T-CELL DYSFUNCTION AND IMMUNE OPTIMIZATION: INSIGHTS INTO PREECLAMPSIA. A SCOPING REVIEW

ABSTRACT

Preeclampsia is a pregnancy complication marked by high blood pressure and endothelial dysfunction, affecting approximately 2–8% of pregnancies globally. Despite extensive research, the immunopathogenesis of preeclampsia remains unclear. Recent studies suggest that immune dysfunction underlying Immune Mediated Inflammatory Diseases (IMIDs) share common epidemiological links and disrupted immune-inflammatory pathways. Lifestyle factors that adversely affect immune health can initiate and worsen T-cell immune dysfunctions. Implementing immune optimization strategies, such as a balanced diet, adequate sleep, and moderate intensity exercise, may be effective adjunctive therapies to prevent and alleviate immune dysfunction. In this review, we searched databases including Google Scholar, PubMed, Biomed Central, and SciELO online, using keywords related to immune optimization, T lymphocyte dysfunction, cytokines, preeclampsia, and systemic inflammation. This scoping review presents a proposed model of T-cell immune dysfunction in preeclampsia and explores the potential of multi-omic studies to validate this model. While it paves the way for new therapeutic approaches that address immune dysfunction, it does not cover the diagnostic and monitoring roles of multi-omic studies for preeclampsia.

Keywords: Pre-eclampsia, Immune dysfunction, systemic inflammation, Inflammatory cytokines, multiomics.

T-CELL DYSFUNCTION AND IMMUNE OPTIMIZATION: INSIGHTS INTO PREECLAMPSIA. A SCOPING REVIEW

ABSTRACT

Preeclampsia is a pregnancy complication marked by high blood pressure and endothelial dysfunction, affecting approximately 2–8% of pregnancies globally. Despite extensive research, the immunopathogenesis of preeclampsia remains unclear. Recent studies suggest that immune dysfunction underlying Immune Mediated Inflammatory Diseases (IMIDs) share common epidemiological links and disrupted immune-inflammatory pathways. Lifestyle factors that adversely affect immune health can initiate and worsen T-cell immune dysfunctions. Implementing immune optimization strategies, such as a balanced diet, adequate sleep, and moderate intensity exercise, may be effective adjunctive therapies to prevent and alleviate immune dysfunction. In this review, we searched databases including Google Scholar, PubMed, Biomed Central, and SciELO online, using keywords related to immune optimization, T lymphocyte dysfunction, cytokines, preeclampsia, and systemic inflammation. This scoping review presents a proposed model of T-cell immune dysfunction in preeclampsia and explores the potential of multi-omic studies to validate this model. While it paves the way for new therapeutic approaches that address immune dysfunction, it does not cover the diagnostic and monitoring roles of multi-omic studies for preeclampsia.

Keywords: Pre-eclampsia, Immune dysfunction, systemic inflammation, Inflammatory cytokines, multiomics.

INTRODUCTION

Preeclampsia is a pregnancy complication characterized by hypertension and endothelial dysfunction, affecting 2–8% of pregnancies globally. The rising incidence of preeclampsia is of public health concern. It is a leading cause of adverse maternal and fetal outcomes worldwide characterized by the onset of hypertension and proteinuria after 20 weeks of gestation. [1, 2]

The pathogenesis of preeclampsia is multifactorial, involving a complex interplay of various biological processes such as T-cell mediated immune dysfunction, placental dysfunction, oxidative stress, angiogenic imbalance, systemic inflammation thereby exposing maternal and fetal health to adverse outcomes. [3, 4, 5] Abnormal trophoblast invasion and impaired angiogenesis exacerbate immune dysfunction leading to increased antiangiogenic factors like soluble fms-like tyrosine kinase-1 (sFlt-1), which inhibit critical endothelial regulators such as Vascular Endothelial Growth (VEGF) and Placenta Growth Factor (PlGF). Furthermore, oxidative stress arising from Reactive Oxygen Species (ROS) is linked to the pathogenesis of preeclampsia. [6, 7]

Maintaining a balance between pro-angiogenic and anti-angiogenic factors is essential for healthy vascular function. In preeclampsia this balance is disrupted by overproduction of anti-angiogenic factors, further fueling systemic inflammation. [8, 9] Women with preeclampsia often exhibit elevated pro-inflammatory cytokines like TNF-α, IL-6, and IFN-γ, worsening endothelial dysfunction and clinical symptoms. [10, 11]

