Systematic Review

Analysis of Risk Factors for Preeclampsia in Pregnant Women with Systemic Lupus Erythematosus: A Systematic Review

.

ABSTRACT

|  |
| --- |
| **Aims:** To review the literature and analyze the main risk factors for the development of preeclampsia in women with Systemic Lupus Erythematosus. **Methodology:** The study consists of a systematic review using the PRISMA 2020 guidelines through the search for articles in the PubMed, BVC/LILACS and Cochrane databases, covering clinical trials and observational studies published between 2013 and 2023. The articles were selected by two authors, using the Rayyan tool, and the divergences were analyzed by a third reviewer. A form previously defined by the authors was used to extract the main data from the studies and the quality of the articles was assessed using the Cochrane tool (ROBINS-I). Of the 171 articles initially selected, 9 met the inclusion and exclusion criteria, covering a total of 500,780 women. **Results:** Lupus activity before and during pregnancy was identified as a risk factor for preeclampsia (95% CI 1.04-7.4 and 95% CI 1.0-9.1), as well as younger age (*P* < 0.01), multiparity (95% CI 0.01-0.95) and high BMI (*P* = 0.026). Renal disease (95% CI 1.944-74.376), pregestational hypertension (95% CI 2.67-125.01), MAP value > 95 mmHg (95% CI 24.39-999.99) and previous hematological disorders (95% CI 1.03-16.67), as well as lower estimated glomerular filtration rate (CI 95% 4.35–80.70), positive aCL-IgM (95% CI 1.11–333.33), serum albumin < 31.5 g/L (95% CI 2.07–47.62), serum uric acid ≥ 303 μmol/L (95% CI 1.40–22.22), and 24-hour proteinuria ≥ 0.286 g (95% CI 2.43–83.33) also increased the risk for preeclampsia. Another predictor of risk was the use of prednisolone (OR=2.33), and a lower risk was identified with the use of antimalarial drugs (95% CI 0.08-0.53). **Conclusion:** Certain factors associated with women with Lupus contribute to the development of preeclampsia and their early identification may allow a targeted follow-up to prevent and treat possible complications early. |

*Keywords: Lupus Erythematosus, Systemic; Pre-Eclampsia; Pregnant Women; Risk Factors*

1. INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune and inflammatory disease characterized by periods of activity and remission. It can affect virtually all organs of the body, including the skin, joints, kidneys, and central nervous system. The etiology of the disease remains unknown, but its pathogenesis is known to involve an immunological cascade triggered by environmental and hormonal factors in genetically susceptible individuals, particularly those with complement deficiency and the HLA DR2 gene (Carvalho *et al.*, 2019). Under certain stimuli, T and B lymphocytes specific to self-antigens become activated due to failures in the mechanisms responsible for self-tolerance, leading to the production of autoantibodies and the formation of immune complexes (Sawada *et al.*, 2019). Environmental and hormonal factors involved in SLE pathogenesis include ultraviolet radiation exposure, smoking, infections, medication use, and stress (Fava and Petri, 2019).

Lupus predominantly affects women, with a 9:1 ratio compared to men, and is most common in young adults of reproductive age, with an average onset between 24 and 32 years (Pons-Estel *et al.*, 2017). Additionally, since SLE does not directly affect fertility, it is quite common to encounter pregnant women with lupus. However, during pregnancy, increased TH2 cell production and hormonal changes, combined with the TH2-predominant immune response in lupus, trigger a pro-inflammatory state, leading to greater disease activation and severity. For this reason, pregnant women with lupus have a higher risk of developing obstetric complications, such as preterm births, miscarriages, and preeclampsia (Maynard *et al.*, 2019).

In this group of patients, preeclampsia (PE) is one of the most significant complications, occurring in 16–30% of pregnant women with lupus, compared to a prevalence of 5–7% in healthy women (Lateef and Petri, 2017). This syndrome is characterized by elevated systemic blood pressure, usually associated with proteinuria or significant target organ dysfunction, in a patient beyond 20 weeks of gestation (ACOG, 2020). Its pathogenesis is not fully understood but is known to involve superficial trophoblast invasion into the uterus and abnormal placentation, resulting in incomplete remodeling of spiral arteries. Consequently, there is an exaggerated maternal inflammatory response and widespread endothelial dysfunction, increasing the risk of potentially severe and fatal events, such as seizures, cerebral hemorrhage, stroke, placental abruption, liver failure, and pulmonary edema (Opichka *et al.*, 2021).

General risk factors for preeclampsia in women include a family history of the condition, advanced maternal age, pre-existing hypertension or diabetes, and obesity, among others. In women with lupus, the reasons for the increased risk are unclear, but some predictors, such as the presence of antiphospholipid antibodies and hypocomplementemia, as well as mechanisms involving inflammation and microangiopathy, may be associated with the development of this hypertensive condition (Dalal *et al.*, 2019; Silva *et al.*, 2021).

Preeclampsia can affect multiple organs and cause severe systemic repercussions for both the mother and fetus, such as disseminated intravascular coagulation, acute kidney injury, acute pulmonary edema, intracranial hemorrhage, and hepatic rupture (Kahhale *et al.*, 2018). Identifying risk factors for preeclampsia in women with systemic lupus erythematosus can help prevent these complications by enabling closer monitoring during pregnancy and the use of specific tests that may facilitate early treatment.

Thus, the objective of this study is to analyze the primary risk predictors for developing preeclampsia in women with systemic lupus erythematosus, aiming to prevent this hypertensive condition and improve the safety and quality of life for these patients.

2. methodology

The present study is a systematic review of the literature, with data obtained from updated sources using systematic methods to identify, select, and critically evaluate the risk predictors for preeclampsia in pregnant women with Systemic Lupus Erythematosus. This review followed the recommendations outlined by the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (Figure 1), and the review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42024581541.

