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Pre-pregnancy kidney function and subsequent adverse pregnancy outcomes

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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,

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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

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≤10^{th} 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/$1.73m^2$ 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.

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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).

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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					
Never	352	67.8	305	58.2	0.17
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
Predictor																		
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
Race = black																		
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
Race = white																		
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

	Low birthweight				Preterm birth				Small-for-gestational-age			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Predictor												
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
Race = black												
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
Race = white												
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
Predictor												
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**
Predictor						
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
Uurinary 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.