Pregnancies complicated by preeclampsia and non-preeclampsia-related nephrotic range proteinuria

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Abstract

Objective: To examine the impact of nephrotic range proteinuria during pregnancy on renal, maternal and fetal outcomes.

Methods: A retrospective study of pregnant women with proteinuria greater than 3 g/24 h. Outcome measures included: gestation and mode of delivery, maternal high dependency unit admission, birth weight, maternal blood pressure and proteinuria at time of last follow-up, renal biopsy.

Results: Two hundred and sixty four pregnancies in 262 women were reviewed. Postnatal data were available in 180; of these 104 (57%) had urinary protein quantified postnatally. Sixty three (60%) were pure preeclampsia and nine (9%) super-imposed preeclampsia. Biopsy-proven renal disease was newly diagnosed in nine (9%). Sixty three per cent required caesarean section and 34% required high dependency unit admission. There were no maternal deaths. Birth weight corrected for gestation was below the fifth centile in 33%.

Conclusions: The incidence of underlying renal pathology in this cohort is significant and highlights the importance of careful follow-up.

Keywords

Nephrology, hypertension, maternal-fetal medicine, pregnancy, proteinuria

Introduction

Preeclampsia is characterised by new onset hypertension and proteinuria in pregnancy. Though reported as early as 15-weeks gestation,¹ international criteria define preeclampsia as only occurring when onset is after 20 weeks.² It complicates 2–8% of pregnancies worldwide³ and is the most common glomerulopathy in pregnancy and the most common cause of nephrotic range proteinuria. Nephrotic syndrome, defined as excretion of more than 3 g of protein in 24 h, is reported to complicate up to 0.025% of pregnancies.⁴ In cases where nephrotic syndrome occurs it can be difficult to distinguish preeclampsia from other glomerulopathies, particularly if hypertension is not marked and there is no evidence of other system involvement. Those with renal or systemic diseases (e.g. diabetes, lupus) are at greater risk of developing preeclampsia⁵ and these pathologies can co-exist. Proteinuria and/or hypertension prior to 20 weeks gestation may be the only clue to a pre-existing renal lesion and a higher risk of preeclampsia, therefore first trimester antenatal clinic visits are a valuable screening opportunity.

In the literature, there are several case reports of nephrotic syndrome occurring in pregnancy due to other causes,^{6–9} two case series of pregnancies complicated by nephrotic proteinuria,^{10,11} and a small retrospective study of 40 cases.¹² Studies to assess whether proteinuria is an independent predictor of maternal and fetal morbidity have produced mixed results.^{13–19}

In this retrospective study spanning 11 years, all pregnancies complicated by nephrotic range proteinuria were reviewed to determine both the extent of other renal pathology and pregnancy outcomes.

Subject and methods

This was a retrospective study of pregnancies complicated by nephrotic range proteinuria over an 11-year period (2000–2011) in a large maternity hospital (6000–8300 births/year).

Cases were identified from the biochemistry laboratory database. Any woman with a maternity unit number having had proteinuria (measured by 24-h urine collection) >3 g/24 h related to pregnancy was included. Case records and the computerised maternity database were identified for each pregnancy and information extracted from each.

Baseline data relate to first antenatal clinic visit which is usually undertaken at approximately 12-weeks gestation.

Maternal outcomes were mode of delivery, hypertension (BP greater than 140/90 mmHg), anti-hypertensive treatment and high dependency unit (HDU) admission. Renal outcomes were persistent postnatal (>6/52 post delivery) hypertension and proteinuria and renal biopsy. Fetal outcomes were gestation at birth, intrauterine death, early neonatal death (<1 week) neonatal intensive care unit (NICU) admission and gestational corrected birth weight. During pregnancy, proteinuria was evaluated by 24-h urine collection; however, as this was a retrospective study, varied methods were used to evaluate proteinuria post partum, urine dipstick, albumin creatinine ratio (ACR), protein creatinine ratio (PCR) and 24-h urine collection.

Birth weights were corrected for gestation using GROW 7.5.1 Data for the total number of births was obtained from annual clinical reports. In view of the limitations of a retrospective study, tests of statistical significance were not applied to compare outcomes between the cohort with nephrotic proteinuria and all births (Table 4). We examined obstetric and perinatal outcomes according to level of proteinuria: 3–4.9 g/24 h, 5–9.9 g/24 h and >10 g/24 h and comparison was made between these. Statistical analysis was performed using the chi-square test and Student's t-test as appropriate. Linear regression was used to assess relationship between proteinuria and gestation at diagnosis and gestation at delivery.

