First-Trimester Fasting Hyperglycemia without Gestational Diabetes Mellitus is not Associated with Adverse Pregnancy Outcomes:A Prospective Cohort Study in China

Zhiheng Guo
Jilin University First Hospital
Yanhong Shan
Jilin University First Hospital
Caifeng Xiu
Jilin University First Hospital
Yi Yang (yi_sj2019@163.com)
Jilin University First Hospital https://orcid.org/0000-0003-4156-6409
Shu Zheng
Jilin University First Hospital
Min Peng
Jilin University First Hospital

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Abstract

Background Gestational diabetes mellitus (GDM) is a common pregnancy-induced metabolic complication worldwide. At present, a variety of strategies for diagnosis and management of GDM have been recommended. Our aim is to investigate the clinical features and pregnancy outcomes among women in whom a first-trimester fasting glucose value (≥ 5.10 mmol/L but < 7.0 mmol/L) was detected and a 2-h 75-g oral glucose tolerance test (OGTT) between 24–28 weeks was negative.

Methods This is a prospective cohort study of women who registered and delivered between June 2016 and November 2019 at First Hospital, Jilin University. Pregnant women who met the inclusion criteria were categorized as normal first-trimester fasting plasma glucose(FPG)(< 5.10 mmol/L) and first-trimester fasting hyperglycemia (≥ 5.10 mmol/L but < 7 mmol/L).Outcomes included weeks at time of delivery, neonatal birth weight, Apgar score at 1 min, Apgar score at 5 min, prevalence of macrosomia, hypertensive disorders of pregnancy ,primary cesarean delivery, preterm delivery ,premature rupture of membranes and sillbirth or neonatal death were compared after women who developed gestational diabetes mellitus (GDM) were excluded.

Results In our population of 2124 eligible subjects, pregnant women with first-trimester fasting hyperglycemia (≥ 5.10 mmol/L but < 7 mmol/L) constituted 20.8% of the total study population and accounted for 27.6% of subsequent GDM diagnosis. The other 1683 had a normal first-trimester FPG (< 5.1 mmol/L), accounting for 11.6% of all subsequent GDM diagnosis ($p < 0.01$).After excluding women with a diagnosis of GDM between 24 and 28 weeks of gestation, we observed no significant difference between groups for adverse maternal and prenatal outcomes.

Conclusion More than two thirds of first-trimester fasting hyperglycemia pregnant women will have a normal OGTT performed at 24–28 week and of these women whom in no increased risk of adverse pregnancy outcomes have been identified.

Background

Gestational diabetes mellitus (GDM) is a common pregnancy-induced metabolic complication worldwide[1]. Patients with GDM are not only associated with increased risks of maternal and perinatal morbidities but also have a high risk of development of type 2 diabetes after delivery[2]. At present, a variety of strategies for diagnosis and management of GDM have been recommended to improve pregnancy outcomes. The most striking distinction is the timing for the screen of GDM. American Diabetes Association(ADA)[3] suggest that the diagnosis of GDM is made either by “one-step strategy” or “two-step strategy” at 24–28 weeks of gestation in women without preexisting diabetes. According to the recommendation, GDM is restricted to second or third trimester of pregnancy. Whereas International Association of Diabetes and Pregnancy Study Groups (IADPSG)[4] support that fasting plasma glucose(FPG) ≥ 5.10 mmol/l but < 7.0 mmol/l as the GDM diagnostic criteria at the first prenatal visit and women with FPG < 5.1 mmol/l are tested for GDM from 24 to 28 weeks’ gestation with a 75-g oral glucose

