Original Article

Associations of family histories of diabetes mellitus and hypertension with the occurrence of gestational diabetes mellitus, gestational hypertension, and preeclampsia : multivariate analysis

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Abstract

Objective：We herein determined whether family histories of hypertension（HT）and diabetes mellitus（DM）were independent risk factors for gestational hypertension（GH）, preeclampsia（PE）and gestational diabetes mellitus（GDM）.

Methods：A prospective cohort study was conducted using 1,737 pregnant women. We evaluated five factors：a family history of HT（father, mother, or both）, a family history of DM, age ≥40 years old, obesity, and high blood pressure（mean blood pressure level ≥90 mmHg at 16-19 gestational weeks）, and three outcomes：GH, PE, and GDM. Univariate and multivariate logistic regression analyses were performed.

Results：High blood pressure was an independent risk factor for the occurrence of PE（OR［95% CI］：4.6［2.3-9.2］）, pre-pregnancy obesity was an independent risk factor for the occurrence of GH（4.4［1.3-15］）, whereas a family history of HT or DM was not an independent risk factor for either PE or GH . Independent risk factors for the occurrence of GDM were a family history of DM（5.5［3.3-9.1］）, age ≥40 years old（2.2［1.1-4.1］）, and pre-pregnancy obesity（4.2［2.5-6.9］）.

Conclusions：After adjusting for other factors, a family history of DM was not associated with the occurrence of either PE or GH. In addition, a family history of HT was not an independent risk factor for GDM.

（Key Words：family history of diabetes mellitus, family history of hypertension, gestational diabetes mellitus, gestational hypertension, preeclampsia）

Introduction

A family history of hypertension（HT）is a well-known risk factor for the occurrence of preeclampsia（PE）[1,2]. However, to the best of our knowledge, it has not been extensively investigated whether a family history of DM is a risk factor for the occurrence of PE or GH[2,3]. Although we previously reported that a family history of HT was an independent risk factor for the occurrence of PE, but not GH[4], we did not investigate whether a family history of DM was a risk factor for PE and GH.

A family history of DM is a well-known risk factor for the occurrence of GDM[5,6]. GDM was associated with the increased risk of PE[7], although it was not associated with GH[8]. Thus, a family history of DM may be a risk factor for the occurrence of PE. In view of pathophysiology of DM and PE, since the first-degree relatives of patients with type 2 DM have insulin resistance long before the development of type 2 DM[9], and since they have diminished beta-cell function when they are not hyperglycemic[10], the pregnant women with a family history of DM may also have insulin resistance and beta cell dysfunction. Maternal insulin resistance in the second trimester is associated with the later occurrence of PE, but not GH[11]. Thus, pregnant women with a family history of DM might develop PE more frequently compared with those without a family history of DM due to relatively high insulin resistance.

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Received：18 April 2016, Accepted：24 October 2016

To the best of our knowledge, it currently remains unknown whether a family history of HT is a risk factor for the occurrence of GDM[12]. In the present study, we evaluated whether family histories of HT and DM were associated with the occurrence of PE, GH, and GDM using univariate and multivariate analyses in a prospective cohort study.

Methods

Subjects

We recruited 2,410 pregnant women into a prospective cohort study to evaluate the effects of blood pressure levels and abnormal uterine artery Doppler findings on the later occurrence of PE/GH, between July 2003 to March 2011. This study was approved by the Ethics Committee of our institute. Written informed consent was obtained from all subjects. This cohort was used in our previous study[4]. In this cross-sectional study, we used 1,737 pregnant women in the cohort between January 2006 to March 2011.

Blood pressure in pregnancy and the puerperal period, and the definition of high blood pressure

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured three times at 1 min interval in every maternal check-up using an Omron HEM-906 automated digital oscillometric sphygmomanometer (OMRON Healthcare, Kyoto, Japan), without conversation, after resting for one minute in a seated position. In this study, the first measurements of SBP and DBP during 16-19 gestational weeks were used for each subject. Although the accuracy of the sphygmomanometer was validated for adults, it has not been validated for pregnancy women.

