Insulin sensitivity, β cell function, and adverse pregnancy outcomes in women with gestational diabetes

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Abstract

Background: The potential impact of β cell function and insulin sensitivity on adverse pregnancy outcomes in women with gestational diabetes mellitus (GDM) remains uncertain. We aimed to investigate the association between β cell dysfunction, insulin resistance, and the composite adverse pregnancy outcomes.

Methods: This observational study included 482 women diagnosed with GDM during pregnancy. Quantitative metrics on β cell function and insulin sensitivity during pregnancy were calculated using traditional equations. The association of β cell dysfunction and insulin resistance with the risk of the composite adverse pregnancy outcomes was investigated using multivariable-adjusted logistic regression models.

Results: Multivariable-adjusted odds ratios (ORs) of adverse pregnancy outcomes across quartiles of homeostatic model assessment for insulin resistance (HOMA-IR) were 1.00, 0.95, 1.34, and 2.25, respectively (*P* for trend = 0.011). When HOMA-IR was considered as a continuous variable, the multivariable-adjusted OR of adverse pregnancy outcomes was 1.34 (95% confidence interval 1.16–1.56) for each 1-unit increase in HOMA-IR. Multivariable-adjusted ORs of adverse pregnancy outcomes across quartiles of homeostatic model assessment for β cell function (HOMA-β) were 1.00, 0.51, 0.60, and 0.53, respectively (*P* for trend = 0.068). When HOMA-β was considered as a continuous variable, the multivariable-adjusted OR of adverse pregnancy outcomes was 0.57 (95% CI 0.24–0.90) for each 1-unit increase in HOMA-β. However, other quantitative metrics were not associated with the composite adverse pregnancy outcomes.

Conclusions: We demonstrated a significant association of β cell function and insulin sensitivity with the risk of adverse pregnancy outcomes. We have provided additional evidence on the early identification of adverse pregnancy outcomes besides the glycemic values.

Keywords: β cell function; Insulin sensitivity; Adverse pregnancy outcomes

Introduction

Gestational diabetes mellitus (GDM) is a specific type of diabetes that affects women during pregnancy who were not diagnosed with diabetes before pregnancy.[1] Women with prior GDM will have a high risk of recurrent GDM after the first pregnancy and postpartum metabolic disorders.[2-5] GDM itself may be associated with a series of adverse pregnancy outcomes including preeclampsia, macrosomia, preterm delivery, and primary cesarean section.[6,7] Previous studies have shown that both β cell function and insulin sensitivity may be involved in the pathogenesis of GDM.[8] For a healthy pregnancy, insulin resistance also occurs in favor of the growth of the fetus.[9] Chronic insulin resistance may occur during early pregnancy, resulting in asymptomatic metabolic disorders even before parturition.[10] A recent study has shown that increased insulin resistance was associated with adverse pregnancy outcomes especially preterm delivery in women with GDM.[11] However, there is always a lack of discussion on β-cell dysfunction in the background of insulin resistance. Hence, we aimed to investigate the

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association of β cell function and insulin sensitivity with the risk of adverse pregnancy outcomes and to further discuss the potential impact of different pathophysiologic patterns on adverse pregnancy outcomes.

Methods

Ethical approval

This study was approved by the Institutional Review Board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (No. 2020-093). All patients signed informed consent.

Study population

This was a single-center, observational study. The detailed information on the study population has been described previously.[6] Women who gave birth to their children in the Department of Obstetrics and Gynecology, Shanghai Jiao Tong University affiliated Sixth People's Hospital during 2015 to 2017 were screened. Women were eligible for the study if they (1) were ≥20 years old; (2) had complete electronic medical records during the whole period of pregnancy; and (3) had received a one-step 2-h 75 g oral glucose tolerance test between 24 and 28 gestational weeks. Women were excluded from the study if they (1) had chronic kidney or liver diseases; (2) had multiple pregnancies; (3) were diagnosed with diabetes before pregnancy; (4) received insulin therapy during pregnancy.

