Gestational Diabetes Mellitus and Renal Function: A Prospective Study With 9- to 16-Year Follow-up After Pregnancy

Diabetes Care 2018;41:1378–1384 | https://doi.org/10.2337/dc17-2629

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Received 15 December 2017 and accepted 11 April 2018.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-2629/-/DC1.

See accompanying articles, pp. 1337, 1339, 1343, 1346, 1362, 1370, 1385, 1391, and e111.

OBJECTIVE

To examine whether gestational diabetes mellitus (GDM), independent of subsequent diabetes, is an early risk factor for renal impairment long term after the index pregnancy.

RESEARCH DESIGN AND METHODS

In the Diabetes & Women's Health (DWH) study (2012–2016), we examined the independent and joint associations of GDM and subsequent diabetes with long-term renal function among 607 women with and 619 women without GDM in the Danish National Birth Cohort (DNBC) index pregnancy (1996–2002). At median follow-up of 13 years after the index pregnancy, serum creatinine (mg/dL) and urinary albumin (mg/L) and creatinine (mg/dL) were measured, from which estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2) and urinary albumin-to-creatinine ratio (UACR) (mg/g) were derived.

RESULTS

Compared with women without GDM or subsequent diabetes, women with a GDM history had significantly higher eGFR even if they had not subsequently developed diabetes (adjusted β-coefficient [95% CI] = 3.3 [1.7, 5.0]). Women who had a GDM history and later developed diabetes (*n* = 183) also had significantly higher UACR [exponent β = 1.3 [95% CI 1.1, 1.6]) and an increased risk of elevated UACR (≥20 mg/g) [adjusted relative risk [95% CI] = 2.3 [1.1, 5.9]) compared with women with neither. After adjusting for potential confounders including prepregnancy BMI and hypertension, GDM without subsequent diabetes was not related to UACR.

CONCLUSIONS

Women who develop GDM in pregnancy were more likely to show increased eGFR levels 9–16 years postpartum, which could indicate early stages of glomerular hyperfiltration and renal damage. However, only those who subsequently developed diabetes showed overt renal damage as evidenced by elevated UACR.

Chronic kidney disease (CKD) is a common condition, with an estimated global prevalence of 13.4% (95% CI 11.7, 15.1) (1). Despite its long-term health consequences, many patients with CKD remain undiagnosed and untreated until the disease has progressed to an advanced stage (2). Currently, the identification and staging of CKD is based on the levels of urinary albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR), which are markers of renal damage. Increasing

evidence supports that both UACR and eGFR are independently associated with higher rates of mortality and end-stage renal disease (3–5). Identifying early risk factors that are associated with these renal function markers and are amenable to screening in primary care settings is hence critical to tackling the global burden of CKD and its adverse health sequelae.

Gestational diabetes mellitus (GDM), defined as glucose intolerance with first onset or recognition during pregnancy, is one of the most common metabolic complications in pregnancy (6). Despite its resolution soon after delivery among the majority of women, accumulating evidence supports that GDM is associated with subsequent dyslipidemia, hypertension, vascular dysfunction, and other cardiometabolic abnormalities (7–11), which are risk factors for renal impairment. Emerging, yet limited, studies (12–16) have reported an association between GDM history and subsequent renal morbidity. However, most of the current evidence has been based on retrospective or cross-sectional analysis, with the most critical limitation being the inadequate control for potential confounding factors including prepregnancy BMI, which is a major risk factor for GDM. Additionally, it is not clear whether GDM, independent of subsequent diabetes, is an early risk factor for renal impairment.

Given the sparse and inconsistent literature, a prospective study with longer follow-up and detailed assessment of potential confounders and renal outcomes was warranted. In the current study, we prospectively investigated the association between history of GDM and clinical markers for renal impairment 9–16 years after the index pregnancy. Further, we examined the independent and joint effect of GDM and subsequent diabetes on long-term renal function to clarify whether GDM, independent of progression to diabetes, is a risk factor for renal impairment.

