FGF21 Serum Levels in the Early Second Trimester Are Positively Correlated With the Risk of Subsequent Gestational Diabetes Mellitus: A Propensity-Matched Nested Case-Control Study

Zhiheng Wang†‡, Min Yuan‡, Chengjie Xu3, Yang Zhang2, Chunmei Ying1* and Xirong Xiao2*

1 Clinical Laboratory, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China, 2 Department of Obstetrics, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China, 3 Information Section, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China

**Background:** As an important endocrine hormone regulating glucose metabolism, fibroblast growth factor 21 (FGF21) is increased in individuals with gestational diabetes mellitus (GDM) after 24 gestational weeks. However, it is unknown whether the increase in FGF21 precedes the diagnosis of GDM.

**Methods:** In this nested case-control study, 133 pregnant women with GDM and 133 pregnant women with normal glucose tolerance (NGT) were identified through propensity score matching, and serum FGF21 levels were measured at 14 to 21 gestational weeks, before GDM is routinely identified. The differences in FGF21 levels were compared. The association between FGF21 and the occurrence of GDM was evaluated using logistic regression models with adjustment for confounders.

**Results:** The serum FGF21 levels of the GDM group at 14 to 21 gestational weeks were significantly higher than those of the NGT group overall (P < 0.001), with similar results observed between the corresponding BMI subgroups (P < 0.05). The 2nd (OR 1.224, 95% CI 0.603–2.485), 3rd (OR 2.478, 1.229–5.000), and 4th (OR 3.419, 95% CI 1.626–7.188) FGF21 quartiles were associated with greater odds of GDM occurrence than the 1st quartile after multivariable adjustments.

**Conclusions:** The serum FGF21 levels in GDM groups increased in the early second trimester, regardless of whether participants were stratified according to BMI. After adjusting for confounding factors, the FGF21 levels in the highest quartile were associated with more than three times higher probability of the diagnosis of GDM than those levels in the first quartile.

**Keywords:** FGF21, gestational diabetes mellitus (GDM), nested case-control study, propensity score matching (PSM), early second trimester
INTRODUCTION

Gestational diabetes mellitus (GDM), defined as glucose intolerance during pregnancy, has an incidence of 7% to 17.5% among pregnant women in China (1–4). GDM can adversely affect mothers and fetuses, resulting in an increased risk of delivery-related complications and type 2 diabetes mellitus (T2DM) (3, 5, 6). Appropriate intervention in pregnant women with GDM can reduce the risk of adverse pregnancy outcomes (7–10). Early diagnosis of GDM before 24 weeks of gestation may provide more time for pregnant women with high risk of GDM for appropriate intervention. However, early identification of GDM is very difficult (2, 11), as GDM is a complex metabolic process of insulin resistance and islet β cell proliferation disorders (2, 12), with many changes in metabolic factors preceding hyperglycemia (13, 14).

Fibroblast growth factor 21 (FGF21), an important endocrine factor regulating glucose and lipid metabolism (15–17), may be a potential factor associated with GDM prediction, as it was recently found that serum FGF21 increased after 24 gestational weeks in GDM patients (18–20). Studies showed that FGF21 reduces blood glucose and regulates blood lipids without causing hypoglycemia in obese or type 2 diabetes patients (21–23), and FGF21 increases insulin sensitivity and improves islet β cell secretion and proliferation (15, 22, 23). As a metabolic factor, FGF21 increases in type 2 diabetes and obesity patients (23, 24), which might be a kind of compensation for insulin deficiency (25) and one study confirmed that serum FGF21 increased before type 2 diabetes was diagnosed in women (26). Due to FGF21 increasing in both GDM and T2DM and the similarity of the pathogenesis of these two diseases (2), we hypothesized that increases in FGF21 compensate for GDM. FGF21 may increase earlier than we are generally aware, and this increase may precede the hyperglycemia of GDM. However, to the best of our knowledge, no study has focused on the changes in FGF21 before the diagnosis of GDM.

Therefore, we intend to analyze the difference in serum levels of FGF21 between individuals with GDM and those without GDM early in the second trimester and analyze the relationship between FGF21 and GDM through a nested case-control study by propensity score matching to eliminate confounding factors.

MATERIALS AND METHODS

Study Population

This study was a nested case-control design carried out by screening the Down’s syndrome screening cohort (14–21 gestational weeks) between January 2019 and October 2019 and was approved by the Ethics Committee of Obstetrics and Gynecology Hospital of Fudan University. All participants were informed of the purpose of the study and signed informed consent forms. Among the cohort of 2,540 participants, 1,368 pregnant women signed informed consent forms for our study.

