Exploring the roles of cytokines and chemokines in toxemia of pregnancy

Running title: Cytokines and Chemokines in Toxemia of Pregnancy

Adedeji Okikiade
[1] Department of Pathology, Clinical Sciences, California Northstate University, Elk Grove, CA, USA and [2] Ejyde International Education and Research Consultancy, USA. 0000-0003-2797-289X

Chidinma Kanu
Ejyde International Education and Research Consultancy, USA.

Oluwadamilare Iyapo
Department of Pathology, Eko University of Medicine and Health Sciences, Lagos, Nigeria.

Ololade Omitogun
Director, Alluring Healthcare Solutions LLC, MD, USA.

Corresponding author: Adedeji Okikiade
Email: okikis@yahoo.com
Tel: +1-443-803-2553.

Abstract

Introduction: Hypertensive disorders, particularly preeclampsia (PE), complicate 2–8% of pregnancies and significantly contribute to maternal and perinatal mortality. PE disproportionately affects low-resource regions, accounting for 26% of maternal deaths in Latin America and 9% in Africa/Asia. Risk factors include extreme maternal age, chronic hypertension, obesity, diabetes, and racial disparities (higher incidence in Black/Hispanic populations). The exact cause remains unclear, but angiogenic imbalance and immune dysregulation play key roles. This review examines cytokine and chemokine involvement in PE pathogenesis.

Methods: A narrative review synthesized studies on PE's immunological and vascular mechanisms, prioritizing recent systematic reviews and high-impact research.

Results: This study identifies a critical imbalance between pro-inflammatory (IL-6, TNF-α) and anti-inflammatory (IL-4, IL-10) cytokines in PE pathogenesis. Notably, reduced second-trimester IL-10 levels may serve as an early predictive biomarker. Endothelin-mediated vasoconstriction and Th1/Th2 immune imbalance further exacerbate endothelial dysfunction, a central feature of PE. While human and animal studies support these findings, precise mechanistic pathways remain elusive.

Conclusion: Cytokine and endothelin dysregulation offer promising biomarkers and therapeutic targets for PE. Early IL-10 detection may improve risk prediction, but causal links need validation. Understanding these mediators could enhance clinical strategies, reducing complications. Future research should validate biomarkers longitudinally and explore anti-inflammatory treatments for PE prevention.

Keywords: Toxemia of pregnancy, Eclampsia, Preeclampsia, Interleukins, TNF, Chemokines, Cytokines.

Introduction

Toxemia of pregnancy is the spectrum of hypertensive disorders in pregnancy, spanning from mild Hypertension and preeclampsia to Eclampsia. Toxemia during pregnancy can be complicated by intrauterine growth restriction, placental abruption, stillbirth, HELLP syndrome (Hemolysis, Elevated Liver Enzymes, and Low Platelets), and DIC (Disseminated Intravascular Coagulation). 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. Other manifestations are intense headaches, visual disturbances like blurring or flashing, discomfort below the ribs, nausea, and abrupt swelling of the face, hands, and feet.

The etiopathogenesis of Toxemia in pregnancy is not fully understood, though it is thought to stem from inflammation, a known pivotal mediator in preeclampsia. A disproportion in lymphocytic (TH1, TH2, and TH17) immune responses and endothelial dysfunction is apparent. Likewise, cytokines such as interleukins and TNF-alpha play crucial roles (2). A dysfunctional placenta and the disruption of the interaction between the fetal blood supply and the maternal circulation are implicated.

Immune-mediated inflammation triggers placental hypoperfusion resulting in low birth weight and intra-uterine growth retardation. The oxidative stress is associated with activation of the maternal inflammatory response such as regulatory T cells, B-cells, macrophages, natural killer cells, and neutrophils are known to have major causative roles in the pathology of preeclampsia and the contributions inflammatory cytokines and anti-angiotensin II type 1 receptor autoantibodies are now recognized.

