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Original Article

Association of gestational diabetes mellitus with preeclampsia: a retrospective cohort study

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Abstract: Objective: To explore the impact of gestational diabetes mellitus (GDM) on preeclampsia. Methods: Singleton pregnant women who registered in our hospital between January 2010 and January 2020 were enrolled in this retrospective cohort study. GDM is diagnosed according to the criteria of the International Association of Diabetes and Pregnancy Study Groups Consensus. Univariate and multivariate logistic regression analyses were conducted to estimate the relative risk between GDM and preeclampsia. Results: Among the 800 singleton pregnancy women analyzed, 66 (8.25%) was diagnosed with GDM. We found that women with GDM had a higher risk of developing preeclampsia than women with non-GDM (12.12% vs. 4.09%, P<0.05). Multivariate analysis showed that GDM (odds ratio [OR] 2.95, 95% confidence interval [CI] 1.28-6.83), pre-pregnancy BMI ≥25 (OR 3.15, CI 1.37-7.28) and dyslipidemia (OR 2.53, CI 1.01-6.33) were significantly associated with preeclampsia. Conclusion: GDM, pre-pregnancy BMI ≥25 and dyslipidemia are significantly associated with preeclampsia.

Keywords: Gestational diabetes mellitus, preeclampsia, prepregnancy BMI, dyslipidemia

Introduction

Preeclampsia is a pregnancy disorder with hypertension after 20 weeks of gestation, often accompanied by proteinuria. Clinical manifestations of preeclampsia include hypertension, edema, proteinuria and vasoconstriction [1]. The pathogenesis of preeclampsia is not clearly known. As one of the causes of poor perinatal outcomes, preeclampsia may develop into eclampsia if not properly treated. In addition, pregnancy with preeclampsia may lead to future cardiovascular disease and metabolic syndrome [2-4]. Gestational diabetes mellitus (GDM) is defined as glucose intolerance first detected during pregnancy [5]. GDM is associated with maternal and neonatal complications in singleton pregnancies [6-8].

There have been some studies on the relationship between GDM and preeclampsia, but the results are controversial or contradictory. Some studies have suggested a correlation between GDM and preeclampsia [1, 9, 10]. But other studies showed no association between gestational diabetes and preeclampsia [11]. However, most of their studies did not adjust for confounders, which could lead to biased results.

The purpose of this study is to evaluate the correlation between GDM and preeclampsia by logistic regression analysis which can adjust the influence of confounding factors on the results, with a hope to provide a reference for clinical prevention and treatment of preeclampsia.

Patients and methods

This study retrospectively included singleton pregnant women who successfully live delivery in Daqing Oilfield General Hospital, from January 2010 to January 2020. The clinical data and outcomes for mothers were obtained from clinical records. The data collected included demographic and obstetric parameters. All patients were screened for GDM at 24 to 28 weeks gestation and for preeclampsia at 20 to 39 weeks of gestation.

GDM is diagnosed according to the criterion of the International Association of Diabetes and

