Risk of gestational diabetes recurrence and the development of type 2 diabetes among women with a history of gestational diabetes and risk factors: a study among 18 clinical centers in China

Yumei Wei[1], Juan Juan[1], Rina Su[1], Geng Song[1], Xu Chen[2], Ruiqin Shan[3], Ying Li[4], Shihong Cui[5], Shangrong Fan[6], Ling Feng[7], Zishan You[8], Haixia Meng[9], Yan Cai[10], Cuilin Zhang[11], Huixia Yang[1]

[1]Department of Obstetrics and Gynecology, Peking University First Hospital, Beijing 100034, China;
[2]Department of Obstetrics, Tianjin Central Obstetrics and Gynecology Hospital, Tianjin 300199, China;
[3]Department of Obstetrics, Jinan Maternal and Child Health Hospital, Jinan, Shandong 250000, China;
[4]Department of Obstetrics, Dalian Maternity Hospital, Dalian, Liaoning 116033, China;
[5]Department of Obstetrics and Gynecology, The Third Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China;
[6]Department of Obstetrics, Shenzhen Peking University Hospital, Shenzhen, Guangdong 518036, China;
[7]Department of Obstetrics and Gynecology, Tongji Hospital Affiliated to Huazhong University of Science and Technology, Wuhan, Hubei 430030, China;
[8]Department of Obstetrics and Gynecology, Suzhou Jiulong Hospital Affiliated to Shanghai Jiaotong University, Suzhou, Jiangsu 320571, China;
[9]Department of Obstetrics, Affiliated Hospital of Inner Mongolia Medical University, Huhhot, Inner Mongolia 010050, China;
[10]Department of Obstetrics and Gynecology, The Fourth Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang 150001, China;
[11]Epidemiology Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20817, USA.

Abstract

Background: Gestational diabetes mellitus (GDM) brings health issues for both mothers and offspring, and GDM prevention is as important as GDM management. It was shown that a history of GDM was significantly associated with a higher maternal risk for GDM recurrence. The incidence of GDM recurrence was unclear because of the incidence of second-child was low before 2016 in China. We aim to investigate the prevalence of GDM recurrence and its associated high-risk factors which may be useful for the prediction of GDM recurrence in China.

Methods: A retrospective study was conducted which enrolled participants who underwent regular prenatal examination and delivered twice in the same hospital of 18 research centers. All participants were enrolled from January 2018 to October 2018, where they delivered the second baby during this period. A total of 6204 women were enrolled in this study, and 1002 women with a history of GDM were analyzed further. All participants enrolled in the study had an oral glucose tolerance test (OGTT) result at 24 to 28 weeks and were diagnosed as GDM in the first pregnancy according to the OGTT value (when any one of the following values is met or exceeded to the 75-g OGTT: 0 h [fasting], ≥5.10 mmol/L; 1 h, ≥10.00 mmol/L; and 2 h, ≥8.50 mmol/L). The prevalence of GDM recurrence and development of type 2 diabetes mellitus were calculated, and its related risk factors were analyzed.

Results: In 6204 participants, there are 1002 women (1002/6204, 16.15%) with a history of GDM and 5202 women (5202/6204, 83.85%) without a history of GDM. There are significant differences in age (32.43 ± 4.03 years *vs.* 33.00 ± 3.34 years *vs.* 32.19 ± 3.37 years, $P < 0.001$), pregnancy interval (4.06 ± 1.44 years *vs.* 3.52 ± 1.43 years *vs.* 3.38 ± 1.35 years, $P = 0.004$), prepregnancy body mass index (BMI) (27.40 ± 4.62 kg/m^2 *vs.* 23.50 ± 3.52 kg/m^2 *vs.* 22.55 ± 3.47 kg/m^2, $P < 0.001$), history of delivered macrosomia (22.7% *vs.* 11.0% *vs.* 6.2%, $P < 0.001$) among the development of diabetes mellitus (DM), recurrence of GDM, and normal women. Moreover, it seems so important in the degree of abnormal glucose metabolism in the first pregnancy to the recurrence of GDM and the development of DM. There are significant differences in OGTT levels of the first pregnancy such as area under the curve of OGTT value (18.31 ± 1.90 mmol/L *vs.* 16.27 ± 1.93 mmol/L *vs.* 15.55 ± 1.92 mmol/L, $P < 0.001$), OGTT fasting value (5.43 ± 0.48 mmol/L *vs.* 5.16 ± 0.49 mmol/L *vs.* 5.02 ± 0.47 mmol/L, $P < 0.001$), OGTT 1-hour value (10.93 ± 1.34 mmol/L *vs.* 9.69 ± 1.53 mmol/L *vs.* 9.15 ± 1.58 mmol/L, $P < 0.001$), OGTT 2-hour value (9.30 ± 1.66 mmol/L *vs.* 8.01 ± 1.32 mmol/L *vs.* 7.79 ± 1.38 mmol/L, $P < 0.001$), incidence of impaired fasting glucose (IFG) (fasting plasma glucose ≥5.6 mmol/L) (31.3% *vs.* 14.6% *vs.* 8.8%, $P < 0.001$), and incidence of two or more abnormal OGTT values (68.8% *vs.* 39.7% *vs.* 23.9%, $P < 0.001$) among the three groups. Using multivariate analysis, the factors, such as age (1.07 [1.02–1.12], $P = 0.006$), prepregnancy BMI (1.07 [1.02, 1.12], $P = 0.003$), and area under the curve of OGTT in the first pregnancy (1.14 [1.02, 1.26],

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002036

Yumei Wei and Juan Juan contributed equally to the work.

