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*Case Report*

# New-onset idiopathic membranous nephropathy in pregnancy

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**Abstract:** Background: Pregnancy with new-onset nephrotic syndrome manifested as idiopathic membranous nephropathy (IMN) is extremely rare. Treatments that improve maternal and fetal prognosis remain controversial. Case presentation: We report the case of a pregnant 23-year-old Chinese woman with IMN who delivered successfully and breastfed her infant. At 16 weeks of gestational age, she experience dedema in her legs following diarrhea, and she was diagnosed with "nephrotic syndrome" at the local hospital. The patient was then admitted to our hospital. After secondary factors were excluded, IMN was confirmed with a renal biopsy, and the patient received supportive treatment. At 35+2 weeks of gestational age, she was unable to achieve a full-term pregnancy because of heart failure after an upper respiratory infection, and a healthy baby girl was delivered via cesarean section and was breastfed. After delivery, the patient's symptoms were relieved, and her urinary protein was significantly reduced. At eight months after delivery, her urinary protein was 1.33 g/day, and this value decreased to an undetectable level after one month of tacrolimus treatment. Conclusion: Renal biopsy is necessary for patients with nephrotic syndrome as a potential primary nephropathy in early pregnancy. Supportive treatment is feasible for IMN patients with mild symptoms during pregnancy and is conducive to fetal development and breastfeeding.

**Keywords:** Idiopathic membranous nephropathy, pregnancy, nephrotic syndrome, renal biopsy

## Introduction

Pregnancy can cause or aggravate renal diseases because of the numerous physiological changes in the body. Approximately 4% of pregnant women develop chronic kidney diseases, including different types of primary renal disease and renal disease secondary to other systemic diseases [1]. Nephrotic syndrome is rare in pregnant women, with a prevalence of approximately 0.012-0.025% [2]; most of these cases are associated with preeclampsia or a history of renal disease, whereas new-onset primary nephropathy is extremely rare. To date, only one case of pregnancy with new-onset idiopathic membranous nephropathy (IMN) has been reported, but the possibility of silent lupus-associated MN could not be completely excluded, and the pregnancy ended with an abortion [3]. In this paper, we report one case of a pregnant patient with new-onset IMN who successfully continued the pregnancy and was cured; the patient was able to breastfeed after childbirth. Moreover, we summarize the characteristics and treatment experience of this case.

## Case presentation

### *General information*

The patient was a 23-year-old, married, nulliparous Chinese woman. She was previously healthy and underwent regular perinatal care and exams with no abnormal results. The time course of patient care is shown in **Figure 1**.

### *Admission condition*

At 16 weeks of gestational age, after consuming contaminated food, the patient experienced diarrhea (watery stools) and fever (up to 38.4°C). Her symptoms improved after three days of treatment; however, she developed edema in her legs. Her condition was diagnosed as "nephrotic syndrome" at the local hospital, and she was admitted to our hospital in June 2014.

