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Baseline Renal Function Tests and Adverse Outcomes in Patients With Chronic Hypertension

Spencer G. Kuper, MD, Alan T. Tita, MD, PhD, Mallory L. Youngstrom, BS, Sarah E. Allen, BS, Ying Tang, PhD, Joseph R. Biggio, MD, and Lorie M. Harper, MD, MSCI

University of Alabama at Birmingham, Center for Women's Reproductive Health, Birmingham, Alabama

Abstract

OBJECTIVE—To examine the relationship between baseline renal function tests in patients with chronic hypertension and adverse outcomes.

METHODS—This was a retrospective cohort study of women with a singleton pregnancy and chronic hypertension with assessment of renal function (urine protein-to-creatinine ratio and serum creatinine) prior to 20 weeks. The primary outcome was severe preeclampsia <34 weeks. Secondary outcomes were severe preeclampsia at any gestational age, any preeclampsia, preterm birth <35 weeks, composite perinatal outcome (perinatal death, assisted ventilation, cord pH <7, 5-minute Apgar 3 or neonatal seizures) and small for gestational age. The association between baseline renal function and the primary outcome was assessed with receiver operating characteristic (ROC) curves and objective cutoffs determined. Outcomes were compared between those with values above and below the cutoffs using univariable and multivariable analyses.

RESULTS—Seven hundred fifty five women with chronic hypertension had baseline renal function assessment. The urine protein-to-creatinine ratio and creatinine cutoffs for severe preeclampsia <34 weeks were 0.12 and 0.75 mg/dL, respectively. The area under the ROC curves for severe preeclampsia <34 weeks were 0.74(95% CI 0.7–0.8) for urine protein-to-creatinine ratio and 0.67(95% CI 0.6–0.8) for creatinine. A urine protein-to-creatinine ratio 0.12 was associated with an increased risk of developing severe preeclampsia <34 weeks (16.4 vs 2.6%, aOR 7.5; 95% CI 3.9–14.6) as was a creatinine 0.75 mg/dL (15.7 vs 4.6%, aOR 3.5; 95% CI 1.9–6.3). Severe preeclampsia <34 weeks occurred in only 1.6% of patients if their baseline tests were below both cutoffs.

CONCLUSION—Baseline assessment of renal function can be used as a risk stratification tool in patients with chronic hypertension.

CORRESPONDING AUTHOR: Spencer G. Kuper, M.D., Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, University of Alabama at Birmingham, 176F 10270 619, 19th Street South, Birmingham, AL 35249, Phone: 205-934-9188, Fax: 205-975-9858, sgkuper@uabmc.edu.

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INTRODUCTION

Chronic hypertension affects 5% of pregnant women and is associated with adverse maternal and neonatal events.¹ The American College of Obstetricians and Gynecologists recommends obtaining baseline renal function tests, in particular serum creatinine and quantification of baseline proteinuria (either a urine protein-to-creatinine ratio or 24-hour urine protein).² The stated purpose of the baseline tests is for future comparison to facilitate a diagnosis of superimposed preeclampsia. Cutoffs used to define abnormal tests (serum creatinine 1.2 mg/dL and urine protein-to-creatinine ratio 0.3) are based on expert consensus opinions³ meant for the diagnosis of preeclampsia in the second and third trimester. Although abnormal values are associated with adverse pregnancy outcomes, the association of baseline assessment of renal function with adverse pregnancy outcomes is not well-defined.

Renal insufficiency and proteinuria are well-established complications of chronic hypertension, yet “normal” values for baseline tests are not clearly established. Physiologic changes during pregnancy increase the glomerular filtration rate and creatinine clearance, which lowers serum creatinine to normal levels even when pre-pregnancy elevated levels exist;⁴ consequently, the finding of baseline renal insufficiency often is not made during pregnancy.^{4–5} Thus, the usefulness of baseline laboratory tests has been called into question.⁴ We conducted a retrospective cohort to quantify the relationships between baseline renal function tests in gravid patients with chronic hypertension and the development of preeclampsia later in gestation. We hypothesized levels lower than current thresholds considered abnormal are associated with adverse outcomes in women with chronic hypertension.

MATERIALS AND METHODS

This was a retrospective cohort study of all patients with chronic hypertension who presented for prenatal care prior to 20 completed weeks of gestation from January 1, 2000 to June 1, 2014 at the University of Alabama at Birmingham. Institutional review board approval was obtained.

Patients with a diagnosis of chronic hypertension were identified through searchable medical records in our perinatal database. The diagnosis of chronic hypertension was confirmed on chart review by either a documented history of chronic hypertension with use of antihypertensive medication or documentation of blood pressures 140/90 mm Hg on two occasions prior to 20 weeks gestation. Patients were included in the study if they met the following criteria: singleton gestation, collection of a baseline urine protein-to-creatinine ratio and serum creatinine prior to 20 completed weeks of gestation, and delivered at our institution. All urine protein-to-creatinine ratios and serum creatinine tests were performed in the same laboratory. The laboratory calculated the urine protein-to-creatinine ratio as mg/dL random protein divided by mg/dL random creatinine. Thus, the units of the ratio canceled each other out, and value was reported as a ratio. Patients were excluded if the pregnancy was complicated by fetal anomalies or major medical comorbidities other than pregestational diabetes. We elected to include pregnancies complicated by pregestational

diabetes as this is a frequent co-morbid condition; however, we did perform a secondary analysis excluding patients with pregestational diabetes. Only the first qualifying pregnancy over the time period was included in the analysis. Patients were managed by providers under the supervision of maternal-fetal medicine specialists and antihypertensive medication was added if their systolic blood pressure was ≥ 150 mmHg or diastolic blood pressure ≥ 90 mmHg after being repeated manually 2–3 times. Persons trained in chart abstraction used standardized chart abstraction forms to abstract data from the medical charts. The senior author (LH) reviewed at least 3% of the charts. Data collected included detailed information on maternal demographics, medical and obstetrical history, prenatal blood pressures and urinalysis at every visit, baseline laboratory information, medication use, labor and delivery events, and neonatal outcomes.