**2.1 Identifying the research question**

The guiding question for this review was formulated using the PICO strategy, which analyzes the relationship between events based on its components. In this acronym, the Population targeted by the research is defined, followed by the Intervention to be studied, the Comparison with other interventions, and the Outcome intended to be achieved. For this study, the "Comparison" component was excluded, as the objective of this review was to analyze the risk factors involved in the occurrence of preeclampsia, making the comparison of different interventions non-essential.

Thus, the guiding question of this review was: “What are the risk factors for the occurrence of pre-eclampsia in pregnant women with Systemic Lupus Erythematosus?”.

**Table 1. Description of the research question formulation strategy**

|  |  |  |
| --- | --- | --- |
| **Acronym** | **Definition** | **Denomination** |
| P | Population | Pregnant women with SLE |
| I | Intervention | Risk factors  |
| O | Outcome | Pre-eclampsia |

**2.2 Search strategy and eligibility criteria**

The article search was conducted in the electronic databases PubMed, BVS/LILACS, and Cochrane using descriptors included in the Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCs), combined with Boolean operators in the following search formula: “Risk factors” AND “Systemic Lupus Erythematosus” OR “SLE” OR “Lupus” AND “Pregnancy” OR “Pregnant” OR “Pregnancy diseases” OR “Pregnancy complications” OR “Adverse pregnancy outcomes” AND “Pre-eclampsia” OR “Preeclampsia”. Clinical trials and observational studies (cohort and case-control) with full text, published in Portuguese, English or Spanish between 2013 and 2023, were included. Exclusion criteria were: duplicate articles, editorials and reviews, studies conducted in animals, and studies reporting risk factors for the development of diverse obstetric complications rather than specifically preeclampsia.

**2.3 Study selection and data extraction**

Two authors independently evaluated the titles and abstracts of the studies identified and selected those that met the inclusion and exclusion criteria. Subsequently, the eligible studies were read in full by the authors, and any disagreements were resolved by a third reviewer. The Rayyan tool was used for article selection, and a pre-defined form was employed to analyze and extract the following data from each study: the name of the first author and year of publication, the country where the study was conducted, study design, sample size, and the variables influencing the occurrence of preeclampsia.

**2.4 Analysis of Bias**

To assess the quality of the included studies, the Cochrane Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used, evaluating the following domains: bias due to confounding factors, bias in the selection of participants, bias in the classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, bias in the selection of reported outcomes, and overall bias. Three reviewers independently assessed the risk of bias and classified it as low, moderate, serious, critical, or no information available. Discrepancies were individually evaluated and resolved through discussion.



**Fig 1. The PRISMA flowchart of search strategy and selection process.**

3. results

**3.1 Included Studies**

The initial search identified 171 records in the databases. After removing 65 duplicates, 106 articles were screened based on their titles and abstracts. Of these, 79 were excluded, leaving 27 publications for full-text review (Figure 1). Ultimately, this systematic review included nine articles involving a total of 500,780 pregnant women with SLE.

In this context, Table 2 details the baseline characteristics of the included studies. The articles were published between 2017 and 2021, with most conducted in European countries (Norway, Sweden, Portugal, Italy), Asian countries (Japan, China, South Korea), and North America (Mexico), representing 44%, 44%, and 11% of the publications, respectively. This review included eight retrospective observational studies (89%) and one prospective study (11%).

**3.2 Systemic Lupus Erythematosus Activity**

SLE activity was identified as a significant risk factor for the development of hypertensive pregnancy outcomes in two included studies: the risk of preeclampsia is higher in women in the active phase of lupus disease (Skorpen *et al.*, 2017), and disease activity both before (relative risk [RR] 2.7, 95% CI 1.04–7.4) and during pregnancy (RR 3.0, 95% CI 1.0–9.1) was associated with the development of preeclampsia (Saavedra *et al.*, 2020).

**3.3 Demographic profile**

The mean ages of patients across all studies ranged from 27.4 to 34.1 years, with an average of 33.5 years for nulliparous women and 34.1 years for multiparous women (Maeda *et al.*, 2020). Additionally, the mean age of women treated with HCQ was 32.8 years, compared to 31.8 years for those not receiving treatment (Seo *et al.*, 2019).

Univariate logistic regression analyses revealed that the gestational age at disease onset increased the risk of preeclampsia/eclampsia (Chen *et al.*, 2021). Furthermore, in pregnancies complicated by preeclampsia, women appeared to be younger (25.3 vs. 29.9 years, p < 0.01) (Reis *et al.*, 2019).

Regarding parity, multiparous women with SLE had a statistically significantly lower risk of preeclampsia compared to nulliparous women with SLE (adjusted odds ratio [aOR]: 0.08; 95% CI: 0.01–0.95) (Maeda *et al.*, 2020). Additionally, in pregnancies complicated by preeclampsia, nulliparous women were more frequently affected, suggesting a potential risk factor for the condition (81.8% vs. 59.6%, p < 0.20) (Reis *et al.*, 2019).

Body Mass Index (BMI) was also evaluated as a significant and independent risk factor for the development of preeclampsia. It was also noted that pregnant women with SLE undergoing hydroxychloroquine treatment had a higher BMI compared to those not treated (24.3 kg/m² vs. 23.0 kg/m², p = 0.026) (Seo *et al.*, 2019).

**3.4 Comorbidities**

Regarding comorbidities, lupus nephritis (LN) is a significant condition, with the presence of pregestational LN serving as an indicator for the development of preeclampsia (PE) (Seo *et al.*, 2019). Women with prior or active LN during pregnancy are more likely to develop PE compared to those with systemic lupus erythematosus (SLE) without renal involvement (25.7% vs. 2.9%, p=0.001) (Bremme *et al.*, 2021). In this context, renal involvement has been identified as an independent risk factor for PE (aOR: 8.380, 95% CI: 1.944–74.376) (Chen *et al.*, 2021), with a high prevalence of LN in pregnancies complicated by PE (81.8% vs. 27.3%, p < 0.01) (Reis *et al.*, 2019).