Correspondence to: Dr. Huixia Yang, Department of Obstetrics and Gynecology, Peking University First Hospital, Beijing 100034, China
E-Mail: yanghuixia@bjmu.edu.cn

Chinese Medical Journal 2022;135(6)

Received: 02-12-2021; **Online:** 07-03-2022 **Edited by:** Yanjie Yin

$P = 0.02$), have an effect on maternal GDM recurrence; the factors, such as age (1.28 [1.01–1.61], $P = 0.04$), pre-pregnancy BMI (1.26 [1.04, 1.53], $P = 0.02$), and area under the curve of OGTT in the first pregnancy (1.65 [1.04, 2.62], $P = 0.03$), have an effect on maternal DM developed further.

Conclusions: The history of GDM was significantly associated with a higher maternal risk for GDM recurrence during follow-up after the first pregnancy. The associated risk factors for GDM recurrence or development of DM include age, high pre-pregnancy BMI, history of delivered macrosomia, the OGTT level in the first pregnancy, such as the high area under the curve of OGTT, IFG, and two or more abnormal OGTT values. To prevent GDM recurrence, women with a history of GDM should do the preconception counseling before preparing next pregnancy.

Keywords: Gestational diabetes mellitus; Recurrence; Risk factors; Multipara; Primipara

Introduction

With the aging of the population, urbanization, and related dramatic changes toward sedentary lifestyle during the past few decades, the prevalence of diabetes mellitus (DM) has been growing rapidly worldwide. Gestational DM (GDM) in both mother and infants has a high risk of development of DM. GDM is one of the most common pregnancy complications and is associated with a higher risk of maternal morbidity and perinatal/neonatal morbidity,[1-5] and it also has long-term consequences for both the mothers and the offspring.[6-8] It has been reported that the prevalence of GDM was 17.5% to 18.9%.[9,10] Therefore, the prevention of GDM is particularly important, as well as the standardized management of GDM for DM prevention in adults.

After the second- and third-child policy was sequentially liberalized, the incidence of high-risk women, such as elder age, pre-pregnancy overweight or obesity, history of GDM, has been increased, and the prevalence of GDM would be increased. It has been proved that the history of GDM was one of the risk factors of GDM and the reported frequency of GDM recurrence ranges widely from 30% to 84%,[11-15] depending on the different population studies and the various diagnostic criteria employed.[11-15] It is reported that the prevalence of GDM recurrence was 43.75% to 55% in some local small sample study in China.[16,17] The limited data were correlated to the Chinese population because of the implementation of the "one-child policy" in China. In 2011, all pregnant women were suggested to do oral glucose tolerance test (OGTT), and the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria[18] were widely adopted for GDM diagnosis in China. With the increasing number of multiparas, the study of GDM recurrence and GDM follow-up would become the research focus. It has been reported that GDM was significantly associated with a higher maternal risk for a disorder of glucose metabolism during long-term follow-up after pregnancy in the hyperglycemia and adverse pregnancy outcomes (HAPO) Study in 2019.[1] However, it did not pay attention to the recurrence of GDM in pregnant women with a history of GDM.

This study examined predictors for recurrence of GDM and development of DM at their next pregnancy in China. Clinical outcomes of women with GDM at the index as well as the subsequent pregnancies were also compared. We aimed to determine the prevalence of GDM recurrence and its related risk factors in China.

Methods

Ethical approval

The study was reviewed and approved by the Institutional Review Board of Peking University First Hospital (2013 [572]). The informed consents were obtained from all the participants.

Study population

A population-based retrospective cohort study was conducted among women of reproductive age who delivered twice in the same hospital from 18 medical centers in this study between 2011 and 2018. Participants were enrolled in our study, and clinical information was collected including age, height, pre-pregnancy weight, OGTT fasting, 1-hour and 2-hour value, gestational interval, weight change between the first and second pregnancy, gestational weeks at delivery, delivered mode, birth weight, blood pressure, and pregnancy outcomes. Women who were diagnosed DM before the first pregnancy or did not do the OGTT during the first pregnancy were excluded from the current study. It compared the adverse pregnancy outcomes, such as GDM, preterm birth (PTB), and macrosomia between multipara and primipara, and the risk factors associated with the probability of GDM recurrence, were analyzed.

Participants and recruitment

There are 18 medical centers (Peking University First Hospital, Tianjin Central Maternity Hospital, Jinan Maternity and Child Care Hospital, Fujian Maternity and Child Care Hospital, Hubei Maternity and Child Care Hospital, Dalian Maternity Hospital, The Third Affiliated Hospital of Zhengzhou University, The First Affiliated Hospital of Zhengzhou University, Shenzhen Peking University Hospital, Tongji Hospital Affiliated of Huazhong University of Science and Technology, Taiyuan Maternity and Child Care Hospital, Qilu Hospital of Shandong University, Kowloon Hospital of Suzhou Affiliated to Shanghai Jiao Tong University, Affiliated of Inner Mongolia Medical University, Hainan General Hospital, The First Affiliated Hospital of Harbin Medical Hospital, The Fourth Affiliated Hospital of Harbin Medical Hospital, and Shunyi Hospital) in the current study (all centers have been standardized trained by the World Diabetes Foundation).