Preeclampsia requires a distinct immunological model compared to other Immune Mediated Inflammatory diseases (IMIDs) due to several unique factors. Firstly, its pathophysiology is pregnancy-specific, involving abnormal trophoblast invasion and impaired spiral artery remodeling. [6] The maternal immune system adapts to tolerate the semi-allogeneic fetus, with

failures in this adaptation leading to excessive inflammation unique to preeclampsia. [12] The cytokine profile associated with preeclampsia, including elevated pro-inflammatory cytokines and anti-angiogenic factors, differs from those in other IMIDs. [9, 13] Additionally, preeclampsia occurs exclusively during pregnancy, highlighting the importance of gestational context, localized placental inflammation, and the interplay between impaired maternal T cell tolerance and maternal-fetal immune maladaptation [14]

In recent years, growing evidence suggests that immune dysregulation plays a crucial role in the development and progression of preeclampsia. [15] Immuno-toxic lifestyle habits like poor diet, lack of sleep, and exercise are implicated in the pathogenesis of Immune Mediated Inflammatory Diseases (IMIDs). [16, 17]

Immune dysfunction in disease pathogenesis determine to some extent, the phenotypic expressions of genetically predisposing IMIDs. [18] The biology and correlation of inflammatory cytokines in relation to immune dysfunction and IMIDs like Metabolic Syndrome Associated Disorders are well established. [16, 18] Although insights into inflammatory dysfunctional immune processes concerning IMIDs and preeclampsia exist, the actual systemic inflammatory dysfunctional disease mechanisms remain unknown. [15, 16]

Epigenetic activation of T cells by dietary factors can alter their permeability and induce signal transductions. [19] Dysfunctional T cells play a central role in the immunopathogenesis of IMIDs like Metabolic Syndrome Associated Disorders (MSADs). [18] Trans-endothelial migration of dysfunctional T cells in disease pathogenesis is mediated by cellular adhesion molecules (CAMs), which are regulated by pro-inflammatory cytokines in immunological processes. [16] Placental ischemia, oxidative stress, and release of damage-associated molecular patterns (DAMPs) trigger the activation of immune cells in preeclampsia. [3]

The morbidity and mortality rate of preeclampsia underscores the limitations of current treatment approaches. Discussing the putative T cell immune dysfunction model of IMIDs using preeclampsia as an example should highlight its pathogenesis concerning immune-toxic lifestyle habits. Insights from the putative disease model can guide effective interventions.

MATERIALS AND METHODS

Online searches were conducted on databases such as Google Scholar, PubMed, Biomed Central, and SciELO. Articles were reviewed using keywords such as preeclampsia, disease mechanisms, cellular adhesion molecules, immune optimization/dysfunction, T lymphocyte activation/dysfunction, and systemic inflammatory cytokines.

RESULTS

Of the 273 articles identified from databases, 17 were duplicates and 11 which did not highlight the role of immuno-toxins in the pathogenesis of IMIDs were excluded. Of the 245 articles assessed for eligibility, 35 articles described immunopathogenesis of T cell dysfunction secondary to immunotoxins, discussed preventive and adjunctive therapeutic roles of immune optimization interventions on IMIDs and were included in the Scoping review [Figure 1].

Key Findings

(1) Immuno-toxic lifestyle habits serve as initiators and consolidators of immune dysfunctional mechanisms underlying IMIDs and preeclampsia.
(2) Similar immune dysfunctional mechanisms underlie a spectrum of IMIDs and preeclampsia.

(3) Immune Optimization Interventions could serve as preventive and therapeutic adjuncts for management of IMIDs and preeclampsia.

