Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: January 31, 2023

Citation: Saklecha A., Smith C.J.F., 2023. Challenges associated with active lupus nephritis in pregnancy and distinguishing between lupus nephritis and preeclampsia: Case report of a high-pressure situation, Medical Research Archives, [online] 11(1). https://doi.org/10.18103/mra.v11i1.3446

DOI: https://doi.org/10.18103/mra.v11i1.3446
ISSN: 2375-1924

CASE REPORT

Challenges associated with active lupus nephritis in pregnancy and distinguishing between lupus nephritis and preeclampsia: Case report of a high-pressure situation

Anokhi Saklecha[1]; ***Chelsey J. F. Smith**[1]

Division of Rheumatology, Allergy and Immunology
University of California, San Diego, USA

*cjs018@health.ucsd.edu

ABSTRACT

Active lupus nephritis poses severe maternal and fetal risks in pregnant patients. Management in pregnancy is challenging and limited by lack of pregnancy-safe medication options. Preeclampsia is an associated maternal risk that shares many clinical features with lupus nephritis, often making it difficult to identify the primary disease process. In this report, we present a case of severe preeclampsia superimposed on active lupus nephritis in a 25-year-old pregnant female. We highlight the risks and management options for lupus nephritis in pregnancy, the overlaps in presentation between lupus nephritis and preeclampsia, and techniques to clinically distinguish between the two.

Introduction

Lupus nephritis (LN) is a subtype of glomerulonephritis associated with systemic lupus erythematosus (SLE). It affects over 50% of SLE patients and most commonly presents as an acute kidney injury with proteinuria, hematuria, and hypertension.[1] The disease is characterized by a type 3 hypersensitivity reaction caused by immune complex depositions in the glomeruli. Definitive diagnosis of LN requires a kidney biopsy exposing these immune deposits.[2]

Immunosuppressive treatment and control of active LN prior to pregnancy is crucial to preserve both maternal and fetal health, as the pregnant state may be associated with flaring kidney disease. If unmanaged, these flares can lead to poor pregnancy outcomes, including preeclampsia, progressive maternal kidney disease, preterm delivery, intrauterine growth restriction, stillbirth, and neonatal death.[3]

Preeclampsia, classically defined as new onset hypertension and proteinuria or other end organ damage after 20 weeks of pregnancy, represents a particularly hazardous risk of LN. It is caused by endothelial dysfunction and systemic vasospasm experienced during pregnancy.[4] Preeclampsia may also be associated with other pregnancy complications, including preterm delivery, intrauterine growth restriction, still birth, HELLP syndrome, and maternal multiorgan failure.[5] If preeclampsia becomes severe, delivery of the fetus is recommended.[6]

Due to the overlaps in presentation between preeclampsia and LN, including hypertension, acute kidney injury, and proteinuria, identifying the primary disease process often presents a diagnostic challenge in cases of coexisting disease. However, as the management of each disease differs, distinguishing between the two becomes critical in providing the best possible care for both the mother and fetus.

In this case, we explore the risks and treatments of LN in pregnancy and the management of cases with coexisting preeclampsia.

Case Summary

A 25-year-old female with a history of SLE, Class III LN, and hypertension, presented to establish care with rheumatology after a positive pregnancy test. Prior extra-renal manifestations of the patient's disease included hypocomplementemia, positive double stranded DNA (dsDNA) antibody, arthritis, oral ulcers, and alopecia. At the time of presentation, she was at 14 weeks' gestation, and this was her first pregnancy. Urinalysis revealed 2+ proteinuria, 2+ hematuria, 6-10 red blood cells, 3-5 white blood cells, and an elevated total protein to creatinine ratio of 1.85. Serum blood work included a creatinine of 1.08 mg/dL, hemoglobin of 7.9 g/dL, and C3 and C4 levels of 131 mg/dL and 25 mg/dL, respectively. Anti-Ro, anti-La antibodies and antiphospholipid antibody panels were negative. Upon review of her record, it was evident that the patient had never completed appropriate induction treatment for her LN prior to pregnancy, and was maintained only on 20 mg prednisone and low dose

azathioprine. Due to active renal disease, the high-risk nature of the pregnancy was discussed with the patient with emphasis on potentially threatened kidney function and risk for serious adverse maternal and fetal outcome; however, she elected against pregnancy termination. The patient was started on hydroxychloroquine 400 mg, labetalol 200 mg and low dose daily aspirin. The azathioprine dose was up-titrated, and prednisone 20 mg was continued.

