Hypertensive Disorders of Pregnancy: Effects on Mother and Baby

Spot urine protein measurements in normotensive pregnancies, pregnancies with isolated proteinuria and preeclampsia

Andrea Kattah,1 Natasa Milic,2 Wendy White,3 and Vesna Garovic1
1Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota; 2Institute for Medical Statistics and Informatics, Faculty of Medicine, University of Belgrade, Belgrade, Serbia; and 3Department of Maternal-Fetal Medicine, Rochester, Minnesota

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Kattah A, Milic N, White W, Garovic V. Spot urine protein measurements in normotensive pregnancies, pregnancies with isolated proteinuria and preeclampsia. Am J Physiol Regul Integr Comp Physiol 313: R418–R424, 2017. First published July 26, 2017; doi: 10.1152/ajpregu.00508.2016.—We performed a prospective, longitudinal study of pregnant women presenting to their first obstetrics visits to characterize the changes in spot urine protein-to-creatinine (UPCR) and albumin-to-creatinine ratios (UACR) in normotensive pregnancies, as well as identify clinical characteristics associated with isolated proteinuria and preeclampsia. We measured spot urinary albumin, protein, and creatinine at the first prenatal visit, end of the second trimester, and at delivery. In the normotensive pregnancies (n = 142), we found that from the beginning of pregnancy to delivery, UACR increased by a median [interquartile range (IQR)] of 14.7 mg/g Cr (3.74–51.8) and UPCR by 60 mg/g Cr (30–130) (P < 0.001 for both changes). Isolated proteinuria (defined as UPCR > 300 mg/g Cr in the absence of hypertension) was identified in 19/142 (13.4%) normotensive pregnancies. Increases in systolic and diastolic blood pressure from early pregnancy to delivery and increases in UACR from early to midpregnancy were associated with isolated proteinuria at delivery. Twelve women developed preeclampsia. Nulliparity, early, and midpregnancy diastolic blood pressures were strongly associated with the development of preeclampsia, but early changes in UACR were not. In conclusion, women who develop isolated proteinuria at delivery have a larger increase in blood pressure than women without proteinuria and have a “microalbuminuric” phase earlier in gestation, unlike women who develop preeclampsia. These findings suggest a different mechanism of urine protein excretion in women with isolated proteinuria as compared with women with preeclampsia, where proteinuria has a more abrupt onset.

albuminuria; proteinuria; pregnancy; preeclampsia

URINE PROTEIN EXCRETION typically increases over the course of normal pregnancy, and therefore the threshold for elevated proteinuria in pregnancy (>300 mg/24 h or urine protein-to-creatinine ratio (UPCR) > 300 mg/g Cr) is higher than outside of pregnancy (1, 10, 16). The physiological increase in proteinuria may be due to changes in either glomerular or tubular handling of proteins (17). Several studies have investigated urinary albumin excretion as a marker of glomerular permeability and found that it does not increase, and may even decrease, in normal pregnancy as compared with nonpregnant controls (4, 18). In contrast, markers of tubular proteinuria, such as retinol-binding protein, may increase in pregnancy (4). In late pregnancy, there is some evidence that the glomerular basement membrane can become more permeable, in which case, an increase in urinary albumin may be expected (22).

The uncertain significance of proteinuria in pregnancy is reflected in the most recent American College of Obstetricians and Gynecologists (ACOG) guidelines on the diagnosis of preeclampsia, a hypertensive condition classically characterized by glomerular endotheliosis and proteinuria. Proteinuria is no longer a requirement to diagnose preeclampsia if a woman has other severe features, such as seizures, low platelets, or elevated liver enzymes (1). The rationale for this change is that preeclampsia is a syndrome of endothelial dysfunction with multiple manifestations, and that the degree of proteinuria is not related to pregnancy outcomes (5). Furthermore, some women may develop significant proteinuria in pregnancy in the absence of hypertension, a phenomenon known as isolated, or gestational, proteinuria (19). These women typically have healthy and otherwise uncomplicated pregnancies (2, 19, 20) though it is a diagnosis that can only be made retrospectively. If a woman with proteinuria develops hypertension, she then fulfills criteria for preeclampsia.

