

Diabetic nephropathy in pregnancy: Report of two cases progressing to end-stage renal disease within one year postpartum

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ARTICLE INFO

Keywords:

Type 1 diabetes mellitus
Diabetic nephropathy
End-stage renal disease
Preterm premature rupture of membranes
Hemodialysis
Peritoneal dialysis
Case report

ABSTRACT

Background: Diabetes mellitus is a leading cause of nephropathy and end-stage renal disease. However, diabetic nephropathy during pregnancy in patients with normal glomerular filtration rate and subsequent progression to end-stage renal disease has not been well studied.

Cases: This report presents two patients with poorly controlled type 1 diabetes mellitus who had diabetic nephropathy with preserved estimated glomerular filtration rate (Case 1: 117 mL/min/1.73m²; Case 2: 79 mL/min/1.73m²) and shared a similar clinical course, with glomerular filtration rates decreasing by approximately one-half during pregnancy and progression to end-stage renal disease within the first year postpartum. Both women had a long history of type 1 diabetes: 18 years and 24 years for case 1 and case 2 respectively. The first patient's course of pregnancy was complicated by difficult-to-control blood glucose and hypertension with subsequent preeclampsia. The second patient's course of pregnancy was complicated by difficult-to-control blood sugars and preterm labor resulting in classical cesarean delivery at 24 weeks. Both patients had renal biopsies shortly after delivery as their renal function continued to worsen postpartum. Both kidney biopsies demonstrated advanced diabetic nephropathy changes and ultimately required chronic renal replacement therapy within 7–9 months postpartum.

Conclusion: Comprehensive family planning discussions with women who have diabetic nephropathy should include the risks of renal disease progression, even in those patients with preserved renal function at the time of conception.

1. Introduction

Diabetic nephropathy (DN) is a well-known micro-vascular complication of type 1 diabetes (T1DM) and a major cause of end-stage renal disease (ESRD) [1–3]. The incidence of pregnancy-associated complications in patients with DN is well established, but the rate of DN progression after pregnancy has not been adequately studied [4]. Although a definitive diagnosis of DN can be made only with a renal biopsy, DN can be identified clinically with a persistent urinary albumin-to-creatinine ratio ≥ 30 mg/gCr and/or sustained reduction in GFR < 60 mL/min along with the assessment of clinical features, such as diabetes duration, diabetic control, and presence of microvascular damage such as diabetic retinopathy [15]. This report presents two cases of young women with uncontrolled T1DM and evidence of DN but

relatively preserved renal function before pregnancy. Both suffered progressive renal decline requiring chronic renal replacement therapy within the first one year postpartum.

2. Case 1

A 36-year-old multiparous Hispanic woman with T1DM (diagnosed at age 18) and hypertension presented to a nephrology clinic at 12 weeks of gestation after she was found to have nephrotic range proteinuria of 7.6 g, and measured creatinine clearance (CCr) of 104 mL/min on 24-h urine collection. Her serum creatinine (SCr) at that time was 0.8 mg/dL. One month before her pregnancy, SCr was 0.61 mg/dL with an estimated glomerular filtration rate (eGFR) of 117 mL/min/1.73m² based on the chronic kidney disease epidemiology collaboration equation

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<https://doi.org/10.1016/j.crwh.2021.e00326>

Received 29 April 2021; Received in revised form 7 May 2021; Accepted 11 May 2021

Available online 14 May 2021

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(CKD-EPI), and urine dipstick demonstrated 2–3+ proteinuria.

Throughout the remainder of her pregnancy, her diabetes remained uncontrolled with a hemoglobin A1c (HbA1c) of 10.1% despite the up-titration of her initial insulin regimen (Levemir 15 units in the morning and 12 units in the afternoon; Humalog: 6 units with breakfast, 7 units with lunch and 20 units with dinner). She continued to have glycosuria of more than 1000 mg/dL on multiple occasions. She was started on labetalol 200 mg twice daily at the beginning of pregnancy for elevated blood pressure. Her blood pressure ranged from 140 to 158 mmHg systolic and from 80 to 98 mmHg diastolic. Her antihypertensive regimen was escalated to labetalol 300 mg twice daily, nifedipine extended-release 60 mg daily and furosemide 80 mg twice daily. Despite these changes, her hypertension remained poorly controlled, with blood pressures ranging from 130 to 184 mmHg systolic and from 68 to 120 mmHg diastolic until delivery. She was also started on aspirin 81 mg daily around 12 weeks of gestation to reduce her risk of preeclampsia.

