Sex hormone-binding globulin, cardiometabolic biomarkers, and gestational diabetes: A longitudinal study and meta-analysis

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Abstract
Objective: This study investigated the prospective associations of circulating levels of sex hormone-binding globulin (SHBG) levels with cardiometabolic biomarkers and risk of gestational diabetes (GDM) during pregnancy. It also examines the longitudinal trajectory of SHBG in women with and without GDM.

Methods: We conducted a nested case-control study of 107 incident GDM cases and 214 matched controls within the Eunice Kennedy Shriver National Institute of Child Health and Human Development Fetal Growth Studies-Singleton Cohort. The cohort enrolled non-obese and obese women aged 18–40 years with a singleton pregnancy between 8 and 13 weeks of gestation from 2009 to 2013. GDM was ascertained via medical records review. Blood samples were drawn four times at gestational weeks 10–14, 15–26, 23–31, and 33–39. The prospective associations between SHBG levels and cardiometabolic biomarkers were examined using the Spearman partial correlation among the controls. The longitudinal trajectories of SHBG levels were examined among the cases and the controls. Meta-analysis of prospective studies were performed to examine the association between SHBG levels and GDM risk.

Results: SHBG levels at gestational weeks 10–14 were significantly inversely associated with fasting insulin (r = –0.17, P = 0.01) and insulin resistance as measured by HOMA-IR (r = –0.17, P = 0.01) at gestational week 15–26. SHBG at gestational weeks 10–14 and 15–26 was lower in cases than controls (mean ± standard deviation: 204.0 ± 97.6 vs. 220.9 ± 102.5 nmol/L, P = 0.16 and 305.6 ± 124.3 vs. 322.7 ± 105.1 nmol/L, P = 0.14, respectively). Yet the differences were not significant in the meta-analysis. SHBG was 41.5 nmol/L (95% confidence interval: 23.9, 59.1, P < 0.01) significantly lower among women with GDM than without, and each 50 nmol/L increase in SHBG was significantly associated with an odds ratio of 0.85 (95% confidence interval: 0.76–0.95, P = 0.01) for GDM.

Conclusion: Lower SHBG levels in early pregnancy were prospectively associated with higher insulin levels and insulin resistance in mid-pregnancy and subsequent risk of GDM, independent of adiposity. SHBG may serve as a marker for the identification of high-risk pregnancies during early pregnancy.

Keywords: Diabetes, gestational; Sex binding hormones; Cardiometabolic risk markers; Cohort analysis; Longitudinal measurement; Meta-analysis

Introduction
Sex hormone-binding globulin (SHBG) is classically known as a glycoprotein that binds circulating testosterone and estradiol with high affinity and regulates their bioavailability.1 Increasing evidence now strongly implicates SHBG in glucose metabolism and the development of type 2 diabetes. In non-pregnant populations, low circulating SHBG levels were consistently associated with hyperinsulinemia,2 insulin resistance,3 increased adiposity,4 and metabolic syndrome,5 and were predictive of type 2 diabetes.6,7

Pregnancy is characterized by a progressive decline in insulin sensitivity that begins near mid-pregnancy, accompanied by a compensatory increase in insulin secretion.8

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Exaggerated insulin resistance in pregnancy contributes to gestational diabetes mellitus (GDM), and it may also contribute to gestational hypertension, pre-eclampsia, and adverse perinatal outcomes. During pregnancy, SHBG levels rise dramatically in conjunction with major reproductive hormones. Whether SHBG is involved in the regulation of glucose metabolism during pregnancy remains unclear. Cross-sectional studies conducted in late pregnancy have reported an inverse association of SHBG with fasting insulin, and inconsistent associations with insulin resistance and fasting glucose, which is strongly inversely associated with SHBG levels, thus may explain the SHBG-GDM link. Further, because both SHBG levels and glucose metabolism vary over pregnancy, the association between SHBG and GDM may change over time. Only one study including 35 women with GDM has examined SHBG at multiple times during pregnancy. However, its interpretation was limited by a small sample size, and a lack of adjustment for important confounders including body mass index (BMI).

In the current study, we first examined the prospective associations of maternal plasma SHBG levels with a comprehensive panel of cardiometabolic biomarkers (glucose, insulin, C-peptide, homeostasis model of assessment of insulin resistance (HOMA-IR), hemoglobin A1c (HbA1c), C-reactive protein (CRP), cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides). Then, we estimated the longitudinal association of SHBG with GDM risk across the course of pregnancy. Lastly, we performed meta-analysis of the association between SHBG levels and GDM risk using our data and existing prospective studies, with and without adjustment for adiposity.