If one considers normotensive pregnancy and preeclampsia to be on a spectrum, women with isolated proteinuria may have an intermediate phenotype. Alternatively, these women may have subclinical renal disease unmasked by the hyperfiltration of pregnancy. As albumin excretion is a more specific marker of glomerular permeability, the relative changes in urine albumin and total protein excretion over the course of normotensive pregnancy may provide insights into the mechanisms of urinary protein excretion in pregnancy and the causes of isolated proteinuria (18, 21, 24).

We had three goals with this study. Our first goal was to define the change in urine albumin-to-creatinine ratio (UACR) and UPCR over the course of normotensive pregnancy. Second, we performed a nested case-control analysis to identify clinical characteristics and changes in urinary protein excretion that are associated with isolated proteinuria at the time of delivery. Finally, we compared the changes in urinary protein excretion and clinical characteristics associated with isolated proteinuria to those seen in preeclampsia that is accompanied by proteinuria. Although preeclampsia can be diagnosed with-
out proteinuria (1), none of our patients met the criteria for preeclampsia in the absence of proteinuria. By clarifying the changes in urinary protein excretion in these clinical settings, we hoped to better understand the various mechanisms of proteinuria in pregnancy.

MATERIALS AND METHODS

Study Design

Participants. We performed a prospective, longitudinal study of pregnant women presenting to their first obstetrics visits from 6/2007 to 7/2010 at Mayo Clinic, Rochester, MN. This study was approved by the Institutional Review Board (IRB no. 2104–05), and all women gave informed consent. Demographic information and obstetrical history were collected from the first prenatal visit.

This cohort of women was initially recruited to study podocyturia as a marker for preeclampsia and detailed methods have been described previously (8). Urine samples were collected at the first prenatal visit [median, 7.8 gestational weeks (GW); interquartile range (IQR) 7.0–9.4], at the end of the second trimester (median, 27.8 GW; IQR 26.7–28.7), and at admission for delivery (median, 39.6 GW; IQR 39.0–40.4); spot urinary albumin, protein, and creatinine were measured. All urine assays were performed on a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN) using standardized methods and routine calibration (creatinine by enzymatic method, albumin by immunoturbidimetry assay, and protein by colorimetric dye assay). Samples were run in duplicate, and the average value was taken for each measurement. UACR (mg/g Cr) and UPCR (mg/g Cr) were calculated. Blood pressure (BP, in mmHg) and weight (in kg) were recorded in early pregnancy, midpregnancy, and at admission for delivery to correspond with the time point when the urine sample was given. Blood pressure was taken at the obstetrics visit by trained clinical assistants using a manual cuff. The BP at the time of delivery was the first blood pressure taken at the triage area before the patient received other interventions that may have interfered with the measurements.

Clinical outcomes. Preeclampsia is a pregnancy-specific hypertensive disorder characterized by hypertension and commonly proteinuria. The American College of Obstetrics and Gynecology has defined hypertension in pregnancy as 2 blood pressure elevations 4 h apart, with a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg (1). Pregnancy outcomes and diagnoses were recorded at the time of hospitalization for delivery and included normotensive pregnancy, preeclampsia, gestational hypertension, and other pregnancy complications [gestational diabetes, intrauterine growth restriction (IUGR), and preterm delivery], as previously described (8). Isolated proteinuria in pregnancy was defined as UPCR >300 mg/g Cr in the absence of blood pressure elevation (1).

We excluded women from our analysis who did not give a urine sample within the first 14 wk of pregnancy and those with baseline elevations in albuminuria or proteinuria, defined as a UACR >25 mg/g Cr or a UPCR >160 mg/g Cr, respectively (15, 23). Women with histories of renal disease were excluded regardless of current levels of proteinuria. We excluded women with preterm delivery due to causes other than preeclampsia and twin gestation from the analysis of isolated proteinuria in normotensive pregnancy given the concern that they did not have the opportunity to reach their peak urine protein excretion at the time of delivery. Similarly, we excluded women with gestational hypertension as they did not have normotensive pregnancy, by definition, and if they had both hypertension and proteinuria, they would be classified as having preeclampsia.

Statistical Analysis

Data are presented as medians with IQRs for continuous variables and absolute numbers with percentages for categorical variables.

