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# *PLACENTAL ALTERATIONS IN SEVERE PREECLAMPSIA AND THEIR MATERNAL AND NEONATAL IMPACTS: INTEGRATIVE LITERATURE REVIEW*

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REVISÃO INTEGRATIVA DA LITERATURA

**ABSTRACT**

Severe preeclampsia remains one of the greatest challenges in obstetrics, with significant impacts on maternal and neonatal morbidity and mortality. This study conducted an Integrative Literature Review with the aim of systematizing evidence on placental alterations associated with the disease and their clinical repercussions. The methodological strategy followed validated steps of Evidence-Based Practice, guided by a structured PICo question (pregnant women with severe preeclampsia; identification of placental alterations; context of maternal and neonatal outcomes). Searches were performed in PubMed, Web of Science, ScienceDirect, and SciELO using DeCS/MeSH descriptors, and included original studies in Portuguese and English. Data were organized into a synthesis matrix, and levels of evidence were classified according to the Joanna Briggs Institute; the selection process was described in accordance with PRISMA. Findings converge toward a pattern of placental impairment characterized by villous infarction, fibrinoid deposition, villous hypoplasia, oxidative stress, and failure in spiral artery remodeling, resulting in uteroplacental hypoperfusion. Clinically, these changes were associated with HELLP syndrome, worsening hypertension, and placental abruption. In neonates, intrauterine growth restriction, prematurity, and perinatal death predominated. Angiogenic biomarkers, particularly PlGF and sFlt-1, have emerged as promising tools for early detection and severity stratification, although they still lack broad multicenter standardization and validation. Recurrent limitations among the studies include methodological heterogeneity, small sample sizes, and the absence of standardized protocols for placental evaluation. It is concluded that the placenta plays a central role in the pathophysiology of severe preeclampsia and in determining clinical outcomes. The adoption of combined biomarker panels, alongside standardized placental analysis protocols and multicenter studies with representative samples, may improve diagnosis, guide early management, and reduce maternal and neonatal morbidity and mortality.

**Keywords**: preeclampsia; placenta; angiogenic biomarkers; maternal outcomes; neonatal outcomes.

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## 1- INTRODUCTION

Preeclampsia is one of the main hypertensive syndromes of pregnancy, characterized by elevated blood pressure after the 20th week, associated with proteinuria or signs of maternal organ dysfunction. It represents a significant cause of maternal and perinatal morbidity and mortality worldwide, particularly in developing countries, where limited access to quality prenatal care hinders early diagnosis and appropriate management. It is estimated that the condition affects 2% to 8% of pregnancies, making it one of the greatest challenges in contemporary obstetrics (WHO, 2025; Dimitriadis et al., 2023).

Within the clinical spectrum of the disease, the severe form carries particular relevance due to the intensity of its systemic repercussions, with an increased risk of eclampsia, HELLP syndrome, placental abruption, and renal, hepatic, and neurological complications. From a pathophysiological perspective, severe preeclampsia is linked to impaired remodeling of the spiral arteries, resulting in uteroplacental hypoperfusion and an imbalance between angiogenic and antiangiogenic factors. These changes directly affect placental structure and function, positioning the placenta as a central axis for understanding the disease (Gathiram; Moodley, 2016; Bisson et al., 2023).

The placenta plays a crucial role at the maternal-fetal interface, ensuring the exchange of nutrients, gases, and hormones. In severe preeclampsia, multiple morphological and functional alterations may be observed, such as placental infarctions, fibrinoid villi, excessive fibrin deposition, villous hypoplasia, and increased oxidative stress (Vornic et al., 2024). These alterations compromise adequate perfusion, promote tissue hypoxia, and impact both maternal clinical evolution and neonatal outcomes, with increased risk of intrauterine growth restriction, prematurity, and perinatal death (Donthi et al., 2020).

