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Association Between Proteinuria and Pregnancy Outcomes in Women With Preterm Pre-Eclampsia Undergoing Expectant Management: Secondary Analysis of Two Randomised Trials

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ABSTRACT

Objective: Evaluate whether proteinuria levels, in women undergoing expectant management for pre-eclampsia, are associated with pregnancy latency and adverse outcomes.

Design: Secondary analysis of data from two randomised trials.

Setting: Tygerberg Hospital, Cape Town, South Africa.

Population: Women undergoing expectant management for pre-eclampsia diagnosed between 26 and 32 weeks.

Methods: Latency was analysed using parametric time-to-event methods to estimate increases. Composite outcomes were assessed using Poisson regression.

Main Outcome Measures: Pregnancy latency Composite adverse maternal or perinatal outcomes.

Results: Two hundred and ninety-one women were included. Women with <3 g/24 h had a median prolongation of 15.3 days (interquartile range (IQR) 4.3 to 25.6), compared to 10.0 days (IQR 5.0 to 19.6) with proteinuria between 3 to 5 g/24 h; and 4.9 days (IQR 3.8 to 11.7) for those with ≥ 5 g/24 h. Increasing levels were also associated with increases in subsequent adverse composite maternal outcomes: 8.8% of women with <3 g/24 h experienced maternal complications, compared to 16.1% with 3 to 5 g/24 h, and 27.9% with ≥ 5 g/24 h. There was no association with composite perinatal adverse outcomes. The sFlt-1/PIGF ratio performed slightly better in predicting latency (area under the receiver operating characteristic curve (AUC) 0.78 vs. 0.67) but similarly in predicting adverse composite maternal outcomes (AUC 0.67 vs. 0.64). Both had poor performance for predicting composite adverse perinatal outcomes (AUC 0.61 vs. 0.56).

Conclusion: Levels of proteinuria strongly correlate with pregnancy latency and adverse maternal outcomes, but not perinatal outcomes, in women with pre-eclampsia undergoing expectant management. They perform similarly to angiogenic markers. Proteinuria levels may confer useful prognostic information to assist clinical decision-making.

The last two authors share senior authorship.

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1 | Introduction

Massive proteinuria (> 5 g/day) arises from significant renal pathology and once was thought to reflect severe pre-eclampsia [1]. But over recent decades, international societies have removed the relative levels of proteinuria as a marker of disease severity [2–6]. There now seems to be near-universal agreement across international societies that the level of proteinuria does not reflect disease severity, confers no prognostic benefit and should not be considered as part of clinical decision-making. The simple presence or absence of proteinuria may be used to diagnose pre-eclampsia, but otherwise, the actual quantities of protein in the urine are no longer listed as a concern.

The American College of Obstetricians and Gynaecologists (ACOG) guideline based its recommendation on two small retrospective studies which reported no association between the degree of proteinuria and poor perinatal outcomes. However, both studies (evaluating 64 and 209 pregnancies, respectively) were particularly underpowered to assess serious adverse outcomes, especially given they were assessed as individual outcomes [7, 8].

In fact, other retrospective studies [9–22], but not all [7, 8, 23], have reported an association between levels of proteinuria at diagnosis and adverse maternal or perinatal outcomes. Many reporting such an association grouped adverse outcomes as a composite. However, all studies so far have been retrospective studies where case notes of pregnancies undergoing regular clinical care were evaluated.

We previously reported two high-quality randomised trials evaluating whether esomeprazole [24] or metformin [25] could be used to treat women with preterm pre-eclampsia undergoing expectant management to prolong gestation. The clinical information, prospectively collected from these trials, provides high-quality data with clinical trial rigour to examine the association between levels of proteinuria at diagnosis and adverse maternal or perinatal outcomes. Importantly, our unit adheres to a strict protocol encouraging pregnancy prolongation in preterm pre-eclampsia [26]. Longer diagnosis-to-birth intervals allow us to better observe the natural evolution of preterm pre-eclampsia.