RESEARCH DESIGN AND METHODS

Study Population

The Diabetes & Women's Health (DWH) study (2012–2016) (17) was a long-term follow-up of women with GDM within the Danish National Birth Cohort (DNBC) and the Nurses' Health Study II. This current analysis is limited to data from the DNBC, which was a longitudinal cohort of 91,827 pregnant women in Denmark (1996–2002) (18). In the DNBC, data on maternal sociodemographics, perinatal exposures, and clinical conditions were collected through four telephone interviews at gestational weeks 12 and 30 and at 6 and 18 months postpartum.

In the DNBC, women were considered to have GDM if they either responded positively to a question about GDM in interviews conducted at gestation week 30 or 6 months postpartum or if they had GDM diagnosis recorded in the National Patient Registry (NPR) for the index pregnancy. The registry extractions used ICD 10 codes (DO24.4 and DO24.9) from the date of last menstrual period prior to the index pregnancy until the day the pregnancy ended. A total of 1,274 women with GDM were identified in the DNBC cohort. Of these, 790 participated in the DWH study at 9–16 years since the index pregnancy, and 607 participated in a clinical exam when biospecimens were collected (19). Out of these 607 women, a subset (n = 361) had clinically verified GDM diagnosis based on expert panel review of medical records (19).

For comparison, 1,457 randomly selected women without GDM, either self-reported or in the NPR, were invited to the study, out of which 619 women participated and provided biospecimens. Major characteristics of the eligible sample were comparable to those who participated in the DWH study. The study was approved by the Regional Scientific Ethical Committee (VEK) of the Capital Region of Denmark (record no. H-4–2013–129). Informed consent was obtained from all women. Study procedures were followed in accordance with the Declaration of Helsinki.

GDM Screening and Diagnosis in Denmark

During the DNBC study period (1996–2002), pregnant women in Denmark were tested for urine glucose levels at every visit during pregnancy (19). GDM screening in Denmark was selective based on presence of risk factors (i.e., glucosuria, family history of diabetes, GDM in previous pregnancy, age >35 years, previous delivery of macrosomic baby, or prepregnancy overweight or obesity) (19). If the fasting glucose exceeded 4.1 mmol/L (corresponding plasma glucose value of 4.7 mmol/L) during initial screening in early pregnancy or repeated screening in the third trimester, a diagnostic 75-g oral glucose tolerance test (OGTT) was performed (19). In most clinics, glucose was measured in capillary blood although venous plasma was used by others, and GDM was diagnosed if two or more OGTT values exceeded thresholds based on corresponding standard curves developed for Danish women (20,21). For venous plasma, mean + 3 SD on the standard curve was 6.2 mmol/L at 0 min, 10.9 mmol/L at 30 min, 11.1 mmol/L at 60 min, 9.2 mmol/L at 90 min, 8.9 mmol/L at 120 min, 8.2 mmol/L at 150 min, and 7.3 mmol/L at 180 min (19).

Ascertainment of Diabetes at Follow-up

At the follow-up clinical exam, on average 13 years after the index pregnancy, women provided fasting blood and morning urine samples and underwent a 75-g OGTT. Blood samples for glucose measurements were drawn in K-oxalat-Na-fluoride vials. Glucose (mmol/L) was measured by standard laboratory methods on the Modular P module (Roche, Mannheim, Germany), with coefficients of variance <4%. Glycated hemoglobin (HbA_{1c}) was measured by means of ion-exchange high-performance liquid chromatography (Tosoh Bioscience, Inc., South San Francisco, CA, and Tokyo, Japan). Type 2 diabetes status at follow-up was either diagnosed based on clinical exam results following the American Diabetes Association criteria [HbA_{1c} levels ≥6.5% (48 mmol/mol), fasting glucose ≥7.0 mmol/L, or 2-h glucose ≥11.1 mmol/L] (22) or was based on self-report (type 1 or type 2 diabetes). Prediabetes was defined according to the American Diabetes Association 2011 criteria [HbA_{1c} 5.7–6.4% (39–46 mmol/mol), fasting glucose 5.7–6.9 mmol/L, and 2-h glucose 7.8–11 mmol/L] (22).