She presented to the hospital at 36 weeks and 0 days of gestation with contractions and was noted to have very high blood pressure, at 170–180 mmHg systolic and 90–100 mmHg diastolic, which was treated with intravenous labetalol. At that time, her SCr was 1.3 mg/dL along with a protein-creatinine ratio of 17 g/gCr. Given her uncontrolled hypertension and proteinuria, she was admitted for superimposed preeclampsia with severe features. Labor induction was initiated with misoprostol for cervical ripening and magnesium sulfate was administered. Shortly after administration of misoprostol, fetal heart rate decelerations were noted, which prompted an urgent cesarean delivery and bilateral tubal ligation. She delivered a viable female infant of low birth weight, 2095 g, yet appropriate for gestational age with Apgar scores of 8 and 9. She remained on magnesium sulfate for 24 h postpartum and blood pressure control was ultimately achieved with amlodipine 10 mg daily, carvedilol 25 mg twice daily, lisinopril 30 mg daily and bumetanide 3 mg daily.

One month after delivery, the patient's SCr had decreased to 1.1 mg/dL, with an eGFR (CKD-EPI) of 65 mL/min/1.73m² and an albumin-creatinine ratio of 9 g/gCr. Given her proteinuria and elevated SCr during her pregnancy, she underwent a renal biopsy, which showed advanced DN (Figs. 1–4). Renal function gradually declined. At 3 months postpartum SCr was 1.6 mg/dL, and by 8 months had risen to 4.3 mg/dL. Table 1 outlines the progression of the patient's estimated renal function and proteinuria. 24-h urine collection at that time revealed CCr of 12.4 mL/min with 20 g of proteinuria. She was diagnosed with ESRD, defined as a GFR of less than 15 mL/min, and was started on hemodialysis.

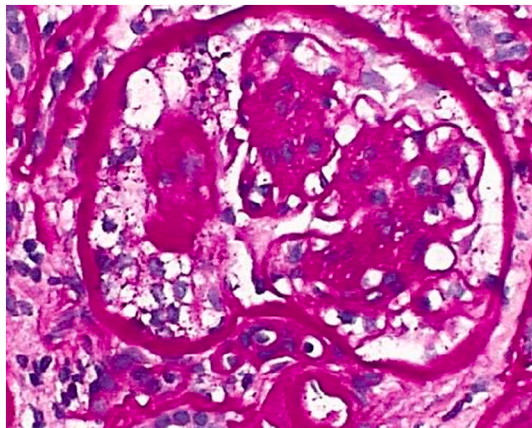


Fig. 1. PAS stain. Glomerulus showing centrilobular nodular sclerosis. Capillary loops around the nodules are patent. The arteriole shows hyaline arteriosclerosis.



Fig. 2. PAS stain. Three glomeruli showing advanced global sclerosis.

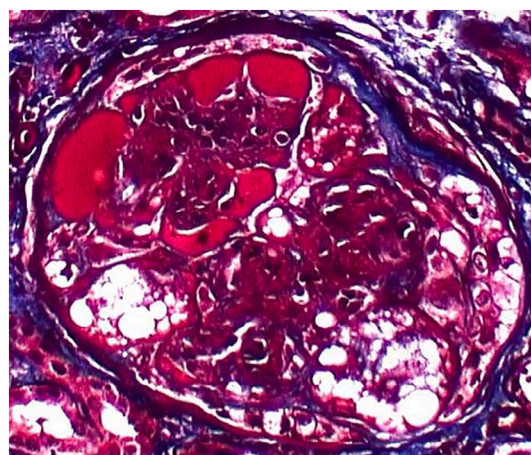


Fig. 3. Elastic trichrome stain. The photo shows endocapillary insudative deposits at 10 to 12 o'clock.

