**An Exploratory overview of Cytokine and Chemokine-driven Inflammatory pathways to decipher the Immune landscape of Pregnancy-induced hypertension**

**ABSTRACT**

Hypertensive disorders of pregnancy and pregnancy-induced hypertension(PIH) are often erroneously often erroneously used interchangeably and in remote past collectively termed "toxemia of pregnancy". This continues to represent a critical global health concern, contributing significantly to maternal and perinatal morbidity and mortality. According to the American College of Obstetricians and Gynecologists (ACOG), these disorders affect approximately 2–8% of pregnancies worldwide, underscoring their clinical relevance. Despite advancements in prenatal care, hypertensive conditions remain a substantial cause of maternal death across both low-resource and high-income settings. Regional data indicate that hypertensive disorders account for approximately 26% of maternal deaths in Latin America and the Caribbean, while in Africa and Asia, they contribute about 9%. Even in high-income countries, where maternal mortality rates have declined considerably due to improvements in obstetric care, 16% of maternal deaths are still attributed to these conditions.

Among the hypertensive disorders of pregnancy, preeclampsia remains the commonest is characterized by new-onset hypertension after 20 weeks of gestation, often accompanied by proteinuria or signs of systemic organ dysfunction and it is associated with adverse outcomes for both mother and fetus. While the precise pathophysiological mechanisms underlying preeclampsia and related hypertensive conditions remain incompletely defined, mounting evidence implicates dysregulated immune and inflammatory responses as central drivers in their development and progression.

One of the prevailing hypotheses posits an imbalance between pro-angiogenic factors (such as vascular endothelial growth factor [VEGF] and placental growth factor [PlGF]) and anti-angiogenic factors (notably soluble fms-like tyrosine kinase-1 [sFlt-1] and soluble endoglin), leading to widespread endothelial dysfunction and impaired placental perfusion. This angiogenic imbalance is believed to be influenced or even triggered by an aberrant maternal immune response to fetal antigens.

Several maternal risk factors have been identified that increase susceptibility to pregnancy-induced hypertension, including extremes of maternal age (particularly under 14 or over 35), a personal or family history of chronic hypertension, preeclampsia, or diabetes, obesity, primigravidity, multiparity, and certain racial/ethnic backgrounds, especially Black and Hispanic populations. Additional risk factors include elevated systolic blood pressure early in pregnancy, high pre-pregnancy body mass index (BMI), a history of smoking, and prior spontaneous abortions or miscarriages.

Increasing attention has been directed toward understanding the immunological landscape of hypertensive pregnancy disorders. In particular, the roles of inflammatory cells (such as macrophages, neutrophils, and T lymphocytes) and their secreted mediators; cytokines (e.g., TNF-α, IL-6, IL-10) and chemokines (e.g., CXCL8, CCL2),have emerged as critical components in the pathogenesis of preeclampsia and other forms of PIH. An exaggerated maternal systemic inflammatory response, coupled with insufficient immune tolerance at the maternal-fetal interface, may contribute to the endothelial injury, placental ischemia, and oxidative stress that characterize these disorders.

This review seeks to provide a mini-comprehensive analysis of the immunopathogenesis of toxemia of pregnancy, with particular emphasis on the interplay between inflammatory cells, cytokines, and chemokines. By elucidating these mechanisms, we aim to enhance our understanding of the disease process and highlight potential avenues for biomarker discovery, risk stratification, and targeted therapeutic interventions.

**Keywords:** Pregnancy-induced hypertension, eclampsia, Preeclampsia, Interleukins, TNF, inflammatory cells, chemokines, cytokines ,Toxemia of pregnancy.

**INTRODUCTION**

Hypertensive conditions during pregnancy, synonymous as toxemia of toxemia, ranges from mild hypertension, preeclampsia, and eclampsia. Toxemia in pregnancy may be complicated by intrauterine growth restriction, placental abruption, stillbirth, HELLP syndrome (Hemolysis, Elevated Liver Enzymes, and Low Platelet), and DIC (Disseminated Intravascular Coagulopathy). Preeclampsia (PE) manifests as high blood pressure and weight gain with protein in the urine after 20 weeks of gestation [1], while the presence of neurological manifestations is termed Eclampsia or imminent Eclampsia. Additional symptoms consist of intense migraines, visual anomalies like blurring or flickering, pain below the ribs, nausea, and rapid swelling of the face, hands, and feet. While the exact cause of Toxemia during pregnancy remains unclear, it is believed to stem from inflammation, which plays a vital role in preeclampsia. A clear disparity exists in the lymphocytic immune responses (TH1, TH2, and TH17) along with evident endothelial dysfunction[2].Similarly, cytokines like interleukins and TNF-alpha are essential[2]. An ineffective placenta and the disruption of the relationship between the fetal blood supply and the maternal blood flow are implicated.

Preeclampsia is the most common of the spectrum and multifactorial hypertensive disorder of pregnancy that typically arises after 20 weeks of gestation. It is characterized by elevated blood pressure, proteinuria, and organ dysfunction[1][2].The guidelines from the American College of Obstetricians and Gynecologists state that a hypertensive emergency in pregnancy is marked by a rapid increase in severe hypertension, with systolic blood pressure exceeding 160 mmHg or diastolic blood pressure going beyond 110 mmHg, particularly in cases of preeclampsia or eclampsia[3][4]. This usually manifests as the onset of new hypertension and protein in the third trimester. Preeclampsia can escalate quickly, leading to serious complications such as reduced uterine blood flow, placental detachment, prompt delivery, and the potential for death for both the mother and the fetus if not managed properly.

