Prepregnancy SHBG Concentrations and Risk for Subsequently Developing Gestational Diabetes Mellitus

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OBJECTIVE

Lower levels of sex hormone–binding globulin (SHBG) have been associated with increased risk of diabetes among postmenopausal women; however, it is unclear whether they are associated with glucose intolerance in younger women. We examined whether SHBG concentrations, measured before pregnancy, are associated with risk of gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS

This was a nested case-control study among women who participated in the Kaiser Permanente Northern California Multiphasic Health Check-up examination (1984–1996) and had a subsequent pregnancy (1984–2009). Eligible women were free of recognized diabetes. Case patients were 256 women in whom GDM developed. Two control subjects were selected for each case patient and were matched for year of blood draw, age at examination, age at pregnancy, and number of intervening pregnancies.

RESULTS

Compared with the highest quartile of SHBG concentrations, the odds of GDM increased with decreasing quartile (odds ratio 1.06 [95% CI 0.44–2.52]; 2.33 [1.07–5.09]; 4.06 [1.90–8.65]; *P* for trend < 0.001), after adjusting for family history of diabetes, prepregnancy BMI, race/ethnicity, alcohol use, prepregnancy weight changes, and homeostasis model assessment of insulin resistance. Having SHBG levels below the median (<64.5 nmol/L) and a BMI ≥25.0 kg/m^2 was associated with fivefold increased odds of GDM compared with normal-weight women with SHBG levels at or above the median (5.34 [3.00–9.49]).

CONCLUSIONS

Low prepregnancy SHBG concentrations were associated with increased risk of GDM and might be useful in identifying women at risk for GDM for early prevention strategies.

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Gestational diabetes mellitus (GDM) is glucose intolerance with onset or first diagnosis during pregnancy. Women with a history of GDM have a sevenfold increased risk of developing type 2 diabetes mellitus after delivery (1), and the children of women with GDM are more likely to become obese and develop diabetes (2,3). The underlying etiology of GDM appears to be similar to the physiological abnormalities that characterize diabetes outside of pregnancy and is thought to be due to an inability of the pancreatic β-cell to compensate for the increased insulin resistance (IR) induced by pregnancy (4,5). The established risk factors for GDM are similar to the factors associated with the development of type 2 diabetes (6). However, recognized clinical risk factors for GDM are absent in up to half of affected women identified by universal screening strategies (7). Therefore, much remains to be learned about why pregnancy induces glucose intolerance in some women. Prepregnancy metabolic indices that have been associated with subsequent GDM pregnancy include low HDL cholesterol levels, impaired fasting glucose levels, elevated random glucose levels, and higher fasting insulin levels, independent of obesity (8,9). These same biomarkers predict type 2 diabetes in adults. There is increasing interest in identifying prepregnancy risk factors and biomarkers for GDM to increase our understanding of the underlying etiology.

Low levels of sex hormone–binding globulin (SHBG) and high levels of testosterone, indicative of serologic hyperandrogenism, have each been associated with incident type 2 diabetes in women (10–12). Sex hormone levels change during early pregnancy because of the pregnancy-induced rise in levels of estradiol, estriol, and SHBG (13), so it is important to understand whether pregravid levels are associated with GDM to ensure that the possible associations are not a consequence of the pregnancy hormone milieu. The aim of this study is to examine the association between prepregnancy SHBG concentrations and the risk of the development of GDM and to determine whether these associations are independent of known risk factors for GDM.

RESEARCH DESIGN AND METHODS

Kaiser Permanente Northern California (KPNC) is an integrated health-care delivery system that provides medical care for about one-third of the underlying population in the San Francisco Bay area. KPNC subscribers are representative of the region (14). The source population for this study consisted of female KPNC members who completed a voluntary Multiphasic Health Checkup (MHC) examination at the Kaiser Permanente Oakland Medical Center between 1984 and 1996. KPNC members at this facility were invited to complete a comprehensive health checkup upon study enrollment. The MHC consisted of a clinic visit for the completion of questionnaires and clinical measurements, including blood pressure, weight, and serum glucose and cholesterol levels (measured in serum obtained from a random blood draw). An extra serum sample was collected and stored at −40°C for future use. The goal of the MHC was to provide health maintenance through early diagnosis (15).

