulation [19, 25-27]. The compensatory activation of the RAAS in response to decreased plasma volume does not occur. It is unclear whether this phenomenon is a cause or consequence of PE.

Importantly, PE women secrete an autoantibody to the angiotensin II type 1 receptor (AT1-AA) [55] (Figure 1). This AT1-AA is agonistic in nature activating the AT1 receptor and may account for the exaggerated pressor sensitivity to infused Ang II PE patients [28] (Figure 1). AT1-AAs increase the production of reactive oxygen species, inflammatory cytokines, and tissue factors through the activation of the AT1 receptor [29-33]. Additionally, these AT1-AAs can be recognized as antibodies bound to cells that should be destroyed by NK cells, contributing to NK cell activation [34]. In rat models of PE, AT1-AA causes hypertension, oxidative stress,
endothelin-1 and cytokine production, and vascular dysfunction[31, 33, 35, 36]. Moreover, when
the two are infused simultaneously there is an additive increase in the secondary responses such
as oxidative stress, endothelin-1 production, and renal vascular dysfunction [33]. Although the
stimulus for the AT1-AA is unknown, the AT1-AA has been shown to be produced by PE
women 6-8 years postpartum [37, 38]. This indicates a long term memory response is at play,
thus indicating a role for lymphoid cells in the pathogenesis of PE.

This review aims to provide insight into mechanics of key lymphoid cells such as T cells,
B cells, and NK cells in normal pregnancy and preeclamptic pregnancies, and also discusses
potential therapeutics in immune system regulation of PE. T cells are a component of the
adaptive immune system and play a central role in modulating the adaptive immune response. B
cells are also part of the adaptive immune system and produce antibodies as well as cytokines to
promote immunity and help clear pathogens. NK cells are part of the innate immune system and
provide a rapid, cytotoxic response to viral or cancerous cells. Therefore, by summarizing studies
examining the role of lymphoid cells in PE, this review will contribute to the collection of
research that could lead to the development of new therapeutics for PE. Importantly, it will aid in
understanding the molecular mechanisms of lymphoid cells in PE, which is necessary for an
adapted approach in diagnosing and treating of PE.
Figure 1: Changes in components of the renin-angiotensin-aldosterone system (RAAS) during pregnancy and preeclampsia (PE). Renin cleaves angiotensin I from angiotensinogen. Angiotensin I is converted to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II binds to the angiotensin II type 1 receptor (AT1-R) which contributes to aldosterone production and vasoconstriction. Ang1-7 binds to the MAS receptor which contributes to vasodilation. PE is associated with increased Angiotensin II sensitivity which is thought to be caused by AT1-AA. This increased sensitivity contributes to increased vasoconstriction which plays a role in placental ischemia, which causes T cell and B cell activation leading to the production of AT1-AA. AT1-AA bound to healthy tissues also contributes to cytolytic NK cell activation.

The role of lymphoid cells in normal pregnancy and preeclampsia

Studies demonstrate shifts in immune cell populations and chronic immune activation in PE women compared to normal pregnancies. During normal pregnancies, populations of anti-inflammatory immune cells are elevated to help the mother tolerate the immunogenic fetus [39,
In pregnancies complicated by PE, there is a shift toward pro-inflammatory immune cell types [41, 42]. The chronic inflammation seen in PE can be sustained postpartum, negatively impacting maternal health and contributing to an increased risk for cardiovascular and metabolic disorders later in life. Studies have shown important roles for multiple cell types in the pathogenesis of PE including T cells, B cells, and Natural Killer cells (Figure 2). Importantly, there is a lack of studies examining the importance of neutrophils, macrophages and dendritic cells to cause the pathology of PE. This lack of knowledge presents an opportunity for researchers to target specific immune cells with immunomodulating therapeutics in animal models or cell culture systems in order to further elucidate their role in the pathophysiology of PE and thus potentially find new treatments for PE.

