Published in final edited form as:

Pregnancy Hypertens. 2019 January ; 15: 195–200. doi:10.1016/j.preghy.2019.01.011.

Pre-pregnancy kidney function and subsequent adverse pregnancy outcomes

Emily W. Harville¹, Janet Catov², C. Elizabeth Lewis³, Kirsten Bibbins-Domingo⁴, and Erica P. Gunderson⁵

¹Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA

²University of Pittsburgh Departments of OB/GYN and Epidemiology, Pittsburgh, PA, catovjm@mail.magee.edu

³Department of Epidemiology, School of Public Health University of Alabama at Birmingham, Birmingham, AL, celewis@uabmc.edu

⁴Department of Epidemiology and Biostatistics, University of California-San Francisco, San Francisco, CA, kirsten.bibbins-domingo@ucsf.edu

⁵Cardiovascular and Metabolism Section, Division of Research, Kaiser Permanente Northern California, Oakland, CA, erica.gunderson@kp.org

Abstract

Background: Renal insufficiency is associated with pregnancy complications including fetal growth restriction, preterm birth (PTB), and pre-eclampsia.

Objective: To determine the effect of preconception kidney function within the normal range on pregnancy outcome.

Method: 1043 (50% black, 50% white) women who participated in the CARDIA study who had kidney function and biochemical analyses measured before at least one pregnancy delivered during the 20 years post-baseline period were included in analysis. Kidney function estimated as glomerular filtration rate (eGFR) via modified CKD-EPI equations, serum creatinine, and urinary albumin/creatinine ratio were evaluated as predictors of infant birthweight, gestational age,

---

Address for correspondence: Emily W. Harville, 1440 Canal St. Ste. 2001 #8318, New Orleans, LA 70112-2714, 504-988-7327, 504-988-1568, harville@tulane.edu.

Authors' Contributions

Study hypothesis, data analysis, and paper drafting: EWH

Study conduct and data collection: CEL, EPG, KBB

Analytic revisions: JC, EPG

Critical reading, suggestions, and approval of final draft: All authors

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Statement of ethics

The CARDIA study data collection was approved by the Institutional Review Boards of the participating organizations, and all participants provided written informed consent in the original study. This secondary data analysis was ruled exempt by the Tulane IRB.

birthweight-for-gestational-age, and hypertensive disorders of pregnancy via self-report, using multiple regression with adjustment for confounders (age, race, smoking, BMI, center, parity, systolic blood pressure at baseline). Serum uric acid was also examined at both baseline and year 10.

Results: Unadjusted pre-pregnancy eGFR (baseline) was associated with lower average birthweight-for-gestational-age, but this disappeared after adjustment for confounders. A decline in GFR from baseline to year 10 was associated with lower birthweight (adjusted estimate -195 g, $p=0.03$ overall), especially among whites. After adjustment for confounders, no association was found with gestational age or hypertensive disorders.

Conclusions: No strong evidence for an association between preconception kidney function in the normal range and birthweight or gestational age was found. Possible racial differences in these relationships warrant further examination.

Keywords

glomerular filtration rate; serum creatinine; birthweight; gestational age; race

Introduction

Kidney function is closely tied to pregnancy outcome, most clearly noted in pre-eclampsia and related complications, which are characterized by high albumin:creatinine ratios.[1, 2] Appropriate response of the renin-angiotensin system may be required for the plasma volume expansion and vascular remodeling needed for healthy pregnancy: reduced plasma volume expansion is associated with pre-eclampsia (PE) and small-for-gestational-age (SGA).[3] Moderate to severe renal insufficiency is associated with a high rate of preterm birth (PTB)/intrauterine growth restriction (IUGR) and pre-eclampsia [4, 5] and pregnancies in kidney transplant recipients are at high risk for PTB and low birthweight (LBW).[6, 7] On a subclinical level, urinary albumin excretion [8] and albumin:creatinine ratio [9, 10] during pregnancy, indicators of kidney function, have been associated with lower gestational age at birth in some studies, though other studies have not confirmed this finding [11], and these tests do not appear to be useful for screening.[12, 13] Microalbuminuria in early pregnancy is associated with the development of later pre-eclampsia [14, 15], which may be the cause of some of the associations seen with PTB. (In at least one study, the relationship between urinary albumin and preterm birth was stronger for medically induced PTB and diminished when cases of pre-eclampsia and other complications were excluded [9].) Uric acid, another possible indicator of kidney disease [16], has been associated with IUGR and PTB in some studies [17–19], while others have not shown a clear difference.[20, 21] Gout, characterized by hyperuricemia, is rare in reproductive-age women, but case reports suggest a high rate of pregnancy complications in such patients, particularly pre-eclampsia.[22]

