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Correlation of Maternal Serum Homocysteine in the First Trimester with the Development of Gestational Hypertension and Preeclampsia

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: This study investigated the relationship of serum homocysteine in early pregnancy with the risk of gestational hypertension (GH) and preeclampsia (PE) and with the severity of preeclampsia.

Material/Methods: In a retrospective cohort study, we identified 147 confirmed cases of preeclampsia (103 with mild PE and 44 with severe PE) and 147 confirmed cases of GH; 4418 women who remained normotensive and nonproteinuric throughout pregnancy served as controls. Maternal blood samples were collected at between 11 and 13 weeks of gestation to test serum concentrations of homocysteine (Hcy), folic acid, and VitB12. A logistic regression model was used to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CIs).

Results: Women who subsequently developed GH and PE were older and had higher body mass indexes (BMIs) than those in the control group. Compared with the control group, women who developed PE were less educated (P=0.031), and more of those who developed GH were primiparas (P=0.012). The serum levels of Hcy in severe PE were significantly higher than those in the control group (median: 8.50 μmol/L *vs.* 7.33 μmol/L, P<0.001). After logistic regression analyses for potential confounding factors, the adjusted odds ratios (aORs) of Hcy was 1.12 for severe PE (95% CI 1.06–1.20). The serum concentrations of folic acid and VitB12 in those with GH and PE were not significantly different from controls.

Conclusions: A high level of Hcy in the first trimester is an independent risk factor for severe PE, although it is not a useful marker for the subsequent development of GH and mild PE.

MeSH Keywords: Folic Acid • Homocysteine • Hypertension, Pregnancy-Induced • Pre-Eclampsia • Vitamin B 12

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Background

Homocysteine (Hcy) is formed during the metabolism of dietary methionine, found largely in animal protein. Folic acid and vitamin B12 (VitB12) are required for Hcy metabolism; deficiencies in these can result in increased Hcy concentrations [1]. Hyperhomocysteinemia is a risk factor for both cardiovascular disease and vasculopathy [2]. A quantitative meta-analysis of mainly retrospective case-control studies demonstrated a positive association between Hcy and cerebrovascular disease [3]. Furthermore, animal studies suggest that hyperhomocysteinemia affects the walls of blood vessels, causing endothelial changes and smooth muscle proliferation.

Concerns regarding Hcy are relatively novel in obstetrics. It has been found that alterations in methionine-Hcy metabolism may be related to systematic vascular damage, which can lead to the classic clinical appearance of hypertensive disorders of pregnancy (HDOP). It has also been assumed that higher levels of Hcy may contribute to the development of placental microvascular diseases and preeclampsia (PE), thus affecting the endothelium adversely [4]. Women diagnosed with PE are at a much greater risk of future cardiovascular or cerebrovascular diseases, with an estimated doubling of odds compared with unaffected women [5]. This association indicates that HDOP and cardiovascular diseases may share common risk factors.

Gestational hypertension (GH) and PE are common complications of HDOP and have a major impact on public health. Currently, controversy remains as to whether GH and PE are separate diseases affecting similar organs or whether they represent varying severities of the same illness [6].

Most studies focused solely on the relationship between serum Hcy concentrations and PE. Khosrowbeygi et al. reported that total maternal serum Hcy level was increased in PE and that hyperhomocysteinemia was associated with the severity of

PE [7]. However, Hogg et al. [8] found that there was no significant difference in Hcy levels at the second trimester among women with pregnancy-induced hypertension plus PE as compared with control subjects.

Because few studies [9] have been conducted to investigate the relationship of serum Hcy in early pregnancy with GH and PE, and due to the contradictory results regarding the relationship of Hcy with PE, the objective of the present study was to investigate the relationship of serum Hcy in early pregnancy with the risk of developing GH and PE, as well as the consequent severity of PE.

Material and Methods

This was a retrospective cohort study performed from January 2016 to June 2016 at the International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University.

The inclusion criteria were as follows: (1) complete and full consent was obtained from each participant; (2) all participants were clinically and thoroughly examined at our hospital; (3) all participants had singleton pregnancies; and (4) all had live births after 28 weeks of gestation.

Exclusion criteria were as follows: (1) women with chronic diseases before pregnancy, such as hypertension, diabetes mellitus, kidney and liver diseases; (2) the presence of fetal abnormalities; (3) women who experienced stillbirth; (4) women with unexplained intrauterine growth restriction (IUGR) and placental abruption were also excluded from the control group.

