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Microalbuminuria is a predictor of adverse pregnancy outcomes including preeclampsia

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ABSTRACT

Objectives: Abnormal urinary protein loss is a marker associated with a diverse range of renal diseases including preeclampsia. Current measures of urine protein used in the diagnostic criteria for the diagnosis of preeclampsia includes urine protein:creatinine ratio and 24-h urine protein. However very little is known about the value of urine albumin:creatinine ratio (uACR) in pregnancy. In this study we examined the prognostic value of microalbuminuria detected antepartum to predict adverse pregnancy outcomes.
Design: This is a single-centre retrospective analysis of 84 pregnant women over the age of 16 attending a tertiary 'high-risk' pregnancy outpatient clinic between July 2010 and June 2013. Utilising medical records, antepartum peak uACR level and pregnancy maternal and fetal outcomes were recorded.
Findings: The primary outcome was a composite of poor maternal and fetal outcomes including preeclampsia, maternal death, eclampsia, stillbirth, neonatal death, IUGR, premature delivery and placental abruption. As the antepartum peak uACR level (in mg/mmol) increased from normoalbuminuria (uACR < 3.5) to microalbuminuria (uACR 3.5–35) to macroalbuminuria (>35), the percentage of women with the primary composite outcome increased in a stepwise fashion (13.8% to 24.1% to 62.1% respectively, $p < 0.001$). After adjusting for covariates including history of hypertension, chronic kidney disease and aspirin therapy during pregnancy, micro- and macroalbuminuria remained significant predictors of the primary outcome.
Conclusions: We have shown that antepartum peak uACR is a useful simple marker to help predict adverse maternal and fetal outcomes. Further studies are required to utilise uACR as a prognostic tool in pregnancy before it can be applied in clinical practice.

1. Introduction

Abnormal urinary protein loss is a marker associated with a diverse range of renal diseases, including diabetes, glomerulonephritis and preeclampsia. Established markers of protein loss in pregnancy include positive protein testing on urinalysis and high (>300 mg) 24 h protein excretion [1]. Uncertainty remains regarding the best method of estimating abnormal urinary protein losses in pregnancy, with the 24 h urine protein measurement used as the gold standard at present. However there are limitations with the 24 h urine protein measurement including incorrect evaluation due to under- and over-collection of urine, and the cumbersome nature of collection, especially during pregnancy. Therefore, other methods of measuring urinary protein, including dipstick urinalysis, urine protein-to-creatinine ratio (uPCR) (laboratory and bedside) and urine albumin- to- creatinine ratio (uACR) have been employed. The dipstick test for proteinuria is easy to perform and is semi quantitative in nature, but suffers from lack of both sensitivity and specificity. The uPCR has been used in more recent years, however a number of systematic reviews [2–4] have shown that as a diagnostic test, it lacks accuracy compared to the "gold standard" 24 h urine protein measurement. Despite this the uPCR is currently part of the diagnostic criteria for the diagnosis of preeclampsia [1].

On the other hand, very little is known about the value of uACR in pregnancy. Current guidelines use uACR in conjunction with estimated glomerular filtration rate (eGFR) to stage chronic kidney disease [5]. The uACR is a well-validated tool in the diagnosis and prognosis of kidney disease outside of pregnancy. There is a scarcity of studies that looked at the utility of uACR in predicting adverse pregnancy outcomes in patients especially those with underlying chronic kidney disease or diabetes.

Therefore, in this study we aimed to examine the ability of microalbuminuria with uACR detected during the antenatal period

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to predict adverse pregnancy outcomes, including preeclampsia. We hypothesized that an elevated uACR is associated with a higher incidence of adverse pregnancy outcomes.

2. Study method

This is a single-centre retrospective analysis utilising medical record review. The study population included pregnant women over the age of 16 attending the renal pregnancy outpatient clinic, also known as the 'high-risk antenatal clinic', at a tertiary public hospital unit (Sydney, Australia) between July 2010 and June 2013. These patients were identified using an existing quality assurance database in the Department of Renal Medicine. To be included in the study, the participant had to have at least one uACR measurement performed during pregnancy (excluding measurements performed at or near to delivery). uACR measurements were obtained at various time points in the pregnancy, from gestational periods 0–19^{+6} weeks, 20–27^{+6} weeks, 28–33^{+6} weeks. As not all participants had uACR measurements at each of these time points, the peak uACR measurement prior to 34 weeks gestation (and prior to delivery date, to ensure that the uACR was not measured at the time of an adverse pregnancy outcome such as preeclampsia) was chosen for the final analysis. Patient characteristics, medications (particularly the use of aspirin and calcium), blood pressure, urinalysis, serum creatinine, fetal and maternal outcomes of the pregnancy were collected from patient medical records and electronic databases. Those patients who did not have at least one uACR performed prior to <34 weeks or did not have data on the pregnancy outcomes of interest were excluded from the study.