tolerance test(OGTT). The FPG diagnostic threshold that they introduced was based on the study by Riskin-Mashiah et al[5]. Similar to the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Research Group report[6], the study showed a strong continuous graded association between higher first-trimester FPG values and adverse pregnancy outcomes. IADPSG recommendation is advantageous in two points to screen for GDM. On one hand, the result of FPG is reliable, reproducible and patients are more compliant[7]. On the other hand, early detection of GDM allows interventions prior to 24–28 weeks and might have a positive effect on maternal and fetal outcomes. Unsurprisingly, previous study[8] presented that there is no complete correspondence in diagnosing GDM between the first-trimester fasting glucose value and the results of a 2-h 75-g OGTT performed early in the third trimester. Therefore more pregnant women are diagnosed of GDM by IADPSG recommendation. It is a matter of debate regarding cost-effectiveness and benefit of detecting and treating early GDM. Since higher first trimester fasting glucose levels are associated with increased risk for the development of GDM[9] and GDM in late pregnancy have been acknowledged deleterious, the association between fasting hyperglycemia in early pregnancy and adverse pregnancy outcomes may be exaggerated. To date, there is no clinical trial addressing the extent to which first-trimester fasting hyperglycemia women without GDM are associated with adverse pregnancy outcomes.

Thus, the aim of the current study was to determine clinical characteristics and pregnancy outcomes among women in whom first-trimester FPG(≥ 5.10 mmol/l but < 7.0 mmol/l) was detected and a 2-h 75-g OGTT between 24–28 weeks was negative.

Methods

Design and setting

This is a prospective cohort study conducted between June 2016 and November 2019. All consecutive pregnant women who registered at our obstetrics clinic and intended to deliver at our hospital were invited to participate in this study, if they had a first-trimester fasting glucose value. Women were excluded if they had preexisting diabetes or overt diabetes, a previous caesarean, hypertension disorder prior to 20 weeks, a history of stillbirth, multifetal gestation, and conception by means of in vitro fertilization. All the women who participated in the study provided written informed consent. The study was approved by the Institutional Review Board.

Eligibility Criteria

In China, FPG test is provided freely to every woman as soon as pregnancy was confirmed. The result and the time of the test will be duly documented in their perinatal manual. Based on the recommendations, overt diabetes was defined as having a fasting blood glucose of ≥ 7.0 mmol/l. Patients with overt diabetes were given instructions to glycemic control, the remainder received no interventions. Participants were required to take an OGTT, with the use of a 75-g dose of glucose, between 24 and 28 weeks of

gestation. GDM diagnosis was established when any one of the following values is met or exceeded in the75-g OGTT: 0 h (fasting), ≥ 5.10 mmol/L; 1 h, ≥ 10.00 mmol/L; and 2 h, ≥ 8.50 mmol/L. Information regarding age, parity, pre-pregnancy body mass index (BMI), family history of diabetes, first-trimester FPG level, and gestational age at delivery was recorded. Pre-pregnancy body mass index(BMI) was self-reported. Gestational age was determined from the date of the last menstrual period. If the date was uncertain, the gestational age of delivery was estimated by means of ultrasound performed between 6 and 13 weeks of gestation.

Data collection and management

For the purpose of analysis, subjects were distributed between two groups: normal first-trimester FPG (< 5.10 mmol/L) and first-trimester hyperglycemia (≥ 5.10 mmol/L but < 7 mmol/L) and basic patient information was compared. Pregnancy outcomes were studied and compared between groups excluding women with a diagnosis of GDM between 24 and 28 weeks of gestation. Maternal outcomes included macrosomia(≥4000g), primary cesarean delivery, gestational age at birth, and preterm birth(< 37 weeks), premature rupture of membranes, hypertensive disorders of pregnancy (defined as pre-eclampsia or systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg in a previously normotensive pregnant woman who is at ≥ 20 weeks of gestation and has no proteinuria or new signs of end-organ dysfunction) .Neonatal outcomes comprised of birth weights, 1 minute and 5 minute Apgar score and stillbirth or neonatal death. Obstetricians were blinded to the first-trimester FPG level when they recorded the pregnancy outcomes. At the end of study period, a special team was assigned and responsible for the final analysis.

Statistical analysis

Statistical analysis was performed with the SPSS computer statistics program (SPSS Inc, Chicago, Ill). Mean and standard deviation are reported for continuous variables, and number and percentage are reported for categorical variables. Chi-square or Fisher's exact tests (for categorical variables) and independent-samples t tests (for continuous variables) were used to compare groups. Reported P-values were two-tailed and P-values < 0.05 were considered to be statistically significant.