The effect of preconception kidney function (when not clinically impaired) on pregnancy outcome is even less clear. We were able to find only one previous study that addressed the question: a Norwegian study found that pre-pregnancy estimated glomerular filtration rate (eGFR) was associated with SGA, preterm birth, and pre-eclampsia, but only in women hypertensive prior to pregnancy.[23] Given the known risk for adverse birth outcomes

associated with impaired kidney function, it is reasonable to ask whether smaller deficits, even if not clinically significant at the time, are also associated with increases in risk. The issue is of importance because, apart from the centrality of preterm birth and reduced fetal growth to infant morbidity and mortality, the disparity in pregnancy outcomes between blacks and whites is mirrored in disparities in renal impairment [24], suggesting that pregnancy disparities may be serving as an early indicator of compromised health. In this analysis, we aimed to address three questions: 1) Does pre-pregnancy kidney function within the normal range predict PTB and/or SGA?; 2) Does the relationship differ between black and white women?; and 3) Is there a link between kidney function and disparities in birth outcomes?

Materials and Methods

Study sample

This analysis uses data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, which is well-described elsewhere.[25, 26] Briefly, this study has been examining the evolution of cardiovascular risk in adulthood, starting in 1985–86 (study baseline), when participants were 18–30 years of age. The study was designed to have equal numbers of black and white participants, and was conducted in four study centers: Minneapolis, MN; Birmingham, AL; Chicago, IL; and Oakland, CA. Participants have been followed up at regular intervals; this analysis uses data from the follow-ups through year 20 (follow-up #7).

Study visit protocols included an extensive medical history; interviews on smoking and other health behaviors; direct measure of blood pressure, height, weight, and other cardiovascular risk factors; and taking of biological samples, including plasma, serum and urine.

For this analysis, we selected women who had at least one kidney function or uric acid measure, and had at least one birth after baseline. Women with diabetes were also excluded. Of the 2787 women at baseline, 1060 were eligible for analysis. Compared to excluded women, included women were more likely to be white (50% vs. 45%) and mean baseline GFR was slightly lower (89.1 vs. 90.6, $p=0.05$). The most common reason for exclusion was no eligible pregnancies ($n=1725$). Included women were less likely to be black (50% vs. 55%), were younger (mean age at baseline 24.6 vs. 26.9) and had lower BMI (23.6 vs. 25.1).

Exposure

At baseline, kidney function was indicated by glomerular filtration rate (GFR), estimated by CKD-EPI equations [27], as well as absolute serum creatinine. At year 10 (visit 5), these measures were repeated, and urinary albumin/creatinine ratio was also measured. Decline in eGFR was dichotomized (eGFR lower at visit 5 than visit 1). Serum uric acid was measured at both baseline and year 10.

Outcomes

At each visit, women were asked about their pregnancies, the outcome of each one, birthweight and gestational age of each baby, and pregnancy complications. Outcomes for

this analysis were self-reported birthweight and gestational age for the first singleton livebirth after the kidney function measurement was taken. Low birthweight was defined as birthweight <2500 g and preterm birth as birth <37 weeks. Birthweight standardized for gestational age was also examined, with small-for-gestational-age defined as birthweight 10th percentile,[28] using the overall study population as the standard. Generally, mother's report of her child's birthweight and gestational age is accurate [29–31], and preterm birth has been validated in CARDIA as well [32]; sensitivity for maternal report of ever delivering preterm was 84% and specificity was 89% (stronger for earlier preterm birth). Women were also asked about their experience of pre-eclampsia and gestational hypertension during each pregnancy, using the wording: “Did you have (Have you had) any of these illnesses or complications during this pregnancy?” with possible responses including “Toxemia including all of the following: high blood pressure, albumin (protein) in urine, and swelling of the ankles?” as well as “High blood pressure without toxemia”.