**T Cells in Normal Pregnancy and Preeclampsia**

T cells play a critical role in regulating and stimulating the adaptive arm of the immune system. CD4+ T cells, also known as T helper cells, can be further classified as T Helper 1 (TH1) cells and T Helper 2 (TH2) cells. In normal pregnancy, the balance between TH1 and TH2 cells is shifted towards TH2 cell types to ensure maternal tolerance towards fetal alloantigens [41, 43]. This shift is likely due to increased progesterone production and elevated production of interleukin-4 (IL-4), an anti-inflammatory cytokine [44]. PE patients produce higher levels of TH1 associated cytokines such as interferon-γ (IFN-γ) [45]. In PE, there is also a shift from TH2 towards predominately TH1 T cells [45]. Furthermore, the predominance of either TH1 immunity or TH2 immunity has been implicated in recurrent spontaneous abortion as well as PE [46, 47].
Figure 2: Lymphoid cell interplay to cause cell death in Preeclampsia. Lymphocytes work in tandem to induce inflammation during preeclampsia (PE). 1. CD4+ T cells activate B cells through TCR-MHCII and CD40L-CD40 crosstalk on T and B cells, respectively. T cell-B cell communication causes B cells to proliferate and transform into memory B cells and Plasma cells. Memory B cells retain long term antigen memory, while plasma cells produce antibodies and secrete them into the circulation. 2. Th1 and TH17 cells produce IL-17, TNF-α, and IFN-γ, which polarize Natural Killer (NK) cells towards the cytolytic NK1 phenotype. In PE, plasma cells produce autoantibodies that can target cells for antibody dependent cellular cytotoxicity through activation of the CD16 receptor on NK cells. (For example, AT1-AA can bind a cell that expresses the AT1 receptor. Once, the Fc region of the AT1-AA is recognized by CD16 on the NK cell surface, perforin and granzymes granules are released from the NK cell that induce apoptosis of the AT1-AA marked cell resulting in death and tissue damage). 3. Antibody mediated cell death alongside AT1 receptor activation leads to vasoconstriction and a continuation of the immune response contributing to chronic inflammation. 4. This leads to vascular dysfunction in the placenta, kidney, and brain and hypertension.
T helper cells can also differentiate into other subtypes such as T Helper 17 (TH17) cells and regulatory T cells (Tregs). TH17s selectively produce the pro-inflammatory cytokine interleukin-17 (IL-17) and they also produce pro-inflammatory cytokines interleukin-21 (IL-21) and interleukin-22 (IL-22) [48, 49]. In contrast, Tregs play a role in immunoregulation and tolerance [50-52]. During normal pregnancy, the Treg population expands both systemically and at the maternal-fetal interface. These cells have protective functions through cell-to-cell interactions and the production of anti-inflammatory cytokines. Tregs produce interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) which can act to suppress the effector functions of other activated immune cell populations. Anti-inflammatory cytokines such as IL-10 and IL-4 play a critical role in successful pregnancies and therefore, Tregs, as well as TH2 cells, are believed to be critical in maintaining immune balance[53]. Moreover, analysis of blood from women with PE shows a significant shift in the populations of circulating T helper cell subtypes. Clinical studies demonstrate an increase in TH17 cells alongside a decrease in Tregs in peripheral and umbilical blood samples [51, 54]. Increased TH17 cells in PE patients are hypothesized to increase the production of cytokines, recruitment of other immune cells, and the generation of oxidative stress in the placenta [55-57] (Figure 2). However Barnie et al. [58] have shown that increases in IL-17 may also be due to elevations in innate lymphoid cell 3s (ILC3s). Additionally, Tregs have been shown to lose their suppressive function and their proliferation is downregulated in autoimmune diseases. This decreased Treg number combined with loss of function contributes to a lack of tolerance towards fetal alloantigens. Interestingly, Tregs adoptively transferred from normal pregnant rats into Reduced Uterine Perfusion Pressure (RUPP) rats improves blood pressure and lowers inflammatory mediators [50]. The RUPP model is a surgically induced model of PE that recaptures many PE symptoms including elevated blood
pressure and inflammatory activation including the predominance of TH1 vs TH2 cells and B cells secreting the AT1-AA. This indicates the downregulation of Tregs in response to placental ischemia plays a role in pathology of the RUPP rat and a protective role during normal pregnancy to control inflammation and production of vasoactive factor.

