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Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

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Case Report / Приказ болесника

Aleksandra Kezić[1,2], Marko Baralić[2], Đina Tomasević[1], Saša Kadija[1,3], Radmila Sparić[1,3,†]

Various faces of the same disease: membranous nephropathy in pregnancy – a case series

Различита лица исте болести: мембранозна нефропатија у трудноћи – серија случајева

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]Clinical Centre of Serbia, Clinic for Nephrology, Belgrade, Serbia;
[3]Clinical Centre of Serbia, Clinic for Gynecology and Obstetrics, Belgrade, Serbia

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†**Correspondence to:**
Radmila SPARIĆ
Clinic for Gynecology and Obstetrics, Clinical Centre of Serbia, Višegradska 26, 11000 Belgrade, Serbia
E-mail: **radmila@rcub.bg.ac.rs**

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SUMMARY

Introduction Pregnancies in women with membranous nephropathy (MN) are usually complicated by increased proteinuria and superimposed preeclampsia, and this frequently results in poor pregnancy outcomes.

The aim of this paper is to present case series of pregnant women with MN and different fetal and maternal outcomes.

Outline of cases Case 1 presents a 25-year-old woman with MN, who had relapsed nephrotic syndrome in early pregnancy with proteinuria of 4.14 g/day and serum albumin of 30 g/L accompanied by hypertension. Due to a missed abortion, the pregnancy was terminated. Three months later her proteinuria was still increased, measuring 3 g/day.

Case 2 presents a 29-year-old woman with a history of diffuse proliferative glomerulonephritis, who conceived with proteinuria below 0.5 g/day. The proteinuria ranged between 1 and 2 g/day from 32nd until 38th gestational week, when she delivered a healthy neonate. After delivery, the woman underwent a kidney biopsy, which revealed MN.

Case 3 presents a 25-year-old woman with MN, whose proteinuria was 1 g/day at the time of conception, but in the 35th gestational week proteinuria of 4.2 g/day was noticed. In the 36th gestational week, increased proteinuria was detected, and a cesarean section was performed with favorable neonatal outcome. After two weeks her proteinuria dropped to 0.6g/day.

Conclusion Pregnancies in women with MN associated with low-grade proteinuria at the time of conception may have a favorable perinatal outcome. Such pregnancies require multidisciplinary management by both obstetricians and nephrologists, and team decision regarding the best timing of delivery.

Keywords: membranous nephropathy; nephrotic syndrome; pregnancy; preeclampsia; hypertension

САЖЕТАК

Увод Уобичајене компликације трудноће код жена са мембранозном нефропатијом (МН) су пораст протеинурије и развој суперпониране прееклампсије, што често резултира неповољним исходом трудноће.

Циљ овог рада је да прикаже серију случајева трудница са МН и различитим феталним и матерналним исходима.

Приказ случајева Случај 1 представља жену са МН стару 25 година која је имала релапс нефротског синдрома у раној трудноћи са протеинуријом од 4,14 г/дан и серумским албуминима од 30 г/л, удруженог са хипертензијом. Због изосталог побачаја учињен је прекид трудноће. Три месеца касније протеинурија је још увек била повишена са вредношћу од 3 г/дан.

Случај 2 представља 29-годишњу жену са историјом дифузно пролиферативног гломерулонефритиса чија је протеинурија у време концепције била мања од 0,5 г/дан. Протеинурија се одржавала у опсегу од 1 до 2 г/дан од 32. до 38. недеље гестације када је рођено здраво новорођенче. Након порођаја биопсија бубрега је показала МН.

Случај 3 представља 25-годишњу жену са МН чија је протеинурија у време концепције била 1 г/дан, али је у 35. недељи гестације уочена протеинурија од 4.2 г/дан. У 36. недељи трудноће уочен је пораст протеинурије и урађен је царски рез са повољним исходом по новорођенче. Након две недеље њена протеинурија се смањила на 0,6 г/дан.