Analysis

Kidney function variables were skewed and so were log-transformed for analysis. Each continuous kidney function variable was examined as a predictor of continuous (birthweight, gestational age, birthweight-for-gestational age z-score) and dichotomous (low birthweight, preterm birth, small-for-gestational-age, pre-eclampsia/toxemia, and high blood pressure during pregnancy) birth outcomes at the first pregnancy after baseline and year 10 (visit 5). If a woman had multiple pregnancies after a given visit, only the first was analyzed. Multiple linear/logistic regression was used to examine these associations, with adjustment for race, center, smoking, age, BMI, parity, and blood pressure (not included in the hypertensive disorder models). The effect estimate from the linear model (beta) is therefore the change in outcomes associated with a one log-unit change in the predictor, while for the logistic regression is it the odds ratio associated with a one log-unit change in the predictor. Participants who were pregnant at time of interview or had diabetes were removed from the analysis; after also omitting those with missing data on covariates, 1018 women were left for analysis of baseline data and 303 for analysis of year 10. As only pregnancies after the measurement were considered, many fewer women had pregnancies after year 10. This gave 1043 total participants as some women had pregnancies during both time periods. With 9–19% LBW/PTB at first pregnancy after baseline, this provided 80% power to find a 0.32 standardized unit or smaller difference, which corresponds to approximately 6 mL/min/1.73m² difference between cases and noncases.

Interactions with age and race were examined. As some of these interactions were significant at $p < 0.05$, stratified analyses were then conducted. As a previous study had found eGFR to be associated with reduced fetal growth and gestational age only in those with hypertension [23], interaction with hypertension status was also examined.

As previous studies have indicated long-term effects of first birth [33], we also ran a sensitivity analysis limiting the population to those nulliparous at baseline ($n=715$).

Finally, we examined whether there might be a cut-off or threshold effect, as kidney disease is often considered in those terms. No women at baseline met the criteria for active kidney

disease based on eGFR, and quartile analysis failed to demonstrate non-linear or threshold effects (data not shown).

The CARDIA study data collection was approved by the Institutional Review Boards of the participating organizations, and all participants provided written informed consent in the original study. This secondary data analysis was ruled exempt by the Tulane IRB.

Results

Participants were evenly split between black and white groups (Table 1). In most cases, the first birth after the baseline exam occurred at ages 25–35, on average 5.7 years post-baseline.

In unadjusted analysis, pre-pregnancy eGFR measured at baseline was associated with lower mean birthweight-for-gestational-age (BWT-GA) (table 2), but adjustment for confounders erased this association. Serum creatinine was associated with lower birthweight among blacks but higher among whites (p for interaction <0.05; table S1). No associations were found with absolute levels for pregnancies after year 10, including for urinary A/C ratio (table 3). One hundred thirty-five (13%) of women had an eGFR at visit 5 lower than that at visit 1. This decline in GFR from visit 1 to 5 was associated with lower birthweight and, possibly, gestational age, among whites. No associations were seen with uric acid at either visit and birthweight/gestational age (table S2). Urinary A/C ratio at year 10 was associated with self-reported gestational hypertension; no other associations were found with either gestational hypertension or pre-eclampsia/toxemia (Table 4). No significant interactions were found between kidney function and baseline hypertension. Sensitivity analysis limiting to women nulliparous at baseline also did not reveal any particular patterns.

Discussion

This analysis largely suggested that pre-pregnancy kidney function does not predict PTB or SGA. The association with GFR was stronger for whites; in blacks, if anything, the association went the opposite direction, indicating that this was unlikely to be a major contributor to racial disparities. In whites, a decline in GFR over time was associated with lower birthweight, which warrants examination in a larger study. In addition, we did not find a pattern of pre-pregnancy kidney function predicting hypertensive disorders of pregnancy, even though pre-eclampsia is characterized by proteinuria, and is associated with later development of renal disease.[34] Previous studies do not provide a clear basis for comparison. The most directly relevant study was conducted in Norway [23], and found pre-pregnancy eGFR to be associated with reduced fetal growth and gestational age only in those with hypertension. Our study is not as large, and few participants had hypertension or microalbuminuria. Studies during pregnancy are also mixed. While clinical kidney disease is associated with increased odds of PTB and LBW [35, 36], and increased creatinine is associated with an increased risk of PTB in renal transplant patients[6], previous studies of microalbuminuria in pregnancy have contradictory results [8–11], with some finding that microalbuminuria early in pregnancy predicts poorer birth outcomes, and others not concurring. Healthy pregnancy requires physiological adaptations that include increased GFR and protein excretion; pregnancy constitutes a significant strain on this system, and in

women with advanced chronic kidney disease, kidney function often worsens and there is a dose-response relationship between worsening in eGFR and gestational age/birthweight.[36] To some degree, this is related to the increased risk of hypertension in these women. Kidney disease may induce placental dysfunction as well [37]. In addition, we found no associations with uric acid in our study, even though such a relationship is plausible: uric acid may might reduce endothelial nitric oxide bioavailability and inhibit endothelial cell proliferation [38], or act as a proinflammatory or vasoconstrictor [39], which might contribute to PTB or IUGR. Our study adds to the literature by considering a US-based population with no overt clinical disease at baseline, including a large proportion of both black and white women, and assessing both planned and unplanned pregnancies. The sample size was moderately large, and the proportion of women with low birthweight and preterm birth (9–19% in a single pregnancy) provided sufficient cases for the analysis.