Results

During the present study period, a total of 3783 consecutive pregnant women registered and resulted in deliver in our hospital. Of these 2124 women met the inclusion criteria.

Table 1 presented the characteristics of whole study population stratified according to first-trimester FPG. Women with first-trimester fasting hyperglycemia constituted 20.8% of the total study population and accounted for 27.6% of subsequent GDM diagnosis. The other 1683 had first-trimester FPG < 5.1 mmol/L, accounting for 11.6% of all subsequent GDM diagnosis ($p < 0.01$). The average (SD) first-trimester fasting FPG was 4.5(0.4)mmol/L and 5.5(0.4)mmol/L respectively ($p < 0.01$).The individual rates of Parity > 1

and family history of diabetes, maternal age, pre-pregnancy BMI, gestational age at fasting glucose did not differ significantly between the groups.

Table 1
Patient information stratified according to first-trimester fasting plasma glucose

Characteristic	FPG < 5.1 mmol/L (n = 1683)	FPG ≥ 5.1 mmol/L (n = 441)	p
Maternal Age (years)	31.2± 3.6	31.5± 4.8	0.48
Prepregnancy BMI (kg/m2)	22.7 ± 3.5	23.5± 4.1	0.04
Parity > 1	102(6.1%)	25(5.7%)	0.76
First-trimester FPG (mmol/L)	4.5± 0.4	5.5± 0.4	0.00
Gestational age at fasting glucose (weeks)	10.2 ± 1.4	10.5 ± 1.3	0.56
Family history of diabetes	188 (11.1%)	46 (10.5%)	0.43
Prevalence of GDM [n (%)]	195(11.6%)	123(27.6%)	0.00
Data are presented as means ± SD or as n (%).; BMI: body mass index; FPG: fasting plasma glucose GDM: gestational diabetes mellitus			

After excluding women with a diagnosis of GDM between 24 and 28 weeks of gestation, patient information stratified according to first-trimester FPG was presented in Table 2. Maternal age and pre-pregnancy BMI in both groups was slightly reduced after women with subsequent GDM was excluded. The prevalence of parity > 1 and family history of diabetes, first-trimester FPG and gestational age at fasting glucose is similar after exclusion. There is no significant difference for all the variables except first-trimester FPG between the groups.

Table 2
Patient information stratified according to first-trimester fasting plasma glucose excluding women with a diagnosis of GDM between 24 and 28 weeks of gestation

Characteristic	FPG < 5.1 mmol/L (n = 1485)	FPG ≥ 5.1 mmol/L (n = 318)	p
Maternal Age (years)	31.1 ± 3.6	31.0 ± 5.1	0.90
Prepregnancy BMI (kg/m2)	22.6 ± 3.4	22.9 ± 3.6	0.36
Parity > 1	85(5.7%)	19(5.9%)	0.76
First-trimester FPG (mmol/L)	4.5 ± 0.4	5.4 ± 0.3	0.00
Gestational age at fasting glucose (weeks)	9.8 ± 1.4	10.3 ± 1.2	0.78
Family history of diabetes	129 (8.7%.)	29 (9.1%)	0.43
Data are presented as means ± SD or as n (%).; BMI: body mass index; FPG: fasting plasma glucose GDM: gestational diabetes mellitus			

Pregnancy outcomes were studied and compared in patients without GDM and the results are shown in Table 3. The rate of macrosomia (4.6% VS 5.9%), preterm delivery (5.0% VS 5.3%), primary cesarean delivery (29.2% VS 31.6%), premature rupture of membranes (18.6% VS 21.7%) were slightly higher for first-trimester fasting hyperglycemia patients but all the differences were statistically insignificant. In contrast, hypertensive disorders of pregnancy (5.9% VS 4.6%) occurred more frequently in normal first-trimester FPG patients, however statistical test also fail to detect a significant difference. The mean birth weight and gestational age at delivery, as well as Apgar score at 1 min or 5 min were similar between the groups. There was no stillbirth or neonatal death in either group.