Закључак Трудноћа код жена са МН и протеинуријом ниског ранга у време концепције може имати повољан перинатални исход. Ове трудноће захтевају мултидисциплинарни приступ акушера и нефролога, као и тимску одлуку о оптималном тренутку порођаја.

Кључне речи: мембранозна нефропатија; нефротски синдром; трудноћа; прееклампсија; хипертензија

INTRODUCTION

The usual complications of pregnancies in women with glomerulonephritis are increased proteinuria, the worsening of hypertension and development of superimposed preeclampsia, frequently resulting in impaired pregnancy outcomes [1]. Moreover, in some instances such pregnancies may result in progressive deterioration of maternal kidney function. Women with nephrotic syndrome are unlikely to carry the pregnancy until term, although there are reported cases with successful pregnancy outcomes [2]. Nevertheless, modern advances in glomerulonephritis treatment, which increases the frequency of complete and partial remissions, and improved perinatal and neonatal care may allow these women to fulfill their reproductive wishes.

Membranous nephropathy (MN) is one of the most common causes of nephrotic syndrome in adults, and frequently affects women of childbearing age [3]. The course of MN is variable. There are spontaneous remissions, although relapses with deterioration of renal function are common, causing end-stage renal disease in about 40% of idiopathic MN [4].

In a review depicting the outcomes of pregnant women with MN more than 30 years ago, the authors reported that the only predictor of an unfavorable maternal or fetal outcome was the presence of nephrotic proteinuria during the first trimester of pregnancy [2]. These findings were confirmed in later studies, which also concluded that the pregnancy outcomes in women with MN or other chronic glomerulonephritis mainly depend on pre-existing proteinuria before pregnancy [5, 6].

Our work aims to report a case series of different pregnancy outcomes in women with MN.

CASE REPORTS

Case 1

A 25-year-old woman was referred to us for generalized body swelling. She was already diagnosed with MN and regularly followed up by a nephrologist for six years. The disease was initially treated with corticosteroids and cyclophosphamide according to the Ponticelli protocol; cyclophosphamide was replaced by mycofenolat mofetil due to recidivant

pneumonia. Partial remission was achieved with sustained proteinuria of 2 g/day. Laboratory investigations revealed proteinuria of 4.14 g/day, serum albumins of 30g/L, with normal parameters of kidney function showing serum creatinine (sCr)-69 μmol/L, blood urea nitrogen-4.2 mmol/L and creatinine clearance (CrCl)-98ml/min and abnormal urinalysis (6-8 leucocytes, 1-2 eritrocytes and 2 granular bodies in a high power field). Her blood pressure was 120/90 mm Hg. The patient reported six weeks amenorrhea. Ultrasonography revealed a normal first trimester pregnancy corresponding to her last menstrual period. Due to an overt nephrotic syndrome, pregnancy termination was advised. However, the patient refused this. Therefore, the therapy with angiotensin-converting enzyme (ACE) inhibitors was discontinued, and methyldopa was introduced. Two weeks later, after episodes of high blood pressure of up to 180/130 mmHg, ultrasonography revealed a missed abortion. Except of proteinuria of nephrotic range with hypoalbuminemia, all other laboratory tests including coagulation status were quite normal. Dilatation and curettage were performed without complications. Three months later her proteinuria, although still increased, was in the subnephrotic range (3 g/day); her serum albumin measured 38 g/L. Her kidney function was stable.

Case 2

A 29-year-old patient with a history of diffuse proliferative glomerolunephritis became pregnant after a regular nephrology check-up documenting stable remission of the disease. She was diagnosed with diffuse proliferative glomerulonephritis by kidney biopsy at the age of 19, when she was presented with nephrotic syndrome requiring treatment with corticosteroids. Systemic lupus erythematosus (SLE) was excluded by thorough investigation . Immunologic analysis showed anti-nuclear antibody (ANA) negativity, and no other laboratory or clinical signs defined by the American Rheumatism Association (ARA) criteria for SLE diagnosis confirmation were detected. Corticosteroid treatment resulted in decreased proteinuria ranging up to 0.6 g/day. At the age of 26, she gave birth to a healthy neonate by cesarean section (CS) in the 36th week of pregnancy due to the development of nephrotic proteinuria, which subsided after delivery to almost a normal range. Afterwards, she was treated only with ACE inhibitors. Before her second pregnancy, her proteinuria was 0.34g/day, with a serum creatinine of 54 μmol/L and CrCl of 102.9 ml/min. ACE inhibitors were replaced by methyldopa. In the 34th gestational week, she exhibited the rise of