The Zenclussen lab demonstrated that the adoptive transfer of activated TH1-like cells into pregnant mice induced a PE-like phenotype including elevated blood pressure, proteinuria, and cytokine production [59]. Our lab performed similar studies showing adoptive transfer of CD4+ T cells from the RUPP rat model of PE into normal pregnant rats increased blood pressure, inflammatory cytokines TNF-α, IL-6 and IL-17, as well as increased production of placental endothelin-1 (ET-1) and circulating soluble fms-like tyrosine kinase 1 (sFlt-1) and AT1-AA [60, 61]. Studies also demonstrate that inflammatory cytokines such as TNF-α, IL-6, and IL-17 play crucial roles in immune activation by increasing the production of vasoactive molecules such as AT1-AA, ET-1 and sFlt-1 [62-64]. Importantly we recently showed that adoptive transfer of CD4+ T cells from placentas of PE patients causes hypertension, IUGR, increased AT1-AA, sFlt-1, ET-1 and the cytokines TNF-α, and IL-17 demonstrating the importance of T cells in causing many characteristics of PE[65].

After a primary antigen response, most activated T cells die off, however some differentiate into memory T cells which remain to provide quicker responses to a secondary antigenic exposure [66]. Memory T cells can fall into subsets, mainly central memory (CM) and effector memory (EM) cells. CM cells differentiate into effector cells upon antigen exposure and EM cells reside in peripheral tissue and conduct the pro-inflammatory response upon antigen exposure [67, 68]. There is a delicate balance of these subtypes in a normal pregnancy that is
usually higher than in non-pregnant women [66]. During complicated pregnancies like PE, this balance is disrupted and these cells contribute to chronic inflammation seen in the disorder [66].

Another important role that T cells play in normal immunity is the co-stimulation of B cells [69] (Figure 2). This interaction occurs between the T cell receptor, CD40 ligand (CD40L), the MHC class II molecule, and CD40 receptor on B cells [70, 71]. Once this activation takes place, B cells proliferate and differentiate into plasma cells and memory B cells[72, 73]. Plasma cells provide short-term, immediate protection while memory B cells provide long-term, persistent protection through antibody production [74].

We have shown that communication between T cells and B cells is crucial for the development of PE symptoms in an adoptive transfer model of PE. T helper cells were isolated from RUPP animals and incubated with anti-CD40L to block communication with B cells prior to transfer into normal pregnant rats [75]. This blockade improved PE characteristics compared to normal pregnant rat recipients of control RUPP T cells. We have also shown that T cells isolated from PE patients can cause PE symptoms in pregnant nude-athymic rats [76]. More recently, we showed that incubation with anti-CD40L prior to adoptive transfer also improved PE symptoms in the nude-athymic model further indicating that T cells co-stimulating B cells is critical to the pathophysiology of PE [65].

**B Cells in Preeclampsia**

B cells are typically divided into two different populations, B1 and B2 cells. B1 cell development occurs during fetal life and their precursors are present in the fetal liver. These cells are typically found in peripheral circulation in humans but found in the peritoneal cavity in murine animals. B1 cells produce “natural antibodies” that do not require an antigenic stimulus. B2 cells are produced from precursors present in the bone marrow and migrate to the spleen where they can then undergo antigen exposure and co-stimulation from T cells.
exposure and co-stimulation, B2 cells undergo Ig class switching and differentiation into plasma
cells and memory B cells. During normal pregnancies, B cells are believed to produce protective
asymmetric antibodies, and the failure to produce these results in a failure of the pregnancy[77].
Canellada et al. [78] showed that B cells isolated from the placenta and stimulated with CD40L
produced a large amount of these protective antibodies. Stimulation with the CD40L also
supports the hypothesis that T cell to B cell communication is key during pregnancy.

