

Early Onset Pre-Eclampsia with Nephrotic Range Proteinuria as the Initial Manifestation of *Lupus Nephritis*

Report of three cases

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تسمم الحمل المبكر مع بيلة بروتينية كلوية كمظهر مبدئي لالتهاب الكلية الذئبي تقرير ثلاث حالات

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ABSTRACT: Early onset pre-eclampsia (pre-eclampsia at less than 34 gestational weeks) is a severe form of pre-eclampsia; in addition, some women may also develop nephrotic range proteinuria. *De novo* diagnosis of *lupus nephritis* (LN) in pregnancy is challenging as it may present with features similar to commonly occurring pre-eclampsia. We report three cases of early onset pre-eclampsia with nephrotic range proteinuria and subsequent diagnosis of LN at the Women and Children hospital attached to Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, between 2014 and 2017. These cases highlight the need for further evaluation of the association between nephrotic-range proteinuria and early onset pre-eclampsia. The index of suspicion for underlying LN of these type of cases should be high. Earlier detection of LN will prompt better management that can avert or delay short- and long-term morbidity.

Keywords: Lupus Nephritis; Pre-Eclampsia; Nephrotic Syndrome; Proteinuria; Case Reports; India.

المخلص: تسمم الحمل ذو البداية المبكرة (تسمم الحمل قبل الاسبوع 34 من الحمل) هو شكل حاد من تسمم الحمل. الى جانب ذلك ، قد تصاب بعض هؤلاء النسوة بروتينية كلوية أيضا. التشخيص الجديد لالتهاب الكلية الذئبي أثناء الحمل يعتبر تحديا لأنه قد يظهر بصفات مماثلة لتسمم الحمل الأكثر شيوعا. نورد هنا ثلاث حالات من تسمم الحمل المبكر مصحوبة ببيلة بروتينية كلوية والتي شخصت لاحقا كالتهاب كلية ذئبي في مستشفى النساء والأطفال الملحق بمعهد جواهرلال للدراسات العليا في التعليم الطبي والبحث، بودوتشيري ، الهند بين الأعوام 2014 و 2017. تسلط هذه السلسلة من الحالات الضوء على الحاجة إلى مزيد من التقييم للعلاقة بين البيلة البروتينية الكلوية وبين تسمم الحمل المبكر. يجب أن يكون مؤشر الشك بوجود ضمني لالتهاب الكلية الذئبي في مثل هذا النوع من الحالات عاليا. ان الكشف المبكر عن التهاب الكلية الذئبي سوف يدفع إلى رعاية أفضل يمكن معها تجنب أو تأخير الإعتلالات ذات الأجل القصيرة والطويلة.

الكلمات المفتاحية: التهاب الكلية الذئبي؛ تسمم الحمل؛ متلازمة كلوية؛ بيلة بروتينية؛ تقارير حالة؛ الهند.

PRE-ECLAMPSIA IS CHARACTERISED BY ABNORMAL placentation and endothelial dysfunction secondary to an imbalance of angiogenic factors occurring early in pregnancy. Early onset pre-eclampsia that develops before 34 gestational weeks represents a severe form of the hypertensive disorders during pregnancy. The presence of significant proteinuria is regarded as one of the diagnostic criteria distinguishing pre eclampsia from gestational hypertension.¹ Systemic *lupus erythematosus* (SLE) is a multi-systemic autoimmune disorder affecting mostly women of child-bearing age. Nearly two-thirds of the women affected have *lupus nephritis* (LN) and usually have nephrotic-range proteinuria (>3.5 g/day) with active urinary sediments.^{2,3} Pre-eclampsia occurs in 10–15% of pregnant women with SLE and is more frequent in those with LN (20–40%).^{4,5}

Women with SLE are reported to have an increased risk of early onset pre-eclampsia. Owing to the similar presentation of pre-eclampsia and LN, it is possible to overestimate this risk due to misclassification of cases.⁴

Nephrotic-range proteinuria complicates 0.32% of pregnancies, of which pre-eclampsia contributes to 0.19%.^{6,7} In women with LN where nephrotic-range proteinuria is a criterion for diagnosis, differentiating new-onset SLE or LN in pregnancy from pre-eclampsia remains a challenge. These cases should be met with a high index of suspicion and require further evaluation with autoantibody screening and a possible renal biopsy for diagnosis.⁸ We report three female patients who presented with early onset pre-eclampsia and nephrotic-range proteinuria and were subsequently diagnosed with LN.