Results

Two hundred and sixty four pregnancies in 262 women were identified. Baseline data were available in all except 12 women who were transferred from outside the region. Postnatal records were available for

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180 (69%) women. Characteristics at booking were as follows: age (mean [standard deviation]) 29 [7] years, primigravida 163 (62%), systolic BP 114 [15] mmHg, diastolic BP 69 [11] mmHg, pre-existing renal or systemic disease 61 (23%). See Table 1. Eleven women were under nephrology care and five had had prior renal biopsy.

BP was recorded at first antenatal visit in 222 (84%) of patients and urinalysis in 175 (67%) of patients. Fifteen (9%) women had dipstick proteinuria >1+. Of these, 10 were in the aforementioned group known to have pre-existing renal disease and under nephrology care.

Urinalysis for protein was negative in 144, trace in 10, 1+ in 4, 2+ in five and 3+ in six. Five patients had dipstick positive glycosuria and one had haematuria.

The median peak proteinuria during pregnancy was 4.7 g/24 h (interquartile range 3.6–6.9). The mean serum albumin was 27 ± 4.3 g/L with 73% (*n* = 184) of patients having serum albumin below 30 g/l at the time of delivery.

Data with regard to BP was complete in 159 patients. The mean BP at the time proteinuria was first noted was 155 [16] mmHg systolic and 93 [12] mmHg diastolic, and the mean increase in BP from booking was 42 [18]/25 [14] mmHg. New hypertension developed in 138 (87%) of

women with complete data. According to NICE definitions,²⁰ 23 (17%) had severe hypertension, 42 (30%) had moderate hypertension and 73 (53%) had mild hypertension.

Renal outcomes

Postnatal records were available in 180 women, of whom 104 (57%) had a recorded urine protein test postnatally, including any booking sample at a subsequent pregnancy. Primary care follow-up data were not available. The mean length of follow-up was 46.5 [3.9] months (93% >6 weeks, 85% >6 months). The majority, 63 of these 104 (60%), had pure preeclampsia with hypertension and proteinuria resolving postnatally. Nine (9%) had superimposed preeclampsia as per WHO definition.² A further nine (9%) had newly diagnosed renal disease of whom three also had superimposed preeclampsia. In six women with known renal disease, proteinuria increased but there was no associated increase in blood pressure. Isolated gestational proteinuria occurred in one pregnancy. The diagnosis was unclear in 16 pregnancies either due to follow-up <6 months or low level proteinuria that persisted but did not merit renal biopsy.

Postnatal urine testing was done by varied methods: PCR (*n* = 5), ACR (*n* = 17), 24-h urinary protein (*n* = 32) and urine dipstick (*n* = 50), 42 of which were negative for protein.

Excluding those with only dipstick evidence of proteinuria (*n* = 8), 21 women had significant proteinuria at the time of last follow-up; (ACR > 30 *n* = 3, PCR > 50 *n* = 2, 24 h Urinary protein > 0.5 g/24 h *n* = 16). Fourteen of these had some pre-existing disease – reflux nephropathy five, hypertension two, diabetes two, tuberous sclerosis one, IgA nephropathy one, Alport's syndrome one, membranoproliferative glomerulonephritis (MPGN) one and unspecified proteinuria two. The greatest elevation in proteinuria occurred during pregnancy in all patients. Table 2 shows there was no clear relationship between the presenting proteinuria, peak proteinuria, pre-existing and subsequent new diagnosis of renal disease.

Nine women had a renal biopsy because of proteinuria identified during their pregnancy, 8 were biopsied postnatally and 1 was biopsied at 19 weeks gestation (see Table 3). Biopsy proven glomerular pathology was newly diagnosed in all 9. Three of these had had a history of proteinuria but were not under nephrology follow up at time of pregnancy and had not been previously biopsied. Of the six women with no

Table 1. Pre-existing renal/systemic disease *n* = 61 by diagnosis.

Diabetes	18
Type 1	16
Type 2	2
Hypertension	26
Systemic lupus erythematosus	2
Urinary tract infection/pyelonephritis/reflux	8
Nephrectomy	3
IgA nephropathy	3
Alport's syndrome	1
Nephrotic syndrome	5
Tuberous sclerosis	1
Congenital renal abnormality	1
Nephrolithiasis	1

Table 2. Proteinuria in 104 patients at booking, in pregnancy and at last follow up.