In this context, understanding placental alterations associated with severe preeclampsia and their impact on maternal and neonatal health is essential to support strategies for prevention, diagnosis, and treatment. Therefore, this study aims to systematize, through an Integrative Literature Review, the available scientific evidence on placental changes in severe preeclampsia and their maternal and neonatal repercussions.

## 2- METHOD

This study is an Integrative Literature Review (ILR) designed to investigate placental alterations in severe preeclampsia and their maternal and neonatal impacts. The ILR is a research method grounded in Evidence-Based Practice (EBP), whose purpose is to systematically gather and analyze findings from different studies, allowing the development of critical and comprehensive syntheses on a given phenomenon. Such an approach not only consolidates existing knowledge but also identifies gaps that may guide future investigations (Ganong, 1987; Souza; Silva; Carvalho, 2010; Lemes et al., 2021).

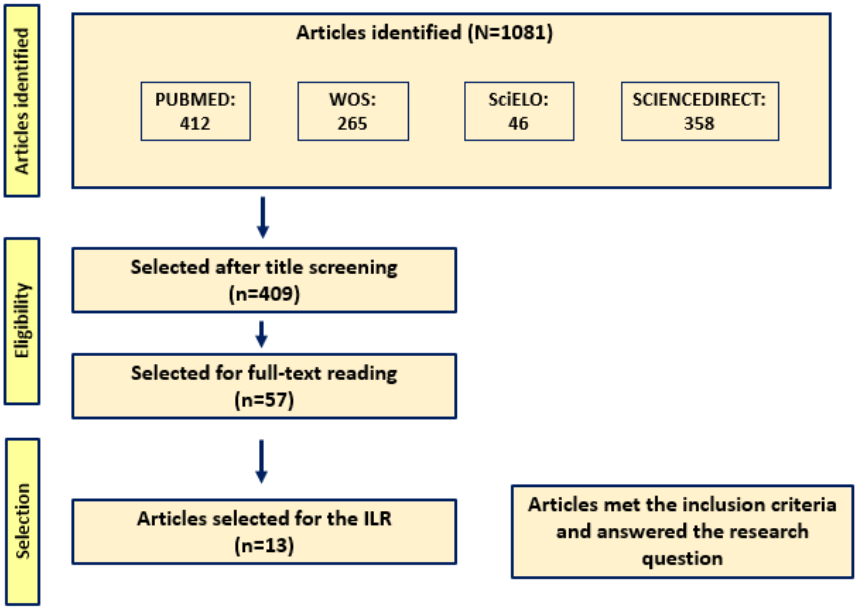
The methodological process followed steps widely validated in the literature: (1) definition of the guiding question; (2) establishment of inclusion and exclusion criteria; (3) search and selection of studies; (4) critical appraisal and categorization of findings according to levels of evidence; (5) interpretation of results; and (6) synthesis and final presentation. To structure the research question, the PICo strategy was applied, where: P = pregnant women with severe preeclampsia; I = identification of placental alterations; Co = context of maternal and neonatal impacts. Thus, the guiding question was formulated as: What placental alterations are observed in severe preeclampsia, and what are their impacts on maternal and neonatal health? (Stern; Jordan; McArthur, 2014; Lockwood; Munn; Porritt, 2015).

The literature search was conducted using controlled descriptors identified in the Health Sciences Descriptors (DeCS) and the Medical Subject Headings (MeSH). The following terms were applied: “Pre-Eclampsia,” “Placenta,” “Placental Pathology,” “Maternal Health,” and “Neonatal Outcomes.” The databases consulted included PubMed, Web of Science (WOS), ScienceDirect, and the Scientific Electronic Library Online (SciELO), selected for their relevance and scope in the maternal–child health field.

Inclusion criteria comprised original articles available in full, published between 2015 and 2025, in Portuguese or English, directly addressing placental alterations in severe preeclampsia and their maternal–neonatal outcomes. Exclusion criteria included books, book chapters, theses, dissertations, editorials, and narrative reviews without

detailed methodological description. The entire selection process followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009), detailed in the methodological flowchart presented in Figure 1 below.

