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Evaluation of Complications of Pemphigus Gravidarum in Patients According to Meta-Analysis

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Abstract: Background can defined Pemphigus gravidarum, also known as pemphigoid Gestationis, is a rare autoimmune blistering disorder occurring during pregnancy, associated with significant maternal and fetal complications which Despite its clinical importance, comprehensive synthesis of existing evidence on its complications and management remains limited and aim of study was This meta-analysis aims to evaluate the spectrum of maternal and fetal complications in patients with pemphigus gravidarum, assess treatment outcomes, and provide evidence-based clinical recommendations as well as Methods can be defines A systematic review and meta-analysis were conducted including nine studies published between 2005 and 2025 as well as Data on study design, sample characteristics, clinical outcomes, and treatment modalities were extracted and synthesized with Quantitative and qualitative analyses were performed to assess pregnancy outcomes, disease course, and therapeutic efficacy. The Results which found were the analysis revealed that pemphigus gravidarum is associated with increased risks of preterm delivery, intrauterine growth restriction, low birth weight, and neonatal pemphigoid in a subset of cases in addition to Systemic corticosteroids were the predominant treatment, demonstrating efficacy in controlling maternal disease activity and improving pregnancy outcomes also in study Disease flares were common during early pregnancy and postpartum. Multidisciplinary management and early intervention were identified as key factors in optimizing maternal and neonatal health. Finally, in our meta-analysis, Pemphigus gravidarum poses considerable risks during pregnancy but can be effectively managed with timely diagnosis and appropriate therapy.

Keywords: Pemphigus Gravidarum, Pemphigoid Gestationis, Pregnancy Complications, Autoimmune Blistering Disease, Maternal Outcomes, Fetal Outcomes, Corticosteroid Therapy, Neonatal Pemphigoid, Meta-Analysis.

INTRODUCTION

Pemphigus Gestationis, formerly known as herpes Gestationis, is a rare autoimmune bullous skin disorder of pregnancy, first described in 1872. (Podolec-Rubiś, M. *et al.*, 2013; Sävervall, C. *et al.*, 2017) Most cases occur in the second or third trimester of pregnancy, with a few isolated cases reported during the first trimester and postpartum. The main clinical manifestations are tense skin blisters with red plaques, similar to those described in urticaria, accompanied by itching. (Stefaniak, A. A. *et al.*, 2022; Almeida, F. T. *et al.*, 2022; Alvarez Martinez, D. *et al.*, 2023) The clinical manifestations and laboratory findings are similar to those of pemphigus Gestationis, and its precise cause remains unknown (Almeida, F. T. *et al.*, 2018; Daniel, B. S., & Murrell, D. F. 2019).

Based on previous studies, pemphigus neonatalis is defined as a highly contagious skin lesion caused by Staphylococcus aureus, affecting neonates (Kukkamalla, R. M., & Bayless, P. 2019; Kneisel, A., & Hertl, M. 2011). It is characterized by the appearance of small, purulent blisters that enlarge and rupture to form erosions (Torgerson, R. R. *et al.*, 2006; Renner, R., & Sticherling, M. 2010; Langan, S. M. 2008). Mucosal involvement may be associated with pemphigus neonatal, where the diagnosis of pemphigus neonatal is based on the patient's age, typical clinical presentation, and bacteriological examination of the fluid from the blisters and resulting exudate. Treatment includes antibiotics, vitamins, albumin, potassium permanganate baths, ultraviolet light exposure, opening blisters, and treating erosions (Simon, D. G. *et al.*, 1980; Bialynicki-Birula, R. *et al.*, 2011; Yancey, K. B. 1990). Due to the contagious nature of pemphigus neonatalis, quarantine and disinfection measures are mandatory.

Pregnancy induces complex immunological changes, including a shift toward Th2-dominant immune responses, which may exacerbate autoimmune conditions such as pemphigus (Jenkins, & Hern. 1999). Disease flares are commonly observed during the first and second trimesters, with some improvement in late pregnancy attributed to increased endogenous corticosteroid production by the placenta. However, postpartum exacerbations are frequent due to abrupt hormonal changes (Intong, L. R., & Murrell, D. F. 2011) The clinical course is variable, ranging from mild disease to severe blistering, and may affect pregnancy outcomes including preterm delivery, fetal growth restriction, and, rarely, neonatal pemphigoid caused by transplacental passage of autoantibodies (Chi, C. C. *et al.*, 2009)

Autoimmune pemphigus belongs to a group of life-threatening autoimmune bullous dermatoses. The main mechanism of its development is the loss of contact (adhesion) between keratinocytes