Proteinuria at last follow up	Booking proteinuria				Pre-existing disease			Mean peak proteinuria g/24 h	Biopsies	
	N	Nil significant	>+1	No result	Renal	Diabetes	Hypertension		Number	Diagnosis
24-h urinary protein <0.5 g/24 h ACR < 30 mg/mmol PCR < 50 mg/mmol Urine dipstick <1+	80	54	2	24	8	10	2	20 6.6	2	MPGN, ^a FSGS/Preeclampsia
24 h urinary protein > 0.5 g/24 h ACR > 30 mg/mmol PCR > 50 mg/mmol Urine dipstick > 1+	24	8	10	6	9	2	2	13 6.9	7	Hypertensive nephropathy, IgAx2, FSGSx2, ^a FSGS Membranous
Total	104	62	12	30	17	12	4	33 6.0	9	As above

ACR: albumin creatinine ratio; PCR: protein creatinine ratio; MPGN: membranoproliferative glomerulonephritis; IgA: IgA nephropathy; FSGS: focal segmental glomerulonephritis.

^aDenotes those patients with prior history of renal disease but no prior biopsy; *n* = 3.

Table 3. Women who underwent renal biopsy during pregnancy^a $n = 1$ (19 weeks gestation) and postpartum $n = 8$.

Biopsy diagnosis	Gestation (weeks)			Blood pressure (mmHg)		Proteinuria		
	Proteinuria first quantified	Urinary protein >3 g/24 h	At delivery	Baseline	At diagnosis	Baseline (dipstick)	Peak in pregnancy g/24 h	Last follow-up
Women with no prior renal disease								
IgA Nephropathy ^a	17	22	31	130/90	135/89	2+	12.2	0.80 g/24 h
FSGS/preeclampsia	23	24	27	102/70	152/95	not done	4.8	ACR 11.
IgA Nephropathy	19	33	33	125/60	128/72	NAD	15.3	2.5 g/24 h
FSGS ^a	29	30	36	153/101	157/100	3+	15.7	2.2 g/24 h
Hypertensive Nephropathy	32	34	34	140/80	No result	3+	6.0	0.8 g/24 h
Membranous nephropathy	28	34	35	120/75	143/80	Trace	6.1	3.24 g/24 h
Women with previous proteinuria $n = 3$								
MPGN	29	29	31	120/80	167/78	Trace	13.8	ACR 6.7
FSGS	23	23	30	100/70	122/80	3+	7.4	1.64 g/24 h
FSGS	25	30	36	120/55	154/99	NAD	12.6	2.16 g/24 h

FSGS: focal segmental glomerular sclerosis; MPGN: membranoproliferative glomerulonephritis; ACR: albumin creatinine ratio.

^aLate booker at 29 weeks gestation.

prior history of renal disease, three had significant proteinuria dipstick >1+ at first antenatal visit.

Of the entire group of 264 pregnancies none required acute renal replacement therapy. The incidence of acute kidney injury was difficult to assess retrospectively as there was no baseline creatinine for comparison in the majority of cases. Four patients have subsequently progressed to end-stage renal disease (ESRD) and all had pre-existing kidney disease with baseline creatinine above 160 $\mu\text{mol/l}$, (3 with reflux nephropathy, 1 with IgA nephropathy) 3 have since been transplanted. One remains on haemodialysis.

Maternal and foetal outcomes

As expected, the study population were more likely than the general population to encounter complications, and deliver a low birth weight, premature infant by caesarean section. (See Table 4.)

We examined obstetric and perinatal outcomes according to level of proteinuria: (see Table 5).

Booking BP was significantly higher in the proteinuria >10 g/24 h group, but pre-delivery blood pressure was not. As proteinuria increased, women were significantly more likely to deliver by caesarean section, although this was not statistically significant for emergency caesarean sections alone.

Those in the higher protein excretion groups presented at significantly earlier gestation and were also significantly more likely to deliver below 37 and 34 weeks but not below 28 weeks. We could not demonstrate any relationship between gestation at diagnosis or delivery and proteinuria. There was no significant relationship between extent of proteinuria and markers of maternal morbidity including serum creatinine, alanine transferase (ALT), platelet count, maternal HDU requirement, eclampsia, pulmonary embolus, need for NICU admission, intrauterine death, early neonatal death or gestation corrected birth weight.

Discussion

The study has all of the limitations and caveats of retrospective cohort methodology with incomplete follow-up, missing and incomplete data. However, there are few studies in the literature on both renal and pregnancy outcomes where pregnancy is complicated by nephrotic proteinuria.^{10,21}

Table 4. Maternal and fetal outcomes: study population vs total births at LWH.

