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Syphilis and Proteinuria in Pregnancy

Jay Jensen, MD[1], Jesse Cottrell, MD[1]

ABSTRACT

Syphilis has the potential to result in serious, irreversible morbidity and mortality during pregnancy and has increased in incidence across the United States. While syphilis is a common disease and a known but rare cause of membranous nephropathy, it can complicate the clinical picture and obscure accurate diagnosis of women presenting with proteinuria during pregnancy. We report a case of proteinuria with syphilis in the second trimester of pregnancy as an educational review.

KEYWORDS

Proteinuria, syphilis, pregnancy, membranous nephropathy

Author affiliations are listed at the end of this article.

Correspondence to:
Jesse Cottrell, MD
Marshall University
Joan C. Edwards
School of Medicine
cottrellje@marshall.edu

INTRODUCTION

Syphilis has increased in incidence across the United States over the past decade despite effective identification and treatment.[1] Untreated syphilis can result in serious, irreversible morbidity during pregnancy via vertical transmission to the fetus and maternal sequelae seen in the secondary and tertiary stages of the disease.[2] There has also been an increase in congenital syphilis, with 8.4 cases per 100,000 live births during 2008–2012 and 11.6 cases per 100,000 live births in 2014, which is the highest rate reported since 2001.[3,4] While pregnancy can present with proteinuria from normal or abnormal physiologic changes during pregnancy, syphilis is a common disease and a known cause of membranous glomerulonephritis; however, the manifestation is rare during pregnancy and not reported in the literature. We report a case of proteinuria with syphilis in the second trimester of pregnancy as a mini-review, as we believe syphilitic membranous glomerulonephritis to be an important addition to the differential diagnosis of proteinuria during pregnancy. The aim of this mini-review is for the education of physicians, residents, and students.

CASE PRESENTATION

A 32-year-old female at 21 weeks gestation presented to the emergency department after being physically and sexually assaulted by her significant other. Physical exam demonstrated bruising and tenderness to the patient's left periorbital and abdominal areas, and vaginal and anal bleeding. The physical exam was otherwise unremarkable, and there were no physical exam findings indicative of syphilitic infection. The patient was admitted for inpatient management and continued maternal and fetal evaluation.

The patient's medical history was significant for a reactive rapid plasma reagin (RPR) of 1:128 three months prior to her current hospital admission, at which time a positive serum pregnancy test was documented. Treatment was arranged at a public health clinic, but the patient did not attend the appointment or receive antibiotic treatment elsewhere. A repeat RPR of 1:132 was present on hospital admission, and syphilis was confirmed with a fluorescent treponemal antibody screening (FTAbS) test. Due to physician concern for neurosyphilis, a lumbar puncture was performed and showed no signs of spirochetal infection in

the cerebrospinal fluid. A 24-hour urine specimen showed subnephrotic proteinuria of 1.5 grams with a urinalysis consistent with an ongoing lower urinary tract infection (Table 1).

Urinalysis Dipstick	11/12/2020	11/15/2020	11/28/2020	12/10/2020
Clarity	clear	clear	clear	clear
Color	yellow	yellow	yellow	yellow
Spec. Grav.	1.014	1.015	1.022	1.019
Bili	Neg	Neg	Neg	Neg
pH	6.5	7.0	6.0	6.0
Urobilinogen	4.0	0.2	0.2	0.2
Occult Blood	neg	neg	neg	neg
Glucose	neg	neg	neg	neg
Ketones	neg	neg	neg	neg
Protein	30	neg	neg	neg
Nitrate	neg	neg	neg	neg
Leuk Est	small	trace	small	moderate
UA micro				
WBC	10-15	3-5	5-10	3-5
RBC	none	0-1	1-3	trace
Bacteria	1+	trace	trace	trace
Epi Cells	15-20	1-3	5-10	5-10

TABLE 1. (UA dipstick and UA micro showing with unrevealing findings except for variant levels of WBCs and leukocyte esterase consistent with urinary tract infection)