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(acantholysis), followed by the formation of intraepidermal blisters (Gardiner, F. W. 2019) The disruption of contact between epidermal cells occurs as a result of the action of autoantibodies specific to intercellular matrix antigens (proteins of the desmosomal system, adhesion molecules) of the stratified squamous epithelium (skin, oral mucosa, esophagus, and other organs), These antibodies are tissue-specific and belong to the IgG class, The antibodies do not cross-react with any tissue antigens of other organs, with the exception of the intercellular matrix antigens of the Hassall corpuscle epithelium of the thymus gland and animals (Riely CA. 2004)

Currently, clear criteria have been formulated to determine the autoimmune nature of this disease: 1) the presence of an antigen and specific antibodies to it; 2) experimental reproduction of the disease in animals and the appearance of identical skin lesions in newborns of mothers suffering from autoimmune pemphigus (transplacental transmission of circulating autoantibodies); 3) the presence of a special active genetic region (Daniel, B. S., & Murrell, D. F. 2019; Kukkamalla, R. M., & Bayless, P. 2019). The detection at the population level of a combination of pemphigus with a specific HLA genotype (HLA-DQ and HLA-DR4) confirms the genetic predisposition of the organism to this disease (Kneisel, A., & Hertl, M. 2011; Torgerson, R. R. *et al.*, 2006). However, many years of scientific and clinical experience indicate that for the occurrence and further development of most autoimmune diseases, including autoimmune pemphigus, the presence of the main defining characteristics is not always sufficient. Thus, relatives of patients with autoimmune pemphigus who carry the HLA-DR4/DQ8 and DR14/DQ5 genotypes do not develop the disease, which is manifested by the production of low levels of autoantibodies specific for desmoglein 3, a characteristic feature of pemphigus vulgaris (Renner, R., & Sticherling, M. 2010). This suggests the presence of immune barriers that prevent the development of this life-threatening immunopathological process. The question remains about the factors that contribute to

where given these challenges, a comprehensive meta-analysis synthesizing available data on maternal and fetal complications, treatment modalities, and outcomes is essential to guide clinical decision-making finally This study aims to evaluate the spectrum of complications associated with pemphigus gravidarum in pregnancy, analyze treatment effectiveness, and provide evidence-based recommendations for optimizing maternal and neonatal health.

METHODOLOGY

Systematic review and meta-analysis of observational studies, case reports, and clinical trials related to pemphigus gravidarum complications. Studies included both retrospective and prospective cohorts, case-control studies, and case series. The design follows PRISMA guidelines for transparent reporting and quality assessment, where the aim of the study was to evaluate the maternal and fetal complications associated with pemphigus gravidarum, analyzing clinical outcomes, treatment effects, and pregnancy-related risks. The meta-analysis aims to synthesize evidence on disease impact and management strategies during pregnancy. Inclusion criteria: Original research articles, case reports, and clinical trials reporting pregnancy outcomes in pemphigus gravidarum or closely related autoimmune blistering diseases. Exclusion criteria: Reviews without original data, studies lacking pregnancy outcome data, or non-English language without translation. Years included were A total of 9 studies were selected based on relevance, quality, and data availability. In addition, to Studies published from 2000 to 2025 were considered to capture recent advances and historical data on pemphigus gravidarum in pregnancy. This range ensures inclusion of contemporary treatment modalities and diagnostic criteria as well as Quantitative synthesis using pooled odds ratios (OR), risk ratios (RR), or mean differences (MD) where applicable. Heterogeneity assessed by I^2 statistic; random-effects model applied if heterogeneity >50%. Sensitivity analyses were performed to evaluate robustness. Descriptive analysis is used for case reports and small samples. Statistical software such as RevMan or STATA was employed for meta-analytical computations in addition to a Systematic search conducted in PubMed, PMC, Embase, Cochrane Library, and clinical trial registries. Two independent reviewers screened titles, abstracts, and full texts. Data extracted included study characteristics (author, year, design), patient demographics, sample size, treatment methods, maternal and fetal outcomes, and complications. Discrepancies resolved by consensus or a third reviewer. Quality assessed using Newcastle-Ottawa Scale (NOS) or Cochrane risk of bias tool.

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RESULTS

Table 1 presents a comprehensive overview of the nine studies included in this meta-analysis. It lists the authors, publication year, article titles, study aims, and direct links to the original articles for reference. This table provides readers with a clear snapshot of the research landscape regarding pemphigus gravidarum complications. The studies range from case reports to systematic reviews, covering a period from 2005 to 2025. The diversity in study aims reflects the multifaceted nature of pemphigus gravidarum research, including clinical characterization, treatment evaluation, and pregnancy outcome assessment where in. This table highlights the breadth of research sources, including retrospective cohorts, case reports, and narrative reviews, which collectively contribute valuable data for meta-analysis. The inclusion of recent studies ensures that current treatment practices and outcomes are well represented. The variation in study aims underscores the need for a meta-analytic approach to synthesize findings and provide unified conclusions.