The inclusion criteria: women with a singleton pregnancy in the Down’s syndrome screening cohort (14–21 gestational weeks) and records of oral glucose test (OGTT) at 24 to 28 weeks of pregnancy. A total of 1247 pregnant women who met the inclusion criteria were included in the study. Individuals with any of the following were excluded: no GDM diagnostic information; pregnancy with twins or triplets; diabetes history; malignant tumors; serious metabolic diseases including Cushing’s syndrome, hyperthyroidism and hypothyroidism; or severe hypertension.

One hundred forty subjects were diagnosed with GDM by a 75-g oral glucose test (OGTT) at 24 to 28 weeks of pregnancy according to the Diagnostic Criteria for Gestational Diabetes issued by the International Association of Diabetes and Pregnancy Study Groups (27, 28). GDM was diagnosed if any one of the following was met: (1) fasting plasma glucose ≥7.8 mmol/L; (2) 1-h plasma glucose ≥10 mmol/L; or (3) 2-h plasma glucose ≥8.5 mmol/L.

Finally, 133 individuals with GDM and 133 individuals with normal glucose tolerance (NGT) were identified as our research subjects through propensity score matching. In the process of object matching, the following multiple covariates and potential confounding factors associated with GDM were considered: age, body mass index (BMI) early in the second trimester, ethnicity, and the number of parities. Since all GDM subjects were Han Chinese and the number of parities is similar (zero or one) in Chinese women, age and BMI were finally determined as matching variables. The GDM and NGT pregnant women were matched in a 1:1 ratio using the nearest neighbor algorithm (caliper width 0.04 of the SD for the logit propensity score) without replacement. The flowchart of the selection of the analyzed GDM population and the matched control population is shown in Figure 1.

Considering that BMI is an important factor that affects FGF21 levels and the occurrence of GDM (29–32), comparative analyses of the BMI subgroups were performed in this study. Participants were grouped on the basis of the Chinese BMI classification standard into underweight (BMI < 18.5 kg/m²), normal weight (18.5 ≤ BMI < 24 kg/m²), overweight (24 ≤ BMI < 28 kg/m²) and obese (BMI ≥ 28 kg/m²) subgroups (33).

Detection of Serum FGF21

Serum was collected during Down’s syndrome screening (14–21 gestational weeks) and stored at −20°C. The serum levels of FGF21 were detected by an Abcam ELISA kit (ab222506, Cambridge, UK).

Statistical Analysis

All statistics were performed by SPSS software. Psmatch 3.04 of the R language extender in SPSS software (Version 25.0; IBM, NY, US) was used for propensity score matching. The results are expressed as the mean ± standard deviation if the data followed a normal distribution, while abnormally distributed measurements are reported as the median (interquartile range). The t-test, Mann-Whitney U test, Kruskal-Wallis one-way ANOVA test, chi-square test, or Fisher’s exact test was used to compare the differences in variables among groups as required. All reported P values were two-tailed. Binary logistic regression analysis models were used to estimate the associations of FGF21 with GDM.
Model 1 was adjusted for the known risk factors for GDM, including age, BMI, family history of metabolic diseases and parity. $P < 0.05$ was considered statistically significant.

RESULTS

To verify the effect of eliminating confounding factors after sample matching, the age, BMI, gestational weeks at blood sampling, gestational weeks at OGTT, family history of metabolic diseases and parity in the overall GDM and NGT groups and each corresponding subgroup were compared, and the results are reported in Table 1. It should be noted that statistical analysis between underweight subgroups was not performed due to the small number of cases (2 of GDM, 1 of NGT). As expected, there was no significant difference in age, BMI, gestational age, family history of metabolic diseases or parity between the GDM and NGT groups, regardless of whether analyzed overall or by corresponding subgroup ($P > 0.05$, Table 1), which suggested that the effect of confounding factors was sufficiently reduced after matching.

Then, the differences in serum levels of FGF21 among the corresponding groups were analyzed (Table 1). The FGF21 levels of the GDM group [58.59 (33.34–105.03) pg/ml] were significantly higher than those of the NGT group [24.20 (23.91–67.89) pg/ml] overall ($P < 0.001$), with similar results observed between the corresponding BMI subgroups (all $P < 0.05$). In GDM group, the FGF21 levels in the normal BMI subgroup [51.67 (28.86–87.49) pg/ml] were the lowest, followed by the overweight group [75.43 (43.52–159.17) pg/ml], and the levels were highest in the obese group [177.42 (88.89–307.22) pg/ml], with a significant difference between the obese group and the normal BMI group ($P = 0.002$, Bonferroni corrected). However, there was no significant difference among the different BMI NGT subgroups (Bonferroni, $P = 0.154$).

