

Gestational Diabetes Mellitus Alone in the Absence of Subsequent Diabetes Is Associated With Microalbuminuria

Results from the Kidney Early Evaluation Program (KEEP)

ANDREW S. BOMBACK, MD, MPH¹
 YELENA REKHTMAN, MD¹
 ADAM T. WHALEY-CONNELL, DO, MSPH²
 ABHIJIT V. KSHIRSAGAR, MD, MPH³
 JAMES R. SOWERS, MD²

SHU-CHENG CHEN, MS⁴
 SUYING LI, PHD⁴
 KAVITHA M. CHINNAIYAN, MD⁵
 GEORGE L. BAKRIS, MD⁶
 PETER A. MCCULLOUGH, MD, MPH⁵

OBJECTIVE — Women with gestational diabetes mellitus (GDM) maintain a higher risk for recurrent GDM and overt diabetes. Overt diabetes is a risk factor for development of chronic kidney disease (CKD), but GDM alone, without subsequent development of overt diabetes, may also pose a risk for CKD.

RESEARCH DESIGN AND METHODS — This cross-sectional analysis included Kidney Early Evaluation Program (KEEP) participants from 2000 to 2009. Patient characteristics and kidney function among three categories (GDM alone, overt diabetes, and no history of diabetes) were compared. The prevalence of microalbuminuria, macroalbuminuria, and CKD stages 1–2 and 3–5 was assessed using logistic regression.

RESULTS — Of 37,716 KEEP female participants, 571 (1.5%) had GDM alone and 12,100 (32.1%) had overt diabetes. Women with GDM had a higher rate of microalbuminuria but not macroalbuminuria than their nondiabetic peers (10.0 vs. 7.7%) that was substantially lower than the 13.6% prevalence in diabetic women. In multivariate analysis, women with GDM alone, compared with nondiabetic women, demonstrated increased odds of CKD stages 1–2 (multivariate odds ratio 1.54 [95% CI 1.16–2.05]) similar to the odds for women with overt diabetes (1.68 [1.55–1.82]). In stratified analyses, age, race, BMI, and hypertension modified the odds for CKD stages 1–2 but not CKD stages 3–5 among women with GDM.

CONCLUSIONS — Women with GDM alone have a higher prevalence of microalbuminuria than women without any history of diabetes, translating to higher rates of CKD stages 1–2. These results suggest that GDM, even in the absence of subsequent overt diabetes, may increase the risk for future cardiovascular and kidney disease.

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Most women who develop diabetes during a pregnancy, gestational diabetes mellitus (GDM), are normoglycemic after delivery but still maintain a higher risk for recurrent GDM, impaired glucose tolerance, and overt diabetes. Indeed, the odds of developing subsequent type 2 diabetes for women with GDM is roughly 5 times higher than that for women with normoglycemic

pregnancies in the first 5 years after delivery; the odds rise to more than 9 times higher in the years afterward (1).

Although overt diabetes is recognized as a potent risk factor for development of chronic kidney disease (CKD), it is currently unclear whether GDM alone, without subsequent development of overt diabetes, also poses any risk to kidney function. Because certain clinical factors (e.g., waist circumference, BMI, and years postdelivery) have been shown to increase the risk for development of overt diabetes in women with GDM (2), these factors could potentially also modify the risk for development of CKD.

We hypothesized that GDM alone would impart an increased risk for CKD and, specifically, that women with GDM would have a level of risk intermediate between that of women without any history of glucose abnormalities and women with overt diabetes. Using data from the National Kidney Foundation's Kidney Early Evaluation Program (KEEP), a program designed to screen participants at higher risk for CKD than the general population, we examined in cross-sectional analyses whether GDM, in the absence of subsequent overt diabetes, increases the odds of abnormal urinary albumin excretion and impaired glomerular filtration rate. In addition, we examined whether age, race, BMI, or hypertension modifies this relationship between GDM and CKD.