Table 3
Pregnancy outcomes stratified according to first-trimester fasting plasma glucose, excluding women with a diagnosis of GDM between 24 and 28 weeks of gestation

Pregnancy outcomes	FPG < 5.1 mmol/L (n = 1485)	FPG ≥ 5.1 mmol/L (n = 318)	p
Weeks at time of delivery	39.2 ± 1.4	39.3 ± 1.3	0.56
Neonatal birth weight (g)	3315.3 ± 460.5	3354.9 ± 485.3	0.36
Macrosomia (> 4000 g)	66(4.6%)	27(5..9%)	0.44
Hypertensive disorders of pregnancy	117(8.1%)	21(6.6%)	0.74
Primary cesarean delivery	423(29.2%)	144(31.6%)	0.78
Preterm delivery (< 37 weeks)	24(5.0%)	8(5.3%)	0.86
Premature rupture of membranes	270(18.6%)	66(21.7%)	0.40
Stillbirth or neonatal death	0	0	
Apgar score at 1 min	9.5 ± 1.0	9.6 ± 0.9	0.45
Apgar score at 5 min	9.9 ± 0.4	9.9 ± 0.4	0.66
Data are presented as means ± SD or as n (%).; BMI: body mass index; FPG: fasting plasma glucose GDM: gestational diabetes mellitus			

Discussion

In this prospective cohort study, we found that patients with first-trimester fasting hyperglycemia have a higher incidence of developing GDM which was diagnosed between 24 and 28 weeks of gestation. Importantly, we also found that first-trimester hyperglycemia is not associated with adverse pregnancy including macrosomia, preterm delivery primary cesarean delivery, premature rupture of membranes and pregnancy hypertension disorders, while subsequent GDM patients were excluded in the analysis.

It is established that overt or preexisting diabetes in early pregnancy is associated with an increase in several adverse maternal outcomes and women at risk may benefit from screening and treatment in early pregnancy[10],however, importance of detecting and regulating degrees of hyperglycemia less severe than “overt” diabetes from early pregnancy is controversial. Advocates[11] argue that traditionally GDM screen which begin at the beginning of the third trimester provide only a brief period for intervention and result in little improvement for pregnancy outcomes. Critics[12] points that mild hyperglycemia does not carry anything like the same degree of risk as overt diabetes. In addition, If IADPSG proposal is adopted, rates of diagnosis of gestational diabetes will increase enormously. Interventions and costs will increase without evident benefits[13].

Our results are consistent with the results of numerous studies which demonstrated that first-trimester FPG level was strongly correlated with GDM diagnosed at 24–28 gestational weeks. In a large retrospective study conducted by Riskin-mashihar et al[9], it is noted that first-trimester FPG level had a continuous associations with increased frequency of GDM development. The incidence of GDM in highest first-trimester hyperglycemia is 11.7% (adjusted odds ratio 11.92 [95% CI 5.39 – 26.37]). F. Corrado et al[8] reported a study including a number (n = 738) of pregnant women in Italy with an 11.9% prevalence of GDM revealed by OGTT between 24 and 28 weeks of gestation. In this study 24(45.3%) women who have a first-trimester FPG greater or equal to 5.1 mmol/L progressed to GDM. In a study of 17,186 pregnancies among Chinese population[14], the incidences of GDM were 37.0, 52.7, and 66.2%, respectively, for women with FPG at the first prenatal visit between 5.10 and 5.59, 5.60 and 6.09, and 6.10–6.99 mmol/L. In light of the high prevalence of GDM in pregnant women with FPG (6.10–6.99 mmol/L), the authors suggested that the same interventions should be provided for them as for GDM.

