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Clinical Report

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Urinary protein selectivity in nephrotic syndrome and pregnancy: resurrection of a biomarker when renal biopsy is contraindicated

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Abstract
Significant proteinuria in pregnancy can indicate the presence of serious conditions requiring investigation and treatment. The nephrotic syndrome in pregnancy presents a multitude of difficulties and is a relative contraindication of renal biopsy, particularly in the third trimester. We present a case of nephrotic syndrome of unknown cause presenting at 33 weeks of pregnancy. With renal biopsy contraindicated, we used the urine protein selectivity test, a largely discarded test predicting steroid-responsive nephrotic syndrome, to help inform the decision to give steroids. This led to a successful clinical outcome including the avoidance of neonatal ICU care for baby.

Keywords: biomarker; nephrotic syndrome; pregnancy; protein selectivity; renal biopsy

Introduction

Significant proteinuria in pregnancy can indicate the presence of serious conditions requiring investigation and treatment. Although pre-eclampsia is the commonest cause of heavy proteinuria and hypoalbuminaemia, potentially treatable primary glomerular disease is an important differential diagnosis. While pre-eclampsia necessitates prompt delivery, nephrotic syndrome in pregnancy due to glomerular disease may allow management aimed at prolonging gestation to improve fetal outcome. Complications of the nephrotic state include those of hypoalbuminaemia and fetal/placental consequences combined with increased tissue fragility and increased thrombotic tendency. There is relative contraindication of renal biopsy, particularly in the third trimester [1, 2], with complications such as post-biopsy haemorrhage that could be catastrophic for both mother and fetus. Therefore biomarkers of primary glomerular disease can be of utmost importance to help guide treatment and management. Unfortunately not all glomerular diseases have routinely available biomarkers, in particular those more common conditions such as minimal change disease, presenting a diagnostic and management dilemma in the pregnant nephrotic patient. Here we present a case of nephrotic syndrome of unknown cause presenting at 33 weeks of pregnancy. With renal biopsy contraindicated, we used the urine protein selectivity test included in a comprehensive range of biomarkers, to attempt to predict the underlying glomerular pathology and guide therapy. This largely discarded test predicting steroid-responsive nephrotic syndrome, commonly associated with minimal change histopathological findings, informed the decision to give steroids and led to a successful clinical outcome including avoidance of need for neonatal ICU care for baby.

Case report

Mrs G, a healthy 38-year-old, gravida 2 para 1, presented with a 2-week history of bilateral leg swelling. Blood pressure was 110/72 mmHg, eGFR >90, serum albumin 13 g/L and urine protein/creatinine ratio (uPCR) 928 mg/mmol. With normal blood pressure, renal function, good urine output and no signs of fetal compromise, pre-eclampsia was clinically excluded by the fetal-maternal-renal multi-disciplinary team following admission.

Within 24 h, in view of the profound proteinuria and hypoalbuminaemia, early induction of labour, with Neonatal Intensive Care Unit (NICU) backup, was considered. With pre-eclampsia excluded clinically, the most likely diagnosis for her proteinuria was a primary renal pathology. At 33 weeks gestation and with renal biopsy contraindicated [1, 2], an alternative investigation was sought to identify the underlying pathology with the potential for prompt response to treatment.

Full autoimmune screen was negative but urine protein selectivity, performed at the Supra-Regional Assay Service (SAS) Protein Reference Unit, Sheffield, demonstrated selective proteinuria (selectivity index) of 0.2 (highly selective <0.16; selective <0.3; non-selective >0.3). Given that the protein selectivity test has a high correlation with steroid responsiveness, Mrs G was commenced on high-dose steroids at 60 mg daily (Day 1). The results of the protein selectivity test also provided further reassurance that this presentation was unlikely to be pre-eclampsia [3–6]. She showed prompt clinical and biochemical

improvement and was discharged on Day 7 with uPCR 51 mg/mmol and albumin 23 g/L.

Mrs G was followed up in the antenatal clinic where she remained in remission. A fetal USS at Week 35 + 5 (Day 21) showed static growth of the abdominal circumference and a decision was made to induce labour. At 35 + 6 (Day 22), Mrs G delivered a healthy baby boy weighing 2.52 kg who did not require admission to NICU.