Outcome Measures

Following a standardized protocol, blood and urine samples were processed and assayed by a certified clinical laboratory at the University of Minnesota. Urine albumin (mg/L), urine creatinine (mg/dL), and plasma creatinine (mg/dL) were measured with the Roche COBAS 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN). The interassay coefficients of variation of all assays were ≤6.7%. UACR was calculated and classified as follows: *1*) elevated UACR defined as ≥20 mg/g according to our laboratory reference range values and as used previously (23–25), and *2*) micro- or macroalbuminuria defined as UACR >30 mg/g (26). eGFR (mL/min/1.73 m^2)

was calculated from the plasma creatinine measurements using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation (27). Glomerular hyperfiltration was defined as eGFR ≥95th percentile (116.4 mL/min/1.73 m^2) (28).

Covariates

Several putative risk factors of kidney function, obtained from questionnaires administered during pregnancy or at the follow-up, were considered. Covariates selected a priori included age at index pregnancy (years), education (high school or less vs. more than high school education), smoking during/at the beginning of pregnancy (yes vs. no), family history of diabetes (yes vs. no), prepregnancy BMI calculated from self-reported height and prepregnancy weight, and hypertension before pregnancy (yes vs. no).

Statistical Methods

Descriptive data were tabulated as mean (SD) for parametric continuous variables and as frequencies for categorical variables. Participant characteristics and markers of kidney function between women with and without GDM history were analyzed by Student *t* test for parametric continuous variables and χ^2 test for categorical variables.

UACR levels were log-transformed to normalize their distribution. General linear models were used to assess unadjusted and adjusted differences in log-transformed UACR and eGFR between women with and without GDM history. Poisson regression models with robust variance estimates were used to estimate adjusted relative risk (RR) and 95% CI for the associations of GDM with respect to elevated UACR and glomerular hyperfiltration. All multivariable models were adjusted for age at index pregnancy, smoking during pregnancy, education, family history of diabetes, prepregnancy BMI, and hypertension before pregnancy. To explore the independent and joint associations of GDM and subsequent diabetes on kidney function, the models also estimated associations of GDM only, subsequent diabetes only, and combined GDM and diabetes on renal function outcomes, using women with neither GDM history nor subsequent diabetes as the reference group.

In sensitivity analyses, multiple imputation (M = 100) was used to impute missing data (8.1%), the majority of which stemmed from the lack of prepregnancy BMI. We also repeated the analyses including women with prediabetes in the diabetes group to examine whether the association between GDM and renal function markers was independent of both prediabetes and overt diabetes. Similarly, we restricted the definition of GDM history to women with verified GDM diagnosis based on medical records from the index pregnancy (*n* = 361) and performed additional analyses restricting the definition of diabetes to self-reported physician-diagnosed type 1 or type 2 diabetes (*n* = 135). In additional sensitivity analyses, we excluded women who reported type 1 diabetes diagnosis after the index pregnancy (*n* = 18), regular use of cholesterol-lowering drugs at follow-up (*n* = 66), or recent use (within the past month) of medications (ACE inhibitors, diuretics, H2 blockers) known to affect renal function markers (*n* = 44). Additionally, women who had registry-verified preeclampsia/eclampsia diagnosis (*n* = 9) or any hypertension complication indicated on their hospital records from index pregnancy (*n* = 43) were also excluded. In order to test the robustness of our findings and examine if the association between GDM and renal markers was modified by clinical and lifestyle characteristics at follow-up, we stratified our analyses by the median age at follow-up (≤43 vs. >43 years), BMI status at follow-up (BMI <25 vs. ≥25 kg/m^2), smoking status at follow-up (current smokers vs. former/never smokers), regular antihypertension medication use at follow-up (yes vs. no), family history of diabetes (yes vs. no), physical activity at follow-up (<3 vs. ≥3 days per week), and median time since GDM-complicated pregnancy (<13 vs. ≥13 years). All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Two-tailed *P* values <0.05 were considered significant.