One-step oral glucose tolerance test

Pregnant women received a one-step 2-h 75 g oral glucose tolerance test after a morning fasting between 24 and 28 weeks of pregnancy. Plasma samples from all subjects were obtained for measurements of plasma glucose levels. Serum samples were obtained for measurements of serum insulin levels. Blood samples at fasting, 30 min post load, 1 h post load, and 2 h post load were collected. Plasma glucose levels were measured by the glucose oxidase method (Kehua China Shanghai Bioengineering Co., Ltd., Shanghai, China) using the Charisma 2000 biochemical automatic analyzer. Serum insulin levels were measured by electro-chemiluminescence immunoassay (Roche insulin assay) via Cobas e 601 automatic analyzer.

Quantitative metrics for β cell function and insulin sensitivity

β cell function was evaluated by the homeostatic model assessment for β cell function (HOMA-β) as HOMA-β = fasting insulin levels × 20/(fasting glucose levels – 3.5).[12] Basal insulin sensitivity was evaluated by the homeostatic model assessment for insulin resistance (HOMA-IR) as HOMA-IR = fasting insulin levels × fasting glucose levels/22.5.[12] Mean glucose or insulin levels were calculated as the mean of all measured glucose levels and insulin levels (ie, fasting, 30 min, 1-h, and 2-h glucose and insulin levels). Insulin sensitivity index (ISI) was calculated as M/(mean glucose levels × lg [mean insulin levels]), in which M stands for the glucose uptake rate that was calculated as 75,000/120 + (fasting glucose levels – 2 h glucose levels) × 1.15 × 180 × 0.19 × body weight/120.[13] Difference in insulin 30 min (ΔI_{30}) was defined as 30-min insulin levels – fasting insulin levels. Difference in glucose 30 min (ΔG_{30}) was defined as 30-min glucose levels – fasting glucose levels.

Routine antenatal care

Women in early pregnancy received their first clinic visit at 6 weeks. Individual electronic medical records were then initiated. Routine antenatal care included follow-up visits every 8 weeks during the first trimester, every 4 weeks during the second trimester, and every week during the third trimester. All the women who were diagnosed with GDM received a comprehensive management including instructions on diet and physical activity. Electronic medical records were obtained by a blinded doctor, including information on height, weight, number of pregnancies, parities, medications, and prior history of diseases.

Definitions

GDM was diagnosed according to the 2010 International Association of Diabetes and Pregnancy Study Group criteria (fasting glucose ≥5.1 mmol/L; or 1-h glucose ≥10 mmol/L; or 2-h glucose ≥8.5 mmol/L).[14]

Outcomes

The composite adverse pregnancy outcomes were defined as maternal outcomes (including primary cesarean section, preeclampsia [systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on two or more occasions with at least 6 h apart and proteinuria ≥1+ on dipstick or ≥300 mg on 24-h urine collection] and postpartum hemorrhage [over 500 mL for vaginal delivery and 1000 mL for cesarean section]) and neonatal outcomes (including large for gestational age [birth weight >90th percentile], small for gestational age [birth weight <10th percentile], macrosomia [birth weight of the newborn ≥4000 g], and preterm delivery).[6,15]

Statistical analysis

The general characteristics (continuous and categorical variables) were investigated using the chi-squared test or Student's *t*-test. Logistic regression models were used to assess the association of metrics of β cell function and insulin sensitivity at 24 to 28 gestational weeks with the risk of adverse pregnancy outcomes. All analyses were adjusted for age (Model 1), and then for pre-pregnancy body mass index, family history of diabetes, infant's sex, and parities (Model 2). $P < 0.05$ was considered statistically significant. All statistical analyses were performed by IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 1976 women underwent screening and 498 were diagnosed with GDM. Finally, 482 women with GDM were included in the present analysis. The characteristics of

Table 1: Characteristics of women with GDM.