Participants who delivered the second-child from January 1, 2018 to December 31, 2018 were enrolled in our study.

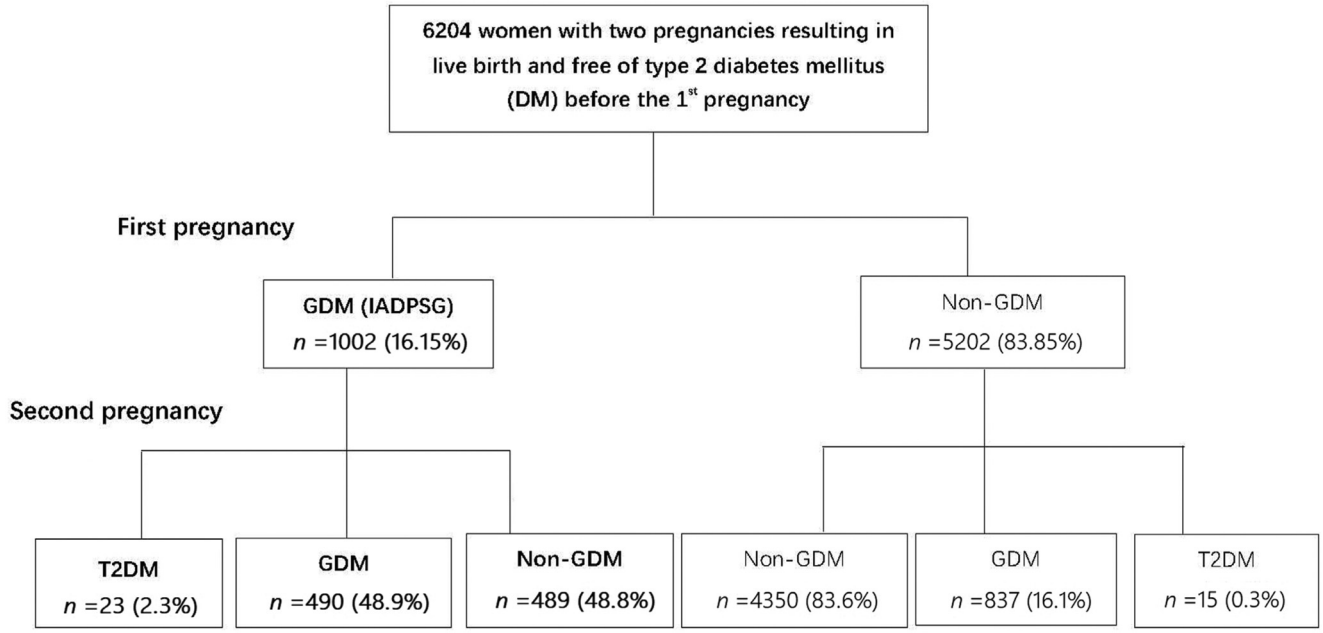

Figure 1: Flowchart of the participants Included in the study. GDM: Gestational diabetes mellitus; T2DM: Type 2 diabetes mellitus; IADPSG: International Association of Diabetes and Pregnancy Study Group.

Then, 6204 women without DM before the first pregnancy were enrolled in this study. All participants had done OGTT in the first pregnancy and delivered the first time after 2011 because the "one-step of GDM diagnostic method" and IADPSG criteria had been adopted since 2011. The range of the gestational interval was 1.0 to 7.1 years. The clinical information was collected including age, height, pre-pregnancy weight, OGTT fasting, 1-hour and 2-hour value, gestational interval, weight change between the first and second pregnancy, delivered weeks, delivered mode, birth weight, blood pressure, etc. All participants had done the OGTT at 24–28th gestational weeks, and the value of OGTT was collected to analyze and calculate the area under the curve of OGTT. Detailed information on the study population recruitment and derivation of the population used in the final analysis are shown in Figure 1.

We compared the incidence of the pregnancy outcomes such as GDM, PTB, and macrosomia between the first and the second pregnancy. The incidence of GDM is significantly higher in multipara, and it is especially higher in women with a history of GDM (48.9%). We would assess the impact of risk factors on GDM recurrence and early type 2 diabetes mellitus (T2DM) onset in women with a history of GDM and search strategies to prevent GDM recurrence.

Outcome measurement

Pre-pregnancy body mass index (BMI) was calculated as the maternal weight in kilograms divided by the height in meters squared (kg/m^2). Overweight and obesity were determined based on the BMI recommendations of the Group of China Obesity Task Force of the Chinese Ministry of Health[19] on account of interracial differences: obese, BMI ≥28 kg/m^2; overweight, 24 ≤ BMI < 28 kg/m^2; normal weig ht, 18.5 ≤ BMI < 23.9 kg/m^2; and underweight < 18.5 kg/m^2.

Macrosomia is defined as newborn birth weight ≥4000 g. PTB was defined as delivery at gestational age between 28 weeks and 42 weeks.

Ascertainment of GDM

All participants enrolled in the study had an OGTT result at 24 to 28 weeks, and GDM was diagnosed according to the OGTT value. GDM diagnosis can be made when any one of the following values is met or exceeded the 75-g OGTT: 0 h (fasting), ≥ 5.10 mmol/L; 1 h, ≥10.00 mmol/L; and 2 h, ≥8.50 mmol/L.

