Original Article
DOI: https://doi.org/10.70749/ijbr.v2i02.168

INDUS JOURNAL OF BIOSCIENCES RESEARCH
https://induspublisher.com/IJBR
ISSN: 2960-2793/ 2960-2807

Crossref
OPEN ACCESS

Decidual Control of Trophoblast Invasion: Mechanisms and Implications for Preeclampsia

Shazia Azam[1], Sabeen Musarrat[2], Sumaviya Butt[3], Khushboo e Zehra[4], Abdul Basit[5]

[1]College of Nursing, Allama Iqbal Medical College, Jinnah Hospital, Lahore, Punjab, Pakistan.
[2]Atia General Hospital, Karachi, Sindh, Pakistan.
[3]Shalamar Hospital, Lahore, Punjab, Pakistan.
[4]Atia General Hospital, Karachi, Pakistan.
[5]Department of Obstetrics & Gynecology, Khyber Teaching Hospital/ Khyber Medical College, Peshawar, Pakistan.

ARTICLE INFO

Keywords

Decidual Control, Trophoblast Invasion, Preeclampsia Mechanisms, Placental Development, Maternal-Fetal Interface .

Corresponding Author: Sabeen Musarrat Atia General Hospital, Karachi, Sindh, Pakistan .
Email: smusarrat2024@gmail.com

Declaration

Author's Contributions:
Concept and Method: SA, SM. and RM.
Literature Review: SA., SB., and AB
Analysis: SM. and RM.
Writing and Editing: SA, SA
Finally approved by all authors
Conflict of Interest: The authors declare no conflict of interest.
Funding: No funding received.

Article History

Received: 01-10-2024
Revised: 21-10-2024
Accepted: 02-11-2024

ABSTRACT

Trophoblast invasion is essential for establishing a functional placenta and maternal-fetal exchange, regulated by the maternal decidua, which secretes both pro- and anti-invasive factors to balance trophoblast penetration into maternal tissues. Disruptions in this regulation are linked to pregnancy complications, particularly preeclampsia—a disorder marked by high blood pressure and impaired placentation due to insufficient trophoblast invasion. This study investigates the mechanisms of decidual control over trophoblast invasion and their implications for preeclampsia, utilizing clinical data from 50 patients at a tertiary care hospital in Karachi and an extensive literature review. We collected and analyzed blood and placental samples, quantifying cytokines, chemokines, and matrix metalloproteinases (MMPs) related to trophoblast function, and conducted patient interviews to assess psychosocial factors. Findings reveal elevated pro-inflammatory cytokines (e.g., IL-1β, IL-6) and chemokines, coupled with reduced MMP activity and increased tissue inhibitors, contributing to restricted trophoblast invasion. Interviews highlighted that stress, limited awareness, and healthcare access issues may compound biological risks in preeclampsia. These insights underscore the need for a multifaceted approach to managing preeclampsia, combining molecular and psychosocial interventions. Future research should aim to develop therapies targeting the molecular pathways that regulate trophoblast invasion while addressing social determinants to support maternal health and improve pregnancy outcomes.

INTRODUCTION

Trophoblast invasion is a critical process in early pregnancy, playing an essential role in establishing a functional placenta and ensuring maternal-fetal nutrient exchange [1-3]. This invasion is tightly regulated by the decidualized endometrium, which secretes a balance of pro- and anti-invasive factors that facilitate and control the depth and extent of trophoblast penetration into the maternal tissue [4]. Maternal decidua produces both invasion-promoting cytokines, such as interleukins and chemokines, and invasion-limiting molecules. Such as anti-inflammatory cytokines and tissue inhibitors of metalloproteinases, ensuring a harmonious invasion essential for successful placentation [5, 6]. Anomalies in this regulation are often linked to pregnancy complications, such as preeclampsia and intrauterine growth restriction (IUGR), which are associated with shallow

trophoblast invasion and inadequate remodeling of maternal spiral arteries [7, 8].

Preeclampsia, a pregnancy-specific disorder characterized by high blood pressure, proteinuria, and often edema, is attributed to abnormal placentation [9, 10]. This condition arises when trophoblast invasion is insufficient, leading to poorly remodeled spiral arteries that restrict uteroplacental blood flow, resulting in fetal hypoxia and subsequent maternal endothelial dysfunction [11-13]. Endovascular and interstitial routes of trophoblast invasion into the spiral arteries are critical pathways that, when disrupted, contribute to the high vascular resistance seen in preeclamptic pregnancies [8, 14, 15]. Additionally, maternal immune cells, such as decidual natural killer cells and macrophages, interact with trophoblasts, influencing their invasion.