Figure 1. PRISMA flowchart of the integrative review on placental alterations in severe preeclampsia




Adapted from: Moher et al., 2009

The systematization of data obtained from the articles included in this review was carried out through a synthesis matrix, which compiled essential information such as title, first author, journal, year of publication, study design, level of evidence, and main findings. For the hierarchy of evidence, the classification proposed by the Joanna Briggs Institute (JBI) was adopted, which organizes studies into six levels: Level I: systematic reviews and randomized controlled trials; Level II: experimental studies; Level III: quasi-experimental research; Level IV: descriptive or qualitative/quantitative investigations; Level V: case reports or experiential accounts; and Level VI: expert opinions (Lockwood et al., 2020). The presentation of results and discussion followed the descriptive and

critical logic recommended for Integrative Literature Reviews, in line with reference authors in the field (Ganong, 1987; Souza; Silva; Carvalho, 2010; Lemes et al., 2021).

## 3- RESULTS

After the careful application of the predefined inclusion and exclusion criteria, 13 articles composed the final sample of this review. The studies analyzed investigated, from different perspectives, the structural and functional modifications of the placenta in cases of severe preeclampsia, as well as their clinical implications for both mother and newborn. Publications were conducted in different countries, ranging from detailed histopathological analyses to clinical correlation studies, highlighting methodological diversity and the breadth of approaches. This body of evidence contributes to a deeper understanding of the central role of the placenta in the pathophysiology of severe preeclampsia and points to gaps that still require further scientific exploration.

Overall, the results demonstrated frequent alterations such as abnormal fibrin deposition, villous infarctions, villous hypoplasia, oxidative imbalance, and failures in the remodeling of spiral arteries. These conditions were directly associated with adverse outcomes, including intrauterine growth restriction, preterm birth, fetal death, and relevant maternal complications such as HELLP syndrome and placental abruption (Pietro et al., 2021; Staff et al., 2022). Some studies also emphasized the value of angiogenic markers in the early detection of placental dysfunction. However, methodological limitations, small sample sizes, and the scarcity of controlled clinical trials remained common challenges across the analyzed publications (Veisani et al., 2019; Zegarra; Ghi; Lees, 2024).

To provide an organized view of the evidence, a synthesis table was developed, compiling the main information from each selected study in order to facilitate critical analysis and comparison of the available findings in the literature.

Table 1. Synthesis of the studies included in the discussion on placental alterations in severe preeclampsia and their maternal and neonatal impacts

| Title | First Author | Journal (Year) | Study Design / Level of Evidence | Main Findings |
|---|---|---|---|---|
| **An objective histopathological scoring system for placental pathology in pre-eclampsia and eclampsia** | Donthi | Cureus (2020) | Descriptive observational study – Level IV | Proposed a histopathological scoring system to assess placental alterations in preeclampsia and eclampsia. |
| **Oxidative stress and placental pathogenesis: a contemporary overview of potential biomarkers and emerging therapeutics** | Vornic | International Journal of Molecular Sciences (2024) | Narrative review – Level VI | Highlighted oxidative biomarkers as potential indicators of placental dysfunction. |
| **Placental findings in preterm and term preeclampsia: an integrative review of the literature** | Pietro | Revista Brasileira de Ginecologia e Obstetrícia (2021) | Integrative review – Level V | Identified common histological findings and clinical implications in pregnancies with preeclampsia. |
| **Preeclampsia pathophysiology and adverse outcomes during pregnancy and postpartum** | Bisson | Frontiers in Medicine (2023) | Narrative review – Level VI | Linked the pathophysiology of preeclampsia to adverse maternal and neonatal outcomes. |
| **Failure of physiological transformation and spiral artery atherosis: their roles in pre-eclampsia** | Staff | American Journal of Obstetrics and Gynecology (2022) | Specialized narrative review – Level VI | Showed failures in spiral artery transformation and their association with disease severity. |
| **Angiogenic factors and the risk of preeclampsia: a systematic review and meta-analysis** | Veisani | International Journal of Reproductive Biomedicine (2019) | Systematic review and meta-analysis – Level I | Demonstrated an association between angiogenic factors and increased risk of preeclampsia. |
| **Does the use of angiogenic biomarkers for the management of preeclampsia and fetal growth restriction improve outcomes?:** | Zegarra | European Journal of Obstetrics & Gynecology and Reproductive Biology (2024) | Critical narrative review – Level VI | Questioned the effectiveness of angiogenic biomarkers in clinical practice for PE and FGR. |