In our previous study, we evaluated whether the high blood pressure in the second trimester is a risk factor for the later occurrence of either PE or GH[13]. The relative risk of either PE or GH was increased 1.5 times for every 5 mmHg increments of SBP, suggesting that the higher the blood pressure level, the more frequently pregnant women develop PE and/or GH. When we evaluated the mean arterial pressure (MAP) of ≥90 mmHg in the second trimester as a risk factor for the development of PE, MAP ≥ 90 mmHg was significantly associated with the occurrence of PE[14]. Therefore, in the current study, we selected MAP ≥ 90 mmHg as an indicator of high blood pressure.

Definition of PE and GH

We defined PE and GH according to the definition and classification of pregnancy-induced hypertension (2004) of the Japan Society for the Study of Hypertension in Pregnancy[15]. In brief, PE was defined as hypertension with proteinuria occurring after 20 gestational weeks. GH was defined as hypertension without proteinuria occurring after 20 gestational weeks. Hypertension was defined as SBP ≥140mmHg and/or DBP ≥90mmHg on at least two consecutive measurements. Proteinuria was defined as ≥ 300mg/day from a 24-h urine collection. If a 24-h urine collection was not available, repeated semi-quantitative test results of 2+ or a urine protein/creatinine ratio of >0.27 g/gCr were considered to constitute a positive result[16,17].

Definition of GDM

The diagnosis of GDM was performed using a stepwise method. We measured random blood glucose levels (cut-off value ≥95 mg/dL) in the early stage of pregnancy and gave pregnant women a 50-g glucose challenge test (GCT ; cut-off value ≥140 mg/dL) in mid-pregnancy (28-29 gestational weeks). We performed a diagnostic test of GDM (75-g oral glucose tolerance test [OGTT]) on all women with a positive screening test result. Threshold values for 75-g OGTT were fasting plasma glucose (PG) ≥100 mg/dL, 1-h PG ≥180 mg/dL 1h after intake, and 2-h PG ≥150 mg/dL. Pregnant women were diagnosed with GDM if two or more threshold values of 75-g OGTT were fulfilled[18].

Risk factors

We evaluated five factors for PE, GH, and GDM in this study : a family history of HT (father, mother, or both), family history of DM (father, mother, or both), age ≥40 years old, obesity (pre-pregnancy body mass index ≥25.0), and high blood pressure (mean MAP level ≥90 mmHg at 16-19 gestational weeks).

Statistical analysis

Data were shown as the mean ± SD, or number (percent). An unpaired *t*-test was used to compare continuous data, and Fisher's exact test was used to compare categorical data. Univariate and multivariate logistic regression analyses were performed to assess risk factors for the occurrence of PE, GH, and GDM, using a family history of HT, family history of DM, age ≥40 years, obesity, and high blood pressure at 16-19 gestational weeks. All analyses were performed using the IBM SPSS software package (version 21 ; IBM, Armonk, NY, USA). $P<0.05$ was considered significant.

Results

The occurrence of PE, GH, and GDM was 2.5%, 1.0%, and 5.2%, respectively. The characteristics of all patients are presented Table 1. The frequencies of a family history of HT, a past history of PE/GH, obesity, high blood pressure, and bilateral notches (bilateral early diastolic notches on the right and left uterine artery Doppler flow velocity waveforms, BN) at 20-23 gestational weeks were significantly higher in women with PE than in those without PE. The frequencies of a past history of PE/GH, obesity, and BN were significantly higher in women with GH than in those without. The frequencies of age ≥40 years old, a family history of HT, family history of DM, obesity, and high blood