Systemic arterial hypertension has also been found to be an independent risk factor for PE, as evidenced by stepwise multiple regression analysis (aOR: 19.185; 95% CI: 3.921–93.868) (Chen *et al.*, 2021). Another study, through multivariate analysis, revealed that a mean arterial pressure (MAP) greater than 96.5 mmHg and the presence of pregestational hypertension were independent risk factors (OR 213.15, 95% CI=24.39–999.99 and OR 18.19, 95% CI=2.67–125.01, respectively) (Jiang *et al.*, 2020).

Pre-gestational hematologic disorders, such as thrombocytopenia, have also been indicated as independent risk factors for the development of PE (OR 4.13, 95% CI=1.03–16.67) (Jiang *et al.*, 2020).

**3.5 Biochemical parameters**

The presence of proteinuria increased the risk of developing preeclampsia (PE) by 2.45 times, while serum creatinine levels greater than 1.2 mg/dL were associated with a 1.25-fold higher risk compared to patients with serum creatinine levels below 1.2 mg/dL. An estimated glomerular filtration rate (eGFR) lower than 90 mL/min/1.73 m² increased the risk of PE by 18.73 times, with the association between eGFR and PE being highly significant (OR: 18.73; 95% CI: 4.35–80.70; p < 0.001), suggesting a strong relationship with the outcome (Mecacci *et al.*, 2017).

According to clinical reference values, positive aCL-IgM (OR 19.85, 95% CI = 1.11–333.33), serum albumin <31.5 g/L (OR 9.88, 95% CI = 2.07–47.62), serum uric acid ≥ 303 μmol/L (OR 5.58, 95% CI = 1.40–22.22), and 24-hour proteinuria ≥ 0.286 g (OR 14.39, 95% CI = 2.43–83.33) were identified as independent risk factors for PE in pregnant women with systemic lupus erythematosus (SLE) (Jiang *et al.*, 2020).

In one study, 25.2% of women had proteinuria, an important marker of renal disorders associated with SLE. It was demonstrated that elevated uric acid levels and lower eGFR before conception or during the first trimester of pregnancy were significantly associated with the development of PE. Multivariate analysis showed that the estimated glomerular filtration rate (OR 0.931, 95% CI: 0.886–0.979, P = 0.005) is an independent risk factor, with reduced eGFR being associated with a higher risk of adverse outcomes (Seo *et al.*, 2019).

**3.6 Pharmacological therapy**

The use of prednisolone was associated with a significant increase in the likelihood of developing preeclampsia (OR = 2.33) (Skorpen *et al.*, 2017), with another study showing that a higher percentage of patients who developed preeclampsia were using prednisone (88.9% vs. 71%, P = 0.01) (Saavedra *et al.*, 2020).

Interestingly, in one study, patients who did not develop preeclampsia received antimalarial medications more frequently than those who did (84.8% vs. 68.2%, P = 0.007). The use of antimalarials during pregnancy was the only factor associated with a lower risk of developing preeclampsia (RR 0.21, 95% CI 0.08–0.53, P < 0.001) (Saavedra *et al.*, 2020). Other authors also demonstrated that HCQ treatment was associated with an 89.4% reduction in the risk of developing preeclampsia in pregnant women with SLE (OR 0.106; 95% CI 0.017–0.671) (Seo *et al.*, 2019).