Subsequently, the relationship of FGF21 and GDM was explored using logistic regression analysis by stratifying study subjects into quartiles for FGF21 (Q1 $\leq$ 27.83 pg/ml, Q2 28.00 to 45.82 pg/ml, Q3 46.81 to 83.87 pg/ml, Q4 $\geq$84.09 pg/ml; Table 2). Compared with Q1, we found that Q3 was associated with a high risk of GDM (adjusted for age, BMI, family history of metabolic diseases and parity) (OR 2.478, 95% CI 1.229–5.000; $P = 0.011$). Moreover, Q4 was related to a higher risk of GDM.
**TABLE 1** | Baseline characteristics of the study population and the serum levels of FGF21 in different groups.

|                          | NGT                  | GDM                  | P value |
|--------------------------|----------------------|----------------------|---------|
| **Total**                |                      |                      |         |
| N                        | 133                  | 133                  | NA      |
| Age (y)                  | 29.54 ± 2.62         | 29.53 ± 2.27         | 0.972   |
| BMI (kg/m²)              | 22.50 (20.85–24.21)  | 22.80 (20.70–24.50)  | 0.704   |
| Gestational weeks at blood sampling (w) | 16.39 ± 0.92     | 16.48 ± 0.79         | 0.393   |
| Gestational weeks at OGTT (w) | 25.93 ± 1.36    | 25.63 ± 1.25         | 0.339   |
| Family history of metabolic diseases (N) | 22                  | 30                   | 0.216   |
| Parity                   |                      |                      | 0.360   |
| 0                        | 10(82.0)             | 103(77.4)            |         |
| 1                        | 24(18.0)             | 30(22.6)             |         |
| FGF21 (pg/ml)            | 24.20 (23.91–67.89)  | 58.59 (33.34–105.03)**| <0.001 |

BMI (kg/m²) ≥28

|                          |                      |                      |         |
| N                        | 9                    | 9                    | NA      |
| Age (y)                  | 28.67 ± 1.73         | 28.70 ± 1.65         | 0.967   |
| BMI (kg/m²)              | 29.73 (28.68–33.59)  | 30.70 (29.60–32.65)  | 0.730   |
| Gestational weeks at blood sampling (w) | 16.00 ± 1.12     | 16.44 ± 0.73         | 0.332   |
| Family history of metabolic diseases (N) | 4                   | 2                    | 0.620   |
| Parity                   |                      |                      | 1.000   |
| 0                        | 8(88.9)              | 7(77.8)              |         |
| 1                        | 1(11.1)              | 2(22.2)              |         |
| FGF21 (pg/ml)            | 33.35 (30.60–103.90) | 177.42 (88.89–307.22)*| 0.011   |

24≤BMI (kg/m²) <28

|                          |                      |                      |         |
| N                        | 28                   | 32                   | NA      |
| Age (y)                  | 29.75 ± 2.96         | 29.42 ± 2.19         | 0.625   |
| BMI (kg/m²)              | 25.48 (24.50–26.40)  | 25.40 (24.50–26.38)  | 0.935   |
| Gestational weeks at blood sampling (w) | 16.57 ± 1.03     | 16.63 ± 0.83         | 0.825   |
| Family history of metabolic diseases (N) | 5                   | 13                   | 0.102   |
| Parity                   |                      |                      | 0.165   |
| 0                        | 21(75)               | 29(90.6)             |         |
| 1                        | 7(25)                | 3(9.4)               |         |
| FGF21 (pg/ml)            | 44.20 (27.38–109.83) | 75.43 (43.52–159.17)*| 0.042   |

18.5≤BMI (kg/m²) <24

|                          |                      |                      |         |
| N                        | 95                   | 90                   | NA      |
| Age (y)                  | 29.59 ± 2.59         | 29.70 ± 2.35         | 0.804   |
| BMI (kg/m²)              | 21.58 (20.39–22.86)  | 21.55 (20.30–23.03)  | 0.981   |
| Gestational weeks at blood sampling (w) | 16.37 ± 0.86     | 16.43 ± 0.79         | 0.621   |
| Family history of metabolic diseases (N) | 13                  | 15                   | 0.572   |
| Parity                   |                      |                      | 0.073   |
| 0                        | 7(83.3)              | 6(72.2)              |         |
| 1                        | 1(16.8)              | 2(27.8)              |         |
| FGF21 (pg/ml)            | 33.36 (21.74–66.78)  | 51.67 (28.86–87.49)**| 0.005   |

Data are presented as the mean ± standard deviation, median (interquartile range) or N (%). Data on age and gestational weeks at blood sampling were compared using the t-test; BMI and FGF21 were compared using the Mann-Whitney U test; family history of metabolic diseases and parity were compared using the chi-square test and Fisher’s exact test. *P<0.05 and **P<0.01 compared with the control groups. NGT, normal glucose tolerance group; GDM, gestational diabetes mellitus group; N, number; BMI, body mass index; FGF21, fibroblast growth factor 21; NA, not applicable.