1.1 | Study Objective

We therefore performed a secondary analysis using data from these two randomised trials to assess whether degree of proteinuria at diagnosis was associated with subsequent adverse maternal or perinatal outcomes. Outcomes examined were pregnancy latency (primary outcome), and composites of adverse maternal or perinatal outcomes (secondary outcomes). We aligned components of the composite outcomes with those published in an international consensus document, generated by Delphi consensus [27]. Angiogenic markers at first diagnosis of pre-eclampsia may confer prognostic benefit [28]. Therefore, we also compared the performance of levels of proteinuria versus angiogenic markers in predicting subsequent adverse outcomes.

2 | Methods

2.1 | Study Design and Study Population

The cohort used in this analysis consisted of data collected from two double-blind, randomised placebo-controlled trials on expectant management of preterm pre-eclampsia conducted at Tygerberg Hospital, Cape Town, South Africa. We previously reported the findings of both trials [24, 25]. The first trial, the PIE trial, randomised 120 women with preterm pre-eclampsia to 40 mg of esomeprazole or placebo. The second trial, PI2, randomised 180 women to up to 3 g of metformin or placebo. For both trials, the main inclusion criteria were women diagnosed with preterm pre-eclampsia at 26–32 weeks of gestation and who were clinically assessed as suitable for expectant management.

PIE recruited women between January 2016 and April 2017, and the PI2 trial recruited women between February 2018 and March 2020. The trials were registered with the Pan African Clinical Trials Registry (PIE: PACTR201504000771349; PI2: PACTR201608001752102). All participants provided written informed consent to participate in this research and for secondary analyses of their data. Both trials received ethics approval from Stellenbosch University's Health Research Ethics Committee (PIE: M14/09/038; PI2: M16/09/037), and this substudy (S22/11/249).

In both trials, pre-eclampsia was defined as a blood pressure (BP) greater than 140/90 mmHg on at least two occasions with proteinuria (more than 0.3 g total urinary protein excreted over a 24-h period). Expectant management involved hospital admission with close maternal and fetal surveillance. Those reaching 34 + 0 weeks' gestation were delivered. The clinical team followed a strict protocol on expectant management with clear indications for delivery [26]. The level of proteinuria did not influence management and was not an indication for delivery. Severe renal disease was an exclusion criterion for both trials.

Data for both trials were collected prospectively and entered into a REDCap database. Plasma samples were collected during the trials and stored. Angiogenic biomarkers were measured once the trials had completed randomisation and all participants had delivered. The case record forms for every participant in the trial were reviewed by CC, a maternal fetal medicine specialist. Patients were not involved in the development of the research.

2.2 | Procedures

Data from both trial groups were combined for analysis. Participants were grouped according to the 24 h protein concentrations in the urine collected at recruitment: Mild (< 3 g/24 h), moderate (3–5 g/24 h), and severe (≥ 5 g/24 h) proteinuria, which are commonly used categories of proteinuria during pregnancy [29, 30]. Proteinuria was also analysed as a continuous variable to identify potential thresholds for poor outcomes. Levels of proteinuria were measured before the participants were enrolled in the trial and before any trial medications (esomeprazole or metformin) were administered.

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We also evaluated the angiogenic biomarkers soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF), individually and in combination with proteinuria, to assess their discriminatory performance in predicting pregnancy latency and adverse pregnancy outcomes in both trials. Blood samples were collected and stored before any trial medications were administered. The samples were only analysed after enrolment was completed. Circulating concentrations of soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PIGF) were measured using the Elecsys electrochemiluminescence immunoassay platform, run on the cobas e411 instrument manufactured by Roche Diagnostics.

2.3 | Outcomes

The primary outcome was prolongation of gestation, measured in days from randomisation until delivery. Gestational age at delivery was also evaluated descriptively. Secondary outcomes were composites of adverse maternal or neonatal outcomes. Outcomes we included in the composites aligned with those listed on the Delphi international consensus on core outcomes for pre-eclampsia research [27]. The composite maternal adverse outcome was any of: Maternal death, eclampsia, a cerebrovascular event, cortical blindness, retinal detachment, pulmonary oedema (oxygen saturation ≤ 90%, with clinical symptoms requiring treatment), severe renal impairment (serum creatinine level ≥ 125 μmol/L), HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome, liver haematoma or rupture, placental abruption, and/or admission to intensive care unit. The composite perinatal adverse outcome was any of: Stillbirth, neonatal death within the six weeks of the expected due date, necrotising enterocolitis (NEC) requiring surgery, neonatal sepsis, intubation and ventilation, Grade III/IV intraventricular haemorrhage (IVH) on cranial ultrasonography, neonatal seizures, bronchopulmonary dysplasia (requiring oxygen at 28 days of life), and/or retinopathy of prematurity. The neonates were followed up until 6 weeks after the expected due date.

