High Level of Complement Factor Ba Within 11 to 17 Weeks of Gestation Increases the Risk of Subsequent Gestational Diabetes: A Propensity Score-Matched Study

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Abstract

Background: Several studies have shown that the over activation of complement factor B(CFB) was related to obesity, insulin resistance(IR) and type 2 diabetes mellitus. This study was to assess whether circulating complement factor Ba (CFBa) within 11 to 17 weeks of gestation is associated with subsequent gestational diabetes mellitus (GDM) or not.

Methods: Biochemical parameters and blood samples were collected from 399 pregnant women within 11 to 17 weeks of gestation. At 24 to 28 weeks of pregnancy, all participants underwent 75-g oral glucose tolerance test (fasting for more than 8 hours before blood sampling) and were assigned to GDM group(n=80) and normal control group(n=319). Perinatal data were collected after delivery. A propensity score-matched (PSM) analysis was performed to reduce the impact of confounding factors on glucose metabolism during pregnancy between the two groups.

Results: Two groups of 74 well-matched patients who maintained balance in terms of baseline characteristics. The levels of CFBa in pregnant women who later developed GDM were significantly higher than those in healthy pregnant women [0.4(0.1-0.8) *vs.* 0.2(0.2-0.3), *P*=0.031]. Logistic regression results confirmed that the level of CFBa was an independent influencing factor for the occurrence of GDM (OR=1.52, 95% CI: 1.25-1.85, *P*=0.000). Further grouping according to the quartile of CFBa level, it was found that the incidence of GDM in category 3 was markedly higher than that in the first and the second categories.

Conclusions: High level of the CFBa within 11 to 17 weeks of gestation increased the risk of subsequent GDM, and maybe a biomarker for predicting GDM.

Background

Gestational diabetes mellitus (GDM) refers to the abnormal glucose metabolism found for the first time during pregnancy without reaching the level of dominant diabetes[1]. The incidence of GDM fluctuates widely due to differences in geographical area, ethnicity and diagnostic criteria[2, 3]. Long-term uncontrolled blood glucose in patients with GDM may have serious adverse effects on the mothers and fetus, such as preeclampsia, cesarean section, macrosomia, premature rupture of membrane, neonatal hypoglycemia and so on[4, 5]. At present, the exact pathogenesis of GDM is still not throughly clear, but the IR and the chronic subclinical inflammatory process caused by immune system dysfunction are considered as the main factors for the development of GDM[6]. In recent years, the innate immune system was shown to be closed related to the metabolic pathway[7].

The complement system is an important part of innate immune system. It can protect host against pathogens and connect innate and adaptive immune response[8]. Abnormal regulation of complement system or deficiency of complement can increase the susceptibility of chronic inflammatory diseases and infections[9]. The complement cascades are activated in three different ways: the classical pathway, the alternative pathway and the mannose binding lectin way. Among them, the alternative pathway has

attracted much more attention because of its potential role in metabolic diseases such as hypertension, type 2 diabetes mellitus, as well as dyslipidemia, and CFB is critical for its activation[10–12]. CFB is a single chain glycoprotein, which consists of five protein domains. After the alternative pathway of complement system was activated, factor B was cleaved into two fragments, Ba and Bb. The molecular weight of Ba fragment is about 30000 dalton, which is composed of 234 amino acids and comes from the N-terminal part of the precursor molecule of factor B[13, 14]. At present, many studies have confirmed that excessive activation of CFB was closely related to obesity, IR and type 2 diabetes mellitus[15, 16]. but its role in GDM has not been elucidated. The main purpose of this study was to assess the effect of circulating CHBa (the activation product of CHB) level within 11 to 17 weeks of gestation on the risk of subsequent GDM.