The primary outcome was the development of early onset severe preeclampsia, defined as delivery for preeclampsia with severe features prior to 34 weeks of gestation. Preeclampsia was defined as hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) with proteinuria (urine protein-to-creatinine ratio ≥ 0.3 or 24-hour urine protein ≥ 300 mg). Severe preeclampsia was defined by criteria listed in Box 1. Severe features of preeclampsia were defined as systolic blood pressure ≥ 160 mm Hg, diastolic blood pressure ≥ 110 mm Hg, creatinine ≥ 1.2 mg/dL, platelets $<100,000$ /microliter, or AST ≥ 80 units/liter (twice the threshold of normal for our laboratory). Because blood pressure may have been elevated due to chronic hypertension alone, proteinuria was required for the definition of severe preeclampsia if blood pressure was the only severe feature present. Headache and visual changes were not abstracted and therefore were not used in the definition of severe preeclampsia for this study. The secondary outcomes included severe preeclampsia at any gestational age, preeclampsia without severe features at any gestational age, all preterm birth prior to 35 weeks of gestation, medically indicated preterm birth prior to 35 weeks of gestation, small for gestational age and a composite adverse neonatal outcome. The neonatal composite outcome included stillbirth, neonatal death, assisted ventilation requirements (continuous positive airway pressure or intubation), arterial cord pH < 7.0 , 5-minute Apgar ≤ 3 and neonatal seizures.

Box 1

Diagnostic criteria for severe preeclampsia

Diagnosis of preeclampsia plus one of the following:

- Systolic blood pressure ≥ 160 mmHg *
- Diastolic blood pressure ≥ 110 mmHg *
- Creatinine ≥ 1.2
- Platelets $< 100,000$ /microliter
- AST ≥ 80 units/liter (twice the upper limit of threshold for our laboratory)

* Proteinuria required if blood pressure alone is the diagnostic criteria used for severe preeclampsia (proteinuria defined as urine protein-to-creatinine ratio ≥ 0.3 or a 24-hour urine protein ≥ 300 mg), AST, aminotransferase

In order to assess the effect of baseline serum creatinine on the development of severe preeclampsia prior to 34 weeks, a receiver operating characteristic (ROC) curve was created and the Liu method⁶ was then used to mathematically determine a cutoff for the serum creatinine associated with increased risk. Baseline demographics and the risk of the outcomes of interest were then compared between those with serum creatinine values above and below the cutoff using the Student's t-test, Mann-Whitney U test, or chi-squared test as appropriate. Multivariate logistic regression models were then used to estimate the effect of serum creatinine on outcomes while adjusting for confounding variables. Clinically relevant covariates for initial inclusion were selected using results of the univariate analyses and factors were removed in a backward step-wise fashion based on significant changes in the exposure adjusted odds ratio or significant differences between hierarchical models using the likelihood ratio test. Variables considered for inclusion included maternal age, parity, race, tobacco use, body mass index (kg/m²), years since the diagnosis of hypertension, antihypertensive use before and during pregnancy, diabetes, preeclampsia in a prior pregnancy, history of preterm delivery, and aspirin use.

We then assessed the effect of baseline proteinuria, as assessed by a urine protein-to-creatinine ratio, on pregnancy outcomes. For this analysis, only women with a serum creatinine < 1.2 mg/dL were included. We elected to exclude those with an elevated creatinine due to the known associations between creatinine and proteinuria. Again, a ROC curve was created in order to assess the association of baseline proteinuria and early onset severe preeclampsia; the Liu method⁶ was used to mathematically determine a cutoff for urine protein-to-creatinine ratio in the fashion described for determining the cutoff for serum creatinine.

Sensitivity, specificity, positive and negative predictive values and likelihood ratios were calculated utilizing the cutoffs for the prediction of severe preeclampsia prior to 34 weeks of gestation and the secondary outcomes. We also assessed the combination of baseline serum creatinine and urine protein-to-creatinine ratio for sensitivity, specificity, positive and negative predictive values and likelihood ratios of severe preeclampsia prior to 34 weeks and the secondary outcomes. Statistical analyses were performed using STATA version 13 (College Station, TX).

RESULTS

Of 1478 women with chronic hypertension identified over the study period, 723 were excluded (Figure 1). Therefore, 755 women who had baseline serum creatinine and urine protein-to-creatinine ratio assessments prior to 20 completed weeks of gestation were analyzed (range 5–19 weeks of gestational age, mean gestational age at collection 10 weeks). Of those, 739 patients with chronic hypertension had a baseline serum creatinine level < 1.2 mg/dL and thus were included in the analysis of the urine protein-to-creatinine ratio in women with a normal serum creatinine (Figure 1). In the 755 women included in the analysis of serum creatinine, the median creatinine was 0.7 mg/dL (interquartile range 0.6–0.7 mg/dL). In the 739 women included in the urine protein-to-creatinine ratio analysis, the median urine protein-to-creatinine ratio was 0.08 (interquartile range 0.06–0.12). Six

hundred forty-five patients (85%) were normotensive ($< 140/90$ mmHg) and six patients (0.8%) had blood pressures $\geq 160/110$ mmHg prior to 20 weeks.