2.4 | Statistical Analysis

Descriptive data were presented as mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables, as appropriate, and as number (percentage) for categorical variables.

The primary outcome, prolongation of gestation, was analysed using parametric time-to-event methods assuming a log-normal distribution, with censoring for deliveries induced at 34 weeks without maternal or fetal indications for delivery. Proteinuria was log-transformed prior to analysis, and results were expressed as fold change (FC; geometric mean ratio) in pregnancy prolongation per 50% increase in proteinuria. Prolongation of gestation and gestational age at delivery were also assessed graphically with Kaplan–Meier curves, stratified by categories of proteinuria (< 3 g/24 h, 3–5 g/24 h, and ≥ 5 g/24 h). We additionally estimated the median prolongation of gestation by proteinuria level using flexible modelling with restricted cubic splines.

The secondary outcomes, adverse maternal and adverse perinatal outcomes, were analysed using Poisson regression with robust standard errors to estimate relative risks (RRs) per 50% increase in proteinuria. The main analyses (time-to-event model and Poisson regression) were conducted both unadjusted and adjusted for maternal age, gestational age at enrolment, body mass index (BMI), trial medication (placebo, esomeprazole, or metformin), mean arterial pressure, fetal growth restriction at enrolment (defined according to a Delphi consensus) [31], and chronic hypertension. These variables were selected a priori based on clinical relevance and their potential to confound the associations of interest.

We finally evaluated the predictive performance of proteinuria, PlGF, and the sFlt-1/PlGF ratio in predicting pregnancy prolongation < 3 days or < 7 days, maternal complications, and perinatal complications. Discriminatory performance was assessed using receiver operating characteristic (ROC) curves, the area under the ROC curve (AUC), and sensitivity (true positive rate, TPR) at 10%, 20%, and 30% false-positive rates (FPR). The FPR thresholds were selected because, in the context of expectant management, it is clinically more important to avoid missing women who may deteriorate than to minimise false positives. Proteinuria, sFlt-1, and the sFlt-1/PlGF ratio were analysed individually and in combination using logistic regression with the log-transformed biomarker values as predictors, without further covariate adjustment, to assess their independent discriminatory performance.

All analyses were conducted at the 5% significance level with corresponding 95% confidence intervals (CIs). Statistical analyses were performed using IBM SPSS Statistics version 26.0. (IBM Corp., Armonk, NY, USA) and SAS/STAT Software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | Results

Three hundred women were recruited across the PIE and PI 2 trials (Figure S1). Women were enrolled between 26 to 32 weeks gestation with a diagnosis of pre-eclampsia and deemed clinically suitable for expectant management. Of these, nine were excluded in the original trials: Five did not meet the requirements for a pre-eclampsia diagnosis, two declined further in-hospital management, one had their diagnosis changed from pre-eclampsia to a systemic lupus erythematosus (SLE) flare after randomisation, and one was under the maternal age range for inclusion. This left 291 participants for the present study, of which 217 (74.6%) had proteinuria < 3 g/24 h at admission, 31 (10.7%) had proteinuria 3–5 g/24 h, and 43 (14.8%) had proteinuria ≥ 5 g/24 h. Participants with higher levels of proteinuria were younger, more frequently nulliparous, and were more likely to have fetal growth restriction at the time of presentation (Table 1). There were no notable differences in body mass index (BMI), blood pressure, or gestational age at inclusion. A total of 81 (28%) women reached 34 + 0 weeks' gestation without a maternal or fetal indication for delivery.

In women undergoing expectant management of pre-eclampsia, the amount of proteinuria in urine collected at first presentation strongly correlated with the length of pregnancy prolongation

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TABLE 1 | Baseline characteristics at enrolment, overall and stratified by level of proteinuria at diagnosis of pre-eclampsia (mild < 3 g/24 h; moderate 3–5 g/24 h; severe ≥ 5 g/24 h).