Methods

Participants

This is a nested case-control study of pregnant women. From February 2017 to April 2019, a total of 399 pregnant women were enrolled in the department of Obstetrics and Gynecology of Jinshan District Central Hospital of Shanghai Jiao-Tong University Affiliated 6th People's Hospital. At 24 to 28 weeks of pregnancy, all pregnant women underwent 75-g oral glucose tolerance test (fasting for more than 8 hours before blood sampling). According to criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and the WHO[17, 18], GDM can be diagnosed when the blood glucose meets or exceeds any of the following values: fasting blood glucose: 5.1 mmol/L, 1-hour blood glucose: 10.0 mmol/L, 2-hour blood glucose: 8.5 mmol/L. According to the above criteria, the pregnant women were divided into two groups including the GDM group (n = 80) and the normal control group (n = 319). The women who started their first prenatal test in early pregnancy until delivery with complete data were included. Pregnant women who meet the following conditions should be excluded: (1)previous history of diabetes; (2)severe acute and chronic infections; (3)autoimmune diseases; (4)multiple pregnancy. The study was approved by the Ethics Committee of Jinshan District Central Hospital of Shanghai Jiao-Tong University Affiliated 6th People's Hospital. Written informed consent was signed by all participants.

Data and serum sample collection

All participants were required to complete a questionnaire to collect background information including family history of diabetes mellitus, previous disease history, current disease, reproductive history and drug treatment. During the examination, Height and weight were assessed in a standard form by the same physician. Body mass index (BMI) was calculated in the following formula: BMI = body weight(Kg)/Height(m)^2. Perinatal data of 399 pregnant women were collected. Newborn with a birth weight of 4000 g or more is defined as macrosomia. Premature rupture of membranes refers to natural rupture of membranes before labor. Blood samples were collected after fasting for more than 8 hours at night before the first antenatal examination and the serum were store at -80℃.

Laboratory measurements

Glycosylated hemoglobin A1c (HbA1c) was detected by high performance liquid chromatography (HPLC). Other indicators used to evaluate liver and kidney function, such as alanine aminotransferase(ALT), aspartate aminotransferase (AST), γ-glutamyltransferase(γ-GT), blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA) and blood lipids including total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C) were all measured by enzymatic method. Blood glucose was measured by glucose oxidase method. The frozen (-80℃) serum was quickly thawed in a 37℃water bath until just thawed, and then transferred to ice. Serum Ba concentrations were measured in duplicate using a MicroVue Ba Enzyme Immunoassay Kit (Quidel Corporation, USA, A033). The linear range of the standard was 0.033–3.239 ng/ml. The intra-assay and inter-assay coefficients of variation (CV) were 2.3% and 8.1% respectively. The control values were in the control range.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) when they conform to normal distribution or as median (interquartile range [IQR] 25th percentile-75th percentile) when they do not. Categorical variables were presented as the number (percentage). Kolmogorov-Smirnov test was used to test whether continuous variables conform to normal distribution. Comparison between the two groups using the two-tailed Student's test or the Mann-Whitney U test depends on whether the continuous variables followed a normal distribution. Categorical variables were compared by chi-squared test or Fisher's exact test. A propensity score-matched (PSM) analysis was done to balance the distribution of baseline characteristics between the two groups. The included covariables were as follows: age, family history of diabetes, prepregnancy BMI, ALT, AST, γ-GT, BUN, Cr, UA, TC, TG, LDL, miscarriage and reproductive history. Pairs of GDM and the control groups were derived using 1:1 greedy nearest neighbor matching with a caliper of 0.05. This strategy resulted in 74 matched pairs in each group. To verify the impact of the level of CFBa on subsequent GDM, a logistic regression analysis performed. All statistical analyses were performed by SPSS 26.0 (SPSS Inc., Chicago, IL). A two-sided *P*-value < 0.05 was considered statistically significant.

Results

The baseline clinical characteristics and biochemical indexes between two groups

The clinical characteristics of all pregnant women were shown in Table 1, including the GDM group (n = 80) and the control group (n = 319). There was no significant difference in AST, γ-GT, BUN, Cr between the two groups. The pregnant women in the GDM group had significantly higher age, incidence of family history of diabetes, prepregnancy BMI, HbA1c, ALT, UA, TC, TG, LDL, reproductive history, fasting blood glucose, 1-hour blood glucose, 2-hour blood glucose levels (all $P < 0.05$). After that, regular follow-up was carried out until delivery. The perinatal data of all pregnant women were shown in Table 2. Gestational age at delivery, the proportion of premature rupture of membranes, the rate of intrauterine distress, amount of postpartum hemorrhage, the weight of newborn, the incidence of caesarean section, apgar

score showed no significant difference between the two groups. The incidence of macrosomia in GDM group was significantly higher than that in control group (11.25% *vs.* 4.39%, $P = 0.037$).