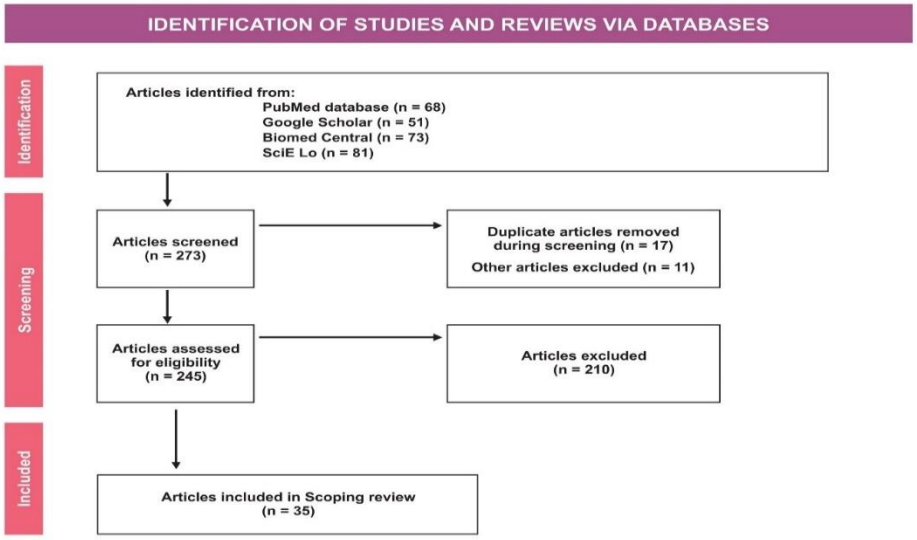


Fig 1: PRISMA flow diagram for the Scoping review detailing the database searches and the number of articles screened.

IMMUNOPATHOGENESIS OF T CELLS IN IMMUNE MEDIATED INFLAMMATORY DISEASES

The coordinated actions of immune system components enable quick, targeted defenses against severe infections and their biologic byproducts and the immune-mediated defense

mechanisms are active in a wide range of medical disorders. [20] The immune system is divided into two main arms; innate and adaptive. Physical barriers such as layers of epithelial cells in the skin act as the primary mediators of the protective action of the innate immune system. The protective function of the adaptive immune system is mediated by intricate interactions between immune system cells, such as B cells, T cells, leukocyte subsets, and the cytokines that these cells synthesized. Additionally, immune cells have receptors for a variety of chemicals that may function as antigens. [21]

Leukocytes and plasma proteins are extracted from the blood and transported to particular parts of the body where they trigger appropriate immune responses. [22] Cytokines are chemicals that resemble hormones and control immune responses in a paracrine manner. They either have anti-inflammatory properties (IL-13, IL-11, and TGF-beta) or pro-inflammatory properties (IL-6, IL-7, and TNF-alpha). [16]

T cells are crucial for immune functions and they maintain a homeostatic milieu and prevent diseases. Their development occurs in a stepwise process in the thymus, which mainly generates CD4+ and CD8+ T cell subsets. [23] Depending on the cytokine milieu present in the disease microenvironment and certain transcription factors, CD4+ T cells can differentiate into several subsets of effector T cells, such as T helper 1 (Th1) cells, T helper 2 (Th2) cells, T regulatory cells (Treg), or cytotoxic T cells. [18] T cells have been shown to play a crucial role in the pathogenesis of hypertension, an IMID. T cell-deficient mice were reported to be resistant to blood pressure elevation, suggesting that these cells play unique roles in the pathogenesis of hypertension. [24, 25, 26] Genetic predisposition, which coordinates and chooses where to direct activated dysfunctional T cells in disease conditions, can influence immune response products and outcomes. They may also mediate distinct disease phenotypes in different regions of the body as well as worsening of clinical symptoms as reported by Okafor et al. [19]

IMMUNE DYSREGULATION IN PREECLAMPSIA

The pathogenesis of preeclampsia involves an interplay between immune cells, placental development, and maternal response to pregnancy. [4] Dysregulation of immune cells is a hallmark of preeclampsia and T helper 1 (Th1) and T helper 17 (Th17) cells were reported to be prominently involved in the inflammatory response associated with preeclampsia. [24] Th1 cells secrete pro-inflammatory cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which have been shown to promote endothelial dysfunction and vascular inflammation. [27] Similarly, Th17 cells produce interleukin-17 (IL-17), a cytokine that enhances inflammatory processes and has been implicated in the pathogenesis of various autoimmune conditions, including preeclampsia. [28]

In contrast, regulatory T cells (Tregs), which typically play a crucial role in maintaining immune tolerance during pregnancy, are often found to be altered in women with preeclampsia. Tregs are essential for preventing excessive immune responses that could harm the fetus, and their dysfunction leads to a failure in maintaining the necessary immune tolerance. [29] Research indicates that the number and activity of Tregs are significantly reduced in women with preeclampsia contributing to the disrupted balance between pro-inflammatory and anti-inflammatory responses. Reduction in Treg activity allows for the unchecked proliferation of pro-inflammatory cells, exacerbating systemic inflammation and endothelial dysfunction. [29] Elevated levels of pro-inflammatory cytokines in the maternal circulation can lead to increased vascular permeability, vasoconstriction, and ultimately, hypertension, hallmark features of preeclampsia. [1] Recent studies have also highlighted the role of the placental microbiome and its interaction with the maternal immune system in preeclampsia. The presence of certain microbial communities within the placenta may

influence immune responses and contribute to inflammatory pathways involved in the condition. [30]