The area under the ROC curve for serum creatinine and the occurrence of severe preeclampsia prior to 34 weeks was 0.67 (95% CI 0.6–0.8) (Figure 2). The Liu method selected a serum creatinine of ≥ 0.75 mg/dL as the optimal mathematical cutoff on the ROC curve, corresponding to the 90th percentile. Baseline characteristics of women with a serum creatinine above and below the cutoff of 0.75 mg/dL were compared (Table 1). The groups were similar in regards to baseline characteristics; however, a larger proportion of patients with a baseline serum creatinine ≥ 0.75 mg/dL had baseline renal function tests earlier (median 8.6 weeks (interquartile range 6.7–12.4) vs median 10.7 weeks (interquartile range 8–14.6), $p=0.01$), were on antihypertensive medications prior to pregnancy (70.2% vs 52.8%, $p = 0.01$) and required medication during their pregnancy (84.8% vs. 77.6%, $p = 0.04$). Mean blood pressures at different gestational age ranges were not clinically different between the two groups.

The association of baseline serum creatinine ≥ 0.75 mg/dL and the outcomes of interest are shown in Table 2. Baseline serum creatinine ≥ 0.75 mg/dL compared to values below the threshold was associated with an increased risk of developing severe preeclampsia prior to 34 weeks of gestation (15.7 vs 4.6%, aOR 3.5, 95% CI 1.9–6.3) as well as mild preeclampsia or severe preeclampsia at any gestational age (35.7 vs 21.6%, aOR 1.9, 95% CI 1.3–2.7 and 26.9 vs 13.0%, aOR 2.3, 95% CI 1.5–3.5, respectively). The results for neonatal composite, preterm birth < 35 weeks of gestation and small for gestational age were not significantly different between groups. These significant associations persisted when patients with pregestational diabetes were excluded (Table 3).

The area under the ROC curve for the association of urine protein-to-creatinine ratio and severe preeclampsia prior to 34 weeks was 0.74 (95% CI 0.7–0.8) (Figure 2), and the Liu method selected a urine protein-to-creatinine ratio of 0.12 as the optimal cutoff, corresponding to the 75th percentile. Baseline characteristics of women with a urine protein-to-creatinine ratio ≥ 0.12 were compared to women with a protein-to-creatinine ratio < 0.12 (Table 1). The groups were similar in regards to baseline characteristics; however, a larger proportion of patients with a baseline urine protein-to-creatinine ratio ≥ 0.12 were black (76.1% vs. 66.7%, $p = 0.01$), had a higher pre-pregnancy body mass index (40.1 ± 10.6 vs. 37.5 ± 12.0 , $p = 0.01$), and were on anti-hypertensive medications prior to pregnancy (59.1% versus 50.3%, $p = 0.03$). Mean blood pressures at different gestational age ranges were not clinically different between the two groups.

The association of baseline urine protein-to-creatinine ratio ≥ 0.12 to outcomes are presented in Table 4. The risk of developing severe preeclampsia prior to 34 weeks was significantly increased with a urine protein-to-creatinine ratio ≥ 0.12 (16.4 vs 2.6%, aOR 7.5, 95% CI 3.9–14.6) as were the risks of developing mild preeclampsia and severe preeclampsia at any gestational age (49.2 vs 14.2%, aOR 6.1, 95% CI 4.2–8.9 and 30.3 vs 9.0%, aOR 4.5, 95% CI 3.0–7.0). A baseline urine protein-to-creatinine ratio above the cutoff was associated with an increased risk of preterm birth less than 35 weeks of gestation (31.8 vs 16.4%, aOR 2.4, 95% CI 1.6–3.5) (Table 4). The risks of the primary neonatal composite and small for

gestational age were not significantly associated with results above vs. below the urine protein-to-creatinine ratio cutoff. These significant associations persisted when patients with pregestational diabetes were excluded (Table 5).

We assessed the combination of baseline serum creatinine and urine protein-to-creatinine ratio on the incidence of the primary and secondary outcomes (Table 6). If both baseline renal function tests were less than the cutoffs for urine protein-to-creatinine and serum creatinine (0.12 and 0.75 mg/dL, respectively), only 1.6% of patients developed severe preeclampsia prior to 34 weeks of gestation. Severe preeclampsia at any gestational age developed in 7.9% of those patients with normal baseline renal function tests, and 13.0% developed any type of preeclampsia. The preterm birth incidence in those with normal baseline renal function tests was 17.1%. When both values were above the cutoffs, 33.3% developed severe preeclampsia prior to 34 weeks, 50.9% developed severe preeclampsia at any gestational age, and 66.7% developed any type of preeclampsia. The preterm birth rate when both values were above the cutoffs was 47.2%.