Area under the curve of OGTT is the area of the OGTT value in the graph and represents the degree of abnormal glucose metabolism. Area under the curve of OGTT = 1/2 (OGTT 0 h value + 2OGTT 1 h value + OGTT 2 h value) × 1 h

Ascertainment of T2DM

A diagnosis of DM was made when anyone's value met the following criteria[20,21]: (1) Glycated hemoglobin (HbA1c) ≥6.5%; (2) fasting plasma glucose (FPG) ≥7.00 mmol/L; (3) 2-h plasma glucose ≥ 11.10 mmol/L during a 75 g OGTT; (4) classic symptoms and a random plasma glucose ≥11.1 mmol/L.

The group of T2DM includes women who developed T2DM in the second pregnancy; the group of GDM includes women who had recurrent GDM in the second pregnancy; the non-GDM group includes women with a normal value of OGTT in the second pregnancy [Figure 1].

Statistical analysis

Baseline characteristics were presented as mean (standard deviation) for continuous variables and number (percentage)

for categorical variables. Paired samples *t* test or χ^2 test were used to compare the differences between characteristics in the first and second pregnancies. The χ^2 test or one-way analysis of variance was used to compare the distributions of baseline characteristics among three groups (DM, GDM, and normal) among women with GDM in the first pregnancy. Logistic regression models were used to examine the risk factors of hyperglycemia (GDM recurrence or early onset of DM) in the second pregnancy among women with GDM in the first pregnancy. We adjusted for various potential confounding factors, including age, pre-pregnancy BMI, area under the curve of OGTT in the first pregnancy, FPG ≥5.6 mmol/L in the first pregnancy, weight change between the twice pregnancy, history of delivered macrosomia, two or more abnormal OGTT value in the first pregnancy, and pregnancy interval in the multivariate model. All the statistical analyses were conducted using SPSS 20.0 statistical software (SPSS Inc., Chicago, IL, USA). A two-sided *P* value < 0.05 indicated statistically significant.

Results

Participants

In the current study, a total of 6204 women without DM before the first pregnancy and who underwent completed pregnancy outcome follow-up in 18 medical centers were finally included in the primary analysis [Figure 1].

The baseline characteristics of the study population between the first and second pregnancy are given in Supplementary Table 1, http://links.lww.com/CM9/A967. It showed that the age (31.91 ± 3.40 *vs.* 28.37 ± 3.22, $P < 0.001$), the pre-pregnancy BMI (22.25 ± 3.26 *vs.* 21.58 ± 3.11, $P < 0.001$), area under the curve of OGTT (13.41 ± 2.26 *vs.* 13.26 ± 2.12, $P < 0.001$), OGTT fasting value (4.56 ± 0.50 *vs.* 4.53 ± 0.46, $P < 0.001$), OGTT 1 hour value (7.81 ± 1.67 *vs.* 7.72 ± 1.58, $P < 0.001$), and OGTT 2-hour value (6.66 ± 1.31 *vs.* 6.57 ± 1.25, $P < 0.001$) are higher in the second pregnancy. In addition, the incidence of pre-pregnancy overweight (20.2% *vs.* 16.0%, $P < 0.001$) or obesity (5.4%*vs.* 3.5%, $P < 0.001$), impaired fasting glucose (IFG) (FPG≥5.6 mmol/L) (2.8% *vs.* 2.1%, $P < 0.001$), and two or more abnormal OGTT value (7.5% *vs.* 5.5%, $P < 0.001$) of the first pregnancy women was higher in multipara. There is also significant difference in birth weight (3342 ± 468 *vs.* 3372 ± 453, $P < 0.001$) and delivered weeks (39.09 ± 1.55 *vs.* 38.66 ± 1.42, $P < 0.001$) between the first and second pregnancy, and it does not have clinical significance. It has been proved that the incidence of GDM (21.4% *vs.* 16.2%, $P < 0.001$), PTB (5.2% *vs.* 4.8%, $P < 0.001$) and macrosomia (7.6% *vs.* 7.3%, $P < 0.001$) is higher in the second pregnancy, especially GDM.

Overall, in 6204 participants, there were 1002 (1002/6204, 16.15%) women with a history of GDM and 5202 (5202/6204, 83.85%) women did not [Table 1]. There were 490 women diagnosed as GDM who had a history of GDM and 837 women did not. The incidence of GDM (48.90% *vs.* 16.09%, odds ratio 5.21, 95% confidence interval [4.50–6.02], $P < 0.001$) in women with a history of GDM was significantly higher than that in women without a history of GDM. Moreover, there were 23 women (23/1002, 2.30%) who developed DM before the second pregnancy with a history of GDM. It has been proved that the history of GDM is one of the most important risk factors for GDM in multipara. The risk

Table 1: Risk factors on GDM recurrence in women with history of GDM.

