

# Management of Membranous Glomerulonephritis in Pregnancy: A Multidisciplinary Approach

Preeti Lewis<sup>1</sup>, Annapurna Brahma<sup>2</sup>

Grant Government Medical College & Sir J.J. Group of Hospitals, Department of Obstetrics and Gynecology, Mumbai, India

Correspondence should be addressed to Annapurna Brahma:

annapurnabrahma2211[at]gmail.com

**Abstract:** We present a case of 21-year-old female, gravid 2, para 1 and intra-uterine fetal demise 1, a biopsy proven case of membranous glomerulonephritis, who had a past obstetrical history complicated by uncontrolled blood pressure, early onset preeclampsia, and a fetal demise at 30 weeks, COVID 19 positive status requiring Ventilatory Support. Her blood pressure normalized after previous pregnancy. In the recent pregnancy, she remained normotensive and initially presented with normal blood urea nitrogen and creatinine levels. However, after the early first trimester, she developed nephrotic range proteinuria, hypoalbuminemia, and peripheral edema which was diagnosed early and managed appropriately. Afterwards, all clinical symptoms resolved and laboratory values normalized and patient delivered vaginally. We review the clinical course, diagnosis, and management of known case of membranous glomerulonephritis in pregnancy.

**Keywords:** Membranous glomerulonephritis, proteinuria, preeclampsia

## 1. Introduction

Membranous glomerulonephritis, one of the causes of nephrotic syndrome, is histopathologically defined by the presence of immune complexes on the extracapillary side of the glomerular basement membrane [1]. Most often this condition is idiopathic; however, it can be secondary to wide spectrum of infections, tumors, autoimmune diseases, or exposure to drugs or toxic agents. Even before conception occurs, adaptive renal changes for a possible pregnancy commence. During the luteal phase of each menstrual cycle, renal blood flow and glomerular filtration rate (GFR) increase by 10–20% [2]. If pregnancy is established, these hemodynamic changes continue. By the mid second trimester, renal blood flow peaks to 70–80% above non pregnant levels, leading to an increase in GFR of approximately 55%. The effect of pregnancy and its associated physiological adaptive changes can unmask occult underlying renal disease with proteinuria. In addition, the presence underlying glomerular disease can lead to increased pregnancy complications and have adverse effect on fetal outcome. [2]

Thus, pregnancy in a young woman with GN increases both maternal and fetal risk. Adverse maternal outcomes include progression of underlying renal dysfunction, worsening of urine protein, and hypertension and the adverse fetal outcomes include fetal loss, intrauterine growth restriction, preterm delivery and increased NICU admissions. Nephrotic syndrome doesn't discourage women to undertake pregnancy.

The obstetrics outcome in women with kidney disease has improved in recent years due to continuous progress in obstetrics and neonatology, as well as better medical management of hypertension and renal disease. However, every pregnancy in these women remains a high risk pregnancy, and hence, the correct management may include a specific evaluation of risk factors and follow-up the adverse

materno-fetal events and/or maternal kidney disease progression.

## 2. Case Report

A 21 years old female who presented at the age of 17 years with edema, proteinuria and hypertension. The serological tests including ASO, Anti DNAase, ANA, Anti DNA, Hep B, Hep C, Viral antibodies were negative. The C3, C4 levels were in the normal range. The other significant lab findings included serum creatinine level- 3.4 mg/dL, serum albumin level- 2.2 g/dl, 24 hr urine protein -3200mg, abnormal urine analysis showing WBC cast and 4+ albuminuria. A percutaneous renal biopsy was performed after the clinical presentation when clinical and serological improvement didn't occur. Biopsy report was suggestive of Membranous Glomerulonephritis with IgG, IgM, C3, C1q and fibrinogen were all negative on Immunofluorescence, minimally involved glomeruli in the presence of proteinuria, the latter may be noted in Minimal Change disease or Focal Segmental Glomerulosclerosis, in view of tubal atrophy, the possibility of Focal segmental glomerulosclerosis cannot be excluded on light microscopy and on Electron microscopy, the glomerulus was normocellular. All the loops showed diffuse foot process flattening. Few subepithelial and intramembraneous electron dense deposits were seen. In regions, these appeared to be resolving. No sclerosis or organised deposits were detected

Over the next year, the patient continued to be mildly nephrotic with edema and hypertension being controlled with diuretics, ACE Inhibitor. Serum creatinine was ranging between 0.7- 0.9 mg/dL and serum albumin ranging from 2.2- 3.1 g/dL. At 19 years of age, the patient became pregnant during the non complaint period and the patient was referred to the Antenatal OPD of tertiary care centre at around 24 weeks of gestation in view of uncontrolled hypertension and progressing edema and proteinuria and breathlessness. The