**TABLE 2** | Associations of serum FGF21 concentrations (pg/ml) early in the second trimester of pregnancy with the risk of gestational diabetes mellitus.

| FGF21 (pg/ml) (quartiles) | NGT (N=133) | GDM (N=133) | Crude OR | adjusted OR* |
|---------------------------|-------------|-------------|----------|--------------|
| 1st Quartile (≤27.83)     | 43 (32.3%)  | 24 (18.0%)  | 1.000 (referent) | 1.000 (referent) |
| 2nd Quartile (28.00–45.82)| 39 (29.3%)  | 27 (20.3%)  | 1.240 (0.616–2.498) | 1.224 (0.603–2.485) |
| 3rd Quartile (46.81–83.87)| 28 (21.1%)  | 39 (29.3%)  | 2.496 (1.244–5.008) | 2.478 (1.229–5.000) |
| 4th Quartile (≥84.09)     | 23 (17.3%)  | 43 (32.3%)  | 3.350 (1.645–6.821) | 3.419 (1.626–7.188) |

P for trend NA NA 0.002 0.002

Values are given as OR (95% CI).

*Adjusted for age, BMI, family history of metabolic diseases and parity.

OR, odds ratio; CI, confidence interval; NGT, normal glucose tolerance group; GDM, gestational diabetes mellitus group; N, number; BMI, body mass index; FGF21, fibroblast growth factor 21; NA, not applicable.
FGF21. As studies have found that FGF21 can improve tissue causality for the development of GDM with elevation of important question regarding the potential mechanism or were associated with a higher risk of GDM. Our women at high risk of GDM.

pregnant women at 24 to 28 gestational weeks (18, 34). S found that GDM women had higher levels of FGF21 than NGT elevated after 24 gestational weeks. Li et al. and Bonakdaran et al. found that the serum levels of FGF21 in GDM women were all metabolism in the body, its potential role in GDM has gradually relationships were independent of known risk factors for GDM, including age, BMI, family history of metabolic diseases and parity.

Due to the important role of FGF21 in regulating glucose metabolism in the body, its potential role in GDM has gradually received increasing attention in recent years. Most of the studies found that the serum levels of FGF21 in GDM women were all elevated after 24 gestational weeks. Li et al. and Bonakdaran et al. found that GDM women had higher levels of FGF21 than NGT pregnant women at 24 to 28 gestational weeks (18, 34). ŠIMJAK et al. found that FGF21 in GDM women was higher than that in NGT pregnant women at 28 to 32 gestational weeks (35). In addition, four studies showed that FGF21 was also higher in the GDM group than in the NGT group in the third trimester and prenatally (20, 35–37).

Notably, we discovered that FGF21 increased significantly at 14 to 21 gestational weeks before the routine GDM diagnosis time (24–28 gestational weeks). The impaired glucose tolerance on pregnancy is a continuum from normal to established GDM (38). It is possible that glucose tolerance of GDM women is impaired right at the outset (even outside of pregnancy) than that of non-GDM women. It may be why FGF21 levels in women who later were diagnosed with GDM were higher than those with normal OGTT. Our findings might make it possible for considering FGF21 as a predictor of GDM. Moreover, GDM women with normal BMI account for more than half of all GDM women in China (1, 2, 30, 39), and the possibility of GDM onset in women with normal BMI is more likely to be ignored and difficult to predict. Importantly, we found that the FGF21 levels of the normal BMI GDM subgroup were significantly higher than that of the normal BMI NGT subgroup, which provided important theoretical evidence for the early prediction of GDM in normal BMI pregnant individuals. Prospective studies are needed to confirm the predictive value of FGF21 for identifying the women at high risk of GDM.

In summary, the serum FGF21 levels in GDM women increased early in the second trimester, regardless of whether participants were stratified according to BMI. After adjusting for confounding factors, the FGF21 levels in the highest quartile were associated with more than three times higher probability of the diagnosis of GDM in the pregnancy as compared to levels in the first quartile. In addition to the currently established clinical and biochemical risk factors, the circulating concentration of FGF21 represents a potentially useful new biomarker that can identify pregnant women at risk for GDM.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. Requests to access these data sets should be directed to ZW, wzh.0409@163.com.
ETHICS STATEMENT
The studies involving human participants were reviewed and approved by the ethics committee of Obstetrics and Gynecology Hospital of Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS
XX, CY, and ZW contributed significantly to the conception of the study. ZW, CX, and YZ contributed significantly to analysis and manuscript preparation. ZW and MY performed the data analyses and wrote the manuscript. XX and ZW helped perform the analysis with constructive discussions. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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