According to the American College of Obstetricians and Gynecologists guidelines, a hypertensive emergency during pregnancy is characterized by the sudden onset of severe Hypertension, with systolic blood pressure exceeding 160 mmHg or diastolic blood pressure surpassing 110 mmHg, especially in the context of preeclampsia or Eclampsia (3,4). This typically presents as the emergence of new-onset Hypertension and proteinuria in the third trimester. Preeclampsia can progress rapidly, causing severe complications, including a decrease in uterine perfusion, placental abruption, premature delivery, and the risk of death for both the mother and the fetus in the absence of proper management (5, 6).

Conceptualized pathophysiology

The pathology of Toxemia of Pregnancy is unclear. Genetic, microbial, and immunological evidence exists in the pathogenesis of Toxemia of Pregnancy (Figure 1). The first step is abnormal placentation, leading to placenta ischemia. Oxidative stress builds up, releasing pro-inflammatory cytokines, increased antiangiogenetic factors, and decreased placental growth factors, followed by 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 an inflammatory response by binding to pattern recognition receptors.RNA, DNA, IL-1 alpha, Reactive oxygen species(ROS), ATP, and Fibronectin are examples of DAMPs released in the placenta and endothelial injury (8, 9).

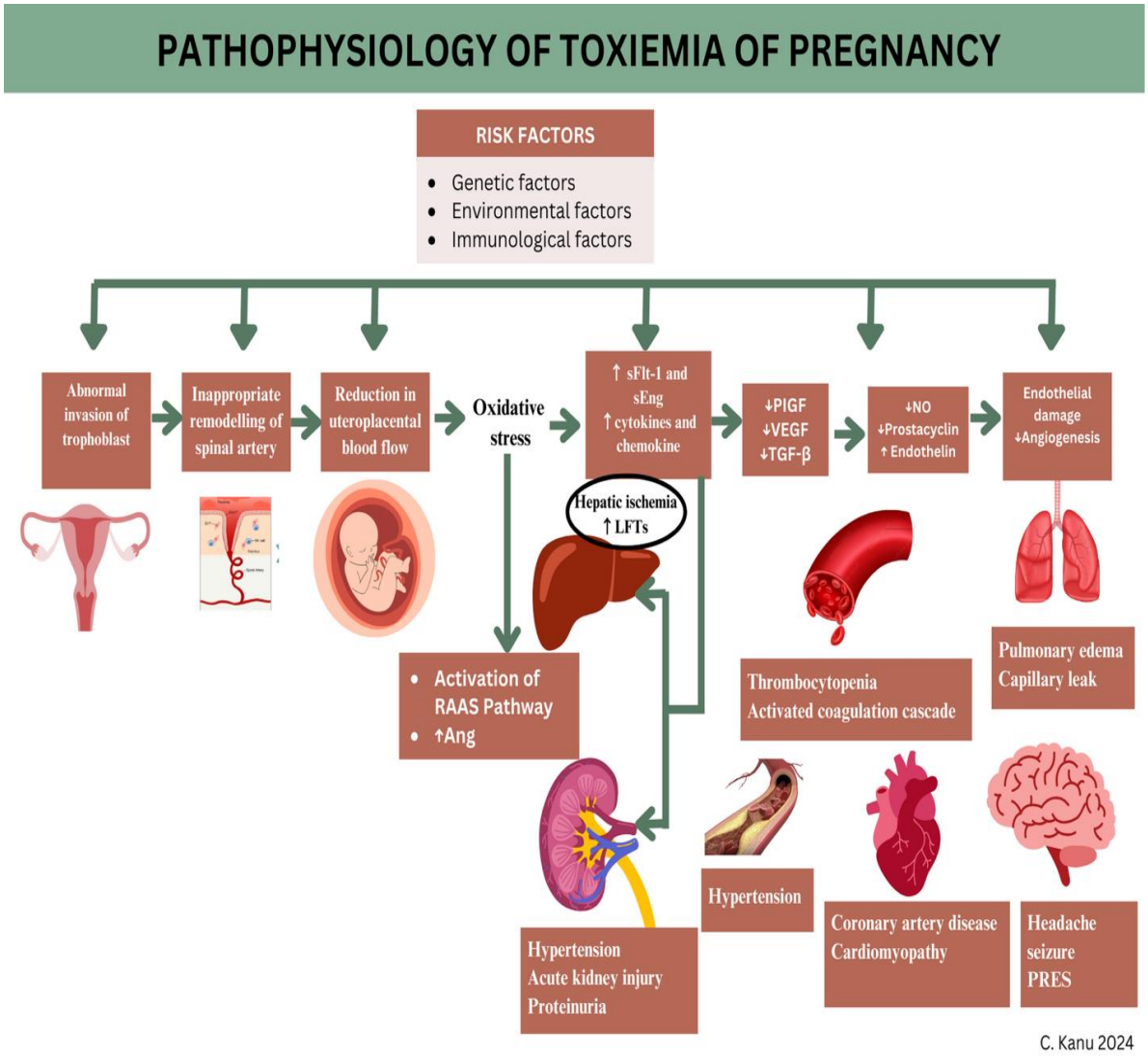

Figure 1. Schematic summary of the Pathogenesis of Toxemia of Pregnancy

The importance of ncRNAs as clinical biomarkers has been explored in an extensive range of human diseases, including pregnancy-related Hypertension. There is evidence of the involvement of placenta-expressed miRNAs and lncRNAs in the immunological regulation of crucial processes of placenta development and function during pregnancy. Abnormal expression of these molecules is related to immune pathophysiological processes that occur during preeclampsia. Multiple ncRNAs are involved in the immune dysregulation of PE, participating in type 1 immune response regulation, immune microenvironment regulation in the 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 in the Pathogenesis of Preeclampsia

