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Risk Factors for Gestational Diabetes Mellitus in the Population of Western China

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Abstract

Objective: We aim to explore the risk factors of gestational diabetes mellitus (GDM) in the population of western China.

Methods: We conducted a prospective cohort study which recruited 908 pregnant females, who were registered in West China Second Hospital of Sichuan University from January 1st to December 31st in 2011. Self-designed questionnaires were used to collect related clinical data. The pregnancies were followed up until 42 days post-partum. We analyzed the data with Mann-Whitney U test, Chi-Square Test, logistic regression analysis and rank correlation coefficient analysis.

Results: Univariate analysis of the data showed that maternal age, leg-to-height percentage, body mass index (BMI) before pregnancy, delivery history, dietary history, family histories of diabetes mellitus (DM), hepatitis B surface antigen (HBsAg) carrier status, serum triglyceride and hemoglobin A1c (HbA1c) levels at first trimester are closely correlated with the incidence of GDM. In addition, logistic regression analysis showed that age (OR=1.081, 95% CI 1.027~1.138), unbalanced diet (OR=3.329, 95% CI 2.167~5.116), fruit intake (OR=2.005, 95% CI 1.447~2.780), fondness for sweet food (OR=1.604, 95% CI 1.129~2.280), pre-pregnancy BMI (OR=1.095, 95% CI 1.008~1.190), gravidity (OR=1.263, 95% CI 1.107~1.442), HBsAg carrier status (OR=3.173, 95% CI 1.387~7.260), family histories of DM (OR=1.798, 95% CI 1.063~3.041), high serum triglyceride level (OR=1.315, 95% CI 1.117~1.548) and HbA1c (OR=10.272, 95% CI 4.719~22.363) are correlated with GDM. Furthermore, bivariate correlation analysis showed that age and pre-pregnancy BMI are positively correlated with the fasting, 1-hour, and 2-hour results of 75 g oral glucose tolerance test (OGTT) while leg-to-height percentage is negatively correlated with the 2-h result of 75 g OGTT.

Conclusion: Advanced maternal age, multigravidity, high pre-pregnancy BMI, low leg-to-height percentage, HBsAg-positive status, matrilineal history of DM, unbalanced diet, high fruit intake, high sweet food intake, and high serum triglyceride and HbA1c levels are risk factors for GDM in western Chinese population.

Keywords: Gestational diabetes; Risk factors; Cohort study

Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1]. GDM could lead to significantly increased incidence of perinatal complications of both mothers and fetuses and recent evidence has corroborated that GDM patients demonstrate higher risk of long-term type 2 diabetes mellitus, cardiovascular diseases, and chronic kidney diseases [2,3]. Nationwide study of China in 2006 by GDM Collaborative Group has shown that western China was one of the cities with highest incidence of GDM [4]. However, there is currently a lack of systematic study of risk factors for GDM so far. Thus, in this study, we aim to assess the potential risk factors of GDM in the population of western China.

Patient and Methods

Study population

Our study prospectively recruited pregnant women registered in Department of Obstetrics of West China Second Hospital, Sichuan University from January 1st to December 31st in 2011. Inclusion criteria included: gestational weeks less than 20; the Han nationality living in western China and single pregnancy. Exclusion criteria included: multiple pregnancies; with pregnancy complications (for instance, chronic hypertension, pre-pregnancy diabetes mellitus, intrahepatic cholestasis of pregnancy, and preeclampsia); on medications which might interfere with glycol-metabolism and lipid metabolism (for instance, indometacin, phentolaminemesilate, furosemide, dilantin, and cortisone) during pregnancy. All participants were assigned oral glucose tolerance test (OGTT) with 75 g glucose during 24 to 28 weeks. GDM was diagnosed based upon diagnostic criteria for gestational diabetes mellitus (WS 331-2011) [5] and we thus divided all participants into two groups: GDM group and non-GDM group, respectively. All participants were under rigorous

prenatal management. We applied self-designed questionnaires to collect related clinical information. As for GDM group, we performed professional weight management and additional nutrition guide programs and followed them up till 42 days post-partum. Written informed consent was obtained from all participants and this study was approved by the Institutional Ethics Committee of Sichuan University, which was in agreement with Helsinki declaration.