RESULTS

Table 1 shows the participant characteristics assessed during the index pregnancy and at 9–16 years' follow-up, by GDM history. At the index pregnancy, women who had GDM were more likely to be older, be parous, and report smoking or drinking alcohol regularly before or during pregnancy, compared with women without GDM. Women with GDM were also more likely to have a higher prepregnancy BMI and hypertension before the index pregnancy. At median follow-up of 13 years postpartum, women with a GDM history remained at higher BMI and were more likely to report a family history of diabetes and were less likely to exercise 3 or more days per week. By follow-up, 192 women had developed diabetes. Among them, 113 women were diagnosed with type 2 diabetes during the follow-up clinical exam, and an additional 79 women reported physician-diagnosed type 1 or type 2 diabetes. Among women with GDM, 183 (30.2%) developed diabetes, whereas only 9 (1.5%) in the non-GDM group developed diabetes.

At follow-up, women with a GDM history had higher UACR and eGFR compared with women without GDM (Tables 2 and 3). After accounting for prepregnancy BMI and other confounders, the difference between the two groups attenuated to nonsignificance for UACR (Table 2) but remained significant for eGFR (Table 3). Similarly, although women with a GDM history had a twofold increased risk (RR = 1.9 [95% CI 1.0, 3.6]) for elevated UACR (≥20 mg/g), the association was not significant after adjusting for potential confounders (Table 4). Women with a GDM history who subsequently developed diabetes (*n* = 183) had higher UACR (exponent β = 1.3 [95% CI 1.1, 1.6]) and an increased risk of elevated UACR (adjusted RR = 2.3 [95% CI 1.1, 5.9]) compared with women who had neither GDM nor diabetes, even after adjusting for major confounders (Tables 2 and 4). However, neither GDM nor diabetes alone was significantly associated with UACR.

Notably, we observed that GDM was associated with higher eGFR irrespective of diabetes status after the index pregnancy. Women with a GDM history who had not developed diabetes by the time of follow-up had higher eGFR (β = 3.3 [95% CI 1.7, 5.0]) compared with women without GDM or subsequent diabetes, even after adjustment for potential confounders (Table 3). Women who had GDM in pregnancy and subsequently developed diabetes had the highest eGFR levels and an increased risk for glomerular hyperfiltration compared with women without GDM or diabetes at follow-up (Tables 3 and 4).

In sensitivity analyses, we repeated the analyses including women with prediabetes in the diabetes category to examine whether the association between GDM and eGFR was independent of prediabetes. Indeed, women with GDM had higher eGFR

Table 1—Characteristics of women with and without GDM in the DWH study (2012–2016)

	GDM (*N* = 607)	No GDM (*N* = 619)	*P* value
Assessed at index pregnancy			
Age (years)	31.6 (4.5)	30.5 (4.2)	<0.0001
Prepregnancy BMI (kg/m^2)	27.1 (5.6)	22.8 (3.9)	<0.0001
Smoking during pregnancy	158 (27.5)	147 (24.0)	0.17
Alcohol consumption (≥1 drink per week) before pregnancy	252 (43.8)	183 (29.9)	<0.0001
Parity			<0.0001
Nulliparous	222 (38.6)	322 (52.6)	
Primiparous	219 (38.1)	195 (31.9)	
Multiparous	134 (23.3)	95 (15.5)	
DNBC enrollment year			0.50
1997	31 (5.1)	31 (5.0)	
1998	112 (18.5)	128 (20.7)	
1999	145 (23.9)	137 (22.1)	
2000	123 (20.3)	115 (18.6)	
2001	112 (18.5)	135 (21.8)	
2002	84 (13.8)	73 (11.8)	
Hypertension before pregnancy	91 (15.8)	49 (8.0)	<0.0001
Preeclampsia	7 (1.1)	2 (0.3)	0.09
Assessed at 9–16 years' follow-up			
Age (years)	43.7 (4.6)	43.4 (4.5)	0.17
Time since index pregnancy (years)	12.7 (1.5)	13.4 (1.5)	<0.0001
BMI (kg/m^2)	29.2 (6.9)	24.9 (7.4)	<0.0001
Family history of diabetes	255 (42.4)	114 (18.6)	<0.0001
Education			0.048
High school or less	96 (15.9)	74 (12.0)	
More than high school	506 (84.1)	541 (88.0)	
Smoking status			0.03
Former smokers	181 (30.0)	207 (33.6)	
Current smokers	110 (18.2)	79 (12.8)	
Never smokers	313 (51.8)	331 (53.6)	
Number of days of exercise per week			0.003
≤3 days per week	237 (39.4)	194 (31.4)	
>3 days per week	364 (60.6)	423 (68.6)	
Diabetes*	183 (30.2)	9 (1.5)	<0.0001
Elevated UACR (≥20 mg/g)	26 (4.4)	14 (2.3)	0.047
Microalbuminuria (UACR >30 mg/g)†	18 (3.0)	10 (1.6)	0.11
Serum creatinine (mg/dL)	0.70 (0.10)	0.75 (0.11)	<0.0001
Glomerular hyperfiltration (eGFR‡ ≥95th percentile)	38 (6.3)	24 (3.9)	0.05