	Women with proteinuria >3 g/24 h during pregnancy	Total births LWH 2000–11
Maternal outcomes		
Number of births	264	81,165
Caesarean section (CS)	165 (63%)	18,623 (23%)
Emergency CS	123 (47%)	10,831 (13%)
Elective CS	42 (16%)	7792 (10%)
Admission to high dependency unit	87 (34%)	2148/47,855 (4.5%) (data only 2005–2011)
Admission to intensive therapy unit	1 (0.4%)	32/47,855 (0.1%) (data only 2005–2011)
Eclampsia	2 (0.8%)	Data not available
Pulmonary embolus	2 (0.8%)	70 (0.1%)
Maternal deaths	0	0
Fetal outcomes		
Delivery <37 weeks	198 (76%)	3253 (4%)
Delivery <34 weeks	146 (56%)	3044 (3.8%)
Delivery <28 weeks	39 (15%)	845 (1%)
NICU admission	35 (13%)	Data not available
Intrauterine deaths	11 (4%)	482 (0.6%)
Early neonatal death <1/52	4 (1.5%)	414 ((0.5%)
Very low birth weight <1500 g	76 (29%)	1140 (1.4%)
Gestational birth weight <5th centile	33%	~5% (absolute data not available)

NICU: neonatal intensive care unit.

Nephrotic proteinuria complicated 0.32% of pregnancies. Pure pre-eclampsia was the commonest cause of nephrotic proteinuria in pregnancy accounting for 60% of cases although levels of pre-existing renal and/or systemic disease in this cohort were high (23%).

Table 5. Maternal and foetal outcomes: with increasing proteinuria.

	Peak proteinuria g/24 h during pregnancy		
	3–4.9 g/24 h	4.9–9.9 g/24 h	>10 g/24 h
Demographics			
Number of births	150	81	33
Mean age years	29 ± 6.4	28 ± 5.2	30.9 ± 7.7
BMI	26.9 ± 6.7	26.9 ± 7.8	27.1 ± 8.6
Nulliparity	93 (62%)	54 (66%)	16 (48%)
Renal/systemic disease	39 (26%)	28 (34%)	8 (24%)
Mean booking BP (mm Hg)	113 ± 13/69 ± 11	112 ± 13/69 ± 11	126 ± 25/74 ± 13 ^a
Mean pre delivery BP (mm Hg)	153 ± 15/93 ± 12	154 ± 15/94 ± 12	157 ± 19/92 ± 14
Maternal outcomes			
Gestation at urinary protein >3 g/24 h	33 ± 5	31 ± 6 ^a	29 ± 4 ^a
Caesarean section (CS) ^a	71 (47%)	56 (69%)	29 (88%)
Emergency CS	59 (39%)	45 (56%)	20 (60%)
Elective CS	22 (15%)	11 (14%)	9 (27%)
Creatinine >100 µmol/L (<i>n</i> = 171)	5 (5%) <i>n</i> = 93	5 (9%) <i>n</i> = 54	5 (20%) <i>n</i> = 24
Platelet count <100 ^a 10 ⁹ /L (<i>n</i> = 183)	3 (3%) <i>n</i> = 97	3 (5%) <i>n</i> = 58	0 <i>n</i> = 28
ALT >50U/l <i>n</i> = 184	10 (10%) <i>n</i> = 98	5 (9%) <i>n</i> = 58	2 (7%) <i>n</i> = 28
Admission to HDU	50 (33%)	23 (28%)	14 (42%)
Admission to ITU	0	1 (1%)	0
Eclampsia	1 (0.7%)	0	1 (3%)
Preeclampsia <i>n</i> = 63	35	22	6
Superimposed preeclampsia <i>n</i> = 9	5	1	3
Newly diagnosed GN <i>n</i> = 9	2	3	4
Pulmonary Embolus	1 (0.7%)	0	1 (3%)
Maternal deaths	0	0	0
Foetal outcomes			
Mean gestation weeks	34 ± 4	33 ± 4	30 ± 3
Delivery <37 weeks ^a	104 (69%)	63 (78%)	31 (94%)
Delivery <34 weeks ^a	54 (36%)	42 (52%)	28 (85%)
Delivery <28 weeks	15 (10%)	10 (12%)	8 (24%)
NICU admission	17 (11%)28	11 (14%)26	7 (21%)8
Intrauterine deaths	9 (6%)	2 (3%)	0
Early neonatal death <1/52	1 (0.7%)	3 (4%)	0
Very low birth weight <1500 g	42 (28%)	28 (35%)	6 (18%)
Gestational birth weight <5th centile	34 (23%)	23 (28%)	7 (21%)

HDU: high dependency unit; ITU: intensive therapy unit; Blood test results were not available for all patients therefore numbers of results available have been included for these (n).

^aStatistical analysis was performed using the chi-squared test and Student's t-test as appropriate. *p* < 0.05.