Genetic and environmental factors play a significant role in the pathogenesis of immune dysfunction in preeclampsia. Recent studies have indicated that these factors not only contribute to the development of immune-mediated inflammatory diseases (IMIDs) but also share common epidemiological associations and similar dysregulated immune-inflammatory pathways. [27] The interaction between genetic predispositions and environmental influences can lead to epigenetic modifications, which further impact immune responses. Specifically, dietary factors such as hydrogenated fats and diacylglycerol (DAG) have been shown to activate epigenetic changes that can disrupt T cell function, altering their permeability and signal transduction mechanisms. [19] This dysregulation of T cells may exacerbate the inflammatory state observed in preeclampsia, contributing to its pathophysiology. [31]

Putative Immunopathogenesis of T-Cell Dysfunction in Preeclampsia.

Activated Dysfunctional T cells (DTCs) are conceived to mediate distinct disease phenotypes depending on genetic predispositions, migrating to diverse places in the body during an immunological dysfunctional state as reported by Okafor et al. [19] DTCs move and adhere with the help of cellular adhesion molecules (CAMs) through chemotaxis mediated by systemic inflammatory cytokines generated by DTCs, participating in cross-talks with the

placenta microenvironment in patients with genetic predisposition to preeclampsia, as shown in Figure 2. When egregious food substances trigger diet-mediated epigenetic activation of T cells, their membranes may become unusually permeable, allowing signal transduction food molecules like DAG to enter and cause malfunction. [19] Moreover, abnormal synthesis of systemic inflammatory cytokines may arise from diet-mediated epigenetic post-translational alteration of proteins, which are enzyme substrates for cytokine generation by DTCs. Enzymes involved in processing these inflammatory cytokines are potential targets for novel drug designs. [31] Furthermore, cross-talks between inflammatory cytokines produced by DTCs and the extracellular matrix of the disease site may exacerbate disease symptoms like ovarian hyper stimulation syndrome. [19, 32]

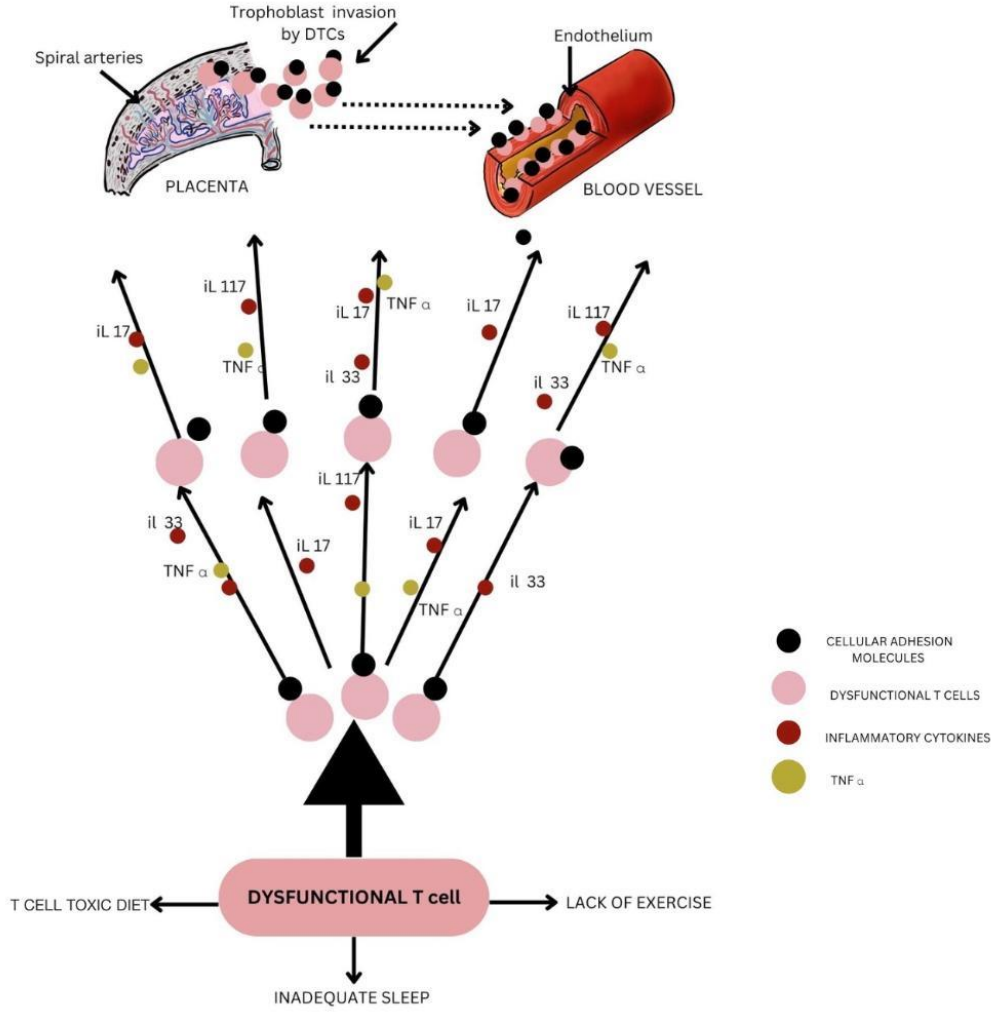
The putative preeclampsia disease model suggests that CAMs and inflammatory cytokines, in immune dysfunction aid DTCs to migrate and adhere to the endothelium of various organs and blood vessels, especially the placental bed. This leads to aberrant trophoblast invasion by DTCs. The placenta and its microenvironment may be pluripotent. Pluripotency is the ability of stem cells to give rise to many cell types. Pluripotency of the placental microenvironment may have a multiplicative effect on DTCs and also serve as their reservoir, from where they migrate to the endothelium of blood vessels, sequestrate, increase vascular resistance, and translate to elevated blood pressure. It is well known that endothelial dysfunction is underlined by impaired bioavailability of nitric oxide, a natural vasodilator that controls vascular tone and blood pressure.

