

# Gestational diabetes mellitus prediction model: A risk factors analysis of pregnant women with gestational diabetes mellitus but have normal oral glucose tolerance test results in the second trimester of pregnancy

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## Abstract.

**BACKGROUND:** Oral glucose tolerance test (OGTT) is a standard for the diagnosis of gestational diabetes mellitus (GDM). However, clinically, some cases with normal results were diagnosed as GDM in the third trimester.

**OBJECTIVE:** To establish a risk model based on energy metabolism, epidemiology, and biochemistry that could predict the GDM pregnant women with normal OGTT results in the second trimester.

**METHODS:** Qualitative and quantitative data were analyzed to find out the risk factors, and the binary logistic backward LR regression was used to establish the prediction model of each factor and comprehensive factor, respectively.

**RESULTS:** The risk factors including the rest energy expenditure per kilogram of body weight, oxygen consumption per kilogram of body weight, if more than the weight gain criteria of the Institute of Medicine, the increase of body mass index between the second trimester and pre-pregnancy, and fasting blood glucose. By comparison, the comprehensive model had the best prediction performance, indicating that 85% of high-risk individuals were correctly classified.

**CONCLUSION:** Energy metabolism, epidemiology, and biochemistry had better recognition ability for the GDM pregnant women with normal OGTT results in the second trimester. The addition of metabolic factors in the second trimester also improved the overall prediction performance.

Keywords: Prediction model, gestational diabetes mellitus, rest energy metabolism

## 1. Introduction

Gestational diabetes mellitus (GDM) is a metabolic disease that is a threat to pregnant women and

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fetal health risk factors, because it may be associated with a variety of perinatal complications, such as ketoacidosis, gestational hypertension, polyhydramnios, macrosomia, fetal congenital malformation, fetal intrauterine death, dystocia, urogenital infection, puerperal infection and neonatal hypoglycemia, respiratory distress syndrome, neonatal low blood calcium disease, and high blood bilirubin [1–3]. The current diagnostic criteria for GDM are an oral glucose tolerance test (OGTT) at 24–28 weeks of gestation. Pregnant women diagnosed with GDM will make timely dietary adjustments and take medication if necessary [4]. In pregnant women with normal OGTT results but at high risk of GDM during pregnancy, blood glucose testing is repeated in the third trimester. Many risk factors for GDM have been identified and incorporated into clinical practice recommendations [5,6], including age, race, BMI, family history of diabetes, previous history of GDM, and multiple pregnancies [7], insulin, fasting glucose, free fatty acids, triglycerides, hepatic lipase, and low-density lipoprotein [8]. Like a metabolic disease, the energy metabolism factor of pregnant women also plays a key role in the control of GDM [9,10].

The object of this study is for GDM pregnant women with normal OGTT results in the second trimester. These data are more clinically meaningful. Meanwhile they are diagnosed by the existing test and non-invasive energy metabolism test. It improves the accuracy of GDM prediction, reduces unnecessary detection, and provides more time for a clinical intervention of GDM. For early prevention and treatment, it is necessary to find a risk model that can accurately and comprehensively predict the risk of the GDM pregnant women with normal OGTT results in the second trimester.

## 2. Materials and methods

### 2.1. Background, population, exclusion, and inclusion criteria

This is a cross-sectional retrospective study. One hundred and sixty-eight pregnant women were randomly recruited from July 2018 to April 2019 for routine prenatal examinations and delivery in Haidian Maternal and Child Health Hospital of Beijing. According to the inclusion and exclusion criteria, a prospective observational cohort was established after obtaining informed consent, and metabolic conditions were detected according to the experimental design until the end of delivery. Ninety pregnant women completed oral glucose tolerance tests and energy metabolic tests at 24–28 weeks. The specific filter flowchart is shown in Fig. 1.