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Table 1: Summary of three cases with early onset pre-eclampsia and *lupus* nephritis

Characteristics	Case 1	Case 2	Case 3
Age in years	26	30	31
Parity index	G1	G4, A3	G2, PL1
Gestational age at presentation in weeks	26	30	29
24 hour urinary protein in mg/day	3,540	4,020	3,800
Serum albumin in mg/dL	2.1	1.9	2.3
Highest serum creatinine in mg/dL	3.4	1.9	2.1
Platelet count in $\times 10^5/\text{mm}^3$	2.05	2.53	2.37
Other obstetric complication	None	None	IUGR
Antibody profile	ANA positive	ANA and dsDNA positive	ANA and dsDNA positive
Timing of renal biopsy	Antenatal (28 gestational weeks)	Postnatal	Postnatal
Renal biopsy finding	Class-IV LN	Class-IV-V LN	Class-IV LN
Treatment received	HCQ and prednisolone	HCQ and prednisolone	HCQ and prednisolone

G = gravida; A = abortion; PL = preterm and living; IUGR = intrauterine growth restriction; ANA = antinuclear antibody; dsDNA = double stranded DNA; LN = *lupus* nephritis; HCQ = hydroxychloroquine.

Case Reports

All three cases presented at Women and Children hospital attached to Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, between 2014–2017 with early onset of pre-eclampsia between 26 and 30 gestational weeks. All cases had nephrotic-range proteinuria and hypoalbuminaemia. Urinary sediments or haematuria were not noted and ultrasound examination showed normal sized kidneys at presentation. None had any clinical symptoms suggestive of any connective tissue disorders. On evaluation, all patients were found to be antinuclear antibody (ANA) positive with low complement levels (C3 and C4). During the antenatal period, all patients were monitored for blood pressure, urine output, renal function and fetal monitoring with ultrasound biometry and non-stress tests [Table 1]. Labour and delivery details were gathered for the three cases [Table 2].

All information was retrieved from medical records without collecting any identifying details, therefore, ethical approval was not sought. However, all patients signed written informed consent forms.

Table 2: Labour and delivery details of three cases with early onset pre-eclampsia and *lupus* nephritis

Variable	Case 1	Case 2	Case 3
Gestational age at delivery in weeks*	34	33	31
Neonatal outcome	Live born	Live born	Stillborn
Birth weight in g	2,100	1,900	980
Apgar score at 5 minutes	9	9	-
Neonatal complications	Low birth weight	Low birth weight and NICU admission	-

NICU = neonatal intensive care unit.

*All labour was induced and mode of delivery was vaginal.

Case One

A 26-year-old *primigravida* woman at 26 gestational weeks presented to the emergency obstetric services in 2014 with a maximum blood pressure of 160/100 mmHg and spot urine protein of 3+; thus, she was diagnosed with early onset pre-eclampsia. She was started on nifedipine 10 mg three times per day. Her laboratory tests revealed raised serum creatinine (1.7 mg/dL) and 24 hour urinary protein of 3,540 mg/day. In view of her rapidly worsening renal function (highest serum creatinine level was 3.4 mg/dL) and nephrotic-range proteinuria, a renal biopsy was performed at 28 gestational weeks which revealed class-IV LN. She was ANA positive and was started on prednisolone (60 mg/day) and hydroxychloroquine (200 mg/day). At the time of delivery, her creatinine levels dropped to 1.4 mg/dL. Labour was induced at 34 gestational weeks in view of the severe early onset pre-eclampsia. She delivered a baby boy weighing 2,100 g with an Apgar score of 9 at 5 minutes. Her post-partum blood pressure returned to normal by the tenth day and her serum creatinine level at discharge was 1.1 mg/dL.

Case Two

A 30-year-old woman with three previous abortions was referred, to the emergency services in 2015, at 30 gestational weeks with early onset pre-eclampsia. She had a blood pressure of 150/90 mmHg and spot urine protein of 4+ on admission and was on nifedipine 30 mg/day. She was started on prednisolone 40 mg/day in view of suspected LN based on positive ANA and dsDNA results. Her blood pressure remained normal and her creatinine levels were stable (1.2–1.4 mg/dL). She was induced at 33 gestational weeks with prostaglandin E2 gel and delivered a baby girl weighing 1,900 g with an Apgar score of 9 at 5 minutes. Her blood pressure

was controlled with nifedipine 30 mg/day. In view of positive autoantibody screening, raised creatinine levels (1.9 mg/dL) and nephrotic-range proteinuria, a renal biopsy was done in the postnatal period which was reported as class-IV and -V LN. Her creatinine level at discharge on the fourteenth postnatal day was 1.1 mg/dL. At discharge, she was on prednisolone, hydroxychloroquine and nifedipine (60, 200 and 30 mg/day, respectively).