| | | | | |
|---|---|---|---|---|
| **challenging the current status quo** | | | | |
| **The clinical heterogeneity of preeclampsia is related to both placental gene expression and placental histopathology** | Benton | American Journal of Obstetrics and Gynecology (2018) | Observational study with molecular analysis – Level IV | Indicated that clinical heterogeneity of preeclampsia is linked to placental gene expression and histopathology. |
| **Early pathways, biomarkers, and four distinct molecular subclasses of preeclampsia: the intersection of clinical, pathological, and high-dimensional biology studies** | Than | Placenta (2022) | Integrative review and molecular analysis – Level V | Defined four molecular subclasses of preeclampsia based on early biomarkers. |
| **Pilot study of placental tissue collection, processing, and measurement procedures for large scale assessment of placental inflammation** | Sjaarda | PLoS ONE (2018) | Pilot methodological study – Level V | Presented a protocol for large-scale placental tissue collection and processing. |
| **Incorporating placental pathology into clinical care and research** | Roberts | Trends in Molecular Medicine (2024) | Methodological update article – Level VI | Reinforced the need to incorporate placental findings into clinical practice and research. |
| **Proteome-based maternal plasma and serum biomarkers for preeclampsia: a systematic review and meta-analysis** | Starodubtseva | Life (2025) | Systematic review and meta-analysis – Level I | Identified promising proteomic biomarkers for early detection of preeclampsia. |
| **A review of omics approaches to study preeclampsia** | Benny | Placenta (2020) | Narrative review – Level VI | Reviewed omics approaches in preeclampsia research, highlighting gaps and advances. |

Table 1. Descriptive synthesis of the studies included in the discussion, presenting title, first author, journal (with year of publication), methodological design, level of evidence according to the Joanna Briggs Institute (JBI), and main findings

## 4- DISCUSSION

The analysis of the studies included in this review reinforces that the placenta plays a central role in the pathophysiology of severe preeclampsia, serving as the link between maternal hemodynamic events and neonatal outcomes. The investigations indicate that placental alterations not only reflect the severity of the hypertensive syndrome but also determine significant clinical consequences for both mother and child. Despite the methodological diversity observed across studies, two main lines of discussion can be identified: (1) placental alterations and their clinical repercussions, and (2) the limitations of current studies, challenges to be addressed, and future perspectives for the field.

### 4.1 Placental alterations and clinical repercussions

In severe preeclampsia, the placenta exhibits a set of structural and functional modifications that mirror disease severity and result in unfavorable maternal and neonatal outcomes. The main morphological findings include villous infarctions, excessive fibrinoid deposition, villous hypoplasia, and increased oxidative stress. Such alterations reduce placental perfusion and lead to tissue hypoxia (Donthi et al., 2020; Vornic et al., 2024).

Maternal repercussions are strongly associated with the intensity of these modifications. HELLP syndrome, placental abruption, and worsening hypertension are among the most severe complications, directly impacting maternal morbidity and mortality (Pietro et al., 2021; Bisson et al., 2023). Neonatal outcomes predominantly include intrauterine growth restriction, prematurity, and fetal death, events linked to the placenta's inability to sustain adequate gas and nutrient exchange (Pietro et al., 2021).