A group of researchers introduced a 2-stage model of preeclampsia. In Stage 1, there is a decrease in placental perfusion, leading to hypoxic injury in the fetus. Brosen et al. proposed that partial persistence initiates a chain of events leading to the emergence of Toxemia during pregnancy in 3 sequential stages (Figure 2). The first stage results in the retention of the "endothelin-producing" endothelium in uteroplacental arteries secondary to the incomplete physiological transformation of the vessels (7-9). Consequently, the uteroplacental vessels are reactive to pathologic signals, which drives local arteriopathy. The second stage starts with a progressive reduction in uteroplacental blood flow, generating oxidative stress in the placenta (Figure 2).

Figure 2. Stages of Pathogenesis of Toxemia of Pregnancy

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 (7-9).

ET-1 is the most abundant and secreted by the syncytiotrophoblast and endothelium on the basolateral side (7-9). It is secreted from the Weibel-Palade 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 ET_A binds mostly to ET-1 and ET-2 than other endothelin receptors, inducing vasoconstriction of 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).

The release of endothelin-1 triggers oxidative stress in the placenta, leading to increased production of factors such as 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, 7-9).

Microbial interplay

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.
The role of γδ T cells has not yet been determined in preeclampsia. However, increases in the production of pro-inflammatory stimuli, interferon (IFN)-γ & 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.

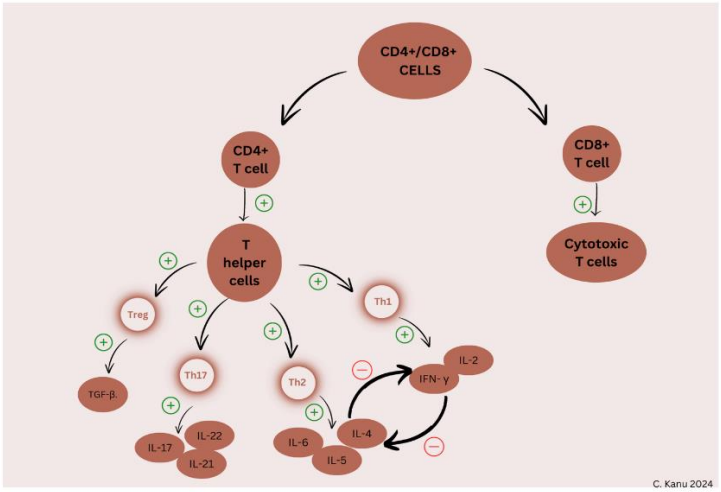

Figure 3. Cytokines production by T cells. (+ Stimulatory, - Inhibitory)

