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Microalbuminuria as an early predictor of preeclampsia in the pre-gestational diabetic population: A prospective cohort study

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ABSTRACT

Objectives: To determine if microalbuminuria can be used as a predictive marker of preeclampsia and adverse pregnancy and neonatal outcomes in women with pre-existing diabetes and to compare the prognostic utility of urinary albumin to creatinine ratio (uACR) and urinary protein to creatinine ratio (uPCR).
Study Design: Multicentre prospective cohort study. Antenatal Diabetes in Pregnancy clinics at three tertiary referral hospitals in Western Sydney, Australia. 158 women with pre-existing diabetes requiring insulin in pregnancy. A spot uPCR and uACR was performed in each trimester. Pregnancy and fetal outcomes were investigated using linear models and receiver-operating characteristic (ROC) curves.
Main outcome measures: The primary outcome was preeclampsia (PE). Secondary outcomes investigated were other adverse pregnancy and neonatal outcomes.
Results: Increased levels of both uPCR and uACR in trimester 3 were associated with the occurrence of PE ($p = 0.007, 0.010$ respectively). In the 113 patients with normal pregnancy uPCR (< 30 mg/mmol) in trimester 1, microalbuminuria was found to be predictive of PE ($p = 0.01$) and need for operative delivery ($p = 0.03$).
Conclusions: In women with pre-existing diabetes, uPCR and uACR appear to have similar ability to diagnose PE, but microalbuminuria demonstrates prognostic ability at a much earlier gestation, prior to the onset of other signs or symptoms of PE. We therefore suggest that assessing microalbuminuria rather than overt proteinuria in trimester 1 provides prognostic information in women with pre-existing diabetes requiring insulin and should be used routinely to evaluate risk of PE in this high-risk cohort of women.

1. Introduction

The worldwide incidence of diabetes is increasing amongst women of reproductive age, with the annual incidence of diabetes in women of child-bearing age in Australia being 0.3% [1]. Compared to the general obstetric population, these women are at significant increased risk of adverse obstetric and neonatal outcomes [2], including an increased risk of developing preeclampsia (PE). Those with diabetic nephropathy are at a particularly high risk [3].

In addition to new-onset elevated blood pressure after 20 weeks gestation, proteinuria is a common accompanying feature in PE. Traditionally, the gold-standard for quantifying proteinuria was the 24-hour urine collection, but ‘spot’ urine specimens provide a prompt diagnosis and greater convenience. The International Society for the Study of Hypertension in Pregnancy (ISSHP) proposed the use of uPCR as an alternative to the 24-hour urinary protein test [4] and uPCR has now become embedded in routine clinical practice. Abnormal protein excretion in pregnancy is defined as > 300 mg per 24 h [4]. However, significant proteinuria or albuminuria should not simply be attributed to the hyperfiltration that accompanies pregnancy. Similar to pregnancy, renal hyperfiltration also occurs with diabetes [5] and its presence has been demonstrated to be a risk factor for progression of diabetic nephropathy [6].

The presence of microalbuminuria is an established marker of systemic endothelial cell dysfunction and micro-vascular disease, and is a hallmark feature of diabetic nephropathy. Outside of pregnancy, uACR

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is a well-validated tool in the diagnosis and prognosis of renal disease [7], with uACR used in diabetic nephropathy to predict poor outcome and guide management [8]. Contrastingly, little is known about the utility of uACR in predicting adverse outcomes within the obstetric population. Whilst antepartum peak uACR correlates with adverse pregnancy outcomes [9], the value of uACR in pregnant women with pre-existing diabetes is uncertain.

At present, uPCR forms part of the diagnostic criteria of PE and aids clinicians in the stratification of perinatal risk, guiding management decisions. We hypothesize that in women with pre-existing diabetes, many cases of nephropathy are missed if uPCR alone is used, and that mild diabetic nephropathy, as assessed by those with elevated uACR, is associated with worse pregnancy outcome. This study aimed to establish whether uPCR and uACR can be used as independent predictive markers for PE and other adverse pregnancy outcomes, and we aimed to compare their respective prognostic abilities.

