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SYSTEMIC LUPUS ERYTHEMATOSUS AND PREGNANCY: STRATEGIES BEYOND THE BASICS TO IMPROVE OUTCOMES IN PREGNANCY

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ABSTRACT

Objectives: To look those available strategies which can improve the outcome of women pregnancies those suffering with SLE.

Materials and Methods: For this review, the two researchers conducted an extensive search across various databases, including Web of Science, PubMed, Scopus, and Medline. In addition, domestic databases such as <https://pakmedinet.com> and Google Scholar were explored. The search strategy involved employing specific keywords like "Systemic lupus erythematosus," "Pregnancy," "Strategies," "Maternal, fetal, or neonatal outcome," and "Improvement." The scope of the search encompassed articles published between January 2010 and January 2022. The PICO framework involves examining which interventions (strategies) are linked to an increased rate of successful normal pregnancies (outcome) in pregnant women with SLE (participants), relative to pregnant women without SLE (comparison).

Results: Based on our total 45 studies, our result demonstrates that pregnancies involving systemic lupus erythematosus (SLE) patients remain high-risk due to increased susceptibility to obstetric and neonatal complications. Maternal mortality rates are over 25-fold higher within SLE pregnancies. Despite vigilant monitoring, maternal and fetal morbidity remains elevated. Immunological changes during pregnancy influence SLE activity, potentially triggering disease flares. Variability exists in SLE flare risk during pregnancy due to diverse definitions and assessment tools. Strategies to improve outcomes involve preconception counseling, multidisciplinary monitoring, disease activity assessment, and postpartum surveillance. Lupus nephritis exacerbates risks, particularly with active disease during conception. Identifying these factors aids in better managing of these SLE women in high-risk pregnancies.

Conclusion: Tailored monitoring and preconception counseling are crucial for improved outcomes. The complex interplay between SLE activity and pregnancy underscores the need for refined assessment tools. Lupus nephritis accentuates risks, particularly with active disease at conception. A holistic, patient-centered approach is paramount to enhance outcomes in these challenging pregnancies.

Key words: Systemic Lupus Erythematosus, SLE, Pregnancy, Maternal-Fetal Outcomes, Preconception Counseling, Multidisciplinary Monitoring, Lupus Nephritis, Perinatal Outcomes.

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INTRODUCTION

SLE, known as systematic lupus erythematosus, is a complex and persistent autoimmune ailment characterized by periods of relapse¹. Predominantly afflicting women, this multisystemic condition often

emerges during the childbearing years, presenting substantial health concerns that can significantly affect functional capacity², mental well-being, and overall survival. The experience of pregnancy among individuals with SLE introduces distinctive hurdles, attributable to the intricate interplay among the maternal immune system, fetal development, and the underlying disease progression³.

SLE affects African, American and Asian more often than people other races. Differences in geographic locations contribute to variations in the estimated occurrence and prevalence of SLE⁴. The annual incidence rate of SLE ranges from 4 to 35 cases per 100,000 individuals⁵ while in United state of America the reported prevalence of SLE is 20 to 150 cases per 100,000 population. But in one meta analysis the prevalence was 73 out of 100,000⁶.

Due to the generalized nature of SLE it influences all aspects of patients life⁷ Exhibiting a lower health-related quality of life in comparison to both the general populace and individuals with other chronic conditions.

Although SLE pregnancies are complicated owing to risk for maternal diseases exacerbation while potential and neonatal complication⁸ but a majority of women with a SLE are to undergo with a successful pregnancy with appropriate planning and management^{5,9} In their study, M. Graça Pereira and colleagues demonstrated an association between disease activity, severity of fatigue, physiological morbidity, and body image with all aspects of quality of life (QoL)¹⁰.

While significant advancements have been made in understanding the basic management of SLE during pregnancy, there is a growing need to explore strategies that extend beyond conventional approaches to further enhance maternal and fetal outcomes^{9,11}. Previous studies has shown systematic lupus erythematosus (SLE) with a severe consequences on pregnancy outcomes. The primary limitations in our specific regions stemmed from an inadequate participant pool and outdated information. Furthermore, the absence of evidence-based analyses to substantiate the systematic literature review presented an additional constraint. So, therefore, we aimed to systematically look those available strategies which can improve the outcome of women pregnancies those suffering with SLE.

MATERIALS AND METHODS

For this review, the two researchers conducted an extensive search across various databases sources by adding Medline, PubMed, Web of Science and Scopus. In addition, domestic databases such as <https://pakmedinet.com> and Google Scholar were explored. The search strategy involved employing specific keywords like "Systemic lupus erythematosus," "Pregnancy," "Strategies," "Maternal, fetal, or neonatal outcome," and "Improvement."

The selection process centered on English articles that incorporated the aforementioned keywords within their titles and abstracts, aligning closely with the research's objectives. The scope of the search encompassed articles published between January 2010 and January 2022.