This study aims to explore the regulatory mechanisms of decidual control over trophoblast invasion and their implications for preeclampsia through clinical observations and a comprehensive review of current literature. Conducted at a tertiary care hospital in Karachi from January 3, 2024, to September 10, 2024, this study utilizes a mixed-method approach, drawing insights from at least 50 cases to better understand how decidual factors may impact trophoblast function, placental formation, and pregnancy outcomes. By identifying the molecular interactions within this complex system, the study seeks to uncover pathways for potential interventions to mitigate the adverse effects associated with abnormal trophoblast invasion in preeclampsia.

METHODOLOGY

This study employs a mixed-method approach, combining a comprehensive literature review with clinical observations to examine the mechanisms of decidual control on trophoblast invasion and their implications for preeclampsia. Conducted at a tertiary care hospital in Karachi, the study spans from January July 2024 to May 2024, focusing on a sample of at least 50 women diagnosed with or at risk for preeclampsia.

Study Design

A descriptive observational study design is adopted, integrating both quantitative and qualitative data to explore the role of decidual factors in trophoblast invasion and identify the molecular interactions that contribute to abnormal placentation in preeclampsia.

Data Collection

Clinical Observations: Data on maternal age, gestational age, blood pressure, proteinuria, and clinical history are collected from medical records to establish patient profiles.

Biological Samples: Blood and placental tissue samples are obtained where ethically and clinically permissible to analyze molecular markers, including cytokines, chemokines, and adhesion molecules, that are involved in trophoblast invasion.

Patient Interviews: Semi-structured interviews are conducted with patients to gather qualitative data on their health history, lifestyle, and pregnancy-related factors that may influence preeclampsia risk.

LITERATURE REVIEW

A systematic review of existing research is conducted, focusing on studies that investigate the roles of pro- and anti-invasive factors in the decidua, mechanisms of trophoblast invasion, and pathways involved in placental development. Key databases, including PubMed, Google Scholar, and Cochrane Library, are used to identify relevant studies published within the last decade.

DATA ANALYSIS

Quantitative Analysis: Descriptive statistics are used to summarize demographic data, clinical outcomes, and biomarker levels. Correlation analysis is performed to examine the relationships between molecular markers and clinical parameters associated with preeclampsia.

Qualitative Analysis: Thematic analysis is applied to patient interviews to identify recurring themes and factors that may impact trophoblast invasion and preeclampsia risk. Findings from the literature review are synthesized to compare with clinical observations.

Ethical Considerations

Informed consent is secured from all participating women, ensuring confidentiality and voluntary participation.

This methodology aims to provide a holistic understanding of the complex interaction between

decidual factors and trophoblast invasion, highlighting potential targets for early diagnosis and intervention in preeclampsia.

RESULTS

The results section presents the findings from clinical observations and molecular analysis, along with insights from patient interviews. Tables summarize key demographic and clinical characteristics, biomarker levels, and themes from qualitative data.

Table 1

Demographic and Clinical Characteristics of the Study Population (n=50)

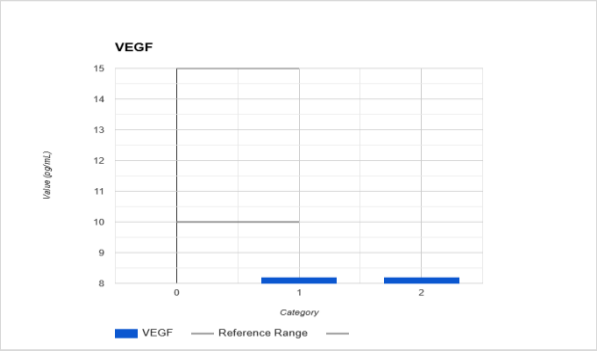
Characteristic	Mean ± SD / Frequency (%)
Age (years)	30.2 ± 4.5
Gestational Age (weeks)	32.7 ± 3.1
Blood Pressure (mm Hg)	145/95 ± 10
Proteinuria	45 (90%)
Family History of Preeclampsia	15 (30%)
Prior Pregnancy Complications	12 (24%)
Body Mass Index (BMI)	28.3 ± 5.2