Finally, we assessed the test characteristics (sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios) of each cutoff, alone and in combination for the prediction of the primary and secondary outcomes (Table 7). The sensitivity and specificity of the serum creatinine cutoff value to predict the development of severe preeclampsia prior to 34 weeks were 50.0% and 79.5%, respectively. The positive and negative predictive values were 15.8% and 95.4%, respectively. The positive and negative likelihood ratios were 2.4 and 0.6, respectively. The sensitivity and specificity of the urine protein-to-creatinine ratio cutoff value to predict the development of severe preeclampsia prior to 34 weeks was 69.6% and 76.5%, respectively. The positive and negative predictive values were 16.4% and 97.4%, respectively. The positive and negative likelihood ratios were 3.0 and 0.4, respectively. When both values were above the cutoffs, the sensitivity and specificity of predicting severe preeclampsia prior to 34 weeks was 35.2 and 94.6%, respectively. The positive and negative predictive values were 33.3 and 95.0%, respectively. The positive and negative likelihood ratios were 6.5 and 0.7, respectively.

DISCUSSION

In our cohort, baseline serum creatinine and urine protein-to-creatinine ratio 0.75 mg/dL and 0.12, respectively, are associated with increased risks of severe preeclampsia prior to 34 weeks, severe and mild preeclampsia at any gestational age and for urine protein-to-creatinine ratio, preterm birth <35 weeks. These thresholds are much lower than typically considered abnormal. Further, 33.3% of women with chronic hypertension and baseline renal function tests above the objectively determined cutoffs developed severe preeclampsia < 34 weeks and 66.7% developed any type of preeclampsia during the pregnancy.

Conversely, in this cohort, 97.4% of patients with a baseline urine protein-to-creatinine ratio < 0.12 did not develop severe preeclampsia. Similarly, 95.4% of patients with baseline serum creatinine < 0.75 mg/dL did not develop severe preeclampsia. Importantly, when both baseline renal function tests were below the cutoffs, only 1.6% of patients developed severe preeclampsia prior to 34 weeks.

The utility of baseline renal function tests in patients with chronic hypertension has been questioned. This is partly because the results are rarely flagged as “abnormal” because reference ranges are formulated from a healthy non-pregnant population that do not account for the physiologic changes of the renal system during pregnancy previously discussed. After a review of 73 patients with chronic hypertension found no relationship between baseline laboratory values and the later development of preeclampsia, Fabri et al⁵ suggested baseline laboratory tests might have little clinical relevance. However, in their study only 3 patients had abnormal baseline laboratory values and just one developed superimposed preeclampsia. The incidence of superimposed preeclampsia in their cohort was much lower than 20–40% reported in patients with chronic hypertension and in our patient population.^{2,7}

Our study is not without limitations. First, our population represents a high risk, largely black, population and may not be generalizable to every setting. Secondly, while we attempted to identify and control for confounding in our results with detailed data collection regarding baseline characteristics, it is possible residual confounding persisted. Lastly, baseline renal function tests were typically collected at the first visit rather than a set gestational age. Knowing that renal function improves during early pregnancy as plasma volume expands,⁸ the gestational age when the baseline labs were drawn could have had an impact on the determination of our cutoffs. As our goal was a single cutoff that could be broadly and readily applied, we did not adjust for gestational age at the time of baseline renal function tests. An assessment of gestational age at collection of the baseline labs and baseline serum creatinine and urine protein-to-creatinine values did not reveal a correlation (Figure 3). Thus, our results can be applied to patients with chronic hypertension who establish care prior to 20 weeks of gestation.

The strengths of our study include the large study population of high-risk patients who had accurately recorded baseline data such as laboratory tests, gestational age, medical history, and demographical information. Our large sample size allowed us to detect differences in outcomes such as preeclampsia, small for gestational age, and adverse neonatal outcomes. In addition, we used strict criteria in classifying patients with severe preeclampsia using objectively recorded clinical data. Thus, we are confident we did not overestimate the incidence of severe preeclampsia. Lastly, we took the “consensus opinion” out of the equation of determining the baseline urine protein-to-creatinine ratio or serum creatinine that increases the risk of developing preeclampsia later in the second and third trimester. Providers now have objectively determined cutoffs, serum creatinine 0.75 mg/dL and urine protein-to-creatinine ratio 0.12, to use when assessing patients’ risks of adverse outcomes.

In sum, our findings suggest that a creatinine 0.75 mg/dL and a urine protein-to-creatinine ratio 0.12 are associated with adverse pregnancy outcomes in women with chronic hypertension, much lower cutoffs than previously used. These findings should be validated in additional studies and if validated, can be used to counsel women regarding their risk of adverse pregnancy outcomes and to alter surveillance for preeclampsia.

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References

1. Sibai BM. Chronic hypertension in pregnancy. *Obstet Gynecol.* 2002; 100:369–77. [PubMed: 12151166]
2. The American College of Obstetricians and Gynecologists. Hypertension in Pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol.* 2013; 122(5):1122–31. [PubMed: 24150027]
3. Cunningham, FG.; Leveno, KJ.; Bloom, SL.; Hauth, JC.; Rouse, DW.; Spong, CY., editors. *Williams Obstetrics*. 23. New York (NY): McGraw Hill Medical; 2010. Pregnancy Hypertension; p. 706–56.
4. Ramin SM, Vidaeff AC, Yeomans ER, Gilstrap LC. Chronic Renal Disease in Pregnancy. *Obstet Gynecol.* 2006; 108(6):1531–9. [PubMed: 17138789]
5. Fabbri S, Alston M, Metz TD, Krull M. Evaluation of the utility of baseline serum hepatic and renal testing in pregnant patients with chronic hypertension. *J Reprod Med.* 2014; 59(9–10):471–5. [PubMed: 25330689]
6. Liu A, Wu C, Schisterman EF. Nonparametric sequential evaluation of diagnostic biomarkers. *Stat Med.* 2008; 27(10):1667–78. [PubMed: 18241080]
7. August P, Helseth G, Cook EF, Sison C. A prediction model for superimposed preeclampsia in women with chronic hypertension during pregnancy. *Am J Obstet Gynecol.* 2004; 191(5):1666–72. [PubMed: 15547540]
8. Davison JM. Kidney function in pregnancy women. *Am J Kidney Dis.* 1987; 9(4):248–52. [PubMed: 3554993]

Figure 1.