When the immune system is not perturbed by harmful dietary substances, the integrity of T cell membranes remains intact. Disruption and permeation of T cell membranes by harmful food substances such as Trans and hydrogenated fats leading to the influx of molecules that prematurely activate them and their migration to disease-predisposing sites, are consequently mitigated. [19] Diet laden with harmful food substances, less than 7-9 hours of sleep and lack

of exercise may be considered initiators and consolidators of immune dysfunction underlying preeclampsia, respectively.

The putative T cell dysfunction disease mediating model in preeclampsia may be postulated as an IMID whereby genetic predisposition determines the disease phenotype. The putative immunopathogenesis of T cell dysfunction described above may be applicable to the pathogenesis of other IMIDs. Phenotypic expression of IMIDs based on genetic predispositions may vary across their spectrum.

Immune optimization interventions with immune optimizers such as a balanced diet, getting 7-9 hours of night sleep and moderate-intensity exercise should be alluring adjunctive therapeutic strategies to prevent and mitigate immune dysfunction underlying IMIDs. Immune optimization interventions are alluring disease prevention strategies. However, their efficacy as therapeutic adjuncts and immuno-prophylaxis may vary depending on how strong the genetic predisposition is. Therefore, IMIDs with very strong genetic predisposition may be less amenable to immune optimization interventions as adjunctive therapeutic interventions as well as immuno-prophylactic measures, especially in the late stages of IMIDs.



220

221

222 Figure 2: Putative immuno-toxiepigenetic disease model of Preeclampsia

223

224

225 **Roles of Multiomic and Radiological Studies for Validation of Putative Immuno-**

226 **toxiepigenetic Model of Preeclampsia**

Immune optimization interventional multiomic (genomic, transcriptomic, proteomic, metabolomic) studies can be used to investigate preeclampsia disease mechanisms and validate our putative disease model.

Gene expression studies may support and partly validate the putative theory of non-expression of disease phenotypes in an immune-optimized state despite preeclampsia genetic predispositions.

Studies on proliferation and migration of DTCs in preeclampsia may validate our theory of migration/aberrant trophoblast invasion by DTCs and to the endothelium of blood vessels.