Changes in UACR and UPCR from early pregnancy to midpregnancy and delivery in women with normotensive pregnancies are presented by line graph where the solid line represents the medians and shaded area represents the IQRs. To evaluate the proportion of total urine albumin that was urine albumin, we took the ratio of urine albumin to urine protein (mg/mg). Paired t-tests were used to test the significance of changes in UACR, UPCR, and the ratio of urine albumin to protein between trimesters. Because the optimal cut-off for UACR in pregnancy has not been determined (7), we used univariate logistic regression and made a receiver-operator characteristic (ROC) curve to determine the value of UACR that had the highest sensitivity and specificity for UPCR >300 mg/g Cr.

Univariate logistic regression was used to assess maternal characteristics associated with isolated proteinuria and preeclampsia in nested case-control analyses. Results are reported as odds ratios (OR) and 95% confidence intervals (CIs). We evaluated whether the change in UACR and UPCR from early to midpregnancy was associated with isolated proteinuria delivery. The predictor variables we used to model the change in UACR and UPCR from early to midpregnancy were the ratios of mid to early pregnancy values. In the analysis of preeclampsia, we only used clinical predictors (blood pressure and weight gain) from early and midpregnancy, before the clinical onset of disease. The P value for significance was determined by the likelihood ratio test and set at 0.05 for all analyses. All analyses were done with JMP Statistical Software, version 10.0.

RESULTS

Studied Population

Figure 1 presents the study participants recruitment in detail. There were 173 women in the study sample (142 with normotensive pregnancy, 12 with preeclampsia, 10 with gestational hypertension, and 9 with preterm delivery) who gave urine samples at each study visit. The women with missing samples (n = 88) did not differ from the women who gave urine samples by any of the baseline demographics (age, gravidity, nulliparity, race, ethnicity, education, or prior pregnancy comp-

![Fig. 1. Women recruited to the cohort and included in the final sample. IUGR, intrauterine growth restriction; DM, diabetes mellitus.](https://api.jpregu.org)
There were 8 women with gestational diabetes and one woman with IUGR, none of whom suffered from a hypertensive pregnancy disorder, all of whom were included in the analysis. Selected blood pressure and pregnancy characteristics are shown in Table 1.

### Change in Spot Urinary Protein Measurements in Pregnancy

In normotensive, term pregnancies ($n = 142$), the median (IQR) UACR values were 3.44 mg/g Cr (1.95–6.05), 3.86 mg/g Cr (2.05–6.13), and 19.20 mg/g Cr (7.47–57.0), in early pregnancy, midpregnancy, and at delivery, respectively ($P < 0.001$ for change from early and midpregnancy to delivery). The median (IQR) UPCR values were 17 mg/g Cr (11–27), 65 (60.5–74.5), and 82 mg/g Cr (43–150), in early pregnancy, midpregnancy, and at delivery, respectively ($P < 0.001$ for all differences). The UACR increased by a median (IQR) of 14.7 mg/g Cr (3.7, 51.8) at the time of delivery. The UPCR increased by a median (IQR) of 64 mg/g Cr (28–132) at delivery. The median (IQR) ratio of urine albumin to urine protein (mg/mg) in early pregnancy was 0.17 (0.10, 0.23), decreased to 0.10 (0.07–0.15) in midpregnancy, and increased at delivery to 0.24 (0.15, 0.37) ($P < 0.0001$ for all differences).

The changes in UACR and UPCR in women with gestational hypertension ($n = 10$) and preterm delivery ($n = 9$) as compared with normotensive, term pregnancies are shown in Fig. 2. Given the small numbers and many missing samples, (5/15 missing in gestational hypertension and 5/14 missing in preterm delivery) further statistical analyses were not performed on these two groups.

We found that a UACR threshold of 125 mg/g Cr was 100% (95% CI 79–100%) sensitive and 98.4% (95% CI 94–100%) specific for UPCR $> 300$ mg/g Cr at delivery. The area under the ROC curve was 0.99. There were 21 women with elevated albuminuria using this threshold (14.8%). With the use of the threshold for microalbuminuria outside of pregnancy in women (UACR $> 25$ mg/g Cr) (15), 44.4% (63/142) of women had elevated albuminuria at delivery.