Among women 15–45 years of age who participated in the MHC from 1984–1996 (n = 27,743 with clinical and questionnaire data, as well as an extra serum sample), we identified 4,098 women who subsequently delivered an infant by 2010 by searching the KPNC hospitalization database and the Pregnancy Glucose Tolerance and GDM Registry (16), an active surveillance registry that annually identifies all pregnancies resulting in a livebirth or stillbirth among KPNC members. Women with recognized prepregnancy diabetes (17) are excluded from the GDM Registry if clinical screening data are available. The registry also captures the results of all screening and diagnostic tests for GDM from the KPNC electronic laboratory database (data available since 1994).

Study Design

We conducted a nested case-control study within a cohort of 4,098 women who took part in an MHC examination, had an extra tube of serum stored for future use, and had a subsequent pregnancy at KPNC. All cohort members in whom GDM developed were included as case patients; two control subjects were selected for each case from among women not meeting the GDM case patient definition.

GDM Case Patient Definition

We identified 267 women with GDM according to the KPNC electronic databases: case patients had either glucose values obtained during a standard 100-g, 3-h oral glucose tolerance test that met the Carpenter and Coustan plasma glucose thresholds for GDM (as outlined by the American College of Obstetricians and Gynecologists) (18) in the laboratory database (n = 228), or a hospital discharge diagnosis of GDM in the electronic hospital discharge database for pregnancies occurring before the electronic laboratory data were available (prior to 1994; n = 39). Standardized medical chart review was conducted by trained abstractors to confirm that these 267 women underwent a 100-g, 3-h oral glucose tolerance test, meeting the American College of Obstetricians and Gynecologists criteria (18) for GDM (plasma glucose thresholds: fasting, 5.3 mmol/L [95 mg/dL]; 1-h, 10.0 mmol/L [180 mg/dL]; 2-h, 8.6 mmol/L [155 mg/dL]; 3-h, 7.8 mmol/L [140 mg/dL]). Case patients were excluded from the study if at the time of the MHC examination they had a random glucose level >200 mg/dL (n = 6), no indication of GDM during the index pregnancy (n = 4), or if they had impaired glucose tolerance with insufficient follow-up testing (n = 1), leaving a total of 256 confirmed cases of GDM. We selected the first diagnosis of GDM after the MHC examination.

Control Subject Selection and Matching Criteria

From among those women without an indication of GDM, control subjects were randomly selected; two control subjects were individually matched to each case patient based on the year of MHC serum collection date (±3 months), age at MHC serum collection (±2 years), number of intervening pregnancies (0, 1, ≥2), and age at delivery of the index pregnancy (±2 years). We matched for the year of serum collection to account for any potential degradation in the quality of the serum over time, thereby assuring that the sample storage time

was approximately the same for case patients and control subjects. Since GDM is more common in older women, we matched on age at serum collection and age at delivery. We also matched on the number of pregnancies to account for any differences in pregnancies between the initial examination and the index pregnancy. Control subjects were excluded from the analysis if they had glucose values diagnostic of GDM found during medical chart abstraction (n = 5), had an abnormal screening glucose level but no follow-up diagnostic glucose test (n = 5), or had one abnormal glucose value on the diagnostic glucose test (n = 5), suggestive of "mild" GDM. Control subjects with glucose levels >200 mg/dL at the time of the examination were also excluded. Of the 512 matched control subjects identified, 497 were eligible.

Exposure Variables

Serum Biomarker Assays

Serum samples were thawed, aliquoted, and transported in batches on dry ice to Dr. Peter Havel's laboratory at the University of California, Davis for analysis. SHBG concentration was measured by ELISA (ALPCO, Salem, NH). Insulin level was measured with a radioimmunoassay (Millipore).