Data are presented as mean (SD) for parametric continuous variables and as *n* (%) for categorical variables. All variables except age (at index pregnancy or follow-up), BMI (prepregnancy or follow-up), time since index pregnancy, and serum creatinine were categorical. *P* values were obtained by Student *t* test for parametric continuous variables and χ^2 test for categorical variables. *Diabetes defined as self-reported physician diagnosis of type 2 or type 1 diabetes or HbA_{1c} ≥6.5% (48 mmol/mol), fasting plasma glucose ≥7.0 mmol/L, or 2-h plasma glucose after 75-g OGTT ≥11.1 mmol/L. †Majority had microalbuminuria with only one person demonstrating macroalbuminuria (UACR >300 mg/g). ‡Calculated by CKD-EPI equation.

compared with those without (adjusted β = 3.0 [95% CI 1.0, 5.0]), even if they did not develop prediabetes or overt diabetes. Similarly, when we restricted the definition of GDM to women with verified GDM diagnosis (Supplementary Table 1) or defined diabetes at follow-up solely based on self-report (data not shown), these findings did not change. The independent association of GDM with eGFR also remained significant when we excluded women with conditions that might influence renal function markers at follow-up, including type 1 diabetes, preeclampsia/eclampsia or any hypertension complication during the index pregnancy, regular use of cholesterol-lowering drugs, or recent use of ACE inhibitors, diuretics, or H2 blockers. Furthermore, no effect modification was observed when we stratified the analyses by clinical and lifestyle characteristics at follow-up, including current BMI, smoking, antihypertension medication use, family history of diabetes, physical activity, and median time since index pregnancy, although associations in some strata became statistically insignificant due to reduced sample size (all *P* for interaction >0.05).

CONCLUSIONS

In the current study, we observed that women with a history of GDM were more likely to have increased levels of eGFR, which could indicate early stages of glomerular hyperfiltration and renal damage (29), compared with women without GDM. Only women who had GDM and developed overt diabetes after pregnancy showed clinically evident renal dysfunction, indicated by elevated UACR. GDM without subsequent diabetes was not significantly related to UACR. These findings were robust even after accounting for factors potentially related to subsequent renal function including prepregnancy BMI, prepregnancy hypertension, family history of diabetes, and hypertension complications during pregnancy. Our findings suggest that in women with a history of GDM, deterioration of renal function may potentially precede the development of overt diabetes, although clinically relevant outcomes such as elevated UACR may manifest only after progression to diabetes.

Few studies have investigated long-term renal outcomes among women with GDM-complicated pregnancies (12–16). Further, most were retrospective or cross-sectional designs. Important confounders such as prepregnancy BMI or hypertension were not accounted for in these studies. Indeed, as shown in our study, these prepregnancy characteristics substantially confounded the association, which was attenuated after adjusting for them. The only prospective study to examine the association between GDM and renal function found that GDM alone, without subsequent diabetes, was not significantly associated with risk of elevated UACR (16). This prospective study included fewer GDM cases (*n* = 100) and had a follow-up period of only 3 years (16). Our results were similar in that we did not observe an independent effect of GDM on UACR, even with a longer follow-up. However, our study additionally assessed eGFR as an outcome and found that GDM was associated with higher eGFR independent of diabetes status at follow-up.