Table 1
Comparison of clinical characteristics and biochemical indexes between GDM group and control group under unmatched

	Total population (n = 399)	Control(n = 319)	GDM(n = 80)	*P* value
Age(years)	28(25–31)	27(25–30)	29(26–31)	0.012
Family history of diabetes; n(%)	11(2.76)	4(1.25)	7(8.75)	0.002
Prepregnancy BMI(Kg/m^2)	21.1(19.5–23.1)	20.8(19.1–22.8)	21.7(20.3–24.7)	0.001
Miscarriage; n(%)	71(17.79)	38(11.91)	33(41.25)	0.000
Reproductive history; n(%)	74(18.55)	34(10.66)	40(50)	0.000
HbA1c(%)	5.1(5.0-5.3)	5.1(4.9–5.2)	5.2(5.0-5.4)	0.000
ALT(U/L)	13.0(9.0–21.0)	12.0(9.0–20.0)	14.5(11.0-27.5)	0.025
AST(U/L)	16.0(13.5–19.3)	16.0(14.0-19.2)	16.0(13.0-20.6)	0.927
γ-GT(U/L)	12.0(8.3–16.6)	12.0(8.3–16.6)	11.5(8.3–16.6)	0.457
BUN(mmol/L)	2.7(2.3–3.1)	2.7(2.3–3.1)	2.8(2.3–3.2)	0.457
Cr(umol/L)	44.0(40.0–48.0)	44.0(40.0–48.0)	44.0(39.0–47.0)	0.230
UA(umol/L)	208.0(178.0-239.0)	205(176.0-236.0)	220.5(190.8–252.0)	0.005
TC(mmol/L)	4.46 ± 0.79	4.41 ± 0.79	4.63 ± 0.79	0.026
TG(mmol/L)	1.3(1.1–1.7)	1.3(1.0-1.7)	1.5(1.1–1.9)	0.020
LDL(mmol/L)	2.39 ± 0.67	2.35 ± 0.66	2.53 ± 0.67	0.034
GDM diagnosis(75-gOGTT)				
OGTT FPG(mmol/L)	4.5(4.3–4.8)	4.5(4.2–4.7)	5.2(4.7–5.4)	0.000
OGTT 1hPG(mmol/L)	7.75 ± 1.80	7.24 ± 1.39	9.79 ± 1.82	0.000

Continuous data were expressed as mean ± standard deviation or as median (interquartile range [IQR] 25th percentile-75th percentile). Categorical data were expressed as n (%). Two-tailed Student's test was used for TC, LDL, OGTT 1hPG. Fisher's exact test was used for family history of diabetes. Chi-squared test was used for miscarriage and reproductive history. Mann-Whitney statistical analysis method was used to analyse the other parameters.

GDM gestational diabetes mellitus, *BMI* body mass index, *HbA1c* glycosylated hemoglobin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *γ-GT* γ-glutamyltransferase, *BUN* blood urea nitrogen, *Cr* creatinine, *UA* uric acid, *TC* total cholesterol, *TG* total triglycerides, *LDL-C* low-density lipoprotein cholesterol.

	Total population (n = 399)	Control(n = 319)	GDM(n = 80)	*P* value
OGTT 2hPG(mmol/L)	6.5(5.6–7.3)	6.31(5.4–6.95)	8.0(6.8–8.9)	0.000

Continuous data were expressed as mean ± standard deviation or as median (interquartile range [IQR] 25th percentile-75th percentile). Categorical data were expressed as n (%). Two-tailed Student's test was used for TC, LDL, OGTT 1hPG. Fisher's exact test was used for family history of diabetes. Chi-squared test was used for miscarriage and reproductive history. Mann-Whitney statistical analysis method was used to analyse the other parameters.