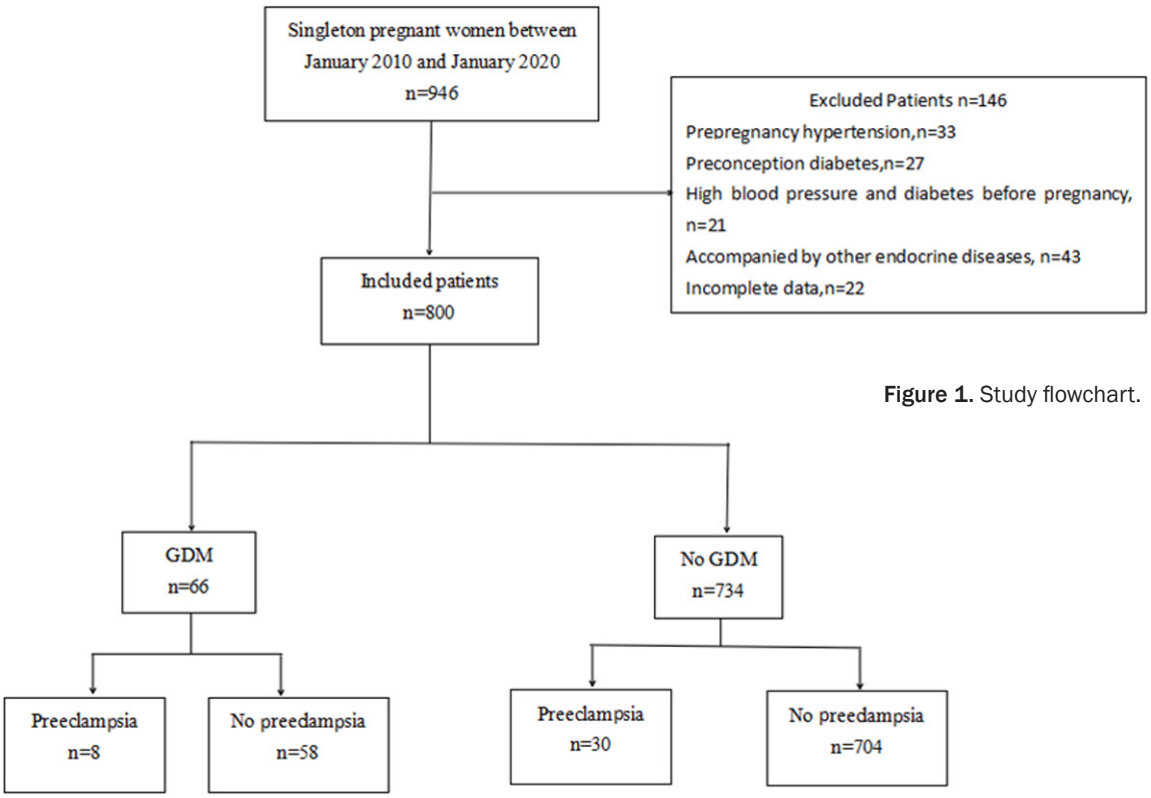

Figure 1. Study flowchart.

Pregnancy Study Groups Consensus [12]. Briefly, GDM received a 75 g oral glucose tolerance test (OGTT) between 24 and 28 weeks gestation and they had fasting blood glucose ≥5.1 mmol/L (92 mg/dL), 1-hour plasma glucose ≥10.0 mmol/L (180 mg/dL) and 2-hour plasma glucose ≥8.5 mmol/L (153 mg/dL).

Preeclampsia was diagnosed at 20 to 39 weeks of gestation and confirmed as preeclampsia if the pregnant women had systolic or diastolic blood pressure of >140/90 mmHg and 24 h urinary albuminuria >300 mg [13].

Inclusion criteria: Singleton pregnant women who successfully live delivery in a hospital. Exclusion criteria: pregnant women with type 1 or type 2 diabetes mellitus diagnosed before pregnancy; pregnant women with hypertension or cardiovascular disease diagnosed before pregnancy; pregnant women with a history of a serious systemic disease, such as cirrhosis, severe anemia, chronic renal failure or immune system disease; pregnant women with untreated endocrine diseases (hyperadrenal, hypoadrenal, hyperthyroidism or hypothyroidism), or patients without complete case data.

The retrospective study conformed with the principles of the Declaration of Helsinki, and obtain approval from an ethics committee of a Daqing Oilfield General Hospital. The study received no special funding from funding agencies in the public, commercial or non-profit sectors.

Statistical analysis was performed using Stata 13.0 software (Stata Corp, USA). Continuous variables were compared using student T-test or Mann-Whitney U test. The Chi-square test and Fisher's exact test were used to compare categorical variables. Associations between GDM and the risk of preeclampsia were tested by univariate analysis and multivariate logistic regression analysis. The dependent variable that we studied was preeclampsia. Results of logistic regression were expressed as adjusted OR with the 95% confidence interval (CI), and potential confounders include age, pregnancy BMI, education level, folic acid supplement, dyslipidemia, family history of hypertension and polycystic ovary syndrome. $P<0.05$ was considered statistically significant.