The design of the study was approved by the Ethics Committee of theInternational Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University. Written consent was obtained from all participants. In all, a cohort of 4712 women remained for analysis.

GH is defined as new-onset hypertension after 20 weeks of gestation without proteinuria [10] with a blood pressure recording of ≥140/90 mm Hg on at least 2 occasions more than 6 hours apart. PE is defined [11] as a sustained increase of blood pressure after 20 weeks of gestation with a pressure recording of ≥140/90 mm Hg together with proteinuria (≥300 mg of protein over 24 hours, or a random dipstick urine determination of ≥1+ protein or ≥30 mg/dL). Blood pressure should be elevated on at least 2 occasions more than 6 hours apart.

The diagnosis of severe PE [11] is considered if 1 or more of the following is present: blood pressure of 160 mm Hg systolic or higher or 110 mm Hg diastolic or higher on 2 occasions at least 6 hours apart while the patient is on bed rest, proteinuria of 2 grams or greater in a 24-hour urine specimen or 3+ or greater in 2 random urine samples collected at least 4 hours apart, oliguria of less than 500 mL in 24 hours, serum creatinine >1.1 mg/dL, cerebral or visual disturbances, pulmonary edema, epigastric or right-upper-quadrant pain, impaired liver function, thrombocytopenia, and fetal growth restriction.

From this cohort, we identified 147 confirmed cases of PE (mild PE n=103, severe PE n=44) and 147 cases of GH. A total of 4418 women remained normotensive and nonproteinuric throughout their pregnancies and served as controls.

Maternal fasting blood samples were collected after an overnight fast of at least 8 hours at a mean gestational age of 11

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to 13 weeks. All samples were analyzed for Hcy, folic acid, and VitB12. Hcy was quantified using the Hcy Assay Kit by Enzymatic Method (Biological & Technological Inc, Wuhan, China). Serum folic acid was quantified using the ARCHITECT Folic Acid Reagent Kit (Abbott, Ireland). VitB12 in serum was quantified using the ARCHITECT B12 Reagent Kit (Abbott).

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. The height and pregestational weight of each patient were recorded.

The data collected were tabulated and analyzed by SPSS (Statistical Package for the Social Sciences) statistical package version 20. Quantitative data were expressed as mean and standard deviation ($\bar{\chi}$±SD). Comparisons of GH *vs.* control and PE *vs.* control were performed. Normal distribution data were analyzed by the *t* test and skewed distribution data by the Mann-Whitney *U* test. Proportional data were compared with the chi-square test. $P<0.05$ was considered significant. Odds ratios, as derived from logistic regression analysis with corresponding 95% confidence intervals (CIs), were used to approximate relative risk. Models were adjusted for other previously identified risk factors, including maternal age, BMI, education level, parity, and delivery week.

Results

1. Figure 1 depicts the study population. We identified 147 cases of PE (103 with mild PE and 44 with severe PE) and 147 cases of GH. A total of 4418 women who remained normotensive and nonproteinuric throughout pregnancy served as control subjects. The incidence of PE and GH was both 3.1%.

2. The clinical and demographic characteristics of the study participants in the various groups are shown in Table 1.

Women who subsequently developed GH and PE were generally older than those in the control group ($P=0.028$ and 0.016, respectively). BMI was higher in women who later developed GH and PE ($P<0.001$). Compared with the control group, women who developed PE were less educated ($P=0.031$), while those who developed GH were more often primiparous ($P=0.012$).

As for the pregnancy outcomes, the delivery weeks in GH and PE were lower than those in the control group. The discrepancies were significant ($P=0.009$ and <0.001 respectively). Furthermore, neonatal birth weights in the PE group were significantly lower than those in the control group ($P<0.001$).

3. Maternal serum concentration of Hcy, folic acid, and VitB12 in the various groups are shown in Table 2.

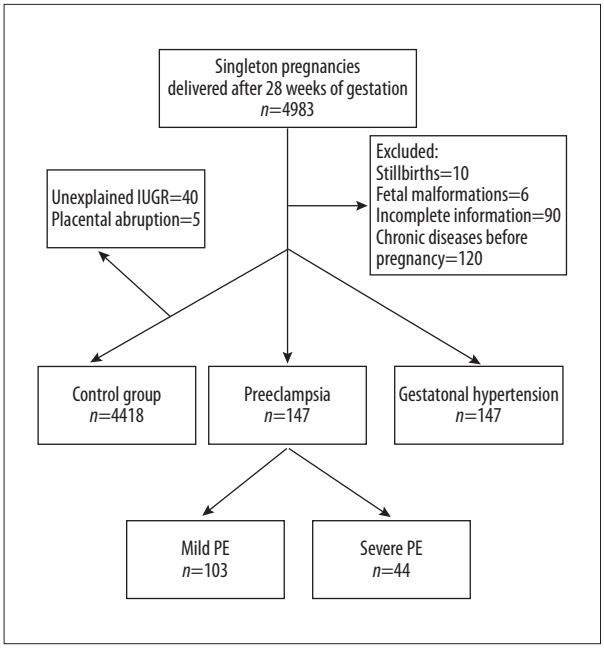

Figure 1. Flowchart depicting the study population.