Table 1 Characteristics of 1,737 women

Characteristics	All women (n = 1737)	PE (n = 43)	GH (n = 18)	GDM (n = 91)	Missing data
Age (yr)	33.3 ± 5.2	32.2 ± 5.1	33.4 ± 5.4	34.7 ± 4.6	-
Age ≥ 40 (%)	143 (8)	7 (16)	3 (18)	16 (18)[c]	-
Japanese (%)	1,720 (99)	43 (100)	18 (100)	90 (99)	-
Family history of HT (%)	464 (27)	19 (44)[a]	5 (28)	34 (37)[c]	-
Family history of DM (%)	236 (14)	7 (16)	2 (11)	40 (44)[c]	-
Nulliparous women (%)	865 (50)	19 (44)	11 (61)	46 (51)	-
Past history of PE/GH (%)	75/1,725 (4)	8/43 (19)[a]	3/18 (17)[b]	6/89 (7)	12
Pre-pregnancy BMI (kg/m2)	22.5 ± 4.6	25.3 ± 6.0	24.7 ± 4.5	26.4 ± 5.9	-
Obesity (%)	379/1,706 (22)	18/42 (43)[a]	8/16 (50)[b]	50/90 (56)[c]	31
Current smoking (%)	89/1,666 (5)	4/43 (9)	1/17 (6)	4/87 (5)	71
MAP at 16-19 wk ≥ 90 mmHg (%)	415/1,731 (24)	26/41 (63)[a]	7/14 (50)	33/82 (40)[c]	84
BN at 20-23 wk (%)	200/1,413 (14)	18/38 (47)[a]	6/17 (35)[b]	10/76 (13)	324
Gestational week at delivery (wk)	38.7 ± 2.2	36.0 ± 4.0	38.0 ± 2.9	38.4 ± 1.6	-
Birthweight (g)	2,911 ± 509	2,348 ± 861	2,614 ± 730	2,980 ± 523	-
Preterm delivery (%)	174 (10)	20 (47)[a]	4 (22)[b]	7 (8)	-
Small-for-gestational-age infant (%)	199/1,736 (12)	12/43 (28)[a]	6/18 (33)[b]	12/91 (13)	1

Abbreviations: PE, preeclampsia; GH, gestational hypertension; GDM, gestational diabetes mellitus; yr; years old; HT, hypertension; DM, diabetes mellitus; BMI, body mass index; MAP, mean arterial pressure; wk, gestational weeks; BN, bilateral notch.

a, significantly different from women without PE.

b, significantly different from women without GH

c, significantly different from women without GDM

pressure were significantly higher in women with GDM than in those without. Preterm delivery occurred more frequently in women with PE and those with GH than in those without.

A family history of HT, obesity, and high blood pressure were associated with the occurrence of PE in a univariate analysis (Table 2). However, only high blood pressure was an independent risk factor for the occurrence of PE. Obesity and high blood pressure were associated with GH ; however, only obesity was an independent risk factor (Table 3). All five risk factors : a family history of HT, family history of DM, age ≥40 years old, obesity, and high blood pressure, were associated with the occurrence of GDM ; however, only three independent risk factors were identified : a family history of DM, age, and obesity (Table 4).

Discussion

Two important results were obtained in the present study. A family history of DM was not associated with the occurrence of either PE or GH. Furthermore, although a family history of HT was associated with the occurrence of GDM, it was not an independent risk factor after adjusting for the associations of the 4 other factors.

A family history of DM was not associated with the occurrence of either PE or GH. To the best of our knowledge, it currently remains unknown whether a family history of DM is a risk factor for the occurrence of PE[2,3]. In a case-control study comparing 190 women with PE and controls, a multivariate logistic regression analysis to investigate the effects of a family history of HT and family history of DM on the occurrence of PE was performed while adjusting for age, race, and obesity ; the crude odds ratio (cOR) of a family history of DM was 1.6 (1.1-2.3) while the adjusted odds ratio (aOR) was 1.9 (1.3-2.9)[2]. In another case-control study comparing 131 women with PE and 262 matched controls, a conditional logistic regression analysis was performed to estimate the OR of various risk factors including a family history of HT and family history of DM for the occurrence of PE ; the cOR of a family history of DM

Table 2 Univariate and multivariate analyses to evaluate effects of 5 risk factors on the occurrence of preeclampsia (PE)

	Univariate analysis			Multivariate analysis		
Risk factors	cOR	(95% CI)	*p* value	aOR	(95% CI)	*p* value
Family history of HT	**2.2**	**(1.2-4.1)**	0.010	1.6	(0.82-3.1)	0.171
Family history of DM	1.2	(0.55-2.8)	0.603	0.81	(0.37-2.2)	0.811
Age ≥ 40 yr	2.2	(0.97-5.1)	0.058	2.0	(0.86-4.8)	0.104
Pre-pregnancy obesity	**2.7**	**(1.5-5.0)**	0.002	1.3	(0.63-2.6)	0.494
MAP at 16-19 wk ≥ 90 mmHg	**5.6**	**(2.9-11)**	<0.001	**4.6**	**(2.3-9.2)**	<0.001

Abbreviations: cOR, crude odds ratio; CI, confidence interval; aOR, adjusted odds ratio; HT, hypertension; DM, diabetes mellitus; yr; years old; MAP, mean arterial pressure; wk, gestational weeks.
Bold font indicates significant risk factors.
The multivariate analysis was performed using 1,635 cases without any missing data for the five variables.