The main risk factors that we assessed were baseline demographic characteristics (like vocation, education, et al.), delivery history, medical history, family history, dietary conditions, physical examination results, biochemical parameters and perinatal outcome. Perinatal outcome includes preterm birth rate, neonatal Apgar scores at 1 min and 5 min scores, birth weight, macrosomia, and neonatal NICU transfer rate. Gestational weight gain is defined as the gap between pre-pregnancy weight and the weight at delivery. Imbalanced diet is defined as lack of daily intake of any one or more of basic food groups (grain and potato, vegetables and fruits, fish-poultry-eggs-meat, oil and fat). Patriarchal family history is referred to as any GDM history and history of diabetes in the father's lineage. Matrilineal family history of DM is referred to as any history of diabetes in the mother's lineage. The formula to calculate leg to height ratio is: leg-to-height percentage=leg length/height × 100% [6]. The formula to calculate BMI is weight/height^2 [7].

Statistical analysis

All data were analyzed with SPSS16.0 statistical software and a P value less than 0.05 was considered statistically significant. In univariate analysis, quantitative data was statistically analyzed with normality test. If it was a normal distribution, the data was described by the "mean ± standard deviation". Otherwise, it was described by the median (range). If it was a normal distribution with homogeneous variance, data was statistically analyzed with analysis of variance. If it was a normal distribution with heterogeneous variance, data was statistically analyzed with t test. However, if it was not a normal distribution, data was statistically analyzed withMann-Whitney U test. Categorical data was analyzed with chi square test. Considering a possible link between the factors, after screening out factors statistically significant in the incidence of GDM by univariate analysis, we further analyzed the data with logistic regression analysis, in which we used odds ratio (OR) to evaluate the correlation between different factors and GDM. In bivariate correlation analysis, bivariate normal distribution data was represented with product-moment correlation coefficient, and non-bivariate normal distribution data was represented with rank correlation coefficient.

Results

Population characteristics

We initially enrolled 908 cases satisfying the inclusion criteria. Among them, 74 cases were complicated with either pre-eclampsia or intrahepatic cholestasis of pregnancy during third trimesters. There are still 712 cases with complete clinical information including 175 cases in GDM group and 537 cases in non-GDM group after elimination of 122 cases lost to follow-up.

Univariate analysis of risk factors for GDM

Univariate analysis results of the categorical data are shown in Table 1. The ratio of several factors in GDM group is significantly higher than that in non-GDM group, which include advanced maternal age, overweight (body mass index (BMI)=24~27.9 kg/m^2) and obesity (BMI ≥ 28 kg/m^2) before pregnancy, HBsAg-positive status, imbalanced diet and fondness of fruit, sweets, hotpot, and stew. In addition, the positive rate of matrilineal family history of diabetes mellitus in GDM group is significantly higher than those in non-GDM group. However, no statistical differences were observed in educational level, vocation, regular diet, staple food, daily meat intake, GDM history, family history of hypertension, family history of hyperthyroidism, family history of hypothyroidism, the positive rate of patriarchal family history of diabetes and other aspects.

Factors	Group		Chi-Square Tests	
	Non-GDM (537)	GDM (175)	χ^2	P
	Cases (%)	Cases (%)		
Age (boundary by 35)				
<35	462(86.0)	128(73.1)	15.447	0
≥35	75(14.0)	47(26.9)		
Age(boundary by 25)				
<25	33(6.15)	7(4.0)	1.146	0.284
≥25	504(93.85)	168(96.0)		
Education				
Primary school education	3(0.6)	1(0.6)	3.844	0.279
Middle school education	6(1.1)	4(2.3)		
High school education	69(12.8)	31(17.7)		
College education	459(85.5)	139(79.4)		