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 IL-1-related group of pro-inflammatory cytokines consists of IL-1α, IL-1β, IL-1 receptor antagonist (IL-1RA) and IL-18 (12) (13). IL-1α and IL-1β are produced mainly by mononuclear and epithelial cells upon inflammation, injury and infection (2, 14). IL-18 shares biological function with IL-12 in that it induces IFN-γ secretion (in synergy with IL-12), enhances natural killer (NK) cell activity, and promotes inflammatory Th1 cell responses (15)**.** IL-2 is commonly regarded as an autocrine or paracrine T cell growth factor, but it affects many cell types, such as B cells, NK cells, macrophages, and neutrophils.IL-12 plays a critical role in cell-mediated immunity by acting as a requisite cytokine in pushing the balance between Th1 cells and Th2 cells towards Th1-type predominance.

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

IL-10, IL-19, and IL-20 are members of a related group of interleukins, homologous to 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 transforming growth factor (TGF)-β family consists of more than 30 members and is involved in the 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 pro-inflammatory 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 affect the function of endothelial cells by making the vessels more permeable and inducing apoptosis of the 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 analysis of ELISA on maternal serum from pre-eclamptic subjects also demonstrated a significant upregulation of 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. Assessment of intracellular cytokines using flow cytometry illustrated a shift 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 et al. presented evidence of increased IL-6 mRNA and protein in leukocyte-free decidual cells from individuals 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 potent pro-inflammatory cytokine that plays a significant role in the pathogenesis of autoimmune diseases (20). The lymphocytic cells exhibiting antagonistic functions include T-regulatory cells (Tregs) and T-helper 17 cells (Th17). Treg is an essential element in pregnancy that plays a vital role in preventing the mother's immune system from attacking the fetal tissue

(21, 22). The decreased amount of Treg is due to improper implantation. Th17 cells contribute to inflammation, autoimmunity, and transplant rejection in humans. Many obstetric complications have been associated with a substantial increase in Th17 cells and a decrease 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 found in CD4+ cells, CD8+ cells, NK cells, and monocytes; human IL-17 functions dynamically in the recruitment and activation processes.

Tumor Necrosis Factor-alpha and Toxemia of Pregnancy

Tumor Necrosis Factor-alpha (TNF-alpha) is a pro-inflammatory cytokine synthesized by macrophages (14, 19, 21), T-lymphocytes, and natural killer cells and monocytes (16, 21, 24). It is released during the acute phase of inflammation, where it orchestrates various signals to facilitate necrosis or apoptosis. Additionally, this protein holds significance in bolstering immunity against infections. Several studies have shown an increase in these cytokines in Toxemia of pregnancy. The generation and release of TNF-α are influenced by hypoxia-reoxygenation resulting from the intermittent perfusion of the placenta (16, 25).

TNF-α binds to two distinct receptors, enabling signal transduction through the pathway and giving rise to diverse cellular responses, which regulate cell survival, differentiation, inflammation, cell defense, and Cell proliferation (Figure 4). An excessive and sustained activation of TNF-α could lead to chronic inflammation, autoimmune diseases, and other complications (26). Knowledge of the TNF-α signaling pathway has expanded and led to the innovation of therapeutic approaches for immunologic diseases, notably 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. Functionally, TNF-α initiates a cascade of inflammatory molecules, including other 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).

