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Identification of significant predictors for the need of insulin therapy and onset of postpartum impaired glucose tolerance in gestational diabetes mellitus patients

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Abstract
Background: Gestational diabetes mellitus (GDM) during pregnancy can greatly increase the risk for a number of adverse prenatal and postpartum consequences. Determining the need for insulin therapy is critical for controlling the glycemic level in GDM patients.
Methods: Here, we performed a retrospective study on 112 GDM patients in China to identify the significant predictors for the need of insulin therapy and onset of postpartum impaired glucose tolerance (IGT) in patients with GDM. During pregnancy, the patients were divided into two groups based on whether insulin therapy was applied for GDM treatment.
Results: Age and gestational weeks at GDM diagnosis, pregestational BMI, family history of diabetes mellitus (DM), plasma glucose levels assessed by 75-g OGTT at both the 1-hour and 2-hour time points (PG-1h and PG-2h) and HbA1c level were all significantly different between the two groups. During postpartum, the same patient population was re-divided into two new groups based on their postpartum PG level. Family history of DM, PG-1h PG-2h and HbA1c level were found to be significantly different between the two groups. More importantly, PG-1h and PG-2h were identified to be significant predictors for both insulin therapy and postpartum IGT.
Conclusions: Our results provide valuable indications on selection of treatment strategy for GDM and GDM-induced postpartum IGT.

Keywords
insulin, glucose, diabetes, pregnancy

Background
Gestational diabetes mellitus (GDM) is a condition in which a woman experiences high blood sugar levels without prior diabetes history. It is a common medical complication associated with pregnancy, especially in elderly women with maternal

obesity and inactivity [1]. Exposure to maternal GDM has been reported to greatly increase the risk of pre-eclampsia and the need for labor induction and cesarean section [2]. GDM also increases the risk of diabetes mellitus (DM) onset in the mother. Over 10% of women with GDM acquired impaired glucose tolerance (IGT) shortly after delivery and 20 to 60% of them developed into DM within 5 to 10 years after pregnancy [3]. Babies born to mothers with poorly managed GDM have a higher tendency of being over weighted, experiencing low blood sugar and acquiring jaundice and type 2 diabetes [2]. Therefore, it is critical to strictly control the maternal blood sugar level during pregnancy.

Medical diet therapy and exercise are the primary treatments for GDM. If these treatments fail to restore the normal glycemic level, insulin therapy should be initiated. However, exogenous insulin has been reported to produce significant side effects on the placental and fetal development, as well as maternal conditions [4]. Therefore, it is important to define the criteria for the initiation of insulin therapy.

In the present study, we performed a retrospective study on GDM patients admitted at our institution to identify the patient characteristics and diagnostic factors that are necessary for the initiation of insulin therapy.

Methods

The study was approved by the ethical committee of Changhai Hospital. Consent has been obtained from all participated patients.

Patients

112 female patients with GDM administered at Changhai Hospital during 2014 and 2019 were enrolled in the present study. GDM was diagnosed via a two-step screening. Pregnant women with any of the following risk factors for GDM were subjected to a 75-g oral glucose tolerance test (OGTT) during their first visit. The risk factors include geriatric pregnancy, pregestational obesity, history of GDM and macrosomia, large for gestational age, glycosuria and a casual plasma glucose level greater than 100 mg/dL. The tested women with a normal 75-g OGTT and pregnant women without any of the above-mentioned risk factors were subjected to a 1-h 50-g oral glucose challenge test between 24 and 28 weeks-of-gestation. If the test result exceeded 10 mg/dL, a diagnostic 75-g OGTT was followed to confirm the onset of GDM. GDM was diagnosed based on the criteria set by the International Association of Diabetes and Pregnancy Study Groups [5]. Patients with overt diabetes during pregnancy or a history of type 1 or type 2 DM before pregnancy were excluded from the study. Dietary therapy was conducted at 30 kcal/kg body weight based on the body mass index (BMI) of 22 kg/m^2 supplemented with 200 kcal. The 212 patients were separated into two groups: the insulin therapy group (n=109) and the diet therapy only group (n=103).

Measurements

Assessed patient data include age and gestational weeks at GDM diagnosis, history of gestation and pregnancy, pregestational and maximum BMI, family history of DM, prior GDM history, plasma glucose levels, and the number of abnormal 75-g OGTT values at GDM diagnosis. A urine test was performed for each patient during their first visit to the hospital. Level of fasting plasma glucose, glycated hemoglobin

(HbA1c), fasting immunoreactive insulin (IRI) and ketone bodies were recorded. The level of ketone bodies of negative, ±, 1+, 2+, 3+ and 4+ were scored as 0, 0.5, 1, 2, 3 and 4, respectively. Levels of plasma glucose and IRI were assessed by a postpartum 75-g OGTT at 0, 30, 60, 90 and 120 min. Homeostatic model assessment for insulin resistance, β-cell function and the insulinogenic index were calculated as previously described [6].