Vocation				
Mental work	156(29.1) 52(29.7) 0.028 0.867			
Manual work	381(70.9) 123(70.3)			
Pre-pregnancy BMI (kg/m^2)				
<18.5	102(19.0)	18(10.3)	18.409	0
18.5~23.9	390(72.6)	124(70.9)		
24~27.9	42(7.8)	31(17.7)		
≥28	3(0.6)	2(1.1)		
HBsAg				
Positive	21(3.9)	15(8.6)	5.973	0.015
Negative	516(96.1)	160(91.4)		
GDM history				
No	531(98.9)	173(98.9)	0	1
Yes	6(1.1)	2(1.1)		
DM family history				
No	468(87.2)	133(76.0)	14.722	0
Maternal	39(7.3)	30(17.1)		
Patrilineal	30(5.6)	12(6.9)	0.384	0.536
Balanced diet1				
No	120(22.3)	71(40.6)	22.334	0
Yes	417(77.7)	104(59.4)		
Regular diet2				
No	33(6.1)	15(8.6)	1.236	0.266
Yes	504(93.9)	160(91.4)		
Staple food				
Mainly in rice	528(98.3)	170(97.1)	0.441	0.507
Mainly in noodles	9(1.7)	5(2.9)		
Daily intake for fruits (g/d)				
<200	54(10.1)	18(10.3)	67.478	0
200~500	363(67.6)	62(35.4)		
≥500	120(22.3)	95(54.3)		
Daily intake for meat (g/d)				
<100	213(39.7)	79(45.1)	1.911	0.385
100~250	306(57.0)	92(52.6)		
≥250	18(3.3)	4(2.3)		
The extent of loving sweets				

Dislike	81(15.1)	29(16.6)	25.005	0
General	393(72.1)	99(56.6)		
Like very much	63(11.7)	47(26.9)		
The extent to loving hot pot and stew				
Dislike	78(14.5)	36(20.6)	21.759	0
General	387(72.1)	94(53.7)		
Like very much	72(13.4)	45(25.7)		

Table 1: Single-factor analysis of the enumeration data within every factor in GDM group and non-GDM group.

Univariate analysis of the quantitative data within every factor is presented in Table 2. The level of several factors in GDM group is significantly higher than that in non-GDM group, which include gravidity and parity, abortion times and cesarean delivery, levels of serum triglycerides and HbA1c at first trimester and prepregnancy BMI, while leg-to-height percentage and gestational weight gain are significantly lower than those in non-GDM group. Nevertheless, no significant difference was observed in economic income (family monthly income per capita), serum total cholesterol and ferritin concentration between the two groups.

	Economic income (RMB)	Leg-to-height percentage (%)*	Gravidity(n)	Parity (n)	Abortion times(n)	C-section (n)	Total cholesterol (nmol/L)	Serum triglycerides (mmol/L)	HbA1c (%)	Pregnancy weight gain(kg)	Ferritin (ng/ml)
GDM Group	6000 (2000~2500)	56 (53~59)	2 (1~8)	0 (0~2)	1 (0~6)	0 (0~2)	6.17 (3.35~10.95)	3.17 (1.03~10.60)	5.30 (4.20~6.70)	13.5 (5.5~33)	30 (5~257)
Mean rank	344.67	322.29	410.78	388.23	405.34	372.37	359.32	429.04	453.22	292.15	381.41
Non-GDM Group	5000(1000~3000)	0.56(0.51~0.59)	2(1~8)	0(0~2)	1(0~6)	0(0~2)	6.11 (2.14~8.96)	2.73 (1.07~7.46)	5.1 (4.30~6.00)	15.50(5~25)	24(5~178)
Mean rank	360.35	367.65	338.81	346.16	340.58	351.33	355.58	332.86	324.98	377.47	348.38
Z	-0.885	-2.535	-4.197	-3.654	-3.803	-2.126	-0.209	-5.372	-7.326	-4.772	-1.845
P	0.376	0.011	0	0	0	0.034	0.835	0	0	0	0.065

Values are given as median (range)
*Leg length: The distance from the heel to the front of the iliac spineleg-to-height percentage=leg length/height × 100%.

Table 2: Single-factor analysis of the enumeration data within every factor in GDM group and non-GDM group#

Multivariate analysis of risk factors for GDM

To further determine the correlation between the risk factors and GDM, we applied forward LR with suitable standard (P<0.05, P>0.10) to perform stepwise logistic regression analysis, using whether the gestation was diagnosed as GDM as a dependent variable and the related factors in univariate analysis as an independent variable. The results show that ten risk factors involved in the analytical model are possibly related the pathogenesis of GDM, which include age , balanced diet, intake of fruits, the fondness for sweet food, pre-pregnancy BMI, gravidity, HBsAg carrier status, family history of DM, glycosylated hemoglobin level, and serum triglyceride level (Table 3).