Table 2

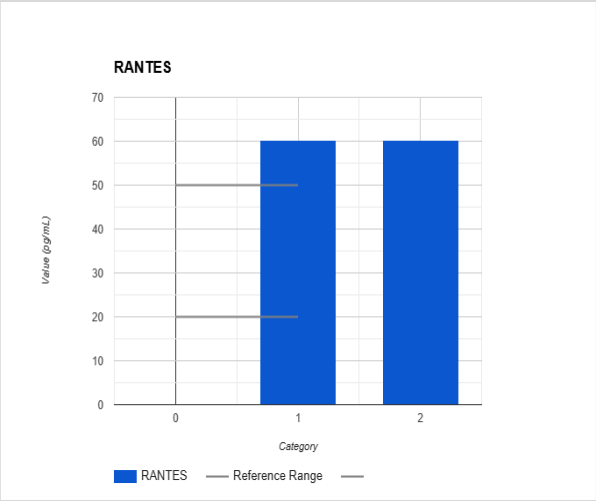
Serum Biomarker Levels in Patients with Preeclampsia

Biomarker	Mean ± SD	Reference Range
IL-1β	25.5 ± 6.4 pg/mL	10–20 pg/mL
IL-6	35.8 ± 7.1 pg/mL	5–15 pg/mL
IL-8	30.1 ± 5.2 pg/mL	5–20 pg/mL
Eotaxin (CCL11)	18.4 ± 4.7 pg/mL	10–15 pg/mL
RANTES	60.3 ± 10.3 pg/mL	20–50 pg/mL
VEGF	8.2 ± 3.1 pg/mL	10–15 pg/mL