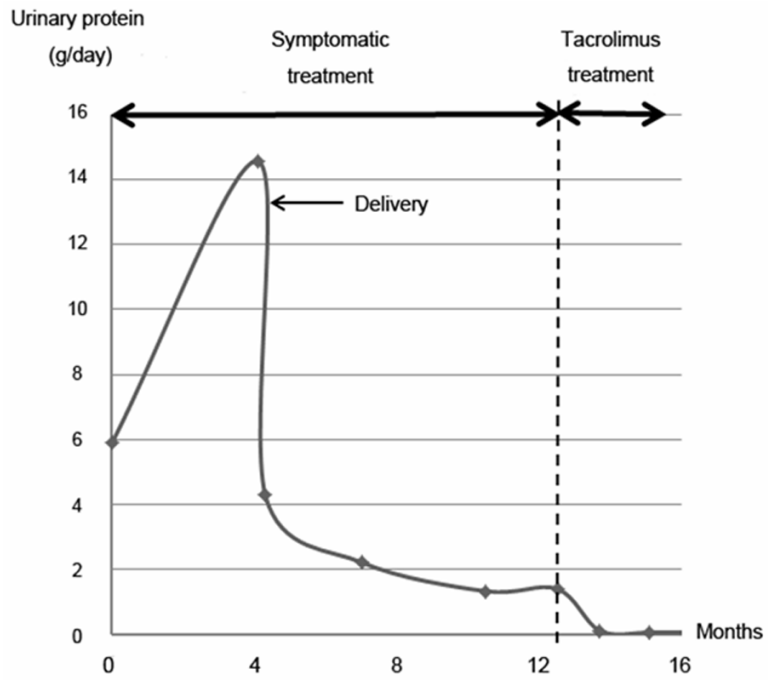


**Figure 1.** The patient's clinical course.

A physical examination upon admission showed the following: temperature (T), 36.5°C; pulse (P), 85 bpm; respiration (R), 22 breaths per minute; and blood pressure (BP), 111/65 mmHg.

The results of a physical examination were normal except for slight limb edema. The following laboratory results were obtained: white blood cell (WBC) count, 9.0 × $10^9$/L; hemoglobin (HGB), 98 g/L; platelets (PLT), 156 × $10^9$/L; albumin (ALB), 21.5 g/L; blood urea nitrogen (BUN), 3.2 mmol/L; serum creatinine (Scr), 37 μmol/L; total cholesterol (TCHO), 7.74 mmol/L; and triglycerides (TG), 1.83 mmol/L. A urine dipstick examination revealed proteinuria (3+), with a 24-hour urine protein level of 5.91 g/day. The urinary sediment contained 170 red blood cells (RBCs) per high-power field (HPF). Liver enzymes, blood electrolytes, and coagulation tests were all within normal ranges. The tests for antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) were negative. No evidence of infection, such as hepatitis B or C virus, was indicated on the blood test. The serum complement levels were within the normal range. A renal ultrasound showed normal kidney size and shape. The echocardiography results were normal. A gynecological ultrasound showed an intrauterine pregnancy, a single live fetus, and a fetal heart rate of 155 bpm.

*Initial treatment protocol*

After consulting with an obstetrician and an ultrasound practitioner, we decided that the patient had no significant contraindications for having a renal biopsy. After communicating with the patient and her family and obtaining signed informed consent, we performed an ultrasound-guided renal biopsy. The procedure went smoothly, the patient did not experience discomfort, and the fetus did not show signs of subsequent distress.

A light microscopic examination of the glomeruli showed diffuse thickening of the capillary basement membrane, spike formation, and granular degeneration of tubular epithelial cells (**Figure 2**). No features of interstitiumor arteritis were identified. Immunofluorescence microscopy indicated granular staining along the capillary wall: IgG (++), IgG1 (±), IgG2 (±), IgG3 (-), IgG4 (++), IgM (-), IgA (-), C3 (+), C4 (-), C1q (-), FRA (-), HBsAg (-), and HBcAg (-) (**Figure 2**). Electron microscopy showed marked subepithelial electron-dense deposits (EDDs) and spike formation (**Figure 2**). The pathological diagnosis was stage II MN.

Based on these results, a diagnosis of IMN (stage II) was indicated. The patient and her familywished to continue the pregnancy. She did notreceive glucocorticoids or immunosuppressive therapy because of their concerns about the sideeffects of the medicine; however, the patient received oral iron supplements. She was also instructed to follow a low-salt, quality protein diet and control fluid intake to manage edema after discharge.

*Disease progression*

After discharge, the patient followed up at the local hospital but not at our hospital. During this period, she experienced worsening edema without dizziness, headache, chest distress,