An array of gene transcript signatures relative to adverse environmental exposures through epigenetic mechanisms may be highlighted by correlative transcriptomic and DTC studies. Two distinct molecular signatures of preeclampsia have been revealed by single cell transcriptomics. [33] It reflected some dysregulations in FLT1 and PGF transcriptions in the syncytium in early preeclampsia. [33] Additionally, comprehensive and correlative analysis of the proteasome for post-translational modifications of substrate enzymes for cytokine production by DTCs may validate and support the putative theory of systemic inflammatory cytokine production by DTCs. Various proteins are detected in preeclampsia. Most frequently detected of these proteins are CLIC3, ALB, FN1, ANXA1 and ANXA2. [34]

Metabolomic studies evaluating the gut microbiome and other biological specimens may highlight metabolites of environmental toxicants suspected to drive adverse gene expressions. The metabolite LysoPE (16:30) have been found to be downregulated in the serum of preeclamsia patients, highlighting its potential role in the pathophysiology of the disease. [35] Furthermore, biological specimens may highlight metabolites associated with T cell dysfunction and further validate the theory of its dysfunction by environmental toxicants through epigenetic mechanisms.

The placenta and its microenvironment may be pluripotent, have multiplicative effect on DTCs and also serve as their reservoir as discussed earlier. Non-invasive radiological scans like Magnetic Resonance Imaging (MRI) can be used to measure the placenta size as a "DTC reservoir" parameter to gauge or predict severity of the disease in preeclampsia immunotoxiepigenetic disease validating studies and future clinical/obstetric practice.

CONCLUSION

This scoping review has discussed a putative immunotoxiepigenetic disease model of preeclampsia and the role of multiomic studies for validation of the disease model.

Insights from the putative disease model as regards the role of immunotoxins in engendering T cell dysfunction should guide therapeutic interventions for IMIDs and their disease spectrum, like preeclampsia. Furthermore, it could pave the way for an emerging field in therapeutics, "immunotoxiepigenetic therapeutics," which takes into account immune dysfunctions underlying IMIDs and the institution of appropriate adjunctive therapeutic immune optimization interventions. Furthermore, immunotoxiepigenetic therapeutics is envisaged to prescribe/proscribe therapeutic interventions in line with rational use of drugs, clinical/laboratory needs of patients, and waxing/waning phenotypic expressions of IMIDs.

Limitation of the review

This mini review did not discuss diagnostic and monitoring roles of multiomic studies for preeclampsia.

Authors' contribution

This manuscript has been read and approved by the authors. The requirements for authorship were met as outlined below.

MTO: Concept, design, definition of intellectual content, literature search, article screening, manuscript preparation, manuscript editing, and manuscript review. Also takes responsibility for the integrity of the content of this manuscript. TUN: Literature search, intellectual content, article screening, data acquisition, manuscript preparation, manuscript review. QCO: manuscript preparation, manuscript editing, manuscript review. MIE: Manuscript preparation, manuscript review. UIN: Intellectual content, manuscript review.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Financial support and sponsorship

No funding was received for reparation of this manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

Informed consent

This is a review article and thus did not require any informed consent

Declaration of Helsinki

The study was conducted according to the ethical principles of Helsinki Declaration.

Availability of research data

The authors are available and ready to supply the data upon any requests through the corresponding author.

Acknowledgment

Nil

References

(1) Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. Nat Rev Nephrol. 2014; 10(8):466-480.

(2) Redman CW, Sargent IL. Placental stress and pre-eclampsia: a revised view. Placenta. 2009; 30 Suppl A: S38-S42.

(3) Agarwal, A., Tvrda, E., & Mulgund, A. (2014). Oxidative Stress in Preeclampsia. *Handbook of Fertility*, 283-290. https://doi.org/10.1016/B978-0-12-800872-0.00026-3

(4) LaMarca B, Cornelius DC, Wallace K. Elucidating immune mechanisms causing hypertension during pregnancy. Physiology (Bethesda). 2013; 28(4):225-233.

(5) Ortved D, Hawkins TLA, Johnson JA, et al. (2019). Cost-effectiveness of first-trimester screening with early preventative use of aspirin in women at high risk of early-onset preeclampsia. *Ultrasound Obstet Gynecol*, 53(2) : 239–44.

(6) Burton GJ, Fowden AL. The placenta: a multifaceted, transient organ. Philos Trans R Soc Lond B Biol Sci. 2015 Mar 5;370(1663):20140066. doi: 10.1098/rstb.2014.0066. PMID: 25602070; PMCID: PMC4305167.