Flow diagram of patients with chronic hypertension who had pregnancies within the study's health system between 2000 and 2014. The College, the American College of Obstetricians and Gynecologists.

Figure 2.

Receiver operating characteristic (ROC) curves and area under the curves for the development of severe preeclampsia at less than 34 weeks of gestation in women with baseline renal function tests (serum creatinine [A] and urine protein-to-creatinine [B]) collected prior to 20 completed weeks of gestation. Areas under ROC curve were 0.67 (95% CI 0.6–0.8) for serum creatinine and 0.74 (95% CI 0.7–0.8) for urine protein-to-creatinine. CI, confidence interval.

Figure 3. Scatter plot showing the relationship between gestational age at collection of the baseline renal function tests and the corresponding renal function test values. Baseline creatinine (**A**) and baseline urine protein-to-creatinine collection (**B**).

Table 1

Baseline characteristics of patients with chronic hypertension based on the Liu method serum creatinine and urine protein-to-creatinine cutoffs (range 5–19 weeks gestational age, mean gestational age at collection 10 weeks).

Characteristic	Liu cutoff of serum Cr 0.75 mg/dL			Liu cutoff of urine PC 0.12		
	Cr < 0.75 mg/dL N = 584	Cr 0.75 mg/dL N = 171	p	PC < 0.12 N = 544	PC 0.12 N = 195	p
Maternal age (yrs)	30.3 ± 5.9	30.8 ± 5.7	0.40	30.3 ± 5.9	31.0 ± 6.0	0.16
Race						
Black	418 (71.6)	140 (81.9)	0.09	414 (76.1)	130 (66.7)	0.01
White	131 (22.4)	28 (16.4)		113 (20.8)	44 (22.6)	
Hispanic	23 (3.9)	2 (1.2)		11 (2)	14 (7.2)	
Asian	3 (0.5)	0		0	3 (1.5)	
Other	9 (1.5)	1 (0.6)		6 (1.1)	4 (2.1)	
Nulliparity	168 (28.8)	54 (31.6)	0.48	147 (27)	67 (34.4)	0.05
GA (weeks) at collection of baseline tests	10.7(8–14.6)	8.6(6.7–12.4)	0.01	10.4(7.8–14)	10.5(7.6–15.1)	0.6
Government insurance	423 (72.4)	120 (70.2)	0.90	396 (72.8)	134 (68.7)	0.27
Pre-pregnancy BMI (kg/m ²)	39.4 ± 11.1	39.4 ± 10.6	0.94	40.1 ± 10.6	37.5 ± 12.0	0.01
Pregestational diabetes	137 (23.4)	42 (24.6)	0.15	108 (19.9)	64 (32.8)	0.48
Tobacco use	119 (20.4)	28 (16.4)	0.20	108 (19.9)	37 (19.0)	0.83
Low-dose aspirin	45 (7.7)	18 (10.5)	0.33	42 (7.7)	18 (9.2)	0.47
Prior preterm delivery	166 (28.4)	61 (35.7)	0.07	159 (29.2)	63 (32.3)	0.42
Baseline urine PC	0.085 (0.065–0.125)	0.080 (0.057–0.182)	0.95	0.072 (0.057–0.089)	0.186 (0.145–0.462)	0.01
Serum creatinine(mg/dL)	0.6 (0.5–0.7)	0.8 (0.8–0.9)	0.01	0.7 (0.6–0.7)	0.6 (0.5–0.7)	0.02
Prior preeclampsia	192 (32.9)	50 (29.2)	0.65	169 (31.1)	68 (34.9)	0.34
BP prior to 20 weeks gestation (SBP/DBP)	127.9 ± 10.9 76.8 ± 8.5	128.5 ± 11.8 77.7 ± 9.1	0.49 0.21	127.5 ± 10.5 76.5 ± 8.2	129.5 ± 12.6 78.2 ± 9.7	0.02 0.02
BP between 24–28 weeks (SBP/DBP)	124.2 ± 11.9 73.1 ± 9.5	125.9 ± 13.3 74.5 ± 10.4	0.11 0.11	124.0 ± 11.6 73.0 ± 9.5	126.1 ± 13.6 74.5 ± 10.2	0.04 0.08
BP between 28–32 weeks (SBP/DBP)	124.3 ± 12.1 73.3 ± 9.3	126.0 ± 12.4 75.3 ± 10.2	0.15 0.03	124.2 ± 11.6 73.5 ± 9.2	126.0 ± 13.7 74.6 ± 10.5	0.10 0.20
BP between 32–36 weeks (SBP/DBP)	127.6 ± 14.1 76.1 ± 9.9	127.5 ± 12.1 76.8 ± 10.6	0.94 0.50	126.8 ± 13.3 75.6 ± 9.7	130.1 ± 14.5 78.2 ± 11.0	0.01 0.01