B cells have been implicated in the pathology associated with PE primarily due to the
production of autoantibodies [79, 80]. Antiphospholipid antibodies have been associated with PE
as well as spontaneous abortion and intrauterine fetal death [81]. Velasquillo et al. [82] have
shown a high number of B1a cells (CD19+CD5+) cells in the peripheral circulation of patients
with antiphospholipid syndrome. B1a cells are fetal in origin and have a role in other
autoimmune diseases including type 1 diabetes and lupus erythematosus [83, 84]. Jensen et al
showed that B1a cells isolated from PE patient blood can produce AT1-AA [85]. Other studies
have shown that autoantibody production is persistent for years after a preeclamptic pregnancy
indicated a potential memory mechanism involved in their production [37, 38]. This would also
implicate B2 cells in the production of autoantibodies during PE. B2 cells are classical B cells
that produce antibodies after T cell dependent activation resulting in long-lived memory B cells
that continue to produce antibodies [74]. This would further implicate B2 cells in chronic
inflammation and increased risk of cardiovascular and metabolic disease later in life after a PE
pregnancy due to the persistent production of AT1-AA.

**NK Cells in Preeclampsia**

Natural killer (NK) cells are a type of ILCs that are important in human pregnancy and
systemic regulation due to their high cytolytic potential against tumor transformed and virus-
infected cells [86]. NK cells develop in the bone marrow from lymphoid progenitor cells and account for approximately 70% of uterine lymphocytes and 5-10% of peripheral lymphocytes during the first trimester of pregnancy [86, 87]. When activated, NK cells release perforin and granzymes that induce cell lysis and they produce pro-inflammatory cytokines IFN-γ and TNF-α [88, 89]. However, uterine NK cells promote placental vascular growth rather than cytotoxic activity [90, 91]. Furthermore, these cells assist with trophoblast invasion and spiral artery remodeling, early processes that are critical for a successful pregnancy, through cytokine production and angiogenic factor secretion [90]. The amount and type of NK cells in the decidua during pregnancy appears to be critical for pregnancy success [90, 92].

Women with pregnancy disorders such as PE have a shift in NK cell populations away from the regulatory uterine NK cells toward pro-inflammatory cytolytic NK cells [42, 92]. Cytolytic NK cell number and activity are elevated in patients with PE[93]. Furthermore, clinical studies have demonstrated that there are shifts in the NK cell population in women with PE due to the upregulation of pro-inflammatory cytokines such as IL-2, IL-17, TNF-alpha, and IFN-γ, which also promotes a TH1 cell response [94, 95]. These elevated cytokines, coupled with increases in other pro-inflammatory cells and a decrease in anti-inflammatory cells, cause NK cells to shift from regulatory uterine NK cells to cytolytic NK cells. [94]. Cytolytic NK cells primary destroy infected or cancer cells through the release of cytolytic enzymes [96]. These activated NK cells also produce TNF-α and INF-γ further contributing to the chronic inflammation in PE [42, 97]. Recent studies from Travis et al. [57, 98] show that NK cells stimulated from the RUPP rat model of PE can cause preeclamptic symptoms in healthy pregnant rats and that NK cells from PE rats have a 5-fold increase in cytolytic activity compared to normal controls. Travis et al. also demonstrated that blockade of IL-17 with its soluble receptor,
IL-17 RC, reduced NK cell activation and improved PE symptoms in RUPP rats [57]. They postulate that activation of NK cells is one mechanism by which IL-17 contributes to hypertension in PE and that activated NK cells are an important cellular mediator in PE pathophysiology.

Based on our previous studies, our overall laboratory hypothesis demonstrates that placental ischemia causes lymphocyte activation which contributes to hypertension through multiple mechanisms. T cells function to activate B cells, but also secrete inflammatory cytokines that lead to endothelial activation and dysfunction thus contributing to hypertension. Furthermore, B cells secrete AT1-AA which directly activate the AT1R resulting in increased vascular resistance but also producing anti-angiogenic factors downstream of AT1R activation. AT1-AA and inflammatory cytokines contribute to the activation of NK cells which can kill AT1AA bound cells which can contribute to increased multi-organ dysfunction and increased vascular tone leading to increased vascular resistance and contributing to hypertension.