RESEARCH DESIGN AND METHODS

KEEP and participants

KEEP is a free, community-based health screening program that targets populations aged ≥ 18 years at high risk for kidney disease, defined as a history of diabetes or hypertension or a first-order relative with diabetes, hypertension, or kidney disease (3). The screening includes informed consent, health screening questionnaire, diagnostic panel, and physician consultation. The study population included eligible KEEP participants

From the ¹Department of Medicine, Division of Nephrology, Columbia University College of Physicians and Surgeons, New York, New York; the ²University of Missouri-Columbia School of Medicine and Harry S. Truman VA Medical Center, Columbia, Missouri; the ³Department of Medicine, Division of Nephrology and Hypertension, University of North Carolina School of Medicine, Chapel Hill, North Carolina; the ⁴Chronic Disease Research Group, Minneapolis Medical Research Foundation, Minneapolis, Minnesota; the ⁵Department of Medicine, Divisions of Cardiology, Nutrition, and Preventive Medicine, William Beaumont Hospital, Royal Oak, Michigan; and the ⁶Department of Medicine, Hypertensive Diseases Unit, University of Chicago, Pritzker School of Medicine, Chicago, Illinois.

Corresponding author: Andrew S. Bomback, asb68@columbia.edu.

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Table 1—Characteristics of KEEP female participants with GDM alone, with overt diabetes, and without diabetes

Characteristics	GDM	Overt diabetes	No diabetes	P value
n	571	12,100	25,045	
Age (years)	51.5 ± 14.5	59.0 ± 13.5	53.4 ± 15.4	<0.0001
Race (%)				0.0003
White	46.8	51.3	50.6	
African American	29.9	32.1	32.9	
Other	23.3	16.6	16.5	
BMI (kg/m ²)	30.0 ± 7.2	32.6 ± 7.5	29.5 ± 6.9	<0.0001
Waist circumference (inches)*	36.6 ± 5.4	41.3 ± 6.7	37.5 ± 6.1	<0.0001
Hypertension (%)	64.6	84.2	67.9	<0.0001
Systolic blood pressure (mmHg)	128.7 ± 19.9	134.7 ± 19.8	130.0 ± 19.3	<0.0001
Diastolic blood pressure (mmHg)	79.0 ± 11.8	78.3 ± 11.5	78.9 ± 11.3	<0.0001
Dyslipidemia (%)	39.2	48.9	34.1	<0.0001
Total cholesterol (mg/dl)	203.0 ± 36.6	196.3 ± 42.7	204.2 ± 39.8	<0.0001
Triglycerides (mg/dl)	149.3 ± 99.9	172.3 ± 121.4	137.8 ± 91.6	<0.0001
Current tobacco use (%)	11.0	8.2	9.3	0.0004
Alcohol use (%)	56.2	46.8	57.5	<0.0001
Family history of kidney disease (%)	15.6	18.3	18.0	0.2,487
Family history of diabetes (%)	51.5	67.9	49.7	<0.0001
Family history of hypertension (%)	86.0	78.4	85.6	<0.0001
Fasting blood glucose (mg/dl)†	96.4 ± 13.0	135.3 ± 60.3	95.0 ± 13.4	<0.0001

Data are means ± SD or %. *Data on waist circumference are available from 2008 (n = 7,070). †Calculation including only participants with fasting glucose data available (n = 9,071).

from August 2000 to May 2009 from 47 National Kidney Foundation affiliates and 2,336 screening programs in 50 states and the District of Columbia. This study cohort included only eligible KEEP female participants divided into three groups: with GDM alone, with overt diabetes, and without diabetes. All participants were screened after their pregnancies, and details of their pregnancies were self-reported.

Definitions

Diabetes was defined as a fasting blood glucose level ≥ 126 mg/dl, nonfasting blood glucose level ≥ 200 mg/dl, self-reported history of diabetes, or taking glucose-lowering medications. GDM alone was defined as self-reported diabetes only during pregnancy without subsequent development of overt diabetes.

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine measured at the KEEP screening using the reexpressed four-variable Modification of Diet in Renal Disease Study equation (serum creatinine was calibrated by the Cleveland Clinic Research Laboratory). Albumin-to-creatinine ratios (ACRs) were calculated from spot urine samples collected at screening and recorded as <30 , 30 – 300 , or >300 mg/g. Microalbuminuria was defined as ACR 30 – 300 mg/g and macroalbuminuria as ACR >300 mg/g. CKD stages were de-

defined as follows: no CKD, eGFR ≥ 60 ml/min per 1.73 m² and no proteinuria; stage 1, eGFR ≥ 90 ml/min per 1.73 m² with ACR ≥ 30 mg/g; stage 2, eGFR 60 – 89 ml/min per 1.73 m² with ACR ≥ 30 mg/g; stage 3, eGFR 30 – 59 ml/min per 1.73 m²; and stage 4–5, eGFR <30 ml/min per 1.73 m².