Characteristic	Total ($n = 291$)	Mild Proteinuria < 3 g/24 h ($n = 217$)	Moderate proteinuria 3–5 g/24 h ($n = 31$)	Severe proteinuria ≥ 5 g/24 h ($n = 43$)
Maternal characteristics				
Age (years)	28.4 (6.5)	29.1 (6.7)	26.2 (5.4)	26.2 (5.0)
Body mass index (kg/m^2)	30.3 (7.3)	30.5 (7.4)	29.7 (7.7)	29.4 (6.3)
Smoking during pregnancy	34 (11.7%)	27 (12.4%)	2 (6.5%)	5 (11.6%)
HIV positive	58 (19.9%)	45 (20.7%)	3 (9.7%)	10 (23.3%)
Chronic hypertension	80 (27.5%)	66 (30.4%)	7 (22.6%)	7 (16.3%)
Nulliparous	101 (34.7%)	69 (31.8%)	13 (41.9%)	19 (44.2%)
Gestation at enrolment (weeks)	29.4 (1.6)	29.4 (1.5)	29.8 (1.7)	29.2 (1.8)
Highest recorded systolic BP before enrolment (mmHg)	168 [17]	168 [17]	169 [14]	167 [17]
Highest recorded diastolic BP before enrolment (mmHg)	102 [13]	101 [13]	105 [12]	105 [13]
Haemoglobin at enrolment (g/dL)	11.8 (1.4)	11.7 (1.4)	11.8 (1.4)	12.1 (1.6)
Platelet count at enrolment (10^9/L)	217 (172–270)	215 (171–273)	231 (177–257)	218 (158–268)
Urea at enrolment (mmol/L)	3.5 (2.8–4.7)	3.3 (2.6–4.3)	4.05 (3.4–5.8)	4.7 (3.4–6.0)
Creatinine at enrolment (μmol/L)	54 (46–64)	52 (45–62)	56 (51–68)	62 (53–72)
Randomised trial medication				
Esomeprazole	58 (19.9%)	44 (20.3%)	7 (22.6%)	7 (16.3%)
Metformin	87 (29.9%)	64 (29.5%)	6 (19.4%)	17 (39.5%)
Placebo	146 (50.2%)	109 (50.2%)	18 (58.1%)	19 (44.2%)
Fetal characteristics				
Estimated fetal weight centile at first ultrasound[a]	10.6 (1.4–29.3)	10.8 (2.1–31.5)	7.0 (0.4–15.1)	9.3 (1.0–26.1)
Fetal growth restriction	128 (44.3%)	91 (42.1%)	17 (54.8%)	20 (47.6%)

Note: Categorical variables are presented as number (percentage); continuous variables as mean (SD) or median (IQR), as appropriate.
Abbreviations: BP = blood pressure; HIV = human immunodeficiency virus; IQR = interquartile range; SD = standard deviation.
[a]Estimated fetal weight centile at first ultrasound calculated using the GROW Customised Centile Calculator [32].

(Figure 1). Women with < 3 g/24 h of proteinuria had a median prolongation of 15.3 days (IQR 4.3–25.6), compared to 10.0 days (IQR 5.0–19.6) in those with proteinuria 3–5 g/24 h and 4.9 days (IQR 3.8–11.7) in those with ≥ 5 g/24 h (Table 2). The median gestation at birth was 32.1 weeks (IQR 30.0–34.0), 32.3 weeks (IQR 29.4–34.1), and 30.4 weeks (28.6–32.1) in women with proteinuria < 3 g/24 h, 3–5 g/24 h, and ≥ 5 g/24 h, respectively (Figure 2). After adjusting for confounders, there was a 15% reduction (95% CI 8%–21%) in length of pregnancy prolongation for every 50% increase in levels of proteinuria (Table 2).

