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Prognostic Value of Cardiovascular Disease Risk Factors Measured in the First-Trimester on the Severity of Preeclampsia

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Abstract: Recent studies have suggested that preeclampsia and cardiovascular disease may share common mechanisms. The purpose of this prospective nested case-controlled study was to characterize a variety of cardiovascular disease risk factors measured during the first trimester of pregnancy in predicting subsequent outcomes and the severity of preeclampsia.

We ascertained the severity of preeclampsia at the onset of the disease, and the presence of intrauterine growth restriction (IUGR). We compared first trimester maternal serum cardiovascular disease risk factors in preeclampsia subjects versus normal pregnancies, early-onset versus late-onset preeclampsia, and preeclampsia with IUGR versus without IUGR. To identify the prognostic value of independent predictors on the severity of preeclampsia, we calculated the area under the receiver operating characteristics curve (AUC) using logistic regression analysis.

There were 134 cases of preeclampsia and 150 uncomplicated pregnancies, and preeclampsia cases were classified as early-onset (53 cases) or late-onset (81 cases), or as with IUGR (44 cases) or without IUGR (90 cases). Among the cardiovascular disease risk factors, maternal serum high-sensitive C-reactive protein (hsCRP) and homocysteine were predictors of both early-onset preeclampsia and preeclampsia with IUGR. For the detection of early onset preeclampsia or preeclampsia with IUGR, the AUC for the combination model (0.943 and 0.952, respectively) was significantly higher than with serum hsCRP or serum homocysteine only.

Patients with preeclampsia can be subdivided into different severities according to time of onset and fetal weight. Cardiovascular risk factors distinguish a subgroup of these patients.

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Abbreviations: AUC = the area under the receiver operating characteristics curve, BMI = body mass index, FOCAS = First Trimester Obstetrical Complications Assessment Study, HbA_{1c} = glycatedhemoglobin, HDL-C = high-density lipoprotein cholesterol, HOMA = homeostasis model assessment index, hsCRP = high-sensitive C-reactive protein, IUGR = intrauterine growth restriction, LDL-C = low-density lipoprotein cholesterol, VLDL-C = very low-density lipoprotein cholesterol.

INTRODUCTION

The identification of predisposing risk factors for the development of preeclampsia could lead to a better understanding of the causality and pathogenesis of this challenging and high-risk disorder. Such knowledge is crucial for the development of an evaluation and management algorithm for the prevention of preeclampsia and its associated complications. Conventional risk factors for preeclampsia included nulliparity, obesity, diabetes, hypertension, thrombophilia, multi-fetal gestations, family history of preeclampsia, and history of prior preeclampsia.[1,2] In addition, the time of onset of the disease and the presence of intrauterine growth restriction (IUGR) are known to be related to the severity of preeclampsia.[1,3–6] Interestingly, recent studies have suggested that preeclampsia and cardiovascular diseases may share common mechanisms,[7,8] and women with a history of preeclampsia have an increased risk of cardiovascular diseases later in life.[9,10] By analogy, we hypothesized that known cardiovascular disease risk factors could represent useful predictors of the risk and severity of preeclampsia. However, data concerning the relationship between cardiovascular disease risk factors that are present during early pregnancy and the occurrence/severity of preeclampsia are scarce. Thus, the aim of this study was to examine the importance of a variety of cardiovascular disease risk factors recorded during the first trimester in predicting the subsequent occurrence and severity of preeclampsia.

MATERIALS AND METHODS

Study Population

In this prospective nested case-controlled study, the population was drawn from participants of the Chang-Gung Memorial Hospital (CGMH) First Trimester Obstetrical Complications Assessment Study (FOCAS) cohort.[11,12] The recruitment of the FOCAS cohort was initiated in 2005 when the first trimester combined screening program for fetal Down syndrome was first provided to women who received prenatal care at CGMH. Pregnant women who presented to the Fetal Medical Center at CGMH for first trimester combined screening were invited to participate if their pregnancies were 11 to 13 weeks' gestation, based on self-reports from the participants. The gestational age

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was later confirmed using last menstrual period and ultrasound crown-rump length estimates. For subjects with both data available, last menstrual period was used if the concordance between the 2 was within 3 days, otherwise the ultrasound crown-rump length estimate was used. Blood samples taken from participants at 11 to 13 weeks' gestation were used for the analysis of biochemical markers and determination of fetal chromosomal aneuploidies. Leftover blood samples were frozen for later analysis. All women gave written informed consent to the scientific processing of their clinic data. The Institutional Review Board at CGMH approved this study (99-3828B).