**Table 2. Baseline Characteristics of Included Studies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Author, year**  | **Type of study** | **Country** | **Date** | **Patients** | **Sample** | **Age (average)** | **Conclusions** |
| Skorpen *et al.*, 2017 | Coorte (Longitudinal Observational) | Norway | 2006 – 2015 | Pregnant women with LES | 180 pregnancies | 31,5 | The risk of preeclampsia is higher in active disease compared to inactive disease (5.33 vs. 3.38). There was a substantially higher probability of PE with the use of prednisolone (OR = 2.33). |
| Bremme *et al.*, 2021 | Observational Retrospective Single-center | Sweden | 2000 - 2017 | Pregnant women with LES | 103 pregnancies (35 women with previous or active NL vs 68 with non-renal SLE) | 31.6 (30.8 with NL and 32 without NL) | Patients with lupus nephritis (either previous or active) had a significantly higher risk of preeclampsia compared to women with SLE without renal involvement (25.7% vs. 2.9%, p = 0.001). |
| Maeda *et al.*, 2020 | Single-Centered Retrospective | Japan | 2002 - 2017 | Pregnant women with LES | 76 (48 nulliparous vs 28 multiparous) | 33.5 (nulliparous) and 34.1 (multiparous) | PE occurred in 22.9% (11/48) of nulliparous women and in 3.6% (1/28) of multiparous women. Multiparity was significantly associated with a lower risk of preeclampsia (OR: 0.08; 95% CI: 0.01–0.95). |
| Jiang *et al.*, 2020 | Randomized Observational Retrospective | China | 2010 - 2018 | Pregnant women with LES | 513 pregnancies | 29,7 | It was observed that mean arterial pressure (MAP) ≥ 96.5 mmHg (OR 213.15, 95% CI 24.39–999.99), pregestational hypertension (OR 18.19, 95% CI 2.67–125.01), a hematologic disorder (OR 4.13, 95% CI 1.03–16.67), positive aCL IgM (OR 19.85, 95% CI 1.11–333.33), serum albumin < 31.5 g/L (OR 9.88, 95% CI 2.07–47.62), serum uric acid ≥ 303 μmol/L (OR 5.58, 95% CI 1.40–22.22), and 24-hour proteinuria ≥ 0.286 g (OR 14.39, 95% CI 2.43–83.33) were considered risk predictors for PE. These factors were included in a prediction model, indicating a high risk of PE. |
| Saavedra *et al.*, 2020 | Prospective Cohort | Mexico | 2009 - 2018 | Pregnant women with LES | 316 pregnancies (46 complicated with PE and 270 without PE) | 28 (without EP) and 29 (with EP) | Multivariate analysis showed that disease activity before (relative risk [RR] 2.7, 95% CI 1.04–7.4) and during pregnancy (RR 3.0, 95% CI 1.0–9.1) was associated with the development of preeclampsia. The use of antimalarial drugs during pregnancy was associated with a lower risk of preeclampsia (RR 0.21, 95% CI 0.08–0.53). |
| MR Seo*, et al.,* 2019 | Retrospective Cohort | South Korea | 1995 - 2018 | Pregnant women with LES | 151 LES pregnancies (80 under HCQ treatment and 71 without HCQ treatment) | 32.8 (with HCQ) and 31.8 (without HCQ) | The incidence of preeclampsia was significantly lower in the HCQ treatment group compared to the non-HCQ group (7.5% vs. 19.7%, p = 0.032). In logistic regression analysis, after adjusting for variables, HCQ treatment was associated with an 89.4% lower risk of PE (OR 0.106, 95% CI 0.017–0.671). Other independent risk factors for PE included high BMI (OR 1.575, 95% CI 1.114–2.227) and low eGFR levels (OR 0.931, 95% CI 0.886–0.979). |
| Chen *et al.,* 2021 | Retrospective Study | China | 2011 - 2018 | Pregnant women with LES | 85 patients | 27,4 | In univariate logistic regression analysis, it was found that gestational age at disease onset, high SLEDAI score, hypertension, renal involvement, and positive aCL and anti-B2GPI increased the risk of preeclampsia and eclampsia.Multivariate regression analysis showed that hypertension (OR 19.185, 95% CI 3.921–93.868) and renal involvement (OR 8.380, 95% CI 1.944–74.376) were independent risk factors for preeclampsia and eclampsia. |
| Reis *et al.,* 2019 | Retrospective Cohort | Portugal | 1994 - 2016 | Pregnant women with LES | 157 pregnancies | 29,6 | In pregnancies complicated by preeclampsia, women tend to be younger (25.3 vs. 29.9 years, p < 0.01) and more frequently nulliparous (81.8% vs. 59.6%, p < 0.20). These women also show a higher prevalence of lupus nephritis (81.8% vs. 27.3%, p < 0.01).After adjusting for maternal age, nulliparity, and chronic hypertension in a logistic regression model, the positive association between lupus nephritis and preeclampsia remained significant, with an OR of 29.78 (95% CI 3.84–281.11, p < 0.01). |
| Meccaci *et al.*, 2017 | Retrospective Cohort | Italy | 2007 - 2015 | Pregnant women with LES | 86 pregnancies (27 with previous NL and 59 without NL) | 32,1 vs. 34,1 | The presence of proteinuria was associated with a 2.45-fold higher risk of preeclampsia, while serum creatinine >1.2 mg/dL was linked to a 1.25-fold higher risk compared to patients with serum creatinine <1.2 mg/dL. A six-month period of inactive disease was associated with better outcomes.An estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m² resulted in an 18.73-fold higher risk of preeclampsia (OR 18.73, 95% CI 4.35–80.7). |

**Table 3.  Prevalence of risk factors in studies**

|  |  |
| --- | --- |
| Risk factors | Proportion of studies |
| Active SLE  | 0,33% (3/9) |
| Age | 0,22% (2/9) |
| Parity | 0,22% (2/9) |
| BMI | 0,11% (1/9) |
| Renal disease | 0,33% (3/9) |
| Hypertension | 0,22% (2/9) |
| Hematologic disorders  | 0,11% (1/9) |
| Serum albumin < 31,5 g/L | 0,11% (1/9) |
| Serum uric acid > 303 μmol/L | 0,11% (1/9) |
| 24-hour proteinuria  | 0,22% (2/9) |
| Estimated glomerular filtration rate (eGFR) | 0,22% (2/9) |
| Serum creatinine  | 0,11% (1/9) |
| Anticardiolipin antibody | 0,11% (1/9) |
| Use of prednisolone | 0,11% (1/9) |
| Use of antimalarial drugs | 0,22% (2/9) |

**3.7 Risk of bias**

Using the ROBINS-I tool, we systematically assessed the risk of bias in all included studies. Of the nine studies evaluated, seven were classified as having "some concerns" due to potential issues in the randomization process and missing outcome data, though they predominantly presented a low risk of bias across various domains. These studies exhibited low bias in areas such as participant selection, intervention classification, deviations from intended interventions, and selection of reported outcomes. This suggests a well-controlled methodology with a lower likelihood of significant bias.

One study was considered to have a "low risk" of bias, indicating a robust methodology and reliable results. The remaining study was classified as having a "high risk" of bias, primarily due to issues in Domain 1 (confounding bias). Additionally, the overall risk for this study was deemed serious. This serious risk suggests that methodological issues could significantly affect the results and interpretation of this study, making it less reliable compared to the others. These classifications were essential in determining the weight and credibility of the synthesized evidence in this review, ensuring that our conclusions are based on high-quality and rigorously assessed research.



**Fig. 2. Risk of bias**

**4. DISCUSSION**

This study evaluated factors associated with the development of preeclampsia (PE) in pregnant women with systemic lupus erythematosus (SLE). The obstetric outcomes of women with SLE have improved over the past decades, primarily due to advancements in treatment and more adequate pregestational counseling (Lazzaroni *et al.*, 2016). However, pregnancies in women with SLE still present higher risks of obstetric and fetal complications compared to pregnancies in women without the disease. For instance, PE occurs in approximately 5% of pregnancies in women without SLE, whereas the risk increases to 26% in women diagnosed with SLE within 0–2 years postpartum, 13% in those diagnosed within 2–5 years, and 16% in women with prevalent SLE (Arkema *et al.*, 2016).

Systemic lupus erythematosus is a chronic autoimmune disease that can affect multiple organ systems, and pregnant women with SLE are at a higher risk of adverse obstetric outcomes compared to those without the disease. The status of SLE—whether the disease remains stable or is active—is closely linked to maternal and neonatal outcomes, as disease activity is associated with various obstetric complications, including PE, primarily due to its potential to cause systemic inflammation and endothelial dysfunction (Li *et al.*, 2022).