Increasing levels of proteinuria at diagnosis were associated with a stepwise increase in rates of adverse composite maternal outcomes. Among women with < 3 g/24 h proteinuria, 8.4% (19/217) experienced maternal complications, compared to 16.1% (5/31) of those with 3–5 g/24 h, and 27.9% (12/43) of those

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with ≥5 g/24 h. Adjusted analyses showed a 19% higher risk of adverse maternal outcomes per 50% increase in proteinuria (aRR 1.19, 95% CI 1.03–1.38). In contrast, there was no association between the level of proteinuria at diagnosis and perinatal adverse outcomes (aRR 1.07, 95% CI 0.97–1.18) (Table 2). There did not appear to be a single maternal organ system driving the results (Table S1). The rates of eclampsia, pulmonary oedema, placental abruption, acute kidney injury, and HELLP syndrome were all more than doubled among those who had proteinuria at diagnosis ≥5 g/24 h, compared to those with <3 g/24 h. There was a potential stepwise increase in rates of adverse outcomes across the three levels of proteinuria studied for pulmonary oedema and HELLP syndrome.

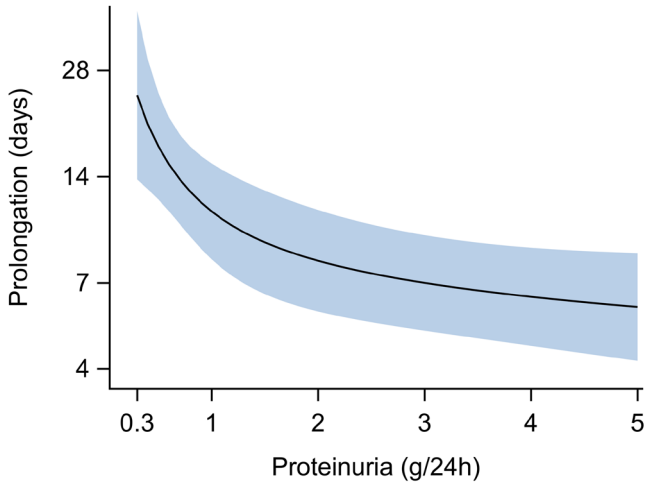

FIGURE 1 | Association between pregnancy prolongation and 24-h urinary protein excretion at diagnosis in women with preterm pre-eclampsia undergoing expectant management. The solid line represents the estimated median prolongation times from parametric time-to-event models fitted with restricted cubic splines, with shaded areas indicating 95% confidence intervals. Higher levels of proteinuria at diagnosis were associated with progressively shorter pregnancy latency ($p < 0.001$). The model was adjusted for trial medication to reflect prolongation expected in the absence of treatment.

Finally, we compared the performance of proteinuria with angiogenic biomarkers in predicting pregnancy complications and early delivery. Levels of proteinuria at first presentation had lower performance than PlGF or sFlt-1/PlGF in predicting prolongation (Table S2). For predicting birth within three days, proteinuria had an AUC of 0.57 (95% CI 0.49–0.66), compared to 0.71 (95% CI 0.63–0.79) for PlGF, and 0.70 (95% CI 0.62–0.78) for the sFlt-1/PlGF ratio (Figure S2). For predicting birth within seven days, levels of proteinuria had an AUC of 0.67 (95% CI 0.61–0.74) compared to 0.73 (95% CI 0.67–0.79) for PlGF, and 0.78 (95% CI 0.72–0.83) for the sFlt-1/PlGF ratio. For both time periods, combining proteinuria with angiogenic biomarkers did not improve performance compared with either biomarker alone.

In contrast, levels of proteinuria at first presentation were similar to the angiogenic biomarkers in predicting adverse maternal outcomes (Table S2). However, none of the biomarker options performed particularly well as lone clinical biomarkers to predict adverse maternal outcomes (all AUCs <0.70). Adding levels of proteinuria to any of the angiogenic biomarkers did not improve performance. All combinations performed poorly at predicting perinatal adverse outcomes (Table S2).

TABLE 2 | Prolongation of gestation and maternal and perinatal complications associated with level of proteinuria at enrolment.