Results

A total of 800 pregnant women were included in this retrospective cohort study from January 2010 to January 2020 (**Figure 1**), including 66

Table 1. Demographics and pregnancy characteristics data

	No. of pregnant women (n = 800)	No preeclampsia (n = 762, [95.25%])	Preeclampsia (n = 38, [4.75%])	*P* value
Age	800	30.62±4.94	31.24±4.17	0.451
Pregnancy BMI (kg/m^2)	800	20.99±2.84	23.31±2.10	0.000
Pregnancy BMI (kg/m^2)				0.002
<25	725	696 (96.00)	29 (4.00)	
≥25	75	66 (88.00)	9 (12.00)	
GDM				0.003
No	734 (91.75)	704 (95.91)	30 (4.09)	
Yes	66 (8.25)	58 (87.88)	8 (12.12)	
Education level				0.471
Junior high school and below	81	75 (92.59)	6 (7.41)	
High school	346	333 (95.24)	13 (3.76)	
University	315	298 (94.60)	17 (5.40)	
Postgraduate and above	58	56 (95.55)	2 (4.75)	
Folic acid supplement				0.166
No	145	135 (93.10)	10 (6.90)	
Yes	655	637 (95.79)	28 (4.21)	
Parity				0.289
Unipara	624	597 (95.67)	27 (4.33)	
Multipara	176	165 (93.75)	11 (6.25)	
Dyslipidemia				0.014
No	664	638 (96.08)	26 (3.92)	
Yes	136	124 (91.18)	12 (8.82)	
Family history of hypertension				0.018
No	611	588 (9624)	23 (3.76)	
Yes	189	174 (92.06)	15 (7.94)	
Polycystic ovary syndrome				0.046
No	711	681 (95.78)	30 (4.22)	
Yes	89	81 (91.01)	8 (8.99)	

Note: BMI, Body mass index; GDM, gestational diabetes mellitus.

pregnant women with GDM (8.25%) and 38 pregnant women with preeclampsia (4.75%). Among women with GDM, 8 patients (8/66, 12.12%) developed preeclampsia; among women with non-gestational diabetes, there were 30 cases (30/734, 4.09%) of preeclampsia (P<0.05). Demographics and pregnancy characteristics are presented in **Table 1**.

Univariate and Multivariate analysis

We first performed a univariate analysis to screen out the potential risk factors for preeclampsia. Multivariate logistic regression analysis was performed on the basis of univariate analysis. Regression analysis was used to adjust the influence of confounding factors, including age, pregnancy BMI, education level, folic acid supplement, dyslipidemia, family history of hypertension and polycystic ovary syndrome, and we assign values to related variables (**Table 2**). Univariate analysis revealed that pregnancy GDM (OR 4.50, CI 2.08-9.74), pre-pregnancy BMI ≥25 (OR 3.57, CI 1.61-7.88), dyslipidemia (OR 2.47, CI 1.21-5.03), and family history of hypertension (OR 2.20, CI 1.13-4.32) as risk factors for preeclampsia (**Table 3**). After adjustment for all confounding factors, GDM (OR 2.95, CI 1.28-6.83), pre-pregnancy BMI ≥25 (OR 3.15, CI 1.37-7.28) and dyslipidemia (OR 2.53, CI 1.01-6.33) were risk factors for preeclampsia (**Table 4**).

Establishment of a prediction model for preeclampsia in singleton pregnant women

A predictive model was established based on independent risk factors for detection of pre-

Table 2. Assignment of related factors

Relevant factor	Variable assignment
Age	Continuous variables
Pregnancy BMI (kg/m^2)	<25 = 0, ≥25 = 1
GDM	Yes = 1, No = 0
Education level	Junior high school and below = 1, High school = 2, University = 3, Postgraduate and above = 4
Folic acid supplement	Yes = 1, No = 0
Parity	Multipara = 1, Unipara = 0
Dyslipidemia	Yes = 1, No = 0
Family history of hypertension	Yes = 1, No = 0
Polycystic ovary syndrome	Yes = 1, No = 0
Preeclampsia	Yes = 1, No = 0

Note: BMI, Body mass index; GDM, gestational diabetes mellitus.