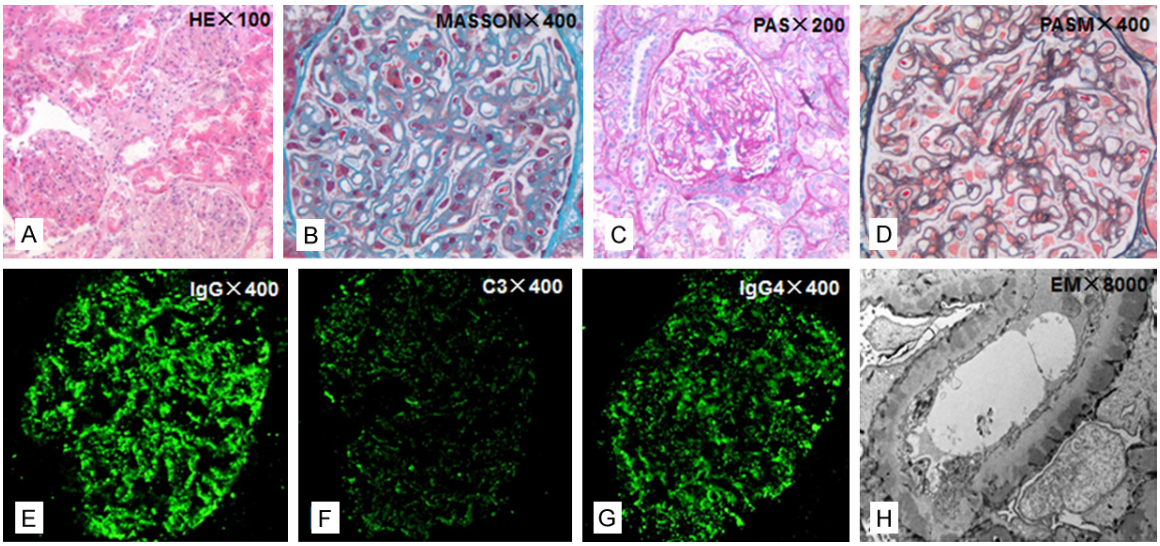


**Figure 2.** (A) Hematoxylin-eosin (HE) stain (original magnification × 100). (B) Masson's trichrome (MASSON) stain (original magnification × 400). (C) Periodic acid-Schiff (PAS) stain (original magnification × 200). (D) Periodic acid-silver methenamine (PASM) stain (original magnification × 400). Examinations of glomeruli show diffuse thickening of the capillary basement membrane and spike formation. (E, G) Immunofluorescence shows moderate granular staining for IgG and IgG4 along the capillary wall and (F) mild staining for C3 (original magnification × 400). (H) Electron microscopy shows marked subepithelial electron-dense deposits and spike formation (original magnification × 8000).

vaginal bleeding, or vaginal discharge, and fetal movement was good. The lab tests performed at the local hospital showed no significant developments.

At 34+2 gestational weeks, the patient experienced chest distress and coughing after a cold and was admitted to the Department of Obstetrics at our hospital. A physical examination upon admission showed the following: T, 36.8°C; P, 96 bpm; R, 22 breaths per minute; BP, 138/84 mmHg; coarse breathing sounds in the lower lungs; severe edema in the lumbosacral area and the legs; fetal heart rate, 133 bpm; and urine output, 800 mL/day. Her test results were as follows: WBC, 14.2 × $10^9$/L; HGB, 112 g/L; PLT, 322 × $10^9$/L; ALB, 20 g/L; BUN, 2.51 mmol/L; Scr, 42 μmol/L; CHO, 7.74 mmol/L; and TG, 1.83 mmol/L. In the urinalysis, the sediment contained 5.94 RBCs/HPF without casts, and the patient had 14.57 g/day of proteinuria. A Doppler ultrasound showed an intrauterine pregnancy, a single live fetus (head down), grade I placental function, no peritoneal effusion, and mild right pleural effusion. The echocardiography results were normal. Ceftriaxone was administered as an anti-infective treatment.

After treatment for 5 days, the patient did not experience a significant improvement in chest distress; she continued to cough and had severe anasarca. At this point, we suggested that she deliver the baby, and the patient agreed. At 35+2 gestational weeks, the patient underwent a successful cesarean section and delivered a healthy baby girl (head down). After the operation, the patient's vital signs were stable. On the day after the operation, her urine output increased to approximately 2500 mL/day. At one week after the operation, her edema was significantly improved, and she had no chest distress, coughing, or other symptoms. A urinalysis showed the following results: urinary protein, 4.29 g/day; WBC, 15.1 × $10^9$/L; HGB, 93 g/L; hematocrit (HCT), 0.31 L/L; PLT, 258 × $10^9$/L; ALB, 20.1 g/L; BUN, 3.06 mmol/L; and Scr, 49 μmol/L. The female infant was healthy and breastfed. Because the symptoms improved and the proteinuria decreased significantly, we continued to provide supportive treatment for this patient.