### Table 1. Characteristics of women with normotensive term pregnancies and with complications of preeclampsia, gestational hypertension, and preterm delivery

<table>
<thead>
<tr>
<th></th>
<th>Normotensive, Term ($n = 142$)</th>
<th>Preeclampsia ($n = 12$)</th>
<th>Gestational Hypertension ($n = 10$)</th>
<th>Preterm Delivery ($n = 9$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td>29.9 (27.1–33.8)</td>
<td>25.2 (22.9–33.7)</td>
<td>28.6 (27.3–29.1)</td>
<td>29.6 (28.8–36.6)</td>
</tr>
<tr>
<td><strong>Gravidity</strong></td>
<td>2 (1–3)</td>
<td>1 (1–1)</td>
<td>1 (1–2.25)</td>
<td>2 (1–4.5)</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td>1 (0–1)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>1 (0–1.5)</td>
</tr>
<tr>
<td><strong>Prepregnancy BMI, kg/m²</strong></td>
<td>24.2 (22.0–29.1)</td>
<td>26.5 (21.7–34.7)</td>
<td>22.6 (21.7–28.2)</td>
<td>24.1 (22.2–29.0)</td>
</tr>
<tr>
<td><strong>Early SBP, mmHg</strong></td>
<td>102 (98–110)</td>
<td>104 (92.5–117)</td>
<td>108 (97–118)</td>
<td>100 (98–113)</td>
</tr>
<tr>
<td><strong>Early DBP, mmHg</strong></td>
<td>60 (60–68)</td>
<td>70 (61–71.5)</td>
<td>65 (61.5–70)</td>
<td>60 (60–66)</td>
</tr>
<tr>
<td><strong>Mid SBP, mmHg</strong></td>
<td>106 (100–110.5)</td>
<td>112 (102.5–123.5)</td>
<td>111 (104–123)</td>
<td>104 (100–113)</td>
</tr>
<tr>
<td><strong>Mid DBP, mmHg</strong></td>
<td>60 (58–66)</td>
<td>65 (60.5–74.5)</td>
<td>66.5 (61–75)</td>
<td>60 (54–60)</td>
</tr>
<tr>
<td><strong>Delivery SBP, mmHg</strong></td>
<td>126 (117–135)</td>
<td>143.5 (133.3–146.2)</td>
<td>144 (140.2–146.3)</td>
<td>130 (120.5–136)</td>
</tr>
<tr>
<td><strong>Delivery DBP, mmHg</strong></td>
<td>77 (69–84)</td>
<td>96.5 (88.8–100.25)</td>
<td>91 (86.5–96)</td>
<td>73 (66.5–78)</td>
</tr>
<tr>
<td><strong>Gestational weight gain, kg</strong></td>
<td>14 (10.6–17.2)</td>
<td>18.9 (14.6–23.6)</td>
<td>18.8 (12.9–24.9)</td>
<td>14.5 (12.6–16.8)</td>
</tr>
<tr>
<td><strong>Gestational age at delivery, days</strong></td>
<td>277 (273–283)</td>
<td>275.5 (273.5–279.8)</td>
<td>278.5 (270.8–283.3)</td>
<td>250 (241.5–254.5)</td>
</tr>
</tbody>
</table>

All data presented as median (interquartile range). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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Isolated Proteinuria

There were 19/142 (13.4%) women with normotensive pregnancies who had isolated proteinuria at delivery. For every 10-mmHg increase in systolic BP from early pregnancy to delivery, the odds of having isolated proteinuria increased by 1.80 times (95% CI 1.25–2.75). We saw a similar association with diastolic BP, as well (OR 1.54 per 10-mmHg increase from early pregnancy to delivery, 95% CI 1.02–2.41). The ratio of mid to early UACR (OR 1.10, 95% CI 1.00–1.27) was also significantly associated with isolated proteinuria at delivery in the univariate analysis (Table 2). Changes in the systolic and diastolic BPs during normotensive pregnancies with and without isolated proteinuria are shown in Fig. 3.