After discharge, the steroids were planned to be reduced over a 6-month period although unfortunately she had three relapses over the subsequent 12 months. A renal biopsy was offered but the patient refused due to family circumstances; however, the relapsing and remitting nature of the disease course and its dramatic response to steroids lends credence to the presumed diagnosis of minimal change disease (MCD).

Discussion

During normal pregnancy proteinuria may increase within modest limits but the presence of significant proteinuria is still an indication that there could be serious complications associated with the pregnancy that require investigation. The vast majority of cases of nephrotic syndrome in pregnancy are caused by pre-eclampsia, which can affect 2–5% of all pregnancies [7, 8], and is associated with nephrotic syndrome and hypertension. It has also been recognized, from as early as 1937, that a primary glomerular disease can cause nephrotic syndrome in a minority of pregnant patients although in these earlier reports histological confirmation was not possible [9, 10].

Over the years, a number of reports described the nephrotic syndrome in pregnancy suggesting that MCD (the most readily treatable of these conditions) is a rare occurrence, especially *de novo* MCD. Indeed, a literature search only revealed two previous case reports of histologically proven *de novo* MCD in pregnancy [11, 12] and one case report consistent with *de novo* MCD but without histological confirmation [13]. Even in case series following the course of patients with previously known primary glomerular disease through pregnancy, those with minimal change disease remain in the minority [14–17].

In the two reports of histologically proven *de novo* MCD the patients presented with oedema early in the course of the pregnancy at 19 weeks gestation, compared with our patient who presented late on in her pregnancy. One patient did require temporary haemodialysis for 17 days early in the disease course for acute kidney injury secondary to her MCD with subsequent renal recovery. Reassuringly though, all three patients had good outcomes for both mother and baby, responding well to steroids both clinically and biochemically. One baby was born via emergency caesarean section at 34 weeks gestation. The other two were born by normal vaginal delivery, again with no fetal compromise [11, 12] (see Table 1).

Proteinuria can occur as a result of damage to any layer of the glomerular filtration barrier. Depending on the level and nature of the damage, differing sizes of protein molecules leak through. In MCD, there is loss of small molecules such as albumin and transferrin via filtration, but larger molecules, such as IgG, are retained.

The cause of nephrotic syndrome is generally diagnosed on renal biopsy but with a higher complication rate in pregnancy this is only undertaken after careful collaborative discussion; and never beyond 30 weeks [1, 2]. An alternative investigation (as in all situations when renal biopsy is contraindicated) was therefore required in our patient if treatment was not to be purely empirical.

Among the many biomarkers of glomerular disease, the use of urinary protein selectivity has declined with the increasing use of renal biopsy as the investigation of choice for the nephrotic syndrome. Given this, protein selectivity is not widely available but can be referred to specialist centres such as the NHS SAS Protein Reference Units.

In the protein selectivity test, the concentrations of a small (albumin or transferrin [18]) and a large molecule (IgG) are measured in serum and urine and the ratio of the clearances calculated which reflects respective glomerular filtration of these molecules [19]. Selective proteinuria (highly selective <0.16; selective <0.3) demonstrates a greater loss of the smaller transferrin molecules compared with the larger IgG molecules and has been shown to have a high correlation with steroid responsiveness; the more selective the proteinuria corresponding to a greater chance of response to steroid therapy. The majority of patients with selective proteinuria also demonstrate MCD on biopsy [20].

While selectivity of proteinuria cannot accurately predict minimal change histology, it has been shown to correlate exceedingly well with steroid responsiveness. In 1964, Joachim *et al.* [21] found that patients with the nephrotic syndrome secondary to intrinsic renal disease demonstrating a high degree of protein selectivity before treatment appear to respond better to steroid therapy regardless of the histological findings. Cameron *et al.* [20] confirmed this, showing that highly selective proteinuria was strongly associated with response to steroids within 8 weeks. This study also found that a response to steroids within 8 weeks is a very good indication that a minimal change lesion is present in the kidney, as this was the only histological finding associated with a complete response to steroid therapy within this time period. In children, it has also been suggested that where such a lesion is expected, in the majority of patients, i.e. those without purpura, hypertension or haematuria, an 8-week trial of steroids may be started without an initial biopsy and with a high expectation of success [20].