Inclusion criteria: (1) Single pregnancy; (2) Regularity of the menstrual cycle; (3) Fetal development and gestational week consistent; (4) No chronic hypertension, diabetes, anemia, and other cardiovascular diseases, normal liver and kidney function; (5) Normal thyroid function, no obvious symptoms of acute or chronic infection, no other obstetric complications and complications; and (6) Pregnant women must not take blood pressure-lowering drugs and cardiovascular drugs. Exclusion criteria: (1) Multiple pregnancy; (2) Pregnancy complications, fetal malformation, and thyroid dysfunction occur during this pregnancy; (3) Termination of pregnancy; and (4) According to the record, during the measurement of metabolic parameters, the mask leakage occurred.

### 2.2. Data collection

#### 2.2.1. Physical measurement

Height in the pre-pregnancy. Weight and body mass index (BMI) of the subjects in the pre-pregnancy and second trimester were recorded. The body surface area (SA) was calculated by Stevenson's formula [11] at the same time.

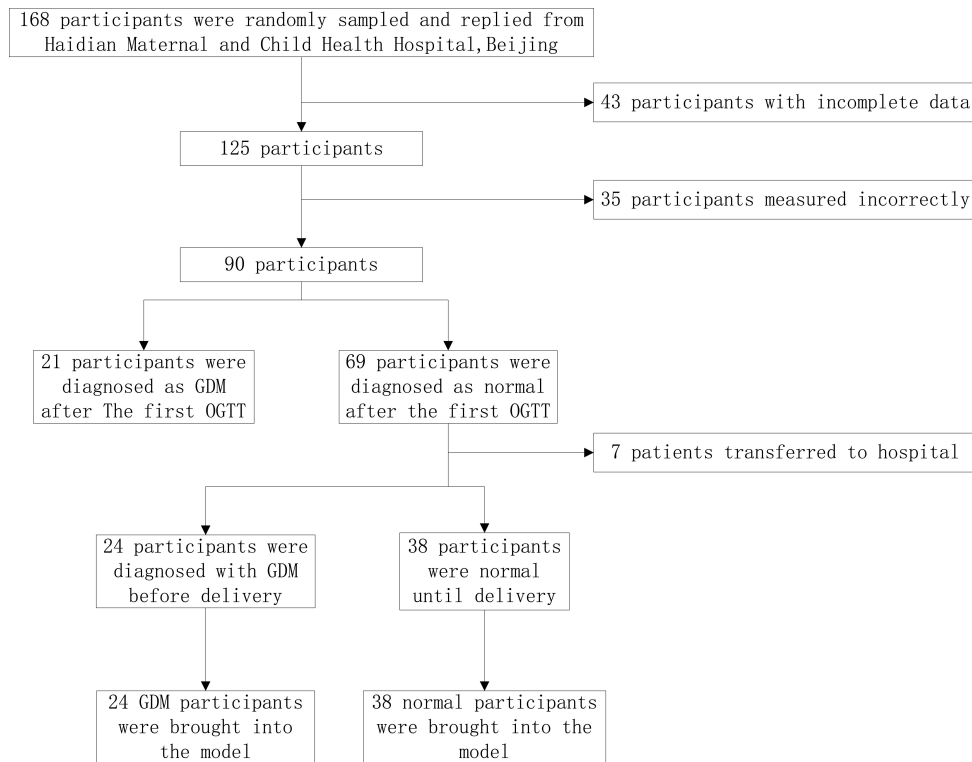


Fig. 1. Flowchart of research object selection.

### 2.2.2. Biochemical measurements

In this study, the 75 g OGTT (fasting blood glucose, 1 h and 2 h blood glucose after drinking oral 75 g anhydrous glucose) was performed at 24–28 weeks of gestation, and the diagnosis was made according to the Health Industry Standard of the People's Republic of China (WS331-2011) diagnostic criteria and the results were recorded. After 30 weeks of gestation to the high risk of normal pregnant women in glucose inspection again. Until delivery, according to the diagnosis, the pregnant women were divided into the GDM pregnant women with normal OGTT results in the second trimester (GDM group) and those who were normal until delivery were analyzed (Normal group).

### 2.2.3. Metabolic measurement

Energy metabolism was measured at 24–28 weeks of gestation. In this study, indirect energy measurement instrument (Breezing, USA) was used to measure rest energy expenditure (REE), oxygen consumption ( $V_{O_2}$ ) and carbon dioxide production ( $V_{CO_2}$ ). Basal metabolic rate (RMR) can be calculated by REE and SA.