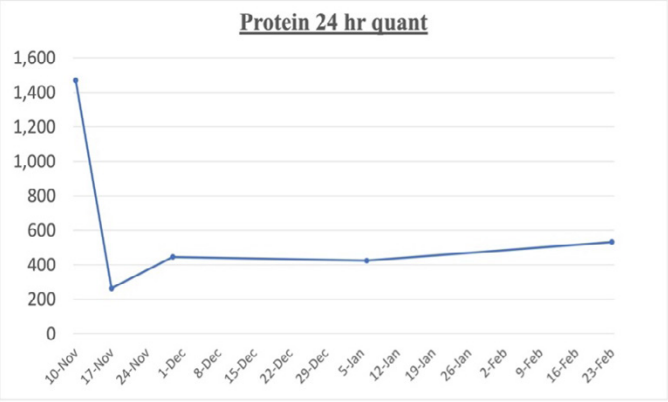

FIGURE 1. 24-hour urine protein collection measured in mg/24hr. Penicillin G Benzathine was given November 10.

Bloodwork was significant for hypoalbuminemia (1.8 gm/dl), elevated creatinine concentration (1.12 mg/dl), low protein (6.3 gm/dl), and E. coli bacteremia. No lipid panel was performed as part of this patient's workup. Pertinent negative findings included normal C3 and C4 levels (146 and 20 mg/dl, respectively), a negative hepatitis panel, and a negative fourth-generation Human Immunodeficiency Virus (HIV) test. Ultrasound of the kidneys revealed an 18mm echogenic mass on the left kidney, interpreted to be an angiomyolipoma. There was no evidence of hydronephrosis or urinary obstruction. A urine culture subsequently demonstrated chlamydial infection without gonorrhea. Antibiotic treatment for chlamydia and E. coli bacteremia was azithromycin and ceftriaxone. The patient refused thromboprophylaxis with low molecular weight heparin. The nephrology service was consulted for the management of acute kidney injury (AKI) while the patient was admitted. The lack of physical exam findings for syphilitic lesions, confirmatory FTAbS, and laboratory values, including the negative HIV test and hepatitis panel, weighted the diagnosis toward membranous nephropathy due to secondary syphilis. However, this diagnosis was not confirmed with renal biopsy.

The patient was started on a weekly course of intramuscular penicillin G benzathine for 3 weeks. RPR trended downward immediately following initiation of penicillin treatment, and a repeat 24-hour urine collection 7 days later showed a sharp downward trending urinary protein. Proteinuria and serum albumin were tracked on follow-up visits over the next 4 months, as shown in Figures 1 and 2.

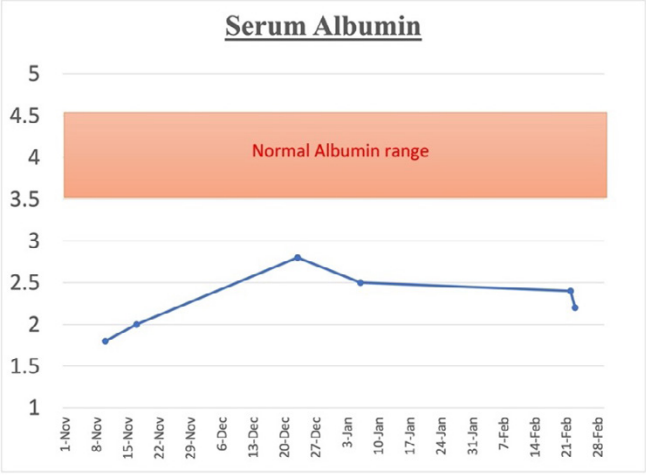

FIGURE 2. Serum albumin measured in mg/dl

The patient left the hospital against medical advice and returned 8 days later for domestic abuse. Urine collection still showed proteinuria of 264 mg/24hr, lower than her previous measurement. She received her final IM penicillin shot during this stay, completing the course of her treatment.

At a follow-up appointment 5 weeks after the initial diagnosis, an RPR titer of 1:64 was documented. The patient continued to be followed in the high-risk obstetric clinic until the delivery of her child at 36 weeks gestation. Her RPR remained reactive, as expected, and lower than previous measurements at 1:32.