Preeclamptic Pregnancies

The baseline characteristics of women with longitudinally collected urinary spot measurements with normotensive pregnancies (n = 142) and women with preeclampsia (n = 12) are shown in Table 3. Clinical characteristics associated with an increased risk of developing preeclampsia were nulliparity (OR 8.40, 95% CI 2.11–56.0), midgestation weight gain (OR 1.15 per 1 kg, 95% CI 1.01–1.33), early and midpregnancy diastolic BP (OR 2.86 per 10 mmHg, 95% CI 1.25–6.93 and OR 2.99 per 10 mmHg, 95% CI 1.10–4.05, respectively) (Table 3). The changes in UACR and UPCR from early to midpregnancy were not significantly associated with the development of pre-eclampsia. The results did not change in a sensitivity analysis.
excluding women with isolated proteinuria \((n = 19)\) from the normotensive pregnancy group.

### DISCUSSION

The clinical characteristics associated with isolated proteinuria have not been explored extensively. In this study, we found that ~13\% of women with normotensive pregnancies developed significant levels of proteinuria at delivery, in the absence of hypertension. The main factor associated with isolated proteinuria at delivery was an increase in blood pressure, although still within the normal range. The increase in UACR from the first prenatal visit to the end of the second trimester was also associated with the development of proteinuria at delivery. These findings mimic the behavior of renal disease outside of pregnancy, where microalbuminuria precedes the development of frank proteinuria, and where proteinuria increases in the setting of increased BP. However, we did not find that an early increase in UACR was associated with the development of preeclampsia, another proteinuric disease of pregnancy. Though our sample size of women who developed preeclampsia was limited, women with preeclampsia and isolated proteinuria did not have the same associated risk factors, such as nulliparity, education, or gestational weight gain, suggesting that isolated proteinuria is not a milder preeclampsia phenotype.

The clinical relevance of isolated, gestational proteinuria has been debated, though whether it represents a pathological state of pregnancy is highly relevant to defining another condition—preeclampsia. The ACOG guidelines have removed proteinuria as a necessary component of the definition of preeclampsia, and our results provide some justification for this decision as nearly 15\% of women had elevated proteinuria at delivery without significant elevations in blood pressure. Another recent prospective study suggested 45\% of women will develop proteinuria >300 mg in 24 hours in late pregnancy in the absence of disease (20). Part of the difficulty in studying this group of women is that underlying renal disease before pregnancy must be excluded, as it is well known that women with glomerular disease will have an increase in proteinuria in pregnancy (2, 19). Similarly, women without hypertension will not routinely have urine protein evaluated in pregnancy; therefore, isolated proteinuria is best studied in a prospective study design. One of the largest prospective studies of isolated proteinuria was published in 2009 by Holston et al., using the Calcium for Preeclampsia Prevention (CPEP) trial database (11). They measured circulating angiogenic factors in nulliparous women with isolated proteinuria \((n = 108)\) and preeclampsia \((n = 319)\), as compared with women with normotensive pregnancies and no proteinuria \((n = 1,564)\). They found that women with isolated proteinuria had lower levels of free placental growth factor early in gestation and transient elevations of soluble fms-like tyrosine kinase and soluble endoglin concentrations 1–2 wk before the onset of proteinuria. Similar to our study, they found that midgestation blood pressure was associated with isolated proteinuria. The authors concluded that gestational proteinuria may be a mild variant of preeclampsia given the modest antiangiogenic factor imbalances. In our study, we found that nulliparity was not associated with isolated proteinuria, unlike preeclampsia, which is an argument against the hypothesis that isolated proteinuria is a mild preeclampsia variant. In addition, by only evaluating nulliparous women, the prevalence of isolated proteinuria in pregnancy may have been underestimated in the CPEP study. Another limitation is that proteinuria was diagnosed by dipstick in the majority of cases, which has quite limited sensitivity and specificity. In our cohort, we were able to measure both UPCR and UACR and therefore better define urine protein changes in pregnancy.