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patient was hospitalized and all the routine investigations were sent. The Obstetrics Ultrasound was suggestive of intrauterine growth restriction with uteroplacental insufficiency. The dosage of anti hypertensive was stepped up and BP monitoring was continued. Meanwhile, the edema was increasing and patient continued to complain about breathlessness and was not maintaining Oxygen saturation in room air. Nasopharyngeal swab was sent for COVID RT-PCR and was tested positive. HRCT thorax was done suggestive of moderate bilateral pleural effusion and ground glass opacities. Then, the patient was shifted to SARI ICU at a COVID dedicated centre and was put on ventilator support. Obstetrics ultrasound was done s/o intrauterine fetal demise. Induction of labor was done with dinoprostone gel and delivered vaginally. Post delivery, patient continued with diuretics, ACE inhibitor and oral steroid. After 11 months, the patient presented at 8 weeks of gestation in the ANC clinic for ANC Registration. All the medications were stopped and patient was started on tab folic acid and tab labetalol as per Nephrology opinion. At around 15 weeks of gestation, the patient was hospitalized for increasing edema, decreased urine output and nephrotic range proteinuria. The patient was started on intravenous methylprednisolone, received antihypertensive, prophylactic anticoagulant therapy and supplemented with fresh frozen plasma (FFP) and albumin. Patient was advised sodium restriction, bed rest with intermittent ambulation and leg elevation. After discharge, the patient routinely followed up in the Department of nephrology and ANC clinic, initially fortnightly followed by weekly visits 32 weeks onwards. In every visit, patient was assessed for clinical signs of anasarca, pallor, proteinuria, urine albumin dipstick, serial weight measurement and the ability to perform daily activity apart from the routine examination. She was watched for any evidence of development of preeclampsia, worsening of symptoms or fetal abnormality. Patient was admitted in the antenatal ward at 36 weeks of gestation and maternal and fetal surveillance was continued.

Patient went into labour spontaneously at 37 (+ 5 days) weeks of gestation. Labour room monitoring was done. Patient delivered vaginally a healthy male child of weight 2.7kg. Delivery was uneventful. Patient was counselled for contraception and PPIUCD was inserted. Post delivery, mother and the baby were both vitally stable and discharged on day 5 post delivery after obtaining fitness from Nephrology. The clinical status of the patient was stable during the entire pregnancy with exception of one period of increased edema and proteinuria despite the presence of nephrotic syndrome, a healthy full term infant was born.

### 3. Discussion

MPGN is a descriptive diagnosis that encompasses a wide variety of underlying etiologies [3]. Most often this condition is idiopathic; however, it can be secondary to wide spectrum of infections, tumors, autoimmune diseases, or exposure to drugs or toxic agents [4]. Idiopathic MPGN is a diagnosis of exclusion in a patient with a distinctive kidney biopsy. Several biopsy patterns have been recognized, the most common

characterized by enlarged glomeruli with diffuse lobular mesangial matrix expansion, hypercellularity, endocapillary proliferation (capillary obliteration), and capillary wall thickening. Immunofluorescence usually reveals diffuse mesangial and capillary staining, predominately with IgG and C3. Electron microscopy usually shows sub-endothelial electrondense deposits with varying amounts of intramembranous, mesangial, and sub-epithelial deposits.[3]

Due to the hemodynamic changes associated with pregnancy, renal disease may initially be masked. The increase in GFR during pregnancy leads to a fall in serum creatinine concentration, so that values that are normal in the nonpregnant state may be considered elevated during pregnancy. Proteinuria increases as pregnancy progresses while serum albumin levels decline by 5–10 g/L. However, the presence of nephrotic range proteinuria with or without hypertension in the first trimester is pathological and may be associated underlying renal disease and a poor prognosis [5]. In patients presenting with significant proteinuria during early gestation, biopsy is necessary as treatment options differ depending on the etiological cause. Although some studies have shown good neonatal outcomes in patients with nephrotic syndrome [4], others have demonstrated rates of fetal loss ranging from 24 to 35% [6-8]. Most of these losses were attributed to first trimester spontaneous abortions. In a systematic review of six studies, Lindheimer and Katz concluded that the average live birth rate in patients with membranous glomerulonephritis was 86.3%, with 4% of the losses occurring after the first trimester [8]. This data is in agreement with a study by Jungers et al. that retrospectively reviewed 43 pregnancies associated with impaired renal function. Of the 43 pregnancies, 13 ended in fetal death (including 5 first-trimester abortions and 8 fetal deaths beyond the 20th gestational week) [6]. Other adverse fetal outcomes that have been associated with nephritic syndrome include preterm delivery and low birth weight; however, results for these outcomes have not been consistent between studies [6].

The influence of MGN on maternal and fetal outcome is controversial, as is the effect of pregnancy on the course of preexisting nephrotic syndrome [6]. Packham et al. [7] concluded that pregnancy in patients with MGN is associated with an increased fetal loss and, in some instances, a worsening in maternal renal function. They also found that the presence of nephrotic range proteinuria during the first trimester correlates with both poor fetal and maternal outcome [7]. On the other hand, Malik et al. [6] reported a good maternal and fetal outcome in patients with primary MGN. Nonetheless, none of their 9 patients were hypertensive at the time of the first pregnancy, after MGN had been diagnosed. Katzir et al. [8] reported a case of successful management of pregnancy in a patient with uncontrolled hypertension and nephrotic range proteinuria.