Excluded from consideration were articles with incomplete data and those not written in English. Initially, a pool of 225 articles was identified by using keyword searches related to "lupus and pregnancy" while 85 were removed by finding duplicates. Among these, 140 articles were screened while 112 articles were located using the keywords "lupus and maternal, fetal, and neonatal outcomes." After the initial screening process, a total of 45 articles were excluded based on an assessment of their titles and abstracts. Subsequently, 22 more articles were eliminated due to their lack of relevance in terms of findings. (Figure1: Prisma flow diagram).

Ultimately, a total of 45 studies were deemed suitable for inclusion in this review. Information pertinent to the study's objectives was extracted using a predefined data extraction form. This form, meticulously crafted by the research team, facilitated the systematic collection of relevant details. Two researchers independently conducted the data extraction process. In cases of divergent extractions, disagreements were resolved through thoughtful deliberation and consensus between the researchers.

Our investigation centered around the PICO question: In cohort, cross-sectional, and case-control study designs, which strategies (Intervention) demonstrate a higher rate of successful normal pregnancy (outcome) among pregnant women with SLE (participants), as opposed to pregnant women without SLE (comparison)?

RESULT

While considerable progress has been achieved globally in terms of diagnostic and therapeutic advancements, pregnancies involving SLE patients continue to be regarded as high-risk endeavors¹². This is primarily due to the heightened susceptibility to major obstetric and neonatal complications associated with SLE. Numerous population-based studies have demonstrated a startling over 25-fold rise in maternal mortality rates within the context of SLE¹³.

Despite the meticulous application of vigilant monitoring protocols during pregnancy and the postpartum phase, along with the adoption of a multidisciplinary approach, observable enhancements in the outcomes of SLE patients have remained elusive^{14,15}. However, findings from recent meta-analyses and systematic reviews underscore that fetal and maternal morbidity remains disproportionately elevated in pregnancies involving women with SLE¹⁶. Furthermore, it's important to highlight that the count of live births in women with SLE is projected to be lower when contrasted with the live births in the broader population¹⁷.

DISCUSSION

ISLE Activity and Its Implications: Influence of Pregnancy on Disease Progression

The adaptations in immunological responses

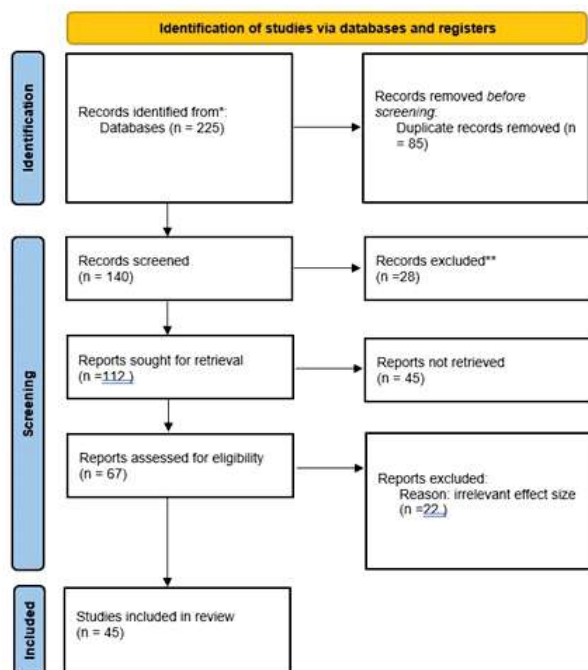


Fig 3: Prisma flow diagram

during pregnancy and postpartum have the potential to exert multifaceted effects on maternal autoimmune conditions³. Considering the predominant Th-mediated nature of SLE, the dynamic shifts in immune activity during pregnancy could theoretically trigger disease initiation or elevate the likelihood of disease flares within this timeframe¹⁸.

The discussion regarding the potential for SLE flares during pregnancy has continued to be intricate. Although several prospective studies on pregnancies in individuals with SLE have suggested an increased likelihood of disease worsening throughout gestation, variations arise due to the diverse definitions of lupus flares and the array of tools employed to evaluate lupus activity¹⁹. Recent inquiries employing thoroughly validated metrics for assessing disease activity have revealed a notable multiple-fold rise in SLE activity throughout pregnancy²⁰. Notably, these flares are often categorized as mild to moderate and frequently involve systems such as the renal, hematological, and musculoskeletal domains. Furthermore, there is an observable trend where prior organ involvement often foreshadows analogous conditions during the pregnancy period²¹.

Different approaches to improve pregnancy outcomes

Perception counseling before pregnancy

To mitigate adverse outcomes in women with SLE, perception counseling plays a crucial role in identifying potential risk factors²². The crucial adoption of these preventative strategies highlights the importance of embracing a patient-centered, multidisciplinary monitoring approach, both prior to and throughout pregnancy. The studies identified various approaches; for instance, one study recommends placing greater emphasis on preconception counseling for women with lupus. The complexities associated with handling high-risk pregnancies in women with SLE, coupled with the lack of unanimous guidance, create obstacles for rheumatologists in delivering family planning counseling. This is exemplified through insights gleaned from semi-structured interviews²³. Facilitating open discussions concerning pregnancy planning and care is pivotal between rheumatologists and female SLE patients in their reproductive years²⁴. Customizing risk assessment is imperative, incorporating a range of factors including comorbidities, disease activity,

organ impairment, and autoantibody profile (such as aPL, anti-Ro/SSA, and anti-La/SSB). In the case of non-primigravida women, a history of past unfavorable pregnancy outcomes plays a pivotal role in evaluating the likelihood of complications in subsequent pregnancies²⁵.