Hypertension was defined as average systolic blood pressure >129 mmHg or diastolic blood pressure >84 mmHg, self-reported history of hypertension, or taking blood pressure-lowering medication. Dyslipidemia was defined as triglycerides >150 mg/dl or HDL level <50 mg/dl. Other measures, including tobacco and alcohol use and family history of diseases and hypertension, were self-reported. Blood pressure, height, weight, and waist circumference were taken from direct measurements for all participants.

Statistical analysis

Patient characteristics and assessment of kidney function among study groups (GDM, overt diabetes, and no diabetes) were compared and tested by ANOVA. Associations of GDM and overt diabetes with respect to microalbuminuria, macroalbuminuria, CKD stages 1–2, and CKD stages 3–5 among KEEP female participants were assessed using univariate and multivariate logistic regressions, respectively. Adjusted odds ratios (ORs) for CKD

stages 1–2 and CKD stages 3–5 among KEEP female participants were stratified by age, race, hypertensive status, and BMI. Covariates in multivariate models included age, race, BMI, current smoking, alcohol use, hypertension, dyslipidemia, and family history of kidney disease.

RESULTS

A total of 37,716 KEEP female participants provided information on glycemic status and were therefore eligible for analysis, of which 571 (1.5%) had GDM alone and 12,100 (32.1%) had overt diabetes (Table 1). Women who reported GDM alone were significantly younger than those with overt diabetes and those without any history of diabetes. Women with GDM and women without diabetes had virtually identical BMI and waist circumference measurements that were significantly lower than those of women with overt diabetes. Likewise, hypertension and dyslipidemia were substantially more prevalent among women with overt diabetes compared with both women with GDM alone and women without any history of diabetes. At the time of the screening visit, fasting blood glucose values were essentially equal for women with GDM and women without diabetes (96.4 ± 13.0 vs. 95.0 ± 13.4 mg/dl) and significantly lower than values for women with overt diabetes (135.3 ± 60.3 mg/dl).

Table 2—Assessment of kidney function in KEEP female participants with GDM alone, with overt diabetes, and without diabetes

Characteristics	GDM	Overt diabetes	No diabetes	P value
n	571	12,100	25,045	
Serum creatinine (mg/dl)	0.81 ± 0.20	0.88 ± 0.31	0.83 ± 0.23	<0.0001
eGFR (ml/min per 1.73 m ²)	85.8 ± 23.4	77.9 ± 23.2	82.5 ± 22.7	<0.0001
eGFR <60 ml/min per 1.73 m ² (%)	11.7	21.0	14.1	<0.0001
ACR (%)				<0.0001
Normal (<30 mg/g)	89.3	84.4	91.7	
Microalbuminuria (30–300 mg/g)	10.0	13.6	7.7	
Macroalbuminuria (>300 mg/g)	0.7	2.0	0.6	
CKD stages (%)				<0.0001
No CKD	78.6	68.7	79.6	
Stage 1	3.8	3.8	2.6	
Stage 2	5.8	6.4	3.8	
Stage 3	11.4	19.8	13.5	
Stage 4–5	0.4	1.3	0.5	

Data are means ± SD or %.

Women who reported GDM alone had lower serum creatinine and higher eGFR measurements than women with or without any history of diabetes (Table 2). Less than 12% of women with GDM had eGFR <60 ml/min per 1.73 m², compared with ~14% of women without any history of diabetes and 21% of women with overt diabetes. These results translated to significantly lower prevalence rates of CKD stages 3–5 for women with GDM alone compared with women with or without diabetes. Although women

with GDM and nondiabetic women had similarly low rates of macroalbuminuria (urinary ACR >300 mg/g), women with GDM had significantly higher rates of microalbuminuria (urinary ACR 30–300 mg/g) than their nondiabetic peers (10.0 vs. 7.7%) that were still substantially lower than the 13.6% prevalence rate seen in diabetic women.

In multivariate logistic regression, the OR for microalbuminuria among women with GDM was 1.36 [95% CI 1.03–1.80] and among women with overt diabetes

was 1.67 [1.55–1.80] using nondiabetic women as the reference group (Table 3). These results translated to increased odds of CKD stages 1–2 for women with GDM alone (multivariate OR 1.54 [95% CI 1.16–2.05]) that approached the odds for women with overt diabetes (1.68 [1.55–1.82]). In univariate and multivariate analyses, women with GDM alone and women without any history of diabetes had similarly lower odds for macroalbuminuria and CKD stages 3–5 than diabetic women.