A growing body of evidence implicates the immune system as a central player in its pathophysiology, particularly through mechanisms involving inflammatory responses, immune cell dysregulation, and oxidative stress. Immune system-related inflammation causes decreased placental blood flow, leading to low birth weight and intrauterine growth restriction. Oxidative stress is linked to the activation of the maternal inflammatory response, with regulatory T cells, B-cells, macrophages, natural killer cells, and neutrophils playing significant roles in the development of preeclampsia, and the roles of inflammatory cytokines and anti-angiotensin II type 1 receptor autoantibodies are now acknowledged[1].

The imbalances in the immunological system contribute to impaired placental development and vascular dysfunction, ultimately leading to adverse pregnancy outcomes such as intrauterine growth restriction (IUGR), low birth weight, maternal and fetal morbidity, and mortality. One of the earliest immune events associated with preeclampsia is the maladaptation of maternal immune tolerance toward the semi-allogenic fetus. Under normal conditions, maternal immune tolerance is mediated through a balance of regulatory immune cells and cytokines that facilitate trophoblast invasion and spiral artery remodeling. However, in preeclamptic pregnancies, this tolerance is disrupted, resulting in a pro-inflammatory environment at the maternal-fetal interface[2][3].

This inflammatory milieu with possible evidence of apoptosis interfere with trophoblast differentiation that further impair the transformation of spiral arteries into low-resistance, high-capacitance vessels, thereby reducing uteroplacental perfusion[1][2][3]. Immune system-related inflammation has been linked to reduced placental blood flow, which limits the supply of oxygen and nutrients to the developing fetus. The ensuing hypoxic and ischemic conditions stimulate the release of various damage-associated molecular patterns (DAMPs), which activate maternal leukocytes that perpetuate systemic inflammation. This cascade significantly contributes to the clinical features of pre-eclampsia, including endothelial dysfunction, hypertension, end-organ damages and complication, fetal growth restriction and maternal demise [3][4].

The regulatory T cells (Tregs) play a pivotal role in promoting maternal-fetal tolerance by suppressing the function of effector T cells and modulating antigen-presenting cells(APC). In women with preeclampsia, both the number and function of Tregs are significantly reduced, leading to a loss of peripheral tolerance and an increase in pro-inflammatory T-helper (Th1 and Th17) responses. This imbalance skews cytokine production toward a pro-inflammatory profile and markers, characterized by elevated levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-17 (IL-17), while anti-inflammatory cytokines such as interleukin-10 (IL-10) are decreased among others [3][4].

B cells also contribute to the immunopathogenesis of preeclampsia through the production of autoantibodies, most notably agonistic autoantibodies against the angiotensin II type 1 receptor (AT1-AA) [4].These autoantibodies mimic the action of angiotensin II by binding to and activating the angiotensin II type 1 receptor (AT1R), resulting in vasoconstriction, sodium retention, and increased blood pressure. Furthermore, AT1-AAs promote the release of soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin, two anti-angiogenic factors that interfere with placental vascular development and exacerbate endothelial dysfunction[4][5]. Their elevation in maternal serum is strongly correlated with the severity of preeclampsia and poor fetal outcomes.

Macrophages, particularly the M1 phenotype, are more prevalent in pre-eclamptic placentas and produce high levels of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6. This contrasts with normal pregnancies, where a balance between M1 and M2 macrophages is necessary for maintaining tissue homeostasis, immune tolerance, and placental remodeling. The predominance of M1 macrophages not only contributes to a sustained inflammatory response but also disrupts tissue repair and angiogenesis within the placenta[5][6].

Natural killer (NK) cells, especially uterine NK (uNK) cells, are integral to spiral artery remodeling. In normal pregnancy, uNK cells produce angiogenic factors like vascular endothelial growth factors (VEGF) and placental growth factors (PlGF) that support trophoblast invasion. However, in preeclampsia, both the number and function of uNK cells are altered. These cells shift toward a cytotoxic phenotype, reducing their secretion of angiogenic mediators and increasing production of inflammatory cytokines and perforins, which may contribute to placental damage and immune rejection[4][5][6].

Typically, at the outset of pre-eclampsia polymorphonuclear cells which are the most abundant circulating leukocytes, are also activated. The activated neutrophils release reactive oxygen species (ROS), matrix metalloproteinases (MMPs), and neutrophil extracellular traps (NETs), which can further cause and worsen endothelial injury and amplify systemic inflammation[4][5][6]. These cytotoxic molecules contribute to oxidative stress within the maternal circulation and the placenta. Importantly, oxidative stress and inflammation form a vicious cycle, with oxidative damage enhancing inflammatory signaling and vice versa[5].

The fetal outcomes have lasting implications, as low birth weight is associated with increased risks of cardiovascular, metabolic, and neurodevelopmental disorders later in life.

Understanding these immune mechanisms offers potential targets for early detection, biomarker development, and novel therapeutic strategies to prevent or mitigate the complications of preeclampsia. In summary, the maternal immune system, while essential for maintaining pregnancy, becomes pathologically activated in preeclampsia. The dysregulation of immune cells, along with excessive inflammatory cytokines, anti-angiogenic factors, and autoantibodies, culminates in placental hypoperfusion, systemic inflammation, and endothelial dysfunction[4][5][6].In prospect continued research into inflammatory ,immunomodulation and angiogenic balance may lead to breakthroughs in improving both maternal and fetal outcomes in hypertensive pregnancies.

### PATHOPHYSIOLOGY

The exact mechanisms behind Toxemia of Pregnancy remain uncertain. Evidence from genetics, microbiology, and immunology exists regarding the pathogenesis of Toxemia of Pregnancy. The first step is abnormal placentation, leading to placenta ischemia[**Figure 1**]. The accumulation of oxidative stress led to the release of pro-inflammatory cytokines, an increase in antiangiogenetic factors, and a reduction in placental growth factors, resulting in endothelial dysfunction[7]. There is the destruction of dendritic cells for implantation support, macrophages for placentation support, and vascular remodeling, which trigger the production of danger signals like Damage-associated molecular patterns (DAMPs)[8].DAMPs are nuclear or cytosolic proteins with defined intracellular functions that promote inflammatory response by binding to pattern recognition receptors. Examples of DAMPs released during placental and endothelial injury include RNA, DNA, IL-1 alpha, Reactive oxygen species (ROS), ATP, and Fibronectin[8][9].