Variables	All participants ($N = 482$)	With adverse pregnancy outcomes ($N = 289$)	Without adverse pregnancy outcomes ($N = 193$)	*P* value
Maternal characteristics				
Age (years)	32.20 ± 4.29	31.90 ± 4.30	32.20 ± 4.28	0.409
Pre-pregnancy BMI (kg/m^2)	23.30 ± 2.94	23.40 ± 2.87	23.10 ± 3.06	0.450
BMI at 24–28 gestational weeks (kg/m^2)	28.10 ± 3.06	28.20 ± 2.99	27.90 ± 3.18	0.353
Number of pregnancies (%)				0.389
1	42.9	42.8	43.0	
2	26.8	28.4	24.4	
≥3	30.3	28.8	32.6	
Parity (%)				0.028
0	67.0	71.6	60.1	
1	30.7	26.6	36.8	
≥2	2.3	1.8	3.1	
Fasting glucose (mmol/L)	4.86 ± 0.62	4.99 ± 0.68	4.68 ± 0.47	<0.001
30-min glucose (mmol/L)	8.27 ± 1.17	8.34 ± 1.27	8.16 ± 1.01	0.099
1-h glucose (mmol/L)	10.10 ± 1.40	10.20 ± 1.45	9.95 ± 1.31	0.063
2-h glucose (mmol/L)	8.68 ± 1.60	8.69 ± 1.71	8.66 ± 1.42	0.800
Fasting insulin (mU/L)	11.50 ± 6.51	12.40 ± 7.31	10.10 ± 4.80	<0.001
30-min insulin (mU/L)	66.7 ± 39.9	67.7 ± 42.3	65.2 ± 36.0	0.490
1-h insulin (mU/L)	90.3 ± 54.7	92.7 ± 57.2	86.7 ± 50.7	0.239
2-h insulin (mU/L)	99.3 ± 65.5	99.8 ± 62.6	98.6 ± 69.7	0.837
HOMA-IR	2.55 ± 1.64	2.82 ± 1.86	2.14 ± 1.15	<0.001
HOMA-β	184 ± 104	185 ± 115	183 ± 86	0.859
ISI	58.5 ± 17.8	58.1 ± 19.3	59.2 ± 15.3	0.474
$\Delta I_{30}/\Delta G_{30}$	20.2 ± 74.5	23.1 ± 95.9	16.0 ± 8.8	0.307
Postpartum hemorrhage (mL)	247 ± 138	268 ± 171	218 ± 47	<0.001
Family history of diabetes (%)	25.7	25.3	26.4	0.156
Newborn				
Birth weight (g)	3422 ± 643	3484 ± 778	3329 ± 337	0.009
Birth length (cm)	49.90 ± 1.65	49.90 ± 2.11	49.90 ± 0.42	0.972
Gestational age at delivery (weeks)	38.60 ± 1.89	38.30 ± 2.25	39.10 ± 1.00	<0.001
Apgar score	9.95 ± 0.38	9.92 ± 0.49	10.00 ± 0.00	0.020
Boys (%)	53.1	54.7	50.8	0.401

BMI: Body mass index; GDM: Gestational diabetes mellitus; HOMA-IR: Homeostatic model assessment for insulin resistance; HOMA-β: Homeostatic model assessment for β-cell function; ISI: Insulin sensitivity index. $\Delta I_{30}/\Delta G_{30}$: Difference in insulin 30 min (ΔI_{30}) was defined as 30-min insulin levels – fasting insulin levels; Difference in glucose 30 min (ΔG_{30}) was defined as 30-min glucose levels – fasting glucose levels.

women with GDM are listed in Table 1. Of 482 women with GDM, 289 (60.0%) had one of the adverse pregnancy outcomes. Compared with women without adverse pregnancy outcomes, those with adverse pregnancy outcomes had higher levels of fasting glucose (4.99 ± 0.68 *vs.* 4.68 ± 0.47 mmol/L, $P < 0.001$) and HOMA-IR (2.82 ± 1.86 *vs.* 2.14 ± 1.15, $P < 0.001$); their offspring had a heavier weight at delivery (3484 ± 778 *vs.* 3329 ± 337 g, $P = 0.009$), had shorter gestational age at delivery (38.30 ± 2.25 *vs.* 39.10 ± 1.00 weeks, $P < 0.001$), and lower Apgar scores (9.92 ± 0.49 *vs.* 10.0 ± 0.00, $P = 0.020$).