*Outcomes*

At three months after delivery, the patient had no significant discomfort or symptoms, and the infant was healthy. Blood tests showed the following: HGB, 123 g/L; ALB, 26.3 g/L; Scr, 44 μmol/L; CHO, 8.3 mmol/L; TG, 1.27 mmol/L; and urinary protein, 2.22 g/day. We did not change the therapy.

At six months after delivery, the patient had no discomfort, her serum albumin and lipid levels were normal, and total urinary protein was 1.33 g/day. The patient was administered oral tripterygium glycosides and irbesartan, and the infant was healthy and converted to artificial feeding.

At eight months after delivery, the lab tests showed that urinary protein was 1.4 g/day, and the patient's treatment was changed tooral tacrolimus (1 mg twice daily). At nine months after delivery, the lab tests showed that total urinary protein was 0.11 g/day and the plasma concentration of tacrolimus was 4.8 ng/dL. At 11 months after delivery, the lab tests showed that urinary protein was 0.06 g/day. Thus, the patient was clinically cured and followed up at the clinic.

*Literature review and discussion*

Nephrotic syndrome in early pregnancy affects the maternal and fetal prognosis [4]. 1. Physiological changes during pregnancy may lead to increased secretion of urinary protein and decreased serum albumin that worsens as the pregnancy advances. Severe hypoproteinemia can lead to fluid retention, infection, pulmonary edema, heart failure, and placental abruption, thereby increasing the caesarean section rate and maternal mortality rate. Moreover, hypoproteinemia [5] affects fetal development, leading to low birth weight and an increase in neonatal asphyxia and mortality. 2. Nephrotic syndrome may also lead to an increase in the occurrence of hypercoagulability, thrombosis, and embolic complications. Thus, care must be taken in selecting an appropriate treatment for patients with nephrotic syndrome during pregnancy. In this case report, by the third trimester, urinary protein had increased significantly, and edema had become more severe; however, the patient's serum albumin level did not decrease significantly, which was thought to be related to her quality protein diet during pregnancy, which also benefited fetal growth.

Most cases of nephrotic syndrome during pregnancy are associated with pregnancy-related hypertension, and primary nephropathy is rare; nephrotic syndrome that occurs during early pregnancy without hypertension often suggests primary nephropathy. The prognoses and responses to medicine are highly variable for primary nephropathies of different pathological types. Lo et al [6] reported a patient with a minimal change disease in early pregnancy who was in complete remission after one month of glucocorticoid treatment, whereas MN [3, 7, 8] responds poorly to glucocorticoids. For pregnant patients with suspected primary nephrotic syndrome, it is necessary to perform a renal biopsy to confirm the pathological type.

Renal biopsy is an invasive examination, and deliberation is necessary prior to operating on a patient during pregnancy. Lindheimer et al [9, 10] noted that a renalbiopsy should be performed in cases of sudden, unexplained renal insufficiency or nephrotic syndrome of unknown origin occurring prior to the final two months of pregnancy. Most cases of primary nephropathy during pregnancy do not present with hypertension, renal failure, severe anemia, or other symptoms that may increase the risk of renal biopsy. In this case report, the patient had nephrotic syndrome in early pregnancy, with the only symptom being mild edema in the legs, and secondary factors were excluded. Therefore, the risk of renal biopsy for this patient, who was considered to have primary nephropathy during pregnancy, was relatively low. A renal biopsy was performed for the patient, and the pathological result was stage II MN; the patient was finally diagnosed as IMN.

Recent studies have shown that phospholipase $A_2$ receptor ($PLA_2R$) [11, 12] is the main antigen involved in the pathogenesis of adult IMN; approximately 70% of IMN patients are positive for the $PLA_2R$ antibody, whereas up to 80% of Chinese IMN patients have the $PLA_2R$ antibody [13]. Hoxha et al [14] showed that $PLA_2R$ antibody level is an independent risk factor for not achieving remission of proteinuria and that a decrease in $PLA_2R$ antibody level is associated with a decrease in proteinuria in patients with primary MN. Moreover, Tomas et al [15] observed thrombospondin type-1 domain-containing 7A (THSD7A), a glomerular protein, in the sera of IMN patients who were negative for the $PLA_2R$ antibody, suggesting that THSD7A is a second antigen involved in the pathogenesis of IMN. Thus, THSD7A antibody-positive patients represent a distinct subgroup of IMN patients. Testing for serum $PLA_2R$ and THSD7A antibodies may contribute to the diagnosis of

IMN and help avoid renal biopsy. However, renal pathological diagnosis remains the gold standard.