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### Figure 1: Schematic summary of the Pathogenesis of Toxemia of Pregnancy. Abnormal invasion of trophoblast → Inappropriate remodeling of spiral artery → Reduction in uteroplacental blood flow → Oxidative stress→ ↑ sFlt-1 and sEng, ↑ cytokines and chemokine → Hepatic ischemia, ↑ LFTs→ ↓ PIGF, ↓ VEGF, ↓ TGF-β→ ↓ NO, ↓ Prostacyclin, → Endothelin→ ↓Endothelial damage and angiogenesis→ Thrombocytopenia, Activated coagulation cascade→ Hypertension. Additional Effects: Activation of RAAS Pathway, ↑ Angiotensin → Hypertension, Acute kidney injury, Proteinuria ,Pulmonary edema, Capillary leak, Coronary artery disease, Cardiomyopathy, Headache, Seizure, PRES.

The significance of ncRNAs as clinical biomarkers has been studied in a broad spectrum of human illnesses, such as pregnancy-associated hypertension. Evidence suggests that miRNAs and lncRNAs expressed in the placenta play a role in the immunological regulation of essential processes related to placenta development and function during pregnancy. The irregular levels of these molecules are associated with immune pathophysiological mechanisms that take place during preeclampsia. Multiple ncRNAs are involved in the immune dysregulation of PE, participating in type 1 immune response regulation, immune microenvironment regulation in placenta promoting inflammatory factors, trophoblast cell invasion in women with Early-Onset PE (EOPE), placental development and angiogenesis and autophagy [8][9].

***Roles of Endothelin (ET) in the Pathogenesis of Preeclampsia***

Researchers have put forward a model consisting of two stages for preeclampsia. In Stage 1, there is a decrease in placental perfusion, leading to hypoxic injury in the fetus. Brosens et al. suggested that partial persistence triggers a series of events that result in the development of Toxemia during pregnancy in three consecutive stages [Figure 2]. The initial phase leads to the preservation of the "endothelin-producing" endothelium in uteroplacental arteries due to the incomplete physiological transformation of the vessels[7][8][9]. As a result, the uteroplacental vessels respond to pathological signals, leading to local arteriopathy. The next stage initiates with a steady reduction in blood circulation to the uteroplacental region, causing oxidative stress within the placenta[Figure 2].

**Environmental factors**

**Immunological factors**

**Genetic factors**

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**Abnormal placental attachment**

**↓ Placental blood flow**

**↑ Release of maternal factors:**

**Increase chemokines and cytokines.**

**Increase sFlt-1 and sEng, ↓PIGF, ↓ VEGE↓, TGF-β**

**STAGE 1**

**(First and second trimester)**

**STAGE 2**

**(Third trimester)**

**Proteinuria**

**Glomerular endotheliosis**

**Hypertension**

**Thrombocytopenia**

**Cerebral edema 🡪 seizure**

**Endothelial dysfunction🡪 vasospasm🡪 capillary leak & vascular damage**

### Figure 2: Stages of Pathogenesis of Toxemia of Pregnancy. STAGE 1 (First and second trimester) with Abnormal placental attachment↓ Placental blood flow and leads to intrauterine growth retardation. STAGE 2 (Third trimester) characterized by Release of maternal factors and Endothelial dysfunction Consequences: Proteinuria, Glomerular endotheliosis, Hypertension, Thrombocytopenia, Cerebral edema (seizure).

### ETs are a family of pro-inflammatory cytokines that consist of several amino acids, of which the major ones include ET-1, ET-2, and ET-3. They are each encoded by different genes (endothelin1,2 and 3). These genes code for the pre-pro form of ETs (pre-pro-ETs), the precursors cleaved by cellular endopeptidases into the inactive big ETs. Additional alteration by one of the ET-converting enzymes (ECEs) will lead to the release of biologically active endothelin products [7][8][9]

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(endothelin1, 2, and 3). These genes code for the pre-pro form of ETs (pre-pro-ETs), the precursors cleaved by cellular endopeptidases into the inactive big ETs. An extra modification by one of the ET-converting enzymes (ECEs) will result in the release of biologically active endothelin products[7][8][9]. ET-1 is the most prevalent and is released by the syncytiotrophoblast and endothelium on the basolateral side. It is secreted from the WeibelPalade bodies of the endothelial cells upon stimulation. Several enzymes, hormones, and cytokines, such as angiotensin II, hypoxia, growth factors, and epinephrine, have been shown to increase the stimulation of ET-1 release [7].

The ETA primarily attaches to ET-1 and ET-2 more than to other endothelin receptors, causing vasoconstriction in both placental and maternal blood vessels. Studies on ET-1 in normal and preeclampsia pregnancies have shown a triple increase in endothelin-1 in women with Toxemia of pregnancy as compared to normal pregnancy. Although the main reason for this is not completely understood [7].

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The release of endothelin-1 initiates oxidative stress in the placenta, resulting in heightened production of elements like soluble FMS-like tyrosine kinase-1 (sFLT-1). Endothelial dysfunction worsens with sFLT-1 secretion into the circulation, where it antagonizes the activity of vascular endothelial growth factor and placental growth factor, as suggested by some researchers [2][7][8].