Statistical analysis

All statistical analysis was performed with the SPS16.0 software. A P-value <0.05 was considered as statistical significance. Data were presented as mean ± standard error. Unpaired t-test, Mann-Whitney U-test and $\chi 2$-test were used to analyze between-group differences for continuous variables, ordinal variables and categorical variables, respectively. Multivariate logistic regression analysis was performed with selected independent variables that were identified to be significantly different in the univariate analysis. Receiver operating characteristic (ROC) curve analysis was performed to identify clinical factors that can predict the need for insulin therapy.

Results

Patient characteristics

The 112 patients were divided into the diet and insulin group depending on whether insulin therapy was initiated. Collected patient characteristics of the two groups were summarized in Table 1. A significant difference was observed in both the age and the gestation length at the time of GDM diagnosis between the two groups. Values for history of pregnancy and gestation were similar between the two groups. In term of BMI, only the BMI value measured at the pregestational stage, but not the BMI at 20-years-of-age or the maximal BMI, was significantly different between the two groups. Significantly more patients in the insulin group were found to have a family history of DM compared to the diet group; while the number of patients with GDM history was similar between the two groups. 75-g OGTT at GDM diagnosis revealed a significant difference in the plasma glucose level at the 1 hour and 2 hour time points between the two groups (PG-1h and PG-2h). In addition, patients in the insulin group had significantly more abnormal 75-g OGTT values than the patients in the diet group. Levels of fasting plasma glucose and HbA1c were both significantly increased in the patients from the insulin group. On the other hand, fasting IRI, urinal ketone bodies, insulin resistance and β-cell function were all similar between the two groups.

Risk factors predicting the need for insulin therapy

To identify the clinical factors that correlate with the need for insulin therapy, we performed logistic regression analysis on the variables that were found to be significantly different between the insulin and diet groups (Table 2). PG-1h and PG-2h were found to be the significant predictor for the need of insulin therapy with an odds ratio of 1.035 and 1.006, respectively. Then, we performed ROC curve analysis on the two plasma glucose levels to determine the cut-off values and revealed a value of 177.4 mg/dL and 154.5 mg/dL, respectively (Table 3).

Postpartum 75-g OGTT analysis

A postpartum 75-g OGTT was performed on the same 112 patients at the 6 to

10-week of the postpartum period. Based on the standard glucose level set for DM diagnosis [7], the patients were re-divided into two groups: the normal glucose tolerance (NGT) group (n=93) and the IGT group (n=19) (Table 4). Age and gestational length at the time of GDM diagnosis, history of gestation and pregnancy and all assessed BMI values were all similar between the two groups. 18 out of 19 patients in the IGT group had a family history of DM, whereas only half of the patients in the NGT group had such a history. Percentage of patients with prior GDM was similar between the two groups. PG-1h and PG-2h , but not fasting PG at the time of GDM diagnosis were significantly higher in the IGT group compared to the NGT group. Logically, the number of abnormal 75-g OGTT values was also significantly higher in the IGT group. In addition, level of HbAc1 was also significantly higher in the patients from the IGT group.

Risk factors predicting the onset of IGT

To identify the clinical factors that indicate the development of IGT, we performed logistic regression analysis on the variables that were found to be significantly different between the NGT and the IGT groups (Table 5). Same as the predicting factors for the need of insulin therapy, PG-1h and PG-2h were also identified as significant predictors for the onset of IGT, with an odd ratio value of 1.043 and 1.001, respectively. ROC curve analysis revealed a cut-off value of 180.5 and 142.3 mg/dL for the two factors, respectively (Table 6).

Discussion

Poor management of GDM during pregnancy can lead to severely adverse perinatal outcomes for both the mother and the baby, including higher risk of developing type 2 diabetes in later life. Therefore, careful treatment of GDM during pregnancy to keep the glycemic level under control is crucial for the pregnant women. Dietary therapy is the first line of treatment for GDM. If failed, insulin therapy will be needed. In the present study, we performed a retrospective study on 112 pregnant women with GDM to identify the risk factors that can be used to predict the need for insulin therapy and the onset of postpartum IGT. We show that PG-1h and PG-2h are significant predictors for both situations.