Our results suggest that there is a “microalbuminuric” phase in women who develop isolated proteinuria at delivery. Women with UPCR >300 mg/g Cr at delivery had a 36\% median increase in urine albumin from early to midpregnancy, whereas women with normal protein at delivery had 5\% median decrease, despite an overall increase in proteinuria in midpregnancy. One explanation for this finding is that women with isolated proteinuria have subclinical renal disease, such as mild reflux nephropathy, secondary focal glomerulosclerosis, or IgA nephropathy, which is uncovered by the hyperfiltration of pregnancy (14). They may not come to provider attention, as UPCR and UACR are not typically measured in women in the absence of hypertension. Alternatively, as others have proposed, women who develop proteinuria without significant

### Table 3. Univariate logistic regression for factors associated with preeclampsia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preeclampsia ((n = 12))</th>
<th>Normotensive ((n = 142))</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>(P) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>25.2 (22.8, 33.7)</td>
<td>29.9 (27.1, 33.8)</td>
<td>0.91</td>
<td>0.78–1.04</td>
<td>0.17</td>
</tr>
<tr>
<td>Race (n, % caucasian)</td>
<td>11 (91.7)</td>
<td>127 (89.5)</td>
<td>1.29</td>
<td>0.23–24.6</td>
<td>0.80</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>10 (83.3%)</td>
<td>53 (37.3%)</td>
<td>8.40</td>
<td>2.11–56.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Education (n, % with college or advanced degree)</td>
<td>4 (33.3)</td>
<td>104 (73.2%)</td>
<td>0.18</td>
<td>0.05–0.61</td>
<td>0.006</td>
</tr>
<tr>
<td>Prepregnancy body mass index, kg/m(^2)</td>
<td>26.5 (21.7, 34.7)</td>
<td>24.0 (22.0, 29.1)</td>
<td>1.05</td>
<td>0.96–1.15</td>
<td>0.24</td>
</tr>
<tr>
<td>Midgestation weight gain (per 1 kg)</td>
<td>10.1 (7.6, 14.1)</td>
<td>8.3 (5.8, 11.2)</td>
<td>1.15</td>
<td>1.01–1.33</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early pregnancy, per 10 mmHg†</td>
<td>104 (93, 117)</td>
<td>102 (98, 110)</td>
<td>1.09</td>
<td>0.63–1.86</td>
<td>0.74</td>
</tr>
<tr>
<td>Midpregnancy, per 10 mmHg†</td>
<td>112 (103, 124)</td>
<td>106 (100, 110)</td>
<td>1.62</td>
<td>0.90–2.84</td>
<td>0.08</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early pregnancy, per 10 mmHg†</td>
<td>70 (61, 72)</td>
<td>60 (60, 68)</td>
<td>2.86</td>
<td>1.25–6.93</td>
<td>0.01</td>
</tr>
<tr>
<td>Midpregnancy, per 10 mmHg†</td>
<td>65 (61, 75)</td>
<td>60 (58, 65.5)</td>
<td>2.99</td>
<td>1.10–4.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Ratio of mid to early pregnancy UACR</td>
<td>0.86 (0.63, 4.5)</td>
<td>1.00 (0.64, 1.67)</td>
<td>1.02</td>
<td>0.86–1.11</td>
<td>0.72</td>
</tr>
<tr>
<td>Ratio of mid to early pregnancy UPCR</td>
<td>1.66 (1.32, 2.08)</td>
<td>1.63 (1.17, 2.25)</td>
<td>1.06</td>
<td>0.58–1.64</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Data presented as median (IQR) unless otherwise specified; \(n\) = number of pregnancies. UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein-to-creatinine ratio. *Likelihood ratio test. †The odds ratio presented shows the increase in odds of having preeclampsia per 10-mmHg increment of blood pressure. Blood pressures at delivery were not included in this analysis as all women with preeclampsia had elevated blood pressures at delivery.
BP elevations may represent a milder preeclampsia phenotype. We found that women with isolated proteinuria had a different clinical phenotype than those with preeclampsia, in terms of the associations with nulliparity, education, and midgestational weight gain. While not conclusive, this would argue that isolated proteinuria is not a mild preeclampsia syndrome, though this will need to be confirmed in a larger population of patients. None of the women with isolated proteinuria developed overt renal disease in our short-term follow-up of this cohort. However, based on studies evaluating the association of preeclampsia and renal outcomes, the occurrence of renal disease may be decades in the future (12, 13, 25).