2. Methods

2.1. Study methodology

This was a prospective multicentre cohort study conducted between June 2013 and May 2016, at three tertiary referral hospitals (in Western Sydney, Australia). The study was approved by the Human Research Ethics Committees of all three hospitals and written consent obtained from all participants. The study population included pregnant women over the age of 16 with singleton pregnancies, who attended the antenatal Diabetes in Pregnancy clinics at the three centres. Patients included had Type 1 or Type 2 diabetes or fell within the 'likely overt diabetes' range with a 75 g oral glucose tolerance test (fasting ≥ 7.0 mmol/L and/or 2 h ≥ 11.1 mmol/L) as per the 2013 World Health Organisation guideline criteria [10]. Since this is a substudy of the Falling Insulin Requirements STudy (FIRST) [11], only women requiring insulin treatment during pregnancy were included in the study.

Random spot urine samples were tested for ACR and PCR in trimester 1 (< 14 weeks), trimester 2 (24 ± 1 weeks) and trimester 3 (36 ± 1 weeks). Quantitative urinary levels were measured for albumin using the ALB Flex® reagent cartridge, creatinine using the ECREA Flex® reagent cartridge and total protein using the TP Flex® reagent cartridge on the Dimension Vista® System (Siemens Ltd). The reference range for uACR in non-pregnant females is 0–3.5 mg/mmol. No normal reference range is available for the pregnant population. The reference range for uPCR in non-pregnant females is 0–20 mg/mmol with < 30 mg/mmol considered normal for the pregnant population. Non-albuminuric proteinuria was defined as the difference between uPCR and uACR measured simultaneously in the same sample.

The primary outcome measured was preeclampsia (PE). Secondary outcomes evaluated included small for gestational age (≤ 5th percentile for gestational age), stillbirth (> 20 weeks), premature delivery (≤ 30 weeks), and neonatal outcomes of hyperbilirubinemia, hypoglycaemia, birth trauma, Apgar scores (1 and 5 min), neonatal admission to neonatal intensive care unit, birth weight and gestation at delivery. Pregnancy complications evaluated included preterm rupture of membranes, antepartum haemorrhage, postpartum haemorrhage, need for induction of labour, mode of delivery and gestational hypertension. Planned pregnancy was defined as women intentionally attempting to conceive, and patients with nephropathy were defined based on patient history or pre-pregnancy uACR or uPCR values. All cases of PE satisfied the ISSHP 2014 criteria [12].

2.2. Statistical methods

uACR was categorized into normal (< 3.5 mg/mmol), microalbuminuria (3.5–35 mg/mmol) and macroalbuminuria (> 35 mg/mmol). Due to low numbers in the macroalbuminuric cohort (n = 2 in Trimester 1), the microalbuminuria and macroalbuminuria groups were pooled for statistical analyses. uPCR was categorised into 2 categories: normal for gestation (< 30 mg/mmol) and proteinuria (≥ 30 mg/mmol).

All data was analysed using the IBM SPSS statistical package version 20 (SPSS Inc. Chicago, IL, USA) or SAS 9.4 (SAS Institute, Cary, NC, USA). Baseline characteristics were compared between those with and without subsequent PE and normal ACR versus microalbuminuria (uACR ≥ 3.5 mg/mmol), with chi-square tests or Fishers exact tests for categorical risks and t-tests or Kruskal-Wallis tests for continuous variables. The primary and secondary outcomes were analysed using chi-square for binary outcomes and *t*-test or Kruskal –Wallis for continuous outcomes. uACR and uPCR have a log normal distribution so were log transformed to assess the change over time and this was analysed using a general linear model to account for the correlation within a woman over time. Differences were considered significant with $p < 0.05$. Receiver operating characteristic (ROC) curves were also calculated to assess the discriminative ability of uACR and uPCR for PE and the area under the curve (AUC), 95% confidence interval (CI) and p-value were reported.

3. Results

192 patients were recruited over the three-year period. After excluding pregnancies that ended in miscarriage, were a multiple gestation, or patients not requiring or non-compliant with insulin therapy, 158 patients remained. Follow-up time was the length of the pregnancy and the immediate postpartum period and no patient was lost to follow-up.

3.1. Baseline characteristics

Patient demographics were similar between women who developed PE and those that did not (Table 1). Of note, the patients who developed PE had a higher HbA1c of 8.8 ± 1.9% versus 7.7 ± 2.1% for those that did not develop PE (p = 0.010) and were less likely to have a planned pregnancy (22.2% versus 45.0%, p = 0.03). Those who planned their pregnancy were more likely to have an HbA1c < 7% ($p < 0.001$). However, we found no relationship between early uACR or uPCR and HbA1c or planning of pregnancy.

