INTERNAL MEDICINE

□ CASE REPORT □

Pregnancy Is a Risk Factor for Secondary Focal Segmental Glomerulosclerosis in Women with a History of Very Low Birth Weight

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Abstract

Low birth weight (LBW) has been known to increase the susceptibility to renal injury in adulthood. A 26-year-old woman developed proteinuria in early pregnancy; she had been born with very LBW. The clinical course was progressive, and an emergency Caesarean section was performed at 36 weeks due to acute kidney injury. A renal biopsy provided a diagnosis of post-adaptive focal segmental glomerulosclerosis. Increased demand for glomerular filtration during early pregnancy appeared to have initiated the renal injury. This report highlights the fact that pregnancy might be a risk factor for renal injury in women born with LBW.

Key words: low birth weight, focal segmental glomerulosclerosis, post-adaptive, pregnancy, glomerular hyperfiltration, two-hit theory

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Introduction

'The fetal origins hypothesis of adult disease' was proposed by David Barker. It states that impaired fetal development increases the susceptibility to chronic disease in adulthood (1). Later studies have reported that low birth weight (LBW) was associated with a reduced nephron number; this reduction results in an inadequate renal reserve capacity. As the reserve capacity is necessary to compensate for extra load, LBW individuals are susceptible to subsequent renal injury (2, 3). We herein report the case of a woman born with very LBW who developed post-adaptive focal segmental glomerulosclerosis (FSGS) and renal insufficiency during pregnancy. This patient's renal system was unable to compensate for physiological glomerular hyperfiltration during pregnancy, likely due to impaired nephrogenesis because of LBW.

Case Report

A 26-year-old woman who had delivered her first baby 4 months previously was referred for evaluation of postpartum persistent proteinuria and mild renal insufficiency. The patient had been born prematurely at 26 weeks, weighing 630 g. Apart from suffering from retinopathy of prematurity, she had been generally healthy. She had been diagnosed with Basedow's disease three years earlier, but it was well controlled with medication. She had no history of proteinuria, hypertension, or renal disease prior to the pregnancy.

In her first trimester, she was found to have mild proteinuria (1+ on a urinary dipstick) with normal blood pressure. Her blood pressure was mildly elevated close to 140 mmHg after 20 weeks of gestation. At 34 weeks, her urinary protein excretion was 1.84 g/day, and her serum creatinine level had increased from 0.60 mg/dL to 1.06 mg/dL, although her blood pressure stabilized at 130-140/80-90 mmHg. After 2 weeks, her serum creatinine continued to increase to 1.91 mg/dL and urinary protein excretion to 2.08 g/day. An emer-

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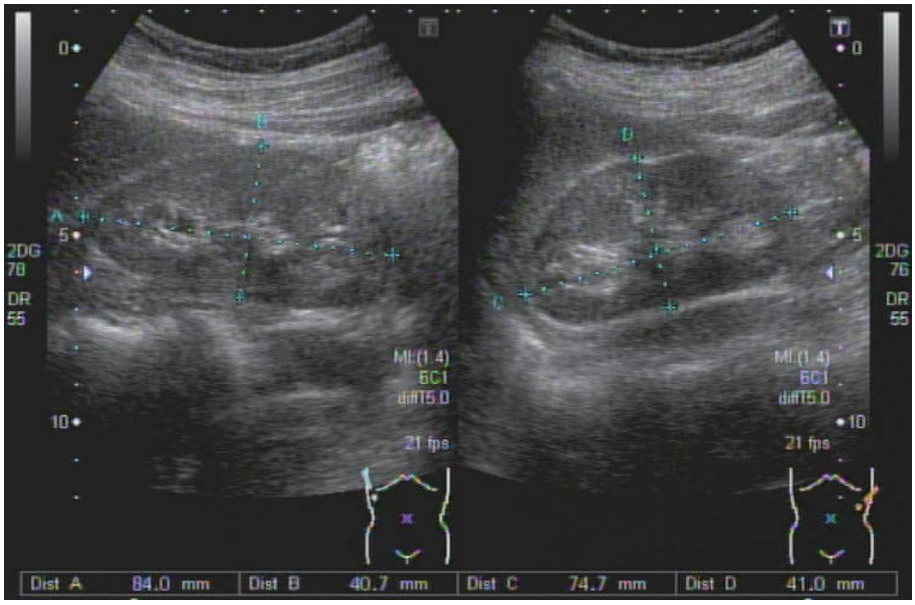