Our study adds to the existing literature in several ways. First, by considering prepregnancy confounders, we were able to account for underlying cardiometabolic

Table 2—Independent and joint association of GDM and subsequent diabetes with log-transformed UACR

	N†	Median (25th−75th percentile)	Crude exponent (β) (95% CI)	Adjusted‡ exponent (β) (95% CI)
GDM status				
GDM (+)	597	2.2 (1.3–3.8)	**1.1 (1.0, 1.3)**	1.0 (0.9, 1.1)
GDM (−)	607	2.0 (1.3–3.3)	Reference	Reference
GDM and DM* status				
GDM (+) DM (+)	179	2.4 (1.5–5.7)	**1.5 (1.3, 1.7)**	**1.3 (1.1, 1.6)**
GDM (+) DM (−)	418	2.1 (1.3–3.3)	1.0 (0.9, 1.1)	0.9 (0.8, 1.1)
GDM (−) DM (+)	9	4.1 (2.4–6.8)	**2.2 (1.2, 4.0)**	1.2 (0.6, 2.3)
GDM (−) DM (−)	598	2.0 (1.3–3.2)	Reference	Reference

Data in boldface type are statistically significant. *Diabetes (DM) defined as self-reported physician diagnosis of type 2 or type 1 diabetes or HbA_{1c} ≥6.5% (48 mmol/mol), fasting plasma glucose ≥7.0 mmol/L, or 2-h plasma glucose after 75-g OGTT ≥11.1 mmol/L. †Sample sizes noted here may not reflect the actual number of women in the corresponding groups due to missing outcome data. ‡Estimates obtained from general linear model adjusting for age at index pregnancy, smoking during pregnancy (yes vs. no), education (high school or less vs. more than high school education), family history of diabetes (yes vs. no), prepregnancy BMI, and hypertension before pregnancy (yes vs. no). Models were run with log-transformed UACR.

risk that may predispose women to GDM and adverse renal outcomes. Second, we characterized renal function by two measures, UACR and eGFR, and separately assessed their association with GDM. eGFR is commonly used in combination with UACR for staging CKD, yet increasing evidence supports that eGFR is an important renal marker that is independently associated with end-stage renal disease, cardiovascular diseases, and all-cause and cardiovascular mortality (3–5). Moreover, glomerular hyperfiltration is considered to be a marker of early renal damage and a precursor to both albuminuria and hypofiltration (29). Last, although prior studies investigated renal outcomes among women with prior GDM who had not yet developed diabetes (13,14,16), we are the first to examine both independent and joint associations of GDM and subsequent diabetes on long-term renal function. In this study, we demonstrated that the adverse impact of GDM on long-term renal function may not be entirely dependent on the progression to overt diabetes, although those with GDM that progressed to diabetes showed greater deterioration in renal function. Given the few cases of diabetes among the non-GDM group, the observed lack of independent association of diabetes may have been due to inadequate power.

Multiple physiological pathways may underlie the observed associations in our study. Increasing evidence has linked GDM with subsequent cardiometabolic stress in women, which is apparent as early as a few months postpartum. Women with GDM are reported to be at increased risk of postpartum metabolic syndrome independent of their progression to diabetes (30–32). Women with GDM are also susceptible to subclinical inflammation and generalized vascular abnormalities, both of which are related to renal dysfunction irrespective of the presence of diabetes (10,33–35). Several studies have noted that markers of inflammation, endothelial dysfunction, and early vascular damage are elevated among women with GDM-complicated pregnancies compared with those without (10,33). The ratio of thromboxane and prostacyclin, which are important regulators of placental vascular tone, has been found to be increased in pregnancies complicated by diabetes, indicating an imbalance in these prostanoids compared with normal pregnancies (36,37). In terms of vascular changes after a GDM-complicated pregnancy, studies have noted impaired endothelium-dependent vasodilatation (38), impaired acetylcholine-induced skin vasodilatation (33,39), and increased peripheral vascular resistance (10), with these changes persisting for months or years after delivery even in the absence of overt diabetes. Other studies have noted that women with GDM history are more likely to have dyslipidemia, higher blood pressure, and other cardiometabolic risk factors (7–9,11,40). Collectively, these findings indicate that GDM may have cardiometabolic implications that persist beyond pregnancy, which in turn may adversely impact long-term renal function.