The baseline characteristics were similar between women with normal Trimester 1 uACR (< 3.5 mg/mmol) and Trimester 1 microalbuminuria (≥ 3.5 mg/mmol), with the exception of the microalbuminuria group having a higher proportion of patients with a history of ischemic heart disease (p = 0.03), and a lower proportion of smokers (p = 0.002) than in the group with normal uACR (Supplementary Table 1). Notably, there was also significant association between women who were categorised as having nephropathy in those with microalbuminuria (47% v 3%) in trimester 1 ($p < 0.001$), but not those with proteinuria (uPCR ≥ 30 mg/mmol; 20% v 7%) in trimester 1 (p = 0.07). Only one patient had a serum creatinine > 90 µmol/L in trimester 1. The incidence of PE within our study cohort of women was 17.1%.

3.2. Change in proteinuria with gestation

There was an increase in uPCR ($p < 0.001$) as pregnancy progressed (Fig. 1A), with a median of 11.0 mg/mmol (IQR: lower quartile 5.0, upper quartile 16.4) in trimester 1, a median of 15.0 mg/mmol (9.0, 22.0) for trimester 2 and 23.0mmg/mmol (16.0, 36.0) in trimester 3, which is a doubling of average levels (2.07 (1.82, 2.35)) between trimester 1 and 3 (Supplementary Table 2). This was not the case with uACR, with median uACR in trimester 1 and 2 being 0.90 mg/mmol (0, 2.0 and 1.8 respectively), which increased to a median of 1.8 mg/mmol (Q1 0.7, Q3 3.9) in trimester 3 (Fig. 1B). The progressive increase in urine protein excretion with advancing pregnancy was also present

Table 1
Baseline characteristics of the study population divided into those with and without preeclampsia (PE).

	Total cohort n = 158	PE negative n = 131	PE positive n = 27	P - Value
Age (years)	32.1 ± 5.6	32.1 ± 5.6	32.0 ± 6.1	0.86
Pre-gravid BMI (kg/m^2)	32.0 ± 8.2	31.9 ± 8.3	32.5 ± 8.1	0.48
Preconception HbA1c	7.9 ± 2.1	7.7 ± 2.1	8.8 ± 1.9	0.01
Type of Diabetes				0.13
Type 1	40 (25)	29 (22)	11 (41)	
Type 2	94 (60)	81 (62)	13 (48)	
Overt in pregnancy	24 (15)	21 (16)	3 (11)	
Metformin use in pregnancy	29 (18)	24 (18)	5 (19)	0.98
Aspirin prior to 14 weeks	15 (10)	10 (8)	5 (19)	0.08
Gravidity	3.0 ± 1.9	3.1 ± 1.9	2.7 ± 1.9	0.17
Multiparity	108 (68)	92 (70)	16 (59)	0.26
Previous miscarriage	60 (38)	50 (38)	10 (37)	0.91
Previous stillbirth	8 (5)	7 (5)	1 (4)	0.72
Previous termination	14 (9)	12 (9)	2 (7)	0.43
Planned pregnancy	65 (41)	59 (45)	6 (22)	0.03
Fertility treatment	10 (6)	9 (7)	1 (4)	0.54
Preconception counselling	66 (42)	56 (43)	10 (37)	0.58
Preconception folate	48 (30)	42 (32)	6 (22)	0.31
Retinopathy	13 (8)	10 (8)	3 (11)	0.55
Nephropathy*	16 (10)	12 (9)	4 (15)	0.38
Neuropathy	6 (4)	3 (2)	3 (11)	0.07
Pre-pregnancy Hypertension	19 (12)	13 (10)	6 (22)	0.07
Previous gestational HT/PE	27 (17)	20 (15)	7 (26)	0.18
Ischemic heart disease	4 (3)	4 (3)	0 (0)	0.36
Hypercholesterolaemia	20 (13)	17 (13)	3 (11)	0.79
Smoker	15 (10)	10 (8)	5 (19)	0.08

Data is presented as n (%) or mean ± standard deviation as applicable.
p-value is a comparison between the groups with and without PE
*Nephropathy defined here is based on history or pre-pregnancy uACR or uPCR values.

when analysing non-albuminuric proteinuria alone ($p < 0.001$), with a doubling in average levels (2.12 (1.82, 2.46)) between trimester 1 and 3. Here we found a median non-albuminuric urine protein of 9.4 mg/mmol (3.6, 15.0), 13.2 mg/mmol (8.1, 20.3) and 20.7 mg/mmol (14.0, 28.9) in trimester 1, 2 and 3 respectively (Fig. 1C). Serum creatinine remained relatively unchanged as pregnancy progressed (Supplementary Fig. 1).