Some limitations are inherent in the study. The time between the measurement and the outcome was not standardized. Both urinary A/C ratio and uric acid were measured fairly late in the study (year 10); there were relatively few pregnancies after that point, so the lack of association may be partly an issue of statistical power or whether it exists in older women. Self-report of hypertensive disorders in pregnancy showed poor sensitivity in CARDIA [40], so results related to this complication are necessarily subject to measurement error (self-report is generally reliable for the other outcomes). All pregnancy outcomes were self-reported, which is subject to errors in recall and lack of precision in reporting.

Overall, we did not find evidence of a strong association between preconception kidney function within the normal range and birthweight, gestational age or hypertensive disorders. It is possible that a study including more subjects with substantially diminished kidney function would find a threshold effect. Possible racial differences in these relationships warrant further examination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Thanks to Katherine Mills for helpful advice.

Funding Sources:

The Coronary Artery Risk Development in Young Adults Study (CARDIA) is supported by contracts HHSN268201300025C, HHSN268201300026C, HHSN268201300027C, HHSN268201300028C, HHSN268201300029C, and HHSN268200900041C from the National Heart, Lung, and Blood Institute (NHLBI), the Intramural Research Program of the National Institute on Aging (NIA), and an intra-agency agreement between NIA and NHLBI (AG0005).

The data collection and derived variables for pregnancy were supported by K01 DK059944, (Gunderson, PI), and R01 DK090047 (Gunderson, PI) from the National Institute of Diabetes, Digestive and Kidney Diseases.

This work was supported by the National Institute of Child Health and Human Development (K12HD043451 to EWH).

Disclosure

None of the authors have a conflict of interest, except Dr. Gunderson receives funding unrelated to the current study from Janssen Pharmaceuticals, Inc. (June 2017).