During the patient's hospitalization, the nephrology service determined it was prudent to defer renal biopsy due to the patient's extenuating physical and social circumstances, as well as the fact that the proteinuria was improving while all underlying causes were being adequately treated.

DISCUSSION

Patients presenting with proteinuria during the later stages of gestation should receive a thorough evaluation. The suspicion of preeclampsia should be foremost. The diagnostic features of preeclampsia described by the American College of Obstetrics and Gynecology are as follows: systolic blood pressure ≥140mmHg or diastolic pressure ≥90mmHg on at least 2 occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive patient and the new onset of 1 or more of the following: proteinuria ≥0.3g in a 24-hour urine specimen or protein/creatinine ratio of ≥0.3mg/mmol in random urine specimen or dipstick ≥2+ (if quant is not available); platelet count <100,000/microL; serum creatinine >1.1mg/dL or doubling of the creatinine concentration in the absence of other renal diseases; liver transaminases at least twice the upper limit of normal concentration; pulmonary edema; new-onset and persistent headache not accounted for by alternative diagnosis, not responding to usual doses of analgesics; visual symptoms (blurred, flashing lights, scotomata).[5] After the diagnosis of preeclampsia is ruled out, and the range of proteinuria is greater than accounted for by physiological changes to the renal filtration system during pregnancy, the renal etiology of proteinuria should be evaluated.

Membranous nephropathy (MN) is the most common nephrotic syndrome of non-diabetic patients, particularly in males above the age of 40.[6] The incidence of the disease in the general population is 1.2/100,000 per year, and end-stage renal disease occurs secondary to membranous nephropathy in 1.9/million per year.[7,8] If present in women under 40, it is suspicious for secondary causes such as lupus nephritis. Patients typically present with proteinuria, hypoalbuminemia, and hyperlipidemia. Idiopathic forms are associated with autoantibody against Phospholipase A2, while secondary causes are most commonly associated with autoimmune diseases and thyroiditis. Membranous nephropathy is also known to occur secondarily to infection (Hepatitis B, Hepatitis C, HIV, and Syphilis) and NSAIDs, gold, penicillamine, and captopril use.[9] It is associated with malignancy in up to a third of cases in patients above the age of 60.[10]

Membranous nephropathy is a rare manifestation of secondary syphilis (albeit the most common form of glomerular pathology seen in syphilitic patients),[11] with most reports of syphilitic nephritis arising from congenital cases of membranous glomerulonephritis with subepithelial deposits or intramembranous deposits. Other manifestations of syphilitic nephropathy include mesangial proliferative glomerulonephritis, post-infectious proliferative glomerulonephritis, rapidly progressive glomerulonephritis with crescents, minimal change disease, renal gumma, and amyloid renal disease.[11] The clinical manifestation of MN is primarily asymptomatic proteinuria that can range from sub-nephrotic levels (<3g/day) to 20g/day.[12] Severe hyperlipidemia can be expected in the majority of cases, but some cases have been reported without hyperlipidemia.[13] Membranous nephropathy is definitively diagnosed using renal biopsy, which was not obtained in this case. It can be noted that renal biopsy is a safe procedure that is not contraindicated during pregnancy.

Some etiologies of nephrotic syndromes are reversible, while others are not. Regardless, the treatment for secondary nephrotic disease is to treat the underlying etiology along with supportive

measures. The treatment of primary membranous nephropathy can be determined using risk stratification based on immunologic parameters (PLA2R antibody) and clinical data (creatinine and eGFR). High or very high-risk patients can be treated using immunosuppression[14]; however, some patients will spontaneously remit.[6]

The known maternal complications to a mother due to membranous nephropathy are not well-documented due to the rarity of this presentation in pregnancy. However, the clinical complications of MN most commonly include thrombotic and thromboembolic events, risk of infection, and cardiovascular disease. Long-term complications of nephrotic syndrome consist of progressive loss of renal function.[6] The rate of fetal loss in primary membranous nephropathy has been documented as high as 24-35%.[15]

Nephrotic syndromes manifesting with proteinuria and hypoalbuminemia have a markedly increased risk of venous thrombosis.[12] Normal pregnancy adaptations predispose to an increased risk of coagulation through the acquired resistance to protein C, a decrease in protein S, and impaired fibrinolysis.[16] Fetal loss associated with thrombophilia has been reported to be as high as 50%,[17] with the hypercoagulable state of pregnancy causing clot formation in placental vessels and restricting blood flow to the fetus.[18] The combined effects of nephrotic syndrome and pregnancy both increasing the risk of thromboembolism can complicate all stages of pregnancy, particularly at or shortly after delivery.