GDM gestational diabetes mellitus, *BMI* body mass index, *HbA1c* glycosylated hemoglobin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *γ-GT* γ-glutamyltransferase, *BUN* blood urea nitrogen, *Cr* creatinine, *UA* uric acid, *TC* total cholesterol, *TG* total triglycerides, *LDL-C* low-density lipoprotein cholesterol.

Table 2
Comparison of pregnancy outcomes between GDM group and control group under unmatched

	Total population (n = 399)	Control(n = 319)	GDM(n = 80)	*P* value
Maternal				
Gestational age at delivery (weeks)	39.0(39.0–40.0)	39.0(39.0–40.0)	39.0(39.0–40.0)	0.118
Caesarean section; n(%)	173(43.36)	134(42.01)	39(48.75)	0.276
Premature rupture of membranes; n(%)	45(11.28)	36(11.29)	9(11.25)	0.993
Intrauterine distress; n(%)	32(8.02)	27(8.46)	5(6.25)	0.514
Amount of postpartum hemorrhage(ml)	300(250–350)	300(250–350)	300(260–350)	0.757
Offspring				
Weight	3.4(3.1–3.7)	3.4(3.1–3.7)	3.5(3.2–3.7)	0.160
Macrosomia; n(%)	22(5.51)	14(4.39)	9(11.25)	0.037
Apgar score	10.0(10.0–10.0)	10.0(10.0–10.0)	10.0(10.0–10.0)	0.272

median (interquartile range [IQR] 25th percentile-75th percentile). Categorical data were expressed as n (%). Chi-squared test was used for caesarean section, premature rupture of membranes, intrauterine distress and macrosomia. Mann-Whitney statistical analysis method was used to analyse the other parameters.

Comparison of clinical characteristics and biochemical indexes between two groups after PSM matching

A PSM analysis was performed using age, family history of diabetes, prepregnancy BMI, ALT, AST, γ-GT, BUN, Cr, UA, TC, TG, LDL, miscarriage, reproductive history as covariates. As a result, there were 148 (74 in each group) well-matched participants who maintained balance in terms of baseline characteristics (P> 0.05) (Table 3). We further detected the levels of CFBa in the two groups and found that the level of CFBa in the GDM group was higher than that in the normal pregnant women group [0.4(0.1–0.8) *vs.* 0.2(0.2–0.3), P = 0.031]. Binary logistic regression was then performed. The results confirmed that the level of CFBa was closely related to the incidence of GDM (OR = 1.52, 95% CI: 1.25–1.85, P = 0.000). The perinatal data of PSM matched pregnant women were shown in Table 4. There was no significant difference in gestational age at delivery, cesarean section rate, incidence of premature rupture of membranes, intrauterine distress rate, neonatal weight, proportion of macrosomia and apgar score between the two groups. The amount of postpartum hemorrhage in normal control group was significantly lower than that in GDM group [280.0(247.5-312.5) *vs.* 300(260.0-352.5), P = 0.042].

Table 3
Comparison of clinical characteristics and biochemical indexes between GDM group and control group after PSM matching

	Control(n = 74)	GDM(n = 74)	*P* value
Age(years)	28.5(25.0–32.0)	29.0(26.0–31.0)	0.669
Family history of diabetes; n(%)	4(5.41)	7(9.46)	0.347
Prepregnancy BMI(Kg/m^2)	21.7(19.9–23.5)	21.35(20.28–23.93)	0.488
Miscarriage; n(%)	38(51.35)	33(44.59)	0.411
Reproductive history; n(%)	34(45.95)	40(54.05)	0.324
HbA1c(%)	5.1(4.9–5.3)	5.2(5.0-5.4)	0.014
ALT(U/L)	14.0(10.8–22.3)	14.5(11.0-26.5)	0.753
AST(U/L)	15.2(13.8–20.0)	16.0(13.0-20.4)	0.852
γ-GT(U/L)	12.0(8.0-17.1)	12.0(8.3–16.6)	0.560
BUN(mmol/L)	2.7(2.2–3.1)	2.8(2.3–3.2)	0.223
Cr(umol/L)	43.0(40.0-47.3)	44.0(39.0–47.0)	0.791
UA(umol/L)	217.28 ± 52.03	220.40 ± 51.12	0.715
TC(mmol/L)	4.60 ± 0.85	4.66 ± 0.79	0.672
TG(mmol/L)	1.4(1.2–1.8)	1.4(1.1–1.9)	0.825
LDL(mmol/L)	2.50 ± 0.73	2.54 ± 0.68	0.705
GDM diagnosis(75-g OGTT)			
OGTT FPG(mmol/L)	4.5(4.3–4.7)	5.1(4.7–5.4)	0.000
OGTT 1hPG(mmol/L)	7.17 ± 1.47	9.73 ± 1.84	0.000
OGTT 2hPG(mmol/L)	6.11 ± 1.24	7.79 ± 1.69	0.000
CFBa(ng/ml)	0.2(0.2–0.3)	0.4(0.1–0.8)	0.031