References

- [1]. Risberg A, Larsson A, Olsson K, Lyrenas S, Sjoquist M, Relationship between urinary albumin and albumin/creatinine ratio during normal pregnancy and pre-eclampsia, *Scand J Clin Lab Invest* 64(1) (2004) 17–23. [PubMed: 15025425]
- [2]. Poon LC, Kametas N, Bonino S, Vercellotti E, Nicolaides KH, Urine albumin concentration and albumin-to-creatinine ratio at 11(+0) to 13(+6) weeks in the prediction of pre-eclampsia, *BJOG* 115(7) (2008) 866–73.
- [3]. Al Kadi H, Nasrat H, Pipkin FB, A prospective, longitudinal study of the renin-angiotensin system, prostacyclin and thromboxane in the first trimester of normal human pregnancy: association with birthweight, *Hum Reprod* 20(11) (2005) 3157–62. [PubMed: 16006463]
- [4]. Jones DC, Hayslett JP, Outcome of pregnancy in women with moderate or severe renal insufficiency, *N Engl J Med* 335(4) (1996) 226–32. [PubMed: 8657238]
- [5]. Alsuwaida A, Mousa D, Al-Harbi A, Alghonaim M, Ghareeb S, Alrukhaimi MN, Impact of early chronic kidney disease on maternal and fetal outcomes of pregnancy, *J Matern Fetal Neonatal Med* 24(12) (2011) 1432–6. [PubMed: 21663522]
- [6]. Sibanda N, Briggs JD, Davison JM, Johnson RJ, Rudge CJ, Pregnancy after organ transplantation: a report from the UK Transplant pregnancy registry, *Transplantation* 83(10) (2007) 1301–7. [PubMed: 17519778]
- [7]. Al Duraihimi H, Ghamdi G, Moussa D, Shaheen F, Mohsen N, Sharma U, Stephan A, Alfie A, Alamin M, Haberal M, Saeed B, Kechrid M, Al-Sayyari A, Outcome of 234 pregnancies in 140 renal transplant recipients from five middle eastern countries, *Transplantation* 85(6) (2008) 840–3. [PubMed: 18360265]
- [8]. Perry IJ, Gosling P, Sanghera K, Churchill D, Luesley DM, Beevers DG, Urinary microalbumin excretion in early pregnancy and gestational age at delivery, *BMJ* 307 (1993) 420–421. [PubMed: 8374454]
- [9]. Franceschini N, Savitz DA, Kaufman JS, Thorp JM, Maternal urine albumin excretion and pregnancy outcome, *Am J Kidney Dis* 45(6) (2005) 1010–8. [PubMed: 15957129]
- [10]. Bahasadri S, Kashanian M, Khosravi Z, Comparison of pregnancy outcome among nulliparas with and without microalbuminuria at the end of the second trimester, *Int J Gynaecol Obstet* 115(1) (2011) 34–6. [PubMed: 21794863]
- [11]. Baker PN, Hackett GA, Urinary microalbumin excretion and preterm birth, *BMJ* 307(6907) (1993) 802.
- [12]. Beunis MH, Schweitzer KJ, van Hooff MH, van der Weiden RM, Midtrimester screening for microalbuminuria in healthy pregnant women, *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology* 24(8) (2004) 863–5. [PubMed: 16147637]
- [13]. Salako BL, Olayemi O, Odukogbe AT, Adedapo KS, Aimakhu CO, Alu FE, Ola B, Microalbuminuria in pregnancy as a predictor of preeclampsia and eclampsia, *West African journal of medicine* 22(4) (2003) 295–300. [PubMed: 15008291]
- [14]. Jensen DM, Damm P, Ovesen P, Molsted-Pedersen L, Beck-Nielsen H, Westergaard JG, Moeller M, Mathiesen ER, Microalbuminuria, preeclampsia, and preterm delivery in pregnant women with type 1 diabetes: results from a nationwide Danish study, *Diabetes Care* 33(1) (2010) 90–4. [PubMed: 19846800]
- [15]. Singh R, Tandon I, Deo S, Natu SM, Does microalbuminuria at mid-pregnancy predict development of subsequent pre-eclampsia?, *J Obstet Gynaecol Res* 39(2) (2013) 478–83. [PubMed: 22925380]
- [16]. Johnson RJ, Nakagawa T, Jalal D, Sanchez-Lozada LG, Kang DH, Ritz E, Uric acid and chronic kidney disease: which is chasing which?, *Nephrol Dial Transplant* 28(9) (2013) 2221–8. [PubMed: 23543594]