(7) Moser G, Windsperger K, Pollheimer J, de Sousa Lopes SC, Huppertz B. Human trophoblast invasion: new and unexpected routes and functions. Histochem Cell Biol. 2018 Oct;150(4):361-370. doi: 10.1007/s00418-018-1699-0. Epub 2018 Jul 26. PMID: 30046889; PMCID: PMC6153604

(8) Helmo FR, Lopes AMM, Carneiro ACDM, Campos CG, Silva PB, Dos Reis Monteiro MLG, Rocha LP, Dos Reis MA, Etchebehere RM, Machado JR, Corrêa RRM. Angiogenic and antiangiogenic factors in preeclampsia. Pathol Res Pract. 2018 Jan;214(1):7-14. doi: 10.1016/j.prp.2017.10.021. Epub 2017 Oct 31. PMID: 29174227

(9) Flint EJ, Cerdeira AS, Redman CW, Vatish M. The role of angiogenic factors in the management of preeclampsia. Acta Obstet Gynecol Scand. 2019;98:700-707. https://doi.org/10.1111/aogs.1354

(10) Cornelius DC. Preeclampsia: From Inflammation to Immunoregulation. Clin Med Insights Blood Disord. 2018 Jan 10;11:1179545X17752325. doi: 10.1177/1179545X17752325. PMID: 29371787; PMCID: PMC5772493.

(11) Redman, C. W., Robertson, S. A., & Taylor, R. N. (2021). The Immunology of Preeclampsia. Chesley's Hypertensive Disorders in Pregnancy (Fifth Edition), 131-153. https://doi.org/10.1016/B978-0-12-818417-2.00021-X

(12) Balasundaram P, Farhana A. Immunology at the Maternal-Fetal Interface. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK574542/

(13) Cornelius DC. Preeclampsia: From Inflammation to Immunoregulation. Clin Med Insights Blood Disord. 2018 Jan 10;11:1179545X17752325. doi: 10.1177/1179545X17752325. PMID: 29371787; PMCID: PMC5772493.

(14) Ives CW, Sinkey R, Rajapreyar I, Tita ATN, Oparil S. Preeclampsia-Pathophysiology and Clinical Presentations: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Oct 6;76(14):1690-1702. doi: 10.1016/j.jacc.2020.08.014. PMID: 33004135.

(15) Luppi P. How immune mechanisms are affected by pregnancy. Vaccine. 2003;21(24):3352-3357

(16) Michael T. Okafor, Samuel I. Ghasi. Preventive and Therapeutic Adjunctive Roles of Immune Optimization on Inflammatory and Infectious Diseases. A Mini Review. Niger J Basic Clin Sci 2024; 21:185-9.

(17) Michael T. Okafor, Queenet C. Onyebuchukwu, Germaine A. Okafor, Samuel C. Niteh, Chikere A. Anusiem. Immune Optimization as a Preventive and Therapeutic Adjunct for the Management of Renin-Angiotensin-Aldosterone System Dysfunction Diseases: A Review. Int J Med Health Dev 2024; 29:161-9.

(18) Okafor MT, Onyebuchukwu QC, Mbah AU. Immune Optimization as a preventive and therapeutic adjunct for management of metabolic syndrome associated disorders: a review of the literature. Afr J Endocrinol Metab 2023; 13: 1-7.

(19) Michael T. Okafor, Uzoamaka A. Okoli, Adaugo G. Okafor. Diet-Mediated Immune Optimization as a Preventive and Therapeutic Adjunct for Management of Multiple Endocrine Neoplasia. Int J Med Health Dev 2023; 28:277-84.

(20) Kay L. Medina. Handbook of Clinical Neurology. Volume 133, 2016, pgs 61-76.

(21) Berkovic MC, Cacev T, Ivkovic TC, Zjacic-Rotkvic V, Kapitanovic S. New insights into the role of chronic inflammation and cytokines in the etiopathogenesis of gastroenteropancreatic neuroendocrine tumors. Neuroendocrinology 2014; 99:75–84. https://doi.org/10.1159/000362339.

(22) Marco A. Moro-Garcia, Juan C. Mayo, Rosa M. Sainz and Rebeca Alonso-Arias. Influence of Inflammation in the Process of T lymphocyte Differentiation: Proliferative, Metabolic and Oxidative changes. Front. Immunol. March 2018. Vol 9.

(23) Toldi G, Rigó J Jr, Stenczer B, Vásárhelyi B, Molvarec A. Increased prevalence of IL-17-producing peripheral blood lymphocytes in pre-eclampsia. Am J Reprod Immunol. 2011;66(3):223-229

(24) Suri-Payer E, Amar AZ, Thornton AM, Shevach EM. CD4+CD25+ T Cells Inhibit Both the Induction and Effector Function of Autoreactive T Cells and Represent a Unique Lineage of Immunoregulatory Cells. The Journal of Immunology 1998; 160:1212–8. https://doi.org/10.4049/JIMMUNOL.160.3.1212.