Table 3 Univariate and multivariate analyses to evaluate effects of 5 risk factors on the occurrence of gestational hypertension (GH)

	Univariate analysis			Multivariate analysis		
Risk factors	cOR	(95% CI)	*p* value	aOR	(95% CI)	*p* value
Family history of hypertension	1.06	(0.37-3.0)	0.918	0.59	(0.15-2.3)	0.588
Family history of diabetes mellitus	0.79	(0.18-3.5)	0.759	0.90	(0.18-4.4)	0.900
Age ≥ 40 yr	2.3	(0.65-7.9)	0.203	1.7	(0.38-8.1)	0.478
Pre-pregnancy obesity	**3.6**	**(1.3-9.5)**	0.012	**4.4**	**(1.3-15)**	0.016
MAP at 16-19 wk ≥ 90 mmHg	**3.1**	**(1.07-8.8)**	0.037	2.2	(0.69-7.3)	0.182

Abbreviations: cOR, crude odds ratio; CI, confidence interval; aOR, adjusted odds ratio; HT, hypertension; DM, diabetes mellitus; yr; years old; MAP, mean arterial pressure; wk, gestational weeks.
Bold font indicates significant risk factors.
The multivariate analysis was performed using 1,635 cases without any missing data for the five variables.

Table 4 Univariate and multivariate analyses to evaluate effects of 5 risk factors on the occurrence of gestational diabetes mellitus (GDM)

	Univariate analysis			Multivariate analysis		
Risk factors	cOR	(95% CI)	*p* value	aOR	(95% CI)	*p* value
Family history of hypertension	**1.7**	**(1.1-2.6)**	0.020	0.78	(0.46-1.3)	0.358
Family history of diabetes mellitus	**5.8**	**(3.7-9.0)**	<0.001	**5.5**	**(3.3-9.1)**	<0.001
Age ≥ 40 yr	**2.6**	**(1.4-4.5)**	0.001	**2.2**	**(1.1-4.1)**	0.020
Pre-pregnancy obesity	**4.9**	**(3.2-7.5)**	<0.001	**4.2**	**(2.5-6.9)**	<0.001
MAP at 16-19 wk ≥ 90 mmHg	**2.1**	**(1.4-3.4)**	0.001	1.1	(0.66-1.8)	0.683

Abbreviations: cOR, crude odds ratio; CI, confidence interval; aOR, adjusted odds ratio; HT, hypertension; DM, diabetes mellitus; yr; years old; MAP, mean arterial pressure; wk, gestational weeks.
Bold font indicates significant risk factors.
The multivariate analyis was performed using 1,635 cases without any missing data for the five variables.

was 1.9 (1.2-3.0), whereas the aOR was not significant[3]. In one of these three studies, including ours, a family history of DM was identified as an independent risk factor for the occurrence of PE[2]. Although our results suggested that a family history of DM was not be a risk factor for PE, the influence of a family history of DM on the occurrence of PE may differ with factors such as race/ethnicity and food habits.

When we searched for studies on a family history of DM and GH in PubMed using the following key words : family history AND gestational hypertension AND diabetes, we were unable to find any studies in which the relationship between a family history of DM and the occurrence of GH was investigated. When we searched PubMed using the key words of gestational hypertension AND multivariate, we again found no studies. In this survey, we found a multicenter cross-sectional retrospective study that analyzed the risk factors for hypertensive disorders of pregnancy (HDP) using 112,386 Chinese pregnant women, including 5,869 women with HDP[19] ; however, this study did not evaluate individual risk factors for PE and GH ; the cOR of a family history of DM for the occurrence of HDP was 2.7 (2.1-3.4) and the aOR was 1.6 (1.2-2.2) after adjusting for 18 risk factors including a family history of HT, age, obesity, and blood pressure levels. Since this study analyzed the effects of a family history of DM on HDP, but not PE or GH separately, it remains unknown whether a family history of DM is truly an independent risk factor for PE or GH.