Risk factors	DM (*n* = 23)	GDM in 2nd pregnancy (*n* = 190)	Normal in 2nd pregnancy (*n* = 489)	*P* value
Age at the first pregnancy	32.43 ± 4.03	33.00 ± 3.34	32.19 ± 3.37	**0.001**
Age ≥35 years	7 (30.4)	140 (28.6)	113 (23.1)	0.130
Pregnancy interval (years)	4.06 ± 1.44	3.52 ± 1.43	3.38 ± 1.35	**0.040**
Pre-pregnancy BMI (kg/m^2)	27.40 ± 4.62	23.50 ± 3.52	22.55 ± 3.47	**<0.001**
Pre-pregnancy BMI ≥ 28 kg/m^2	7 (43.8)	42 (9.6)	28 (6.8)	**<0.001**
Pre-pregnancy BMI 24–28 kg/m^2	6 (37.5)	140 (32.0)	92 (22.3)	
Area under the curve of OGTT in the first pregnancy	18.31 ± 1.90	16.27 ± 1.93	15.55 ± 1.92	**<0.001**
OGTT fasting value in the first pregnancy (mmol/L)	5.43 ± 0.48	5.16 ± 0.49	5.02 ± 0.47	**<0.001**
OGTT 1 h value in the first pregnancy (mmol/L)	10.93 ± 1.34	9.69 ± 1.53	9.15 ± 1.58	**<0.001**
OGTT 2 h value in the first pregnancy (mmol/L)	9.30 ± 1.66	8.01 ± 1.32	7.79 ± 1.38	**<0.001**
FPG ≥5.6 in the first pregnancy	5 (31.3)	67 (14.6)	40 (8.8)	**0.003**
Two or more abnormal OGTT value in the first pregnancy	11 (68.8)	182 (39.7)	109 (23.9)	**<0.001**
History of macrosomia (macrosomia of the first pregnancy)	5 (22.7)	53 (11.0)	30 (6.2)	**0.003**
Weight gain between the two pregnancies (kg)	3.09 ± 6.19	1.64 ± 6.49	1.32 ± 6.46	0.510
Birth weight of the second pregnancy (g)	3576 ± 579	3410 ± 518	3402 ± 455	0.250
Delivered weeks (of the second pregnancy)	38.17 ± 1.21	38.52 ± 1.66	38.58 ± 1.43	0.420
PTB	2 (8.7)	38 (7.8)	26 (5.3)	0.280
Macrosomia	3 (13.0)	51 (10.4)	41 (8.4)	0.470

Data are shown as n (%), mean ± standard deviation. BMI: Body mass index; DM: Diabetes mellitus; FPG: Fasting plasma glucose; GDM: Gestational diabetes mellitus; OGTT: Oral glucose tolerance test; PTB: Preterm birth.

Table 2: Multiple-factor analysis of GDM recurrence in women with history of GDM.

	GDM				DM			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Risk factors	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.08 (1.04, 1.12)	**<0.001**	1.07 (1.02, 1.12)	**0.006**	1.02 (0.90, 1.15)	0.740	1.28 (1.01, 1.61)	**0.040**
Pre-pregnancy BMI	1.08 (1.04, 1.13)	**<0.001**	1.07 (1.02, 1.12)	**0.006**	1.29 (1.15, 1.43)	**<0.001**	1.26 (1.04, 1.53)	**0.020**
Area under the curve of OGTT in the first pregnancy	1.22 (1.14, 1.31)	**<0.001**	1.14 (1.02, 1.26)	**0.020**	2.13 (1.54, 2.93)	**<0.001**	1.65 (1.04, 2.62)	**0.030**
IFG (FPG ≥5.6) in the first pregnancy	1.77 (1.17, 2.68)	**0.007**	1.28 (0.79, 2.06)	0.310	4.69 (1.55, 14.18)	**0.006**	1.43 (0.24, 8.60)	0.690
Two or more abnormal OGTT value in the first pregnancy	2.09 (1.57, 2.78)	**<0.001**	1.28 (0.84, 1.96)	0.250	7.00 (2.38, 20.60)	**<0.001**	3.49 (0.48, 25.18)	0.220
History of macrosomia	1.85 (1.16, 2.95)	**0.010**	1.64 (0.95, 2.83)	0.080	4.42 (1.53, 12.81)	**0.006**	–	–
Weight change between twice pregnancy	1.01 (0.99, 1.03)	0.480	1.01 (0.98, 1.03)	0.700	1.04 (0.97, 1.12)	0.310	1.00 (0.91, 1.11)	0.960
Gestational interval	1.07 (0.98, 1.17)	0.140	1.02 (0.91, 1.14)	0.790	1.41 (1.05, 1.88)	0.020	1.56 (0.93, 2.61)	0.090

BMI: Body mass index; CI: Confidence interval; DM: Diabetes mellitus; FPG: Fasting plasma glucose; GDM: Gestational diabetes mellitus; OGTT: Oral glucose tolerance test; OR: Odds ratio.

factors of GDM recurrence would be analyzed further in the current study.