### *Microbial interplay*

### The mechanism of the interplay of the pathogenesis of microbial infestation and PE remains unclear, but the postulations are the destruction of immune tolerance and induction of cascade of inflammatory processes and metabolic imbalances[9].However, gut microbiota can regulate blood pressure by modulating the host’s inflammatory response and altering endothelial function. Other postulations are that probiotics, low fat diet, steroids ,aldosterone, angiotensin-converting enzyme inhibitors, renin inhibitors, antioxidant molecules during mucin digestion and reduction of excessive fructose consumption are associated with hypertension in pregnancy and lactation by causing increase in intestinal flora leading to PE[9]. Resveratrol, a phytochemical, and an antioxidant is known for the treatment of preeclampsia especially hypertension caused by Asymmetric dimethylarginine (ADMA)-related nitric oxide deficiency and gut microbiota-derived metabolite trimethylamine-N-oxide (TMAO)[9].

### Toll-like receptor Signaling (TLRs) activate nuclear factor-κB (NF-κB) dependent and NF-κB independent pathways to generate cytokines and chemokines. Trophoblast TLR-3 and TLR-4 activation by microbial byproducts and chemokine secretion initiates the innate immune response, and the decidua becomes infiltrated with pNK cells and macrophages (Can be induced by microbes). Double-stranded RNA (dsRNA) and single-stranded RNA (ssRNA) were shown to upregulate expressions of TLR3, TLR7, and TLR8 in mouse placentae, leading to pregnancy-associated Hypertension, endothelial dysfunction, and placental inflammation[10].

The role of gamma delta (γδ) T cells has not yet been determined in preeclampsia. However, increases in the production of pro-inflammatory stimuli, interferon (IFN)-γ and IL-17, by γδ T cells, have been reported in women with idiopathic recurrent pregnancy loss [10].

**CYTOKINES**

Cytokines function by enabling cell interactions and communication. They can be grouped into chemokines (cytokines with chemotactic activities) and interleukins (cytokines produced by leukocytes). The effects can be seen in diverse ranges of cells of the kidneys, brain, liver, heart, and blood. These proteins mediate inflammatory responses and promote the synthesis of other interleukins. An abnormal balance of these cytokines can cause several complications, such as disruption of the vascular system leading to Toxemia during pregnancy. The ratios of Th2 to Th1 cytokines show significantly higher Th1-proinflammatory cytokine production in preeclampsia [10]. The measurement of cells using flow cytometry proved that there is a shift toward Th1-type reactivity in preeclampsia.

These interacting biological signals have remarkable capabilities, such as influencing growth and development, hematopoiesis, lymphocyte recruitment, T cell subset differentiation, and inflammation. Mature CD4 and CD8 T cells leave the thymus with a naive phenotype and produce a variety of cytokines. In the periphery, these T cells encounter antigen-presenting cells (APCs) displaying either major histocompatibility complex (MHC) class I molecules (present peptides generated in the cytosol to CD8 T cells) or MHC class II molecules (present peptides degraded in intracellular vesicles to CD4 T cells). Following activation, characteristic cytokine and chemokine secretion profiles allow the classification of CD4 T helper (Th) cells into two significant subpopulations in mice and humans. Th1 cells secrete IL-2, interferon-γ (IFN-γ) and tumor necrosis factor-β (TNF-β), whereas Th2 cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13[11] **[Figure 3].** Th1 cells support cell-mediated immunity and promote inflammation, cytotoxicity, and delayed-type hypersensitivity (DTH). Th2 cells support humoral immunity and downregulate the inflammatory actions of Th1 cells**[Figure 3].**

A diagram of a cell cycle

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### Figure 3: Flow chart of cytokines production by T cells. [+ Stimulatory, - Inhibitory] CD4+ T cell (T helper):Treg → →  TGF-β.Th17→ → IL-17, IL-22, IL-21. Th2→ → IL-4, IL-5, IL-6.Th1→ → IL-2, IFN-γ. IFN-γ ⊖ inhibits IL-4, IL-5.IFN-γ ⊖ inhibited by IL-4.

### The function of Cytokines

Cytokines and chemokines are related structures and/or functions clustered into groups of interdependent homologs. They exhibit functional redundancy and have a widespread impact on other groups of cytokines or chemokines.

***IL-1/IL-18/IL-12***

The group of pro-inflammatory cytokines related to IL-1 includes IL-1α, IL-1β, IL-1 receptor antagonist (IL-

1RA), and IL-18. IL-1α and IL-1β are primarily generated by mononuclear and epithelial cells during inflammation, injury, and infection[2][14].IL-18 has a biological function similar to IL-12 as it stimulates IFN-γ secretion (in conjunction with IL-12), boosts natural killer (NK) cell activity, and fosters inflammatory Th1 cell responses[15]. IL-2 is often considered an autocrine or paracrine growth factor for T cells, but it also influences various cell types, including B cells, NK cells, macrophages, and neutrophils. IL-12 is crucial for cell-mediated immunity, serving as an essential cytokine that shifts the balance between Th1 and Th2 cells towards Th1 dominance.

***IL-10, IL-6, TNF, and related family***

IL-10, IL-19, and IL-20 belong to a related category of interleukins and share homology with IL-10. IL-10 plays a crucial role in suppressing inflammatory responses. It does this by inhibiting the synthesis of IFN-γ IL-2, IL-3, TNF-α, and GM-CSF by cells such as macrophages and Th1 cells [14)(15)[16]. The TNF family has been expanding a great deal recently; examples are TNF-α, TNF-β, and lymphotoxin (LT)-β [17]. The TGF-β family, which includes over 30 members, plays a role in development, immune regulation, immune tolerance, carcinogenesis, tissue repair, and the generation and differentiation of cells[2].

The consequent decrease in uteroplacental blood flow gives rise to a decreased oxygen delivery to the placenta, leading to impaired placental function [18]. This causes the placenta to express antiangiogenic factors and proinflammatory cytokine, thereby playing a role in developing Toxemia during pregnancy [2]. IL-6 and TNFα are the primary and most abundant pro-inflammatory cytokines mediating the maternal immune system [2]. These cytokines influence endothelial cell activity by increasing vessel permeability and triggering apoptosis in trophoblastic cells. There are significantly higher levels of these pro-inflammatory cytokines produced by women with Toxemia of pregnancy compared to average pregnant women, who, on the contrary, showed significantly greater production of the Th2 cytokines IL-4 and IL-5 compared to normal pregnancies.