Multivariable-adjusted (age, pre-pregnancy body mass index, family history of diabetes, infant's sex, and parities) odds ratios (ORs) of the composite adverse pregnancy outcomes across quartiles of HOMA-IR were 1.00, 0.95 (95% confidence interval [CI] 0.56–1.60), 1.34 (95% CI 0.78–2.30), and 2.25 (95% CI 1.28–3.96), respectively (P for trend = 0.011) [Table 2]. When HOMA-IR was considered as a continuous variable, the multivariable-adjusted OR of the composite adverse pregnancy outcomes was 1.35 (95% CI 1.18–1.55) for each 1-unit increase in HOMA-IR. Multivariable-adjusted ORs of the composite adverse pregnancy outcomes across quartiles of HOMA-β were 1.00, 0.51 (95% CI 0.29–0.89), 0.60 (95% CI 0.50–1.05), and 0.53 (95% CI 0.30–0.91), respectively (P for trend = 0.068). When HOMA-β was considered as a continuous variable, the multivariable-adjusted OR of adverse pregnancy outcomes was 0.57 (95% CI 0.24–0.90) for each 1-unit increase in HOMA-β. However, neither ISI nor $\Delta I_{30}/\Delta G_{30}$ was associated with the composite adverse pregnancy outcomes in quartiles and in continuous variables.

When HOMA-IR, HOMA-β, ISI, and $\Delta I_{30}/\Delta G_{30}$ were analyzed in the logistic regression models of the specific adverse pregnancy outcomes, each 1-unit increase in HOMA-IR was associated with the risks of preterm delivery (OR 1.23, 95% CI 1.07–1.41). However, no association between HOMA-IR and other specific adverse

Table 2: ORs of the composite adverse pregnancy outcomes by different metrics of β cell function and insulin sensitivity.

Items	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* value for trend	Each 1-unit increase
HOMA-IR						
Model 1	1.00	1.04 (0.63–1.73)	1.58 (0.95–2.64)	2.44 (1.43–4.18)	0.003	1.37 (1.19–1.58)
Model 2	1.00	0.95 (0.56–1.60)	1.34 (0.78–2.30)	2.25 (1.28–3.96)	0.011	1.34 (1.16–1.56)
HOMA-β*						
Model 1	1.00	0.51 (0.30–0.87)	0.64 (0.38–1.09)	0.59 (0.35–1.01)	0.084	0.64 (0.32–0.96)
Model 2	1.00	0.51 (0.29–0.89)	0.60 (0.35–1.05)	0.53 (0.30–0.91)	0.068	0.57 (0.24–0.90)
ISI*						
Model 1	1.00	0.99 (0.58–1.70)	0.51 (0.30–0.85)	0.72 (0.42–1.21)	0.030	0.34 (0.07–1.64)
Model 2	1.00	1.00 (0.57–1.76)	0.53 (0.31–0.90)	0.82 (0.47–1.42)	0.059	0.47 (0.09–2.40)
$\Delta I_{30}/\Delta G_{30}$*						
Model 1	1.00	0.56 (0.33–0.94)	0.85 (0.50–1.43)	1.02 (0.60–1.73)	0.078	1.06 (0.56–2.02)
Model 2	1.00	0.46 (0.27–0.80)	0.76 (0.44–1.31)	0.89 (0.51–1.55)	0.029	0.94 (0.49–1.80)

Model 1 adjusted for age. Model 2 adjusted for age, pre-pregnancy BMI, family history of diabetes, infant's sex, and parities. * Data were analyzed after logarithmic transformation. BMI: Body mass index; HOMA-β: Homeostatic model assessment for β cell function; HOMA-IR: Homeostatic model assessment for insulin resistance; ISI: Insulin sensitivity index; ORs: Odds ratios. $\Delta I_{30}/\Delta G_{30}$: Difference in insulin 30 min/difference in glucose 30 min.