3.3. Primary outcome analysis

In trimester 3, the risk of PE in patients with uPCR ≥ 30 mg/mmol was 3.04 (1.49, 6.20) times higher than with uPCR < 30 mg/mmol and with uACR ≥ 3.5 mg/mmol was 2.82 (1.30, 6.11) times higher than with uACR < 3.5 mg/mmol ($p = 0.007$ and 0.001 respectively). 21 patients delivered at ≤ 36 weeks, with 33.3% (n = 7) diagnosed with PE.

While the overall numbers of women with an outcome of PE was low (n = 27), there was a doubling in cases of PE in the micro-albuminuric cohort (Fig. 2A) compared to those with no albuminuria in trimester 1 (RR 2.19 (0.99, 4.85), $p = 0.06$) and trimester 2 (RR 2.21 (1.00, 4.79), $p = 0.06$). This trend was not present with Trimester 1 uPCR levels ≥ 30 mg/mmol (Fig. 2B and Table 2).

A receiver operator curve (ROC) curve was generated for uACR (Fig. 3A) and uPCR (Fig. 3B) in each trimester for the outcome of PE. uPCR was a poor predictor of PE with 95% confidence intervals (CI) for the area under the curve (AUC) crossing 0.5 for all trimesters (Table 2). In contrast, uACR in trimester 1 and 2 was found to be predictive for PE. The AUC for Trimester 1 was 0.71 (0.57–0.85 95% CI, $p = 0.009$), for Trimester 2 was 0.77 (0.65–0.88 95% CI, $p = 0.001$) and for Trimester 3 was 0.63 (0.47–0.79 95% CI, $p = 0.10$).