Women who subsequently developed severe PE had higher concentrations of Hcy than those in the control group ($P<0.001$). Women with GH and mild PE had slightly higher concentrations of Hcy as compared with control subjects; however, this did not reach statistical significance. Serum concentrations of folic acid and VitB12 were similar among the various groups.

4. In addition, multiple regression analysis indicated that elevated Hcy was an independent predictor of severe PE (Table 3).

Table 3 lists results from logistic regression analyses in which we estimated the odds ratios (ORs) of GH, mild PE, and severe PE associated with different concentrations of Hcy. After adjusting for confounders, we found that women with higher concentrations of Hcy had a 1.12-fold increased risk of severe PE as compared with those in the control group (aOR 1.12, 95% CI, 1.06–1.20).

Discussion

GH and PE are common disorders of HDOP, which is considered to be a leading cause of obstetric complications leading to high maternal and neonatal mortality and morbidity worldwide. It is reported that GH affects about 2% to 17% of pregnant women, while PE complicates 2% to 7% of pregnancies [12]. In our study, the incidence of GH and PE was both 3.1%.

The concordance of some risk factors suggests the existence of a similar disease process in these 2 conditions [6]. For example, GH and PE are both influenced by the same demographic

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Table 1. Characteristics of the women enrolled in the various subgroups.

Characteristics	Control	GH	PE	GH *vs.* control	PE *vs.* control
	4418	147	147		
Maternal age (years)	30.37±3.73	31.15±4.18	31.20±3.73	0.028	0.016
BMI (kg/m^2)	20.84±2.52	23.57±3.58	22.37±3.31	<0.001	<0.001
Parity				0.012	0.082
Primiparous	3396 (76.87)	126 (85.7)	122 (82.99)		
Mutilparous	1022 (23.13)	21 (14.3)	25 (17.01)		
Education level				0.115	0.031
High school or low	1190 (27.00)	49 (33.30)	54 (36.70)		
Bachelor	2356 (53.30)	77 (52.40)	69 (46.90)		
Postgraduate	872 (19.70)	21 (14.30)	24 (16.40)		
Delivery, weeks	38.81±1.36	38.51±1.29	37.63±1.93	0.009	<0.001
Birth weight (kg)	3.35±0.43	3.42±0.47	3.11±0.66	0.057	<0.001

GH – gestational hypertension; PE – preeclampsia.

Table 2. Hcy, VitB12 and folic acid in different subgroups (GH, mild PE, severe PE).

	Control	GH	PE		GH *vs.* control	Mild PE *vs.* control	Severe PE *vs.* control
			Mild PE	Severe PE			
Hcy (μmol/L)	7.33±1.53	7.49±1.25	7.49±1.45	8.50±1.18	0.210	0.301	<0.001
VitB12* (pmol/L)	420.0 (325.0, 500.0)	389.0 (289.0, 494.0)	394.0 (306.0, 488.0)	357.0 (290.0, 538.0)	0.051	0.342	0.236
Folic acid (nmol/L)	30.96±4.87	31.51±4.66	30.40±6.11	30.61±6.22	0.151	0.358	0.648

GH – gestational hypertension; PE – preeclampsia. * Shown as median (quartiles).

factors, such as advanced maternal age [13], high BMI [14], and primiparity. In our study, women who developed GH and PE also were significantly older and had higher BMIs. Most of the women who developed GH were primiparous, while the women who developed PE tended to be less educated.

High levels of Hcy may damage the structure of blood vessels and thus promote thrombosis and atherosclerosis [15]. It has also been hypothesized that high maternal concentrations of Hcy are associated with PE [16]. Finally, it has been reported that women who develop severe PE have higher serum levels of Hcy in early pregnancy as compared with women who remain normotensive throughout pregnancy [17]; this was in agreement with our results.