In stratified analyses, age, race, BMI, and the presence of hypertension modified the odds for CKD stages 1–2, but not for CKD stages 3–5, among women with GDM. These results imply that women with GDM were at highest risk for abnormal urinary albumin excretion if they were younger, African American, obese, and/or hypertensive (Table 4). For example, whereas white women with GDM did not appear to have increased odds of CKD stages 1–2 compared with white women without any history of diabetes, African American women with GDM had more than twice the odds for CKD stages 1–2 (multivariate OR 2.32 [95% CI 1.50–3.60]) than African American women without diabetes. Furthermore, the presence of obesity (defined as BMI >30 kg/m²) and hypertension imparted essentially identical odds for CKD stages 1–2 among women with GDM and women

Table 3—Association of GDM and overt diabetes with prevalent microalbuminuria, macroalbuminuria, CKD stages 1–2, and CKD stages 3–5 among KEEP female participants

Condition	GDM	P value	Overt diabetes	P value	No diabetes
Microalbuminuria vs. normal (n = 37,305)					
Univariate analysis	1.34 (1.02–1.77)	0.04	1.93 (1.80–2.07)	<0.001	1.00 (referent)
Multivariate analysis*	1.36 (1.03–1.80)	0.03	1.67 (1.55–1.80)	<0.001	1.00 (referent)
Macroalbuminuria vs. normal (n = 34,101)					
Univariate analysis	1.13 (0.42–3.07)	0.8	3.51 (2.87–4.29)	<0.001	1.00 (referent)
Multivariate analysis*	1.13 (0.41–3.09)	0.8	2.68 (2.16–3.31)	<0.001	1.00 (referent)
Macroalbuminuria vs. microalbuminuria (n = 4,026)					
Univariate analysis	0.85 (0.30–2.36)	0.7	1.82 (1.47–2.24)	<0.001	1.00 (referent)
Multivariate analysis*	0.93 (0.33–2.64)	0.9	1.56 (1.25–1.96)	<0.001	1.00 (referent)
CKD stages 1–2 vs. no CKD (n = 31,581)					
Univariate analysis	1.54 (1.16–2.05)	0.003	1.89 (1.75–2.04)	<0.001	1.00 (referent)
Multivariate analysis†	1.54 (1.16–2.05)	0.003	1.68 (1.55–1.82)	<0.001	1.00 (referent)
CKD stages 3–5 vs. no CKD (n = 34,833)					
Univariate analysis	0.84 (0.65–1.09)	0.2	1.73 (1.64–1.83)		1.00 (referent)
Multivariate analysis†	0.94 (0.71–1.25)	0.7	1.20 (1.12–1.28)	<0.001	1.00 (referent)
CKD stages 3–5 vs. stages 1–2 (n = 9,018)				<0.001	
Univariate analysis	0.55 (0.38–0.79)	0.001	0.92 (0.84–1.00)	0.06	1.00 (referent)
Multivariate analysis†	0.70 (0.46–1.05)	0.08	0.75 (0.68–0.84)	<0.001	1.00 (referent)

Data are ORs (95% CI). *Adjusted for age, race, BMI, current smoking, alcohol use, hypertension, dyslipidemia, eGFR, and family history of kidney disease. †Adjusted for age, race, BMI, current smoking, alcohol use, hypertension, dyslipidemia, and family history of kidney disease.

Table 4—Adjusted odds ratios for CKD stages 1–2 and CKD stages 3–5 among KEEP female participants, stratified by age, race, and BMI