- [17]. de Weerd S, Steegers-Theunissen RP, de Boo TM, Thomas CM, Steegers EA, Maternal periconceptional biochemical and hematological parameters, vitamin profiles and pregnancy outcome, *Eur J Clin Nutr* 57(9) (2003) 1128–34. [PubMed: 12947432]
- [18]. Powers RW, Bodnar LM, Ness RB, Cooper KM, Gallaher MJ, Frank MP, Daftary AR, Roberts JM, Uric acid concentrations in early pregnancy among preeclamptic women with gestational hyperuricemia at delivery, *Am J Obstet Gynecol* 194(1) (2006) 160.
- [19]. Amini E, Sheikh M, Hantoushzadeh S, Shariat M, Abdollahi A, Kashanian M, Maternal hyperuricemia in normotensive singleton pregnancy, a prenatal finding with continuous perinatal and postnatal effects, a prospective cohort study, *BMC Preg Childbirth* 14 (2014) 104.
- [20]. Roberts JM, Bodnar LM, Lain KY, Hubel CA, Markovic N, Ness RB, Powers RW, Uric acid is as important as proteinuria in identifying fetal risk in women with gestational hypertension, *Hypertension* 46(6) (2005) 1263–9. [PubMed: 16246973]
- [21]. Ekblom P, Damm P, Feldt-Rasmussen B, Feldt-Rasmussen U, Molvig J, Mathiesen ER, Pregnancy outcome in type 1 diabetic women with microalbuminuria, *Diabetes Care* 24(10) (2001) 1739–44. [PubMed: 11574435]
- [22]. Batt RE, Cirkse WJ, Lebherz TB, Gout and Salt-Wasting Renal Disease During Pregnancy; Diagnosis, Management, and Follow-Up, *JAMA* 186 (1963) 835–8. [PubMed: 14061065]
- [23]. Munkhaugen J, Lydersen S, Romundstad PR, Wideroe TE, Vikse BE, Hallan S, Kidney function and future risk for adverse pregnancy outcomes: a population-based study from HUNT II, Norway, *Nephrol Dial Transplant* 24(12) (2009) 3744–50. [PubMed: 19578097]
- [24]. Stehman-Breen CO, Gillen D, Steffes M, Jacobs DR Jr., Lewis CE, Kiefe CI, Siscovick D, Racial differences in early-onset renal disease among young adults: the coronary artery risk development in young adults (CARDIA) study, *J Am Soc Nephrol* 14(9) (2003) 2352–7. [PubMed: 12937313]
- [25]. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR Jr., Liu K, Savage PJ, CARDIA: study design, recruitment, and some characteristics of the examined subjects, *J Clin Epidemiol* 41(11) (1988) 1105–16. [PubMed: 3204420]
- [26]. Cutter GR, Burke GL, Dyer AR, Friedman GD, Hilner JE, Hughes GH, Hulley SB, Jacobs DR Jr., Liu K, Manolio TA, et al., Cardiovascular risk factors in young adults. The CARDIA baseline monograph, *Control Clin Trials* 12(1 Suppl) (1991) 1s–77s. [PubMed: 1851696]
- [27]. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, A new equation to estimate glomerular filtration rate, *Ann Intern Med* 150(9) (2009) 604–12. [PubMed: 19414839]
- [28]. Lausman A, Kingdom J, Intrauterine growth restriction: screening, diagnosis, and management, *Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC* 35(8) (2013) 741–748.
- [29]. Adegboye AR, Heitmann B, Accuracy and correlates of maternal recall of birthweight and gestational age, *BJOG* 115(7) (2008) 886–93. [PubMed: 18485168]
- [30]. Rice F, Lewis A, Harold G, van den Bree M, Boivin J, Hay DF, Owen MJ, Thapar A, Agreement between maternal report and antenatal records for a range of pre and peri-natal factors: the influence of maternal and child characteristics, *Early Hum Dev* 83(8) (2007) 497–504. [PubMed: 17071023]
- [31]. Troude P, L'Helias LF, Raison-Boulley AM, Castel C, Pichon C, Bouyer J, de La Rochebrochard E, Perinatal factors reported by mothers: do they agree with medical records?, *Eur J Epidemiol* 23(8) (2008) 557–64. [PubMed: 18560979]
- [32]. Catov JM, Lewis CE, Lee M, Wellons MF, Gunderson EP, Preterm birth and future maternal blood pressure, inflammation, and intimal-medial thickness: the CARDIA study, *Hypertension* 61(3) (2013) 641–6. [PubMed: 23319540]
- [33]. Gunderson EP, Jacobs DR Jr., Chiang V, Lewis CE, Tsai A, Quesenberry CP Jr., Sidney S, Childbearing is associated with higher incidence of the metabolic syndrome among women of reproductive age controlling for measurements before pregnancy: the CARDIA study, *Am J Obstet Gynecol* 201(2) (2009) 177e1–9. [PubMed: 19560114]
- [34]. Vikse BE, Irgens LM, Leivestad T, Skjaerven R, Iversen BM, Preeclampsia and the risk of end-stage renal disease, *N Engl J Med* 359(8) (2008) 800–9. [PubMed: 18716297]

- [35]. Kendrick J, Sharma S, Holmen J, Palit S, Nuccio E, Chonchol M, Kidney disease and maternal and fetal outcomes in pregnancy, *Am J Kidney Dis* 66(1) (2015) 55–9. [PubMed: 25600490]
- [36]. Piccoli GB, Fassio F, Attini R, Parisi S, Biolcati M, Ferraresi M, Pagano A, Daidola G, Deagostini MC, Gaglioti P, Todros T, Pregnancy in CKD: whom should we follow and why?, *Nephrol Dial Transplant* 27 Suppl 3 (2012) iii111–8. [PubMed: 22773243]
- [37]. Piccoli GB, Alrukhaimi M, Liu ZH, Zakharova E, Levin A, What We Do and Do Not Know about Women and Kidney Diseases; Questions Unanswered and Answers Unquestioned: Reflection on World Kidney Day and International Women's Day, *Kidney diseases (Basel, Switzerland)* 4(1) (2018) 37–48.
- [38]. Thadhani RI, Johnson RJ, Karumanchi SA, Hypertension during pregnancy: a disorder begging for pathophysiological support, *Hypertension* 46(6) (2005) 1250–1. [PubMed: 16246974]
- [39]. Kang DH, Finch J, Nakagawa T, Karumanchi SA, Kanellis J, Granger J, Johnson RJ, Uric acid, endothelial dysfunction and pre-eclampsia: searching for a pathogenetic link, *J Hypertens* 22(2) (2004) 229–35. [PubMed: 15076175]
- [40]. Gunderson EP, Chiang V, Lewis CE, Catov J, Quesenberry CP Jr., Sidney S, Wei GS, Ness R, Long-term blood pressure changes measured from before to after pregnancy relative to nonparous women, *Obstet Gynecol* 112(6) (2008) 1294–302. [PubMed: 19037039]