Covariates

BMI at the time of MHC examination was calculated in kilograms per square meter; height was measured using a stadiometer, and weight was measured using a balance beam scale. Information on age, sex, race/ethnicity, education level, cigarette smoking, family history of diabetes, medical history, alcohol consumption, coffee consumption, use of medications, and hours since last food ingestion was collected using self-administered questionnaires during the MHC examination (15). Serum glucose level was measured in serum obtained from a random blood draw using the hexokinase method, and total cholesterol was assessed using a Kodak Ektachem Chemistry analyzer by the regional laboratory of KPNC at the time of the MHC examination. This laboratory participates in the accreditation and monitoring program of the College of American Pathologists.

We searched outpatient databases to identify women who received at least one outpatient diagnosis of polycystic ovary syndrome (ICD-9 code 256.4). Prepregnancy weight was abstracted from the medical record, and weight change (in kilograms/year) from the MHC examination to prepregnancy was calculated.

IR was calculated based on the homeostasis model assessment of IR (HOMA-IR) using the following equation: fasting glucose (in mmol/L) × fasting insulin (in mU/L)/22.5 (19).

Statistical Analysis

Conditional logistic regression was used to obtain odds ratios (ORs) to estimate the relative risk of GDM in relation to prepregnancy SHBG levels. Associations of prepregnancy SHBG levels with prepregnancy BMI, age, and glucose, insulin, cholesterol, and HOMA-IR levels were estimated with Pearson correlation coefficients for normally distributed variables and Spearman correlation coefficients for non-normally distributed variables. We examined the association with 1 SD of SHBG concentration and categorized women by quartile of SHBG levels as defined among control subjects. Variables evaluated for confounding included race/ethnicity, prepregnancy BMI (in kilograms per square meter), parity, cigarette smoking, alcohol use, and family history of diabetes, all assessed at the time of SHBG measurement. To assess confounding, we entered covariates into a logistic regression model, one at a time, and compared the adjusted and unadjusted estimates. We first included covariates that altered unadjusted estimates by ≥10%. We then added a potential intermediary variable of the effects of SHBG level on GDM: prepregnancy HOMA-IR levels among the subset who had been fasting for ≥6 h (149 case patients and 269 control subjects). To examine the effects of weight gain after the MHC examination to the index pregnancy, we added weight change from the MHC examination to prepregnancy to the fully adjusted conditional logistic regression model (20).

To assess the potential modifying effects of prepregnancy BMI (overweight or obese [≥25 kg/m^2] vs. not overweight or obese [<25 kg/m^2]), race-ethnicity (white, Asian, Hispanic, and African American), and the median time since MHC examination (≥6.2 vs <6.2 years), we included appropriate interaction terms in regression models with 1 SD decrease of SHBG levels.

For power calculations, minimum detectable OR calculations were based on the likelihood ratio test of the association between quartiles of exposure and GDM in a logistic regression analysis, assuming a graded, linear trend in (log) ORs across categories and a test for trend (21,22). With 256 case patients and 512 control subjects, there is sufficient power (0.80) to detect a pattern of ORs of 1.00 (reference value), 1.21, 1.47, and 1.79 across quartiles 1 through 4.

This study was approved by the human subjects committee of the Kaiser Foundation Research Institute.

RESULTS

Table 1 summarizes the demographic, anthropometric, reproductive, and metabolic characteristics of the study participants, by case-control status. Women in whom GDM developed were more likely to have <12 years of education, to be Asian or Hispanic, to have two or more children at the time of the examination, to abstain from alcohol, and to have a family history of type 2 diabetes, compared with women in whom GDM did not develop. Women in whom GDM developed also had higher levels of several cardiometabolic risk factors including BMI at the MHC examination, serum glucose and total cholesterol levels, systolic and diastolic blood pressure, serum insulin concentrations, HOMA-IR, and weight gain from the MHC examination to the index pregnancy. Mean prepregnancy SHBG concentrations were significantly lower in women in whom GDM developed, when compared with those in whom GDM did not develop (57.69 vs. 79.68 nmol/L, respectively; P value <0.001).