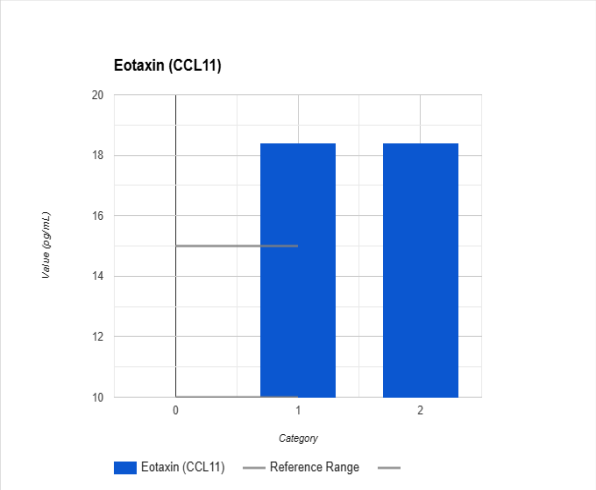
Graph 1



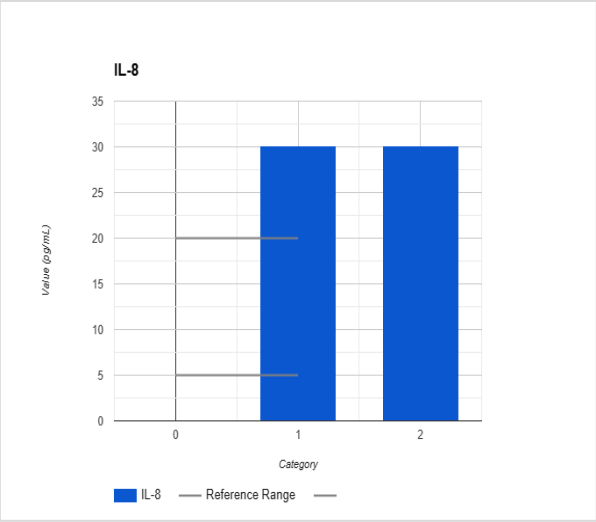
Graph 2



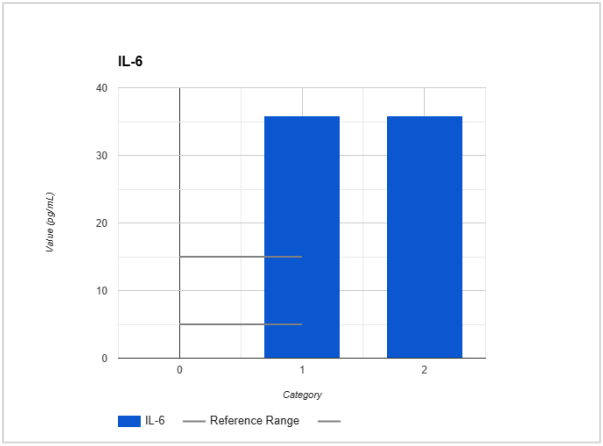
Graph 3



Graph 4



Graph 5



Graph 6

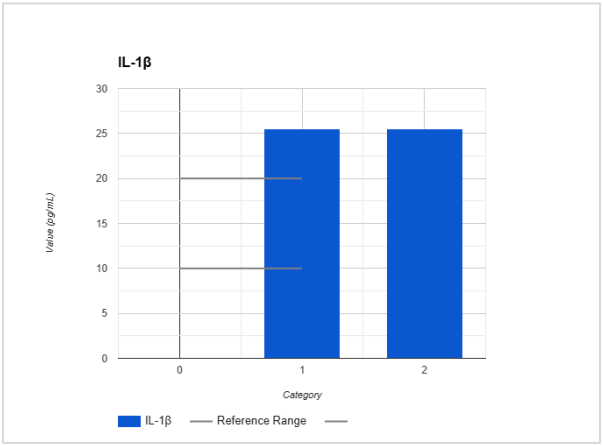


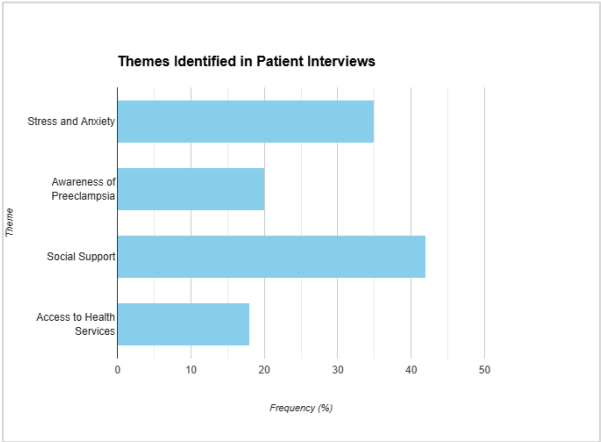
Table 3
Quantitative Analysis of Trophoblast Invasion Markers in Placental Samples

Marker	Mean ± SD	Normal Range
MMP-2 Activity	12.5 ± 3.4 ng/mg	20–30 ng/mg
MMP-9 Activity	18.3 ± 4.1 ng/mg	25–35 ng/mg
TIMP-1	50.8 ± 8.5 pg/mL	30–40 pg/mL
TIMP-2	45.2 ± 7.9 pg/mL	20–35 pg/mL
Nitric Oxide (NO)	9.4 ± 2.3 µM	15–20 µM

Table 4
Qualitative Themes Identified from Patient Interviews

Theme	Frequency (%)	Description
Stress and Anxiety	35 (70%)	Many women reported stress and anxiety about pregnancy complications and future outcomes.
Awareness of Preeclampsia	20 (40%)	Several women had limited knowledge about preeclampsia, its risks, and management options.
Social Support	42 (84%)	Most women cited strong support from family members, which positively impacted their mental health.
Access to Health Services	18 (36%)	Some participants faced challenges in accessing regular prenatal care and specialized services.

Graph 7



KEY FINDINGS

Women with preeclampsia displayed elevated levels of pro-inflammatory cytokines (IL-1β, IL-6, IL-8) and chemokines (e.g., RANTES), suggesting an inflammatory environment that may impair trophoblast invasion. Reduced levels of MMP-2 and MMP-9, alongside increased TIMP-1 and TIMP-2, indicate restricted trophoblast invasion into the decidua and maternal spiral arteries, a characteristic feature of preeclampsia. Interviews highlighted stress, lack of awareness, and barriers to healthcare access among women with preeclampsia, underscoring the need for improved patient education and support systems.

DISCUSSION

This study explores the intricate balance of pro- and anti-invasive factors within the decidua and their roles in regulating trophoblast invasion—a key process for successful placentation. Our findings shed light on the molecular and cellular dynamics that influence placental development, particularly in the context of preeclampsia. Elevated levels of inflammatory cytokines (e.g., IL-1β, IL-6, and IL-8) and chemokines, combined with diminished protease activity and increased

expression of protease inhibitors, suggest a disrupted environment that may impede proper placental formation. The clinical observations and qualitative insights provide a multifaceted perspective on the physiological and social factors influencing preeclampsia.