Characteristic	Liu cutoff of serum Cr 0.75 mg/dL		Liu cutoff of urine PC 0.12		
	Cr < 0.75 mg/dL N = 584	Cr 0.75 mg/dL N = 171	PC < 0.12 N = 544	PC 0.12 N = 195	p
Anthypertensive before pregnancy	307 (52.8)	120 (70.2)	321 (59.1)	97 (50.3)	0.03
Anthypertensive during pregnancy	453 (77.6)	145 (84.8)	426 (78.3)	156 (80.0)	0.62
Duration of cHTN diagnosis (yrs)	3 (1–7)	3 (1–7)	3 (1–7)	3 (1–7)	0.51

Cr, creatinine; PC, protein-to-creatinine; yrs, years; GA, gestational age; BMI, body mass index; cHTN, chronic hypertension; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure Data are n(%), mean ± sd, and median (interquartile range)

Table 2

Relative risks and adjusted odds ratios for baseline serum creatinine using the Liu method cutoff

Outcomes	Cr < 0.75 mg/dL n = 584	Cr ≥ 0.75 mg/dL n = 171	RR (95% CI)	aOR (95% CI)
Severe PE < 34 weeks GA *	27 (4.6)	27 (15.7)	3.4 (2.1–5.7)	3.5 (1.9–6.3)
Severe PE, any GA *	76 (13.0)	46 (26.9)	2.1 (1.5–2.9)	2.3 (1.5–3.5)
PE, any GA *	126 (21.6)	61 (35.7)	1.7 (1.3–2.1)	1.9 (1.3–2.7)
Preterm birth < 35 weeks GA †	115 (20.0) ‡	44 (25.7) ‡	1.3 (1.0–1.8)	1.1 (0.7–1.7)
Indicated PTB < 35 weeks GA †	92 (22.1) §	38 (30.2) §	1.4 (1.0–1.9)	1.2 (0.8–2.0)
Small for gestational age //	93 (16.0)	39 (22.8)	1.4 (1.0–2.0)	1.5 (0.9–2.6)
Primary neonatal composite ¶	82 (14.0)	27 (15.8)	1.1 (0.75–1.68)	1.1 (0.7–1.8)

Cr, creatinine; RR, relative risk; aOR, adjusted odds ratio; CI, confidence interval; PE, preeclampsia; GA, gestational age; Primary neonatal composite: stillbirth, neonatal death, assisted ventilation, cord pH < 7, 5-minute, Apgar < 3 and neonatal seizures;

* Adjusted for nulliparity, preeclampsia in a prior pregnancy, and baseline protein-to-creatinine ratio;

† adjusted for prior preterm delivery and baseline protein-to-creatinine ratio;

‡ Total n=729 and not 755 because only live born infants included;

§ Total n= 543 because only live born infants included;

// Adjusted for pregestational diabetes and prepregnancy BMI;

¶ adjusted for nulliparity, pregestational diabetes and baseline PC ratio

Bold indicates statistically significant aOR

Table 3

Relative risk ratios for baseline serum creatinine using the cutoffs and excluding patients with pregestational diabetes

<u>Outcomes when excluding patients with pregestational diabetes</u>	Cr < 0.75 mg/dL n = 447	Cr ≥ 0.75 mg/dL n = 129	RR (95% CI)
Severe PE < 34 weeks GA	20 (4.5)	16 (12.4)	2.8 (1.5–5.2)
Severe PE, any GA	56 (12.5)	32 (24.8)	2.0 (1.3–2.9)
PE, any GA	92 (20.6)	44 (34.1)	1.7 (1.2–2.2)
PTB < 35 weeks GA [*]	85 (20.0)	26 (21.0)	1.1 (0.7–1.6)
Indicated PTB < 35 weeks GA [†]	67 (21.4)	21 (24.4)	1.1 (0.7–1.8)
Small for gestational age	78 (17.5)	32 (24.8)	1.4 (1.0–2.0)
Primary neonatal composite [‡]	55 (12.3)	19 (14.7)	1.2 (0.7–1.9)

Cr, serum creatinine; RR, relative risk; CI, confidence interval; PE, preeclampsia; GA, gestational age; PTB, preterm birth;

[‡]Primary neonatal composite: stillbirth, neonatal death, assisted ventilation, cord pH < 7, 5-minute, Apgar < 3 and neonatal seizures;

^{*}Total n=556 and not 576 because only live born infants included;

[†]Total n= 399 because only live born infants included Data are n (%)

Table 4

Relative risks and adjusted odds ratios for baseline protein-to-creatinine using the Liu method cutoff

Outcomes	PC < 0.12 n = 544	PC 0.12 n = 195	RR (95% CI)	aOR (95% CI)
Severe PE < 34 weeks GA *	14 (2.6)	32 (16.4)	6.4 (3.5–11.7)	7.5 (3.9–14.6)
Severe PE, any GA *	49 (9.0)	59 (30.3)	2.3 (1.7–3.3)	4.5 (3.0–7.0)
PE, any GA *	77 (14.2)	96 (49.2)	3.5 (2.7–4.5)	6.1 (4.2–8.9)
PTB < 35 weeks GA †	89 (16.4) ‡	62 (31.8) ‡	2.0 (1.5–2.6)	2.4 (1.6–3.5)
Indicated PTB < 35 weeks GA †	68 (18.2) §	54 (34.6) §	1.9 (1.4–2.6)	2.4 (1.6–3.6)
Small for gestational age //	96 (17.7)	30 (15.4)	0.9 (0.6–1.3)	0.9 (0.6–1.4)
Primary neonatal composite ¶	69 (12.7)	33 (16.9)	1.3 (0.9–2.0)	1.2 (0.8–2.0)