Research demonstrated an elevation in the levels of IL-6 and TNF-α in pre-eclamptic placental tissues compared to the control group. The examination of ELISA on maternal serum from pre-eclamptic individuals also revealed a notable increase in cytokines. Consequently, the concentrations of pro-inflammatory cytokines exhibited a continuous rise from the 28th week of gestation until term in both the placenta and serum of mothers with pre-eclampsia. The evaluation of intracellular cytokines through flow cytometry demonstrated a transition towards Th1-type in Toxemia of pregnancy. Numerous studies have explored cytokine production by peripheral blood mononuclear cells (PBMC). Maternal PBMCs generate elevated levels of pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-2, IL-1, IL-6, and IL-8.

Lockwood and colleagues provided proof of elevated IL-6 mRNA and protein levels in leukocyte-free decidual cells from patients with PE. Recent research has revealed the capacity of human endometrial endothelial cells to phagocytose apoptotic trophoblasts and subsequently release the pro-inflammatory cytokine IL-6. This mechanism may contribute to the observed inflammatory response in pre-eclamptic placentas [19].

***IL-17 and T lymphocytes***

IL-17 is a powerful pro-inflammatory cytokine that significantly contributes to the development of autoimmune diseases[20]. The lymphocytic cells exhibiting antagonistic functions include T-regulatory cells (Tregs) and T-helper 17 cells (Th17). Treg is a crucial component during pregnancy that significantly helps in stopping the mother's immune system from attacking the fetal tissue[21]22].. The decreased amount of Treg is due to improper implantation. Th17 cells play a role in promoting inflammation, autoimmune disorders, and the rejection of transplants in humans. Numerous obstetric issues have been linked to a significant rise in Th17 cells and a reduction in Tregs. Maintaining a balance and correlation between Th1 cells, Th2 cells, Th17 cells, and Tregs is imperative for creating a secure environment for the fetus and ensuring safe delivery [23]. Interleukin-17, an inflammatory cytokine, is secreted by Th17 cells. It plays a significant role in the progression of numerous inflammatory processes. It is present in CD4+ cells, CD8+ cells, NK cells, and monocytes; human IL-17 plays a dynamic role in the processes of recruitment and activation.

***Tumor Necrosis Factor-alpha and Toxemia of Pregnancy***

Tumor Necrosis Factor-alpha (TNF-alpha) is a cytokine that promotes inflammation, produced by macrophages, T-lymphocytes, natural killer cells, and monocytes(14)(19)(21),. It is released in the acute stage of inflammation, where it coordinates various signals to promote necrosis or apoptosis. Furthermore, this protein plays a crucial role in enhancing the immune response to infections. Several studies have shown an increase in these cytokines in Toxemia of pregnancy. The production and secretion of TNF-α are affected by hypoxia-reoxygenation caused by the intermittent perfusion of the placenta[16][25].

TNF-α interacts with two separate receptors, facilitating signal transduction via the pathway and resulting in various cellular responses that govern cell survival, differentiation, inflammation, cell defense, and cell proliferation. Prolonged and excessive stimulation of TNF-α may result in chronic inflammation, autoimmune disorders, and various complications[26]. Understanding the TNF-α signaling pathway has progressed, resulting in the development of innovative therapeutic strategies for immunological disorders, particularly TNF-α inhibitors. TNF-α is a cytokine that works on different types of cells to regulate inflammatory responses [24]. It also plays a vital role in the pathogenesis of certain inflammation, cancers, and autoimmune diseases. TNF-α effectively triggers a series of inflammatory substances, which encompass various cytokines and chemokines. It exists in both a soluble and transmembrane form, with transmembrane TNF-α (tmTNF-α) representing the initially synthesized precursor that requires processing by TNF-α-converting enzyme (TACE), a membrane-bound metalloproteinase, to be released as soluble TNF-α (sTNF-α). The soluble TNF-α is released and binds to the receptors, initiating a cascade of reactions leading to the release of molecules that stimulate apoptosis, inflammation, and cell survival [27].

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### Figure 4: TNF-α cascade pathway. Soluble TNF-α formation: Precursor TNF-α → (via TACE) → Soluble TNF-α.TNFR1 Pathway: Soluble TNF-α binds to TNFR1, triggering: TRADD activation → Activates Caspase-8 → Apoptosis. TRADD also activates TRAF → Activates MEKK 1/4 → AP-1 → Contributes to Apoptosis → Activates RIP → Activates MAPK→ Activates NF-κB.TNFR2 Pathway: Soluble TNF-α binds to TNFR2, also leading to downstream signaling. Outcomes are cell survival regulation, Inflammation, host defense and cell proliferation.

These processes culminate in placenta hypoxia, subsequently leading to ischemia. This reduction in oxygen levels within the placental tissue may initiate the production and release of cytotoxic factors, hypothesized to affect the maternal blood supply during gestation. In the human placentas of patients experiencing Toxemia of pregnancy, inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) are produced and released, leading to endothelial cell dysfunction.

Recent findings suggest that hypoxia elevates the levels of TNF-α and IL-1 produced by the human placenta. Placental cells also express erythropoietin (EPO), a molecule regulated transcriptionally by hypoxia in mammals [25][28]. Notably, TNF-α and IL-1 show DNA sequences that are either homologous or similar to the hypoxia-responsive enhancer element of the EPO gene, indicating a possible, though unverified, molecular connection between placental hypoxia and cytokine production stimulation. Inflammatory cytokines excessively produced by the placenta in response to hypoxia may consequently elevate plasma levels and induce endothelial activation and dysfunction in preeclampsia.