	B	S.E.	Wald	Df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Age	0.078	0.026	8.738	1	0.003	1.081	1.027	1.138

Unbalanced diet	1.203	0.219	30.116	1	0	3.329	2.167	5.116
Intake of fruits	0.696	0.167	17.445	1	0	2.005	1.447	2.78
Love sweets	0.473	0.179	6.953	1	0.008	1.604	1.129	2.28
Pre-pregnancy BMI	0.091	0.042	4.617	1	0.032	1.095	1.008	1.19
Gravidity	0.234	0.067	12.052	1	0.001	1.263	1.107	1.442
HBsAg	1.155	0.422	7.477	1	0.006	3.173	1.387	7.26
HbA1c	2.329	0.397	34.442	1	0	10.272	4.719	22.363
Triglyceride	0.274	0.083	10.777	1	0.001	1.315	1.117	1.548
Family history of DM	0.587	0.268	4.784	1	0.029	1.798	1.063	3.041
Constant	18.499	2.235	68.483	1	0	0	—	—
B: Partial regression coefficient; S.E.: The standard error of partial regression coefficient; Exp (B): odds ratio, OR.								

Table 3: The stepwise logistic regression analysis of related factors for GDM.

Correlation analysis of risk factors of GDM

While performing bivariate correlation, we choose nonparametric coefficient of rank correlation because several factors (maternal age, leg-to-height percentage, pre-pregnancy BMI and blood glucose level of OGTT) fail to follow Gaussian distributions. Results in Table 4 show that age of pregnancy, pre-pregnancy BMI are positively correlated with the fasting, 1-hour and 2-hour results of 75 g OGTT while the leg-to-height percentage of pregnant woman is negatively with the 2-hour result of 75 g OGTT.

	FPG		1 h blood glucose level		2 h blood glucose level	
	r	P	r	P	r	P
Age (years)	0.169	0.000*	0.221	0.000*	0.232	0.000*
Leg-to-height percentage	0.087	0.068	0.088	0.063	0.199	0.000*
Pre-pregnancy BMI (kg/m^2)	0.251	0.000*	0.208	0.000*	0.13	0.006*
*P<0.05: The two factors have correlativity.						

Table 4: The correlation analysis between pregnant woman age, leg-to-height percentage, pre-pregnancy BMI and blood glucose levels of 75 g OGTT.

Perinatal outcome

In this study, preterm birth rate of GDM group (7.43%, 13/175) was higher than that of non-GDM group (2.79%, 15/537), and the difference was statistically significant (χ^2=7.506, P=0.006). In regard to the cesarean section rate (χ^2=0.095, P=0.757), neonatal Apgar scores at 1 min (Z=-1.444, P=0.149) and 5 min (Z=-1.614, P=0.107) scores, birth weight (Z=-1.790, P=0.073), macrosomia (χ^2=2.237, P=0.135), and neonatal NICU transfer rate (χ^2=1.853, P=0.173) and the difference between the two groups was statistically insignificant.

Discussion

In this study, we conducted a prospective cohort study explored the potential risk factors of GDM in western China. We found that the incidence of GDM was closely correlated with such factors as maternal age, pre-pregnancy BMI, leg-to-height percentage, dietary conditions, delivery history, HBsAg carrier status, and DM family history, all of which may be potential causal factors for GDM pathogenesis in the population of western China.

Maternal age

Lao and his colleagues retrospectively investigated 15,827 cases of women from 1998 to 2001 in Hong Kong and found that the risk of GDM increased significantly with maternal age after 25 years old [8]. The Fourth International Conference of gestational diabetes and the ADA (American Diabetes Association) recommended that since the incidence is quite low, pregnant women aged less than 25 years need not be screened for GDM if without risk factors [9]. However, in this study, the proportion of pregnant women under 25 years old between the two groups was statistically insignificant, and the proportion of GDM group was higher than that of non-GDM group only in elder pregnant women (over 35 years old), and the fasting, 1-hour and 2-hour results of 75 g OGTT in pregnant women were positively correlated with their age. In addition, binary multivariate logistic regression analysis also confirmed that maternal age may be one of the risk factors for GDM morbidity. Therefore, the optimal gestational age for women of childbearing age should be 23 to 30 years old in order to reduce the incidence of pregnant complications due to advanced age.