Continuous data were expressed as mean ± standard deviation or as median (interquartile range [IQR] 25th percentile-75th percentile). The two-tailed Student's test was used for UA, TC, LDL, OGTT 1hPG, OGTT 2hPG. Chi-squared test was used for family history of diabetes, miscarriage and reproductive history. Mann-Whitney U test was used to analyse the other parameters.

GDM gestational diabetes mellitus, *BMI* body mass index, *HbA1c* glycosylated hemoglobin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *γ-GT* γ-glutamyltransferase, *BUN* blood urea nitrogen, *Cr* creatinine, *UA* uric acid, *TC* total cholesterol, *TG* total triglycerides, *LDL-C* low-density lipoprotein cholesterol, *PSM* propensity score matching, *CFBa* complement factor Ba.

Table 4
Comparison of pregnancy outcomes between GDM group and control group after PSM matching

	Control(n = 74)	GDM(n = 74)	*P* value
Maternal			
Gestational age at delivery (weeks)	39.0(39.0–40.0)	39.0(39.0–40.0)	0.073
Caesarean section; n(%)	36(48.65)	35(47.30)	0.869
Premature rupture of membranes; n(%)	13(17.57)	9(12.16)	0.355
Intrauterine distress; n(%)	4(5.41)	5(6.76)	1.000
Amount of postpartum hemorrhage(ml)	280.0(247.5-312.5)	300(260.0-352.5)	0.042
Offspring			
Weight	3.4(3.1–3.5)	3.4(3.2–3.7)	0.154
Macrosomia; n(%)	4(5.41)	4(5.41)	1.000
Apgar score	10.0(10.0–10.0)	10.0(10.0–10.0)	0.379

median (interquartile range [IQR] 25th percentile-75th percentile); Categorical data were expressed as n (%). Chi-squared test or Fisher's exact test was used for caesarean section, premature rupture of membranes, intrauterine distress and macrosomia. Mann-Whitney U test method was used to analyse the other parameters.

Effect of complement factor Ba on the incidence of GDM

ROC curve analysis showed that the area under curve (AUC) of CFBa for predicting GDM was 0.602 (95% CI, 0.499–0.704; P = 0.033). According to the quartile of CFBa level, we divide it into three groups, category 1(< 0.16 ng/ml, n = 39), category 2 (0.16–0.41 ng/ml, n = 73), category 3(> 0.41 ng/ml, n = 36), as shown in Fig. 1. The results indicated that the incidence of GDM in category 3 was markedly higher than that in the first and the second categories.

Discussion

This is the first study to assess the effect of CFBa level within 11 to 17 weeks of gestation on the risk of subsequent GDM. In this study, a propensity score-matched analysis was used, which could balance the distribution of baseline characteristics among groups, reduce the influence of bias and confounding variables in non-random studies and make more reasonable comparison between the experimental group and the control group[19]. Before PSM, the age, family history of diabetes, prepregnancy BMI, reproductive history, ALT, UA, TC, TG, LDL in GDM group were higher than those in normal pregnant group. After PSM, there was no significant difference of the above indexes between the two groups. We found that the levels of CFBa in pregnant women who later developed GDM were significantly higher than those in healthy pregnant women. Logistic regression results confirmed that the level of CFBa was an independent risk factor for the occurrence of GDM. Further grouping according to the quartile of CFBa

level, it was found that the incidence of GDM in category 3 was markedly higher than that in the first and the second categories.