Table 3: ORs of specific adverse pregnancy outcomes by different metrics of β cell function and insulin sensitivity.

Items	Primary cesarean section	Preeclampsia	Postpartum hemorrhage	LGA	SGA	Preterm delivery
HOMA-IR						
Model 1	1.05 (0.94–1.18)	1.04 (0.81–1.34)	1.07 (0.75–1.51)	1.12 (0.94–1.33)	1.05 (0.85–1.29)	1.23 (1.08–1.40)
Model 2	1.08 (0.96–1.22)	0.99 (0.75–1.30)	1.02 (0.70–1.48)	1.11 (0.93–1.32)	1.04 (0.84–1.28)	1.23 (1.07–1.41)
HOMA-β*						
Model 1	0.75 (0.32–1.74)	1.12 (0.14–9.09)	6.74 (0.42–108)	2.03 (0.42–9.66)	0.30 (0.06–1.56)	0.71 (0.53–0.89)
Model 2	0.61 (0.25–1.50)	0.82 (0.09–7.18)	9.79 (0.47–206)	2.12 (0.43–10.4)	0.29 (0.06–1.55)	0.75 (0.54–0.96)
ISI*						
Model 1	2.97 (0.60–14.8)	0.29 (0.01–18.1)	0.06 (0.01–20.8)	0.16 (0.10–3.64)	0.03 (0.01–0.98)	0.68 (0.08–5.98)
Model 2	3.97 (0.69–22.8)	0.48 (0.10–32.0)	0.11 (0.01–41.1)	0.17 (0.10–4.36)	0.03 (0.01–1.04)	0.71 (0.08–6.62)
$\Delta I_{30}/\Delta G_{30}$*						
Model 1	1.39 (0.72–2.68)	1.23 (0.26–5.83)	4.26 (0.82–22.3)	0.66 (0.20–2.22)	0.18 (0.05–1.62)	0.90 (0.37–2.18)
Model 2	1.27 (0.64–2.53)	1.02 (0.21–5.08)	6.50 (0.11–38.0)	0.69 (0.20–2.40)	0.17 (0.05–1.63)	0.99 (0.40–2.46)

Model 1 adjusted for age. Model 2 adjusted for age, pre-pregnancy BMI, family history of diabetes, infant's sex, and parities. * Data were analyzed after logarithmic transformation. BMI: Body mass index; HOMA-β: Homeostatic model assessment for β cell function; HOMA-IR: Homeostatic model assessment for insulin resistance; ISI: Insulin sensitivity index; LGA: Large for gestational age; ORs: Odds ratios; SGA: Small for gestational age. $\Delta I_{30}/\Delta G_{30}$: Difference in insulin 30 min/difference in glucose 30 min.

pregnancy outcomes was observed including the primary cesarean section (OR 1.08, 95% CI 0.96–1.22), preeclampsia (OR 0.99, 95% CI 0.75–1.30), postpartum hemorrhage (OR 1.02, 95% CI 0.70–1.48), LGA (OR 1.11, 95% CI 0.93–1.32), and SGA (OR 1.04, 95% CI 0.84–1.28). Each 1 SD increase in HOMA-β was also associated with the risk of preterm delivery after multivariable adjustment (OR 0.75, 95% CI 0.54–0.96) [Table 3]. Neither ISI nor ΔI30/ΔG30 was associated with the specific adverse pregnancy outcomes.