GDM recurrence and its related risk factors

Relevant factors for GDM recurrence are shown in Table 1. The multipara with a history of GDM was grouped into group DM, group GDM, and group normal according to the status of glucose metabolism after the first pregnancy. There are significant differences in age (32.43 ± 4.03 years *vs.* 33.00 ± 3.34 years *vs.* 32.19 ± 3.37 years, $P < 0.001$), pregnancy interval (4.06 ± 1.44 years *vs.* 3.52 ± 1.43 years *vs.* 3.38 ± 1.35 years, $P = 0.04$), pre-pregnancy BMI (27.40 ± 4.62 kg/m^2 *vs.* 23.50 ± 3.52 kg/m^2 *vs.* 22.55 ± 3.47 kg/m^2, $P < 0.001$), history of macrosomia (22.7% *vs.* 11.0% *vs.* 6.2%, $P = 0.003$) in the DM, GDM, and normal groups. Moreover, it seems more important in the OGTT levels of the first pregnancy, such as area under the curve of OGTT value (18.31 ± 1.90 mmol/L *vs.* 16.27 ± 1.93 mmol/L *vs.* 15.55 ± 1.92 mmol/L, $P < 0.001$), OGTT fasting value (5.43 ± 0.48 mmol/L *vs.* 5.16 ± 0.49 mmol/L *vs.* 5.02 ± 0.47 mmol/L, $P < 0.001$), OGTT 1-hour value (10.93 ± 1.34 mmol/L *vs.* 9.69 ± 1.53 mmol/L *vs.* 9.15 ± 1.58 mmol/L, $P < 0.001$), OGTT 2-hour value (9.30 ± 1.66 mmol/L *vs.* 8.01 ± 1.32 mmol/L *vs.* 7.79 ± 1.38 mmol/L, $P < 0.001$), incidence of IFG (FPG≥ 5.6 mmol/L) (31.3% *vs.* 14.6% *vs.* 8.8%, $P = 0.003$), and incidence of two or more abnormal OGTT values (68.8% *vs.* 39.7% *vs.* 23.9%, $P < 0.001$) among them to predict GDM recurrence or DM.

However, there was no difference in weight change between the two pregnancies (3.09 ± 6.19 *vs.* 1.64 ± 6.49 *vs.* 1.32 ± 6.46, $P = 0.51$). There are also differences in pregnancy outcomes such as PTB (8.7% *vs.* 7.7% *vs.* 5.3%) and macrosomia (13.0% *vs.* 10.4% *vs.* 8.4%), but it is not significant.

Risk factors of GDM recurrence and early DM onset following a GDM pregnancy

In the further analysis [Table 2], compared with glucose metabolism in normal women, there are some high-risk factors of GDM recurrence or early DM onset during the second pregnancy. In univariate analysis, the risk factors, such as age (1.33 [1.00, 1.77], $P = 0.05$), pre-pregnancy BMI (1.08 [1.04, 1.13], $P < 0.001$), area under the curve of OGTT in the first pregnancy (1.22 [1.14–1.31], $P < 0.001$), IFG in the first pregnancy (1.77 [1.17–2.68], $P = 0.007$), two or more abnormal OGTT value in the first pregnancy (2.09 [1.57–2.78], $P < 0.001$), and history of delivered macrosomia (1.85 [1.16–2.95], $P = 0.01$), are different significantly to GDM recurrence. To early DM onset, it is different in pre-pregnancy BMI (1.29 [1.15, 1.43], $P < 0.001$), area under the curve of OGTT in the first pregnancy (2.13 [1.54–2.93], $P < 0.001$), IFG in the first pregnancy (4.69 [1.55–14.18], $P = 0.006$), two or more abnormal OGTT value in the first pregnancy (7.00 [2.38–20.60], $P < 0.001$), history of delivered macrosomia (4.42 [1.53–12.81], $P = 0.006$), and gestational interval (1.41 [1.05–1.88], $P = 0.02$).

Using multivariate analysis, the factors, such as age (1.07 [1.02–1.12], $P = 0.006$), pre-pregnancy BMI (1.07 [1.02, 1.12], $P = 0.003$), and area under the curve of OGTT in the first pregnancy (1.14 [1.02, 1.26], $P = 0.02$), have an effect on maternal GDM recurrence; the factors, such as age (1.28 [1.01–1.61], $P = 0.04$), pre-pregnancy BMI (1.26 [1.04, 1.53], $P = 0.02$), and area under the curve of OGTT in the first pregnancy (1.65 [1.04, 2.62], $P = 0.03$), have an effect on maternal DM developed further.

Discussion

Women with GDM have a higher chance of developing type 2 diabetes, the burden of which is also increasing in China. It has been reported that GDM was significantly associated with a higher maternal risk for a disorder of glucose metabolism during long-term follow-up after pregnancy by the HAPO study.[1] However, after the second-child policy was fully liberalized in China, the rate of GDM recurrence may be a more important problem in the GDM follow-up study. Given that most of the risk factors for GDM persist or become worse in subsequent

pregnancies, it is not surprising that GDM has a high recurrence rate.[22] In the current study, the rate of GDM recurrence was 48.90%, which is significantly higher than that of women without a history of GDM. Therefore, the history of GDM is one of the most important risk factors for GDM in multipara.

Meanwhile, it is particularly important to reduce the risk of adverse pregnancy outcomes as the proportion of high-risk pregnant women, such as advanced age, obesity, and history of GDM, was further increased. In the current study, the incidence of adverse pregnancy outcomes, such as GDM, PTB, and macrosomia, is higher in multipara, especially GDM. GDM prevention, especially in women with a history of GDM, is particularly important to improve pregnancy outcomes in multipara.