Our results reveal high concentrations of pro-inflammatory cytokines (IL-1β, IL-6, IL-8) and chemokines (RANTES, Eotaxin) in preeclamptic women, which aligns with findings from previous research indicating that an inflammatory environment is detrimental to trophoblast invasion. In typical pregnancies, a balanced cytokine profile supports controlled invasion, enabling trophoblast cells to remodel spiral arteries and ensure adequate blood flow to the fetus. However, in preeclamptic cases, heightened inflammation creates an environment that favors restricted invasion, as noted by Saito et al. (2020), who reported similar findings in relation to trophoblast behavior and cytokine interactions. This inflammatory milieu may contribute to the limited remodeling of uterine arteries, leading to the narrow and unconverted spiral arteries characteristic of preeclampsia.

Our study demonstrates reduced activity of MMP-2 and MMP-9 alongside elevated levels of TIMP-1 and TIMP-2, which suggests that preeclampsia is associated with a suppression of proteolytic pathways necessary for trophoblast invasion. Matrix metalloproteinases (MMPs) are essential for degrading extracellular matrix (ECM) components, allowing trophoblast cells to invade the maternal uterine tissues and establish adequate placental blood flow. Elevated TIMPs, which inhibit MMPs, appear to counteract this invasion process, supporting the hypothesis that a tightly controlled balance between MMPs and TIMPs is critical for proper placental development. This finding is consistent with Chen et al. (2021), who noted that excessive TIMP expression can disrupt trophoblast migration and reduce placental vascular remodeling, contributing to conditions like preeclampsia.

Nitric oxide (NO), produced by extravillous trophoblast cells, is another factor observed to be lower than typical in our preeclamptic sample. NO plays a role in vascular dilation and facilitates endovascular invasion by acting on smooth muscle cells in the uterine arteries. Its diminished synthesis may further restrict spiral artery remodeling, leading to higher uteroplacental resistance. Our results are supported by findings from Dunk et al. (2023), which demonstrated that reduced NO levels correlated with impaired placental vascularization in preeclampsia.

Implications of Patient Experiences

The qualitative findings from patient interviews underscore the psychosocial dimensions of preeclampsia. The frequent reports of stress, limited awareness of preeclampsia, and barriers to accessing prenatal care suggest that alongside biological factors, social determinants play a significant role in the management and prognosis of this condition. Previous studies (e.g., Johnson et al., 2019) highlight that social support and timely access to healthcare are vital for reducing adverse pregnancy outcomes, suggesting that public health initiatives could help alleviate some psychosocial burdens linked to preeclampsia.

Study Limitations

Our study has certain limitations, including a relatively small sample size and reliance on a single healthcare setting, which may limit generalizability. Furthermore, the lack of a control group of normotensive pregnant women prevents a direct comparison of biomarker levels in preeclampsia versus healthy pregnancies. Future studies should consider larger, multi-center designs with control groups for more robust analysis.

CONCLUSION

This study highlights the complex interplay of molecular, cellular, and psychosocial factors that govern trophoblast invasion and placental development, with direct implications for preeclampsia. Key findings reveal that an imbalance of pro- and anti-invasive cytokines, reduced protease activity, elevated protease inhibitors, and diminished nitric oxide synthesis in preeclamptic cases contribute to impaired trophoblast invasion and limited spiral artery remodeling. These biological disruptions are compounded by psychosocial stressors and barriers to prenatal care, underscoring the multifaceted nature of preeclampsia.

The insights gained from this study underscore the importance of both biological and social interventions. Future research should focus on

developing therapies that can restore the balance of molecular factors involved in trophoblast invasion and address psychosocial elements to support maternal health. Effective management and prevention of preeclampsia will require a holistic approach, encompassing molecular insights, patient-centered care, and accessible healthcare services to improve outcomes for both mothers and infants.