**Evidence-based Research on Interleukin-17 interplay**

A case-control study was conducted at Zagazig University Hospitals, involving the recruitment of 40 cases from the antenatal outpatient clinics within the Obstetrics and Gynecology department. The sample size was determined using open EPI with a 95% confidence interval and 80% study power. The study involved two distinct groups: a control group consisting of 20 pregnant women at a gestational age of 28 to 34 weeks and a preeclampsia group made up of 20 women diagnosed based on the guidelines set by the American College of Obstetricians and Gynecologists (ACOG). The preeclampsia cases were further classified as severe based on specified criteria (systolic blood pressure greater than or equal to 160 and diastolic blood pressure was greater than or equal to 110 mmHg and proteinuria ≥5 mg/24 hr [29]30][31]. Every four hours, beginning at 10:00 each day, healthcare providers monitored patients, considering the circadian rhythm. The preeclampsia group was managed using antihypertensive medication, antioxidants, and close follow-up for two weeks. The infusion of magnesium sulfate was specifically administered in instances of severe preeclampsia to avert neurological impairment. IL-17 serum concentration was measured after the 2 weeks following additional blood pressure assessment. The average IL-17 level in the preeclampsia group was 18.5 pg/mL, compared to 4.3 pg/mL in the control group, demonstrating a statistically significant difference between the two groups. The receiver operating characteristic (ROC) curve identified the optimal cutoff value for IL-17 in preeclampsia as 8.2 pg/mL, demonstrating a sensitivity of 100%, specificity of 80%, and accuracy of 89% P<0.00001.[29]30][31].

Studies revealed that IL-17 concentrations were elevated in 34 individuals diagnosed with pre-eclampsia when compared to 35 healthy pregnant women, associating these findings with an exacerbation of the typical inflammatory response that occurs prior to childbirth in cases of preeclampsia. This result shows a significant difference in IL-17 levels before and after controlling preeclampsia, with a noteworthy positive association with systolic blood pressure. This will prove beneficial for the prognosis and subsequent tracking of the disease. A separate set of researchers conducted a similar study to assess cytokines associated with T-helper 17 (IL-17, IL21, IL-23, and TGF-β) during the third trimester of pregnancy. The research involved three groups: 30 patients with preeclampsia, 30 pregnant women with normal blood pressure, and 30 healthy subjects.[29] Researchers noted that the serum levels of IL-17 and TGF-β were markedly higher in patients with preeclampsia compared to both normotensive and healthy individuals [29]30][31].

Conrad et al. (23) utilized Enzyme-Linked Immunosorbent Assays (ELISAs) and subjected them to thorough validation studies. The findings indicated a twofold increase in the median concentration of plasma TNF-α in women with preeclampsia compared to normal third-trimester pregnancy (P < 0.001) and in women with gestational Hypertension (P < 0.04) [29][30][31].

**Table 1:** Summary of common cytokines and their function.

| CYTOKINES | FUNCTIONS | SECRETED BY |
| --- | --- | --- |
| IL-1 | Activates lymphocytes, macrophage stimulation, increased leukocyte/endothelial adhesion, and release of acute phase reactants. It causes fever and inflammation. | T cells, B cells, Endothelial cells |
| IL-2 | Increases T-cell proliferation. Stimulates proliferation of NK cells and cytotoxic and helper T-cells. Inhibit TH2 responses. | T cells |
| IL-4 | Stimulates B-cell differentiation and class switching to IgE and IgG. Enhances Th2 differentiation, inhibits IFN-γ activation of macrophages. | B cells, T cells, NK cells |
| IL-5 | Induces B cell growth and differentiation, activates eosinophils, and enables class switching to IgA. | B cells |
| IL-6 | It causes fever and stimulates the release of acute phase proteins. | Monocytes |
| IL-10 | Inhibits IL-2 and IFN-γ. Reduces antigen presentation and MHC class II expression by dendritic cells. Suppresses TH1 response. | Macrophages |
| IL-12 | Stimulates T cells to differentiate into Helper T cells. | Macrophages |
| TNF-Alpha | Increases vessel permeability, adhesion molecule expression, and WBC recruitment. Maintains granulomas. | Endothelial cells, Macrophages, B cells |
| Interferon-γ | Promotes Th1 cell growth and inhibits Th2. Stimulates macrophages to kill phagocytosed pathogens. | NK cells, TH1 cells |

IL-13 Induces mucus production and airway hyperresponsiveness All cells

(Same as IL-4)

**Anti-inflammatory cytokines in Toxemia of Pregnancy**

In cases of pregnancy-related toxemia, there is an increase in placental cytokines, including pro-inflammatory cytokines, while the secretion of anti-inflammatory cytokines like IL-10 and IL-4 decreases[11][12]. The essential role of anti-inflammatory cytokines (IL-4 and IL-10) is pivotal for the proper functioning of T helper cell 2 (Th2) and regulatory T cells (Treg) in ensuring a successful pregnancy and smooth progression to delivery [24]. It functions as a vital modulator of the immune system, serving as an immunomodulator and directly improving vascular health while promoting effective cellular interactions at the maternal-fetal interface.IL-2 promotes T cell proliferation. Alterations in the levels of these cytokines may impact on the operation of the major apoptotic and inflammatory pathways to balance cell mediated and humoral immunity , thus affect the smooth progression of pregnancy and lead to pregnancy-associated complications such as Toxemia of pregnancy.