The results demonstrated a significant association between lupus activity and the risk of PE, with an estimated threefold increase in risk for women with active lupus compared to those with inactive disease. These findings align with the literature, which also reports a high prevalence of PE in pregnant women with active lupus (Miranda-Hernandez *et al.*, 2020). Therefore, it is crucial for women with active lupus to be closely monitored during pregnancy to prevent disease exacerbations and to promptly manage potential complications. However, the use of different scoring systems to quantify lupus activity, such as the Lupus Activity Index in Pregnancy (LAI-P) or the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), may impact result consistency and comparability.

Increased body mass index (BMI) is associated with a higher risk of PE, as it contributes to increased systemic inflammation and oxidative stress, in addition to being linked to maternal hyperinsulinemia. Obesity leads to elevated leptin and insulin levels, which contribute to defective placental implantation, resulting in endothelial dysfunction and a predisposition to hypertensive disorders such as PE (Wang *et al.*, 2024). In this study, a high BMI was identified as an independent risk factor for PE, supporting findings from another study that also reported a significant association between elevated BMI and the occurrence of maternal complications, including PE (Normand *et al.*, 2019).

Pregnancy in women over 35 years of age is associated with an increased risk of obstetric complications, both due to ovarian aging and the higher prevalence of pre-existing chronic diseases (Alves *et al.*, 2018). It has been reported that the risk of PE increases by approximately 4% for each additional year of maternal age beyond 32 years (Poon *et al.*, 2019). However, in pregnancies complicated by PE in women with SLE, affected individuals tend to be younger, contradicting findings from studies that indicate an increased risk of PE with advancing maternal age (Ferreira *et al.*, 2019). This discrepancy may be explained by the heterogeneity of maternal ages in different studies. For example, in this review, the mean maternal age was 25.3 years in pregnancies complicated by PE and 29.9 years in those without PE. In contrast, other studies have reported mean maternal ages ranging from 35 to 40 years, demonstrating an increased prevalence of complications in older age groups.

Parity is also a relevant factor for the occurrence of complications, as multiparity has been significantly associated with a lower risk of preeclampsia. In contrast, nulliparous women have an increased risk of PE, as described in the literature, with one study demonstrating an almost threefold higher risk of preeclampsia in primigravidae (Grum *et al.*, 2017). The reason why the first pregnancy predisposes to the development of PE is not yet fully elucidated, but one hypothesis suggests that the absence of maternal tolerance to paternal antigens may play a role in the pathogenesis of the disease (Febrasgo, 2019).

Another important consideration is the comorbidities present in these women, such as renal disease, hypertension, and hematologic disorders. In lupus nephritis, there is a reduction in regulatory T cells (Tregs), which play a crucial role in the development and maintenance of immune tolerance by suppressing an aggressive allogeneic response against the fetus. This process contributes to the development of complications such as preeclampsia (Gluhovschi *et al.*, 2015). The results revealed that women with a prior history of lupus nephritis or active LN had a higher risk of developing preeclampsia compared to those with non-renal lupus. This finding aligns with the literature, which demonstrates a significant association between a previous diagnosis of lupus nephritis and the development of preeclampsia (Braga *et al.*, 2021).

Furthermore, chronic arterial hypertension represents a significantly increased risk for the onset of PE, being approximately five times higher compared to women without this condition (Bartsch *et al.*, 2016). The results confirmed this association in pregnant women with SLE, showing that those with preexisting hypertension and a mean arterial pressure (MAP) greater than or equal to 96.5 mmHg had an increased risk of pregnancy complicated by preeclampsia.

Hematologic disorders were also identified as independent risk factors for the development of preeclampsia in pregnant women with SLE. A similar finding was reported in a study demonstrating that the presence of cytopenias increased the risk of obstetric complications in women with lupus by approximately threefold (Tedeschi *et al.*, 2016). Platelet reduction impairs the ability to repair or form clots in response to endothelial injuries (Robbins *et al.*, 2015), contributing to endothelial dysfunction or increased vulnerability to damage. This, in turn, leads to a dysfunctional placenta, a fundamental factor in the pathogenesis of preeclampsia.

Beyond comorbidities, the presence of clinical biomarkers such as proteinuria can also be a relevant risk indicator. Proteinuria, along with changes in glomerular filtration rate (GFR) and serum creatinine levels, reflects potential glomerular dysfunction that can lead to renal function deterioration and be associated with the pathogenesis and prognosis of preeclampsia (Facca *et al.*, 2012). The results demonstrated that the presence of proteinuria, elevated serum creatinine and uric acid levels, decreased serum albumin levels, and a low estimated GFR were classified as independent risk factors for the development of PE. These findings are consistent with the literature, which identifies proteinuria as a risk factor for obstetric complications, including PE (Kim *et al.*, 2020; Vicoveanu *et al.*, 2022).

Another finding was the increased risk of preeclampsia in women with positive anticardiolipin antibody (aCL), in line with studies reporting anticardiolipin and lupus anticoagulant positivity as predictors of PE (Ong and Ding, 2021). Antiphospholipid antibodies, including anticardiolipin, lupus anticoagulant, and anti-beta2-glycoprotein I (anti-B2GPI), are present in one-quarter to half of SLE patients and significantly increase the risk of adverse obstetric outcomes (Lateef and Petri, 2017). These autoantibodies bind to platelets and endothelial cells, inducing a procoagulant state by activating them, as well as stimulating the complement system, leading to the recruitment of inflammatory cells, endothelial injury, and thrombosis (Mayor *et al.*, 2016).