Strengths of this study include prospective data collection, long-term follow-up, a large number of GDM cases, and detailed data on prepregnancy confounders, lifestyle and clinical characteristics, and medication use at follow-up. Additionally, GDM history was well characterized in this study based on interviews and registry data, and a subset was previously verified against hospital records (19). Despite the lack of universal screening for GDM in Denmark at the time of study, misclassification of GDM diagnosis is likely to be very low in our sample of non-GDM women. Further, due to our prospective study design, we expect misclassification, if any, to be nondifferential, which would yield a bias toward the null, thus attenuating the observed associations. Another strength of the study was that undiagnosed diabetes cases at follow-up were carefully captured based on HbA_{1c}, fasting glucose, and OGTT results (22).

Table 3—Independent and joint association of GDM and subsequent diabetes with eGFR†

	N‡	Mean (SD)	Crude β (95% CI)	Adjusted§ β (95% CI)
GDM status				
GDM (+)	601	101.8 (11.7)	**4.7 (3.3, 6.1)**	**4.6 (3.0, 6.1)**
GDM (−)	613	97.1 (13.2)	Reference	Reference
GDM and DM* status				
GDM (+) DM (+)	181	105.6 (10.8)	**8.5 (6.4, 10.6)**	**9.2 (6.8, 11.6)**
GDM (+) DM (−)	420	100.1 (11.8)	**3.0 (1.5, 4.6)**	**3.3 (1.7, 5.0)**
GDM (−) DM (+)	9	97.3 (25.7)	0.2 (−8.0, 8.3)	0.01 (−8.5, 8.5)
GDM (−) DM (−)	604	97.1 (13.0)	Reference	Reference

Data in boldface type are statistically significant. *Diabetes (DM) defined as self-reported physician diagnosis of type 2 or type 1 diabetes or HbA_{1c} ≥6.5% (48 mmol/mol), fasting plasma glucose ≥7.0 mmol/L, or 2-h plasma glucose after 75-g OGTT ≥11.1 mmol/L. †Calculated by CKD-EPI equation. ‡Sample sizes noted here may not reflect the actual number of women in the corresponding groups due to missing outcome data. §Estimates obtained from general linear model adjusting for age at index pregnancy, smoking during pregnancy (yes vs. no), education (high school or less vs. more than high school education), family history of diabetes (yes vs. no), prepregnancy BMI, and hypertension before pregnancy (yes vs. no).

Table 4—RRs for elevated UACR and glomerular hyperfiltration at 9–16 years postpartum according to GDM history and subsequent diabetes status

	Elevated UACR*				Glomerular hyperfiltration†			
	Present (*n*)	Absent (*n*)	Crude RR (95% CI)	Adjusted RR‡ (95% CI)	Present (*n*)	Absent (*n*)	Crude RR (95% CI)	Adjusted RR‡ (95% CI)
GDM status								
GDM (+)	26	571	**1.9 (1.0, 3.6)**	1.4 (0.6, 2.9)	38	563	**1.6 (1.0, 2.7)**	1.1 (0.6, 2.1)
GDM (−)	14	593	1.0	1.0	24	589	1.0	1.0
GDM and DM§ status								
GDM (+) DM (+)	14	165	**3.6 (1.7, 7.6)**	**2.3 (1.1, 5.9)**	22	159	**3.2 (1.8, 5.7)**	**3.2 (1.4, 7.0)**
GDM (+) DM (−)	12	406	1.3 (0.6, 2.9)	1.0 (0.4, 2.3)	16	404	1.0 (0.5, 1.9)	0.8 (0.4, 1.6)
GDM (−) DM (+)	1	8	5.1 (0.7, 39.1)	—	1	8	3.0 (0.4, 21.6)	5.0 (0.6, 44.8)
GDM (−) DM (−)	13	585	1.0	1.0	23	581	1.0	1.0