	Mild proteinuria (<3 g/24 h)	Moderate proteinuria (3–5 g/24 h)	Severe proteinuria (≥5 g/24 h)	crude FC/ RR (95% CI)	*p*	aFC/aRR (95% CI)	*p*
Gestation at delivery (weeks)[a]	32.1 (30.0–34.0)	32.3 (29.4–34.1)	30.4 (28.6–32.1)	—		—	
Prolongation of gestation (days)[b]	15.3 (4.3–25.6)	10.0 (5.0–19.6)	4.9 (3.8–11.7)	0.83 (0.77, 0.89)	<0.001	0.85 (0.79, 0.92)	<0.001
Maternal complications[c,d]	19 (8.8%)	5 (16.1%)	12 (27.9%)	1.20 (1.06, 1.36)	0.005	1.19 (1.03, 1.38)	0.021
Perinatal complications[c,e]	42 (19.4%)	9 (29.0%)	10 (23.3%)	1.07 (0.98, 1.17).	0.12	1.07 (0.97, 1.18).	0.17

Note: Continuous variables are presented as median (IQR); categorical variables as number (percentage). Descriptive results are stratified by mild (<3 g/24 h), moderate (3–5 g/24 h) and severe (≥5 g/24 h) proteinuria, while analyses were performed treating proteinuria as a continuous variable. Fold changes and relative risks are expressed per 50% increase in proteinuria. All analyses were performed both unadjusted and adjusted for maternal age, gestation at enrolment, BMI, trial medication (placebo, esomeprazole, or metformin), mean arterial pressure, fetal growth restriction, and chronic hypertension.
Abbreviations: aFC = adjusted fold change; aRR = adjusted relative risk; CI = confidence interval; FC = fold change; IQR = interquartile range; RR = relative risk.
[a]Gestational age at delivery is reported descriptively only.
[b]Prolongation of gestation was analysed using parametric time-to-event models with a log-normal distribution. Deliveries were censored at 34 + 0 weeks' gestation if induction occurred without other maternal or fetal indications. Results are expressed as fold change (FC; geometric mean ratio) in pregnancy prolongation per 50% increase in proteinuria.
[c]Adverse maternal and perinatal outcomes were analysed using Poisson regression with robust standard errors. Results are expressed as relative risk (RR) of complication per 50% increase in proteinuria.
[d]Composite maternal adverse outcome included maternal death, eclampsia, a cerebrovascular event, cortical blindness, retinal detachment, pulmonary oedema, severe renal impairment, HELLP syndrome, liver haematoma or rupture, placental abruption, and admission to intensive care unit.
[e]Composite perinatal adverse outcome included stillbirth, neonatal death within the six weeks after the expected due date, necrotising enterocolitis requiring surgery, neonatal sepsis, intubation and ventilation, Grade III/IV intraventricular haemorrhage on cranial ultrasonography, neonatal seizures, bronchopulmonary dysplasia (requiring oxygen at 28 days of life), and retinopathy of prematurity.

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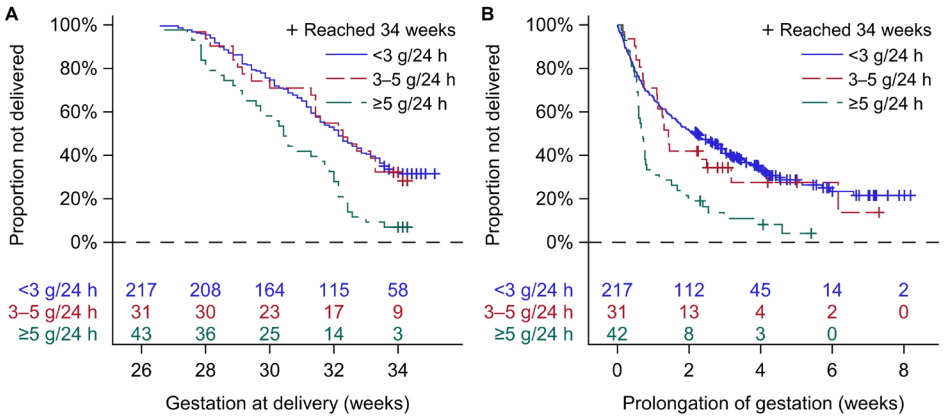

FIGURE 2 | Kaplan–Meier curves for (A) gestation at delivery and (B) pregnancy prolongation according to levels of proteinuria at diagnosis, stratified as < 3 g/24 h, 3–5 g/24 h, and ≥ 5 g/24 h. Deliveries were censored at 34 + 0 weeks' gestation if induction occurred without other maternal or fetal indications. Numbers below the curves indicate women remaining undelivered at each time point.