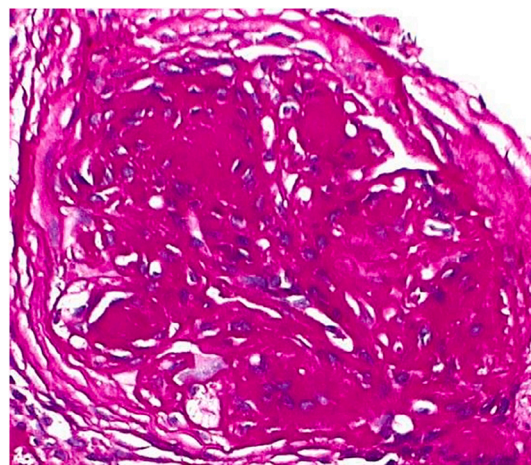


Fig. 4. PAS stain. Glomerulus showing advanced global sclerosis. A nodular character to the glomerular lobules is still appreciable.

3. Case 2

A 32-year-old Hispanic nulliparous woman with T1DM (diagnosed at age 8) and hypertension was referred by a primary care clinic to an obstetrical care provider at 10 weeks of gestation with poor glycemic

Table 1
Renal function summary table.

| Case 1 | Baseline | During Pregnancy: 12 weeks of gestation | After Pregnancy: 1 month postpartum | Time to ESRD: 8 months postpartum |
|--------------------|--------------------------------------|---|-------------------------------------|-------------------------------------|
| Creatinine | 0.61 mg/d L | 0.8 mg/d L | 1.1 mg/d L | 4.3 mg/d L |
| Proteinuria | 2+ to 3+ proteinuria | 7.6 g | ACR – 9 g/g | 20 g |
| eGFR (CKD-EPI)/CCr | eGFR – 117 mL/min/1.73m ² | CCr - 104 mL/min | eGFR - 65 mL/min/1.73m ² | CCr - 12.4 mL/min |
| Case 2 | Baseline | During Pregnancy: 10 weeks of gestation | After Pregnancy: 1 month postpartum | Time to ESRD: 9.5 months postpartum |
| Creatinine | 0.96 mg/dL | 1.3 mg/dL | 1.9 mg/dL | 6 mg/dL |
| Proteinuria | 2+ proteinuria | 9.4 g | 7.5 g | 10 g |
| eGFR (CKD-EPI)/CCr | eGFR - 79 mL/min/1.73 m ² | CCr - 73 mL/min | CCr - 28 mL/min | CCr - 9 mL/min |

eGFR - estimated glomerular filtration rate, ESRD – end stage renal disease, CCr – creatinine clearance, ACR – albumin-to-creatinine ratio.

control. She had a history of non-adherence with her home insulin regimen (NPH insulin: 5 units in the morning; 12 units in the afternoon, Humalog insulin: 5 units three times daily before meals). Her HbA1c was 9.9% at that time. She had previously been diagnosed with diabetic retinopathy requiring laser phototherapy. She was taking lisinopril for her hypertension but was transitioned to labetalol 200 mg twice daily shortly after conception. At 10 weeks and 2 days of gestation, the patient was admitted to the hospital for optimization of poor glycemic control and blood pressure. On admission, fasting blood glucose levels were noted to be around 300 mg/dL and her 2-h post-prandial glucose levels were around 400 mg/dL. Her SCr was 1.3 mg/dL and 24-h urine collection resulted in a CCr of 73 mL/min and 9.4 g of protein. Before pregnancy, her baseline SCr was 0.96 mg/dL with an eGFR (CKD-EPI) of 79 mL/min/1.73 m², and 2+ proteinuria on urine dipstick. She was evaluated by endocrinology and her insulin regimen was further optimized with improvement in her glycemic control. She was started on aspirin 81 mg daily to reduce her preeclampsia risk and her labetalol was increased to 400 mg twice daily with good control at the time of discharge.