Condition	GDM	P value	Overt diabetes	P value	No diabetes
CKD stages 1–2 vs. no CKD					
Age*					
<50 years (n = 12,326)	1.72 (1.17–2.53)	0.006	1.69 (1.46–1.95)	<0.0001	1.00 (referent)
≥50 years (n = 19,255)	1.33 (0.87–2.04)	0.2	1.74 (1.57–1.93)	<0.0001	1.00 (referent)
Race†					
White (n = 15,066)	1.12 (0.68–1.84)	0.7	1.45 (1.28–1.65)	<0.0001	1.00 (referent)
African American (n = 10,945)	2.32 (1.50–3.60)	0.0002	1.92 (1.68–2.19)	<0.0001	1.00 (referent)
Other (n = 5,570)	1.35 (0.75–2.42)	0.3	1.83 (1.52–2.21)	<0.0001	1.00 (referent)
BMI‡					
<30 kg/m ² (n = 16,964)	1.25 (0.82–1.89)	0.3	1.54 (1.36–1.74)	<0.0001	1.00 (referent)
≥30 kg/m ² (n = 14,617)	1.93 (1.30–2.86)	0.001	1.89 (1.69–2.11)	<0.0001	1.00 (referent)
Hypertension§					
No (n = 16,964)	1.24 (0.82–1.88)	0.3	1.60 (1.41–1.81)	<0.0001	1.00 (referent)
Yes (n = 14,617)	1.91 (1.29–2.84)	0.001	1.86 (1.66–2.08)	<0.0001	1.00 (referent)
CKD stages 3–5 vs. no CKD					
Age*					
<50 years (n = 11,796)	0.66 (0.31–1.42)	0.3	1.10 (0.90–1.36)	0.4	1.00 (referent)
≥50 years (n = 23,037)	0.97 (0.72–1.30)	0.8	1.32 (1.24–1.41)	<0.0001	1.00 (referent)
Race†					
White (n = 17,942)	0.83 (0.58–1.19)	0.3	1.07 (0.98–1.16)	0.1	1.00 (referent)
African American (11,187)	1.66 (0.96–2.88)	0.07	1.43 (1.26–1.62)	<0.0001	1.00 (referent)
Other (n = 5,704)	0.64 (0.29–1.43)	0.3	1.39 (1.16–1.66)	0.0003	1.00 (referent)
BMI‡					
<30 kg/m ² (n = 18,774)	1.01 (0.70–1.44)	1.0	1.18 (1.07–1.29)	0.0006	1.00 (referent)
≥30 kg/m ² (n = 16,059)	0.89 (0.56–1.39)	0.6	1.25 (1.14–1.36)	<0.0001	1.00 (referent)
Hypertension§					
No (n = 18,774)	0.99 (0.69–1.4)	0.9	1.19 (1.09–1.31)	0.0002	1.00 (referent)
Yes (n = 16,059)	0.87 (0.56–1.38)	0.6	1.22 (1.12–1.33)	<0.0001	1.00 (referent)

Data are ORs (95% CI). *Adjusted for race, BMI, current smoking, alcohol use, hypertension, dyslipidemia, and family history of kidney disease. †Adjusted for age, BMI, current smoking, alcohol use, hypertension, dyslipidemia, and family history of kidney disease. ‡Adjusted for age, race, current smoking, alcohol use, hypertension, dyslipidemia, and family history of kidney disease. §Adjusted for age, race, BMI, current smoking, alcohol use, dyslipidemia, and family history of kidney disease.

with overt diabetes, compared with those for nondiabetic women.

CONCLUSIONS— In this cross-sectional study of >37,000 KEEP female participants, we report that women with GDM alone have higher prevalence rates of microalbuminuria than women without any history of diabetes, translating to higher rates of CKD stages 1–2. The odds for this early stage of CKD among women with GDM alone fall roughly midway between the odds for disease among women without any diabetes and women with overt diabetes. In stratified analyses, younger age, African American race, obesity, and hypertension substantially increased the odds for CKD stages 1–2 among women with GDM alone, virtually matching the odds for disease among women with overt diabetes.

GDM is clearly recognized as an important disease entity with health implications that persist well beyond the gestational period. As is appropriate, the

most attention is paid to the increased risk for recurrent GDM, impaired glucose tolerance, and overt diabetes in women with prior episodes of GDM (1,4,5). However, an episode (or episodes) of GDM also may impart increased risk for disease beyond mere blood glucose abnormalities. Several reports have demonstrated an increased risk of metabolic syndrome in women with GDM as early as 3 months postpartum and as far as 11 years after the index pregnancy, independent of subsequent overt diabetes (5–7). Women with GDM have also demonstrated a higher risk for subsequent cardiovascular events than women with euglycemic pregnancies in two large population-based cohorts, although this risk was somewhat attenuated after adjustment for subsequent diabetes (8,9).