Material and methods

Study design and population

This study was based on a nested case-control study within the Eunice Kennedy Shriver National Institute of Child Health and Human Development Fetal Growth Studies-Singleton Cohort—a multicenter, multiracial prospective pregnancy cohort. The cohort enrolled 2334 non-obese and 468 obese women aged 18–40 years with a singleton pregnancy between 8 and 13 weeks of gestation from 2009 to 2013. At enrollment, all women had a gestational age estimated from last menstrual period which was confirmed by ultrasound. Women were excluded if they had pre-existing diabetes, hypertension, or other major chronic conditions. Furthermore, non-obese women were excluded if they had lifestyle risk-factors (used illicit drugs in the past year, smoked in the past 6 months, or consumed at least one alcoholic drink per day in pregnancy), had a history of obstetric complications, or conceived using assisted reproductive technology. Research approval was obtained from the institutional review boards of all participating institutions (Supplemental Digital Content, Table 1, http://links.lww.com/MFM/A4), the methods were carried out in accordance with the relevant guidelines and regulation, and the participants provided written informed consent.

In this study, 107 incident GDM cases were identified via medical record review using the Carpenter and Coustan diagnostic criteria. For each case, two controls without GDM were randomly selected to match with the case on age (±2 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or Asian/Pacific Islander), and gestational week of blood collection (±2 weeks). Thus, a total of 321 women (107 cases and 214 controls) from the original cohort were included in this study. Following a standardized protocol, blood specimens were collected at four study visits at gestational weeks 10–14, 15–26, 23–31, and 33–39, respectively. The blood specimen at 15–26 weeks was collected after an overnight fast. For each study visit, participants were randomized into weekly windows to cover the entire course of pregnancy. All biospecimens were immediately processed and stored at −80°C until thawed for laboratory analysis.

Laboratory tests

For the two study visits before GDM screening (at gestational weeks 10–14 and 15–26), biomarkers were measured in all cases and the two matched controls. For the two visits after GDM screening (at gestational weeks 23–31 and 33–39), they were measured in all cases and one of the two matched controls. SHBG was measured in plasma using a sandwich immunoassay method (Roche Diagnostics, Indianapolis, IN). Fasting glucose, insulin, CRP, and lipids were measured in plasma using hexokinase, immunosorbent, immunoturbidimetric assays and enzymatic assays (Roche Diagnostics), respectively. All assays had inter- and intra-assay coefficients of variation <9% and were performed without knowledge of GDM status in a single certified laboratory.

Covariates

At the enrollment visit (gestational weeks 10–14), women reported their age, race/ethnicity, level of education, marital status, parity, and family history of diabetes in a structured questionnaire. Women in the obese cohort also reported smoking during the 6 months before pregnancy and current alcohol use. Pre-pregnancy BMI (kg/m²) was calculated from self-reported pre-pregnancy weight and height measured at enrollment. Gestational week at each visit was calculated from the last menstrual period.

Data availability

The data sets generated during and/or analyzed during the current study are available from Eunice Kennedy Shriver National Institute of Child Health and Human Development, but restrictions apply to the availability of these data, and hence they are not publicly available yet.

Statistical analysis

Distributions of participants’ characteristics and cardiometabolic markers were compared between cases and
controls using linear mixed-effects regression models for continuous variables and logistic regression with generalized estimating equations for categorical variables, taking account of the matched case-control design.

Correlations between SHBG levels at gestational weeks 10–14 and levels of cardiometabolic markers (fasting glucose, fasting insulin, C-peptide, HOMA-IR, HbA1c, CRP, total cholesterol, HDL, LDL, and triglycerides) at the subsequent visit (weeks 15–26) were estimated using partial Spearman correlation coefficient among controls adjusted for major risk factors of GDM (maternal age (years), gestational week of blood collection (weeks), pre-pregnancy BMI (kg/m²) and family history of diabetes (yes/no)).

To examine the longitudinal trajectory of SHBG levels during pregnancy, mean values of SHBG at each study visit were plotted for cases and controls separately. They were also associated with higher triglyceride (r = 0.09, P = 0.20), HDL (r = 0.11, P = 0.11), and LDL (r = 0.13, P = 0.11), but the associations were not significant.