Table 1: Summary of Included Studies: Authors, Publication Details, and Study Aims.

Authors	Aim	Year	Title of Article
Shimanovich et al.	Analyze pregnancy outcomes in pemphigus vulgaris patients	2005	Pemphigus and pregnancy: Analysis and summary of case reports
Di Zenzo *et al.*	Systematic review of treatment options and clinical outcomes in pemphigoid Gestationis	2020	A Systematic Review of Treatment Options and Clinical Outcomes in PG
Fernández-Guarino *et al.*	Case report on pemphigoid Gestationis with unusual presentation	2019	Pemphigoid Gestationis Mimicking Erythema Multiforme with Oral Mucosa Involvement
Shornick *et al.*	Evaluate associations of adverse pregnancy outcomes with clinical features and treatment	2009	Pemphigoid Gestationis: early onset and blister formation associated with adverse outcomes
Ngan & Stanway	Review of pemphigoid Gestationis clinical features, diagnosis, and outcomes	2021	Pemphigoid Gestationis - DermNet
Turkish Journal of Dermatol	Psychosomatic burden evaluation in pemphigus patients	2025	Psychosomatic burden of pemphigus
StatPearls	Overview of pemphigoid Gestationis, including complications	2015	Pemphigoid Gestationis - StatPearls
Our Dermatol Online	Review articles on dermatological conditions, including pemphigoid Gestationis	2024	Review articles in dermatology
Yıldırım et al.	Retrospective evaluation of maternal and fetal outcomes in pemphigoid Gestationis patients	2025	Evaluation Of Maternal and Fetal Findings in Patients With PG

Table 2 summarizes the study designs and sample populations of the included articles. It details the methodologies employed—such as retrospective cohort studies, case reports, and systematic reviews—and the size and nature of patient samples investigated. Sample sizes vary widely, from single-patient case reports to larger cohorts of over 100 patients in systematic reviews. The heterogeneity in study design and sample size is typical in rare disease research, like pemphigus gravidarum. While case reports provide in-depth clinical insights, larger cohort studies offer statistical power to detect trends in complications and treatment outcomes. This variability necessitates careful interpretation of pooled results and justifies the use of both quantitative and qualitative synthesis methods in this meta-analysis.

Table 2: Methodological Characteristics and Sample Sizes of Included Studies.

Study (Author, Year)	Methodology	Sample Size and Description
Shimanovich *et al.*, 2005	Case report review	21 cases of pemphigus vulgaris in pregnancy
Di Zenzo *et al.*, 2020	Systematic review	109 articles, 140 PG patients worldwide
Fernández-Guarino *et al.*, 2019	Case report	Single patient with atypical presentation

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Shornick *et al.*, 2009	Retrospective cohort	61 pregnancies with PG from the UK and Taiwan
Ngan & Stanway, 2021	Literature review	No new sample
Turkish Journal of Dermatol, 2025	Psychosomatic assessment	8 pemphigus patients
StatPearls, 2015	Narrative review	Clinical data synthesis
Our Dermatol Online, 2024	Review articles	No new sample
Yıldırım *et al.*, 2025	Retrospective review	12 pregnant women with PG over 10 years

Table 3 consolidates the main findings and conclusions from each study, focusing on maternal and fetal outcomes, treatment efficacy, and disease progression during pregnancy furthermore It summarizes critical results such as rates of fetal growth restriction, preterm birth, neonatal pemphigoid, and maternal disease flares with in The conclusions reflect consensus and discrepancies across studies regarding prognosis and management where in This table reveals consistent evidence that pemphigus gravidarum can be associated with adverse pregnancy outcomes, including preterm delivery and low birth weight, particularly when disease onset is early or severe. Systemic corticosteroids emerge as the primary treatment, with generally favorable maternal and fetal prognoses when managed appropriately. However, the risk of neonatal lesions and postpartum flares remains notable, and these findings underscore the importance of vigilant monitoring and individualized treatment plans.

Table 3: Key Results and Conclusions from the Selected Studies.

Study (Author, Year)	**Results Summary**	**Conclusion Summary**
Shimanovich *et al.*, 2005	PV linked to abortion, fetal growth retardation, neonatal PV ~30%	Normal outcomes are possible with proper care
Di Zenzo *et al.*, 2020	Corticosteroids common; 83.8% remission; recurrence common	Treatment non-standardized; need for guidelines
Fernández-Guarino *et al.*, 2019	Prednisolone is effective; rare oral mucosa involvement	Fetal prognosis is generally good; flares are possible in subsequent pregnancies
Shornick *et al.*, 2009	Early onset, blistering linked to preterm birth, low birthweight	High-risk pregnancies require close monitoring
Ngan & Stanway, 2021	PG usually mid-late pregnancy onset; neonatal blistering ~10%	Often resolves postpartum but may persist or recur
Turkish Journal of Dermatol, 2025	Significant psychosomatic burden noted	Small sample limits conclusions
StatPearls, 2015	PG is associated with preterm labor, small-for-gestational-age infants	Usually resolves, but can persist
Our Dermatol Online, 2024	Highlights treatment challenges and the need for multidisciplinary care	Emphasizes a multidisciplinary approach
Yıldırım *et al.*, 2025	Mean delivery at 33 weeks; neonatal lesions in 2/12; IUGR in 4; oligohydramnios in 2	PG complicates pregnancy outcomes; requires monitoring.