The study population of this report was recruited from participants who enrolled in the FOCAS during the period from 2007 to 2013 and had singleton pregnancy. During this period, 2931 eligible women were informed of the study, and 2611 individuals (~89%) agreed to participate. Of them, a total of 2536 participants provided fasting blood samples. Pregnancies with chronic hypertension (n = 91), pregestational diabetes mellitus (n = 13), significant medical complications (n = 7), or fetal chromosomal abnormalities (n = 22) were excluded. Also excluded were individuals whose pregnancy outcome was unknown as a result of change in residence, delivery elsewhere, or missing medical records (n = 65). Hence, a cohort of 2338 women with complete pregnancy outcomes was available for the analysis. Given the unique profile of the prospective FOCAS cohort, we consider it is apt to discover early gestational risk factors for maternal-fetal complications that occur later in pregnancy.

Data Collection

The diagnosis criteria of preeclampsia followed international classification systems, and the diagnosis was defined as a sustained increase of blood pressure after 20 weeks of gestation with a systolic pressure of 140 mmHg or higher or a diastolic pressure of 90 mmHg or higher 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 6 hours apart.[1] From this cohort, we identified 134 confirmed cases of preeclampsia. These cases were classified as either early-onset (≤34 weeks of gestation; 53 cases) or late-onset (>34 weeks of gestation; 81 cases) according to the gestational age at which preeclampsia was diagnosed. These cases were also classified as with IUGR (44 cases) or without IUGR (90 cases). IUGR was defined as a birth weight below the 10th percentile for the gestational age according to the national birth weight distribution database of the Taiwanese population. The severity of IUGR was assessed by analysis of neonatal birth weight percentile discrepancy.

A total of 150 uncomplicated pregnancies randomly selected from women who participated over the same period of time were used as controls. All controls had normal blood pressures throughout gestation.

From antepartum electronic medical records, we obtained covariate information including maternal age, height, prepregnancy weight, reproductive and medical history, and medical histories of first-degree family members. Prepregnancy body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

The serum samples were thawed at room temperature, vortexed, and centrifuged prior to the analysis of high-sensitive C-reactive protein (hsCRP), glucose, glycatedhemoglobin (HbA_{1c}), homocysteine, insulin, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and very low-density lipoprotein cholesterol (VLDL-C) using standard methods. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation for samples with <400 mg/dL triglycerides, and by the beta-quantification procedure for samples with ≥400 mg/dL triglycerides. The homeostasis model assessment index (HOMA) = (fasting glucose × fasting insulin)/404 was used as an indicator of insulin resistance. All assays were performed without knowledge of case–control status.

Statistical Analysis

Results were expressed as mean ± standard deviation (SD) for continuous variables and number (percent) for categorical variables. Discrete variables were analyzed by the χ^2 test. A $P < 0.05$ was considered statistically significant. Simple linear regression was used for continuous variables. For incremental data, the Spearman correlation analysis was applied. All variables with a $P < 0.15$ in the univariate analysis were examined by linear or logistic multivariate stepwise regression analysis. The sensitivity and specificity for different cut-offs of independent predictors were calculated. Receiver operating characteristics curves were assessed for the analysis of the prognostic value of independent predictors on the severity of preeclampsia. Logistic regression was used to determine the area under the receiver operating characteristics curve (AUC) and the probabilities of outcomes (eg, early onset preeclampsia or preeclampsia with IUGR).