The energy metabolism parameters met the following conditions: (1) Fasting for 12 hours; (2) No vigorous exercise and no caffeine intake within 12 hours; (3) Sit quietly for 30 minutes before measurement; and (4) The room temperature should be kept at about 25°C to ensure that the subject will not lose heart or heat.

### 2.3. Statistical analysis

SPSS 20.0 software was used for statistical analysis of the data in this study. Participant characteristics

Table 1  
Baseline characteristics of pregnant women

Characteristic	GDM group <i>N</i> = 24	Normal group <i>N</i> = 38	<i>P</i> <sup>a</sup>
Age (years)*	31.3 ± 4.1	29.5 ± 2.4	0.007
Height (m)	1.63 ± 0.03	1.63 ± 0.05	0.060
Pre-pregnancy weight (kg)	58.1 ± 8.0	55.2 ± 6.7	0.303
Pre-pregnancy BMI (kg/m <sup>2</sup> )	21.9 ± 2.8	20.9 ± 2.3	0.259
First pregnancy, n yes (%)	18 (29.0)	27 (43.5)	0.485
Family history of diabetes, n yes (%)	3 (4.8)	3 (4.8)	0.438
History of spontaneous abortion, n yes (%)	11 (17.7)	13 (21.0)	0.258
Family history of GDM, n yes (%)	4 (6.5)	3 (4.8)	0.428

Continuous variables are presented as mean ± SD and categorical variables as absolute numbers (%). BMI, body mass index; GDM, gestational diabetes mellitus. <sup>a</sup>95% confidence interval. \**P* < 0.05.

are displayed as mean with SD, or frequencies with percentages. To develop the prediction model, firstly, independent-samples *T* test and binary multivariable logistic regression analysis was used to choose the predictors for GDM prediction model with univariate odds ratios (ORs), 95% confidence intervals (95% CI), and *p*-values. Due to the small amount of experimental data, the predictive variables of OR > 1, *P* < 0.05, and clinical high-risk factors were selected from the three groups.

The binary logistic backward LR regression was used to establish the prediction model of the three factor groups, the model without energy metabolism and the overall factor model to choose the best threshold performance comparison, and test whether after joining energy metabolic parameters model performance ascension with AUC [12,13]. In binary multivariable logistic regression analysis with stepwise backward selection, a covariate was retained if the statistical significance of 15% was reached because of avoiding the inaccurate exclusion of potential predictive variables [14,15].

### 3. Results

A total of 62 pregnant women were included in this study, including 24 normal and 38 GDM pregnant women with normal OGTT results in the second trimester, and the basic baseline information was shown in Table 1. The age of pregnant women in the GDM group was higher than that in the normal group (29.5 ± 2.4 vs. 31.3 ± 4.1), and there was no significant difference in other factors.

Table 2 shows the correlation of energy metabolism factors, epidemiological factors, and biochemical factors with GDM. Due to the small amount of experimental data, the predictive variables of OR > 1, *P* < 0.05, and clinical high-risk factors were selected from the three groups. Vo<sub>2</sub>, REE/kg, RMR/kg, BMI, BMI-LP, IOM recommendations, and GLU were selected according to OR, *P*-value, and clinical suggestions. There was no data below the IOM recommendations, so the data of IOM recommendations only contains the within and above the IOM.

Table 3 shows the performance comparison results of the five models. By comparison, for GDM pregnant women with normal OGTT results in the second trimester, the model with the combined performance of the three factors was the most stable, with better prediction accuracy and ability. The models with and without energy metabolism factors were compared. After the addition of energy metabolism factors, the performance of the model is more stable, the sensitivity is higher, and the accuracy is better than the model without energy metabolism. It has been proved that energy metabolism is valuable for the inclusion of predictive models.