IMN has a long natural course and may lead to worsening kidney function or spontaneous remission [16]. Approximately 30-60% of patients achieve spontaneous remission; gender (female) and age (< 50 years) are predictors of spontaneous remission [17-21]. Previously [22], most researchers thought that patients with mild or moderate proteinuria were more likely to experience spontaneous remission, which was less common if urinary protein was > 8 g/day or if the patient had renal failure. Recent studies have shown that 31.7% of IMN patients with nephrotic syndrome achieve spontaneous remission and that approximately 25% of patients with urinary protein > 8 g/day also achieve spontaneous remission [23]. Moreover, IMN patients with nephrotic syndrome and renal impairment may also achieve spontaneous remission [24]. Thus, based on the IMN characteristics and suggestions from the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [25], early aggressive treatment may not improve the prognosis of IMN patients with no significant symptoms.

IMN treatment during pregnancy remains controversial. Currently, large clinical trials on this subject are absent, and most reported patients are described in case reports [3, 7, 8] with unsatisfactory treatment outcomes. Furthermore, most researchers believe that the remission rate among patients with IMN is low with glucocorticoid treatment alone and that combination therapy with glucocorticoids and cytotoxic medicines has some effect [22]. However, because of the severe teratogenic effects, immunosuppressants, such as cyclophosphamide (CTX) and cyclosporin A (CsA), are contraindicated in women in early pregnancy; thus, medicinal treatment for IMN during pregnancy is often limited to steroids. Previous studies of patients with MN during pregnancy [3, 7, 8] demonstrated that glucocorticoid therapy reduced urinary protein levels but that urinary protein levels remained extremely high until after the pregnancy was terminated. In addition, glucocorticoid therapy may increase the risks to the mother and unborn baby, resulting in adverse consequences [26]. Therefore, care is necessary when using glucocorticoids to treat patients with IMN during pregnancy.

The rate of spontaneous remission is high among IMN patients. However, there is no evidence of spontaneous remission in pregnant patients, and the effect of glucocorticoid treatment in pregnant patients has not been established; terminating pregnancy is effective and helpful for remission. In this case, the patient had mild symptoms, including urinary protein < 8 g/day, and the KDIGO guidelines [25] suggest that IMN patients without serious symptoms can be observed for at least six months. If we had followed these guidelines in this case, the unborn baby would have been fully developed after six months, so we administered supportive treatment and thus prevented adverse medicinal reactions. Because no specific medicine was administered, the patient could breastfeed her baby for six months after childbirth, which promoted the growth and development of her child.

Unfortunately, the patient did not follow up at our hospital during her pregnancy, and therefore, we did not have the chance to extend her pregnancy to full term. The patient followed the instructions to consume a proper diet and control fluid intake; thus, the serum albumin level did not progressively decrease during the third trimester, which was beneficial for fetal development. However, she continued to experience a decrease in urine output, worsening edema, and infection-induced heart failure and was unable to carry the baby to full term. If we had administered albumin and diuretics to reduce edema in this patient at an early timepoint, she may have been able to carry the baby to full term.

## Conclusions

For patients in early pregnancy with nephrotic syndrome as a potential primary nephropathy, renal biopsy is necessary for diagnosis and treatment. New-onset IMN during pregnancy is extremely rare, and the benefits of glucocorticoid treatment have not been established; terminating pregnancy is effective and helpful for remission. In this case, the patient delivered successfully after supportive treatment, suggesting that this type of treatment is applicable for pregnant IMN patients with mild symptoms and is conducive to breast feeding, but patients

should be monitored closely. To the best of our knowledge, no similar cases have been reported previously in the literature.

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## Disclosure of conflict of interest

None.

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