Previous studies have suggested that only PG-1h, but not PG-2h was an independent predictor for the need of insulin therapy [8-10]. In addition, gestational weeks at the time of GDM diagnosis and the HbA1c level were also shown to be the prediction factor for insulin therapy [9], while neither of the factor was identified positive in the present study. These differences could be due to the different analyzed patient population, where all those previous studies were performed on pregnant women from Japan while our study is the first one performed on pregnant women from China. Indeed, ethnicity has been suggested to be a key factor that affects the prediction for the need of insulin therapy [11]. Other possible predicting factors, such as pregestational BMI, maternal age and family history of diabetes have also been implicated as potential predicting factors [12-14]. Although these factors were not identified in the present study as significant predicting factors for insulin therapy, they were all found to be significantly different between the diet and insulin groups. In

addition, gestational weeks at GDM diagnosis and HbA1c level were also significantly different between the two groups. PG-1h and PG-2h were also identified as the only significant predictors for postpartum IGT, indicating that these two factors are indeed critical for GDM-induced glucose levels.

The underlying mechanism for GDM involves impaired pancreatic β-cell function, resulting in increased insulin resistance during pregnancy. Surprisingly, homeostatic model assessment for insulin resistance, β-cell function and the insulinogenic index did not reveal any significant predictors for either insulin therapy or postpartum IGT. The reason behind this unexpected phenomenon is unclear. The retrospective nature of the present study on patients treated at a single cohort might generate possible selection bias. Further studies on patients of different ethnicity and treated at different institutions are required.

Conclusions

In summary, PG-1h and PG-2h are significant predictors for both the need of insulin therapy and onset of postpartum IGT in GDM patients. Therefore, extreme care should be taken for these parameters in pregnant women diagnosed with GDM.

List of abbreviation

Gestational diabetes mellitus (GDM), impaired glucose tolerance (IGT), diabetes mellitus (DM), plasma glucose levels assessed by 75-g OGTT at both the 1-hour and 2-hour time points (PG-1h and PG-2h), oral glucose tolerance test (OGTT), glycated hemoglobin (HbA1c), fasting immunoreactive insulin (IRI), Receiver operating characteristic (ROC), body mass index (BMI), normal glucose tolerance (NGT)

Declarations

Ethics approval and consent to participate

The study was approved by the ethical committee of Changhai Hospital. Consent has been obtained from all participated patients.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

XH, LY and YW collected, analyzed and interpreted the data. YQ designed the study

and wrote the manuscript. All authors read and approved the final manuscript.

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Table 1: Characteristics of the GDM patients in the diet and insulin groups.
Data are mean ± standard error of the mean. BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; IR, insulin resistance; IRI, immunoreactive insulin; OGTT, oral glucose tolerance test; PG, plasma glucose.

	Diet group (n=53)	Insulin group (n=59)	P-value
Age at GDM diagnosis (years)	29.5 ± 0.41	34.3 ± 0.89	0.023
Gestational weeks at GDM diagnosis (weeks)	24.77 ± 0.46	21.19 ± 0.89	0.004
History of gestation	1.56 ± 0.12	1.33 ± 0.24	0.542
History of pregnancy	0.87 ± 0.07	0.82 ± 0.09	0.921
BMI at 20 years-of-age	20.85 ± 0.35	21.62 ± 0.53	0.877
Pregestational BMI	21.32 ± 0.34	24.72 ± 0.88	0.018
Maximum BMI	24.65 ± 0.77	25.11 ± 0.97	0.662
Family history of DM, n (%)	23 (43.4%)	37 (62.7%)	<0.001
Prior GDM, n (%)	7 (13.2%)	9 (15.2%)	0.152
PG in 75-g OGTT at GDM diagnosis (mg/dL)			
Fasting	92.3 ± 0.54	94.8 ± 1.23	0.105
At 1 h	148.5 ± 2.3	189.3 ± 5.9	<0.001
At 2 h	133.2 ± 2.4	160.3 ± 4.6	<0.001
No. of abnormal 75-g OGTT values at GDM diagnosis	1.2 ± 0.12	1.9 ± 0.22	<0.001
Fasting PG (mg/dL)	78.5 ± 0.98	80.6 ± 1.35	0.097
HbA1c (%)	5.15 ± 0.08	5.52 ± 0.11	0.003
Fasting IRI (μU/mL)	5.72 ± 0.39	5.81 ± 0.86	0.219
Insulin resistance	1.15 ± 0.08	1.32 ± 0.11	0.243
β-cell function	132.76 ± 5.76	130.65 ± 9.65	0.765
Ketone bodies in urine	0.98 ± 0.12	1.03 ± 0.21	0.812

Table 2: Logistic regression analysis of the variables that were significantly different between the diet and insulin groups.
BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PG, plasma glucose.