There has been a reported reduction in IL-10 production in trophoblasts derived from patients with Toxemia of pregnancy in a hypoxia state [32]. This finding indicates that the placenta affected by pre-eclampsia inadequately produces IL-10 and IL-4 in response to hypoxia. As a result, this unusual reaction might lead to an increased production of inflammatory cytokines, thus influencing the onset of maternal intravascular disease. A noteworthy finding indicated a negative correlation between blood pressure and circulating IL-10 levels. This correlation has been experimentally verified in non-human primates. Consequently, these findings suggest the potential association of Toxemia of pregnancy with diminished systemic IL-10 bioactivity, a proposition supported by certain segments, if not the entirety in existing literature [33][34].

In another study, variations in IL-10 levels were observed, with an increase in the first and second trimesters but a decline in the third trimester of normal pregnancies [2]. However, in the present study, the levels and expressions of IL-4 and IL-10 were diminished in both sets of pre-eclamptic placental tissues, contrasting with an upregulation in control samples [35]. Maternal serum samples exhibited similar trends, revealing reduced levels in preeclampsia when compared to the control group. These findings suggest that in Toxemia of pregnancy, IL-10 and IL-4 may not effectively suppress the pro-inflammatory cytokines, potentially leading to heightened inflammatory responses [33][35].

### CHEMOKINES

Chemokines represent a group of small chemotactic cytokines that influence the movement of leukocytes by interacting with rhodopsin-like G protein-coupled transmembrane receptors. Chemokines have significant structural homology and overlapping functions and can often bind to more than one receptor [36][37][38]. Chemokine receptors facilitate various signaling pathways that influence different cellular activities.

The most studied chemokines are CC(β-chemokines), CXC (α-chemokines), CX3C, and C subfamilies. The C group of chemokines has recently been described. It has at least two ligands (XCL) and lacks cysteines [38]. Examples are lymphotactin/XCL1 and SCM1β/XCL2, which bind XCR1 receptors. Lymphotactin is coded for on human chromosome 1 and attracts lymphocytes, not monocytes or neutrophils. XCR1+cells depend on growth factor FtL3 ligand, so more studies need to be done to establish its potential roles in Toxemia of pregnancy [34][38]. The human CC chemokine group with no intervening amino acid includes at least 27 members (CCL), most encoded on human chromosome 17, and binds at least 10 receptors (CCR). CC chemokine targets include monocytes, T cells, dendritic cells, eosinophils, and NK cells [38].

IL-8/CXCL8 (ELR), monokine-induced by IFN-γ (MIG)/CXCL9 (nonELR), IFN-γ inducible protein-10 (IP-10)/CXCL10 (nonELR) and stromal cell-derived factor-1 (SDF-1)/CXCL12 (nonELR) can be theoretically inferred to play a role in the pathogenesis of inflammatory changes of the placenta. Lastly, the “sole CX3C chemokine” (three intervening amino acids), namely fractalkine/CX3CL1, is encoded on human chromosome 16, binds CX3CR1 and attracts T cells and monocytes but not neutrophils [38]. Fractalkine/CX3CL1 is found in humans and can be theoretically assumed to play a role in the neurological manifestations of Toxemia during pregnancy.

Research involving 309 pregnant women across three groups (Uncomplicated Preeclampsia with both normal and abnormal angiogenic profiles) further substantiates the existence of intravascular inflammation, cytokines, and chemokines within the study cohorts. The study revealed plasma concentrations of cytokines (interleukin-6, interleukin-8, interleukin12/interleukin-23p40, interleukin-15, and interleukin-16) and chemokines (eotaxin, eotaxin-3, interferon-γ inducible protein-10, monocyte chemotactic protein-4, macrophage inflammatory protein-1β, macrophage-derived chemokine) are higher in pre-eclamptic women compared to uncomplicated subgroup, except in preeclampsia with average angiogenic profile where monocyte chemotactic protein 4 is the only elevated chemokine [35]. A relationship was identified between the intensity of the antiangiogenic condition, blood pressure, and the plasma levels of certain cytokines.

**DISCUSSION**

In addition to the cytokine and chemokines interplay above, it is imperative to have a wholistic approach to their roles in the development of the spectrum of pregnancy induced hypertension.

There is tendency of intrauterine fetal death in normal pregnancy as a result of elevated level Th2-type immunity (stimulated by IL-18) and suppression of cytotoxic(Th1) cells[39][40]. Though, the stimulator ,IL-18 shares similar homologous structure to Il-1 and uses IL-1R/Toll-like receptor (TLR) superfamily[40][41].Typically ,IL-18 has a different function as IL-1 but both can function to stimulates Th1-mediated immune responses [42].The balance is mediated by cytokines such as IL-2,IFN-γ,IL-18, and IL-12. Th2 -type immune is stimulated also by high level IL-18 and decreased IL-12( reduced IL-12p70/IL-12p40 ratios) in healthy pregnant patients[39][40]. In pre-eclampsia , IL-1α ,IL-1β,IL-6,IL-8,IP-10,MCP-1,ICAM-1,VCAM-1, TNF-α,IL-12p70 and IL-18 levels are markedly elevated[39][40][41].

Elevated MCP-1 and ICAM-1 correlate with the presence of acute phase reactant like C-reactive protein (CRP) suggesting their implications in hepatocellular injury and hypertension seen in pregnancy induced hypertension[39][40][41].

The entire cascade of pathophysiological process ends up as anatomical abnormalities and vice versa. The interplay of pathogenic pathways and mechanisms are complex and not well understood. The anatomical pathology of preeclampsia is documented to be associated with extensive programmed cell death of placental cytotrophoblasts within the uterus despite the numerous evidence and study indicative in the inflammatory changes in the pathogenesis without obvious mitosis [42][43]. The findings in pre-eclampsia in most studies and literature revealed shallow and rudimentary endovascular invasion, fibrin deposition on maternal surface, and abnormal differentiation contributing to reducing blood flow to the placenta[42][44]. There are resultants effects further downregulate adhesions molecules like E-cadherin and integrin α6β4 with upregulations of VE-cadherin, integrin αVβ3, α1β1 meant for endothelial cell activities leading to or worsening a state of hypertensive state in pregnancy and leveraging a wanton complication in the mother and fetus[44][45][46].Experimental model further supported the up-regulation of integrin α1β1 once there is proposed inflammatory process that leads to hypoxic injury in the cytotrophoblast, asserting the role of oxygen tension in the determination of its ability to proliferate and invade the uterine wall[46][47][48][49].