Data in boldface type are statistically significant. *Elevated UACR defined as ≥20 mg/g (based on laboratory reference range). †Hyperfiltration defined as eGFR (calculated by CKD-EPI equation) ≥95th percentile or 116.4 mL/min/1.73 m^2. ‡Poisson regression models adjusted for age at index pregnancy, smoking during pregnancy (yes vs. no), education (high school or less vs. more than high school education), family history of diabetes (yes vs. no), prepregnancy BMI, and hypertension before pregnancy. §Diabetes (DM) defined as self-reported physician diagnosis of type 2 or type 1 diabetes or HbA_{1c} ≥6.5% (48 mmol/mol), fasting plasma glucose ≥7.0 mmol/L, or 2-h plasma glucose after 75-g OGTT ≥11.1 mmol/L.

Some potential limitations are worth mentioning. We could not evaluate effect modification by GDM severity as glucose measurements in our cohort were captured by different methods and at different time points during pregnancy and data on treatment modalities were also lacking. Currently, there are no established guidelines for the diagnosis of glomerular hyperfiltration (29). In our study, we defined hyperfiltration as eGFR ≥95th percentile (116.4 mL/min/1.73 m^2), whereas other cutoffs ranging from 125 to 140 mL/min/1.73 m^2 have been used previously (28). Our results were similar when we used an alternative cutoff of ≥125 mL/min/1.73 m^2, although they were statistically nonsignificant likely due to the lower number of hyperfiltration cases (data not shown). Although we controlled for major confounders, given the observational design, we cannot exclude the possibility of residual confounding. However, we conducted a series of sensitivity analyses to account for potential factors that may affect renal function, such as hypertension complication during the index pregnancy and regular use of cholesterol-lowering drugs following the index pregnancy. As our study population was predominantly composed of non-Hispanic white women, generalizability to other racial/ethnic groups may be limited. Last, renal markers were assessed only once after the index pregnancy. Future studies with longitudinal measurements of these markers are warranted to further clarify the association of GDM with renal function after the index pregnancy.

In summary, using prospective data that included a large number of women who developed GDM, we demonstrated that GDM may be an early indicator of subsequent subclinical renal dysfunction. These findings suggest that women with GDM-complicated pregnancies may represent a high-risk group that could benefit from regular monitoring for early-stage renal damage, timely detection of which may help clinicians initiate treatment to prevent or delay further disease progression.

Funding. This research was supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at the National Institutes of Health (contract numbers HHSN275201000020C, HHSN275201500003C, HHSN275201300026I, HHSN275201100002I). Financial support for the DNBC was received from the Innovation Fund Denmark (grant numbers 09-067124 and 11-115923, Centre for Fetal Programming), March of Dimes Birth Defects Foundation (6-FY-96-0240, 6-FY97-0553, 6-FY97-0521, 6-FY00-407), Health Foundation (11/263-96), Heart Foundation (96-2-4-83-22450), and European Union (FP7-289346-EarlyNutrition).

Duality of Interest. A.V. is an employee of AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. S.R. analyzed the data and wrote the manuscript. S.F.O., F.B.H., and C.Z. contributed to the study design and implementation, data interpretation, and manuscript revisions. L.G.G., R.C.M., S.N.H., C.G., J.W., E.Y., J.L.M., Y.Z., W.B., S.H.L., P.D., A.V., and M.Y.T. contributed to data acquisition or interpretation of data analyses and reviewed the manuscript. C.Z. obtained funding, designed and oversaw the study, and revised the manuscript. All authors contributed to the critical interpretation of the results, reviewed the manuscript for important intellectual content, and approved the final version of the manuscript. S.R. and C.Z. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 77th Scientific Sessions of the American Diabetes Association, San Diego, CA, 9–13 June 2017.

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