RESULTS

The clinical data of patients with preeclampsia and healthy controls are shown in Table 1. There was no statistical difference between women with or without preeclampsia with respect to maternal age, parity, BMI, HbA_{1c}, total cholesterol, LDL-C,

TABLE 1. Characteristics of the Study Patients and Controls

Characteristics	Preeclampsia (n = 134)	Control (n = 150)	*P* Value
Age, year	31.0 (7.3)	30.3 (6.7)	0.4
Nulliparous, %	70	67	0.3
hsCRP, mg/L	9.97(4.79)	3.91 (1.19)	<0.0001
Homocystine, μmol/L	7.88 (3.80)	5.81 (1.75)	<0.0001
Fasting glucose, mg/dL	83 (23)	74 (18)	0.0004
HbA_{1c}, %	5.71 (1.84)	5.58 (1.43)	0.49
Fasting insulin, mU/L	9.81 (2.3)	8.5 (2.5)	<0.0001
HOMA	2.0 (1.0)	1.7 (1.1)	0.02
Total cholesterol, mg/dL	179 (49)	171 (48)	0.185
Triglycerides, mg/dL	165 (46)	144 (54)	0.0006
HDL-C, mg/dL	64.8 (10.3)	65.5(10.8)	0.62
LDL-C, mg/dL	86.9 (19.0)	85.5 (20.0)	0.53
VLDL-C, mg/dL	30.3 (6.6)	27.0 (6.1)	0.0001
Body mass index, kg/m^2	22.9 (3.4)	22.2 (3.4)	0.11
Infant birth weight, g	2410 (689)	3060 (645)	0.0001

Data are presented as mean (SD) unless otherwise indicated. HOMA = [fasting glucose (mg/dL) × fasting insulin (mU/L)]/404. HbA_{1c} = glycatedhemoglobin, hsCRP = high-sensitive C-reactive protein, HDL-C = high-density lipoprotein cholesterol, HOMA = homeostasis model assessment index, LDL-C = low-density lipoprotein cholesterol, SD = standard deviation, VLDL-C = very low density lipoprotein cholesterol.

TABLE 2. Univariate Analysis of Risk Factors Related to the Time of Onset and the Presence of IUGR in Pregnancies With Preeclampsia

Variables	Early-Onset (n = 53)	Late-Onset (n = 81)	*P* Value	With IUGR (n = 44)	Without IUGR (n = 90)	*P* Value
Age, year	32.3 (10.1)	30.3 (7.9)	0.06	32.9 (9.6)	30.2 (8.4)	0.09
Nulliparous, %	81	63	0.0001	68	71	0.1
hsCRP, mg/L	12.25 (4.94)	8.48 (4.08)	0.0001	13.05 (4.57)	8.47 (4.15)	0.0001
Homocystine, μmol/L	10.43 (3.49)	6.22 (3.0)	0.0001	10.62 (2.76)	6.55 (3.52)	0.0001
Fasting glucose, mg/dL	78 (18)	86 (25)	0.025	78 (18.7)	85 (25)	0.08
HbA_{1c}, %	5.62 (1.22)	5.77 (2.16)	0.65	5.75 (1.98)	5.69 (1.78)	0.85
Fasting insulin, mU/L	9.87 (1.85)	9.77 (2.59)	0.82	9.12 (1.95)	10.14 (2.4)	0.02
HOMA	2.1 (1.15)	1.9 (0.9)	0.28	1.69 (0.79)	2.1 (1.1)	0.03
Total cholesterol, mg/dL	168 (54)	186 (45)	0.035	157 (45.9)	189(48)	0.0003
Triglycerides, mg/dL	162 (49)	167 (43)	0.58	134 (48.2)	180 (36)	0.0001
HDL-C, mg/dL	65 (12)	65 (9.4)	0.80	62.4(12.9)	66 (8.6)	0.053
LDL-C, mg/dL	79.2 (20.6)	92 (16.1)	0.0001	78.1 (17.9)	91.2 (18.1)	0.0001
VLDL-C, mg/dL	28.7 (5.9)	31.39 (6.8)	0.012	29.1 (5.8)	31.0 (6.86)	0.11
Body mass index, kg/m^2	22.8 (3.8)	22.9 (3.1)	0.92	21.7 (4.1)	23.4 (2.9)	0.0043