During pregnancy, her spot albumin-creatinine ratio was reported as 5 g/gCr. Her peak SCr rose to 1.8 mg/dL with an eGFR (CKD-EPI) of 37 mL/min/1.73m². Her blood pressure remained well controlled on her new dose of labetalol, consistently ranging from 94 to 137 mmHg systolic and from 58 to 81 mmHg diastolic. Urinalysis documented glucosuria up to 250 mg/dL. At 22 weeks and 2 days of gestation, she presented to the hospital with vaginal leakage of fluid and was diagnosed with a previable premature rupture of membranes. An ultrasound scan documented a singleton fetus in breech presentation with an estimated fetal weight of 492 g and anhydramnios. Maternal-fetal medicine and neonatology were consulted. The patient was extensively counseled regarding her prognosis; however, she wished to continue the pregnancy. There was no clinical evidence of labor or intraamniotic infection. She received a course of betamethasone and completed a course of latency antibiotics. The patient remained stable without evidence of intraamniotic infection or preterm labor until 24 weeks and 2 days of gestation, when she was noted to have a fever of 101.2 °F. She began experiencing painful contractions. The patient was started on a magnesium sulfate infusion for fetal neuroprotection and a rescue dose of betamethasone was administered. The fetal heart rate tracing was initially reassuring for gestational age; however, a few hours later minimal variability and recurrent variable decelerations were noted. A

decision was made to proceed with cesarean delivery for non-reassuring fetal status, suspected intraamniotic infection, and breech presentation. The patient underwent an uncomplicated classical cesarean delivery of a viable 500 g male infant with Apgar scores of 1, 6, and 7. The patient's postpartum course was uncomplicated and she was discharged home on postoperative day 4. The infant was admitted to the neonatal intensive care unit for 8 months before being discharged home.

One month postpartum, SCr was 1.9 mg/dL and 24-h urine collection resulted in a CCr of 28 mL/min and 7.5 g of protein. Over the following 9 months, her blood pressure ranged from 123 to 180 mmHg systolic and from 88 to 98 mmHg diastolic, for which her anti-hypertensive regimen was changed from labetalol to amlodipine 5 mg daily, losartan 25 mg daily, and torsemide 10 mg daily. At 5 months postpartum, her SCr was 2.7 mg/dL and by 7 months had increased to 5.1 mg/dL. A kidney biopsy was consistent with advanced DN (Figs. 5–8). By nine and half months postpartum, SCr had worsened to 6 mg/dL and 24-h urine collection resulted in a CCr of 9 mL/min with 10 g of proteinuria. She was diagnosed with ESRD and started on peritoneal dialysis.

4. Discussion

Diabetic nephropathy is a major cause of ESRD in patients with T1DM. The physiological burdens of pregnancy, such as insulin resistance, glomerular hyper-filtration, and increase in proteinuria, are plausible mechanisms contributing to a potential decline in renal function in an already compromised kidney [1–4].

Women with DN can be considered as a group of patients with the highest propensity for worse pregnancy-associated outcomes. For example, rates of preeclampsia are noted to be 35–64% in patients with DN and 9–17% in diabetic women without DN, compared with 7% in women with lupus nephritis [5,6]. Other adverse pregnancy outcomes include small for gestational age (15–39%), preterm delivery <37 weeks (73–77%), and cesarean delivery (70–100%).

Prior literature has suggested that patients with DN and relatively preserved renal function do not experience faster progression of kidney disease as a consequence of pregnancy [7]. Rossing et al. investigated the long-term impact of pregnancy on the progression of DN in 93 patients with T1DM over a 16-year follow-up. They compared ever-pregnant and never-pregnant women who received similar medical therapy and who had similar baseline degrees of renal function at the start of the study. At the end of the follow-up, 35% (95% CI:17–53) of the ever-pregnant women had died while 19% (95% CI: 7–39) had developed ESRD, whereas 34% (95% CI:23–45) of the never-pregnant women had died while 24% (95% CI,14–34) had developed ESRD. This suggests that pregnancy neither altered the time course of renal