Studies suggest alteration of adhesion molecules maybe involve in generation of invasive phenotype of cytotrophoblasts that could be seen in preeclampsia and choriocarcinoma[50][51][52][53].The cytotrophoblast villous processes and other parts are attached to the basement membrane by alpha-5/6, beta-1/4 integrins, Tenascin, merosin and A-chain-containing laminin ,all of which are required for adequate regulations and modification for effective adaptation[50][51][54][55].**Tenascin**, a highly specialized extracellular oligomeric glycoprotein, plays a crucial role in **cellular differentiation** and has been shown to influence cytotrophoblast development [50][56][57][58].The adhesion molecules play important roles in the implantation of the placenta, and it is important to understand the function as it may be responsible for development of hypertension in pregnancy should there is any abnormality or maladaptation[59][60].

**CONCLUSION**

In this review, we delve into the pivotal role of cytokine ; particularly interleukins such as IL-6, IL-4, IL-10, tumor necrosis factor-alpha (TNF-α), and endothelin in the immunopathogenesis of toxemia of pregnancy, a term historically used to describe preeclampsia. Preeclampsia remains a significant obstetric complication with complex etiologies involving immune dysregulation, endothelial dysfunction, and impaired placental development. Cytokines, as key mediators of inflammation and immune signaling, are central to understanding the multifaceted nature of this condition.

Cytokines exert diverse biological effects that influence both maternal immune adaptation to pregnancy and placental vascular remodeling. For instance, IL-6 ,TNF-α and several others are pro-inflammatory cytokines often found elevated in pre-eclamptic patients, contributing to systemic inflammation, endothelial activation, and increased vascular resistance. In contrast, IL-10, an anti-inflammatory cytokine, plays a regulatory role by suppressing excessive immune activation and promoting tolerance to the semi-allogeneic fetus. Several studies suggest that lower maternal serum levels of IL-10, particularly in the second trimester, are associated with an increased risk of developing preeclampsia, making it a potential early biomarker for the disease. IL-4, another anti-inflammatory cytokine, supports Th2-type immune responses essential for fetal tolerance, and its imbalance may also contribute to the inflammatory state observed in preeclampsia.

Endothelin, a potent vasoconstrictor, has emerged as a critical effector molecule in the endothelial dysfunction characteristic of preeclampsia. Elevated levels of endothelin-1 have been correlated with hypertension, proteinuria, and impaired uteroplacental blood flow, further exacerbating placental ischemia and oxidative stress. These cytokine and vasoactive pathways intersect, forming a feedback loop that amplifies the inflammatory milieu and endothelial damage seen in preeclamptic pregnancies.

Experimental studies in both human and animal models have significantly enhanced our understanding of cytokine-mediated mechanisms in pregnancy toxemia. Rodent models, particularly those involving immune manipulation or placental ischemia, have demonstrated altered cytokine profiles consistent with those observed in human preeclampsia. These findings underscore the translational relevance of cytokine research and support the immunological hypothesis of disease progression.

Despite the considerable progress in cytokine research, the definitive pathophysiological mechanism of preeclampsia remains elusive. The interplay between maternal genetics, immune response, placental development, and environmental triggers suggests a multifactorial origin that is yet to be fully deciphered. This ongoing uncertainty continues to challenge early diagnosis, risk prediction, and the development of targeted therapeutics.

Nevertheless, advancing our understanding of the cytokine and chemokine networks implicated in pregnancy-induced hypertension holds immense clinical promise. Early identification of cytokine imbalances may facilitate the development of predictive biomarkers and risk assessment tools. Additionally, therapeutic modulation of specific cytokines or their signaling pathways could offer new strategies to mitigate disease severity, improve placental function, and reduce maternal and fetal morbidity. Moreover, raising clinical and research awareness of the immunoinflammatory basis of preeclampsia can promote multidisciplinary collaboration among obstetricians, immunologists, and vascular biologists. Such collaboration is vital for translating bench-side discoveries into bedside applications, ultimately enhancing prenatal care and long-term health outcomes for both mothers and their offspring.

In conclusion, cytokines are not merely bystanders but active contributors to the pathogenesis of preeclampsia. Continued exploration of their roles offers a pathway toward more precise diagnostic and therapeutic approaches, thereby transforming the landscape of maternal-fetal medicine and addressing one of the leading causes of maternal mortality and morbidity worldwide.

**Conflict of Interest**

This is an output of intra-faculty and international collaboration of medical educators and mentees as part of continuous medical education necessitating the need for republishing of this review. All authors declare no conflict of interest.

**Abbreviations**

Th, Helper T cell; RNA, Ribonucleic acid; DNA, **Deoxyribonucleic acid;** IL, Interleukins; ATP, Adenosine triphosphate; (uNK),uterine NK cells ROS, Reactive oxygen species; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-γ; CXCL, chemokine (C-X-C motif) ligand; Chemokine (C-C motif) ligand; TLR, Toll-like receptor; DAMPS, Damage-associated molecular pattern; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; ETA ,endothelin receptors A ;TNF, Tumor necrosis factor; TGF-β, Transforming growth factor-β; PIGF, Placental growth factor; VEGF, **Vascular endothelial growth factor;** TGF, Transforming growth factors; sFlt, Soluble fms-like tyrosine kinase-1; NO, Nitous oxide; RAAS, renin–angiotensin–aldosterone system; ANG, angiotensin; LFT, Liver function tests; PRES, posterior reversible encephalopathy syndrome.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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