As GDM was manifested with β cell dysfunction on the basis of insulin resistance, we further performed a subsequent analysis based on the 50th percentile (P_{50}) of HOMA-IR and HOMA-β (Group 1: HOMA-IR ≥ P_{50} and HOMA-β < P_{50}, Group 2: HOMA-IR ≥ P_{50} and HOMA-β ≥ P_{50}, Group 3: HOMA-IR < P_{50} and HOMA-β < P_{50}, Group 4: HOMA-IR < P_{50} and HOMA-β ≥ P_{50}). GDM women with HOMA-IR < P_{50} and HOMA-β ≥ P_{50} had the lowest odds of preterm delivery (OR 0.30, 95% CI 0.12–0.76) and the composite adverse pregnancy outcome (OR 0.29, 95% CI 0.15–0.56) [Table 4].

Discussion

In this observational study of 482 women with GDM during pregnancy, we demonstrated a significant association of HOMA-IR and HOMA-β with the risk of adverse pregnancy outcomes. However, ISI and $\Delta I_{30}/\Delta G_{30}$ were not associated with the risk of adverse pregnancy outcomes. As expected, we demonstrated a significant negative association between HOMA-β and adverse pregnancy outcomes. This study has added new evidence to the pathophysiologic background of GDM and has provided new insights that β cell function may be also important during the course of GDM.

GDM is a common disease during the perinatal period in women of child-bearing. Epidemiologic studies have shown that the prevalence of GDM in China was 8.1% in 2012 and this prevalence has an increasing tendency during recent years.[16] Traditional risk factors associated with the occurrence of GDM include overweight or obesity before pregnancy, excessive gestational weight gain, family history of diabetes, elderly pregnancy

Table 4: ORs of adverse pregnancy outcomes among patients with different subgroups of β cell function and insulin sensitivity.

Items	Group 1	Group 2	Group 3	Group 4
Primary cesarean section				
Model 1	1.00	0.90 (0.52–1.56)	0.87 (0.50–1.51)	0.90 (0.48–1.66)
Model 2	1.00	0.82 (0.46–1.48)	0.85 (0.47–1.54)	0.70 (0.36–1.34)
Preeclampsia				
Model 1	1.00	1.28 (0.32–5.10)	1.39 (0.35–5.56)	0.61 (0.10–3.77)
Model 2	1.00	1.29 (0.31–5.27)	1.61 (0.39–6.55)	0.61 (0.10–3.86)
Postpartum hemorrhage*				
Model 1	1.00	2.14 (0.43–10.6)	0.28 (0.03–3.16)	–
Model 2	1.00	2.72 (0.51–14.4)	0.32 (0.03–3.76)	–
LGA				
Model 1	1.00	1.44 (0.53–3.88)	0.86 (0.30–2.50)	0.79 (0.23–2.70)
Model 2	1.00	1.46 (0.54–3.96)	0.85 (0.29–2.50)	0.82 (0.24–2.84)
SGA				
Model 1	1.00	0.38 (0.14–1.04)	0.60 (0.25–1.48)	0.38 (0.12–1.27)
Model 2	1.00	0.38 (0.14–1.05)	0.61 (0.24–1.51)	0.39 (0.12–1.31)
Preterm delivery				
Model 1	1.00	0.62 (0.32–1.20)	0.53 (0.27–1.04)	0.29 (0.12–0.73)
Model 2	1.00	0.63 (0.32–1.24)	0.51 (0.26–1.01)	0.30 (0.12–0.76)
All outcomes				
Model 1	1.00	0.52 (0.29–0.94)	0.35 (0.20–0.63)	0.32 (0.17–0.61)
Model 2	1.00	0.50 (0.27–0.91)	0.35 (0.19–0.63)	0.29 (0.15–0.56)

Model 1 adjusted for age. Model 2 adjusted for age, pre-pregnancy BMI, family history of diabetes, infant's sex, and parities. Group 1: HOMA-IR ≥ P_{50} and HOMA-β < P_{50}. Group 2: HOMA-IR ≥ P_{50} and HOMA-β ≥ P_{50}. Group 3: HOMA-IR < P_{50} and HOMA-β < P_{50}. Group 4: HOMA-IR < P_{50} and HOMA-β ≥ $P_{5.0}$. *There is no case in Group 4. BMI: Body mass index; HOMA-β: Homeostatic model assessment for β cell function; HOMA-IR: Homeostatic model assessment for insulin resistance; LGA: Large for gestational age; ORs: Odds ratios; P_{50}: 50th percentile; SGA: Small for gestational age.