Iwakura et al. described membranous nephropathy in the pregnancy of a 30-year-old female at 26 weeks gestation with thrombospondin type-1 domain-containing 7A (THSD7A) in the glomeruli.[19] The diagnosis was made when further evaluation of her proteinuria was done, and a renal biopsy was performed, revealing subepithelial deposits in the glomerular basement membrane. The patient's 24-hour collection of total urine protein was 7.8g/day, serum albumin was 1.8g/dL, and total cholesterol was 435mg/dL. Aoshima et al. also described a case of a 37-year-old female developing MN at 17 weeks gestation.[20] The patient first presented with lower extremity edema, proteinuria, and microscopic hematuria. Laboratory workup revealed a 24-hour urinary protein of 2.26g/day, serum albumin of 1.9g/dL, and total cholesterol of 394mg/dL. Renal biopsy one week after abortion showed subepithelial and paramesangial electron-dense deposits. Guillén et al. described a post-infectious sequala of syphilis infection in association with Acute IgA dominant glomerulonephritis in a 16-year-old female who delivered at 29 weeks, demonstrating that renovascular disease due to syphilis is not limited to membranous nephropathy.[21] The patient presented to the hospital due to seizures and unknowingly being pregnant.

Of interest to this case was a report of a female patient who also presented with non-gonococcal chlamydia infection; some forms of glomerular disease have been associated with bacterial antigens from chlamydia, such as IgA nephropathy and mesangiocapillary glomerulonephritis.[22] Without biopsy, these alternative diagnoses cannot be definitively ruled out. Furthermore, our patient endorsed the recreational use of methamphetamine. To our knowledge, there are currently no reports of membranous nephropathy secondary to methamphetamine use.

CONCLUSION

Nephrotic syndromes such as membranous nephropathy should be expeditiously evaluated and treated during pregnancy. All pregnant patients at greater than 20 weeks gestation should be evaluated for preeclampsia, but the differential diagnosis should not stop there, especially in high-risk patients. Nephrotic syndromes convey an increased risk for coagulopathy and other adverse maternal and fetal outcomes. Membranous nephropathy secondary to syphilis is rare, but it is becoming increasingly important to keep it on the differential diagnosis, as the incidence of syphilis continues to rise. Although this patient could not be definitively diagnosed with membranous nephropathy secondary to syphilis as the kidney biopsy was deferred, the potential diagnosis was reasonably considered. A high level of suspicion should be kept for patients at risk of syphilis infection presenting with proteinuria at any point during pregnancy, even in high-income and developed nations. As nephrotic syndromes

share important diagnostic markers with gestational pathologies, such as preeclampsia, practitioners must be aware that syphilis can cause proteinuria. A missed diagnosis or inappropriate treatment for proteinuria could lead to serious complications for the mother and fetus both during and after pregnancy.