proteinuria to the values of about 1 g/day. The patient's blood pressure was normal. The proteinuria ranged between 1 and 2g/day until the 38th week of gestation. By a planned CS she gave birth to a healthy neonate with birth weight of 2.85 kg and Apgar score 10. As her proteinuria did not decrease below 1 g/day for six months, and occasionally even was above 2 g/day, a kidney biopsy was performed again. Histopathology revealed MN with immunofluorescence showing a "full house" pattern. Again, SLE was not confirmed.

Case 3

A 25-year-old patient was followed up during her first pregnancy by a nephrologist due to a history of MN, which had been diagnosed by kidney biopsy ten years ago. She was successfully treated with corticosteroids and cyclosporine A by a pediatrician nephrologist, and complete remission of nephrotic syndrome was achieved. At 18, when she was presented to an adult nephrologist, her proteinuria level was 0.2g/day, and normal kidney function and urinalysis were detected. In the further course of the disease, at the age of 23, her proteinuria increased up to 1 g/day without any deterioration of kidney function and impairment of blood pressure control. Since her proteinuria remained stable for two years, and her kidney function was normal (serum creatinine was 58 μmol/L and CrCl was 126.7 ml/min), ACE inhibitors were replaced by methyldopa therapy before being given consent to become pregnant. Until the third trimester her blood pressure was up to 130/80 mm Hg and proteinuria was stable. In the third trimester continuous rise of proteinuria was observed. Simultaneously, she required higher doses of methyldopa to control her blood pressure that was 150/90 mm Hg. The patient was admitted in the obstetric department in the 35th week of gestation, when her proteinuria was 4.2 g/day. The other laboratory tests showed sCr-54 μmol/L, blood urea nitrogen-3.5 mmol/L, CrCl-163 ml/min, total proteins-53 g/L. The ultrasound revealed intrauterine fetal growth restriction with olygohydramnion and adequate fetal morphology and oxygenation. In the 36th week of gestation, her proteinuria further increased up to 6g/day and was associated with a decrease in serum proteins to 48 g/L and albumin to 24 g/L. After a dexamethason treatment for fetal lung maturity, a CS was performed in the 36th week of pregnancy and a healthy neonate was born. The birth weight of neonate was 2.85 kg and Apgar score was 8. Two weeks later her proteinuria dropped to 0.6g/day, and the patient remained with normal kidney function.

The treatment of all presented patients and reporting of data are in accordance with the ethical standards and the Helsinki Declaration as revised in 2013.

DISCUSSION

Partial remission of nephrotic syndrome i.e. a fast decrease in proteinuria after abortion indicates a detrimental role of a pregnancy for sustaining a stable proteinuria level and MN remission. This once again confirms the literature data that the only predictor of a poor maternal and fetal outcome is the presence of nephrotic proteinuria during the first trimester, although the presence of a lower degree of proteinuria is also associated with higher risk pregnancies [2]. Chronic kidney disease (CKD), even with normal renal function with low-degree proteinuria, represents a substantial risk for adverse maternal and fetal outcomes, predominantly preeclampsia and iatrogenic preterm delivery. The exact mechanism as to why women with glomerulonephritis in remission, who have normal renal function and physiologic proteinuria, are much more prone to adverse pregnancy outcomes is not clear. Case 2 and Case 3 have conceived while being in long-time stable remission with normal kidney function and proteinuria up to 1g/day. However, in the last trimester, Case 3 developed a progressive increase of proteinuria accompanied by a drop in the serum albumin and proteins and a rise in blood pressure. These two associated events contributed to intrauterine fetal growth restriction and necessitated preterm delivery.