Table 4 shows the results of the comprehensive model. After the reverse elimination method is adopted,

Table 2  
Potential predictors of GDM and their Odds ratios, coefficients, and p-value

	GDM group N = 24	Normal group N = 38	Univariate model		
			OR <sup>a</sup> (95% CI) <sup>b</sup>	β <sup>c</sup>	P <sup>d</sup>
Intercept					
Vo <sub>2</sub> (ml/min)	247.42 ± 53.18	255.32 ± 40.67	1.00 (0.99–1.00)	0.00	0.506
Vo <sub>2</sub> /kg (ml/kg/min)*	3.66 ± 0.66	4.04 ± 0.66	0.38 (0.15–0.95)	−0.96	0.039
Vco <sub>2</sub> (ml/min)	180.58 ± 47.70	177.34 ± 35.72	1.00 (0.99–1.01)	0.00	0.758
REE (kcal/day)	1715.79 ± 272.72	1718.16 ± 282.64	1.00 (0.99–1.00)	0.00	0.974
REE/kg (kcal/kg/day)	25.52 ± 3.24	27.18 ± 4.45	0.89 (0.77–1.03)	−0.11	0.127
RMR (kcal/m <sup>2</sup> /day)	1005.05 ± 127.89	1040.18 ± 161.03	1.00 (0.99–1.00)	−0.00	0.998
RMR/kg (kcal/kg/m <sup>2</sup> /day)	15.07 ± 2.30	16.57 ± 3.33	0.82 (0.67–1.01)	−0.20	0.066
BMI	25.38 ± 2.80	24.10 ± 2.63	1.20 (1.01–1.46)	0.18	0.079
BMI-LP	3.62 ± 1.24	3.43 ± 0.91	1.19 (0.73–1.94)	0.17	0.494
IOM recommendations, n within (%) <sup>*</sup>	8 (33.3)	26 (68.4)	2.04 (1.18–3.54)	0.71	0.011
GLU (μmol/L) <sup>*</sup>	4812 ± 220	4531 ± 183	1.01 (1.00–1.01)	0.01	0.003
Plasma glucose 1 h after 75 g anhydrous glucose (μmol/L)	7621 ± 1337	7068 ± 1338	1.00 (1.00–1.01)	0.00	0.120
Plasma glucose 2 h after 75 g anhydrous glucose (μmol/L)	6343 ± 960	6152 ± 1033	1.00 (1.00–1.01)	0.00	0.461

Vo<sub>2</sub>, oxygen consumption in the second trimester; Vo<sub>2</sub>/kg, oxygen consumption per kilogram in the second trimester; Vco<sub>2</sub>, carbon dioxide production in the second trimester; REE, resting energy expenditure in the second trimester; REE/kg, resting energy expenditure per kilogram in the second trimester; RMR, relative metabolic rate in the second trimester; RMR/kg, relative metabolic rate per kilogram in the second trimester; BMI, body mass index in the second trimester; BMI-LP, change in body mass index between the second trimester and before pregnancy; GLU, fasting plasma glucose; IOM, Institute of Medicine. <sup>a</sup>odds ratio. <sup>b</sup>95% confidence interval. <sup>c</sup>log OR/coefficient. <sup>d</sup>significance level.

Table 3  
Comparison of single factor and multiple factor models

Model	Performance evaluation indicators						
	AUC <sup>a</sup> (95% CI) <sup>b</sup>	P <sup>c</sup>	AC <sup>d</sup>	SE <sup>e</sup>	SP <sup>f</sup>	PPV <sup>g</sup>	NPV <sup>h</sup>
Model-M	0.64 (0.49–0.79)	0.001	0.710	0.417	0.895	0.714	0.708
Model-E	0.71 (0.59–0.85)	0.030	0.677	0.583	0.737	0.583	0.737
Model-B	0.77 (0.64–0.90)	0.001	0.774	0.625	0.868	0.750	0.785
Model-E+B	0.80 (0.68–0.92)	0.001	0.790	0.625	0.895	0.789	0.791
Model-M+E+B	0.85 (0.76–0.95)	0.000	0.820	0.750	0.865	0.783	0.842

Model-M, model based on energy metabolism factors; Model-E, model based on epidemiological factors; Model-B, model based on biochemical factors; Model-E+B, model based on epidemiological and biochemical factors; Model-M+E+B, model based on all factors. <sup>a</sup>area under the ROC curve. <sup>b</sup>95% confidence interval. <sup>c</sup>significance level. <sup>d</sup>accuracy. <sup>e</sup>sensitivity. <sup>f</sup>specificity. <sup>g</sup>positive predictive value. <sup>h</sup>negative predictive value.