Table 2 shows the correlation of serum SHBG levels with several metabolic covariates, separately for case patients and control subjects. SHBG concentration was negatively correlated with age, BMI, and HOMA-IR in both case patients and control subjects (Table

Table 1—Characteristics of case patients and control subjects

Characteristics	GDM case patients (n = 256)	Control subjects (n = 497)	P value
Age at MHC examination	28.2 ± 5.5	28.4 ± 5.2	0.78[a]
Age at delivery (years)	35.4 ± 5.1	35.1 ± 4.9	0.43[b]
<30	39 (15.2)	80 (16.1)	
30–34	73 (28.5)	145 (29.2)	
35–39	102 (39.8)	183 (36.8)	
≥40	42 (16.4)	89 (17.9)	
Time between examination and delivery	7.1 ± 4.4	6.7 ± 4.4	0.21[a]
Education (years)			0.24[b]
≤12	74 (28.9)	119 (23.9)	
13–15	85 (33.2)	157 (31.6)	
≥16	92 (35.9)	214 (43.1)	
Unknown	5 (2.0)	7 (1.4)	
Race/ethnicity			<0.001[b]
Non-Hispanic white	50 (19.5)	186 (37.4)	
African American	91 (35.5)	184 (37.0)	
Asian/Pacific Islander	80 (31.3)	84 (16.9)	
Hispanic	35 (13.7)	43 (8.7)	
Parity			<0.001[b]
0	142 (55.5)	278 (55.9)	
1	47 (18.4)	106 (21.3)	
≥2	44 (17.2)	70 (14.1)	
Unknown	23 (9.0)	43 (8.7)	
Gestational age at birth (weeks)			0.01[b]
≥37	218 (84.8)	460 (90.7)	
<37	39 (15.2)	39 (7.7)	
Large-for-gestational age at birth[c]			<0.01[b]
No	198 (81.1)	427 (89.5)	
Yes	46 (18.9)	50 (10.5)	
Alcohol			<0.001[b]
None	74 (28.9)	81 (16.3)	
Occasional or more drinks/day	149 (58.2)	346 (69.6)	
Unknown	33 (12.9)	70 (14.1)	
Smoking			0.40[b]
Never	150 (58.6)	277 (55.7)	
Former	37 (14.5)	92 (18.5)	
Current	38 (14.8)	61 (12.3)	
Unknown	31 (12.1)	67 (13.5)	
Hypertension status at index pregnancy			<0.001[b]
No hypertension	138 (53.9)	326 (65.5)	
Pre-existing hypertension[d]	28 (10.9)	18 (3.6)	
Gestational hypertension	33 (12.9)	68 (13.7)	
Pre-eclampsia	42 (16.4)	37 (7.4)	
Family history of diabetes			<0.001[b]
Yes	151 (59.0)	192 (38.6)	
BMI (kg/m^2)	26.0 ± 6.5	23.7 ± 4.6	<0.001[b]
Weight change from MHC to pregnancy (kg)	8.9 ± 9.9	4.4 ± 8.2	<0.001[a]
Rate of gestational weight gain (kg/week)[e]	0.3 ± 0.2	0.4 ± 0.2	<0.05[b]
Serum glucose (mg/dL)	89.6 ± 13.5	83.6 ± 8.3	<0.001[a]
Serum cholesterol (mg/dL)	182.9 ± 33.2	176 ± 32.6	<0.01[a]
Systolic blood pressure (mmHg)	115.6 ± 14.7	113.3 ± 13.4	<0.05[a]
Diastolic blood pressure (mmHg)	69.9 ± 10.4	68.3 ± 9.0	<0.05[a]
White blood cell count (1,000 cells/mm^3)	6.9 ± 1.9	6.5 ± 1.9	<0.01[a]
SHBG (nmol/L)	57.7 ± 45.1	79.7 ± 58.5	<0.001[a]
HOMA-IR index	4.1 ± 3.5	2.9 ± 2.9	<0.001[a]
Insulin (μU/mL)	25.8 ± 28.6	17.5 ± 16.7	<0.001[f]