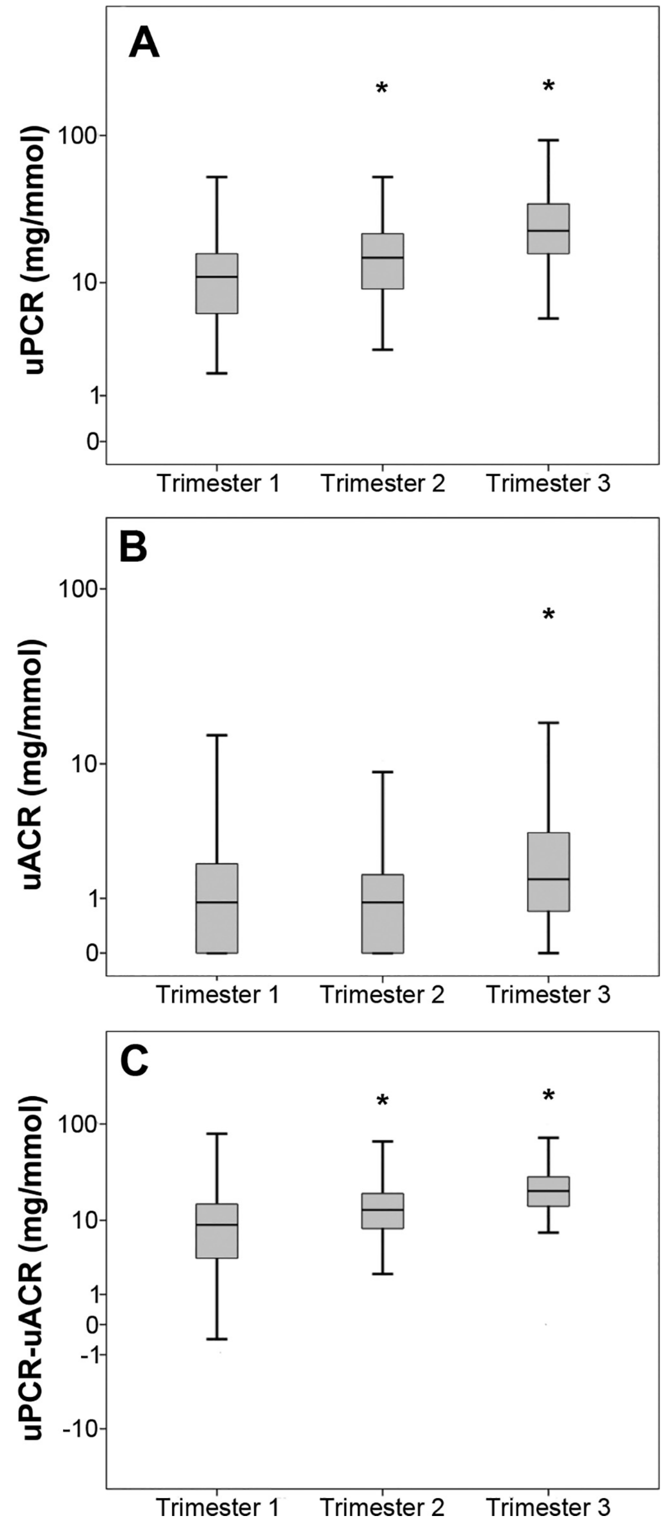

Fig. 1. Distribution of (A) uPCR, (B) uACR and (C) non-albuminuric proteinuria for entire cohort per trimester, presented on a log scale. Both uPCR and non-albuminuric proteinuria show a stepwise increase as pregnancy progresses, which does not occur with uACR. *significant increase in levels $p < 0.001$.

Subgroup analysis of the 113 patients with normal uPCR (< 30 mg/mmol) in Trimester 1 demonstrated that the presence of micro-albuminuria at this timepoint (n = 10) was predictive of an outcome of PE ($p = 0.005$), with 50% of patients with microalbuminuria developing PE compared to 14.6% of those with normal uACR. For this