In the present study, a family history of HT was identified as a risk factor for the occurrence of GDM in a univariate analysis, but was not an independent risk factor after adjusting for the associations of the 4 other factors. To the best of our knowledge, it has not yet been established whether a family history of HT is a risk factor for the occurrence of GDM . In a cohort study using pregnant women with 75-g OGTT between 24 and 28 gestational weeks, a multivariate logistic regression analysis was performed to evaluate risk factors for GDM ; although the cOR of a family history of HT was 2.9 (1.1-7.4) , a family history of HT was not an independent risk factor after adjusting for age, obesity, a family history of DM, a past history of GDM, socioeconomic status, weight gain during pregnancy, and educational status.[12] These findings of univariate and multivariate analyses were consistent with our results. Taken together, a family history of HT appeared to be a risk factor for GDM. However, because the relationship between a family history of HT disappeared after adjusting for at least three risk factors of age, obesity, and a family history of DM, a family history of HT may not be clinically important for evaluating the risk of GDM.

MAP at 16-19 gestational weeks of ≥90 mmHg was only an independent risk factor for the occurrence of PE, after adjusting for the effects of a family history of HT, family history of DM, age ≥40 years old, and pre-pregnancy obesity. In our previous study, we evaluated the effects of pre-pregnancy obesity and high blood pressure levels at 16-23 gestational weeks on the occurrence of PE and GH[13]. Normal blood pressure, high-normal blood pressure, and hypertension were independent risk factors for the occurrence of both PE and GH, after adjusting for the effect of pre-pregnancy BMI ; MAP at 16-23 gestational weeks of ≥80 mmHg was also an independent risk factor for the occurrence of both PE and GH, after adjusting for pre-pregnancy BMI ≥23.6 ; in addition, although pre-pregnancy BMI as continuous data was not associated with the occurrence of either PE or GH, SBP as continuous data was associated with the occurrence of both PE and GH[13]. Thus, high blood pressure level may be a very strong risk factor for the occurrence of PE and GH, whereas the effect of pre-pregnancy obesity on the occurrence of either PE and GH may disappear if high blood pressure level is included in the multivariate analyses.

This study had several limitations. Detailed data of a family history of DM and HT, such as medication and clinical stage in the family members, were not investigated. In addition, we restricted the survey for the family history of either DM or HT to the first degree of a relationship. Therefore, we did not evaluate the severity of the disease or the strong relationship of a family history in this study.

In conclusion, a family history of DM was not associated with the occurrence of either PE or GH. In addition, a family history of HT was not an independent risk factor for GDM.

Declaration of interest

The authors have no conflict of interest to declare.

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糖尿病家族歴，高血圧家族歴の妊娠糖尿病，妊娠高血圧，及び，妊娠高血圧腎症発症に及ぼす影響

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要　　約

糖尿病家族歴，高血圧家族歴が，妊娠糖尿病（gestational diabetes mellitus：GDM），妊娠高血圧（gestational hypertension：GH），妊娠高血圧腎症（preeclampsia：PE）に及ぼす影響について検討した。妊娠24週以前の妊婦1,737例を対象に妊娠高血圧症候群のリスク因子に関する前向きコホート研究を行った。リスク因子として糖尿病家族歴，高血圧家族歴，年齢≥40歳，肥満，血圧高値を評価した。解析は単変量解析，多変量解析を用いた。糖尿病家族歴はGDM発症の独立リスク因子であったが，GHあるいはPE発症の独立危険因子ではなかった。高血圧家族歴は，GDM，GH，PEの何れにおいても独立リスク因子ではなかった。

（キーワード：糖尿病家族歴，高血圧家族歴，妊娠糖尿病，妊娠高血圧，妊娠高血圧腎症）

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受付：2016年４月18日，受理：2016年10月24日