Figure 1. **Renal ultrasonography findings. Both kidneys are small but normally shaped.**

gency Caesarean section was performed at 36 weeks due to acute kidney injury. She delivered a healthy male baby with a birth weight of 2,036 g, which was in the 10th percentile for the gestational age. Her renal function gradually improved to 0.87 mg/dL of serum creatinine 4 months after delivery; however, a urinary protein excretion of about 1 g/gCre persisted, prompting a nephrology consultation.

Physical examination revealed a blood pressure of 117/78 mmHg, a pulse rate of 76 beats/minute, a height of 149 cm, a weight of 46 kg, and a body mass index (BMI) of 20.7 kg/m^2. There was no peripheral edema. A urinalysis revealed a protein level of 2+ and trace blood without cellular casts. The 24-h urine protein excretion was 0.71 g/day, and her renal function was slightly impaired (serum creatinine: 0.89 mg/dL, estimated glomerular filtration rate: 69 mL/min/1.73 m^2). Her serum albumin was 3.7 g/dL and uric acid 4.5 mg/dL. A complete blood count and clotting and liver function test results were normal. Her HbA1c level was 5.9%. Connective tissue disease screening was negative, and serum complement levels were in the normal range. Ultrasonography showed that her kidneys were small, namely the right kidney being 8.7 cm long and the left one being 7.5 cm long, with an almost normal appearance (Fig. 1).

A percutaneous renal biopsy was performed on her left kidney at 10 months postpartum. Two biopsy specimens of the corticomedullary tissue, including the renal capsule, were obtained (Fig. 2a). Eighteen glomeruli were seen on light microscopy, four of which were globally sclerosed. Most glomeruli were enlarged (Fig. 2b), and the largest glomerulus reached a diameter of 308 μm. One glomerulus showed perihilar segmental sclerosis with adhesion to the Bowman's capsule (Fig. 2c). Focal interstitial fibrosis and tubular atrophy were seen; the arteries and arterioles were unremarkable. Immunofluorescence studies were all negative, and electron microscopy showed mild segmental foot process effacement (Fig. 2d). Electron-dense deposits, endothelial cell swelling, double contour of glomerular basement membrane (GBM), and mesangial interposition were not present in the glomeruli. These biopsy findings supported a diagnosis of post-adaptive FSGS.

We proposed renin-angiotensin-aldosterone system blockade therapy in order to improve the glomerular hyperfiltration and proteinuria, but the patient refused medical treatment. Two years after the renal biopsy, her proteinuria and mild renal insufficiency persisted.

Discussion

Several morphometric analyses have demonstrated that LBW is associated with a small kidney size, low nephron number, and glomerulomegaly (4-6). In general, the left kidney is slightly larger, at 11 to 12 cm in length, than the right (7). Some cohorts of individuals born with LBW have shown small kidney size, particularly pronounced in the left kidney, although the mechanisms leading to this lateralization are unknown (6, 8). The present case had small kidneys, with the left kidney smaller than the right, despite a relatively preserved renal function. She also had a larger mean glomerular diameter of 232±45 μm than the previously published mean diameter of 168±12 μm for normal adults (9). Therefore, she was likely to have impaired nephrogenesis associated with premature birth and very LBW.