**Experimental Therapeutics Targeting Lymphoid Cells**

Due to the critical role that immune cells play in the pathogenesis of PE, numerous therapeutics targeting the immune system have been tested with in vivo or in vitro models of PE. A current preventative for women at high risk of PE is a low-dose course of aspirin that inhibits prostaglandin thromboxane A2 [99]. Aspirin use early in pregnancy can prevent or delay the onset of PE [99]. Aspirin is a cyclooxygenase inhibitor which prevents the production of prostaglandins and thromboxanes. The exact mechanism by which aspirin prevents PE is unknown, but current hypothesis is that it improves the placentation process, inhibits placental infarct by reducing platelet aggregation through inhibition of thromboxane production, and reduces inflammation and stabilizes the endothelium through inhibition of prostaglandin [100,
Low molecular weight heparin has also been used to prevent PE through its anti-inflammatory, anticoagulant, and immunomodulatory effects [102]. Systemic lupus erythematosus patients continue on hydroxychloroquine, an antimalarial drug that has immunosuppressive effects, during their pregnancy to reduce the risk of PE by reducing T cell activation [103].

Preclinical studies modulating lymphoid cells in the RUPP rat model of PE demonstrate potential therapy that could be attempted in PE patients. Rituximab, an anti-CD20 monoclonal antibody that depletes B cells, improved PE symptoms in the RUPP model of PE [104]. B cell depletion correlated with reduced circulating AT1-AA, circulating inflammatory cytokines, and maternal blood pressure. Importantly, Rituximab exposure during pregnancy does not increase the rate of preterm delivery or congenital malformations and there is no evidence the incidence of PE increased in this patient population [105, 106]. Orencia, a fusion molecule that inhibits co-stimulation of T cells by binding to CTLA-4, has shown beneficial effects in RUPP rats and in another model of PE rats [107, 108]. Orencia improves maternal blood pressure, oxidative stress in the placenta and kidney, and anxiety-related behaviors[109]. Investigators have also looked for ways to block the actions of IL-17 as TH17s seem to play a crucial role in PE pathophysiology. Infusion of soluble IL-17 receptor C (IL-17RC) into RUPP rats decreased TH17 cell population, AT1-AA production, blood pressure, and improved pup weight [110]. AT1-AA has been targeted directly with a seven amino acid sequence peptide that binds to AT1-AA on its binding region in animal and cell culture models [111, 112]. This blockade improves blood pressure, NK cell activation, mitochondrial oxidative stress, as well as decreasing circulating sFlt-1 and ET-1. Etanercept, a soluble receptor for TNF-α, also demonstrated positive effects in RUPP rats by improving maternal blood pressure, circulating inflammatory cytokines,
natural killer cell activation, and ET-1 [113, 114]. Although there are preclinical studies and
some clinical situations in which lymphoid modulating drugs show promise to alleviate PE
phenotypes, the effects and safety of immune-modulating therapeutics on fetal health is still
under investigation and requires further study before they can become options for clinical use.

Summary

PE is defined as new onset hypertension with multi-organ dysfunction including the
brain, liver, kidney, cardiovascular system, and the placenta. PE is also associated with abnormal
changes in expression of renin-angiotensin-aldosterone system components that could contribute
to the overall pathophysiology of the disorder. Moreover, compelling evidence suggests that PE
is also associated with chronic immune activation characterized by a shift towards pro-
inflammatory cytokines and lymphoid cell types and away from anti-inflammatory cytokines and
regulatory lymphoid cells. While the mechanisms that cause PE are still unclear, the contribution
of the immune system to preeclamptic symptoms is unfolding. Multiple cell types contribute to
endothelial dysfunction, tissue damage, and further immune activation to cause hypertension in
pregnancy. Additionally, autoantibodies play a clear role in contributing to the tissue damage and
elevated blood pressure that characterize PE. Better understanding the role of the immune system
in the pathophysiology of PE is critical as it allows researchers and clinicians new possibilities
for therapy.
Disclosures

B. LaMarca reports the following: Honoraria: NIH; UAB; Advisory or Leadership Role: UMC; DOJ; and Speakers Bureau: UAB. The remaining authors have nothing to disclose.

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Author Contributions

Nathan Campbell: Conceptualization; Project administration; Writing - original draft; Writing - review and editing. Evangeline Deer: Conceptualization; Writing - original draft; Writing - review and editing. Owen Herrock: Conceptualization; Writing – original draft. Babbette LaMarca: Conceptualization; Writing - original draft; Writing - review and editing.
Works Cited