Values are given as n (%) or mean ± SD, unless otherwise stated. [a]t test to compare differences in mean values of continuous variables except as noted below for Wilcoxon test. [b]χ^2 test for categorical variables. [c]Subset of women with singleton births; large-for-gestational age >90th percentile based on race and gestational age-specific quantiles. [d]Includes women who experienced pre-eclampsia superimposed on pre-existing hypertension. [e]Weight change (in kilograms per week) from the beginning of index pregnancy until screening glucose (measurement obtained 1 h after the 50-g oral challenge). Data were available for 226 case patients and 407 control subjects. [f]Wilcoxon test for differences in median values.

Table 2—Correlation coefficients of prepregnancy SHBG and maternal characteristics

	SHBG	
Characteristics	GDM case patients (n = 256)	Control subjects (n = 497)
Maternal age at examination	−0.15 (0.02)	−0.17 (<0.001)
BMI (kg/m^2)	−0.17 (<0.01)	−0.16 (<0.001)
Serum glucose (mg/dL)	−0.07 (0.30)	−0.22 (<0.0001)
Serum insulin (μU/mL)	−0.05 (0.45)	−0.08 (0.09)
Serum cholesterol (mg/dL)	−0.09 (0.16)	0.12 (<0.01)
HOMA-IR index[a]	−0.16 (0.05)	−0.12 (0.04)

Values are given as r value (P value). [a]Subset of women fasting for >6 h at the time of MHC examination (case patients, n = 149; control subjects, n = 269); Spearman correlation coefficient for non-normally distributed variables.

2). As presented in Table 3, a 1 SD decrease in SHBG concentration was associated with an OR of 1.93 (95% CI 1.33–2.10) for GDM, after adjusting for race/ethnicity, BMI, family history of diabetes, alcohol use at the time of MHC examination, weight change, and HOMA-IR among the subset of case patients and control subjects who were fasting for >6 h. Women in the lowest quartile of SHBG concentration distribution (8.0–44.2 nmol/L) prior to pregnancy experienced a fourfold increased risk of GDM, compared with women whose values fell within the highest quartile (99.7–537.6 nmol/L) (OR 4.06 [95% CI 1.90–8.65]), after adjusting for race/ethnicity, BMI, parity, family history of diabetes, smoking status at the time of MHC examination, weight change, and HOMA-IR (Table 3).

When the combined effects of SHBG levels and maternal BMI were examined, among normal-weight women (BMI <25.0 kg/m^2), having low concentrations of SHBG (defined as <64.5 nmol/L, below the median) was associated with a 2.6-fold (95% CI 1.54–4.28) increased risk of GDM compared with having high concentrations of SHBG (defined as ≥64.5 nmol/L, at or above the median). Women who were overweight or obese (BMI ≥25.0 kg/m^2) and had high SHBG concentrations had a 2.2-fold (95% CI 1.11–4.54) increased risk of GDM compared with normal-weight women with the same SHBG concentrations. Women who were both overweight and had low SHBG concentrations had a 5.3-fold (95% CI 3.00–9.49) increased risk of GDM (Fig. 1).

In a stratified analysis, examining SHBG concentration and GDM risk, the ORs for 1 SD of SHBG concentration were similar when the time since initial examination was <6.2 years (the median time since the examination) (OR 1.73 [95% CI 1.16–2.59], compared with when it had been >6.2 years since the examination (1.74 [1.22–2.48]); there was no significant interaction by time since examination (P = 0.40). There was also no significant interaction by pregravid BMI. There was a suggestive interaction by race-ethnicity (P = 0.10); it appears that the association between SHBG concentration and GDM risk may be stronger for nonwhite racial-ethnic groups (ORs [95% CIs] for 1 SD of SHBG concentration, as follows: white, OR 1.20 [95% CI 0.70–2.04]; black, 2.10 [1.35–3.26]; Asian/Pacific Islander, 2.83 [1.38–5.82]; and Hispanic, 2.39 [0.84–6.80]), after adjusting for prepregnancy BMI, family history, alcohol use, and prepregnancy weight change.