4 | Discussion

4.1 | Main Findings

Among women with preterm pre-eclampsia undergoing expectant management, there was a strong correlation between increasing levels of proteinuria at diagnosis and reduced pregnancy latency and adverse maternal outcomes, but not perinatal outcomes. Levels of proteinuria performed similarly to angiogenic biomarkers for predicting adverse maternal and perinatal outcomes. Combining proteinuria with angiogenic biomarkers did not improve performance.

4.2 | Interpretation

A summary of findings from 12 previous studies examining associations between levels of proteinuria and outcomes is shown in Table S3. Unlike our study, all but one were retrospective studies. Nearly all examined a mix of maternal or perinatal outcomes; only two examined the prediction of pregnancy prolongation. Significantly, ours is the first to compare the performance of proteinuria with angiogenic biomarkers to predict adverse outcomes.

The two studies that assessed prolongation of pregnancy associated with proteinuria level at diagnosis yielded conflicting results. One that examined 209 women diagnosed with pre-eclampsia before 37 weeks showed no difference in prolongation of pregnancy [7]. The other included 94 women diagnosed with pre-eclampsia after 22 weeks and showed a significant decrease in prolongation if proteinuria was above 5 g/24 h. Our study, examining 291 women recruited prospectively, found results consistent with findings of the latter publication.

Most studies examined proteinuria levels and adverse maternal outcomes. Most studies examining composite maternal outcomes reported positive associations between levels of proteinuria and poor outcomes (Table S3) [10, 13, 16, 17, 21, 33]. This concurs with our findings of a strong correlation between levels of proteinuria and composite adverse maternal outcomes.

In contrast, studies reporting individual maternal outcomes often reported no associations. This is unsurprising as they were likely underpowered to examine single outcomes as they occur relatively rarely [7, 14, 18]. Some studies did identify differences in individual maternal outcomes such as eclampsia [16, 21, 22], HELLP syndrome [19, 21, 22], pulmonary oedema [19], placental abruption [21], severe hypertension [13, 22], severe features of pre-eclampsia [21, 22], intensive care unit admissions [21, 22], haemodialysis [21] and other individual outcomes (Table S3).

In contrast to our study, which did not find a correlation between levels of proteinuria and a composite of poor perinatal outcomes, many of the prior studies did report a correlation. (Table S3) [7, 10, 13, 14, 17–22, 33]. Our study only included perinatal outcomes that were listed in a Delphi consensus paper on important adverse outcomes in pre-eclampsia [27]. It is difficult to reconcile the differences we found with these prior studies. A probable explanation is that levels of proteinuria likely reflect vascular injury in the maternal compartment, but it is difficult to explain how maternal proteinuria would reflect the fetal condition.

There did not appear to be a single maternal organ system driving the composite maternal adverse outcome. Rates of eclampsia, pulmonary oedema, placental abruption, acute kidney injury, and HELLP syndrome were all more than doubled among women with proteinuria ≥ 5 g/24 h compared with those with < 3 g/24 h at diagnosis. This suggests that high levels of proteinuria may help identify women at increased risk of serious maternal complications. Further research is needed to determine its value as a potential predictor for risk stratification in expectant management.

Our study is the first to compare the performance of angiogenic markers such as the sFlt-1/PIGF ratio with levels of proteinuria to predict outcomes. Recently, it was proposed that measuring sFlt-1 and PIGF in women diagnosed with pre-eclampsia may have a role in predicting who are at risk of developing adverse outcomes. A secondary analysis of a prospective cohort showed that a ratio < 38 was good at ruling out the development of pre-eclampsia with severe features

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within two weeks (defined according to the ACOG guidelines) [34]. They also showed that a ratio > 85 performed fairly at ruling in pre-eclampsia with severe features within 2 weeks when pre-eclampsia had already been confirmed in patients at < 35 weeks. The most common adverse outcome was severe hypertension, a readily treatable condition [34]. In contrast, our study was able to examine far more severe maternal outcomes (such as eclampsia, pulmonary oedema, acute liver injury and HELLP), albeit as part of a composite. In our study, we found that levels of proteinuria performed similarly or just slightly worse than angiogenic markers. Angiogenic markers were moderately better predictors of delivery within three days but were similar to proteinuria in predicting delivery within seven days and maternal complications.