The patient developed FSGS during her pregnancy. Several reports indicate that FSGS may occur *de novo* during pregnancy with preeclampsia (10, 11), so we must consider the possibility of preeclampsia-associated FSGS. Preeclampsia is defined as new-onset hypertension (≥140/90 mmHg on 2 separate occasions) and proteinuria (≥0.3 g/day) after 20 weeks of gestation (12). The characteristic pathologic feature of preeclampsia is prominent glomerular endothelial

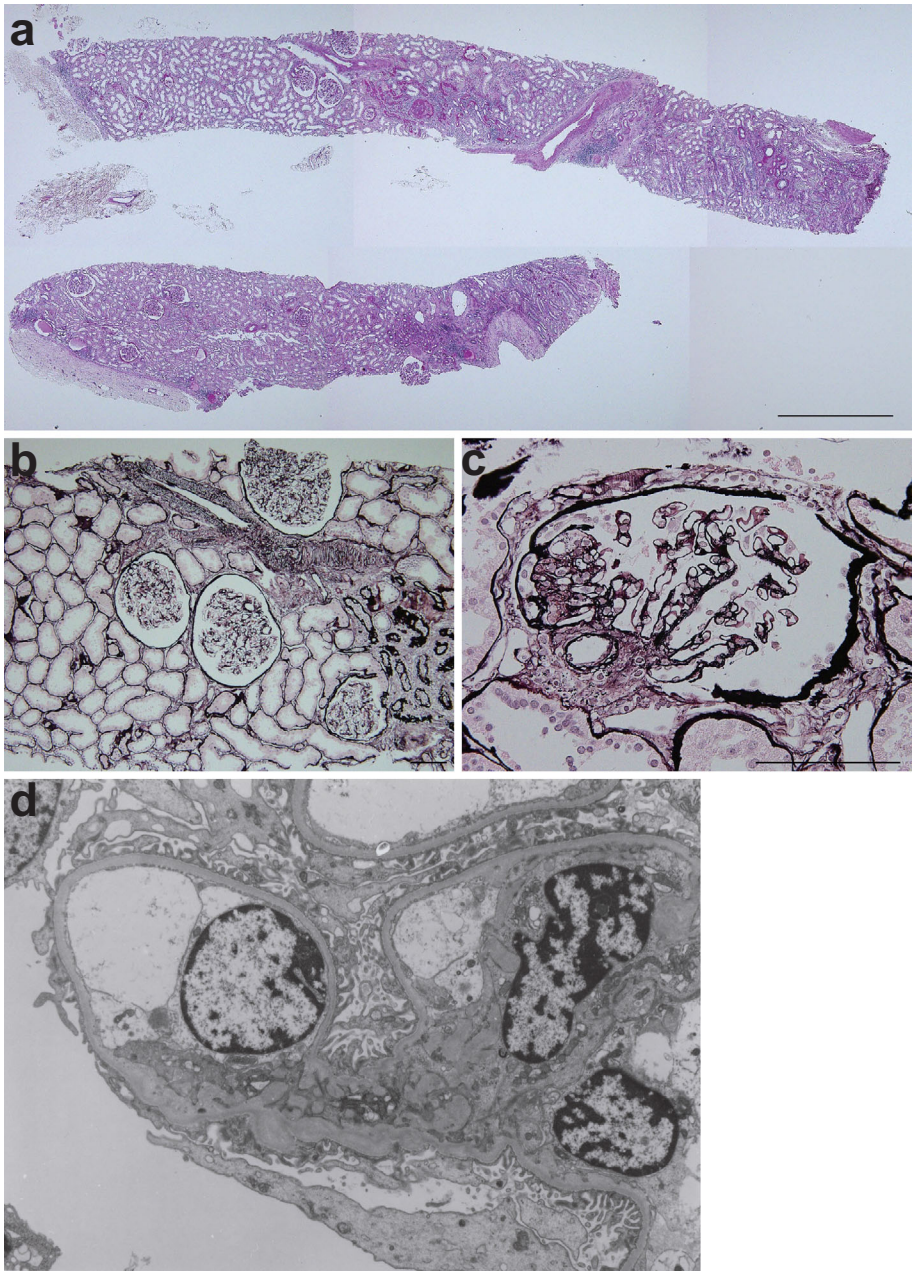

Figure 2. **The renal biopsy findings are consistent with post-adaptive focal segmental glomerulosclerosis (FSGS). (a) The length of the renal cortex appears to be short (periodic acid-Schiff stain, Scale bar=1 mm). (b) The glomeruli are moderately enlarged (periodic acid-methenamine-silver stain, Scale bar=100 μm). (c) The glomerulus shows perihilar FSGS (periodic acid-methenamine-silver stain, Scale bar=100 μm). (d) Electron microscopy shows the relatively-preserved podocyte foot processes. Electron-dense deposits and endothelial cell swelling are not present (original magnification, × 5,750).**