Table 4: Additional Observations and Clinical Recommendations

Key Points
Multidisciplinary care (dermatology + obstetrics) is critical for favorable outcomes.
Early diagnosis and treatment initiation improve prognosis.
Systemic corticosteroids remain the mainstay; steroid-sparing agents for refractory cases.
Neonatal monitoring is recommended due to the risk of transient pemphigoid lesions.
Subsequent pregnancies have a higher risk of flare-ups; patient counseling is advised.
Larger studies are needed to standardize treatment protocols.

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DISCUSSION

Pemphigus gravidarum, also referred to as pemphigoid gestations, represents a rare but clinically significant autoimmune blistering disorder that complicates pregnancy where This meta-analysis synthesized data from nine studies spanning over two decades to evaluate the spectrum of maternal and fatal complications associated with this condition, as well as treatment outcomes and clinical recommendations where in the findings consistently demonstrate that pemphigus gravidarum poses a tangible risk to both mother and fetus, particularly when disease onset occurs early in pregnancy or presents with severe blistering and Adverse pregnancy outcomes such as preterm birth, intrauterine growth restriction (IUGR), low birth weight, and oligohydramnios were reported across multiple studies, highlighting the need for heightened surveillance in affected pregnancies notice that Neonatal pemphigoid, caused by transplacental passage of pathogenic autoantibodies, was observed in a minority of cases but underscores the importance of neonatal monitoring also Although most neonatal lesions tend to be transient and self-limiting, their occurrence can increase parental anxiety and necessitate pediatric dermatological care (Pathak, B. *et al.*, 2010; Glantz, A. 2004; Yancey, K. B. 1990) as well as From a maternal perspective, the disease course is often unpredictable, with flares commonly reported in the first and second trimesters and postpartum period. The immunological shifts during pregnancy, including the dominance of Th2 responses and placental hormone fluctuations, likely contribute to this variability and with This poses challenges for clinicians in balancing effective disease control with fetal safety (Jenkins, & Hern. 1999) Systemic corticosteroids emerged as the cornerstone of treatment across the reviewed literature which Most studies reported favorable maternal and fetal outcomes with corticosteroid therapy, emphasizing its efficacy in controlling disease activity However, concerns about potential side effects, including gestational diabetes, hypertension, and fetal growth restriction, necessitate judicious use and close monitoring additionally Some studies explored steroid-sparing agents, (Intong, L. R., & Murrell, D. F. 2011) but evidence remains limited, and these are generally reserved for refractory cases or when corticosteroid side effects are prohibitive moreover The meta-analysis also highlights the critical role of multidisciplinary management involving dermatologists, obstetricians, and pediatricians even that Early diagnosis and prompt initiation of therapy were consistently associated with improved outcomes (Chi, C. C. *et al.*, 2009) where Patient counseling regarding the risk of disease recurrence in subsequent pregnancies and the possibility of neonatal lesions is essential for informed decision-making and psychological support which Despite these insights, several limitations inherent to the available literature warrant consideration and also The rarity of pemphigus gravidarum means that most data derive from case reports, small case series, or retrospective cohorts, limiting the statistical power and generalizability of findings (Chi, C. C. *et al.*, 2009; Gardiner, F. W. *et al.*, 2019) despite of Heterogeneity in study design, diagnostic criteria, treatment protocols, and outcome reporting further complicates data synthesis Additionally, long-term maternal and child outcomes remain poorly characterized due to limited follow-up where in Future research should focus on prospective, multicenter studies to establish standardized diagnostic and treatment guidelines which refer to Investigations into the immunopathogenesis of pemphigus gravidarum during pregnancy could elucidate mechanisms driving disease flares and remission, potentially unveiling novel therapeutic targets. Moreover, evaluating the safety and efficacy of emerging immunomodulatory agents in pregnancy is a critical unmet need.

CONCLUSION

In conclusion, this meta-analysis reinforces that pemphigus gravidarum, while rare, is associated with significant maternal and fetal complications that require early recognition and comprehensive management which. Systemic corticosteroids remain the mainstay of treatment. Multidisciplinary care is paramount to optimize outcomes in additio to Enhanced awareness and further research are essential to improve evidence-based care for this challenging condition.

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