Table 3—GDM association with SHBG concentrations

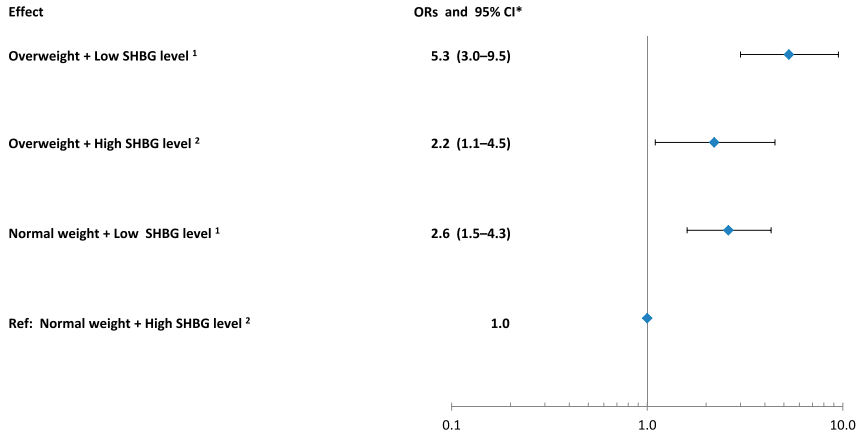
Prepregnancy risk factor SHBG (nmol/L)	Crude	Multivariable-adjusted[a]	Multivariable-adjusted[b]
1 SD (58.5)	1.85 (1.46–2.34)	1.58 (1.24–2.02)	1.93 (1.33–2.80)
Quartile 1 (8.04–44.23)	4.40 (2.69–7.19)	3.34 (1.94–5.75)	4.06 (1.90–8.65)
Quartile 2 (44.24–64.53)	1.70 (1.03–2.80)	1.89 (1.09–3.28)	2.33 (1.07–5.09)
Quartile 3 (64.54–99.73)	1.18 (0.69–2.02)	1.25 (0.70–2.24)	1.06 (0.44–2.52)
Quartile 4 (99.74–537.57)	1.00	1.00	1.00

Values are given as OR (95% CI). [a]Adjusted for race-ethnicity, prepregnancy BMI, family history of diabetes, and alcohol use. [b]Further adjusted for HOMA-IR index and weight change between MHC examination and index pregnancy; subset of women fasting for >6 h at the time of MHC examination (case patients, n = 149; control subjects, n = 269).

In a sensitivity analysis excluding women who had received a diagnosis of polycystic ovary syndrome, similar results were observed (Supplementary Data). The analysis was rerun excluding women who used hormonal contraceptives at the time of the MHC examination, and similar results were observed (Supplementary Data). Finally, to determine whether SHBG levels could be useful in identifying women without other known risk factors for GDM, we examined the association between SHBG concentration and GDM among a subset of women without the strongest risk factors for GDM, women who were of normal weight (BMI <25.0), and women who had no family history of GDM (n = 55 case patients and n = 224 control subjects). Among this subset of low-risk women, the OR associated with a 1 SD decrease in SHBG concentration was 2.02 (95% CI 1.11–3.68), after adjusting for matching variables BMI (continuous), parity, alcohol use, weight change from MHC to pregnancy, and race-ethnicity.