One of the central mechanisms underlying these alterations is the failure of spiral artery remodeling, characterized by incomplete trophoblastic invasion and persistently elevated vascular resistance. This process compromises uteroplacental perfusion and directly correlates with clinical severity (Staff et al., 2022).

Beyond morphological findings, angiogenic biomarkers, particularly placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1), have gained

increasing relevance. The imbalance between these markers reflects endothelial dysfunction and placental hypoxia, and is considered a promising tool for early detection and disease severity stratification (Veisani et al., 2019; Zegarra; Ghi; Lees, 2024).

Thus, placental alterations in severe preeclampsia not only express the severity of the hypertensive disorder but also result in significant clinical repercussions for both mother and infant, reinforcing the need to expand the use of biomarkers in diagnosis and early management. Nevertheless, despite advances, methodological limitations still hinder the standardization of findings, as will be discussed in the next section.

### 4.2 Limitations, challenges, and future perspectives

Although the reviewed studies have contributed to expanding understanding of placental alterations in severe preeclampsia, methodological and structural limitations still compromise the consolidation of scientific knowledge in the area. The heterogeneity of approaches was one of the most recurrent issues, ranging from traditional histopathological analyses to molecular investigations, making direct comparison of findings difficult. In addition, many studies relied on small samples, restricting the generalizability of results and weakening the external validity of conclusions (Benton et al., 2018; Than et al., 2022).

Another identified challenge relates to the absence of standardized protocols for placental evaluation in cases of severe preeclampsia. This methodological gap undermines the establishment of consistent markers applicable in both clinical practice and multicenter research. Added to this are the ethical and logistical difficulties in collecting placental material and conducting longitudinal follow-up of pregnant women and newborns, which limits the production of relevant and comparable evidence across different contexts (Sjaarda et al., 2018; Roberts et al., 2024).

Despite these obstacles, future perspectives are promising. Advances in molecular biology, proteomics, and genomics open pathways for a more detailed characterization of the mechanisms underlying placental alterations, enabling the identification of potential early biomarkers of dysfunction. Furthermore, conducting multicenter studies with larger and more representative samples could strengthen the reliability of findings (Starodubtseva et al., 2025). The integration of these advances has the potential not

only to enhance early diagnosis but also to support new therapeutic strategies aimed at preventing and managing severe preeclampsia, with direct impacts on reducing maternal and neonatal morbidity and mortality (Benny et al., 2020).

## 5- FINAL CONSIDERATIONS

Severe preeclampsia is one of the most challenging pregnancy complications, whose understanding inevitably involves the study of placental alterations. This integrative review demonstrated that structural and functional placental findings, such as villous infarctions, fibrinoid deposition, villous hypoplasia, oxidative stress, and failures in spiral artery remodeling, not only express the severity of the hypertensive syndrome but also determine relevant clinical repercussions for both mothers and newborns.

On the maternal side, complications include increased risk of HELLP syndrome, worsening hypertension, and placental abruption, underscoring the direct association between the degree of placental impairment and morbidity and mortality. On the neonatal side, intrauterine growth restriction, prematurity, and perinatal death stand out, highlighting the impact of impaired perfusion and placental exchange of gases and nutrients.

Despite progress made, methodological limitations such as heterogeneity of study designs, small sample sizes, and lack of standardized protocols for placental evaluation still restrict the consolidation of robust evidence. In this scenario, the study of angiogenic biomarkers such as PlGF and sFlt-1 emerges as a promising tool for early diagnosis, severity stratification, and therapeutic guidance, although their widespread incorporation into clinical practice still requires greater scientific validation.

Therefore, the findings of this review reiterate the need to expand multicenter research with integrated methodologies and representative samples, capable of consolidating reliable indicators for clinical practice. Investment in this field may not only improve the diagnosis and management of severe preeclampsia but also significantly contribute to reducing maternal and neonatal morbidity and mortality, reaffirming the centrality of the placenta as an essential link in the health of the mother–infant dyad.

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