(25) Ghiadoni L, Taddei S, Virdis A. Hypertension and endothelial dysfunction: therapeutic approach. Curr Vasc Pharmacol 2012;10:42–60. https://doi.org/10.2174/157016112798829823.

(26) Rana, S., Lemoine, E., Granger, J., and Karumanchi, S. A. (2019). Compendium on the pathophysiology and treatment of hypertension. Preeclampsia pathophysiology, challenges, and perspectives. Circ. Res. 124, 1094–1112. doi: 10.1161/CIRCRESAHA.118.313276

(27) Saito S, Nakashima A, Shima T, Ito M. Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. Am J Reprod Immunol. 2010; 63(6):601-610.

(28) Shigeru Saito, Sayaka Tsuda, Akitoshi Nakashima. T cell Immunity and Etiology and Pathogenesis of Preeclampsia. Journal of Reproductive Immunology. Vol 159, Sep 2023, 104125.

(29) Aagaard, K., Ma, J., Antony, K. M., Ganu, R., Petrosino, J., and Versalovic, J. (2014). The placenta harbors a unique microbiome. Sci. Transl. Med. 6, 237–265. doi: 10.1126/scitranslmed.3008599

(30) Derek Miller, Kenichiro Motomura, Jose Galaz, Meyer Gershater, Eun D. Lee, Roberto Romero, and Nardhy Gomez-Lopez. Cellular Immune Responses in the Pathophysiology of Preeclampsia. J Leukoc Biol. 2022 Jan; 111(1): 237-260.

(31) C.A. Dinarello and N.H. Margolis. Cytokine Processing Enzymes: Stopping the cuts. Current Biology. Volume 5, Issue 6, June 1995. Pages 587 – 590.

(32) Abramov Y, Schenker JG, Lewin A, Friedler S, Nisman B, Barak V. Plasma inflammatory cytokines correlate to the ovarian hyperstimulation syndrome. Hum Reprod 1996; 11:1381–6. https://doi.org/10.1093/OXFORDJOURNALS.HUMREP.A019404.

(33) Inbal Admati, Niv Skarbianskis, Hannah Hochgerner, Osnat Ophir, Zeev Weiner, Simcha Yagel, Ido Solt, Amit Zeisel. Two distinct molecular faces of

preeclampsia revealed by single cell transcriptomics. Med. Volume 4, Issue 10, 13 October 2023, Pages 687-709.e7

(34) Navajas, R., Corrales, F. and Paradela, A. Quantitative proteomics-based analyses performed on preeclampsia samples in the 2004-2020 period: a systematic review. Clin Proteom 18, 6 (2021).

(35) Zhongxiao Zhang, Ping He, Danni Chen, Yan Tan, Ailan Chen, Zheng Bian, Tingting Chen. Active metabolomics identify functional metabolites for preeclamsia prevention, Clinica Chimica Acta. Volume 560, 15 June 2024, 119717

17th March, 2025

The Editor in Chief,

Dear Sir/Madam

RE: CORRECTIONS FOR OUR SUBMITTED MANUSCRIPT

We write in response to the reviewer's comments for the manuscript submitted to your journal with the title: **T-CELL DYSFUNCTION AND IMMUNE OPTIMIZATION: INSIGHTS INTO PREECLAMPSIA. A SCOPING REVIEW** as follows:

Reviewer 1 comments

(1) Tracked changes have been accepted.
(2) The putative mechanism of T cell dysfunction in preeclampsia are original viewpoints of the authors and were not referenced.
(3) Insights into the putative disease model that can guide therapeutic interventions have been added to the conclusion.

Reviewer 2 comments

(1) The manuscript is a scoping review and did not carry out any form of inferential statistics.
(2) The manuscript have addressed/highlighted its novelty as regards putative mechanism for pathogenesis of preeclampsia.
(3) Exclusion/inclusion criteria of reviewed papers have been described in the method section and ethical clearance was not required for the review manuscript.
(4) The manuscript is not a primary study and no potential confounders were envisaged.
(5) Repetitive statements in the manuscript have been expunged.
(6) The conclusion of the manuscript have made suggestions as regards how putative preeclampsia disease mode may guide therapeutic interventions.

We hope our manuscript receives further consideration for publication in your journal.

Kind regards,

Corresponding author.