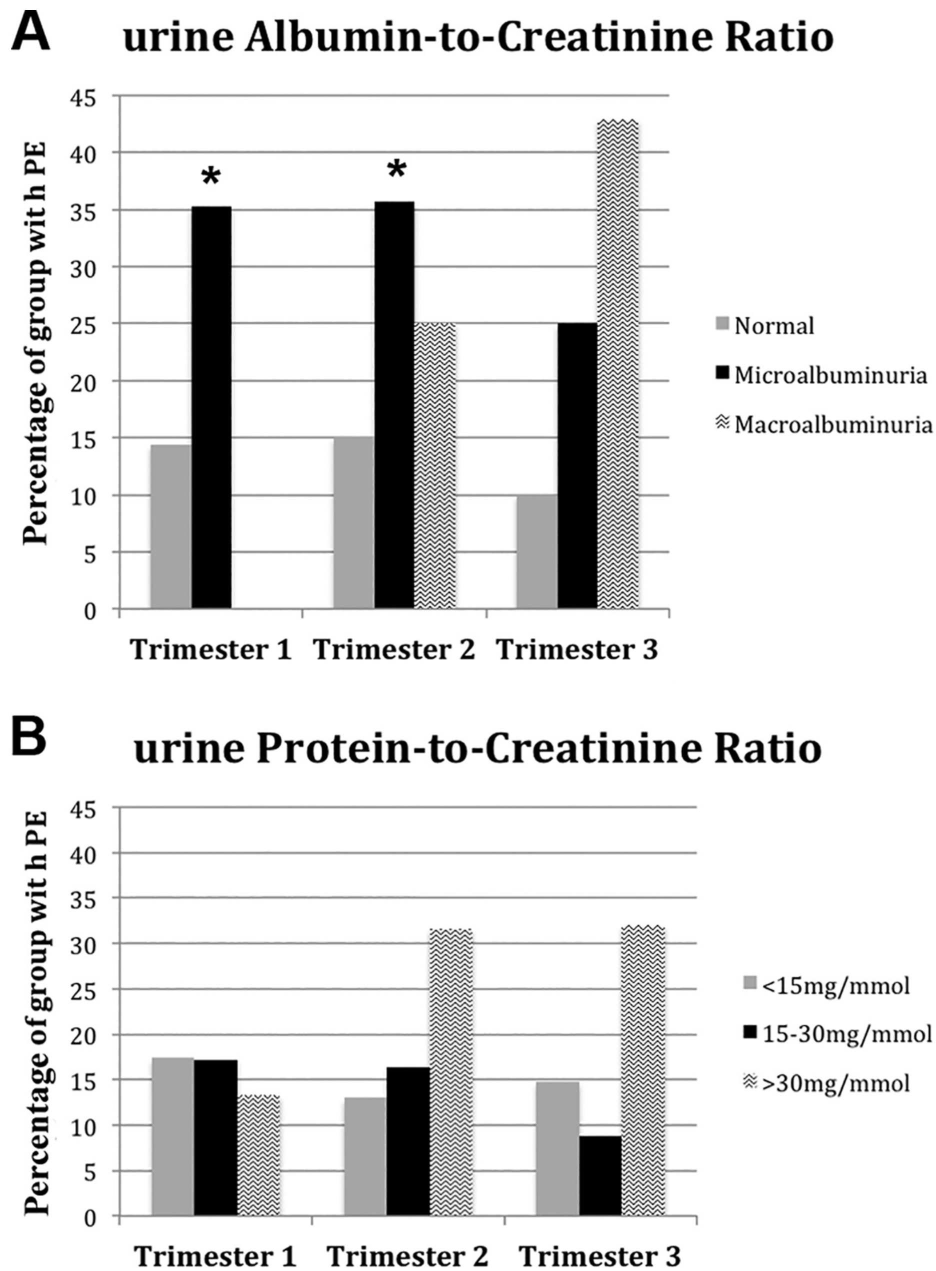

Fig. 2. Percentage of patients with the outcome of PE within each category of (A) uACR and (B) uPCR, with RR and 95% Confidence Interval. *significant increase in the relative risk of preeclampsia $p < 0.05$.

Table 2
Percentage of patients with the outcome of PE within each category and ROC curves for prediction of preeclampsia for uACR and uPCR, with Relative Risk (RR), Area under curve (AUC) and 95% confidence level (CI). *Statistical significance $p < 0.05$.

	Trimester 1	Trimester 2	Trimester 3
uACR	2.19 (0.99, 4.85)	2.21 (1.00, 4.79)	2.82 (1.30, 6.11)
(Relative Risk)	p = 0.06	p = 0.06	p = 0.007 *
uPCR	0.77 (0.20, 2.96)	2.16 (0.99, 4.72)	3.04 (1.49, 6.20)
(Relative Risk)	p = 1.00	p = 0.06	p = 0.001 *
uACR	0.71 (0.57–0.85)	0.77 (0.65–0.88)	0.63 (0.47–0.79)
(Area under the curve (95% CI)	p = 0.009	p = 0.001	p = 0.10
uPCR	0.53 (0.40–0.65)	0.57 (0.44–0.70)	0.64 (0.50–0.79)
(Area under the curve (95% CI)	p = 0.73	p = 0.30	p = 0.04

cohort of 113 patients, a ROC curve was generated for uACR for the outcome of PE (Fig. 4), which demonstrated an AUC of 0.69 (0.56 – 0.83 95% CI, p = 0.007).

3.4. Secondary outcome analysis

Analysis of all secondary outcomes demonstrated no statistically significant relationships with uACR or uPCR measurements in any trimester (all $p > 0.05$). In the trimester 1 subgroup analysis of 113 patients with normal uPCR (< 30 mg/mmol), microalbuminuria was related to the need for delivery via caesarean section (p = 0.03), with 100% of patients with microalbuminuria (n = 10) delivered via LSCS compared to 66% of those with normal uACR.