At 16 weeks' gestation, the patient developed a creatinine rise from 1.08 to 1.67 mg/dL, as well as elevated blood pressures and dysuria. Urine protein levels and complement levels were stable, and there were no new systemic lupus symptoms at the time. A diagnosis of preeclampsia was considered, though not favored due to early gestational age. Leading differentials included progression of LN despite non-elevated lupus markers or active SLE symptoms, concomitant urinary tract infection, and/or worsening hypertension. The patient's azathioprine dose was increased further, blood pressure medications were adjusted, antibiotics were prescribed, and prednisone dose was increased to 1 mg/kg dosing for possible flaring kidney disease. By 20 weeks of gestation, the patient was maintained on prednisone 60 mg, azathioprine 125 mg, hydroxychloroquine 400 mg, amlodipine 5 mg, and labetalol 200 mg, and serum creatinine improved back to baseline.

At 22 weeks and 5 days of gestation, the patient was seen in rheumatology clinic with new onset shortness of breath, lower extremity edema, and elevated blood pressure after missing three days of amlodipine. She was sent to the emergency department and admitted for hypertensive urgency, with blood pressures ranging from 160-180/70-90 mmHg, requiring intravenous labetalol and hydralazine. On exam, she exhibited shortness of breath with gross anasarca, including sacral and pedal edema. Her creatinine was 1.30 mg/dL, 24-hour urine protein was greater than 6 grams and total protein to creatinine ratio had raised to 10.89. Lupus markers were stable, and a chest x-ray showed cardiomegaly with pulmonary edema.

The patient was admitted to the hospital and transferred to the intensive care unit for administration of a nicardipine drip and close cardiac monitoring. Given progressive hypertension, edema, nephropathy, and proteinuria beyond 20 weeks of gestation, a diagnosis of severe preeclampsia was suspected. Despite aggressive blood pressure control, the patient's blood pressures repeatedly remained 160-180/80-90 mmHg. Additionally, she experienced progressively worsening renal function, with a serum creatinine of 1.61 mg/dL and potassium of 5.6 mmol/L with peak T waves on EKG. The decision was made to expedite fetal delivery and pursue a classical cesarean section at 23 weeks and 5 days of gestation. The patient gave birth to a viable fetus, which passed away at day three of life. Post-operatively, the patient's blood pressures were managed with a nicardipine drip for two days until able to titrate to an oral regimen. Her creatinine suffered an initial jump to 1.9

mg/dL after delivery, and remained elevated for up to two months postpartum. The creatinine subsequently down trended over time, although still not back to normal range.

Discussion

This case highlights the challenges of managing active LN in pregnancy, and demonstrates the potential for poor maternal and fetal outcomes when disease is not controlled, including the increased risk for superimposed severe preeclampsia. In this case, the very preterm infant unfortunately passed away, and the mother required multiple hospitalizations and days in the intensive care unit, with resultant progressive renal failure, despite aggressive medical management.

This case also brings into question the timing of preeclampsia onset, which can be insidious and difficult to pinpoint, particularly in the setting of known active kidney disease.

Active Lupus Nephritis in Pregnancy

Lupus nephritis affects more than 50% of SLE patients and presents with flares of progressive kidney injury characterized by proteinuria, hematuria, leukocyturia, and/or hypertension.[1,7] LN is caused by immune complex depositions throughout the kidney, resulting in tissue damage and inflammation. There are six histological classes of LN, based upon the distribution and location of the immune complexes.[8] In anywhere from 10 to 30% of cases, LN can lead to end stage renal disease with a high level of mortality.[9]

The presence of LN poses additional risk during pregnancy. Active LN has been associated with poor fetal outcomes, including intrauterine growth restriction, miscarriage, preterm delivery, and intrauterine death.[10] In women with SLE, pregnancy itself may trigger a flare of LN, thereby exacerbating levels of proteinuria and hypertension and accelerating further renal dysfunction. While all pregnant SLE patients are at an increased risk for developing preeclampsia, pregnant patients with LN are up to 8.8 times more likely to develop preeclampsia as compared to those without LN.[11] Chronic kidney disease, thrombocytopenia, and decreasing complement levels have all been associated with increased risk of preeclampsia in this population.[12] Due to the excess maternal and fetal risk associated with active LN in pregnancy, patients are advised to wait at least six to nine months following a LN flare before conceiving. If serum creatinine is markedly elevated, it is recommended to consider avoiding pregnancy altogether.[10]