At present, insulin resistance and low-grade inflammation caused by immune imbalance are the important reasons for the formation and development of GDM[20]. The chronic inflammation may lead to increased expression of complement gene and activation of complement pathway. Many studies have investigated the role of CFB in metabolic syndrome including type 2 diabetes mellitus, hypertension and insulin resistance. Moreno-navarrete JM et al. [21] found that the circulating CFB concentration was closely related to IR. The CFB gene expression is highly in omentum tissue, which is positively correlated with BMI, log fasting triglycerides and fasting glucose. Fujita T et al.[22] conducted a study including 32 obese patients with type 2 diabetes mellitus and 32 healthy people showed that the circulating level of CFB was significantly higher in type 2 diabetes mellitus than that in healthy people, and it was also associated with IR, atherosclerosis and diabetic microangiopathy. It is suggested that the activation of the alternative complement pathway can enhance the sustained mild inflammation and insulin resistance, thus inducing the activation of macrophages and accelerating tissue damage. In recent years, an animal experiment was carried out by Coan PM et al.[11] to confirm the role of serum CFB in metabolic syndrome. They knocked out the CFB gene in rats and found that the glucose tolerance and insulin sensitivity of rats were improved. As the activation product of CFB, CFBa has been rarely reported in the population.

GDM can lead to a series of maternal and fetal complications, such as macrosomia, preterm birth and cesarean section[23]. In our study, before PSM, the incidence of macrosomia in GDM group was higher than that in normal pregnant women group (11.25% vs. 4.39%, $P = 0.037$). After PSM, compared with the normal control group, the amount of postpartum hemorrhage of GDM group was more. The percentage of cesarean section in the GDM group was also higher than that in the normal pregnant women group, but it did not reach statistical significance. This may be due to the psychosocial factors, such as maternal anxiety about delivery or the mother's desire to have cesarean section without any medical indications[24–26], or it may be due to the small sample size of our study.

There are some limitations in the study. First, due to the lack of serum insulin data, it is impossible to calculate the homeostasis model assessment of insulin resistance index (HOMA-IR) and the homeostasis model assessment of beta cell insulin secretion (HOMA-β), so the relationship between CFBa and IR could not be further evaluated. In addition, the sample size of the study was relatively small. More patients are needed to enroll and follow up in the future and confirm these findings.

Conclusion

In summary, this study revealed that the level of CFBa within 11 to 17 weeks of gestation in the GDM group was significantly higher than that in the normal pregnant women, which was an independent risk factor for subsequent GDM. Pregnant women with a high level of CFBa within 11 to 17 weeks of gestation were more likely to develop GDM.

Abbreviations

CFB: Complement factor B; IR: Insulin resistance; GDM: gestational diabetes mellitus; PSM: Propensity score-matched; BMI: Body mass index; HbA1c: Hemoglobin A1c; HPLC: High performance liquid chromatography; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; γ-GT:γ-glutamyltransferase; BUN: Blood urea nitrogen; Cr: Creatinine; UA: uric acid; TC: Total cholesterol; TG: triglycerides; LDL-C: Low density lipoprotein cholesterol;CV: Coefficients of variation.

Declarations

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Authors' contributions

FL designed the study. YS, HRT and $JXL^{2\#}$ contributed to sample collection and data analysis. YS drafted the manuscript. FL reviewed and edited the manuscript. JXL^{2} and HJL measured biochemical indices, HRT, $JXL^{2\#}$, YS, YJ, ZYL and BL collected all samples, the clinical data and took responsibility of data integrity. All authors reviewed the manuscript.

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Availability of data and materials

The data of this study are available from the corresponding authors upon reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Jinshan District Central Hospital of Shanghai Jiao-Tong University Affiliated 6th People's Hospital. Written informed consent was signed by all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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