It is the fact that a wide range of GDM recurrence rates have been reported [11] in various studies. The rate is 48.90% in our study, which is similar to that of the other studies in China.[16,17] Clinically, identifying women who are more likely to have GDM recurrence may be important in planning future pregnancies. It has been reported that the risk factors include ethnic characteristics of the first pregnancy (maternal age, BMI, weight gain during pregnancy, insulin use, glucose levels, fetal weight, or history of macrosomia) and the characteristics of the second pregnancy (BMI, weight gain during pregnancy, gestational interval, and weight retention).[11,23-25]

It is suggested to have the preconception counseling for women with a history of GDM before they planned subsequent pregnancy. It should carefully assess the effect of the first pregnancy status on the subsequent pregnancy. In our study, we found that the risk factors, such as age, pre-pregnancy BMI, area under the curve of OGTT in the first pregnancy, had the greatest effect on GDM recurrence and early DM onset. Women with a history of GDM should do their best to lose weight to a normal pre-pregnancy BMI. It was found other risk factors of GDM recurrence including FPG≥5.6 mmol/L in the first pregnancy, history of macrosomia, two or more abnormal OGTT value in the first pregnancy, and pregnancy interval in this study. For the high-risk women, lifestyle management should be suggested to prevent GDM recurrence. It is supposed that the glycemic control status might be not very well in most women with a history of macrosomia, and it had an effect on the infant. Therefore, their lifestyle postpartum may be not better than pregnancy, and the risk of GDM recurrence would be increased in the subsequent pregnancy. International Federation of Obstetrics and Gynecology suggested that GDM women should be advised repeatedly during pregnancy to continue the same healthy lifestyle after delivery to reduce the risk of future obesity, T2DM, and cardiovascular diseases.[19]

Meanwhile, the prevalence of DM has risen dramatically as the economy and lifestyles of people have changed in China over recent decades.[3] It has been reported that GDM women had an increased risk (relative risk = 7.43)[26] of developing type 2 diabetes compared with those normoglycemic women. The incidence of early onset of DM in our study is also lower than that of the systematic review of Kim *et al*,[27] which has showed that the cumulative incidence of diabetes ranged from 2.6% to over 70% in studies. Its reason may be that all participants have done OGTT and DM women before the first pregnancy have been excluded.

However, it has been reported[3] that the awareness rate of DM status among reproductive-aged women was extremely low, and the management of DM remained unsatisfactory, even in patients who are aware of their DM status. Preconception counseling to the history of GDM is one of the most important aspects to prevent GDM recurrence, improve maternal and neonatal outcomes, and reduce the maternal and neonatal risk of DM.

To our knowledge, this is the first and largest population-based study to investigate the GDM recurrent rate and its associated risk factors in China. It would be valuable to explore the GDM recurrent prevention strategies. However, some limitations should be mentioned. The follow-up time since the first pregnancy is up to 7 years, which is relatively short. Continuation of following up the women is ongoing.

Conclusions

The increasing prevalence of gestational diabetes has become a huge burden after the second-child policy was fully liberalized in China. GDM brings health issues for both mothers and offspring, and GDM prevention is as important as GDM management. History of GDM was significantly associated with a higher maternal risk for GDM recurrence during follow-up after the first pregnancy. The associated risk factors for GDM recurrence or early onset of DM include age, high pre-pregnancy BMI, history of macrosomia, and the characteristics of the glucose metabolism in the first pregnancy (such as high area under the curve of OGTT, IFG, and two or more abnormal OGTT value). To prevent GDM recurrence, women with a history of GDM should do the preconception counseling before preparing next pregnancy. GDM women should be suggested to keep healthy lifestyle, especially those with a second-child plan.

Acknowledgements

This study was based in part on data provided by the Peking University First Hospital, Tianjin Central Maternity Hospital, Jinan Maternity and Child Care Hospital, Fujian Maternity and Child Care Hospital, Hubei Maternity and Child Care Hospital, Dalian Maternity Hospital, The Third Affiliated Hospital of Zhengzhou University, The First Affiliated Hospital of Zhengzhou University, Shenzhen Peking University Hospital, Tongji Hospital Affiliated of Huazhong University of Science and Technology, Taiyuan Maternity and Child Care Hospital, Qilu Hospital of Shandong University, Kowloon Hospital of Suzhou Affiliated to Shanghai Jiao Tong University, Affiliated of Inner Mongolia Medical University, Hainan General Hospital, The First Affiliated Hospital of Harbin Medical Hospital, The Fourth Affiliated Hospital of Harbin Medical Hospital, and Shunyi Hospital.

Funding

This study was supported by grants from the National Key Research and Development Program of China (No. 2021YFC2700700), the National Natural Science Foundation of China (No. 81801467) and the State Key Development Program for Basic Research of China (No. 2015CB943304).

Conflicts of interest

None.