cell swelling, termed "glomerular endotheliosis" (13). Endotheliosis tends to disappear within a few weeks after delivery, whereas double contour of GBM, mesangial interposition, and endothelial cell vacuolation may occur in the healing stage (14). The present case had an early onset of proteinuria before 20 weeks gestation, and persistent hypertension exceeding 140/90 mmHg was absent during her pregnancy. Furthermore, the typical pathologic findings of preeclampsia described above were not obtained. These results suggested that FSGS seemed unrelated to the preeclampsia in this patient.

The absence of full nephrotic syndrome, pathological findings of perihilar FSGS, glomerulomegaly, and a relatively preserved foot process led to the diagnosis of post-adaptive FSGS (15). Post-adaptive FSGS results from the structural and functional adaptations to nephron loss and glomerular hypertension. Representative conditions associated with post-adaptive FSGS include unilateral renal agenesis, surgical renal ablation, advanced renal diseases with reduced numbers of functioning nephrons, obesity, increased

lean muscle mass, hypertensive arterio-nephrosclerosis, and cyanotic congenital heart disease (16).

Recently, LBW has also been recognized as a contributing factor to post-adaptive FSGS. Although the exact mechanism is uncertain, the two-hit theory seems to be the most widely accepted hypothesis (2). In an individual born with LBW, a congenital deficit of nephrons results in compensatory hyperfiltration of the remaining glomeruli, leading to an increased susceptibility to additional injury. Therefore, a 'second hit' exposure could trigger the initiation of renal injury and development of post-adaptive FSGS. Hodgin et al. reported a series of six patients with a history of very LBW who developed post-adaptive FSGS (3). Their mean age was 32 years (range: 15 to 53). Five cases had an elevated BMI over 25 kg/m^2, and 1 of them was obese, with a BMI of 31.9 kg/m^2. The sixth case had incidental IgA nephropathy. The authors suspected that obesity or primary glomerulonephritis might have acted as a second hit. Since then, several reports have shown that obesity can accelerate the post-adaptive FSGS in individuals born with LBW (17, 18); however, whether or not pregnancy can act as a second hit is unknown.

Pregnancy is characterized by a physiological hyperdynamic state. The glomerular filtration rate (GFR) rises as early as 4 weeks into gestation and peaks at 150% above prepregnancy levels by approximately 9 weeks' gestation. The GFR then remains elevated throughout pregnancy, returning to normal 1 month postpartum (19). Glomerular hyperfiltration during pregnancy generally produces no ill consequences due to renal adaptation (20). In the present case, proteinuria appeared around the time of the increasing GFR during early pregnancy, and no other known conditions that could cause post-adaptive FSGS were observed. We therefore speculated that physiological glomerular hyperfiltration due to pregnancy might have overloaded the impaired nephrogenesis associated with LBW and triggered the development of post-adaptive FSGS by acting as a 'second hit.'

Advances in neonatal care have led to an improved survival among infants born prematurely, and the prevalence of LBW in infants has been steadily rising over the last 30 years. Japan had the highest increase in the rate of LBW infants worldwide, from 6.3% in 1990 to 9.6% in 2011, and now the proportion of LBW infants far exceeds the OECD average of 6.7% (21). An increasing number of surviving LBW women are now reaching reproductive age. Therefore, it is important to recognize pregnancy as a triggering event of renal injury in women born with LBW and closely monitor their renal function during pregnancy and after delivery.

To our knowledge, this is the first report describing a case where physiological glomerular hyperfiltration during pregnancy likely triggered and accelerated the development of post-adaptive FSGS in a woman born with LBW. We need to pay attention to the birth history in women developing gestational proteinuria and maintain close follow-up for signs of initiation of renal injury until after delivery.

The authors state that they have no Conflict of Interest (COI).

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