First line induction therapy for LN Class III, IV, or V includes high dose corticosteroids in addition to immunosuppression with either cyclophosphamide or mycophenolate mofetil.[8,10] These medications, however, are not safe in the pregnant state. Therefore, alternatives must be used for pregnant women, and may not be as effective. Pregnancy-safe treatment options include azathioprine, hydroxychloroquine, and corticosteroids.[7] Tacrolimus may be helpful with proteinuria and is considered safe in pregnancy, with close monitoring of blood pressure. Newer approved adjunctive therapies for LN induction such as belimumab

and voclosporin have minimal safety data in pregnancy and should currently be avoided. Cyclophosphamide may be reserved for life-threatening or organ-threatening disease in the second and third trimesters. Rituximab and IV immunoglobulin may also be considered as last resorts, though these treatments are not proven to be as effective for LN. When possible, it is recommended that steroid-sparing medication be utilized during pregnancy, as high doses of steroids may also contribute to excess maternal and fetal risk.[13] Additionally, it is recommended that all pregnant patients with SLE, with or without kidney disease, be placed on low-dose aspirin to reduce the risk of preeclampsia.[14]

Because treatment options are limited in pregnancy, and because active disease may increase the risk for pregnancy complications, it is advised that SLE and LN be well-controlled for months prior to conceiving, on pregnancy-compatible medications. If disease activity is unable to be controlled on these medications alone, then pregnancy is not recommended.[13] Counseling prior to pregnancy is therefore crucial to optimize maternal and fetal outcomes.

Once becoming pregnant, it is recommended that LN patients undergo frequent monitoring throughout pregnancy of their serum creatinine, urine protein level, electrolytes, and blood pressure. Intermittent evaluation of lupus markers, including anti-dsDNA and complement levels may also be helpful; however, these markers naturally rise during pregnancy, so interpreting their trends is often more useful than the absolute values.[10,15]

Differentiating between Lupus Nephritis and Preeclampsia

As both preeclampsia and LN during pregnancy may present with hypertension, kidney injury, and proteinuria, distinguishing between the two clinical scenarios often poses a diagnostic challenge. This is further complicated by their possible coexistence. As in our patient, LN and preeclampsia often occur together; in fact, LN can increase the risk of superimposed preeclampsia by nearly 10 times.[11] Because the treatments differ, however, differentiating between them is imperative to quality care.

The timeline and history of symptoms may be helpful in identifying the primary disease process. Classically, preeclampsia is defined as occurring after 20 weeks of gestation.[10] Therefore, if a pregnant SLE patient experiences increased proteinuria and hypertension prior to 20 weeks of gestation, it is more likely due to renal disease rather than preeclampsia. However, there have been reports of preeclampsia occurring prior to 20 weeks, namely in individuals with trophoblastic disease or antiphospholipid syndrome, although also seen rarely in otherwise healthy individuals.[16] Kidney biopsy may be considered for these atypical cases to differentiate between new glomerular disease and preeclampsia, but this is a controversial procedure in the setting of pregnancy and elevated blood pressures.[10] Upon reflection of our case, it is possible that our patient exhibited signs of preeclampsia as early as 16

weeks' gestation, although her clinical presentation could also have been entirely attributed to active kidney disease alone.

Following 20 weeks, discriminating between LN and preeclampsia becomes progressively complicated. Analyzing the trend of lupus markers may be of assistance; if there is a rise in anti-dsDNA and/or drop in complement levels, a LN flare may be considered more likely, although on their own, these markers can be difficult to interpret in the context of pregnancy.[15] If the patient experiences other symptoms of an SLE flare, such as joint pain, swelling, rashes, oral ulcerations, or fever, this may help to support a diagnosis of active SLE and LN. Finally, the presence of isolated hematuria or urinary casts may also suggest LN over preeclampsia.[10]

The clinical utility of measuring serum uric acid levels is unclear, but has also been posed as a potential diagnostic tool in this setting. Increased levels are associated with preeclampsia; however, they are also seen in the setting of kidney disease, and may also rise prior to 20 weeks' gestation, possibly confounding the clinical picture.[17]

With any instance of worsening hypertension, proteinuria, edema, or electrolyte disturbances past 20 weeks of pregnancy, it is important to keep preeclampsia on the differential. The reverse also holds true; if preeclampsia is initially suspected in a pregnant patient with SLE, LN should also be on the differential, regardless of history. One study found that for over half of SLE patients thought to have preeclampsia with subsequent preterm delivery, a diagnosis of lupus nephritis was not properly considered, according to EHR records.[18]

Conclusion

Our case emphasizes the high-risk nature of a pregnancy with active LN, which creates significant risk both to the mother and the fetus. Pre-pregnancy counseling and pregnancy-safe medical management prior to conception are highly encouraged to optimize pregnancy outcomes.