Case Three

A 31-year-old multiparous woman with chronic hypertension was admitted to the antenatal wards in 2016, at 29 gestational weeks for evaluation of superimposed pre-eclampsia. She was on alpha-methyldopa 250 mg three times a day and to control her high blood pressure, nifedipine 10 mg three times a day was added. Investigations revealed normal liver function, serum creatinine (1.22 mg/dL), platelet count ($2.05 \times 10^5/\text{mm}^3$) and a normal peripheral smear. Her 24-hour urine protein excretion was 3,800 mg/day. At 30 gestational weeks and 6 days she developed nausea and vomiting and had a blood pressure of 190/110 mmHg. After consulting a neonatologist, a caesarean section was ruled out due to the neonate's growth restriction and prematurity. Labour was induced with misoprostol (prostaglandin E1) and resulted in intrapartum stillbirth. Her autoantibody screen was positive and in view of nephrotic-range proteinuria with persistent renal dysfunction (serum creatinine levels: 1.8–2.1 mg/dL), a renal biopsy was performed in the postnatal period which revealed class-IV LN.

Discussion

Pregnancy leads to changes in the immune system and hormonal profile to promote immune tolerance to sustain pregnancy. Diagnosis of new onset SLE presenting as LN during pregnancy is challenging as it simulates the commonly occurring pre-eclampsia during this period. Presence of medical disorders, especially those associated with autoimmune pathology or vasculopathy are considered risk factors of pre-eclampsia; recent studies have reported similarities in pathogenesis of pre-eclampsia and SLE.^{9–11}

The elevated levels of interferon- α found in SLE have anti-angiogenic and anti-proliferative properties that lead to endothelial cell dysfunction mimicking the endothelial-*milieu* as in pre-eclamptic women.¹² Similar to pre-eclampsia, angiogenic factors like vascular endothelial growth factor and placental growth factor decrease and levels of anti-angiogenic factors such as soluble fms-like tyrosine kinase 1 increase in

those with active *lupus* and LN.^{13,14} Due to a multi-system involvement similar to *lupus*, pre-eclampsia might represent the initial manifestation of an autoimmune disorder.

Studies have found that pregnant women with SLE have worse manifestations than pregnant women without SLE and due to the hormonal changes and the increase in cytokines during pregnancy this disease may only be diagnosed for the first time during pregnancy.^{9,10} Most women with new-onset SLE are found to have a lower frequency of common symptoms suggestive of *lupus* at presentation, such as fever, arthritis, arthralgia, alopecia, oral ulcers and/or hypocomplementaemia, compared to those diagnosed in a non-pregnant state.^{2,3} Thrombocytopenia is reported to occur in 10–40% of cases of new-onset *lupus* but in all present cases platelet counts were normal.⁵ However, more women have nephrotic syndrome when diagnosed during pregnancy making it difficult to differentiate from pre-eclampsia, which complicates pregnancy.^{2,5}

Indications for a renal biopsy in pregnant women include unexplained rapidly progressive renal failure and symptomatic nephrotic syndrome; it may also be used as a guide in managing patients with LN.¹⁵ As there is a risk of maternal-fetal morbidity, any procedure is usually deferred until the post-partum period, unless it requires management before delivery. The risk of various complications following a renal biopsy is higher during pregnancy compared to the post-partum period (7% versus 1%).¹⁶ The presence of a *gravid* uterus makes it difficult for patients to lie prone so alternative positions, such as sitting upright or lying in the lateral *decubitus* position, may be preferred.^{15,16} In the current case report, due to rapidly deteriorating renal function, a biopsy was performed at 28 gestational weeks in one case, whereas it was deferred until delivery in the other two.

Miyamoto *et al.* found eight out of 11 patients diagnosed with new-onset SLE during pregnancy had pre-eclampsia upon initial presentation, while three developed pre-eclampsia after SLE was diagnosed.³ All cases except one, who developed SLE post-partum, had pre-eclampsia detected in the third trimester of pregnancy. Termination of pregnancy for treating pre-eclampsia resulted in premature births in six out of seven cases. Renal haemodynamic changes along with the hormonal changes of pregnancy may accelerate the decline in renal function and worsen hypertension and proteinuria, as was seen in the current case report. Unless the index of suspicion is high, this can be misinterpreted as worsening pre-eclampsia resulting in iatrogenic premature birth, especially if no prenatal or early pregnancy reports of normal renal function are available. Zao *et al.*'s study on new-onset SLE in pregnancy observed that two-thirds (68.8%) of the patients diagn-

osed in pregnancy had LN; this was a much higher rate than among those who were not pregnant.² Women who developed LN had nephrotic-range proteinuria and low serum albumin levels compared to non-pregnant control cases with SLE.² All three of the current patients who presented with pre-eclampsia had nephrotic-range proteinuria and serum hypoalbuminaemia. All current patients had autoantibodies present and underwent a renal biopsy according to the American College of Rheumatology guidelines, two cases during the post-natal period and one case during the antenatal period, confirming the diagnosis of LN.⁸

Conclusion

The index of suspicion of underlying LN should be high upon presentation of early-onset pre-eclampsia with nephrotic-range proteinuria and hypoalbuminaemia. Autoantibody screening should be performed and if positive, a renal biopsy may be considered. Early detection of LN would lead to better management that can avert or delay short- and long-term morbidity.

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