(maternal age), etc.[1,17,18] Women with GDM have a tremendously increased risk of adverse pregnancy outcomes and later postpartum metabolic disorders such as diabetes and metabolic syndrome.[2,19,20] Genetic susceptibility, insulin resistance, and chronic inflammation are commonly considered the main basis of pathogenesis and etiology of GDM.[8] However, one human glucose clamp study found that women with GDM had a 67% reduction in pancreatic β cell compensation for insulin resistance at the late stage of pregnancy compared with normal pregnant women.[21] Decreased β cell function is always not mainly discussed in many population-based studies. In this study, in addition to insulin resistance, we also found that improved β cell function during pregnancy was protective against adverse pregnancy outcomes.

The evidence linking the contribution of insulin resistance during pregnancy to maternal or offspring outcomes is concrete. One study of 2647 Chinese women diagnosed with GDM has confirmed the association between insulin resistance and adverse pregnancy outcomes.[22] The findings were independent of pre-pregnancy body mass index. However, maternal β cell function during pregnancy was not considered in that study. Another study of 710 women with GDM from China also demonstrated a significant association between HOMA-IR and adverse pregnancy outcomes, especially hypertensive disorders of pregnancy and large for gestational age.[11] The investigators did not consider maternal β cell function in the analysis either. We presented a supplementary result that both insulin sensitivity and β cell function during pregnancy were involved in the occurrence of adverse pregnancy outcomes. A beneficial pattern that women were represented with lower HOMA-IR and higher HOMA-β during the second trimester of pregnancy may finally result in a better outcome especially for preterm delivery and large for gestational age.

Another two metrics of β cell function and insulin sensitivity (ISI and $\Delta I_{30}/\Delta G_{30}$) showed negative results in the analysis. ISI indicates the insulin sensitivity at postprandial status while $\Delta I_{30}/\Delta G_{30}$ is the pancreatic insulin response to glucose load within 30 min. These results supported the hypothesis that post load insulin sensitivity and β cell function were not the key factors that affected glycemic homeostasis. Physiological insulin resistance might be observed during a healthy pregnancy. β cells can compensate for the reduced insulin sensitivity either in size or in mass.[8] Progressive β cell dysfunction accompanied by chronic insulin resistance may eventually result in uncompensated hyperglycemia and contribute to the presence of GDM. Given the pathophysiology of GDM, it is not rigorous to analyze insulin resistance independently of β cell function. Actually, a recent study has shown that insulin-resistant gestational glucose intolerance is a high-risk subtype for adverse pregnancy outcomes in the US population.[23] In the present study with a comprehensive analysis among Chinese women with GDM, insulin sensitivity and β cell function in terms of both basal and post load status were investigated, of which the basal insulin sensitivity and β cell function were superior to the post load metrics in the association with adverse pregnancy outcomes.

The major strength of the study is that we have used traditional equations that have already been well established and have provided sufficient information on the association between insulin sensitivity, β cell function, and adverse pregnancy outcomes in women with GDM. Lifestyle intervention should be initiated as early as possible to improve insulin sensitivity and preserve the residual β cell function. Several limitations should also be indicated. Firstly, a moderately limited sample size in one single center may bias the external generalization. Secondly, there is a lack of information on lifestyle and medications after the diagnosis of GDM. Finally, the prevalence of adverse pregnancy outcomes (~60%) was a bit higher in our study population than the average level that was previously reported in a systematic review,[7] representing a population of pregnant women at high risk. Our findings should thus be validated in other populations with a larger sample size and a more proper prevalence of outcomes.

In conclusion, we demonstrated a significant association between β cell function, insulin sensitivity, and adverse pregnancy outcomes. We have provided new evidence on the early identification of adverse pregnancy outcomes independent of the glycemic values.

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Conflicts of interest

None.

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