AUTHOR AFFILIATIONS

1. Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia

REFERENCES

1. Schmidt R, Carson PJ, Jansen RJ. Resurgence of Syphilis in the United States: An Assessment of Contributing Factors. Infect Dis (Auckl). 2019;12:1178633719883282.
2. Su JR, Brooks LC, Davis DW, Torrone EA, Weinstock HS, Kamb ML. Congenital syphilis: trends in mortality and morbidity in the United States, 1999 through 2013. Am J Obstet Gynecol. 2016;214(3):381 e381-389.
3. Congenital syphilis in the USA. Lancet. 2018;392(10154):1168.
4. Bowen V, Su J, Torrone E, Kidd S, Weinstock H. Increase in incidence of congenital syphilis - United States, 2012-2014. MMWR Morb Mortal Wkly Rep. 2015;64(44):1241-1245.
5. "Gestational Hypertension and Preeclampsia: Acog Practice Bulletin, Number 222." Obstet Gynecol 135, no. 6 (Jun 2020): e237-e60. https://doi.org/10.1097/AOG.0000000000003891. https://www.ncbi.nlm.nih.gov/pubmed/32443079.
6. Couser WG. Primary Membranous Nephropathy. Clin J Am Soc Nephrol. 2017;12(6):983-997.
7. McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transplant. 2011;26(2):414-430.
8. Cattran DC, Brenchley PE. Membranous nephropathy: integrating basic science into improved clinical management. Kidney Int. 2017;91(3):566-574.
9. Cahen R, Francois B, Trolliet P, Gilly J, Parchoux B. Aetiology of membranous glomerulonephritis: a prospective study of 82 adult patients. Nephrol Dial Transplant. 1989;4(3):172-180.
10. Glassock, R. J. "Diagnosis and Natural Course of Membranous Nephropathy." Semin Nephrol 23, no. 4 (Jul 2003): 324-32. https://doi.org/10.1016/s0270-9295(03)00049-4. https://www.ncbi.nlm.nih.gov/pubmed/12923720.
11. Hunte W, al-Ghraoui F, Cohen RJ. Secondary syphilis and the nephrotic syndrome. J Am Soc Nephrol. 1993;3(7):1351-1355.
12. Wasserstein AG. Membranous glomerulonephritis. J Am Soc Nephrol. 1997;8(4):664-674.
13. Shearn, M. A. "Normocholesterolemic Nephrotic Syndrome of Systemic Lupus Erythematosus." Am J Med 36 (Feb 1964): 250-61. https://doi.org/10.1016/0002-9343(64)90087-7. https://www.ncbi.nlm.nih.gov/pubmed/14124691.
14. De Vriese, A. S., R. J. Glassock, K. A. Nath, S. Sethi, and F. C. Fervenza. "A Proposal for a Serology-Based Approach to Membranous Nephropathy." J Am Soc Nephrol 28, no. 2 (Feb 2017): 421-30. https://doi.org/10.1681/ASN.2016070776. https://www.ncbi.nlm.nih.gov/pubmed/27777266.
15. Malik GH, Al-Harbi AS, Al-Mohaya S, et al. Repeated pregnancies in patients with primary membranous glomerulonephritis. Nephron. 2002;91(1):21-24.
16. Townsley DM. Hematologic complications of pregnancy. Semin Hematol. 2013;50(3):222-231.
17. Brenner B, Sarig G, Weiner Z, Younis J, Blumenfeld Z, Lanir N. Thrombophilic polymorphisms are common in women with fetal loss without apparent cause. Thromb Haemost. 1999;82(1):6-9.
18. Colman-Brochu S. Deep vein thrombosis in pregnancy. MCN Am J Matern Child Nurs. 2004;29(3):186-192.
19. Iwakura T, Fujigaki Y, Katahashi N, et al. Membranous Nephropathy with an Enhanced Granular Expression of Thrombospondin Type-1 Domain-containing 7A in a Pregnant Woman. Intern Med. 2016;55(18):2663-2668.
20. Aoshima Y, Iyoda M, Nakazawa A, et al. Membranous nephropathy that first presented in pregnancy. Intern Med. 2013;52(17):1949-1952.
21. Orozco Guillen AO, Velazquez Silva RI, Moguel Gonzalez B, et al. Acute IgA-Dominant Glomerulonephritis Associated with Syphilis

Infection in a Pregnant Teenager: A New Disease Association. J Clin Med. 2019;8(1).
22. Nagy, J., I. Sarov, J. Samik, C. Trinn, L. Kun, T. Burger, and B. Sarov. "[Iga and Igg Antibodies to Chlamydia in Iga Nephropathy as Well as in Mesangiocapillary and Membranous Glomerulonephritis]." Orv Hetil 130, no. 29 (Jul 16 1989): 1527-30. Chlamydia elleni IgA es IgG antitestek IgA nephropathias, mesangiocapillaris es membranosus glomerulonephritises betegekben. https://www.ncbi.nlm.nih.gov/pubmed/2671859.