Association Between Gestational Diabetes and Incident Maternal CKD: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

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Background: Gestational diabetes mellitus (GDM) is associated with increased risk for diabetes mellitus, metabolic syndrome, and cardiovascular disease. We evaluated whether GDM is associated with incident chronic kidney disease (CKD), controlling for prepregnancy risk factors for both conditions.

Study Design: Prospective cohort.

Setting & Participants: Of 2,747 women (aged 18-30 years) enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) Study in 1985 to 86, we studied 820 who were nulliparous at enrollment, delivered at least 1 pregnancy longer than 20 weeks' gestation, and had kidney function measurements during 25 years of follow-up.

Predictor: GDM was self-reported by women for each pregnancy.

Outcomes: CKD was defined as the development of estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or urine albumin-creatinine ratio ≥ 25 mg/g at any one CARDIA examination in years 10, 15, 20, or 25.

Measurements: HRs for developing CKD were estimated for women who developed GDM versus women without GDM using complementary log-log models, adjusting for prepregnancy age, systolic blood pressure, dyslipidemia, body mass index, smoking, education, eGFR, fasting glucose concentration, physical activity level (all measured at the CARDIA examination before the first pregnancy), race, and family history of diabetes. We explored for an interaction between race and GDM.

Results: During a mean follow-up of 20.8 years, 105 of 820 (12.8%) women developed CKD, predominantly increased urine albumin excretion (98 albuminuria only, 4 decreased eGFR only, and 3 both). There was evidence of a GDM-race interaction on CKD risk ($P = 0.06$). Among black women, the adjusted HR for CKD was 1.96 (95% CI, 1.04-3.67) in GDM compared with those without GDM. Among white women, the HR was 0.65 (95% CI, 0.23-1.83).

Limitations: Albuminuria was assessed by single untimed measurements of urine albumin and creatinine.

Conclusions: GDM is associated with the subsequent development of albuminuria among black women in CARDIA.

Complete author and article information provided before references.

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Am J Kidney Dis. 71(1): 112-122. Published online November 8, 2017.

doi: 10.1053/j.ajkd.2017.08.015

Gestational diabetes mellitus (GDM), that is, glucose intolerance with onset or first recognition during pregnancy, affects ~6% of pregnancies in the United States, where the prevalence of GDM has been increasing over time.[1,2] GDM is known to be associated with the subsequent development of cardiovascular risk factors, including type 2 diabetes mellitus[3-6] and metabolic syndrome,[7,8] as well as subclinical atherosclerosis[8,9] and manifest cardiovascular disease.[10-12] Chronic kidney disease (CKD), defined by increased urine albumin excretion (albuminuria) and/or reduced estimated glomerular filtration rate (eGFR), affects ~13.6% of US adults (2007-2012).[13] Reduced eGFR and albuminuria are independent risk factors for all-cause mortality, cardiovascular mortality, and end-stage renal disease in the general population.[14,15]

The relationship between GDM and subsequent CKD is unclear. Studies have reported an association between GDM and early-stage CKD,[16] increased albuminuria among women with a history of GDM compared with those without a GDM history,[17,18] and a higher prevalence of albuminuria among women with a GDM history who later developed diabetes compared with normoglycemic women.[19] Other studies have not found differences in albuminuria between women with and without a GDM history,[20,21] although the cross-sectional nature, lack of prepregnancy measurement of shared risk factors for GDM and CKD, or short duration of follow-up since pregnancy constrained several studies. The aim of this study was to estimate the association between GDM and CKD in a longitudinal prospective population-based study of young adults that includes prepregnancy assessments of kidney function and shared risk factors for GDM and CKD.

Methods

Study Design

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a prospective population-based cohort study that enrolled 5,115 black and white participants aged 18 to 30 years in 1985 to 1986.[22] Follow-up examinations occurred at 2, 5, 7, 10, 15, 20, and 25 years (2010-2011) after the initial examination. Participants were recruited from Birmingham, AL; Chicago, IL; Minneapolis, MN; and

Oakland, CA. All participants gave informed consent, and the appropriate institutional review boards approved this study.