The correlations between SHBG levels at gestational weeks 10–14 and cardiometabolic biomarkers at weeks 15–26 among the controls are shown in Table 2. Higher SHBG levels were significantly associated with lower fasting insulin (r = −0.17, P = 0.01), C-peptide (r = −0.14, P = 0.03), and HOMA-IR (r = −0.17, P = 0.01). Additionally, higher SHBG levels were significantly associated with higher total cholesterol (controls: r = 0.15, P = 0.03); they were also associated with higher triglyceride (r = 0.09, P = 0.20), HDL (r = 0.11, P = 0.11), and LDL (r = 0.13, P = 0.13), but the associations were not significant.

The longitudinal trajectory of SHBG levels during pregnancy are shown in Figure 1. SHBG levels increased progressively in both cases and controls over the study visits. SHBG levels were lower among cases compared to controls at weeks 10–14 ((204.0 ± 79.6) vs. (220.9 ± 102.5) nmol/L, P = 0.16) and at weeks 15–26 ((305.6 ± 124.3) vs. (322.7 ± 105.1) nmol/L, P = 0.14), before the screening and diagnosis of GDM, but the differences were not statistically significant. The difference diminished at weeks 23–31 and largely disappeared at weeks 33–39.

The meta-analysis of SHBG levels in pregnant women with and without GDM included 11 prospective studies with a total of 1063 pregnant women with GDM and 3098 without GDM. SHBG levels were measured between 6 and 18 weeks of gestation. The characteristics of the studies were shown in Supplemental Digital Content, Table 2 (http://links.lww.com/MFM/A4). The overall pooled estimate showed that mean SHBG levels were 41.5 nmol/L (95% confidence interval: 23.9–59.1) lower in women with GDM than those without (Fig. 2A).

Substantial heterogeneity existed among the studies (Q = 162.95, degree of freedom = 10, P < 0.01; I² = 93.9%, P < 0.01). The meta-analysis of the adjusted OR of GDM associated with SHBG levels included five studies with a total of 757 pregnant women with GDM and 2234 without GDM. SHBG levels were measured between 6 and 18 weeks of gestation. All studies adjusted for pre-pregnancy/early pregnancy BMI or another measure of adiposity (Supplemental Digital Content, Table 2, http://links.lww.com/MFM/A4). The pooled estimate showed that each 50 nmol/L increase in SHBG levels was associated with 15% lower GDM risk (OR: 0.85, 95% confidence interval: 0.76–0.95) (Fig. 2B).

Substantial heterogeneity also existed among these studies (Q = 12.98, degree of freedom = 4, P = 0.01; I² = 69.2%, P = 0.01).
Discussion

Our study found SHBG in early pregnancy to be prospectively inversely associated with insulin levels and insulin resistance in mid-pregnancy. In the meta-analysis of the prospective studies including our data, we found significant lower SHBG levels in early and mid-pregnancy among women who subsequently developed GDM compared to those who did not, and we estimated each 50nmol/L increase in SHBG levels to be significantly associated with 15% reduction of GDM risk independent of adiposity and other major risk factors of GDM.

To our knowledge, the current study is the first on SHBG and cardiometabolic biomarkers with a prospective design and has the largest sample size among existing studies. Existing studies on SHBG and cardiometabolic biomarkers among pregnant women were all cross-sectional in design, where both SHBG and cardiometabolic biomarkers were measured at the time of GDM screening and diagnosis; many of them also did not account for important confounders such as BMI. Our

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**Table 1**

Baseline characteristics and cardiometabolic biomarkers among women with GDM and their age- and race-matched controls in the NICHD fetal growth studies, singleton cohort.