Here, we present data suggesting that GDM is associated with microalbuminuria and, by extension, CKD stages 1–2. Microalbuminuria is a marker of endothelial dysfunction and an independent risk

factor for cardiovascular events (10,11). Thus, the presence of microalbuminuria clearly marks a patient for whom lifestyle (e.g., low-salt diet) or medical (e.g., renin-angiotensin system blockade) intervention can be beneficial. The results presented here suggest that women with GDM may represent a group for whom such an intervention may prove beneficial. Indeed, we have previously shown that the overlap between microalbuminuria and reduced eGFR is very low among younger individuals in KEEP (12); thus, the finding of microalbuminuria offers the best chance not only to detect kidney damage associated with GDM but also the potential to intervene long before significant dysfunction ensues.

The finding of a greater risk for microalbuminuria, but not macroalbuminuria, also suggests that GDM may be a transient manifestation of preexisting and persistent metabolic dysfunction. The later development of overt cardiovascular disease among these women, indepen-

dent of overt metabolic syndrome or diabetes, lends support to the hypothesis that women with previous GDM are at risk for cardiovascular disease because of subclinical inflammation and enduring, generalized vascular dysfunction. Inflammatory markers that have been shown to be independent predictors of future cardiovascular events, including C-reactive protein, interleukin-6, and plasminogen activator inhibitor-1, are significantly elevated in women with previous GDM compared with control women (13). Women with previous episodes of GDM also exhibit lower levels of plasma adiponectin, an anti-inflammatory peptide (14), and have higher central systolic pressure, higher mean arterial pressure, higher peripheral resistance, lower mean stroke volume, lower cardiac output, and higher carotid intimal-medial thickness than normoglycemic women without previous GDM (15).

The strength of this study lies in the large size and diversity of the cohort assembled by KEEP screening activities. Friedman et al. (16) previously reported higher risk for microalbuminuria in women with GDM compared with control women, but this observation was based on data from only 72 individuals. Go et al. (17), in an entirely African American cohort of 289 women with GDM assessed at a median of 11 years after delivery, reported an 11% prevalence of microalbuminuria in normoglycemic women versus 36% prevalence in women who had developed overt diabetes after GDM. Our large cohort of 571 women with GDM alone allows us to find meaningful relationships within subgroups. Indeed, stratified analyses (Table 4) suggest that GDM may be a different, and more harmful, disease for African American women and women with obesity compared with white women and nonobese women, respectively. As demonstrated in recent reports from KEEP (18,19), these patient groups may derive extra benefit from screening for albuminuria in the setting of preserved GFR. Our data also suggest that this screening is crucial when hypertension, with or without concomitant diabetes, has developed in the years after delivery.

The study has limitations, however. Because the analysis is cross-sectional, microalbuminuria could have preceded (and been responsible for) GDM in many of the cases analyzed here rather than have resulted from prior GDM. Previous reports have suggested that microalbu-

minuria is associated with insulin resistance in nondiabetic subjects and can augur the arrival of subsequent diabetes (20,21). We did not have data on the exact date of pregnancy for these participants, and therefore inferences about the effect of age may not be valid. Younger women with GDM appeared to have a higher risk for CKD stages 1–2 than older women with GDM, but this may simply represent closer proximity to the pregnancy. Older women may have progressed to overt diabetes by the time they presented for screening activities and been equally or more likely to have renal dysfunction. In addition, although we had data on BMI for all participants, we only had limited data on waist circumference. Abdominal adiposity has been shown to predict the development of abnormal urinary albumin excretion and may have better identified a subgroup at risk than BMI in this cohort (22). Finally, KEEP was designed to screen participants at higher risk for CKD than the general population, and therefore the results presented here may not be generalizable to women with GDM and otherwise low-risk profiles. Further studies into the link between GDM and CKD ideally should be longitudinal, include waist circumference as a covariate, and include women at various levels of risk for chronic disease.

In summary, in a national cohort of >37,000 KEEP female participants, women with GDM alone demonstrated a greater prevalence of microalbuminuria than normoglycemic women. African American and obese women with prior GDM emerged as having the highest odds of CKD stages 1–2, comparable to that of women with overt diabetes. These results suggest that GDM, even in the absence of subsequent overt diabetes, is marked by generalized endothelial dysfunction and may place women at increased risk for future cardiovascular and kidney disease.

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A.S.B. conceived the study concept and wrote the manuscript. Y.R. researched data and reviewed/edited the manuscript. A.T.W.-C., A.V.K., J.R.S., K.M.C., G.L.B., and P.A.M. reviewed/edited the manuscript. S.-C.C. and S.L. performed the statistical analyses.

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