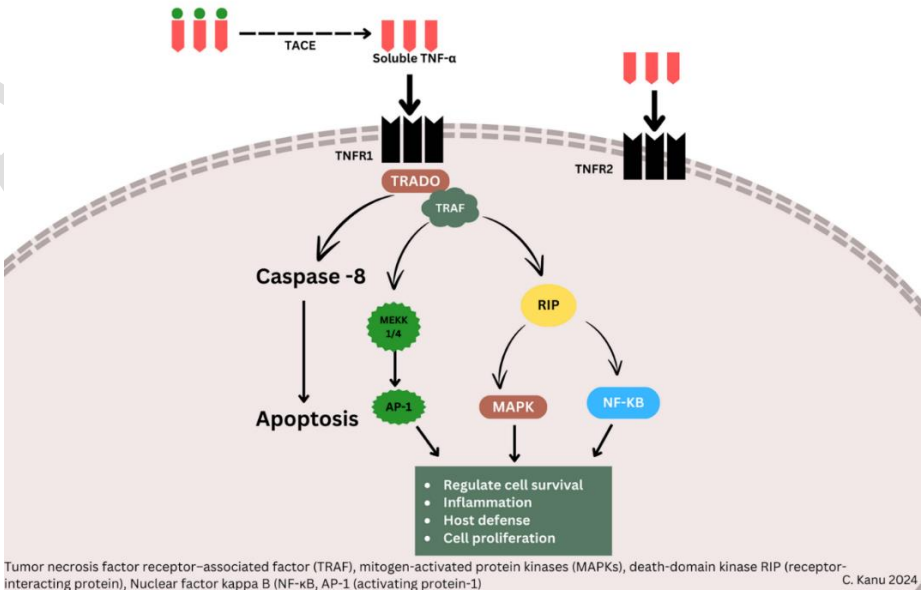

Figure 4. TNF-α cascade

The sequel of these processes is placental hypoxia, 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. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), known to induce dysfunction in endothelial cells, are synthesized and released in the human placenta of patients with Toxemia of pregnancy.

Recent reports indicate that hypoxia increases the production of TNF-α and IL-1 from the human placenta. Placental cells also express erythropoietin (EPO), a molecule regulated transcriptionally by hypoxia in mammals (25, 28). Intriguingly, TNF-α and IL-1 exhibit DNA sequences homologous or homologous to the hypoxia-responsive enhancer element of the EPO gene, suggesting a potential, albeit untested, molecular link between placental hypoxia and the stimulation of cytokine production. 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

A prospective case-control study was conducted at Zagazig University Hospitals, recruiting 40 cases from antenatal outpatient clinics in the Obstetrics and Gynecology department. The sample size was determined using open EPI with a 95% confidence interval and 80% study power. The participants were divided into two groups: a standard (control) group of 20 pregnant women at a gestational age of 28–34 weeks and a preeclampsia group comprising 20 women diagnosed according to the American College of Obstetricians and Gynecologists (ACOG) guidelines. 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 (29-31).

Patients were monitored every 4 hours starting at 10:00 daily, considering the circadian rhythm. The preeclampsia group was managed using antihypertensive medication, antioxidants, and close follow-up for two weeks. Magnesium sulfate infusion was selectively used for cases of severe preeclampsia to prevent neurologic deficit. IL-17 serum concentration was measured after the 2 weeks following additional blood pressure assessment. In the preeclampsia group, the mean IL-17 value was 18.5 pg/mL, while in the control group, it was 4.3 pg/mL, indicating a statistically significant difference between the 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% (29- 31).

A study showed an elevation in IL-17 levels in 34 pre-eclamptic patients compared to 35 healthy pregnant women, attributing their findings to an exacerbation of the normal inflammatory response preceding birth in preeclampsia patients. 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 be very valuable for both prognosis and follow-up of the disease (29- 31). Another group of researchers undertook a comparable investigation to evaluate cytokines linked with T-helper 17 (IL-17, IL-21, IL-23, and TGF-β) during the third trimester of pregnancy. The study included three cohorts: 30 preeclampsia patients, 30 normotensive pregnant women, and 30 healthy individuals (29). They observed that the serum concentrations of IL-17 and TGF-β were significantly elevated levels observed in preeclampsia patients in comparison to both the normotensive and the healthy individuals($P<0.0001$) (29- 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- 31).