3. Data & statistical analysis

Peak uACR was divided into 3 categories: <3.5 mg/mmol, 3.5–35 mg/mmol (microalbuminuria) and >35 mg/mmol (macroalbuminuria), categorised as per the Australasian Proteinuria Consensus Working Group [7].

The primary outcome was a composite of any one of the following maternal and fetal outcomes – maternal death, stillbirth, neonatal death (within 7 days of birth), preeclampsia (PE) (defined by ISSHP 2014 criteria: blood pressure >140/90 mmHg after 20 weeks gestation with either proteinuria >300 mg/day (or equivalent) or presence of any maternal organ dysfunction i.e. renal insufficiency, liver involvement, neurological or hematological complications) [8], eclampsia, Intra Uterine Growth Restriction (IUGR – defined by fetal weight <5th centile and abnormal uterine doppler), premature delivery (<32 weeks) or placental abruption.

Secondary outcomes included the individual components of the primary outcome, poor maternal outcome (including maternal death, preeclampsia or eclampsia), and poor fetal outcome (including miscarriage, stillbirth, neonatal death (within 7 days of birth), IUGR, premature delivery (<32 weeks), placental abruption, neonatal hypoglycaemia (defined as BSL < 2.5 mmol/L), neonatal hyperbilirubinemia (defined as clinical jaundice and/or total serum bilirubin > 86 μmol/L)), neonatal intensive care unit (NICU) or Special Care for Neonates (SCN) admission, birth injuries or congenital malformations.

Data analysis was performed by comparing the primary outcome between the 3 uACR categories using Pearson's Chi square for 3 way comparison of normoalbuminuria vs. microalbuminuria vs. macroalbuminuria. Covariates including age, body mass index (BMI), pre-existing hypertension or chronic renal disease (as recorded in medical records), history of preeclampsia, multiparity (defined by parity $\geqslant 1$), multiple pregnancy, smoking before or during pregnancy, peak serum creatinine during pregnancy (prior to last trimester <34 weeks gestation or prior to onset of pre eclampsia) and use of aspirin or calcium supplement (anytime through the pregnancy) were examined to assess an association with the primary outcome [9]. Multiple logistic regression analysis was used to identify the independent predictors of the composite primary outcome. Candidate variables for inclusion in the model were those risk factors significant at p-value $\leqslant 0.05$ in the univariate analysis. Backward stepwise variable selection was then used to identify the independent predictors of composite primary outcome. Statistician support was used (with SPSS Statistics version 22 for data analysis).

4. Results

Out of 116 patients attending the renal pregnancy clinic between July 2010 and June 2013, 33 patients were excluded due to absence of at least one uACR performed prior to <34 weeks or missing data on the pregnancy outcomes, leaving 83 patients for the final analysis. The baseline characteristics of the patients in this study are outlined in Table 1. The women had a mean age of 33.1 (±5.4) years. Mean BMI was 29.4 (±8.1) kg/m^2. Almost half the population (47.6%) had a previous history of hypertension, one fifth (20.2%) had a previous history of preeclampsia, and more than a

Table 1
Baseline characteristics of study population divided into those with primary outcome and those without.

	$N = 83$	Primary outcome –positive $N = 29$	Primary outcome – negative $N = 54$	p-Value*
Age (years)	33.1 ± 5.4	33.7 ± 5.4	32.8 ± 5.5	–
BMI (kg/m^2)	29.4 ± 8.1	29.8 ± 7.6	29.2 ± 8.4	–
Gravida	3.4 ± 2.3	3.8 ± 3.0	3.1 ± 1.8	–
Peak serum creatinine (μmol/L)	68.6 ± 46.9	90.7 ± 56.1	56.1 ± 40.3	–
Multiple pregnancy	4 (4.8%)	1 (3.4)	3 (5.6)	0.564
History of hypertension	40 (47.6%)	20 (69)	20 (36.4)	0.004
History of preeclampsia	17 (20.2%)	8 (27.6)	9 (16.4)	0.224
History of chronic kidney disease	31 (36.9%)	15 (51.7)	16 (29.1)	0.041
Diabetes mellitus (DM)				0.351**
Gestational DM	12 (14.3%)	6 (20.7)	6 (10.9)	
Type 2 DM	10 (11.9%)	5 (17.2)	5 (9.1)	
Type 1 DM	9 (10.7%)	2 (6.9)	7 (12.7)	
Smoking before pregnancy	12 (4.3%)	7 (24.1)	5 (9.1)	0.098
Smoking during pregnancy	10 (11.9%)	6 (20.7)	4 (7.3)	0.087
Use of aspirin during pregnancy	26 (31%)	14 (48.3)	12 (21.8)	0.013
Use of calcium supplement during pregnancy	14 (17.1%)	4 (14.3)	10 (18.5)	0.762

Data is presented as n (%) or mean ± standard deviation as applicable.
* p-Value is a comparison between the groups with and without primary outcome.
** p-Value for all diabetic groups.