Our results are inconsistent with three previous reports which found that fasting hyperglycemia in early pregnancy is associated with adverse pregnancy. J. Seth Hawkins et al[15] described that women with an earlier diagnosis of diet-treated GDM were at increased risk of preeclampsia and the delivery of large infants compared with women who received the diagnosis at 24 weeks of gestation. Women with early diagnosis were more likely to be older, multiparous, and obese. When differences in maternal characteristics and glycemic control were adjusted, there is still a higher risk of preeclampsia in earlier diagnosis group (odds ratio, 2.4; 95% CI, 1.5, 3.8). Similar results were reported in the study of Maisa N et al[16]. In contrast with women who received a diagnosis for GDM at or after 24 weeks, women diagnosed with GDM before 24 weeks were associated with an increased risk for macrosomia (OR 2, 95% 1-4.15, p = 0.0498), but relationship with other adverse outcomes was not found. Women diagnosed with GDM before 24 weeks were more likely to be obese and they were less likely to have excess gestational weight gain. A large multiethnic cohort study conducted by Sweeting et al[17] showed that incidence of macrosomia, large for gestational age and neonatal intensive care admission in women in whom GDM was diagnosed at < 12 weeks of gestation was high and even comparable to women with pre-existing diabetes. Difference in definitions of gestational diabetes is a potential reason for differences in study findings. Ours have been described above, whereas their approach was based on the Carpenter-Coustan Criteria that if either a 50-g one-hour glucose challenge test (GCT) that exceeded 200 mg/dL, or if they had two or more abnormal values on a 3 hour, 100 gram oral glucose tolerance test (OGTT). Other important distinctions between the current study and that of prior reports include populations studied and study design. All of these studies were made retrospectively and in two of the three studies only patients with high risk was included in the analysis. Maternal baseline characteristics including pre-pregnancy weight, maternal age and parity, which have previously been reported to be associated with adverse pregnancy outcomes in these studies were not comparable and strategies to control the confounders was vague and poorly explained.

Our study has several strengths, to our knowledge, it is the first prospective study with regard to the association between first-trimester fasting hyperglycemia and adverse pregnancy outcomes while

important confounder as subsequent GDM was excluded from the analysis, particularly all women were followed at a single university clinic and also delivered in the same institution warranting the consistency of results. Other strengths included the relatively large patient sample size compared to earlier studies and inclusion criteria which the HAPO Study has adopted. However, we acknowledge our study also has several limitations. First, Pre-pregnancy BMI, which is a known confounding factor for adverse pregnancy outcomes, was self-reported. Its accuracy depended on the participants' ability of memory and evidences showed[18] adults are willing to overestimate their height and underestimate their weight. Notwithstanding, we do not believe this will bias our study dramatically as pre-pregnancy BMI was comparable in the two groups. Another problem is the test of first-trimester FPG level which was performed in different community center. The measurement lacks a standardized protocol and laboratory quantity control is impossible. Finally, our results are exclusively from Chinese population and may not be generalizable to other ethnicities. However, as Asians are more inclined to develop GDM[19], and we supposed that fewer patients with first-trimester fasting hyperglycemia will suffer from GDM among other races.

Conclusion

In summary, majority of first-trimester fasting hyperglycemia pregnant women will have a normal OGTT performed at 24–28 week and of these women whom in no additional risk for adverse outcomes have been observed. To classify fasting hyperglycemia in early pregnancy as GDM proposed by IADPSG is not appropriate. Medical intervention and close monitoring should only be applied to those with "standard" GDM.

Abbreviations

GDM
Gestational diabetes mellitus; OGTT:oral glucose tolerance test (OGTT); FPG:fasting plasma glucose

Declarations

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Availability of data and materials

The data are available from the corresponding author on reasonable request.

Authors' contributions

Conceptualization: YY; Data acquisition: ZG; Formal analysis: YY; Investigation: YS, Yi Yang; Methodology: YY; Software: MP; Supervision: CX, YS; Writing – original draft: YY, SZ

Writing – review & editing: Yi Yang, ZG

All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Institutional Review Board of the First Hospital of Jilin University reviewed and approved the study protocol. Written informed consent was obtained from all participants.

Consent for publication

All authors read and approved the final manuscript for publication.

Competing interests

The authors declare that they have no competing interests.

Author details

[1] Department of Obstetrics, The First Hospital of Jilin University, Changchun, Jilin, China . [2] Department of Gynecology II, The First Hospital of Jilin University, Changchun, Jilin, China. [3] Center of Reproductive Medicine and Center of Prenatal Diagnosis, The First Hospital of Jilin University, Changchun, Jilin, China.

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