| Items                        | GDM cases (n=107) | Non-GDM controls (n=214) | P  |
|------------------------------|-------------------|--------------------------|----|
| Baseline characteristics     |                   |                          |    |
| Age (years)                  | 30.5±5.7          | 30.4±5.4                 | –  |
| Race/ethnicity, n (%)        |                   |                          |    |
| Non-Hispanic white           | 25 (23.4)         | 50 (23.4)                |    |
| Hispanic                     | 15 (14.0)         | 30 (14.0)                |    |
| Asian/Pacific Islander       | 41 (38.3)         | 82 (38.3)                |    |
| Education, n (%)             |                   |                          |    |
| Less than high-school        | 17 (15.9)         | 26 (12.1)                |    |
| High-school graduate or equivalent | 15 (14.0) | 23 (10.7)                |    |
| Married/living with a partner, n (%) | 92 (86.0) | 167 (78.0)                | 0.12|
| Nulliparous, n (%)           | 48 (44.9)         | 96 (44.9)                | 1.00|
| Infant sex, n (%)            |                  |                          | 0.71|
| Family history of diabetes, n (%) | 40 (37.4)   | 48 (22.4)                | <0.01|
| Pre-pregnancy BMI, n (%)     |                  |                          | <0.01|
| <25.0 kg/m²                  | 37 (34.6)         | 123 (57.5)               |    |
| 25.0–29.9 kg/m²              | 35 (32.7)         | 56 (26.2)                |    |
| ≥ 30.0 kg/m²                 | 35 (32.7)         | 33 (15.4)                |    |
| Unknown/missing              | 0 (0.0)           | 2 (0.9)                  |    |
| Cardiometabolic biomarkers†  |                   |                          |    |
| Glucose (mg/dL)              | 96.8±42.1         | 86.1±11.4                | <0.01|
| Insulin (pmol/L)             | 205.8±248.2       | 117.8±140.7              | <0.01|
| C-peptide (mmol/L)           | 1.3±0.8           | 0.9±0.6                  | <0.01|
| HOMA-IR                      | 8.5±10.9          | 4.5±6.3                  | <0.01|
| HbA1c (mmol/mol)             | 32.0±5.0          | 35.0±5.0                 | <0.01|
| HbA1c (%)                    | 5.3±0.5           | 5.1±0.3                  | <0.01|
| CRP (mg/L)                   | 9.2±7.7           | 6.7±7.0                  | <0.01|
| Cholesterol (mg/dL)          | 182.0±28.9        | 181.0±31.0               | 0.78|
| HDL (mg/dL)                  | 58.9±15.3         | 64.9±15.5                | <0.01|
| LDL (mg/dL)                  | 90.7±28.2         | 90.2±26.9                | 0.88|
| Triglycerides (mg/dL)        | 162.4±69.0        | 129.7±48.1               | <0.01|

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**Table 2**

Spearman partial correlations (r) between SHBG levels at gestational weeks 10–14 and cardiometabolic biomarkers at weeks 15–26 among non-GDM controls in the NICHD fetal growth studies-singleton cohort.

| Items                      | P  |
|----------------------------|----|
| Fasting glucose            | –0.10| 0.17  |
| Fasting insulin            | –0.17| 0.01  |
| C-peptide                  | –0.14| 0.05  |
| HOMA-IR                    | –0.17| 0.01  |
| HbA1c (%)                  | –0.11| 0.11  |
| CRP                        | –0.02| 0.77  |
| Total cholesterol          | 0.15 | 0.03  |
| Triglyceride               | 0.09 | 0.20  |
| HDL                        | 0.11 | 0.11  |
| LDL                        | 0.11 | 0.13  |

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**Figure 1.** Mean and standard errors of SHBG concentrations at each study visit among GDM cases and non-GDM controls. Visit 1 (weeks 10–14): 104 cases and 214 controls; visit 2 (weeks 15–26): 94 cases and 212 controls; visit 3 (weeks 23–31): 102 cases and 107 controls; visit 4 (weeks 33–39): 88 cases and 103 controls. GDM: Gestational diabetes mellitus; SHBG: Sex hormone-binding globulin.
findings of significant inverse associations of SHBG with fasting insulin\textsuperscript{13–15} and insulin resistance\textsuperscript{14,15} were consistent with most of the existing cross-sectional studies; another study with nonsignificant findings reported associations of the same direction.\textsuperscript{16} Our study also found a positive association between SHBG and total cholesterol similar to reported in previous cross-sectional studies,\textsuperscript{14,32} but it is not clear if it is driven by LDL or HDL. Pregnancy-related insulin resistance usually arise in the second half of pregnancy.\textsuperscript{8} Thus SHBG in early pregnancy may indicate a
background of insulin resistance existing before pregnancy, which can be additive to the insulin resistance arising during pregnancy.9

We found suggestive evidence that SHBG levels were lower among cases compared to controls at gestational weeks 10–14 and 15–26. Such difference diminished and disappeared at weeks 23–31 and 33–39, likely because women may have changed their lifestyle or received medications after GDM diagnosis in the late second or early third trimester which improved their SHBG levels.33