Table 3. Univariate risk analyses for preeclampsia

	Preeclampsia (n = 38, [4.75%])	Univariate analysis	
		P value	OR (95% CI)
Age	38	0.451	1.03 (0.96-1.10)
Pregnancy BMI (kg/m^2)		0.002	
<25	29 (4.00)		1
≥25	9 (12.00)		3.57 (1.61-7.88)
GDM		0.000	
No	30 (4.09)		1
Yes	8 (12.12)		4.50 (2.08-9.74)
Education level		0.482	
Junior high school and below	6 (7.41)		1
High school	13 (3.76)		0.49 (0.18-1.325)
University	17 (5.40)		0.71 (0.27-1.87)
Postgraduate and above	2 (4.75)		0.45 (0.09-2.30)
Folic acid supplement		0.183	
No	10 (6.17)		1
Yes	28 (4.39)		0.60 (0.29-1.27)
Parity		0.292	
Unipara	27 (4.33)		1
Multipara	11 (6.25)		1.47 (0.72-3.03)
Dyslipidemia		0.013	
No	26 (3.92)		1
Yes	12(8.82)		2.47 (1.21-5.03)
Family history of hypertension		0.021	
No	24 (3.92)		1
Yes	14 (7.45)		2.20 (1.13-4.32)
Polycystic ovary syndrome		0.052	
No	30 (4.22)		1
Yes	8 (8.99)		2.24 (0.99-5.06)

Note: BMI, Body mass index; GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval.

eclampsia in women with singleton pregnancy: Logit P = (-3.542 + 1.212 × Pre-BMI + 1.348 × GDM + 0.709 × Dyslipidemia). Hosmer-lemeshow test concluded that the goodness of fit of the prediction model was relatively high (P = 0.756). The ROC curve shows that the maximum value of the Yoden index is 0.445, in this case, the sensitivity of the prediction model is 86.80% and the specificity is 57.7%. The area under the curve (AUC) is 0.767 (**Figure 2**).

Discussion

GDM and preeclampsia are common complications which are harmful to the health of pregnant women. In this retrospective cohort study, we aim to explore the correlation between GDM and preeclampsia. We found that 66 pregnant women with GDM (8.25%) and 38 pregnant women with preeclampsia (12.12%). In addition, among women with GDM, 8 patients (8/66, 12.12%) developed preeclampsia and among women with non-gestational diabetes, there were 30 cases (30/734, 4.09%) of preeclampsia

Table 4. Multivariate risk analyses for preeclampsia

	Preeclampsia (n = 38, [4.75%])	Multivariate analysis	
		Adjusted OR (95% CI)	*P* Value
Age	38	1.04 (0.96-1.11)	0.352
Pregnancy BMI (kg/m^2)			0.007
<25	29 (4.00)	1	
≥25	9 (12.00)	3.15 (1.37-7.28)	
GDM			0.011
No	30 (4.09)	1	
Yes	8 (12.12)	2.95 (1.28-6.83)	
Education level			0.357
Junior high school and below	6 (7.41)	1	
High school	13 (3.76)	0.66 (0.22-1.98)	
University	17 (5.40)	1.21 (0.39-3.74)	
Postgraduate and above	2 (4.75)	0.37 (0.06-2.50)	
Folic acid supplement			0.084
No	10 (6.17)	1	
Yes	28 (4.39)	0.42 (0.16-1.13)	
Parity			0.739
Unipara	27 (4.33)	1	
Multipara	11 (6.25)	1.17 (0.47-2.93)	
Dyslipidemia			0.048
No	26 (3.92)	1	
Yes	12 (8.82)	2.53 (1.01-6.33)	
Family history of hypertension			0..241
No	24 (3.92)	1	
Yes	14 (7.45)	1.58 (0.74-3.39)	
Polycystic ovary syndrome			0.311
No	30 (4.22)	1	
Yes	8 (8.99)	1.58 (0.65-3.83)	

Note: BMI, Body mass index; GDM, gestational diabetes mellitus; OR, odds ratio; CI, confidence interval.

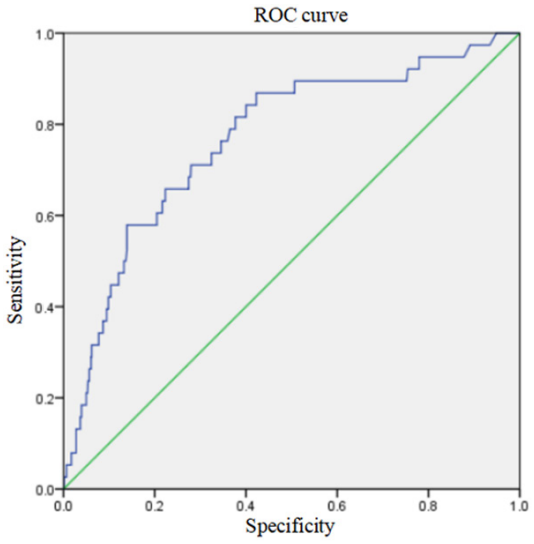

Figure 2. ROC curve of prediction model.