4. Discussion

In this multi-centre prospective cohort study, we sought to

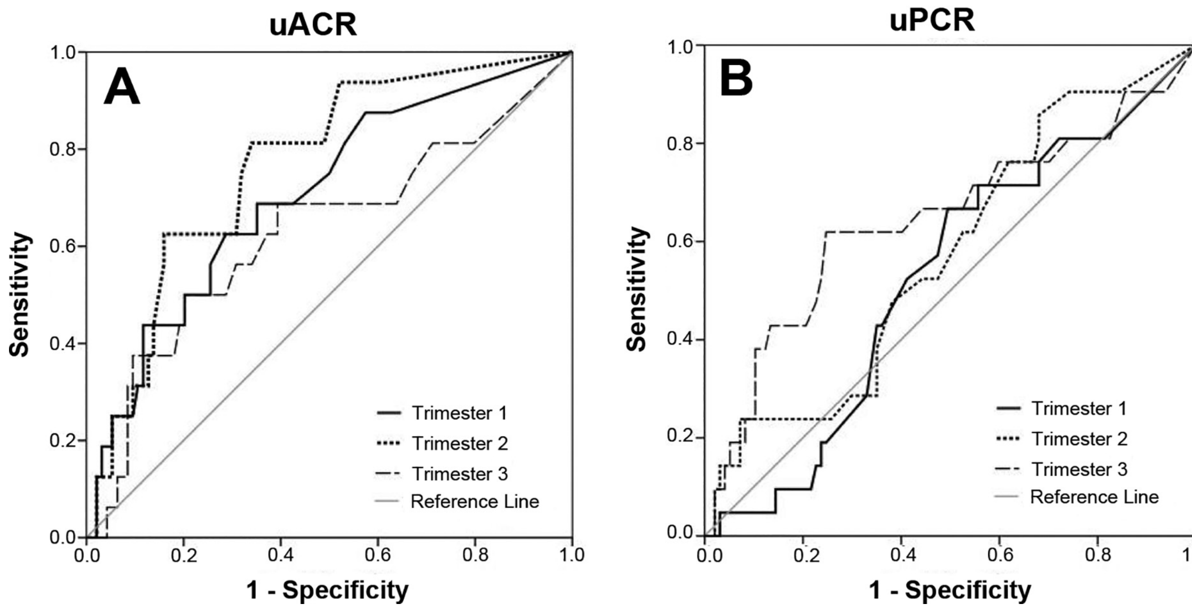

Fig. 3. ROC curves for prediction of preeclampsia based on the (A) uACR and (B) uPCR in each trimester.

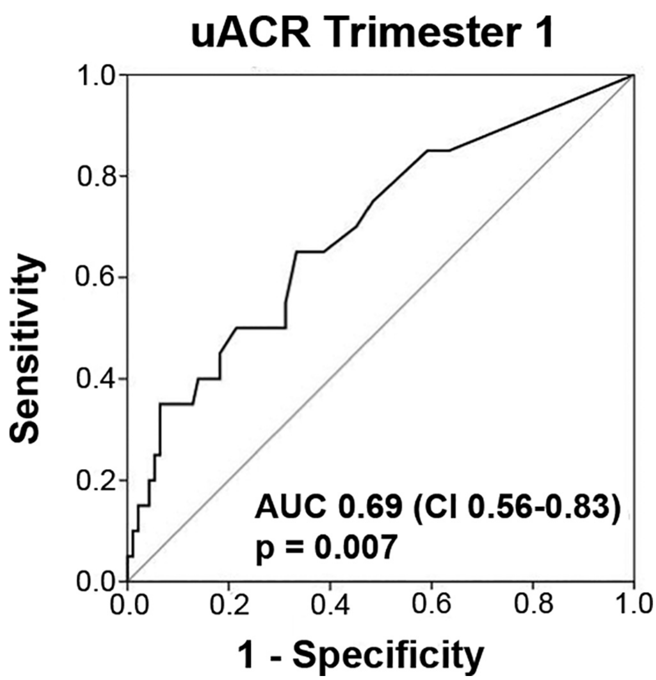

Fig. 4. ROC curve for prediction of preeclampsia based on first trimester uACR in the cohort of women with normal uPCR (< 30 mg/mmol).

determine if uPCR and uACR were good predictive tests for PE and other adverse pregnancy and neonatal outcomes in a cohort of women with pre-existing diabetes requiring insulin during pregnancy. Indicative of the high-risk nature of this cohort, the incidence of PE was found to be 17.1%, which is more than triple that of the general population [13], and is in keeping with published literature [3].

Data on urinary protein excretion in women with diabetes as pregnancy progresses has not previously been described. Within our select cohort of women, irrespective of pregnancy outcome, there was an incremental rise in uPCR as pregnancy progressed. This is in keeping with the literature in the general obstetric population [14]. However, in contrast to literature in the general obstetric population [15], and interestingly given the renal hyper perfusion that accompanies not only pregnancy but also diabetes, we did not observe an incremental rise in uACR as pregnancy progressed, but rather a small rise in late pregnancy. Discrepancy between gestational rise in uPCR and uACR is likely due to renal excretion of non-albumin proteins such as uromodulin in pregnancy, and the fact that pregnancy changes the properties of renal protein excretion. These results suggest that uACR is less vulnerable to the hyperfiltration associated with pregnancy, suggesting it may be a better predictor of pathology, with the small rise in trimester 3 uACR within our cohort likely representing the manifestations of the PE disease process.

Our data demonstrated that Trimester 3 levels of both uACR and uPCR correlated with the outcome of PE. Given the trimester 3 urinary measurements were performed at a predetermined time-point unrelated to timing of PE diagnosis, it is likely that at this time-point, increased uACR and uPCR is reflective of PE disease manifestation, suggesting that uACR performs similarly to uPCR as a diagnostic indicator of PE. Contrastingly, the percentage of the cohort who developed PE was double in the trimester 1 micro-albuminuric group compared to normal uACR, a trend not seen with the trimester 1 proteinuric (uPCR ≥ 30 mg/mmol) cohort. The ROC curves for Trimester 1 and 2 uACR were similar to that of the Trimester 3 uACR and outperformed uPCR in all trimesters. These results suggest that compared to uPCR, uACR may be a better screening test in early pregnancy in this cohort, and likely performs similarly to uPCR as a diagnostic test. Trimester 1 micro-abuminuria correlated with women with a history of nephropathy, while Trimester 1 proteinuria did not, and of the women with normal uPCR in trimester 1, those with microalbuminuria had a 1 in 2 risk of developing PE, a significantly at-risk cohort that would be missed if uPCR alone were used.