	B	Standard error	P-value	Odds ratio (95% CI)
Age at GDM diagnosis	0.552	0.933	0.113	0.922 (0.856-1.112)
Gestational weeks at GDM diagnosis	−0.047	0.03	0.121	0.971 (0.912–0.998)
History of pregnancy	−0.351	0.185	0.133	0.732 (0.443–1.085)
Family history of DM (1: no, 2: yes)	0.571	0.316	0.097	1.853 (0.913–3.573)
Pregestational BMI	0.028	0.029	0.533	0.996 (0.921–1.112)
PG at 1 h in 75-g OGTT at GDM diagnosis	0.022	0.009	0.002	1.035 (1.001–1.048)
PG at 2 h in 75-g OGTT at GDM diagnosis	0.012	0.006	0.008	1.006 (0.989–1.056)
No. of abnormal 75-g OGTT values at GDM diagnosis	-0.185	0.331	0.634	0.856 (0.498–1.587)
HbA1c	1.235	0.576	0.057	3.233 (1.566–8.233)

Table 3: ROC curve analysis of PG-1h and PG-2h between the diet and insulin groups.
GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PG, plasma glucose.

	cut-off value (mg/dL)	area under curve	sensitivity	specificity
PG at 1 h in 75-g OGTT at GDM diagnosis	177.4	0.772	62%	77.90%
PG at 2 h in 75-g OGTT at GDM diagnosis	154.5	0.801	59%	74.30%

Table 4: Characteristics of the GDM patients in the NGT and IGT groups.
Data are mean ± standard error of the mean. BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; IR, insulin resistance; IRI, immunoreactive insulin; OGTT, oral glucose tolerance test; PG, plasma glucose; NGT, normal glucose tolerance; IGT, impaired glucose tolerance.

	Normal glucose tolerance (n=93)	Impaired glucose tolerance (n=19)	P-value
Age at GDM diagnosis (years)	31.8 ± 0.9	32.2 ± 1.2	0.533
Gestational weeks at GDM diagnosis (weeks)	23.54 ± 0.79	22.95 ± 1.32	0.145
History of gestation	1.41 ± 0.15	1.44 ± 0.37	0.843
History of pregnancy	0.89 ± 0.15	0.85 ± 0.24	0.685
BMI at 20 years old	21.03 ± 0.35	20.97 ± 0.46	0.913
Pregestational BMI	22.85 ± 1.21	22.79 ± 1.15	0.435
Maximum BMI	24.76 ± 1.86	25.03 ± 1.92	0.911
Family history of DM, n (%)	46 (49.4)	18 (94.7)	<0.001
Prior GDM, n (%)	13 (14.0)	3 (15.8)	0.321
PG in 75-g OGTT at GDM diagnosis (mg/dL)			
Fasting	93.12 ± 1.6	92.91 ± 1.8	0.786
At 1 h	148.6 ± 3.2	196.5 ± 5.2	<0.001
At 2 h	128.9 ± 4.2	166.3 ± 5.7	<0.001
No. of abnormal 75-g OGTT values at GDM diagnosis	1.1 ± 0.02	2 ± 0.0	< 0.001
Fasting PG (mg/dL)	79.2 ± 0.8	80.1 ± 3.3	0.867
HbA1c (%)	5.25 ± 0.43	5.43 ± 0.59	0.012
Fasting IRI (μU/mL)	5.74± 0.87	5.80 ± 1.12	0.932
Insulin resistance	1.19 ± 0.44	1.28 ± 0.56	0.232
β-cell function	129.34 ± 6.12	132.97 ± 10.30	0.321
Ketone bodies in urine	1.01 ± 0.08	1.02 ± 0.11	0.653

Table 5: Logistic regression analysis of the variables that were significantly different between the NGT and IGT groups.

BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PG, plasma glucose; NGT, normal glucose tolerance; IGT, impaired glucose tolerance.

	B	Standard error	P - value	Odds ratio (95% CI)
Family history of DM (1: no, 2: yes)	0.532	0.437	0.178	1.253 (0.812-2.913)
PG at 1 h in 75-g OGTT at GDM diagnosis	0.028	0.009	0.03	1.043 (1.002–1.065)
PG at 2 h in 75-g OGTT at GDM diagnosis	0.024	0.005	0.02	1.001 (0.980–1.023)
No. of abnormal 75-g OGTT values at GDM diagnosis	0.451	0.379	0.064	1.562 (0.721–3.314)
HbA1c	1.076	0.731	0.112	2.865 (0.798–10.654)

Table 6: ROC curve analysis of PG-1h and PG-2h between the NGT and IGT groups.

GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PG, plasma glucose; NGT, normal glucose tolerance; IGT, impaired glucose tolerance.

	cut-off value (mg/dL)	area under curve	sensitivity	specificity
PG at 1 h in 75-g OGTT at GDM diagnosis	180.5	0.753	67%	79.60%
PG at 2 h in 75-g OGTT at GDM diagnosis	142.3	0.786	62%	75.70%