Fetal and maternal monitoring during pregnancy to improve outcome

The collected set of studies recognized a multi-disciplinary strategy involving a team comprising a rheumatologist, obstetrician, maternal-fetal medicine physician, and additional specialists based on the specific organ involvement²⁶. It is recommended to maintain close monitoring by both obstetricians and rheumatologists, involving initial and routine clinical assessments. A rheumatologist should conduct disease activity evaluations at the outset and periodically every few weeks, adapting to disease status and risk categorization. This proactive approach aids in promptly detecting potential disease exacerbation or pregnancy-related complications²⁷. Some studies added that during the initial assessment, predictive elements for Adverse Pregnancy Outcomes (APOs) need to be pinpointed. Subsequent visits should prioritize monitoring blood count, renal, blood pressure and hepatic functionality, urinalysis, and proteinuria²⁸. Additionally, the measurement of complement C3, anti-dsDNA antibodies and complement C3 is recommended on a trimester basis²⁹.

Assessment of disease activity and SLE outcome

Due to physiological changes during pregnancies can be challenging when we recognize the disease during pregnancies. Thus, clinical and laboratory data should interpret to indicate the classical features of SLE³⁰. During a typical pregnancy, thrombocytopenia, mild anemia, and increased erythrocyte sedimentation rate often manifest. However, the usefulness of complement levels in identifying or confirming disease activity is constrained by their physiological rise during pregnancy. Nevertheless, differentiating complications such as preeclampsia from SLE activity could potentially be aided by observing a decrease of $\geq 50\%$ in C3 and C4 levels relative to baseline and an increase in anti-dsDNA antibodies³¹. Some studies proposed modified pregnancy scores to assess disease activity in pregnancy, factoring in physiological gestational alterations and conditions that may mimic SLE. However, these tools are not

commonly employed in rheumatological practice. Instead, clinical attention typically centers around new organ involvements, exacerbation of existing disease manifestations, or alterations in immuno-suppressive medication³².

Postpartum surveillance after pregnancy

The postpartum period, which is characterized by increased lupus flares, is acknowledged as a time of heightened risk. A recent retrospective study involving 398 SLE pregnancies from the Hopkins Lupus Cohort highlighted a higher frequency of flares in the early postpartum months compared to non-pregnant individuals³³. Importantly, a protective effect was noted with hydroxychloroquine therapy, reducing flare risks during both pregnancy and postpartum to levels comparable to non-pregnant SLE patients³⁴.

Among the chosen studies, a prospective cohort encompassing 145 pregnancies revealed heightened disease activity at 6 and 12 months postpartum, in contrast to the third trimester and the initial 6 weeks postpartum. This emphasizes the importance of ongoing monitoring and surveillance during the postpartum period³⁵.

lupus nephritis and Perinatal outcomes

A higher prevalence of maternal complications and preterm delivery has been observed in SLE women with lupus nephritis when compared to patients without a history of renal involvement³⁶.

However, recent data have shown that the risk is associated with the activity of lupus nephritis at the beginning of pregnancy, rather than being solely linked to the presence of lupus nephritis^{37,38}. In a study involving a prospective cohort of 119 lupus pregnancies, individuals with a prior history of lupus nephritis displayed an elevated occurrence of maternal complications, specifically notable for renal flares (50% vs. 27%, $p = .001$)³⁸. However, these differences dissipated when individuals with renal flares during the months preceding pregnancy were excluded³⁹. Wagner's research underscores the significance of active lupus nephritis (LN) at the time of conception as a notable risk factor for maternal complications such as preeclampsia, eclampsia, and HELLP syndrome^{25,40}. On the fetal side, prevalent complications encompassed miscarriage, small for gestational age, intrauterine growth restriction (IUGR), preterm

delivery, and stillbirth²⁶. A prospective multicenter study encompassing 71 pregnancies (78.9% of which exhibited complete renal remission before pregnancy) revealed that patients with stable lupus nephritis, who had undergone pregnancy counseling, did not demonstrate an increased likelihood of experiencing renal flares during pregnancy^{41,42}.

CONCLUSION

Our result showed that SLE pregnancies remain high-risk due to obstetric complications. Recent data show persistent maternal and fetal morbidity, fewer live births among SLE women. Pregnancy-related immunological shifts can trigger SLE flares. Validated metrics indicate a significant increase in disease activity during pregnancy. Tailored risk assessment, perception counseling, and multidisciplinary care enhance outcomes. Vigilant monitoring and biomarker assessment aid postpartum care. Hydroxychloroquine protects against postpartum flares. Active LN at pregnancy onset elevates maternal risks. Collaboration and ongoing research offer hope for safer SLE pregnancies, emphasizing tailored strategies and vigilant monitoring.

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