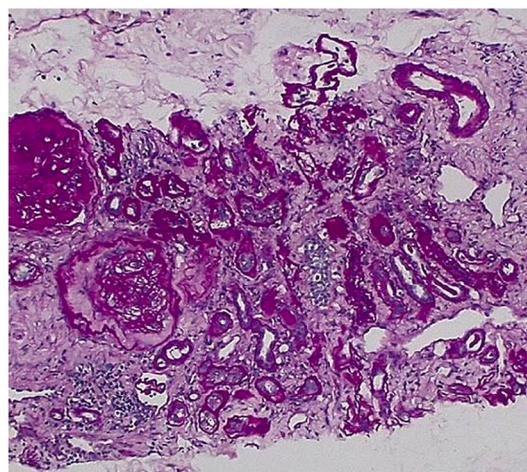


Fig. 5. PAS stain. Three glomeruli are globally sclerosed. There is severe tubular atrophy/interstitial fibrosis.

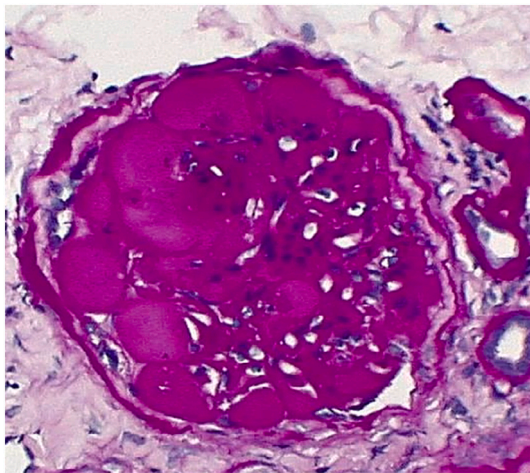


Fig. 6. PAS stain. Global glomerular sclerosis/obsolescence with many endocapillary insudative/hyalinosis 'deposits'.

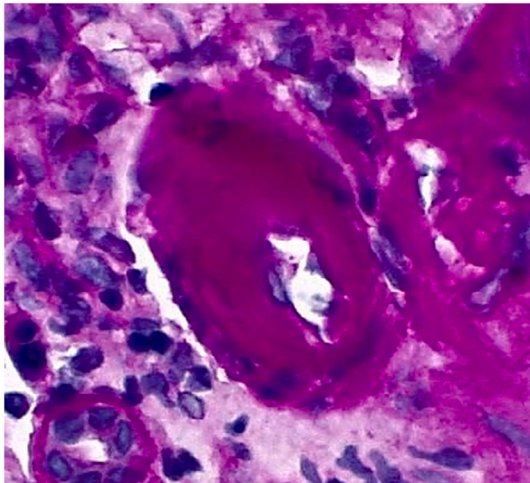


Fig. 7. PAS stain. Hyaline arteriolosclerosis.

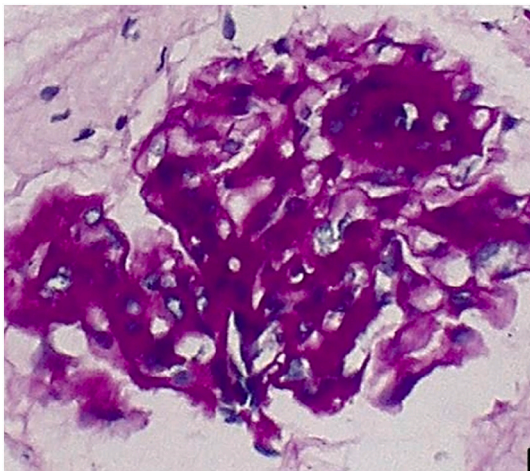


Fig. 8. PAS stain. Non-globally sclerosed glomerulus showing centrilobular nodular sclerosis lesion (2 o'clock) with peripheral patent capillary loops.

disease nor increased the likelihood of developing ESRD [9].