Pre-pregnancy BMI and weight gain during pregnancy

Accumulating epidemiological data confirmed that regardless of racial difference, maternal obesity was an important risk factor of GDM morbidity and also increased the probability of macrosomia and childhood obesity [7,10-12]. According to Shin's study, women with obese prepregnancy BMI (≥30 kg/m^2) had increased odds of gestational diabetes mellitus (2.78; 2.60-2.96) compared to women with normal prepregnancy BMI (18.5-24.9 kg/m^2) [13]. In our study, the mean maternal pre-pregnancy BMI of GDM group was

significantly higher than that of non-GDM group (Z=-3.803, P=0.000), and the proportion of pregnant women with BMI of overweight (BMI=24~27.9 kg/m^2) and obesity (BMI ≥ 28 kg/m^2) was also significantly higher than that of non-GDM group. We also found that the fasting, 1-hour and 2-hour glucose values of 75 g OGTT were positively correlated with maternal pre-pregnancy BMI. Consequently, in clinical practice, it will help reduce the incidence of GDM for women of childbearing age while having proper diet, doing adequate exercise, and controlling pre-pregnancy weight prior to pregnancy.

Recently, some researchers demonstrated that excessive weight gain during first trimester increased the morbidity of GDM [7]. Although we did not take into account the body weight gain level during the first trimester, we analyzed the weight gain value of the entire pregnancy and found that weight gain value in non-GDM group was significantly higher than that in the GDM group (P=0.000). This phenomenon might be attributed to the scientific guidance of weight management and nutrient intake by the clinicians and nutritionists once the pregnant women were diagnosed with GDM. In order to make the gestational weight gain close to the standard value as recommended by the guidelines, we provided professional guidance for GDM patients on dietary history, exercise, blood glucose monitoring, and medication, mainly based upon the Pregnant Dietary Guidelines issued by the Women and Children Branch of Chinese Nutrition Society and the Gestational Diabetes Diagnosis and Treatment guidelines issued by Perinatal Medicine Branch of the Chinese Medical Association [14]. We did not take any mandatory intervention on the pregnant women with normal glucose tolerance, and as a consequence, weight gain during pregnancy of non-GDM group was distinctly higher than that of GDM group. A recent study suggested that the reasonable control of weight gain during pregnancy could significantly improve mother-child perinatal outcome [15]. In addition, our results showed that after weight management and nutritional guidance, mother-child perinatal outcome of GDM group was similar to that of non-GDM group except preterm labor.

Leg-to-height percentage

Mose et al. recently performed researches on Australian pregnant females to analyze the correlation between leg length and abnormal glucose tolerance. Interestingly, they found that women with GDM were a mean of 2.8 cm shorter than women who were glucose tolerant, due primarily to their leg lengths being a mean of 3.2 cm shorter. They also discovered that there were significantly negative correlation between the leg-to-height percentage and the 2-hour result of 75 g OGTT after adjustment for age and for BMI. Hence, they supposed that leg-to-height percentage was an independent impact factor of the 2-hour glucose value of 75 g OGTT [16]. Our study gave additional support to their conclusion. Therefore, pregnant women with shorter leg should be paid more attention to and their glucose tolerance screening should be taken at the early stage in order to reduce the incidence of adverse perinatal outcomes.