Sample Selection Criteria

Women were asked at each cohort examination whether they were currently pregnant or breastfeeding and about the number of pregnancies, abortions, miscarriages, stillbirths, and live births since the last examination. The first reported pregnancy longer than 20 weeks' gestation was treated as the index pregnancy. Women were included in our analytic cohort at the examination before the index pregnancy, and all covariates were selected from that examination. For example, for a woman who reported her first birth at CARDIA examination year 15, prepregnancy covariates were selected from the prior examination in year 10. Urine specimens used to define our outcome were collected at CARDIA years 10, 15, 20, and 25. Women who reported a first birth before the 10-year follow-up examination had their covariates assessed at the first CARDIA examination. As shown in Figure 1, we excluded women who were parous at the initial CARDIA examination (n = 1,008), women with zero births at the end of CARDIA follow-up (examination year 25; n = 862), women with CKD before or at the baseline examination (n = 7), women with diabetes mellitus before any pregnancy (n = 3), women missing measures of baseline CKD or missing measures of both albuminuria and eGFR at all 4 examinations at which the outcome was measured (n = 25), and women missing data for covariates of interest (n = 30). Baseline CKD was defined as GFR < 60 mL/min/1.73 m^2 or self-reported kidney disease other than nephrolithiasis or pyelonephritis or urine albumin-creatinine ratio (ACR) ≥ 25 mg/g adjusted for race and sex (urine ACR was not measured at the year 0 examination). Compared with women included in these analyses, women excluded from this study were more likely to be older and black, with higher systolic blood pressure (SBP), body mass index (BMI), low-density lipoprotein cholesterol concentration, eGFR, and fasting plasma glucose concentration at enrollment into CARDIA (Table S1). The women excluded also were more likely to be smokers and have less education, while being more likely to have metabolic syndrome and a family history of CKD compared with the included study population.

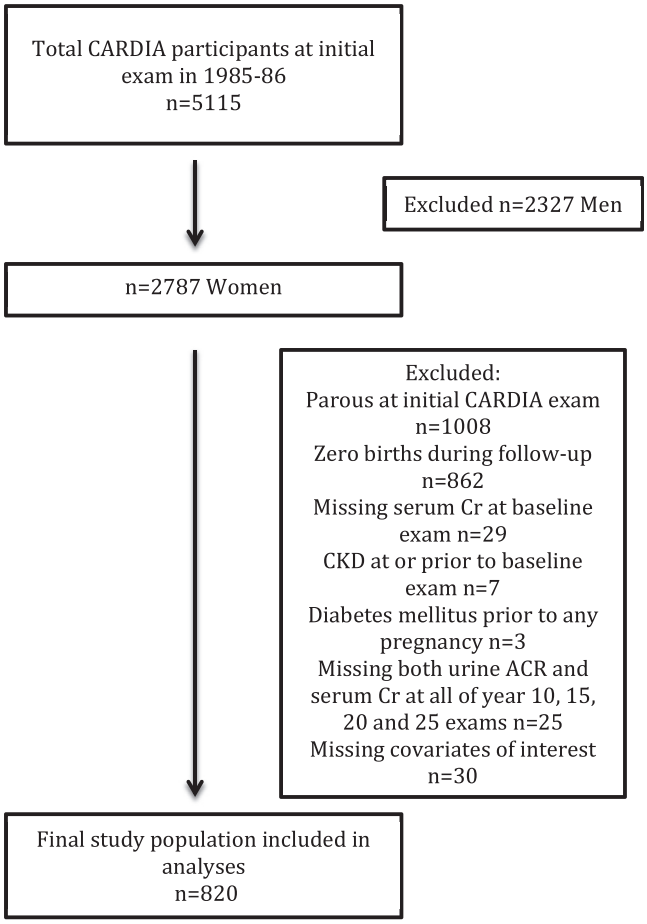

Figure 1. Study population selection. Abbreviations: ACR, albumin-creatinine ratio; CARDIA, Coronary Artery Risk Development in Young Adults; CKD, chronic kidney disease; Cr, creatinine; exam, examination.

Parity and GDM

At each examination, women were asked if they had diabetes and whether they had diabetes only during pregnancy. Self-report of GDM was validated for 200 births between baseline and year 10 in 165 CARDIA women by medical record abstraction of laboratory data. The sensitivity of reports of ever having GDM was 100% (20 of 20) and specificity was 92% (134 of 145).[3]

Women were included if nulliparous (no live births of >20 weeks' gestation) at baseline and transitioned across follow-up intervals (0-10, >10-15, >15-20, and >20-25) in which the number of births (parity) and GDM status were updated. The number of births was cumulative to the end of follow-up (ie, examination year of development of CKD or year 25). When women developed GDM, they were classified as having GDM for all subsequent follow-up time (which may have included additional pregnancies).

Chronic Kidney Disease

Single untimed urine specimens were collected for measurement of urine albumin and creatinine at the year 10, 15, 20, and 25 examinations. Urine albumin was measured by nephelometry with a specific anti-albumin monoclonal antibody. In years 10, 15, and 20, urine creatinine was measured by the Jaffé method. In year 25, urine creatinine was measured by the Roche enzymatic method. Based on creatinine excretion across 3 days of 24-hour urine collections obtained in a CARDIA subsample (n = 839),[23] calibration constants were used in our study to adjust for sex- and race-specific differences in urinary creatinine excretion as in Murtaugh et al[24] using the formula albumin/(k × creatinine), where k = 0.88 in black women (no adjustment needed for female sex).