Regarding pharmacological therapy, the antimalarial drug hydroxychloroquine (HCQ) is used in the treatment of SLE, both for managing cutaneous and musculoskeletal lesions and for preventing relapses and cardiovascular disease. According to the 2020 guidelines of the American College of Rheumatology (ACR), all women with lupus are recommended to use HCQ during pregnancy, and if they were not taking it before conception, they should initiate treatment as soon as possible (ACOG, 2020). The results demonstrated that the use of antimalarial drugs was associated with a lower risk of developing preeclampsia, a finding consistent with studies showing a reduction in PE incidence in pregnant women with SLE treated with hydroxychloroquine (Braga *et al.*, 2021; Duan *et al.*, 2021).

The literature also demonstrates an association between the development of preeclampsia and treatment with prednisolone (Braga *et al.*, 2021), a finding corroborated by the results, which indicated an approximately twofold increase in PE risk with corticosteroid use. Glucocorticoids, such as prednisolone, can interfere with placental angiogenesis by altering the expression of certain factors, resulting in improper endothelial cell formation and migration (Ozmen *et al.*, 2017). This may lead to a less efficient and possibly dysfunctional placenta, contributing to the development of preeclampsia. However, it is important to note that prednisolone is generally prescribed to treat lupus exacerbations in more severe cases, which may contribute to a higher risk of complications.

This review aimed to synthesize the risk factors associated with the development of preeclampsia in pregnant women with Systemic Lupus Erythematosus and to expand the understanding of the topic, although some limitations were identified.

First, there was a high degree of heterogeneity among the patients in the included studies, with geographical variability due to the participation of multiple countries. Additionally, the limited number of studies that met the inclusion criteria may have influenced the results obtained. Finally, another important limitation is the risk of bias in some of the included studies, particularly due to issues with randomization and missing data. Seven studies were rated as having "some concerns," and one was classified as having a "high risk" of bias due to confounding, which may compromise the reliability and accuracy of the review's conclusions. This heterogeneity in the risk of bias reduces the overall credibility of the synthesized evidence, requiring caution in the interpretation of results.

Despite these limitations, the review process was conducted rigorously to ensure study quality, excluding articles that addressed multiple complications and focusing solely on the occurrence of preeclampsia. Furthermore, study selection, data extraction, and methodological quality assessment were performed independently by more than one author, reducing the risk of bias that could occur if these steps were conducted by a single individual.

5. Conclusion

Based on the studies included in this review, we identified that certain factors associated with women with Systemic Lupus Erythematosus (SLE) have a significant impact on their obstetric outcomes, increasing the risk of developing preeclampsia. Patient characteristics such as elevated BMI, age, and multiparity, as well as active SLE, comorbidities (renal disease, hypertension, hematologic disorders), biochemical alterations (decreased albumin and estimated glomerular filtration rate, increased uric acid, creatinine, and proteinuria), anticardiolipin antibody positivity, and the use of prednisolone were identified as independent risk factors for the development of PE. Additionally, the use of hydroxychloroquine was observed as a protective factor.

Early identification of these factors during preconception evaluation or prenatal care in women with SLE may enable a more targeted follow-up throughout pregnancy, allowing for the implementation of preventive measures and specific care strategies for these patients.

Consent AND ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Authors hereby declare that no generative AI technologies such as large language models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

References

1. Carvalho, M. A. P., Lanna, C. C. D., Bertolo, M. B. & Ferreira, G. A. (2019). Reumatologia: diagnóstico e tratamento (5 ed.). Rio de Janeiro. Guanabara Koogan.

2. Sawada, T., Fujimori, D. & Yamamoto, Y. (2019). Systemic lupus erythematosus and immunodeficiency. Immunological Medicine, 42(1),1-9. https://doi.org/10.1080/25785826.2019.1628466.

3. Fava, A., & Petri, M. (2019). Systemic lupus erythematosus: diagnosis and clinical management. Journal Of Autoimmunity, 96, 1-13. Elsevier BV. https://doi.org/10.1016/j.jaut.2018.11.001.

4. Pons-Estel, G. J., Ugarte-Gil, M. F., & Alarcón, G. S. (2017). Epidemiology of systemic lupus erythematosus. Expert Review Of Clinical Immunology, 13(8), 799-814. Informa UK Limited. https://doi.org/10.1080/1744666x.2017.1327352.

5. Maynard, S., Guerrier, G., & Duffy, M. (2019). Pregnancy in Women With Systemic Lupus and Lupus Nephritis. Advances In Chronic Kidney Disease, 26(5), 330-337. Elsevier BV. https://doi.org/10.1053/j.ackd.2019.08.013.

6. Lateef, A., & Petri, M. (2017). Systemic Lupus Erythematosus and Pregnancy. Rheumatic Disease Clinics Of North America, 43(2), 215-226. Elsevier BV. https://doi.org/10.1016/j.rdc.2016.12.009.

7. Gestational Hypertension and Preeclampsia: ACOG Practice Bulletin, Number 222. (2020). Obstetrics and gynecology, 135(6), 237–260. https://doi.org/10.1097/AOG.0000000000003891.

8. Opichka, M. A., Rappelt, M. W., Gutterman, D. D., Grobe, J. L., & Mcintosh, J. J. (2021). Vascular Dysfunction in Preeclampsia. Cells, 10(11), 3055. MDPI AG. https://doi.org/10.3390/cells10113055.

9. Dalal, D. S., Patel, K. A., & Patel, M. A. (2019). Systemic Lupus Erythematosus and Pregnancy: A Brief Review. Journal of obstetrics and gynaecology of India, 69(2), 104-109. https://doi.org/10.1007/s13224-019-01212-8.

10. Silva, M. B. G., Alves, N. F., Vidal, I. H., Ramos, S. S. R., Oliveira, M. D. G., Pereira, M. L. V. B. A., *et al.* (2021). Atualizações sobre a abordagem da pré-eclâmpsia e o manejo dessa síndrome. Brazilian Journal Of Surgery And Clinical Research, 37(1), 70-78.

