Nephrotic syndrome due to focal segmental glomerulosclerosis occurring in early pregnancy

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Summary: Physiological proteinuria is common during pregnancy, but pathological proteinuria may also occur. Nephrotic range proteinuria most commonly occurs due to preeclampsia, but primary renal disease may also occur. We present a case of a woman who presented with nephrotic range proteinuria and nephrotic syndrome at an early stage of her second pregnancy. Due to proteinuria, haematuria, progressive symptoms and high need for medical treatment, renal biopsy was performed and she was noted to have focal segmental glomerulosclerosis (FSGS). She commenced immunosuppression but remained nephrotic during pregnancy. She delivered a healthy baby boy at 35 weeks gestation. Postpartum she remained nephrotic, and developed further complications requiring renal replacement therapy. Despite a successful pregnancy, this case of FSGS highlights that despite aggressive treatment FSGS in pregnancy is often associated with adverse renal outcome. We discuss investigations, including renal biopsy and empiric treatment options in this report.

Keywords: nephrology, maternal–fetal medicine, high-risk pregnancy, general medicine, drugs (medication)

INTRODUCTION

Physiological proteinuria, defined as less than 300 mg of urinary protein in 24 hours, is common during pregnancy, but pathological proteinuria may also occur and is most frequently associated with preeclampsia. However, primary or secondary renal disease may occur during pregnancy with pathological proteinuria as the presenting feature. Pregnancies associated with renal disease are high risk, and management is complex due to higher rates of maternal and fetal complications.¹

CASE PRESENTATION

A 32-year-old Caucasian woman presented at 14 weeks gestation with shortness of breath at rest. She had paroxysmal nocturnal dyspnoea, four pillow orthopnoea, cough productive of frothy sputum and pitting oedema to mid abdomen. She was normotensive. Urinalysis revealed 4+ proteinuria and 2+ haematuria. At her first antenatal visit, at eight weeks, she was normotensive with 2+ proteinuria. She had one previous successful pregnancy that was uncomplicated with no previous history of preeclampsia. Medical history was remarkable for severe psoriasis and she was taking no regular medications.

Investigations showed urea 2.7 mmol/L (1.1–4.1 mmol/L), creatinine 30 µmol/L (36–77 mmol/L) and albumin 19 g/L (27–39 g/L). Full blood count showed haemoglobin 8.9 g/dL (9.8–13.7 g/dL) and other parameters were normal.

A 24-hour urine collection showed 9 g protein. No casts were demonstrated on urine microscopy. Renal ultrasound was normal. Serum protein electrophoresis revealed hypogammaglobulinaemia. Autoimmune and viral screens were negative. A diagnosis of nephrotic syndrome was made.

She remained an inpatient throughout her pregnancy. Management included fluid restriction, low sodium diet and increasing doses of intravenous diuretics for worsening volume overload with evidence of pulmonary oedema on serial chest radiographs. She was anticoagulated with prophylactic dose tinzaparin. Renal biopsy was performed under real-time ultrasound guidance at 16 weeks gestation in the prone position. Histology showed features of focal segmental glomerulosclerosis (FSGS) including diffuse foot process effacement on electron microscopy, consistent with a diagnosis of primary FSGS. Features were consistent with the cellular variant of FSGS.²

The patient was commenced on prednisolone 40 mg and azathioprine 100 mg daily. There was no clinical response and she remained heavily nephrotic throughout pregnancy, requiring repeated intravenous diuretics and albumin to manage gross peripheral oedema and pleural effusions. Prednisolone was slowly tapered due to the absence of clinical response. Proteinuria remained over 9 g in 24 hours with a serum albumin of 23 g/L prior to delivery. The safety of cyclophosphamide administration during pregnancy is controversial and after discussion of the risks and benefits with the patient, a decision was made not to proceed. No other immunosuppression was initiated during pregnancy due to lack of clinical response to prednisolone.

Because of the high-risk nature of the pregnancy, she was reviewed weekly in the antenatal clinic with alternate week fetal growth scans. Polyhydramnios was not noted at any

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point during the pregnancy, nor were there any features of intrauterine growth restriction. Due to persistent difficulties with management of maternal nephrotic syndrome and evidence of fetal maturity, a multidisciplinary team decided on planned induction of labour to occur at 35 weeks gestation. Methods included artificial rupture of membranes, syntocinon and prostaglandin E. Fetal distress was noted on the cardiotocograph and she subsequently underwent emergency caesarean section. She was delivered of a baby boy weighing 1890 g (20th centile for gestation). The umbilical cord was found around the fetal neck but liquor was clear. APGAR score at one minute was six, and at five minutes was nine. The baby was transferred to the Special Care Baby Unit but had no acute complications. Placental delivery was uncomplicated and histology showed evidence of impaired placental circulation but no preeclamptic changes.