Highlights

- Kidney function within the normal range, prior to pregnancy, has seldom been examined as a predictor of birth outcomes.
- In this analysis, unadjusted pre-pregnancy eGFR was associated with lower average birthweight-for-gestational-age (-0.04 change in z-score per log-unit eGFR), but this disappeared after adjustment for confounders.
- Possible racial differences in these relationships warrant further examination, as GFR decline at visit 5 relative to visit 1 was associated with lower birthweight and gestational age only in whites.

Table 1

Study population, women in the CARDIA study with at least one kidney mea-sure and one birth after baseline (n = 1043).

	Black		White		p
	N	%	N	%	
Educational level					< 0.01
< =12	184	38.9	95	18.9	
Associates or some college	201	42.6	119	23.7	
College degree	68	14.4	180	35.9	
> college	19	4.0	108	21.5	
Age at baseline					< 0.01
18–25	331	64.2	229	43.7	
25–30	161	31.2	248	47.3	
30–35	24	4.7	47	9.0	
Marital status at baseline					< 0.01
Married	94	18.2	181	34.6	
Living with partner	45	8.7	50	9.6	
Separated/divorced/widowed	31	6.0	21	4.0	
Never married	347	67.1	271	51.8	
Smoking at baseline					0.17
Never	352	67.8	305	58.2	
Former	36	6.9	99	18.9	
Current	131	25.2	120	22.9	
BMI at baseline					< 0.01
< =18.5	36	7.0	42	8.0	
18.5–25	286	55.4	393	75.1	
> 25–30	104	20.2	65	12.4	
> 30	90	17.4	23	4.4	
High blood pressure diagnosis at baseline	51	10.0	30	5.8	0.01
Parity at baseline					< 0.01
Nulliparous	287	55.3	428	81.7	
Multiparous	232	44.7	96	18.3	
Parity post-baseline					< 0.01
1	285	54.9	193	36.8	
2	152	29.3	244	46.6	
3	59	11.4	72	13.7	
4+	23	4.4	15	2.9	
Age at first pregnancy after baseline					< 0.01
18–25	135	26.0	27	5.2	
> 25–30	170	32.8	155	29.6	
> 30–35	155	29.9	233	44.5	
> 35	59	11.4	109	20.8	

	Black		White		p
	N	%	N	%	
	Mean	SD	Mean	SD	
eGFR (CKD-Epi equation)	102.2	19.7	88.0	15.0	< 0.01
Any LBW	79	15.2	28	5.3	< 0.01
Any PTB	165	31.8	79	15.1	< 0.01
Any gestational diabetes	41	7.9	53	10.1	0.21
Any gestational hypertension	69	13.3	44	8.4	0.01
Any pre-eclampsia	103	19.9	62	11.8	< 0.01
Systolic blood pressure at baseline	107.1	9.1	104.3	8.9	< 0.01

Table 2

Association between kidney function at baseline and later pregnancy outcome.