We did not see the same “microalbuminuric” phase in the women who developed preeclampsia, which may reflect a different mechanism of proteinuria. Women with preeclampsia develop glomerular endotheliosis, glomerular injury, and proteinuria (2). None of the women who developed preeclampsia in our cohort had developed elevated proteinuria (UPCR > 0.3) or albuminuria (>125 mg/g Cr) by the end of the second trimester, suggesting a more abrupt onset of glomerular injury. Others have found that microalbuminuria may be a marker for adverse pregnancy outcomes (3, 9, 21). A study by Poon et al. (21) evaluated the urine albumin concentrations and UACR at 11–13 gestational weeks in greater than 2,000 normal singleton and preeclamptic pregnancies. They found that UACR was higher at 11–13 gestational weeks in pregnancies that subsequently developed preeclampsia, but that the addition of the UACR did not improve the model to predict preeclampsia in combination with other maternal factors. They did not, however, have early pregnancy measurements of urine albumin to exclude women with renal disease, who are at an increased risk of preeclampsia at baseline. We excluded women with baseline proteinuria and studied the change in UACR in pregnancy, rather than to study a single urine protein measurement, to take into account a woman’s baseline level of albuminuria in interpreting values later in pregnancy.

Finally, our study brings up some interesting observations about the mechanisms of proteinuria in pregnancy. The hyperfiltration of pregnancy is often invoked as the cause of increased protein excretion in pregnancy, but there are likely several contributing factors (2, 17). Several studies have shown an increase in retinol-binding protein excretion in pregnant women compared with nonpregnant controls, suggesting that tubular proteinuria, or the decreased reabsorption of tubular proteins, accounts for some of the increase in protein excretion (4, 6). In a study by Beetham et al. (4), the authors measured urinary excretion of albumin as a ratio of creatinine concentration and found that it was not significantly different from nonpregnant control groups and did not increase across the trimesters, though retinol-binding protein excretion was increased throughout pregnancy. In our study, the women with normotensive pregnancy had little change in the UACR from early to midpregnancy, whereas the UPCR increased (Fig. 2), which would support the hypothesis that glomerular permeability is unchanged, whereas tubular proteinuria may increase, at least in early pregnancy. This may not be true, however, in late pregnancy. In a classic study of renal physiology in pregnancy, Roberts et al. (22) evaluated the clearance of neutral dextrans in 11 normotensive, otherwise healthy, pregnant women. They found that there was a relative increase in the flux of large to small dextrans across the glomerular basement membrane in late pregnancy (36 wk), which corresponded to an increase in both proteinuria and albuminuria. While it is impossible to measure glomerular permeability directly in this scenario, by using mathematical modeling to assess determinants of GFR, the authors concluded that the ultrafiltration coefficient (Kf) is increased in late pregnancy. We found increases in both urinary albumin and protein excretion at the time of delivery, supporting the hypothesis that glomerular permeability is increased.

This study has several limitations. We had few pregnancies with preeclampsia and therefore limited power to detect differences in urine albumin excretion in that population. Spot urine protein measurements are subject to variability throughout the day, although 24-h urine collections have limitations as well, such as under collection and retention of urine in the collecting system (17). Another potential limitation is that Mayo Clinic is a tertiary care center, so there is a concern for referral bias. However, the vast majority of patients in obstetrics are from the surrounding community, so we feel the results are generalizable.

**Perspectives and Significance**

We believe that our study adds interesting insights into the mechanisms of protein excretion during normotensive pregnancies. We found that total proteinuria increased in midpregnancy and at delivery in normotensive pregnancies, but that urinary albumin excretion only increased at the time of delivery, which may reflect an increase in glomerular permeability late in pregnancy. Women with isolated proteinuria, however, had early increases in urinary albumin excretion, whereas women who developed preeclampsia did not, suggesting different mechanisms of proteinuria in these two states. The clinical significance of isolated proteinuria is still unknown and future studies on the association of isolated proteinuria with maternal outcomes may provide opportunities to identify women at future risk for renal disease.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**

A.K., W.M.W., and V.D.G. conceived and designed research; A.K. and N.M. prepared figures; A.K., N.M., and V.D.G. interpreted results of experiments; A.K. and N.M. analyzed data; A.K., N.M., and V.D.G. drafted manuscript; A.K., N.M., W.M.W., and V.D.G. edited and revised manuscript; A.K., N.M., W.M.W., and V.D.G. approved final version of manuscript; V.D.G. performed experiments.

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