REFERENCES

1. Cindrova-Davies, T., & Sferruzzi-Perri, A. N. (2022). Human placental development and function. in Seminars in cell & developmental biology. *Seminars in Cell & Developmental Biology*, *131*, 66–77. https://doi.org/10.1016/j.semcdb.2022.03.039
2. Chen, Y., Ye, Z., Lin, M., Zhu, L., Xu, L., & Wang, X. (2024). Deciphering the Epigenetic Landscape: Placental Development and Its Role in Pregnancy Outcomes. *Stem Cell Reviews and Reports*, *20*(4), 996–1014. https://doi.org/10.1007/s12015-024-10699-2
3. Yu, X., Wu, H., Yang, Y., Wang, F., Wang, Y.-L., & Shao, X. (2021). Placental Development and Pregnancy-Associated Diseases. *Maternal-Fetal Medicine*, *4*(1), 36–51. https://doi.org/10.1097/fm9.0000000000000134
4. Khorami-Sarvestani, S., Vanaki, N., Shojaeian, S., Zarnani, K., Stensballe, A., Jeddi-Tehrani, M., & Zarnani, A.-H. (2024). Placenta: an old organ with new functions. *Frontiers in Immunology*, *15*. https://doi.org/10.3389/fimmu.2024.1385762
5. Dutta, S., Sengupta, P., & Liew, F. F. (2024). Cytokine landscapes of pregnancy: mapping gestational immune phases. *Gynecology and Obstetrics Clinical Medicine*, *4*(1), e000011–e000011. https://doi.org/10.1136/gocm-2024-000011
6. Li, X., Zhou, J., Fang, M., & Yu, B. (2020). Pregnancy immune tolerance at the maternal-fetal interface. *International Reviews of Immunology*, *39*(6), 247–263. https://doi.org/10.1080/08830185.2020.1777292
7. Farah, O., Nguyen, C., Tekkatte, C., & Parast, M. M. (2020). Trophoblast lineage-specific differentiation and associated alterations in preeclampsia and fetal growth restriction. *Placenta*, *102*, 4–9. https://doi.org/10.1016/j.placenta.2020.02.007
8. Staff, A. C., Fjeldstad, H. E., Fosheim, I. K., Moe, K., Turowski, G., Johnsen, G. M., Alnaes-Katjavivi, P., & Sugulle, M. (2020). Failure of physiological transformation and spiral artery atherosis: their roles in preeclampsia. *American Journal of Obstetrics & Gynecology*, *226*(2), S895–S906. https://doi.org/10.1016/j.ajog.2020.09.026
9. Erez, O., Romero, R., Jung, E., Chaemsaithong, P., Bosco, M., Suksai, M., Gallo, D. M., & Gotsch, F. (2022). Preeclampsia and eclampsia: the conceptual evolution of a syndrome. *American Journal of Obstetrics and Gynecology*, *226*(2), S786–S803. https://doi.org/10.1016/j.ajog.2021.12.001
10. Jena, M. K., Sharma, N. R., Petitt, M., Maulik, D., & Nayak, N. R. (2020). Pathogenesis of Preeclampsia and Therapeutic Approaches Targeting the Placenta. *Biomolecules*, *10*(6), 953. https://doi.org/10.3390/biom10060953
11. Sato, Y. (2020). Endovascular trophoblast and spiral artery remodeling. *Molecular and Cellular Endocrinology*, *503*, 110699. https://doi.org/10.1016/j.mce.2019.110699
12. Obeagu, E. I., & Obeagu, G. U. (2024). Maternal Hypoxia and Placental Dysfunction: Insights from Molecular Biology. *Elite Journal of Health Science*, *2*(8), 58-69. https://epjournals.com/journals/EJHS

13. James, J. L., Boss, A. L., Sun, C., Allerkamp, H. H., & Clark, A. R. (2022). From stem cells to spiral arteries: A journey through early placental development. *Placenta*, *125*, 68–77. https://doi.org/10.1016/j.placenta.2021.11.004
14. Gusella, A., Martignoni, G., & Giacometti, C. (2024). Behind the Curtain of Abnormal Placentation in Pre-Eclampsia: From Molecular Mechanisms to Histological Hallmarks. *International Journal of Molecular Sciences*, *25*(14), 7886. https://doi.org/10.3390/ijms25147886
15. Brennan, L. J., Morton, J. S., & Davidge, S. T. (2014). Vascular Dysfunction in Preeclampsia. *Microcirculation*, *21*(1), 4–14. https://doi.org/10.1111/micc.12079