Table 1. Summary of common cytokines and their function

Cytokine	Function	Secreted By
IL-1	Activates lymphocyte, macrophage stimulation, increased leukocyte/endothelial adhesion, and release of acute phase reactant. Causes fever, acute inflammation.	T cells, B cells, Endothelial cells, Macrophages
IL-2	Increases T-cell proliferation. Stimulates the proliferation of NK cells and cytotoxic and helper T-cells.	T cells
IL-4	Stimulates B-cell differentiation and class switching to IgE and IgG. Causes Th2 differentiation and proliferation, and inhibits IFN gamma-mediated activation on macrophages.	B cells, T cells, NK cells
IL-5	Induces the growth and differentiation of B cells, triggers the activation of eosinophils and enables class switching to IgA.	B cells
IL-6	Causes fever and release of acute phase protein.	Monocytes
IL-10	Causes inhibition of IL-2 and interferon gamma. Reduces the presentation of antigens and the expression of MHC class II by dendritic cells. Stimulates T cells to differentiate into Helper T cells.	Macrophages
IL-12	Stimulates T cell to differentiate into Helper T cell	Macrophages
TNF-Alpha	Makes the vessels more permeable, enables expression of adhesion molecules, activates endothelial cells, increases recruitment of White blood cells to site of infection, and maintains granuloma.	Endothelial cells, Macrophages, B cells
Interferon-γ	Promotes growth of Th1 cells and inhibits the growth of Th2 cells. Stimulates macrophages to kill phagocytosed pathogens.	NK cells and T cells

Anti-inflammatory cytokines in Toxemia of Pregnancy

In Toxemia of pregnancy, there is an elevation in placental cytokines (such as pro-inflammatory cytokines) alongside a diminished secretion of cytokines, such as IL10 and IL-4, which typically serves to inhibit inflammation (11, 32). 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 also serves as a crucial immune system modulator, acting as an immunomodulator and directly enhancing vascular health, fostering effective cellular interactions at the maternal-fetal interface. Alterations in the levels of these cytokines may impact the operation of the major apoptotic pathway, thus affecting the smooth progression of pregnancy and leading 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 observation suggests that the pre-eclamptic placenta responds to hypoxia by producing inadequate levels of IL-10 and IL-4. Consequently, this abnormal response may contribute to the heightened production of inflammatory cytokines, thereby playing a role in the development of maternal intravascular disease. An interesting observation was noted, which proved that there is a negative association between blood pressure and the levels of circulating IL-10. 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 expression of IL-4 and IL-10 were diminished in both sets of pre-eclamptic placental tissues, contrasting with an upregulation in control samples (3\\5). Similar patterns were observed in maternal serum samples, with lower levels detected in preeclampsia 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 are a family of low-molecular-weight chemotactic cytokines that regulate leukocyte migration through interactions 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- 38). Chemokine receptors mediate multiple signaling pathways that regulate various cellular responses.

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 SCM-1β/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.

A study of 309 pregnant women in 3 clusters (Uncomplicated Preeclampsia with normal and abnormal angiogenic profile) further confirms the presence of intravascular inflammation, cytokines, and chemokines among the study groups. The study revealed plasma concentrations of cytokines (interleukin-6, interleukin-8, interleukin-12/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 correlation was observed between the severity of the antiangiogenic state, blood pressure, and plasma concentrations of a subset of cytokines.

Conclusion

In this study, we aimed to investigate the role of cytokines such as IL-6, IL-4, IL-10, TNF- α, and endothelin in the pathophysiology of pregnancy toxemia. There is evidence that lower levels of maternal IL-10 concentrations in the second trimester could potentially serve as an early predictor for the development of pre-eclampsia. Research conducted in both human and animal models has collectively aimed to unravel the role of cytokines in pregnancy toxemia, contributing to a broader understanding of its pathogenesis. However, despite extensive research, a conclusive mechanism underlying pre-eclampsia remains elusive, leading to more questions and further investigations.

Continually pursuing knowledge in this area directs us toward making accurate diagnoses and formulating appropriate management plans. Increased awareness of the involvement of chemokines and cytokines in the pathophysiology of pregnancy toxemia holds the potential to prevent obstetric complications and assist in effective management and follow-up.

Acknowledgement

The authors would like to express their sincere gratitude to all those who contributed to the completion of this research.

Author Contributions

All authors contributed to the article and unanimously approved the submitted version.
CK created the diagrams and figures.

Funding

None

Conflict of Interest

Authors declare no conflict of interest

Abbreviations

Th, Helper T cell; RNA, Ribonucleic acid; DNA, Deoxyribonucleic acid**;** IL-1, Interleukins; ATP, Adenosine triphosphate; 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; 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.

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