(P<0.05). Our study found that GDM was significantly associated with preeclampsia, women with GDM are 2.95 times more likely to show preeclampsia than women without GDM. We also found that women with a pre-pregnancy BMI ≥25 kg/m^2 were 3.15 times more likely to develop preeclampsia than women with a BMI<25 kg/m^2, and compared with pregnant women with normal blood lipid level, pregnant women with dyslipidemia were 2.53 times more likely to develop preeclampsia. After adjusting for relevant confounding factors, the conclusions are consistent.

Our study found that GDM was significantly associated with preeclampsia, consistent with previous researches [1, 9, 10]. Hiersch et al. reported a retrospective cohort study that in singleton pregnant woman, GDM was associat-

ed with preeclampsia (1.26 [1.06-1.50]) [14]. At present, the reason for the higher risk of preeclampsia in patients with gestational diabetes is still unclear. Beysel et al. reported that the HNF1αp.I27L TT genotype was associated with preeclampsia risk in patients with GDM [15]. A study suggests that GDM combined with preeclampsia may be involved in the endothelial injury [16]. On the other hand, patients with GDM have a higher risk of preeclampsia, which might be related to insulin resistance [17].

Compared with pregnant women and with normal blood lipid level, pregnant women with dyslipidemia were more likely to develop preeclampsia. Cao et al. found that pregnant women's dyslipidemia is related to GDM and preeclampsia [16]. In a study done by Kandimalla, et al., 156 pregnant women were included prior to 20 weeks of gestation and their lipid levels were detected. They found that the mean TG levels were found to be significantly higher in the preeclampsia group, and women with TG levels above 130 mg/dL had an increased risk of developing preeclampsia compared with those with TG levels of 91 mg/dL or less [18]. A retrospective analysis of 9911 pregnant women found that dyslipidemia was significantly associated with preeclampsia after adjustment for confounding factors [19].

Studies from different populations have consistently reported that elevated pre-pregnancy BMI is associated with an increased risk of preeclampsia [20-26]. Our study found that the risk of preeclampsia in women with pre-pregnancy BMI ≥25 kg/m^2 is 3.15 times than that of those with pre-pregnancy BMI<25 kg/m^2. Košir et al. reported that pre-pregnancy obese patients are 1.6 times more likely to develop preeclampsia [11]. It was indicated that high BMI may be associated with the pathogenesis of GDM and preeclampsia.

In order to better predict the risk of preeclampsia in women with singleton pregnancy, this study established a prediction model based on independent risk factors. Hosmer-lemeshow test concluded that the goodness of fit of the prediction model was relatively high. The ROC curve shows that the maximum value of the Yoden index is 0.445 and the sensitivity of the prediction model is 86.80%, while the specificity is 57.7%. The area under the curve (AUC) is 0.767, indicating that the prediction model established in this study has high predictive value.

Through this retrospective cohort study, we explored the association between gestational diabetes and preeclampsia, and adjusted the influence of confounding factors on the outcome. But there are still some limitations in our research. Firstly, this study is a retrospective cohort study, there may be bias in the process of collecting patient data, which may affect the accuracy of the results. Secondly, although our study shows that gestational diabetes is associated with preeclampsia, the sequential relations between preeclampsia and GDM remains unclear. Thirdly, we don't know whether patients with GDM can effectively control their blood sugar, and we cannot compare the effect of blood sugar control on the results. Fourthly, we adjusted the impact of some confounding factors on the results, but there may still be some confounding factors missing.

In summary, GDM, pre-pregnancy BMI ≥25 kg/m^2 and dyslipidemia are significantly associated with preeclampsia. Pregnant women with GDM or who are obese before pregnancy or dyslipidemia have a significantly increased risk of developing preeclampsia. We suggest that patients with GDM should be actively tested for preeclampsia, and it is recommended to reduce weight and regulating dyslipidemia before pregnancy to reduce the risk of preeclampsia.

Disclosure of conflict of interest

None.

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