Birthweight (g)										Gestational age (weeks)										Birthweight for gestational age (z-score)									
Unadjusted					Adjusted [†]					Unadjusted					Adjusted [†]					Unadjusted					Adjusted				
Beta [‡]	SE	p-value	Beta	SE	p-value	Beta	SE	p-value	Beta	SE	p-value	Beta	SE	p-value	Beta	SE	p-value	Beta	SE	p-value	Beta	SE	p-value	Beta	SE	p-value			
<i>Predictor</i>																													
GFR	-18	11	0.10	8	12	0.49	-0.04	0.05	0.49	0.03	0.06	0.65	-0.04	0.02	0.04	-0.01	0.02	0.77											
<i>Race = black</i>																													
GFR	24	17	0.15	25	17	0.14	0.09	0.08	0.27	0.06	0.08	0.45	0.00	0.02	0.90	0.01	0.02	0.68											
<i>Race = white</i>																													
GFR	-19	16	0.25	-22	17	0.18	-0.02	0.07	0.80	-0.04	0.07	0.60	-0.03	0.03	0.31	-0.03	0.03	0.24	Small-for-gestational-age										
Low birthweight															Preterm birth														
Unadjusted					Adjusted					Unadjusted					Adjusted					Unadjusted					Adjusted				
OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI				
<i>Predictor</i>																													
GFR at baseline	1.10	0.98–1.23	0.99			0.87–1.13	1.10	1.02–1.19	1.05	0.96–1.14	1.01	0.90–1.13	0.93	0.82–1.06															
<i>Race = black</i>																													
GFR at baseline	0.98	0.85–1.12	0.97			0.84–1.12	1.03	0.93–1.14	1.05	0.95–1.17	0.93	0.80–1.07	0.90	0.78–1.05															
<i>Race = white</i>																													
GFR at baseline	1.09	0.83–1.44	1.10			0.83–1.47	1.02	0.87–1.21	1.04	0.87–1.23	1.00	0.78–1.26	1.00	0.78–1.27															

[†] Adjusted for race, center, smoking, age, BMI, parity, and blood pressure. Race appears to be the strongest confounder.

[‡] Change in outcome associated with a one log-unit increase in the predictor.

Table 3

Kidney function at year 10 (visit 5) as a predictor of later birth outcomes (n = 303).

	Birthweight (g)						Gestational age (weeks)					
	Unadjusted			Adjusted [†]			Unadjusted					
	Beta [‡]	SD	p-value	Beta	SD	p-value	Beta	SD	p-value	Beta	SD	p-value
<i>Predictor</i>												
GFR	−18	20	0.36	9	20	0.66	−0.07	0.07	0.37	0.02	0.08	0.80
Serum creatinine	−426	302	0.16	−161	281	0.57	−0.59	1.13	0.60	−0.29	1.09	0.79
Urinary A/C	−43	46	0.35	−32	43	0.45	−0.08	0.18	0.67	−0.01	0.18	0.94
GFR lower at visit 5 than visit 1	−107	100	0.28	−195	91	0.03	−0.02	0.39	0.95	−0.41	0.37	0.27
Black	63	195	0.75	−25	178	0.89	0.85	0.80	0.29	0.41	0.70	0.56
White	−246	98	0.01	−241	96	0.01	−0.60	0.39	0.12	−0.70	0.39	0.08
p for interaction			0.12			0.12			0.07			0.05
Birthweight for gestational age (z-score)												
	Unadjusted			Adjusted								
	Beta	SD	p-value	Beta	SD	p-value	Beta	SD	p-value	Beta	SD	p-value
<i>Predictor</i>												
GFR	−0.01	0.03	0.66				0.02	0.30	0.60			
Serum creatinine	−0.77	0.49	0.12				−0.34	0.48	0.48			
Urinary A/C	−0.03	0.07	0.70				−0.02	0.07	0.79			
GFR lower at visit 5 than visit 1	−0.19	0.16	0.24				−0.28	0.16	0.08			
Black	−0.11	0.30	0.71				−0.19	0.30	0.52			
White	−0.30	0.18	0.09				−0.27	0.17	0.11			
p for interaction			0.57						0.65			

[†] Adjusted for race, center, smoking, age, BMI, parity, and blood pressure.[‡] Change in outcome associated with a one log-unit increase in the predictor GFR, glomerular filtration rate; A/C, albumin/creatinine.

Table 4

Association between kidney function and later hypertensive complications of pregnancy (pregnancy-induced hypertension and/or pre-eclampsia).

	Unadjusted		Adjusted [†]	
	OR	95% CI	OR	95% CI
GFR at baseline	1.05	0.96–1.14	1.03	0.94–1.13
Serum creatinine at baseline	0.93	0.30–2.92	0.73	0.23–2.35
Uric acid at baseline	1.02	0.86–1.21	0.91	0.76–1.10
GFR at year 10	1.13	0.95–1.33	1.02	0.85–1.23
Serum creatinine at year 10	0.81	0.06–10.92	0.75	0.05–11.04
Urinary A/C ratio at year 10	1.16	0.80–1.69	1.21	0.81–1.80

[†] Adjusted for race, center, smoking, age, BMI, and parity. GFR, glomerular filtration rate; OR, odds ratio; CI, confidence interval; A/C, albumin/creatinine; BMI, body mass index.