Consistent with the published literature in women with diabetes [16], we found higher HbA1c levels in the cohort of women that developed PE. We found a higher rate of unplanned pregnancy in women who developed PE, likely due to those with unplanned pregnancies having more poorly controlled diabetes with significantly higher preconception HbA1c. Compared to the group of women that did not develop PE, we found a higher percentage of women who were smokers, had pre-gestational hypertension, and had a previous history of gestational hypertension, within the group of women that developed PE. This is in keeping with previous studies that have demonstrated these factors to be independent risk factors for the development of PE [17]. We found a higher percentage of women with aspirin use commencing in early pregnancy within the cohort that developed PE compared to the women that did not. Current evidence is conflicting as to whether the use of low dose aspirin reduces the risk of PE in women with diabetes [3,18,19]. However, these results should be interpreted with caution in light of the low absolute numbers of women using aspirin in this study, and the likelihood that aspirin was commenced because of perceived higher risk in these individuals.

This study was performed in a specific high-risk obstetric population, and as such, results are not representative of the utility of uACR in the general obstetric population. Statistical significance was unable to be reached in most analyses due to small absolute outcome numbers. However, the prospective nature of this study adds to its strengths, and serial urinary measurements have not previously been published in this select high-risk obstetric cohort.

Current clinical practice involves the use of uPCR to screen high-risk obstetric patients and diagnose PE. There is limited evidence demonstrating the value of uACR in pregnancy and conflicting data regarding its utility in predicting PE. This is likely a consequence of the vast heterogeneity in previous studies, with differing study populations, varied methods of urine albumin measurement and cutoffs used to define the screen positive cohort, and differing definitions of PE being used. Despite this, a handful of prospective studies have demonstrated a statistically significant association between first and second trimester microalbuminuria and subsequent development of PE [20–23].

At present, the literature is lacking studies investigating the utility of uACR in pregnant women with pre-existing diabetes. A systematic review and meta-analysis in 2012 [24] examining the diagnostic accuracy of uPCR and uACR for adverse pregnancy outcomes, found no study in patients with underlying chronic kidney disease or diabetes. Two studies have investigated the prognostic utility of pre-pregnancy uACR in women with type 1 diabetes [25,26]. A 4-fold increase risk of PE was found in women with microalbuminuria pre-pregnancy or at booking, with PE being associated with a 3-fold higher risk of delivery before 34 weeks [26]. A few smaller studies in women with pre-existing or gestational diabetes have also found an association between microalbuminuria in pregnancy and PE [27–29].

Microalbuminuria in early pregnancy likely represents a cohort of women with early diabetic nephropathy. Our results are consistent with previous studies that have found that in a cohort of women with pre-existing diabetes, those with nephropathy are at significantly increased risk of PE [3], and those with microalbuminuria are at increased risk of developing PE [19]. In addition to the current literature, our results highlight that using uPCR alone does not capture the entire cohort of women with early diabetic nephropathy, further emphasizing the importance of uACR measurement in early pregnancy to identify this cohort of women at significantly higher risk of developing PE. Our results suggest that the prognostic utility of uACR is greater and diagnostic utility similar to that of uPCR within this cohort.

5. Conclusion

We have demonstrated that uACR is a useful simple marker in early pregnancy to predict PE in women with pre-existing diabetes. The results of this study suggest that uACR should be used routinely to evaluate the risk of PE in trimester 1 amongst women with insulin requiring diabetes, and a particularly at-risk cohort of women would be missed in its absence. Validation is required amongst women who do not require insulin. As this test is inexpensive, simple and fast, and given the impact of PE across the globe, further larger studies evaluating the utility of uACR within the general population would also be indicated.

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Conflict of interest

None of the authors have any conflicts of interest to declare.

Author contributions

M.Z. designed the study, analysed the data and wrote the manuscript. V.W.L. and T.I.A. designed the study and reviewed and edited the manuscript. S.P designed the original cohort study, collected the data and reviewed and edited the manuscript. N.W.C and V.W.L. designed the original cohort study and reviewed and edited the manuscript. A.K validated the statistical analysis and reviewed and edited the manuscript. S. J. reviewed and edited the manuscript. M.Z. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.01.010.

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