References

1. Lowe WL Jr, Scholtens DM, Lowe LP, Kuang A, Nodzenski M, Talbot O, *et al*. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. JAMA 2018;320:1005–1016. doi: 10.1001/jama.2018.11628.
2. Farrar D, Simmonds M, Bryant M, Sheldon TA, Tuffnell D, Golder S, *et al*. Hyperglycaemia and risk of adverse perinatal outcomes: systematic review and meta-analysis. BMJ 2016;354:i4694. doi: 10.1136/bmj.i4694.
3. Wei Y, Xu Q, Yang H, Yang Y, Wang L, Chen H, *et al*. Preconception diabetes mellitus and adverse pregnancy outcomes in over 6.4 million women: a population-based cohort study in China. PLoS Med 2019;16:e1002926. doi: 10.1371/journal.pmed.1002926.
4. Alexopoulos AS, Blair R, Peters AL. Management of preexisting diabetes in pregnancy: a review. JAMA 2019;321:1811–1819. doi: 10.1001/jama.2019.4981.
5. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, *et al*. HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002. doi: 10.1056/NEJMoa0707943.
6. Juan J, Yang HX, Su RN, Kapur A. Diagnosis of gestational diabetes mellitus in China: perspective, progress and prospects. Matern Fetal Med 2019;1:31–37. doi: 10.1097/FM9.0000000000000008.
7. Li M, Rawal S, Hinnkle SN, Zhu YY, Tekola-Ayele F, Tsai MY, *et al*. Sex hormone-binding globulin, cardiometabolic biomarkers, and gestational diabetes: a longitudinal study and meta-analysis. Matern Fetal Med 2020;2:2–9. doi: 10.1097/FM9.0000000000000037.
8. Shou C, Wei YM, Wang C, Yang HX. Updates in long-term maternal and fetal adverse effects of gestational diabetes mellitus. Matern Fetal Med 2019;1:91–94. doi: 10.1097/FM9.0000000000000019.
9. Zhu WW, Fan L, Yang HX, Kong LY, Su SP, Wang ZL, *et al*. Fasting plasma glucose at 24-28 weeks to screen for gestational diabetes mellitus: new evidence from China. Diabetes Care 2013;36:2038–2040. doi: 10.2337/dc12-2465.
10. Wei Y, Yang H, Zhu W, Yang H, Li H, Yan J, *et al*. International Association of Diabetes and Pregnancy Study Group criteria is suitable for gestational diabetes mellitus diagnosis: further evidence from China. Chin Med J (Engl) 2014;127:3553–3556. doi: 10.3760/cma.j.issn.0366-6999.2014 0898.
11. Kim C, Berger DK, Chamany S. Recurrence of gestational diabetes mellitus: a systematic review. Diabetes Care 2007;30:1314–1319. doi: 10.2337/dc06-2517.
12. MacNeill S, Dodds L, Hamilton DC, Armson BA, VandenHof M. Rates and risk factors for recurrence of gestational diabetes. Diabetes Care 2001;24:659–662. doi: 10.2337/diacare.24.4.659.
13. Kruse AR, Darling MS, Hansen MKL, Markman MJ, Lauszus FF, Wielandt HB. Recurrence of gestational diabetes in primiparous women. Acta Obstet Gynecol Scand 2015;94:1367–1372. doi: 10.1111/aogs.12764.
14. Bottalico JN. Recurrent gestational diabetes: risk factors, diagnosis, management, and implications. Semin Perinatol 2007;31:176–184. doi: 10.1053/j.semperi.2007.03.006.
15. Getahun D, Fassett MJ, Jacobsen SJ. Gestational diabetes: risk of recurrence in subsequent pregnancies. Am J Obstet Gynecol 2010;203:467.e1–467.e6. doi: 10.1016/j.ajog.2010.05.032.
16. Wang N, Lu W, Xu Y, Mao S, He M, Lin X, *et al*. Recurrence of diet-treated gestational diabetes in primiparous women in northern Zhejiang, China: epidemiology, risk factors and implications. J Obstet Gynaecol Res 2018;44:1391–1396. doi: 10.1111/jog.13688.
17. Wang YY, Liu Y, Li C, Lin J, Liu XM, Sheng JZ, *et al*. Frequency and risk factors for recurrent gestational diabetes mellitus in primiparous women: a case control study. BMC Endocr Disord 2019;19:22. doi: 10.1186/s12902-019-0349-4.
18. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, *et al*. International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676–682. doi: 10.2337/dc09-1848.
19. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–163. doi: 10.1016/S0140-6736(03)15268-3.
20. Standards of medical care in diabetes-2017: summary of revisions. Diabetes Care 2017;40:S4–S5. doi: 10.2337/dc17-S003.
21. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, *et al*. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: a pragmatic guide for diagnosis, management, and care. Int J Gynaecol Obstet 2015;131:S173–S211. doi: 10.1016/S0020-7292(15)30033-3.
22. Wei Y, Yang H. Perspectives on diagnostic strategies for hyperglycemia in pregnancy - Dealing with the barriers and challenges in China. Diabetes Res Clin Pract 2018;145:84–87. doi: 10.1016/j.diabres.2018.04.005.
23. Schwartz N, Nachum Z, Green MS. The prevalence of gestational diabetes mellitus recurrence - Effect of ethnicity and parity: a metaanalysis. Am J Obstet Gynecol 2015;213:310–317. doi: 10.1016/j.ajog.2015.03.011.
24. Wong VW, Chong S, Chenn R, Jalaludin B. Factors predicting recurrence of gestational diabetes in a high-risk multi-ethnic population. Aust N Z J Obstet Gynaecol 2019;59:831–836. doi: 10.1111/ajo.12973.
25. Schwartz N, Nachum Z, Green MS. Risk factors of gestational diabetes mellitus recurrence: a meta-analysis. Endocrine 2016;53:662–671. doi: 10.1007/s12020-016-0922-9.
26. Bellamy L, Casas JP, Hingorani AD, Willisams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 2009;373:1773–1779. doi: 10.1016/S0140-6736(09)60731-5.
27. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care 2002;25:1862–1868. doi: 10.2337/diacare.25.10.1862.

How to cite this article: Wei Y, Juan J, Su R, Song G, Chen X, Shan R, Li Y, Cui S, Fan S, Feng L, You Z, Meng H, Cai Y, Zhang C, Yang H. Risk of gestational diabetes recurrence and the development of type 2 diabetes among women with a history of gestational diabetes and risk factors: a study among 18 clinical centers in China. Chin Med J 2022;135:665–671. doi: 10.1097/CM9.0000000000002036