Table 1. *De Novo* minimal change disease in pregnancy case reports

Reference	Year	Gestation	Proteinuria[a]	Prednisone	Tapering	Delivery	Induced	Method	Fetal weight	Renal biopsy	Comments
T.C McCleave	1951	24 weeks	8.8 g	–	–	Term	–	–	–	No	Low Na, high protein diet
D.B. Nelson	2003	19 ½ weeks	3.5 g	30 mg BD	4 months	34 weeks	Yes	C-section	2086 g	Yes	
Lo *et al.*	2013	19 weeks	15.4 g	1 mg/kg OD	6 months	35 + 6/7th	Yes	Vaginal	2740 g	Yes	HD for 17 days
Current case	2014	33 weeks	9.28 g	60 mg OD	>12 months	35 + 6th	Yes	Vaginal	2520 g	No	

[a]Proteinuria on admission.

Cameron's study found that a highly selective pattern of differential protein clearance was associated with a minimal change or mild proliferative lesion and poorer selectivity with the more severe forms of glomerulonephritis. A selectivity index of <0.1 makes a minimal change likely and >0.3 makes minimal change disease a remote possibility [20].

Pre-eclampsia is the most common cause of nephrotic syndrome in pregnancy and can have drastic consequences if not diagnosed and treated promptly. This diagnosis was excluded by the fetal-maternal-renal MDT as a differential in our patient because her blood pressure and renal function remained normal throughout.

There have been a number of studies looking at protein selectivity in pregnancy, which have not found a correlation between the level of selectivity, and the underlying renal pathology although it has been found that pre-eclampsia shows intermediate range selectivity and is never selective [3–6].

In the setting of previous reports demonstrating intermediate or poor urine protein selectivity in pre-eclampsia [3–6, 17], Wood and colleagues used the now considered unacceptable technique of radiolabelled tracer polymer studies to address the glomerular permeability in women with pre-eclampsia of varying severity. They described varying patterns of glomerular protein/molecular selectivity in pre-eclampsia [22]. Therefore evidence of selective proteinuria, as in our case, not only supports the diagnosis of MCD but also provides reassurance that the clinical signs are not caused by pre-eclampsia.

Our case highlights the difficulty in diagnosis that the nephrotic syndrome presents in pregnancy, especially in the patient in whom a renal biopsy is contraindicated. Protein selectivity has proven value in the diagnosis of a steroid-responsive glomerular disease, as in our case, even though this does not always correlate well with a histological diagnosis. Given the availability and stability of urine it is little wonder that urine examination has been used as a diagnostic tool for thousands of years. Urinoscopy (the art of examining the appearance of urine) is the origin and mainstay of laboratory medicine, dating back to Hippocrates and before [23]. With the advances in technology and understanding, urinalysis has progressed over the years through the protein selectivity test to modern day urinalysis such as urinary protein: creatinine and urinary albumin:creatinine ratios that are in routine use in clinical practice today. We now stand on the cusp of another step in the evolution of urinalysis with the rapidly expanding study of urinary proteins, known as urinary proteomics. There have been a number of small studies recently that have shown promise in accurately diagnosing specific diseases such as minimal change disease, IgA nephropathy and pre-eclampsia by identifying disease-specific urinary proteins [24–31]. However the numbers of patients in these studies have been small and the accuracy is still inferior to renal biopsy, but with continued technological advances and further validation studies this gap is likely to diminish with not only proteomic prediction of glomerular pathology but perhaps also proteomic analysis correlating with differing degrees of severity of pre-eclampsia as suggested by Wood's studies in the 1970s [22]. With this evolution in urinalysis, many of the renal diseases we see today may in the future be diagnosed with this non-invasive investigation of urine that was once championed by Hippocrates, without the need for a renal biopsy, helping the physician of the future to 'do no harm'.

Conclusion

The nephrotic syndrome in pregnancy has a range of causes, some of which can only be confirmed by renal biopsy. Although immunosuppression comes with risk, such as an increased risk of infections and malignancies, correct specific treatment can confer a safer outcome for mother and baby, with NICU care spared by safer prolongation of gestation. In nephrotic patients with no other signs of pre-eclampsia (hypertension, biochemical or haematological derangements), the use of the non-invasive urinary protein selectivity test should be considered together with other readily available biomarkers of glomerular diseases.

Conflict of interest statement. None declared.

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