5 variables are taken in the model. Including the Vo<sub>2</sub>/kg, REE/kg, BMI-LP, the IOM recommendations, and fasting plasma glucose. REE/kg, IOM recommendations, and GLU were significant risk factors for GDM pregnant women with normal OGTT results in the second trimester. However, Vo<sub>2</sub>/kg and BMI-LP were also protective of normal pregnant women. The regression equation was established according to the results:

$$\text{Logit}(P) = \ln\left(\frac{P}{1-P}\right) = -28.67 - 4.84 \times \frac{\text{Vo}_2}{\text{kg}} + 0.7 \times \frac{\text{REE}}{\text{kg}} + 0.98 \times \text{IOM recommendations} - 0.67 \times \text{BMI-LP} + 0.01 \times \text{GLU}$$

The prediction model of the GDM pregnant women with normal OGTT results in the second trimester was:

Table 4  
Risk variables factors in the multivariate logistic model

Variables	Multivariate model		
	OR <sup>a</sup> (95% CI) <sup>b</sup>	$\beta^c$	P <sup>d</sup>
Intercept	0.00	-28.67	0.006
Vo <sub>2</sub> /kg (ml/kg/min)	0.08 (0.00–0.40)	-4.84	0.015
REE/kg (kcal/kg/day)	2.01 (1.01–7.07)	0.70	0.026
IOM recommendations	2.67 (1.09–3.72)	0.98	0.048
BMI-LP (kg/m <sup>2</sup> )	0.51 (0.21, 1.23)	-0.67	0.135
GLU ( $\mu$ mol/L)	1.01 (1.00, 1.01)	0.01	0.003

Vo<sub>2</sub>/kg, oxygen consumption per kilogram in the second trimester; REE/kg, resting energy expenditure per kilogram in the second trimester; IOM, Institute of Medicine; BMI-LP, change in body mass index between the second trimester and before pregnancy; GLU, fasting plasma glucose. <sup>a</sup>odds ratio. <sup>b</sup>95% confidence interval. <sup>c</sup>log OR/coefficient. <sup>d</sup>significance level.

$$P(Y = 1) = \frac{e^{-m}}{1 - e^{-m}}$$

$$P(Y = 0) = \frac{1}{1 - e^{-m}}$$

$$m = -28.67 - 4.84 \times \frac{\text{Vo}_2}{\text{kg}} + 0.7 \times \frac{\text{REE}}{\text{kg}} + 0.98 \times \text{IOM recommendations} - 0.67 \times \text{BMI-LP} + 0.01 \times \text{GLU}$$

#### 4. Discussion

The decisive factors for GDM pregnant women with normal OGTT result in the second trimester are various. In this study, Vo<sub>2</sub>/kg, REE/kg, BMI-LP, the IOM recommendations, and fasting plasma glucose is proven to be effective in predicting the diagnosis of GDM in the third trimester of pregnancy. Among the pregnant women included in the experiment, although they were all normal pregnant women in the second trimester, there are still differences between pregnant women who were normal before delivery and pregnant women diagnosed with diabetes in the third trimester. But due to the small number of samples, normal pregnant women and GDM pregnant women with normal OGTT results in the second trimester could not be well represented. The sensitivity and positive prediction rate of the model were low, and most of the clinical high-risk factors in this study did not show the same high risk as other studies. However, the inquiry is in the middle of pregnancy is normal pregnant women, so in the middle of pregnancy is smaller for part of the risk factors related. More conclusions can be drawn if more sample sizes can be included to discuss the differences in risk factors between GDM and normal pregnant women with OGTT in the second trimester.

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**Conflict of interest**

None to report.

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