11. Kahhale, S., Francisco, R. P. V., & Zugaib, M. (2018). Pré-eclâmpsia. Revista de Medicina, 97(2), 226. Universidade de São Paulo, Agencia USP de Gestão da Informação Acadêmica (AGUIA). <https://doi.org/10.11606/issn.1679-9836.v97i2p226-234>.

12. Skorpen, C. G., Lydersen, S., Gilboe, I. M., Skomsvoll, J. F., Salvesen, K. Å., Palm, Ø., *et al.* (2017). Influence of disease activity and medications on offspring birth weight, pre-eclampsia and preterm birth in systemic lupus erythematosus: a population-based study. Annals Of The Rheumatic Diseases, 77(2), 264-269. BMJ. https://doi.org/10.1136/annrheumdis-2017-211641.

13. Saavedra, M. A., Miranda‐Hernández, D., Lara‐Mejía, A., Sánchez, A., Morales, S., Cruz‐Reyes, C., *et al.* (2020). Use of antimalarial drugs is associated with a lower risk of preeclampsia in lupus pregnancy: a prospective cohort study. International Journal Of Rheumatic Diseases, 23(5), 633-640. Wiley. https://doi.org/10.1111/1756-185x.13830.

14. Maeda, Y., Kaneko, K., Ogawa, K., Sago, H., & Murashima, A. (2020). The effect of parity, history of preeclampsia, and pregnancy care on the incidence of subsequent preeclampsia in multiparous women with SLE. Modern Rheumatology, 31(4), 843-848. Oxford University Press (OUP). https://doi.org/10.1080/14397595.2020.1830466.

15. Seo, M. R., Chae, J., Kim, Y. M., Cha, H., Choi, S. J., Oh, S., *et al.* (2019). Hydroxychloroquine treatment during pregnancy in lupus patients is associated with lower risk of preeclampsia. Lupus, 28(6), 722-730. SAGE Publications. https://doi.org/10.1177/0961203319843343.

16. Chen, J., Xiao, Z. Z., Shi, Q., Wang, H. M., He, F., & Zhang, J. Y. (2021). Risk factors associated with adverse pregnancy outcomes in patients with new-onset systemic lupus erythematosus during pregnancy. Lupus, 30(3), 393-402. SAGE Publications. https://doi.org/10.1177/0961203320980531.

17. Reis, C. R. P., Cardoso, G., Carvalho, C., Nogueira, I., Borges, A., & Serrano, F. (2019). Prediction of Adverse Pregnancy Outcomes in Women with Systemic Lupus Erythematosus. Clinical Reviews In Allergy & Immunology, 59(3), 287-294. Springer Science and Business Media LLC. https://doi.org/10.1007/s12016-019-08762-9.

18. Bremme, K., Honkanen, S., Gunnarsson, I., & Chaireti, R. (2021). The presence of lupus nephritis additionally increases the risk of preeclampsia among pregnant women with systemic lupus erythematosus. Lupus, 30(7), 1031-1038. SAGE Publications. https://doi.org/10.1177/09612033211004716.

19. Jiang, M., Wang, Y., Fu, Q., Lin, S., Wu, J., & Di, W. (2020). Preeclampsia Risk Prediction Model for Chinese Pregnant Patients With Systemic Lupus Erythematosus. Arthritis Care & Research, 72(11), 1602-1610. Wiley. https://doi.org/10.1002/acr.24265.

20. Mecacci, F., Simeone, S., Cirami, C. L., Cozzolino, M., Serena, C., Rambaldi, M. P., *et al.* (2017). Preeclampsia in pregnancies complicated by systemic lupus erythematosus (SLE) nephritis: prophylactic treatment with multidisciplinary approach are important keys to prevent adverse obstetric outcomes. The Journal Of Maternal-Fetal & Neonatal Medicine, 32(8), 1292-1298. Informa UK Limited. https://doi.org/10.1080/14767058.2017.1404570.

21. Lazzaroni, M. G., Dall’ara, F., Fredi, M., Nalli, C., Reggia, R., Lojacono, A., *et al.* (2016). A comprehensive review of the clinical approach to pregnancy and systemic lupus erythematosus. Journal Of Autoimmunity, 74, 106-117. Elsevier BV. https://doi.org/10.1016/j.jaut.2016.06.016.

22. Arkema, E. V., Palmsten, K., Sjöwall, C., Svenungsson, E., Salmon, J. E., & Simard, J. F. (2016). What to Expect When Expecting With Systemic Lupus Erythematosus (SLE): a population-based study of maternal and fetal outcomes in sle and pre-sle. Arthritis Care & Research, 68(7), 988-994. Wiley. https://doi.org/10.1002/acr.22791.

23. Li, J., Li, Z., Yu, L., & Su, J. (2022). Maternal and neonatal outcomes of pregnancy complicated with Systemic Lupus Erythematosus. Food Science And Technology, 42, 1-6. FapUNIFESP (SciELO). https://doi.org/10.1590/fst.56921.

24. Miranda-Hernández, D., Sánchez, A., Sánchez-Briones, R. E., Rivas-Ruiz, R., Cruz-Reynoso, L., Cruz-Domínguez, P., *et al.* (2020). Impact of Systemic Lupus Erythematosus on Pregnancy. Journal of Clinical Rheumatology, 27(6), 217-223. Ovid Technologies (Wolters Kluwer Health). https://doi.org/10.1097/rhu.0000000000001626.

25. Wang, Y., Ssengonzi, R., Townley-Tilson, W. H. D., Kayashima, Y., Maeda-Smithies, N., & Li, F. (2024). The Roles of Obesity and ASB4 in Preeclampsia Pathogenesis. International Journal Of Molecular Sciences, 25(16), 9017. MDPI AG. https://doi.org/10.3390/ijms25169017.

26. Normand, G., Sens, F., Puthet, J., Jourde-Chiche, N., Lemoine, S., Chauveau, D., *et al.* (2019). Not only disease activity but also chronic hypertension and overweight are determinants of pregnancy outcomes in patients with systemic lupus erythematosus. Lupus, 28(4), 529-537. SAGE Publications. https://doi.org/10.1177/0961203319832097.