HBsAg

Lao et al. conducted a retrospective study on 767 nonanemic pregnant women in Hong Kong and found that HBsAg-positive females had a significantly higher incidence of GDM than HBsAg-negative ones (RR 3.51, 95% CI 1.83-6.73). Furthermore, the HBsAg-positive women with GDM had remarkably increased prevalence of high serum ferritin compared with the HBsAg-negative ones. They reasoned that chronic HBV infection might cause inflammatory necrosis of hepatocytess and increase the level of iron releasing from secondary cells, which might result in higher concentration of serum ferritin in HBsAg-positive population. Elevated serum ferritin level could lead to increased incidence of insulin resistance and GDM pathogenesis [17]. Our study analyzed the HBsAg carrier status of enrolled participants at the first trimester and found that the percentage of HBsAg-positive women in the GDM group was significantly higher than that in the non-GDM group 8.57% vs. 3.91%, P=0.015). Binary logistic regression analysis revealed that HBsAg carrier status is an independent risk factor for GDM (OR 3.173, 95%CI 1.387-7.260). However, no significant difference was observed in the serum ferritin levels between the two groups. Therefore, the underlying mechanisms for HBsAg-related GDM remains to be further explored.

Multigravidity and multiparity

Studies on pregnant women in the Arabian region suggested that multiparous women were 8.29 times more likely to have GDM than nulliparous women. However, after adjustment for maternal age and history of abortion, nulliparous women were 2.95 times more likely to develop GDM than parous women. Thereby, they postulated that high rate of GDM among grand multiparas might be due to the confounding effect of maternal age [18]. However, in our study, gravidity and parity of GDM group pregnant women were much higher than that of non-GDM group. The mechanisms of correlation between multigravidity and GDM remains to be further elucidated. Besides, excluding maternal age, BMI and other relevant factors through binary multivariate logistic regression analysis, more pregnancies are also considered to be one of the leading risk factors for GDM.

GDM history and DM family history

Getahun et al. pointed out that the risk of GDM was 13.2-fold higher in women who had history of GDM once than the ones without GDM history and even 25.9-fold higher in women who had history of GDM twice [19]. In our study, however, the majority of the pregnant women failed to undergo GDM screening during previous pregnancy, and thus our conclusion was relatively nugatory. However, our finding that the proportion of positive matrilineal family history of DM was much higher in GDM group than that in non-GDM group was consistent with other studies. In clinical practice, it is advisable to strengthen screening and management of pregnancies who had GDM history and/or DM family history at the early stage of pregnancy [20,21].

Dietary during pregnancy

We conducted a detailed survey on the dietary during pregnancy and found that the GDM pregnancies were much more inclined to have an unbalanced dietary, fondness for sweets and hotpot than the non-GDM ones. In addition, the percentage of enrolled participants whose daily intake of fruits greater than 500 g was higher in GDM group than that in non-GDM group. Accumulating evidence suggested that high-fat diet (high saturated fatty acids and low unsaturated fatty acids), sweet food, and high intake of fruits or cholesterol were prominent risk factors for GDM pathogenesis [22-24]. The main carbohydrate ingredients in fruit included glucose, sucrose, fructose, starch and the glycemic index of each was high. Thus, excessive intake of high glycemic index food is one of the reasons that caused abnormal glucose metabolism during pregnancy.

Intake of hot pot and stew food which contained a lot of saturated fat could also lead to elevated blood glucose, resulting in relative lack of insulin secretion and consequently insulin resistance. Due to the changes in hormonal levels during pregnancy, pregnancy itself could increase the risk of insulin resistance. The above dietary additionally posed high pressure on insulin secretion, leading to the occurrence of abnormal glucose metabolism [25]. The cuisine of western China was mostly spicy and greasy, which might increase the risk of abnormal glucose metabolism. Therefore, lifestyle and dietary guidance during pregnancy could help reduce the incidence of GDM and even reduce or delay type II diabetes.

The limitations for this study lies in the fact that this study was performed in the same centre and that a proportion of the data were obtained from patient questionnaires, which might compromise the accuracy and objectiveness of the data obtained.

Taken together, our study conducted a prospective cohort study in a population of western China that aimed to explore the risk factors for GDM and we found that advanced maternal age, multigravidity, high pre-pregnancy BMI, low leg-to-height percentage, HBsAg-positive status, positive matrilineal family history of diabetes, unbalanced diet, high fruit intake, high sweet food intake, high serum triglyceride and HbA1c levels are risk factors for GDM in western Chinese population. Our study might provide novel insight into the pathogenesis of GDM pathogenesis and could also help reduce the incidence of GDM, thus ultimately improving maternal and prenatal outcome.

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