In our study, women who subsequently developed severe PE had higher concentrations of Hcy than those in the control group. The logistic regression model demonstrated that Hcy was an independent risk factor for the development of severe PE (aOR 1.12, 95% CI, 1.06–1.20). Acilims et al. [18] also showed that maternal and fetal serum Hcy levels were significantly higher in their group with severe PE as compared with their mild PE and control group, suggesting that elevated level of serum Hcy may be associated with the severity of PE.

Another study has reported that elevated Hcy levels in early pregnancy have been associated with the later development of mild PE [19]. However, we failed to note a significant increase in serum Hcy of early pregnancy in women with mild PE. Our data are similar to those of Yelikar et al. [20], who reported a significant difference between severe PE and controls (P<0.001), while there was no difference in Hcy levels between women with mild PE and the control group. The reason for this could

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Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) of the association between GH, PE risk, and maternal plasma Hcy, VitB12, and folic acid.

Characteristic	OR (95% CI)	*p*	aOR (95% CI)	*P*
GH *vs.* control				
Hcy	1.05 (0.97, 1.13)	0.214	1.05 (0.98, 1.14)	0.182
VitB12	0.88 (0.76, 1.00)	0.054	0.97 (0.85, 1.10)	0.617
Folic acid	1.04 (0.98, 1.08)	0.072	1.03 (0.99, 1.07)	0.097
Mild PE *vs.* control				
Hcy	1.04 (0.94, 1.15)	0.433	1.05 (0.95, 1.15)	0.368
VitB12	0.93 (0.80, 1.08)	0.346	1.00 (0.86, 1.16)	0.949
Folic acid	0.98 (0.95, 1.02)	0.386	0.98 (0.94, 1.02)	0.299
Severe PE *vs.* control				
Hcy	1.10 (1.04, 1.16)	0.001	1.12 (1.06, 1.20)	<0.001
VitB12	1.01 (0.81, 1.25)	0.954	1.08 (0.86, 1.35)	0.516
Folic acid	0.99 (0.93, 1.05)	0.670	0.97 (0.92, 1.03)	0.374

GH – gestational hypertension; PE – preeclampsia. Odds ratios adjusted for BMI, age, education level, delivery week, and parity.

be that the low concentration of Hcy affects the endothelium only slightly and plays a subtle role in occurrence of mild PE.

There have been few studies on the correlation between Hcy and GH. In a prospective cohort study, Dodds et al. [21] reported that there was no significant association between Hcy concentration within 20 weeks of gestation and the risk of developing GH. In our study, we failed to find a significant difference between Hcy concentrations in the GH and control groups.

Folic acid and VitB12 are required for DNA synthesis and cell growth and are involved in Hcy metabolism. Without adequate folic acid and VitB12, Hcy concentrations increase. It has been shown that an increase in dietary folic acid results in a corresponding decrease in serum Hcy. Researchers have also reported that folic acid supplementation decreases the levels of Hcy as well as the risk of developing PE [22]. However, Murphy et al. reported that folic acid supplementation had no effect on decreasing high levels of Hcy [23]. Similar findings were observed by Makedos et al. [24], who reported that there was no difference in folic acid and VitB12 levels between normal and preeclampsia women. In our study, the serum concentrations of folic acid and VitB12 in GH and PE were not significantly different from those in the control group. The possible explanation may be that some of the women studied were already aware, before they became pregnant, of the importance of folic acid and various vitamin supplements.

Our study has several limitations. First, although we assessed some potential confounding factors that had previously been reported to influence GH and PE, there were several other potential confounders, such as smoking status and family history of hypertension, that were not included in our database. Additionally, we obtained only a single serum Hcy sample in the first trimester for each patient; this may be regarded as another limitation of the study. Finally, we were unable to determine whether our subjects had taken a folic acid supplement before or during pregnancy; this deserves further research.

Our study revealed that Hcy in the first trimester significantly increased in those who developed severe PE. The possible mechanism maybe that homocysteine in the first trimester may cause endothelial dysfunction and, with the progression of pregnancy, this homocysteine-related endothelial injury may aggravate the placental ischemia, thus leading to the development of severe preeclampsia. However, we did not find a relationship between Hcy and GH. The possible mechanism should be confirmed in future extensive studies.

Conclusions

Our study reveals that elevated plasma Hcy concentration in the first trimester of pregnancy is an independent risk factor for severe PE; however, it is not a useful marker for the subsequent development of GH or mild PE. Further studies are needed to address the role of Hcy in the pathogenesis of gestational hypertension and preeclampsia, especially in severe preeclampsia.

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Conflict of interests

The authors declare no conflicts of interest.

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