27. Alves, N. C. C., Feitosa, K. M. A., Mendes, M. E. S., & Caminha, M. F. (2018). Complicações na gestação em mulheres com idade maior ou igual a 35 anos. Revista Gaúcha de Enfermagem, 38(4), 1-8. FapUNIFESP (SciELO). https://doi.org/10.1590/1983-1447.2017.04.2017-0042.

28. Poon, L. C., Shennan, A., Hyett, J. A., Kapur, A., Hadar, E., Divakar, H., *et al.* (2019). The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre‐eclampsia: a pragmatic guide for first-trimester screening and prevention. International Journal Of Gynecology & Obstetrics, 145(1), 1-33. Wiley. https://doi.org/10.1002/ijgo.12802.

29. Ferreira, E. T. M., Moura, N. S., Gomes, M. L. S., Silva, E. G., Guerreiro, M. G. S., & Oriá, M. O. B. (2019). Maternal characteristics and risk factors for preeclampsia in pregnant women. Rev Rene, 20, 1-7. Rev Rene - Revista da Rede de Enfermagem de Nordeste. https://doi.org/10.15253/2175-6783.20192040327.

30. Grum, T., Seifu, A., Abay, M., Angesom, T., & Tsegay, L. (2017). Determinants of pre-eclampsia/Eclampsia among women attending delivery Services in Selected Public Hospitals of Addis Ababa, Ethiopia: a case control study. Bmc Pregnancy And Childbirth, 17(1), 1-7. Springer Science and Business Media LLC. https://doi.org/10.1186/s12884-017-1507-1.

31. Fernandes, C. E., & Sá, M. F. S. (Eds.). (2019). Tratado de Obstetrícia FEBRASGO (1st ed.). Elsevier.

32. Gluhovschi, C., Gluhovschi, G., Petrica, L., Velciov, S., & Gluhovschi, (2015). A Pregnancy Associated with Systemic Lupus Erythematosus: immune tolerance in pregnancy and its deficiency in systemic lupus erythematosus⠴an immunological dilemma. Journal Of Immunology Research, 2015, 1-11. Hindawi Limited. https://doi.org/10.1155/2015/241547.

33. Braga, A., Barros, T., Faria, R., Marinho, A., Carvalheira, G., Rocha, G., *et al.* (2021). Systemic lupus erythematosus and pregnancy: a retrospective single-center study of 215 pregnancies from portugal. Lupus, 30(13), 2165-2175. SAGE Publications. https://doi.org/10.1177/09612033211050340.

34. Bartsch, E., Medcalf, K. E., Park, A. L., & Ray, J. G. (2016). Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ, 353, 1-10. https://doi.org/10.1136/bmj.i1753.

35. Tedeschi, S. K., Guan, H., Fine, A., Costenbader, K. H., & Bermas, B. (2016). Organ-specific systemic lupus erythematosus activity during pregnancy is associated with adverse pregnancy outcomes. Clinical Rheumatology, 35(7), 1725-1732. Springer Science and Business Media LLC. https://doi.org/10.1007/s10067-016-3270-5.

36. Robbins, S. L., Cotran, R. S., & Kumar, V. (2015). Robbins and Cotran pathologic basis of disease (9th ed). Elsevier.

37. Facca, T. A., Kirsztajn, G. M., & Sass, N. Pré-eclâmpsia (indicador de doença renal crônica): da gênese aos riscos futuros. (2012). Jornal Brasileiro de Nefrologia, 34(1), 87-93. FapUNIFESP (SciELO). https://doi.org/10.1590/s0101-28002012000100015.

38. Kim, J. W., Jung, J. Y., Kim, H. A., Yang, J. I., Kwak, D. W., & Suh, C. H. (2020). Lupus Low Disease Activity State Achievement Is Important for Reducing Adverse Outcomes in Pregnant Patients With Systemic Lupus Erythematosus. The Journal Of Rheumatology, 48(5), 707-716. The Journal of Rheumatology. https://doi.org/10.3899/jrheum.200802.

39. Vicoveanu, P., Vasilache, I. A., Nemescu, D., Carauleanu, A., Scripcariu, I. S., Rudisteanu, D., *et al.* (2022). Predictors Associated with Adverse Pregnancy Outcomes in a Cohort of Women with Systematic Lupus Erythematosus from Romania—An Observational Study (Stage 2). Journal Of Clinical Medicine, 11(7), 1964. MDPI AG. https://doi.org/10.3390/jcm11071964.

40. Ong, S. G., & Ding, H. J. (2021). Predictors of adverse pregnancy outcome in a cohort of women with systemic lupus erythematosus in Malaysia. Med J Malaysia, 76(4), 466-473.

41. Mayor, J. S., Robalo, M., Pacheco, A., Esperança, S., & Capela, C. (2016). Antiphospholipid Syndrome: Report of Three Cases and Review of the Literature. Gazeta Médica, 3(3), 122-127.

42. Duan, J., Ma, D., Wen, X., Guo, Q., Gao, J., Zhang, G., *et al.* (2021). Hydroxychloroquine prophylaxis for preeclampsia, hypertension and prematurity in pregnant patients with systemic lupus erythematosus: a meta-analysis. Lupus, 30(7), 1163-1174. SAGE Publications. https://doi.org/10.1177/09612033211007199.

43. Ozmen, A., Unek, G., & Korgun, E. T. (2017). Effect of glucocorticoids on mechanisms of placental angiogenesis. Placenta, 52, 41-48. Elsevier BV. https://doi.org/10.1016/j.placenta.2017.02.015.

44. Mcguinness, L. A., & Higgins, J. P. T. (2020). Risk‐of‐bias VISualization (robvis): An r package and shiny web app for visualizing ris-of-bias assessments. Research Synthesis Methods, 12(1), 1-7. https://doi.org/10.1002/jrsm.1411.