The most important finding of this study is that biopsy-proven renal disease was newly diagnosed in 9%, eight of these had a primary glomerulonephritis and one had hypertensive renal disease. The incidence of primary glomerulonephritis in this cohort is approximately 0.7/100/year in comparison to estimates of population incidence of 0.2–2.5/10⁵/year.²² In their study of 75 postpartum renal biopsies, Day et al.²³ found glomerular pathology in 64%, however only six of these patients had nephrotic range proteinuria.

Four women progressed to ESRD, all of these had a baseline creatinine above 160 µmol/L, this is in keeping with the findings of Jones et al.²⁴

Vikse et al.²⁵ have shown an increased population risk of ESRD in women with a history of preeclampsia, and as in our cohort with

nephrotic proteinuria, these women may represent the highest risk group. The degree of proteinuria was not predictive of underlying renal disease nor was proteinuria at booking a consistent finding in those with underlying renal disease. In four of the women who had proven glomerulonephritis, proteinuria was not detected until after 20 weeks.

This study shows the difficulty of separating renal disease from preeclampsia where there is this degree of nephropathy. It is unclear how long it takes for the glomerulopathy of preeclampsia to heal and for proteinuria to resolve completely; Hladunewich et al.²⁶ demonstrated that the functional manifestations of preeclampsia largely resolve in four weeks. Others have shown complete resolution may take as long as two years.²⁷

Work demonstrating that preeclampsia is associated with an increased risk of early onset cardiovascular disease and increased mortality²⁸ suggests the effects are longer lasting or the underlying aetiology of preeclampsia has wider vascular effects.

Current NICE guidelines for hypertensive disorders in pregnancy²⁰ recommend follow-up urine dipstick testing for women with preeclampsia at 6–8 weeks following delivery and if $\geq 1+$, further assessment of renal function at three months. Renal disease can be completely asymptomatic until late in the disease process. Proteinuria is a predictor of progressive renal disease but also of cardiovascular risk and mortality. Appropriate referral and follow-up of this cohort would identify those with progressive disease and allow for interventions to slow progression. It is well-documented that those who “crash land” requiring dialysis fare worse than their peers who commence renal replacement therapy in a planned fashion.^{29,30} It is important that women with persistent proteinuria following pregnancy are identified and referred for nephrological assessment.

There has been debate over the effect of nephrotic range proteinuria in preeclampsia on both maternal and perinatal outcomes. Chan¹⁴ and colleagues suggested a linear relationship between maternal outcomes and urinary protein with values of greater than 5 g and 10 g per 24 h being important. Others have not confirmed this association, with Newman and colleagues suggesting that the association is with earlier onset disease and if correction was made for this, proteinuria itself did not influence outcomes. Buchbinder et al.³¹ showed an association of outcomes with the severity of hypertension rather than with proteinuria and Hall et al.¹⁸ could not demonstrate an association between outcomes and either amount of protein or change in protein excretion. A recent systematic review showed very weak associations with perinatal outcomes.³²

Our study reinforces the view that it is the presence of proteinuria rather than the amount that increases morbidity and that the degree of proteinuria should not influence the decision to deliver a woman with preeclampsia or nephrotic syndrome.

Caesarean section rates are higher, but this is a consequence of the gestation at which these births occur. Planned vaginal birth is uncommon in severe preterm preeclampsia. We used admission to HDU as a surrogate measure of overall maternal morbidity; the degree of proteinuria has never been a selection criterion for HDU admission in our service. We could demonstrate no differences, although numbers are small. Other local audits³³ have shown that the extent of proteinuria, particularly increasing proteinuria within the nephrotic range, was used by some clinicians as a trigger for delivery. We therefore cannot exclude confounding from this practice. Using customised birth weight centiles, the degree of proteinuria was not related to fetal growth restriction. There was no association between amount of protein and perinatal mortality.

Conclusions

This study emphasises the need for vigilance in performing urinalysis for protein at all first pregnancy visits and the need, emphasised in the recent NICE guidance on hypertensive disorders during pregnancy,²⁰ for confirmation in the postnatal period that proteinuria has resolved. In those with confirmed proteinuria, it also important to assess and monitor renal function. In our cohort of women with nephrotic range proteinuria, preeclampsia was the predominant cause, however, the risk of undiagnosed nephropathy was 9%. It is important that this is identified as early diagnosis improves outcome.

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Contributorship

MLPH and SAW conceived the study, RAB undertook data retrieval, data analysis and wrote the first draft of the manuscript. GJK advised with regard to statistical analysis. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Disclosure of interests

None

Ethical approval

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