CONCLUSIONS

In this nested case-control study, we found that lower SHBG concentrations measured, on average, 6 years before pregnancy were associated with more than fourfold increased odds of the development of GDM. The associations were even stronger when the serum measurement occurred ≥6 years before pregnancy, confirming the robustness of the association and suggesting the presence of an androgenic hormonal profile even years before pregnancy in some women in whom GDM develops. Of note, these relationships were independent of known risk factors for GDM, including BMI, age, and race-ethnicity, as well as markers of IR (specifically HOMA-IR) and subsequent weight gain. Our findings are among the



*adjusted for race/ethnicity, family history of diabetes, alcohol use, prepregnancy serum glucose, insulin, and fasting status.
[1] Quartiles 1 and 2; [2] Quartiles 3 and 4

Figure 1—ORs (95% CIs) for the association between joint effects of prepregnancy SHBG concentration and BMI and the risk of GDM.

first to suggest that low circulating SHBG concentrations, measured years before pregnancy, are associated with an increased risk of GDM.

Our findings are consistent with previous studies of SHBG and type 2 diabetes. Low levels of SHBG and high levels of testosterone, indicative of serologic hyperandrogenism, have both been prospectively associated with incident type 2 diabetes in women (12). Specifically, the MESA (Multi-Ethnic Study of Atherosclerosis) cohort of postmenopausal women found that women with more androgenic profiles, as represented by low SHBG concentrations and high bioavailable testosterone levels, were at greater risk for diabetes (23). Similarly, in the DESIR (Data from an Epidemiological Study on the Insulin Resistance Syndrome) cohort, low SHBG levels were associated with increased odds of future impaired fasting glucose levels among women aged 30–64 years (24). Pregnant (25) and postpartum (26) women with histories of GDM have decreased SHBG concentrations compared with women without such histories, suggesting that women with histories of GDM have a more androgenic profile after pregnancy.

One small study (27) found that low levels of SHBG measured early in pregnancy were associated with GDM, whereas the HAPO (Hyperglycemia and Adverse Pregnancy Outcome) study found that SHBG levels measured during pregnancy were not independently associated with C-peptide levels (28). However, conflicting findings may be due to the fact that, during pregnancy, SHBG levels change significantly and are influenced by a number of factors (13). Our study adds to this knowledge by clarifying that the altered SHBG levels are present even before pregnancy.

We found that the association between SHBG levels and subsequent GDM was stronger among nonwhite women. These findings are consistent with findings from the BioCycle study, which found that, despite similar levels of SHBG, racial differences exist in the relationships between SHBG concentrations and adiposity among premenopausal women (29). The BioCycle study found that among whites all adiposity measures were significantly and inversely associated with SHBG concentration. However among blacks, BMI, waist circumference, and trunk-to-leg fat ratio were significantly inversely associated with SHBG concentration, and among Asians only measures of central and upper body fat were significantly associated with SHBG concentration, not overall BMI. Our study adds evidence to the idea that the association between SHBG and subsequent metabolic disorders may also differ by race-ethnicity.

There is biologic plausibility for an important role of SHBG concentration in GDM risk. SHBG levels in women are thought to be an indirect measure of androgenicity as levels of free estrogen and androgens determine its concentration (30). Plasma levels of SHBG are determined by the ratio of androgens to estrogens in the body and are extremely sensitive to changes in androgen balance, with even small decreases in SHBG indicating a relative increase in androgenic action (30–32). Studies of the direct administration of testosterone to female rats found that excess androgen impaired peripheral insulin–stimulated glucose uptake and glycogen synthesis (33). The skeletal muscle is responsible for the majority of peripheral glucose disposal, suggesting that sex steroids have a direct action on the skeletal muscle to reduce insulin sensitivity. The underlying etiology of GDM is believed to be diminished insulin secretion before pregnancy coupled with pregnancy-induced IR (5). And other prepregnancy markers that are routinely measured, including HDL cholesterol and fasting and random glucose levels, have been previously reported to be highly predictive of GDM (8,9). This study provides evidence that hyperandrogenism before pregnancy may also reduce insulin sensitivity and thereby increase the risk of subsequent GDM.