We also highlight the spectrum of disease between lupus nephritis and preeclampsia, and the resulting challenges with both diagnoses. Thoughtful consideration of both diagnoses in pregnant patients with SLE can lead to more rapid and appropriate management, thereby minimizing both obstetric and fetal harm.

Corresponding author:
Chelsey J. F. Smith
Division of Rheumatology, Allergy and Immunology
University of California
San Diego, USA
Email: cjs018@health.ucsd.edu

Conflict of interest statement:
None

Acknowledgements:
None

Funding
None.

References:

1. Cervera R, Khamashta MA, Font J, et al. Morbidity and Mortality in Systemic Lupus Erythematosus During a 10-Year Period. *Medicine*. 2003;82(5):299-308. doi:10.1097/01.md.0000091181.93122.55

2. Musa R, Brent LH, Qurie A. Lupus Nephritis. StatPearls. Published January 2020. https://www.ncbi.nlm.nih.gov/books/NBK499817/

3. Stanhope TJ, White WM, Moder KG, Smyth A, Garovic VD. Obstetric Nephrology: Lupus and Lupus Nephritis in Pregnancy. *Clinical Journal of the American Society of Nephrology*. 2012;7(12):2089-2099. doi:10.2215/CJN.12441211

4. Wagner LK. Diagnosis and Management of Preeclampsia. *American Family Physician*. 2004;70(12):2317-2324. https://www.aafp.org/pubs/afp/issues/2004/1215/p2317.html

5. Pankiewicz K, Szczerba E, Maciejewski T, Fijałkowska A. Non-obstetric complications in preeclampsia. *Menopausal Review*. 2019;18(2). doi:10.5114/pm.2019.85785

6. Varnier N, Brown MA, Reynolds M, et al. Indications for delivery in pre-eclampsia. *Pregnancy Hypertension*. 2018;11:12-17. doi:10.1016/j.preghy.2017.11.004

7. Saxena R, Mahajan T, Mohan C. Lupus nephritis: current update. *Arthritis Research & Therapy*. 2011;13(5):240. doi:10.1186/ar3378

8. Gasparotto M, Gatto M, Binda V, Doria A, Moroni G. Lupus nephritis: clinical presentations and outcomes in the 21st century. *Rheumatology (Oxford, England)*. 2020;59(Suppl 5):v39-v51. doi:10.1093/rheumatology/keaa381

9. Tektonidou MG, Dasgupta A, Ward MM. Risk of End-Stage Renal Disease in Patients With Lupus Nephritis, 1971-2015: A Systematic Review and Bayesian Meta-Analysis. *Arthritis & Rheumatology*. 2016;68(6):1432-1441. doi:10.1002/art.39594

10. Lightstone L, Hladunewich MA. Lupus Nephritis and Pregnancy: Concerns and Management. *Seminars in Nephrology*. 2017;37(4):347-353. doi:10.1016/j.semnephrol.2017.05.006

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

12. Chakravarty EF, Colón I, Langen ES, et al. Factors that predict prematurity and preeclampsia in pregnancies that are complicated by systemic lupus erythematosus. *American Journal of Obstetrics and Gynecology*. 2005;192(6):1897-1904. doi:10.1016/j.ajog.2005.02.063

13. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the

Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. *Arthritis Care & Research*. 2020;72(4):461-488. doi:10.1002/acr.24130

14. Davidson KW, Barry MJ, Mangione CM, et al. Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality. *JAMA*. 2021;326(12):1186. doi:10.1001/jama.2021.14781
15. Buyon JP, Cronstein BN, Morris M, Tanner M, Weissmann G. Serum complement values (C3 and C4) to differentiate between systemic lupus activity and pre-eclampsia. *The American Journal of Medicine*. 1986;81(2):194-200. doi:10.1016/0002-9343(86)90251-2
16. Tanaka M, Tsujimoto Y, Goto K, et al. Preeclampsia before 20 weeks of gestation: a case report and review of the literature. *CEN Case Reports*. 2014;4(1):55-60. doi:10.1007/s13730-014-0140-3
17. Bainbridge SA, Roberts JM. Uric Acid as a Pathogenic Factor in Preeclampsia. *Placenta*. 2008;29:67-72. doi:10.1016/j.placenta.2007.11.001
18. Falasinnu T, Simard JF. 283 Supporting evidence to differentiate preeclampsia from nephritis in lupus pregnancy: an electronic health records review. *Lupus Science & Medicine*. 2019;6(Suppl 1). doi:10.1136/lupus-2019-lsm.283