Managing nephrotic syndrome in pregnancy is difficult. The patient's intravascular fluid status, as opposed to the severity of peripheral edema, needs to be assessed when administering diuretic therapy. Many patients with a low serum albumin may

have gross peripheral edema but may have diminished intravascular volume. Aggressive diuresis will worsen the intravascular depletion, causing poor placental perfusion and increasing the risk of acute renal failure. Adequate anticoagulation in pregnant patients with nephrotic range proteinuria is important, as renal vein thrombosis has been reported [9]. Nephrotic syndrome is associated with hypercoagulability due to increased clotting factors V, VII, and VIII, fibrinogen, and 2-antiplasmin and depletion of factors IX and XII, antithrombin III, and plasminogen. Adaptations of pregnancy, including increased fibrinogen, factors VII, VIII, and X, and decreased fibrinolytic activity, also increase hypercoagulability [8]. In order to optimize both maternal and fetal outcomes in patients with known renal disease, preconceptional counseling is essential. Malik et al. retrospectively reported outcomes of repeated pregnancies in patients with known primary membranous [6]. Of the 30 pregnancies, there was a 90% live birth rate with only one perinatal mortality reported [6]. Jungers et al. demonstrated higher live birth rates in pregnancies that started with serum creatinine levels less 0.20mmol/L than in those with serum creatinine greater than 0.20mmol/L. The presence of maternal hypertension was the major factor influencing fetal prognosis, as the relative risk of fetal loss was 10.6 times higher when hypertension was present at conception or early in pregnancy compared to when blood pressure was normal or well-controlled by therapy [7]. In patients that had both uncontrolled hypertension and proteinuria at conception, an accelerated course toward end-stage renal failure was observed in 7 patients (23%) [7]. Therefore, the differences seen in previous reports regarding maternal and fetal prognosis might be explained by the different severity of glomerulonephritis and the differences in renal follow-up and compliance prior to pregnancy and appropriate timing of pregnancy and optimization of both maternal blood pressure and renal function can allow better outcomes.

Thus, in our case, fetal outcome in MPGN was good despite severe proteinuria and renal dysfunction in the mother when our patient conceived during the phase of remission. First, therapy may be limited to antihypertensive agents alone when renal function is stable and proteinuria is minimal. Later on, when renal function worsened and proteinuria became severe, "pulse" corticosteroid therapy with methylprednisolone followed by high dose oral prednisone therapy was safe and may be the most appropriate initial strategy. While other therapies have been reported in MPGN, no conclusions can be drawn regarding their efficacy. Finally, our patient required precise coordination of care from a multi-disciplinary team that communicated effectively regarding all therapeutic decisions, the prognosis of the mother and the baby.

#### **4. Conclusion**

During the preconceptional period, the disease activity has to be assessed with repeat biopsy confirmation, if necessary. Main goal should be optimization of BP control and change to non teratogenic medications and reassurance about

continuation of safe medications in pregnancy. Risk of pregnancy complications and need for heightened surveillance to be explained. Once the patient conceives, she should be encouraged to register at a tertiary hospital preferably and consult the nephrologist as well. Our target BP should be less than 140/90 mmHg, low dose Aspirin to be considered along with vitamin D and calcium. Patient should be advised baseline and serial renal function, proteinuria (albumin to creatinine or protein to creatinine ratios or 24hr collections), Oral glucose tolerance test especially important in women taking steroids or calcineurin inhibitors. Frequent fetal monitoring for fetal wellbeing like upto twice weekly Biophysical profile and upto to weekly placental Dopplers, weekly growth scans. VTE Prophylaxis to be considered if risk factors like nephrotic syndrome, previous VTE, high BMI. Termination of pregnancy by either induction of labour or C-section, whenever indicated should be considered if presence of fetal or maternal decompensation is noticed. Corticosteroid administration for fetal lung maturation at least 24 hrs and upto 7 days prior to anticipated delivery if < 34weeks gestation. Ideal, Vaginal delivery is preferred. In the post partum period, patient should be encouraged for breast feeding. Careful surveillance for active GN should be continued. VTE Prophylaxis to be continued for atleast 6 weeks if necessary. Finally the role of emotional support by the family members and proper counseling by the obstetrician and the neonatologist should not be undermined.

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## Author Profile

**Dr Preeti Frank Lewis** works as an Associate Professor and Head of the Unit in the Department of Obstetrics and Gynaecology in Grant Government Medical College & Sir J. J. Group of Hospitals, Mumbai. Apart from being an academician and a surgeon, she has keen interest and expertise in the field of high risk obstetrics and medicolegal cases and audits. She has been acted upon as a member of medical board for various High court medical termination of pregnancy, RTI cases, maternal mortality and near miss cases review and audit. She has been the Guide and chief mentor of many post graduate students and mentors the post graduate and under graduate students for research work, paper publication, dissertation and thesis publication.

**Dr Annapurna Brahma** works as a Junior Resident in the Department of Obstetrics and Gynaecology in Grant Government Medical College & Sir J. J. Group of Hospitals, Mumbai. She has a keen interest in the field of High Risk Obstetrics, medical disorders in pregnancy and critical care management of Obstetric patients.