Pre-existing vascular disease generally portends a higher risk of preeclampsia (35–64%) and it is considered an established complication in DN [7,8]. However, nephrotic-range proteinuria with preserved GFR and rapid progression to ESRD post-pregnancy has not been well documented [9]. Previous studies showed no increased risk of overt DN or ESRD in women with preserved GFR at conception, and proteinuria generally returns to baseline postpartum [10].

The 2 patients presented in this case report fit the criteria for early-stage CKD (including SCr < 1.4 mg/dL, CCr of >70 mL/min or CKD Stage I/II) with favorable long-term renal outcomes as compared with moderate to severe CKD (SCr >1.4 mg/dL, CCr <70 mL/min or CKD Stage III/IV/IV) [7]. However, both patients experienced an accelerated decline in renal function as well as worsening proteinuria leading to ESRD postpartum. The difficulties in controlling their blood pressure and blood glucose during pregnancy likely played a major role in progression of their renal disease.

Several studies have shown significantly worse outcomes in diabetic ESRD patients than in non-diabetic patients, with one study demonstrating a 1.9 times higher risk of death compared with non-diabetics over 28-month follow-up [11]. Of the two patients presented in this case report, one has died of diabetes-related complications. Patients with T1DM and DN experience large variations in disease manifestation, ranging from rapid progression of preserved renal function to ESRD within 2–3 years versus progression over 20–40 years. Patients with rapid decline are termed “fast decliners” and usually have higher HbA1c levels and proteinuria [12]. There is a higher rate of fetal malformations with higher HbA1c levels and the clinical data suggest that women with HbA1c greater than 10% should be recommended to avoid conception [13].

Even as renal failure develops, the kidneys have the ability to compensate and there may be significant kidney fibrosis unaccompanied by measurable changes in GFR [14]. Patients with preserved GFR and DN manifested only by proteinuria might mask the risk of progression to severe kidney disease and possibly even ESRD. In the absence of non-invasive tools to evaluate underlying disease burden, aggressive glycemic and blood pressure control serve as the only proven modalities to slow renal disease progression postpartum.

Since kidney fibrosis is a key component of the final common pathway leading to ESRD, several attempts have been made to utilize non-invasive imaging to measure the degree of kidney fibrosis. A recent study demonstrated the ability to use magnetic resonance elastography (MRE) combined with magnetic resonance arterial kidney blood flow to predict decreasing renal cortical tissue perfusion, without the need for intravenous contrast; the results correlated with increasing fibrosis on renal biopsy [14]. In patients at risk of disease progression, non-invasive determination of the degree of renal fibrosis burden before apparent reductions in GFR could allow for more accurate renal evaluations without the need for renal biopsy.

Aside from better glycemic and blood pressure control, reducing activation of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers has been clearly shown to be beneficial in slowing the progression of diabetic nephropathy. Although contraindicated in pregnancy due to their effects on the fetus, these medications should be initiated postpartum [15]. Many of these agents, however, have been noted in very small quantities in breast milk [16]. Enalapril is often the preferred option since it has the most published data supporting its use. One study calculated the level of infant exposure to enalapril as 0.16% of the maternal weight-adjusted dose [16]. Given the clinically demonstrated benefit of RAAS blockade, a risk/benefit discussion regarding their usage should be held during breastfeeding period.

5. Conclusion

Despite a preserved GFR at the time of conception, poorly controlled

risk factors can result in the rapid progression of DN to ESRD. Additional studies with a larger sample size are needed to understand the nature of the disease behavior in this subpopulation. Furthermore, new non-invasive screening tools that assess underlying fibro-sclerotic disease burden can provide valuable information regarding risk of disease progression.

Contributors

Hassan Bin Attique was involved in patient care and writing the manuscript.

Deep Phachu was involved in patient care and writing the manuscript.

Alexandra Loza assisted in writing and revising the manuscript.

Winston Campbell assisted in writing and revising the manuscript.

Erica Hammer assisted in writing and revising the manuscript.

Ibrahim Elali finalized the manuscript.

Funding

No funding from an external source supported the publication of this case report.

Patient Consent

Patient consent was obtained for case description and images.

Provenance and Peer Review

This case report was peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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