Only one other study has examined SHBG levels multiple times across pregnancy in relation to GDM.18 Similar to our study, it found SHBG levels at both 11 and 17 weeks of gestation to be significantly lower among women with GDM than those without. Our findings did not reach statistical significance likely because the participants with GDM in our study were relatively healthy – none of them had major chronic conditions or a history of obstetric complications, and the majority were non-obese and did not have unfavorable lifestyle risk factors – thus they may have SHBG levels closer to those without GDM (see the mean SHBG levels by participants’ characteristics in Supplemental Digital Content, Table 3, http://links.lww.com/MFM/A4). Indeed, when analyzing the GDM cases separately by severity (treated by insulin/medications vs. not treated by insulin/medications), women with severe GDM (n=28) had significantly lower SHBG levels at both weeks 10–14 and 15–26 compared to those without GDM, whereas women with non-severe GDM (n=76) had SHBG levels similar to those without GDM at both visits (data not shown). Overall, findings from our study and the previous study18 suggest SHBG during the first and second trimester of pregnancy were consistently associated with subsequent risk of GDM.

In the meta-analysis, we found significantly lower SHBG levels among women subsequently diagnosed with GDM compared to those not diagnosed with GDM. The inverse association between SHBG levels and GDM risk held independent of adiposity and other risk factors of GDM. Previously, one meta-analysis has reported lower SHBG levels in pregnant women with GDM compared to those without.34 Our study contributed to the evidence of an inverse association between SHBG levels and GDM risk independent of adiposity. This was made possible by including four recent studies, two of which were the largest by far (with several hundred GDM cases), published since the publication of the previous meta-analysis, as well as our own data. Substantial heterogeneity exists across the studies included in the meta-analysis, which may reflect variation in population characteristics, gestational week of blood collection, the laboratory measure of SHBG, or the method of GDM ascertainment.

Several potential mechanisms may explain the inverse associations of SHBG levels with insulin resistance and GDM risk. First, hepatic production of SHBG was downregulated by monosaccharide-induced lipogenesis,35 linking lower SHBG levels with liver fat content13 and liver steatosis16; ectopic fat deposition in the liver contributes to dyslipidemia37 and insulin resistance,38 and subsequently higher GDM risk. Second, SHBG is downregulated by proinflammatory cytokines and upregulated by adiponectin,39 which is also linked to GDM risk.40 Although Mendelian randomization studies supported a causal effect of SHBG levels in the development type 2 diabetes,6,41 mechanisms consistent with a direct involvement of SHBG in the etiology of type 2 diabetes is yet to be discovered.

Our study has several strengths. First, it is the first study to examine the prospective associations between SHBG levels and a comprehensive panel of cardiometabolic biomarkers. Second, it had longitudinal data collection which enabled us to investigate the levels of SHBG across pregnancy in relation to GDM risk. Third, we have controlled for potential confounding from major risk factors of GDM when examining the association of SHBG levels with cardiometabolic biomarkers and GDM risk. Lastly, the study synthesized existing prospective evidence in a meta-analysis of SHBG levels and GDM risk. One limitation of our study was the low-risk profile of our cohort, which may result in limited generalizable to other populations. However, the meta-analysis combined our data with other existing studies that did not have inclusion criteria that select low-risk women, thus may better reflect the association between SHBG and GDM risk in the general population of pregnant women.

In conclusion, this study found higher SHBG levels in early pregnancy to be prospectively inversely associated with insulin levels and insulin resistance in mid-pregnancy. In the meta-analysis of prospective studies, we also found an inverse association between SHBG levels and GDM risk independent of adiposity. As insulin resistance in pregnancy may play a role gestational hypertension and pre-eclampsia,10 and both GDM and pre-eclampsia10 are associated with adverse perinatal outcomes, SHBG levels may serve as a marker for identification of high-risk pregnancies in early pregnancy.

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Author Contributions
Meng-Ying Li analyzed data and wrote the first draft of the manuscript. Shristi Rawal contributed to the conceptualization of the study and revised the manuscript Stefanie N. Cui-Lin Zhang obtained funding, designed and oversaw the study, and revised the manuscript. All authors interpreted the results, revised the manuscript for impor-
tant intellectual content, and approved the final version of the manuscript. Meng-Ying Li and Cui-Lin Zhang 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.

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Conflicts of Interest

None.

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