Data are presented as mean (SD). HOMA = [fasting glucose (mg/dL) × fasting insulin (mU/L)]/404. HbA_{1c} = glycatedhemoglobin, hsCRP = high-sensitive C-reactive protein, HDL-C = high-density lipoprotein cholesterol, HOMA = homeostasis model assessment index, IUGR = intrauterine growth restriction, LDL-C = low-density lipoprotein cholesterol, SD = standard deviation, VLDL-C = very low density lipoprotein cholesterol.

and HDL-C. The mean infant birth weight of women with preeclampsia was significantly lower than that of the control group. In women with preeclampsia, plasma levels of hsCRP, homocysteine, fasting glucose, triglycerides, VLDL-C, fasting insulin, and HOMA were all higher than that of the control group (Table 1).

Univariate analysis revealed that nulliparous status, high hsCRP level, high homocysteine level, and high fasting glucose level were significant predictors of early-onset preeclampsia. On the other hand, LDL-C and VLDL-C were significantly lower in pregnancies with early-onset preeclampsia as compared to pregnancies with late-onset preeclampsia (Table 2).

Multivariate logistic regression analysis further revealed 2 independent predictors of early-onset preeclampsia, homocysteine, and hsCRP (Table 3). In addition, stepwise multiple regression analysis indicated that homocysteine and hsCRP were independent predictors of the gestational age at which preeclampsia was diagnosed (Table 3).

Univariate analysis also indicated that pregnancies with preeclampsia and IUGR had higher plasma levels of hsCRP and homocysteine than pregnancies with preeclampsia without IUGR. Women with preeclampsia without IUGR had higher plasma levels of fasting insulin, LDL-C, total cholesterol, and triglycerides, and higher HOMA and BMI as compared to those with preeclampsia with IUGR group (Table 2). After adjustment for these factors, hsCRP and homocysteine were identified as independent predictors of pregnancies with preeclampsia with IUGR (Table 4).

Furthermore, stepwise multiple regression analysis indicated that hsCRP and homocysteine were predictors of birth weight in pregnancies with preeclampsia (Table 4). On the other hand, there was a negative correlation ($r = -0.28$; $P = 0.001$) between homocysteine level and the gestational age at which preeclampsia was diagnosed, as well as between homocysteine level and birth weight ($r = -0.16$; $P = 0.008$).

The detection rate of early-onset preeclampsia and preeclampsia with IUGR for different false positive rates by the final independent predictors (ie, plasma hsCRP only, plasma homocysteine only, and the combination of hsCRP and homocysteine) are shown in Figures 1 and 2. The AUC for the detection of early-onset preeclampsia were significantly higher with the combination model (AUC, 0.943) than with either

TABLE 3. Multivariate Analysis of Risk Factors Related to the Time of Onset of Preeclampsia

	Early-Onset Preeclampsia			Gestational Age at Onset of Preeclampsia	
Variables	Odds Ratio	95% CI	*P* Value	F Value	*P* Value
Homocysteine	1.54	1.30–1.84	0.0000	28.40	0.001
hsCRP	1.23	1.09–1.39	0.0007	8.11	0.008

CI = confidence interval, hsCRP = high-sensitive C-reactive protein.

TABLE 4. Multivariate Analysis of Risk Factors Related to the Presence and Severity of IUGR in Pregnancies with Preeclampsia

	Presence of IUGR			Severity of IUGR	
Variable	Odds Ratio	95% CI	*P* Value	F Value	*P* Value
Homocysteine	1.52	1.24–1.86	0.0001	21.38	0.001
hsCRP	1.33	1.14–1.55	0.0003	26.84	0.001

CI = confidence interval, hsCRP = high-sensitive C-reactive protein, IUGR = intrauterine growth restriction.