4.3 | Strengths and Limitations

A major strength of this study is its use of high-quality, prospectively collected data within a rigorous clinical trial framework. Although preterm pre-eclampsia is a relatively rare condition, our dataset includes a substantial sample of almost 300 participants. Further strengths include using a Delphi consensus to define adverse outcomes, composite endpoints to enhance statistical power, and a pre-specified statistical analysis plan. At the same time, we acknowledge that using a composite outcome may have the disadvantage of limiting clinical specificity. The single-centre design in a low-middle-income country may limit generalisability, although our referral centre's broad catchment area of more than 2 million people enhances external validity. Expectant management protocols and indications for delivery may differ in other settings, particularly where there is increased access to neonatal intensive care.

5 | Conclusion

5.1 | Practical Clinical Implications

We have shown that levels of proteinuria at the time of diagnosis of preterm pre-eclampsia are associated with pregnancy prolongation and risk of severe adverse maternal outcomes in women undergoing expectant management. Measuring proteinuria is not only cheap, but the information is often readily available as it is obtained as part of disease diagnosis. Given the cost and limited availability of angiogenic biomarkers in resource-constrained settings, proteinuria remains a practical and accessible biomarker. The clinical implication is that the level of proteinuria should be noted as it may inform clinical management.

We encourage international clinical guidelines to reconsider their recommendations. In contrast to current recommendations, we propose that noting the level of proteinuria may be considered as part of clinical decision-making, especially in situations where clinicians are at equipoise whether to deliver or hold off.

Furthermore, in contrast with most international clinical guidelines, it is likely that the level of proteinuria indeed correlates with disease severity. The presence of massive proteinuria (≥ 5 g/d) should trigger a heightened sense of anticipation that severe adverse maternal outcomes may occur. Also, the timing of steroid administration for accelerating fetal lung maturity could be guided by the level of protein excretion.

5.2 | Research Recommendations

Future studies in other settings are needed to validate our findings and evaluate generalisability. It is also important to assess whether proteinuria, alone or in a multivariate model, may be used as a predictor for adverse outcomes and if this improves outcomes. Another research avenue would be to examine whether an acute increase in proteinuria levels during expectant management signifies a change in the risk of adverse maternal outcomes and disease severity. Future studies should also explore whether spot protein-to-creatinine ratio at diagnosis is similarly predictive of adverse outcomes.

Author Contributions

C.A.C., S.T., S.P.W. and L.B. conceived the idea. A.R., C.A.C. and L.B. wrote the first draft of the manuscript. H.I. did the statistical analysis. All authors reviewed the manuscript and approved it for publication.

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Disclosure

Levels of proteinuria at diagnosis offer a simple, widely available measure associated with pregnancy latency and serious adverse maternal outcomes in preterm pre-eclampsia. Our findings challenge the current stance of major international guidelines, which no longer consider proteinuria a marker of disease severity, and suggest levels of proteinuria may offer valuable prognostic information for women undergoing expectant management of preterm pre-eclampsia. This measure may be particularly useful in low- and middle-income countries, where access to angiogenic markers is limited, and the burden of disease is greatest.

Conflicts of Interest

S.T., S.W., L.B., C.C., and H.I. provide consultancy service for Diamedica Therapeutics; S.T. and C.C. provide consultancy services for Avilar Therapeutics and Beech Biotech. AvR and D.S. report no Conflicts of Interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Individual maternal and perinatal complications and mode of delivery according to proteinuria at enrolment. **Table S2:** Predictive performance of proteinuria, PlGF, and the sFlt-1/

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PlGF ratio for delivery within 3 or 7 days, maternal complications, and perinatal complications. **Table S3:** Summary of studies assessing proteinuria at diagnosis of pre-eclampsia and adverse maternal, pregnancy and perinatal outcomes. The blue text shows the results that were statistically significant. **Figure S1:** Flowchart showing eligibility, exclusions, and final numbers from the PIE and PI2 trials included in the current analysis. **Figure S2:** Receiver operating characteristic (ROC) curves of proteinuria, placental growth factor (PlGF), and soluble fms-like tyrosine kinase-1 (sFlt-1) to PlGF ratio, shown individually and all three in combination, measured at diagnosis of preterm pre-eclampsia.

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