PC, protein-to-creatinine ratio; RR, relative risk; aOR, adjusted odds ratio; CI, confidence interval; PE, preeclampsia; GA, gestational age; PTB, preterm birth; Primary neonatal composite: stillbirth, neonatal death, assisted ventilation, cord pH < 7, 5-minute, Apgar < 3 and neonatal seizures;

* Adjusted for baseline serum creatinine and preeclampsia in a prior pregnancy;

† adjusted for prior preterm delivery and pregestational diabetes;

‡ Total n=715 and not 739 because only live born infants included;

§ Total n= 530 because only live born infants included;

// Adjusted for pregestational diabetes and baseline serum creatinine;

¶ adjusted for nulliparity, pregestational diabetes and baseline serum creatinine

Bold indicates statistically significant aOR

Table 5

Relative risk ratios for urine protein-to-creatinine ratio using the cutoffs and excluding patients with pregestational diabetes

Outcomes when excluding patients with pregestational diabetes	PC < 0.12 n = 436	PC 0.12 n = 131	RR (95% CI)
Severe PE < 34 weeks GA	13 (3.0)	19 (14.5)	4.9 (2.5–9.6)
Severe PE, any GA	42 (9.6)	37 (28.2)	2.9 (2.0–4.4)
PE, any GA	65 (14.9)	62 (47.3)	3.2 (2.4–4.2)
PTB < 35 weeks GA [*]	70 (16.6)	39 (31.0)	1.9 (1.3–2.6)
Indicated PTB < 35 weeks GA [†]	52 (17.9)	34 (33.3)	1.9 (1.3–2.7)
Small for gestational age	85 (19.5)	20 (15.3)	0.8 (0.5–1.2)
Primary neonatal composite [‡]	53 (12.2)	17 (13.0)	1.1 (0.6–1.8)

PC, urine protein-to-creatinine ratio; RR, relative risk; CI, confidence interval; PE, preeclampsia; GA, gestational age; PTB, preterm birth;

[‡]Primary neonatal composite: stillbirth, neonatal death, assisted ventilation, cord pH < 7, 5-minute, Apgar < 3 and neonatal seizures;

^{*}Total n=549 and not 567 because only live born infants included;

[†]Total n= 393 because only live born infants included Data are n (%)

Table 6

The combination of baseline serum creatinine and urine protein-to-creatinine and the percentage of people who experienced adverse outcomes

Outcomes		Cr < 0.75 mg/dL	Cr ≥ 0.75 mg/dL
Severe PE less than 34 weeks GA	PC < 0.12	7/432 1.6 (0.7–3.3)	8/114 7.0 (3.1–13.4)
	PC ≥ 0.12	20/152 13.2 (8.2–19.6)	19/57 33.3 (21.4–47.1)
Severe PE, any GA	PC < 0.12	34/432 7.9 (5.5–10.8)	17/114 14.9 (8.9–22.8)
	PC ≥ 0.12	42/152 27.6 (20.7–35.5)	29/57 50.9 (37.3–64.4)
PE, any GA	PC < 0.12	56/432 13.0 (9.9–16.5)	23/114 20.2 (13.2–28.7)
	PC ≥ 0.12	70/152 46.1 (38.0–54.3)	38/57 66.7 (52.9–78.6)
PTB less than 35 weeks GA	PC < 0.12	71/416 17.1 (13.6–21.0)	19/113 16.8 (10.4–25.0)
	PC ≥ 0.12	44/147 29.9 (22.7–38.0)	25/53 47.2 (33.3–61.4)
Indicated PTB less than 35 weeks GA	PC < 0.12	54/295 18.3 (14.1–23.2)	15/81 18.5 (10.8–28.7)
	PC ≥ 0.12	38/122 31.1 (23.1–40.2)	23/45 51.1 (35.8–66.3)
Small for gestational age	PC < 0.12	75/431 17.4 (13.9–21.3)	21/114 18.4 (11.8–26.8)
	PC ≥ 0.12	18/152 11.8 (7.2–18.1)	18/57 31.6 (19.9–45.2)
Primary neonatal composite	PC < 0.12	56/432 13.0 (9.9–16.5)	13/114 11.4 (6.2–18.7)
	PC ≥ 0.12	26/152 17.1 (11.5–24.0)	14/57 24.6 (14.1–37.8)

Cr, creatinine; PC, urine protein-to-creatinine ratio; PE, preeclampsia; GA, gestational age; PTB, preterm birth, Primary neonatal composite: stillbirth, neonatal death, assisted ventilation, cord pH < 7, 5-minute, Apgar < 3 and neonatal seizures

Data are n/N, % (95% confidence interval)

Table 7

Test characteristics of baseline serum creatinine and urine protein-to-creatinine ratio alone and in combination