We found that the association between SHBG and GDM was independent of weight gain from the MHC examination to prepregnancy. There have only been a few studies to date on the potential effects of lifestyle factors on SHBG levels in women. Data from an ecological study of women in rural China provided evidence that intake of rice, fish, and possibly green vegetables may elevate SHBG concentrations independent of weight or smoking habits (34). A small crossover design study of 33 women with dysmenorrhea found that women who followed a low-fat vegetarian diet for two menstrual cycles had increased serum SHBG concentrations, and reductions in body weight and dysmenorrhea duration, suggesting dietary influences on estrogen activity (35). A study of 267 postmenopausal women randomly selected from the Women's Health Initiative Dietary Modification Trial

found that women who had the lowest BMI and highest physical activity had the highest levels of SHBG (36). A study of premenopausal glucose-intolerant women who participated in the Diabetes Prevention Program found that an intensive lifestyle intervention increased SHBG levels, whereas no significant changes in SHBG levels were observed among women in the metformin arm of the Diabetes Prevention Program study (37). While this provides some preliminary evidence that SHBG levels can be modified by lifestyle changes, more information is needed to determine strategies for increasing circulating SHBG concentrations to better inform possible prevention strategies for both GDM and type 2 diabetes.

Low levels of prepregnancy SHBG remained a significant risk factor for GDM among the subset of women who were normal weight and had no family history of GDM, two main risk factors for GDM. This finding is of clinical relevance because it suggests that SHBG may help to identify a group of high-risk women who may otherwise not be identified as being at high risk for the development of GDM. These study findings add to the growing body of evidence suggesting that women in whom GDM develops may have signs of altered metabolic parameters even years before pregnancy. Future studies designed to be able to assess the sensitivity and specificity of SHBG concentration in predicting GDM will be valuable to help further clarify the clinical utility of this biomarker. It will be important to determine the effectiveness of using SHBG or other biomarkers clinically to identify at-risk women who may benefit from early interventions designed to prevent GDM.

The strengths of this study include our ability to exclude women with glucose values indicative of recognized, pregestational diabetes. We had the unique ability to look at SHBG levels measured several years before pregnancy on a large number of GDM case patients and matched control subjects. We were able to control for markers of IR (HOMA-IR) among a fasting subset, and our findings remained when adjusted for potential mediators. The study was limited by the lack of data on more informative measures of adiposity in addition to BMI, such as waist circumference or percentage of body fat, and we therefore were not able to assess whether the association between SHBG concentration and GDM was possibly mediated by increased visceral fat. We also lacked information on diet and physical activity changes that may have occurred from the baseline examination to the subsequent pregnancy; therefore, we were unable to assess the impact of lifestyle changes on GDM risk in this study. We only had a single measurement of SHBG, which was not timed to the menstrual cycle, and SHBG levels may be subject to variation depending on a woman's menstrual cycle; however, such misclassification would be nondifferential and bias our results toward the null hypothesis. We did not measure testosterone; however, the binding of testosterone to SHBG has been suggested to be one mechanism by which higher SHBG levels decrease IR and type 2 diabetes risk (12).

In summary, after adjusting for potential confounding factors and clinical factors known to be related to IR, we found that low SHBG concentrations were associated with a fourfold increased risk of GDM. Circulating concentrations of SHBG represent a potentially useful new biomarker identifying who is at risk for GDM beyond the currently established clinical and demographic risk factors. This finding highlights the importance of the preconception period as an etiologically relevant time period for the subsequent risk of GDM. It will be important to determine whether prepregnancy lifestyle interventions improve SHBG levels and other important biomarkers of metabolic risk and may be used to ultimately attempt to prevent subsequent GDM.

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Author Contributions. M.M.H. designed the study, oversaw the data collection, and wrote the manuscript. F.X. and J.A.D. conducted the data analysis and contributed to the writing of the manuscript. C.P.Q. contributed to the study design, provided statistical expertise, and contributed to the writing of the manuscript. S.S. assisted with the data collection, and contributed to the writing and editing of the manuscript. C.K. and E.P.G. contributed to the writing of the manuscript. A.F. designed the study and edited the manuscript. M.M.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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