Only Case 1 had first trimester pregnancy loss. According to the available studies, the rates of fetal loss in pregnancies complicated by MN range from 24 to 35%, and these occur mostly in the first trimester [1, 7, 8]. A systematic review of six studies showed that the average live birth rate in patients with MN was 86.3%, with only 4% of the fetal losses occurring after the first trimester [8]. However, results regarding adverse maternal or fetal outcomes in pregnant women with MN in the literature are inconsistent. For instance, Packham et al. [2], who analyzed 33 pregnancies, reported a total of 24% of fetal losses, a 43% prematurity rate, and a 33% live birth rate with full-term deliveries.

The severity of glomerulonephritis induced complications in pregnancy can vary with different pregnancies even in the same woman. The course of the second pregnancy in Case 2 was less complicated than the course of her first pregnancy. Regarding this patient there is an open question whether she conceived with underlying MN, or it was developed during

pregnancy. However, the presented course did not urge kidney biopsy during pregnancy, or even therapy with corticosteroids or some immunosuppressive agents.

If nephrotic syndrome is manifested in the first trimester, kidney biopsy can be performed; the treatment of MN can be attempted bearing in mind the possible complications such as, in addition to fetal loss with or without the worsening of maternal kidney function, the appearance of adverse effects associated with immunosuppressive therapy itself [9]. The least toxic immunosuppressive agents used to treat various diseases in pregnancy are azathioprine and cyclosporine. There are several reported cases regarding the treatment of MN in pregnancy, mainly with corticosteroids, which all ended either with preterm delivery or with early elective termination of pregnancy [5, 10-12]. Cyclosporine used in post-transplant maintenance therapy may be used to treat some forms of glomerulonephritis in pregnancy, including MN [13]. Whether the physician will advise either immunosuppressive therapy or termination of pregnancy in women with high-grade proteinuria depends on several factors. The presence of nephrotic proteinuria in the first trimester poses a high risk for the pregnancy outcome even if immunosuppressive therapy is implemented. If there is hypertension that requires high doses of methyldopa and nifedipine along with nephrotic proteinuria, the chances for a successful pregnancy outcome, even with applied immunosuppressive therapy, is almost negligible. Progression of proteinuria regardless of whether corticosteroids and/or other immunosuppressive medications were applied is an indication for pregnancy termination.

Women with MN are less able to accomplish physiological renal adaptations that are essential for a favorable perinatal outcome, particularly in cases when the MN is not in stable remission. Besides the efforts towards decreasing proteinuria in pregnancy, the control of hypertension plays an extremely important role. Superimposed preeclampsia, apart from maternal complications, frequently impairs fetal growth and oxygenation, thus indicating iatrogenic preterm delivery. Despite renal disease, its etiology and duration, the presence of hypertension at the time of conception carries a 10.6 times higher relative risk of fetal loss compared to when blood pressure is well-controlled by therapy, or even when it is normal without therapy [7]. Anyway, the impact of MN on maternal and fetal outcomes of pregnancy is still unclear given the observed different courses of subsequent pregnancies in patients with MN, or even the spontaneous remission of nephrotic syndrome in pregnant women with MN [14, 15].

In conclusion, preconceptional counseling is essential in women with MN in order to optimize both maternal and fetal outcomes. These patients require multidisciplinary management by both obstetricians and nephrologists along with careful follow-up, before and after delivery. Women with MN who still have nephrotic proteinuria in spite of conducted immunosuppressive therapy should not be encouraged to become pregnant. In pregnant women, close monitoring is essential to detect the signs of fetal or maternal compromise in a timely manner. One must bear in mind that for a woman with progressive CKD who conceives, the index pregnancy might be the last opportunity for childbearing. Timely referral of such patients to tertiary care centers with appropriate neonatal care, due to risks associated with prematurity, is warranted. The appearance of nephrotic proteinuria in pregnant women with previously diagnosed MN poses a significant challenge and requires team decision regarding the best timing of delivery, while still leaving an open question regarding the implementation of immunosuppressive therapy.

Conflict of interest: None declared.

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