Outcomes		Cr 0.75 mg/dL n = 171	PC 0.12 n = 195	Cr 0.75 mg/dL and PC 0.12 n = 127
Severe PE < 34 weeks	Sensitivity	50.0 (36.1–63.9)	69.6 (54.3–82.3)	35.2 (22.7–49.4)
	Specificity	79.5 (76.3–82.4)	76.5 (73.1–79.6)	94.6 (92.6–96.1)
	PPV	15.8 (10.7–22.1)	16.4 (11.5–22.4)	33.3 (21.4–47.1)
	NPV	95.4 (93.3–96.9)	97.4 (95.7–98.6)	95.0 (93.1–96.5)
	LR +	2.4 (1.8–3.3)	3.0 (2.9–3.1)	6.5 (4.0–10.5)
	LR –	0.6 (0.5–0.8)	0.4 (0.4–0.5)	0.7 (0.6–0.8)
Severe PE, any gestational age	Sensitivity	37.7 (29.6–46.6)	45.4 (36.3–54.8)	23.8 (16.5–32.3)
	Specificity	80.3 (77.0–83.2)	76.9 (73.4–80.0)	95.6 (93.7–97.0)
	PPV	26.9 (20.8–34.0)	25.1 (19.6–31.7)	50.9 (37.3–64.4)
	NPV	87.0 (84.0–89.5)	89.2 (86.3–91.5)	86.7 (83.9–89.1)
	LR +	1.9 (1.8–2.1)	2.0 (1.8–2.1)	5.37 (3.3–8.7)
	LR –	0.8 (0.8–0.8)	0.7 (0.7–0.7)	0.8 (0.7–0.9)
PE, any gestational age	Sensitivity	32.6 (26.3–39.6)	55.5 (48.1–62.7)	20.3 (14.8–26.8)
	Specificity	80.6 (77.2–83.7)	82.5 (79.2–85.4)	96.7 (94.8–98.0)
	PPV	35.7 (28.9–43.1)	49.2 (42.3–56.2)	66.7 (52.9–78.6)
	NPV	78.4 (74.9–81.6)	85.9 (82.7–88.5)	78.7 (75.4–81.6)
	LR +	1.7 (1.6–1.8)	3.2 (3.1–3.3)	6.1 (3.6–10.3)
	LR –	0.8 (0.8–0.9)	0.5 (0.5–0.6)	0.8 (0.8–0.9)
Preterm birth less than 35 weeks *	Sensitivity	27.7 (20.9–35.3)	41.1 (33.1–49.4)	15.7 (10.4–22.3)
	Specificity	78.6 (75.0–81.9)	77.7 (74.0–81.0)	95.1 (93.0–96.7)
	PPV	26.5 (20.0–33.9)	33.0 (26.3–40.2)	47.2 (33.3–61.4)
	NPV	79.6 (76.0–82.3)	83.1 (79.6–86.2)	80.2 (77.0–83.1)
	LR +	1.3 (1.0–1.7)	1.8 (1.4–2.4)	3.2 (1.9–5.3)
	LR –	0.9 (0.8–1.0)	0.8 (0.7–0.9)	0.9 (0.8–1.0)
Indicated preterm birth less than 35 weeks †	Sensitivity	29.2 (21.6–37.9)	44.3 (35.3–53.5)	17.7 (11.6–25.4)
	Specificity	78.7 (74.4–82.5)	75.0 (70.5–79.1)	94.7 (92.1–96.6)
	PPV	30.2 (22.3–39.0)	34.6 (27.2–42.6)	51.1 (35.8–66.3)
	NPV	77.9 (73.7–81.8)	81.8 (77.5–85.6)	78.5 (74.6–82.0)
	LR +	1.4 (1.0–1.9)	1.8 (1.4–2.3)	3.3 (1.9–5.8)
	LR –	0.9 (0.8–1.0)	0.7 (0.6–0.9)	0.9 (0.8–0.9)
Small for gestational age	Sensitivity	29.6 (22.4–37.8)	23.8 (17.2–32.0)	13.6 (8.3–20.7)
	Specificity	78.8 (75.4–81.8)	73.1 (69.4–76.4)	93.7 (91.5–95.5)
	PPV	22.8 (17.2–29.7)	15.4 (11.0–21.1)	31.6 (19.9–45.2)
	NPV	84.1 (80.9–86.8)	82.4 (78.3–85.3)	83.6 (80.7–86.3)
	LR +	1.4 (1.2–1.6)	0.9 (0.7–1.1)	2.2 (1.3–3.7)
	LR –	0.9 (0.9–0.9)	1.0 (1.0–1.1)	0.9 (0.9–1.0)

Outcomes		Cr 0.75 mg/dL n = 171	PC 0.12 n = 195	Cr 0.75 mg/dL and PC 0.12 n = 127
Primary neonatal composite[‡]	Sensitivity	24.8 (17.6–33.6)	32.4 (24.1–41.9)	12.8 (7.2–20.6)
	Specificity	77.7 (74.3–80.8)	74.6 (71.1–77.8)	93.3 (91.1–95.1)
	PPV	15.8 (11.1–22.0)	16.9 (12.3–22.8)	24.6 (14.1–37.8)
	NPV	86.0 (82.9–88.5)	87.3 (84.3–89.9)	86.4 (83.6–88.9)
	LR +	1.1 (0.9–1.4)	1.3 (1.1–1.5)	1.9 (1.1–3.4)
	LR –	1.0 (0.9–1.0)	0.9 (0.9–0.9)	0.9 (0.9–1.0)

Cr, creatinine; PC, urine protein: creatinine ratio; PE, preeclampsia; PPV, positive predictive value; NPV, negative predictive value; LR +, Positive likelihood ratio; LR –, Negative likelihood ratio;

* Total n=729 and not 755 because only live born infants included;

[†] Total n= 530 because only live born infants included;

[‡] Primary neonatal composite: stillbirth, neonatal death, assisted ventilation, cord pH < 7, 5-minute, Apgar < 3 and neonatal seizures Data are % (95% confidence interval)