Postpartum, nephrotic range proteinuria (12 g in 24 hours) persisted and she became hypertensive. She was counselled against further pregnancies and tacrolimus and antihypertensive agents were initiated. Despite nine months of treatment, she remained severely nephrotic and serum creatinine rose to over 300 $\mu\text{mol/L}$, consistent with persistent renal impairment. Unfortunately she developed severe *Salmonella* gastroenteritis with dialysis-requiring acute kidney injury. There was no recovery of renal function and she remains dialysis dependent awaiting renal transplant.

DISCUSSION

Management of nephrotic syndrome during pregnancy is focused on identifying and treating the cause of renal disease. If caused by preeclampsia, definitive treatment is delivery. Oedema can be reduced using fluid restriction, low salt diet and parenteral albumin administration. Diuretics are often avoided due to an increased risk of fetal and maternal complications secondary to reduced plasma volume,³ but there is no evidence of significant effects on perinatal mortality.⁴ In our case, diuretics were used for symptomatic relief due to profound volume overload.

Pregnancy itself has been associated with an elevated risk of thromboembolic disease.⁵ Similarly, nephrotic syndrome is associated with an increased risk of deep venous thrombosis, renal vein thrombosis, pulmonary embolism and arterial thromboembolism.⁶ This is felt to occur due to increased prothrombotic factors such as fibrinogen, factor VIII and platelet adhesiveness, in addition to reduced protein C, protein S and antithrombin III levels.⁷ As our patient had both conditions, she was treated with prophylactic dose low molecular weight heparin during the pregnancy.

For optimum management of primary renal disease during pregnancy, it is important to identify the underlying aetiology in order to initiate potential disease-modifying treatments. As such, renal biopsy should be considered when sudden unexplained deterioration in renal function or symptomatic nephrotic syndrome occurs. A previous series of renal biopsies performed during pregnancy showed high complication rates including haematuria, peri-renal haematoma and maternal death,⁸ but more recent studies have shown similar complication rates in pregnant and non-pregnant patients with well-controlled blood pressure and normal coagulation parameters.^{9,10} Our patient underwent renal biopsy in line with this evidence, and experienced no complication.

Historically, renal biopsy specimens taken from preeclamptic subjects have shown lesions that closely resemble FSGS,¹¹ but usually remit postpartum when preeclampsia has resolved.¹² Due to the very early onset and persistence of pathological proteinuria, presence of haematuria (which is not typical of preeclampsia), progressive symptoms and lack of response to empiric treatment, the working diagnosis in this case was against preeclampsia and renal biopsy was performed. As she remained heavily nephrotic for nine months postpartum, a diagnosis of FSGS was confirmed. A case of nephrotic syndrome in the 17th week of pregnancy due to FSGS complicated by intrauterine death has been reported.¹³ Significantly, the risk of progression to advanced chronic kidney disease varies with individual variants of FSGS, although data are somewhat limited. Low glomerular filtration rate (GFR) and proteinuria appear to increase the risk of progression to end stage renal disease.¹⁴ Consistent with this research, our patient had this degree of low estimated GFR postpartum and persistent proteinuria.

Traditional agents to treat FSGS, including glucocorticoids, are safe for use in pregnancy as prednisone, prednisolone and methylprednisolone cross the placenta at very low concentrations, with no significant fetal effects. Prednisolone use has been reported to be associated with preterm delivery¹⁵ and gestational diabetes.¹⁶ Although not currently part of standard non-pregnant management of FSGS, azathioprine is also safe for use in pregnancy, as active metabolites do not cross the placenta. Tacrolimus is considered safe for use during pregnancy, but mycophenolate mofetil is absolutely contraindicated for use during pregnancy due to increased rate of first trimester pregnancy loss and congenital malformations.¹⁷

Cyclophosphamide was traditionally avoided during pregnancy. It is occasionally used when there is no alternative for life-threatening maternal disease as there is a very high fetal loss rate, with one study showing no live births following administration.¹⁸ A number of studies on the management of breast cancer in pregnancy demonstrate safe cyclophosphamide in usage during the second and third trimester without significant complications for the majority of children exposed.¹⁹⁻²¹ Many physicians continue to avoid the use of cyclophosphamide in pregnant patients. In our case, a detailed discussion was had with our patient and an informed decision was made.

In our case, no response to immunosuppression occurred, and due to potential associated risks, therapy was withdrawn during pregnancy. Further therapy was trialled after pregnancy and no response was seen. FSGS occurring during pregnancy frequently does not respond to standard medical therapy,²² and although pregnancy may be successful, poor renal outcomes may occur.

CONCLUSION

This case highlights the difficulties in management of nephrotic syndrome during pregnancy, including timing of renal biopsy and treatment options. Although preeclampsia is the most common underlying condition presenting with nephrotic range proteinuria, this case highlights the fact that primary renal disease may also present during pregnancy. When these cases are managed aggressively, pregnancy outcome may be good, but renal outcome may not be favourable. We suggest that cases are jointly managed by obstetricians and nephrologists with an interest in obstetric nephrology.

DECLARATIONS

The authors report no conflicts of interest and have no other declarations. This manuscript is not currently under consideration for publication in any other journal, nor has it been published, in part or its entirety, in any other journal.

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