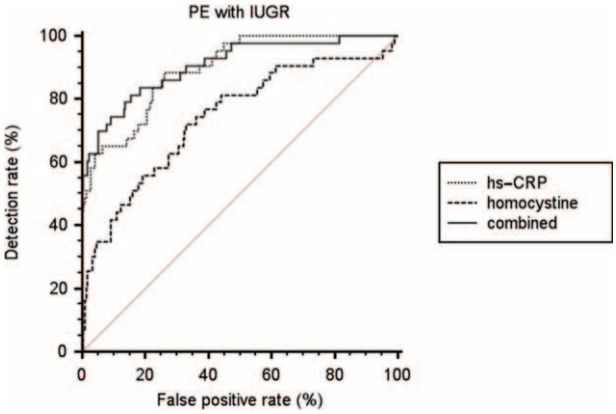

FIGURE 1. Receiver operating characteristics curves of high-sensitive C-reactive protein (hsCRP), homocysteine, and the combination of the 2 in the prediction of early-onset preeclampsia.

plasma hsCRP only (AUC, 0.900; $P = 0.004$) or plasma homocysteine only (AUC, 0.868; $P = 0.0037$). Similarly, for the detection of preeclampsia with IUGR, the AUC for the combination model was significantly higher (AUC, 0.952) than that of hsCRP only (AUC, 0.900; $P = 0.0008$) or homocysteine only (AUC, 0.902; $P = 0.0043$).

DISCUSSION

Preeclampsia is one of the most common life-threatening complications of pregnancy. It affects 3% to 5% of all pregnancies and is one of the leading causes of maternal mortality and preterm delivery.[1] Given the high maternal-fetal mortality and morbidity associated with severe preeclampsia, the ability to predict and recognize the severity of preeclampsia early during pregnancy could have important implications for timely intervention and management. Recently, based on the observation that women with a history of preeclampsia are predisposed to heart diseases later in life;[9,10] it has been hypothesized that preeclampsia and maternal cardiovascular diseases could share common risk factors, underlying mechanism, or predisposing factors.[7,8] With this knowledge, we hypothesized that cardiovascular risk factors that were present during early pregnancy could be risk factors for preeclampsia. In the present study, we assessed the role of a variety of cardiovascular disease risk factors that can be routinely determined to identify predictors for preeclampsia based on disease severity.

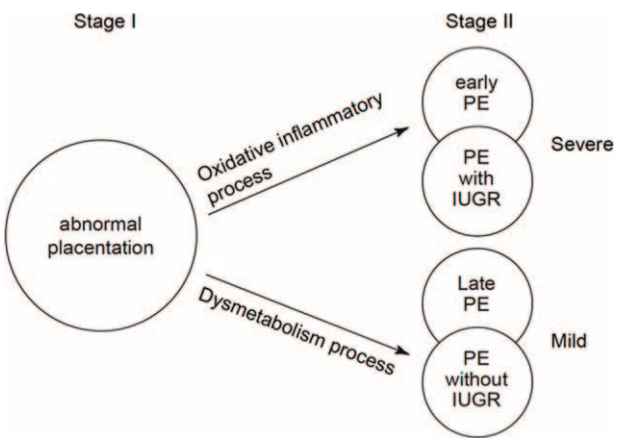

FIGURE 2. Receiver operating characteristics curves of hsCRP, homocysteine, and the combination of the 2 in the prediction of preeclampsia with IUGR. hsCRP = high-sensitive C-reactive protein, IUGR = intrauterine growth restriction.

Because the analyzed cardiovascular risk factors also represent indicators of oxidative stress, dysglycemia, and dyslipidemia, our analyses could provide assessment of these processes in the occurrence/severity of preeclampsia. For example, our data showed that hsCRP and homocysteine levels, measures of the cardiac oxidative response, are higher in women prone to preeclampsia before the onset of clinical syndromes as compared to pregnant women without preeclampsia. Additionally, we have shown that pregnant women who subsequently develop preeclampsia have cardiovascular diseases associated metabolic features such as insulin resistance (elevated fasting insulin levels and HOMA), and dyslipidemia(elevated plasma total cholesterol, triglycerides, LDL-C, and VLDL-C, and lower plasma HDL-C) during the first trimester of pregnancy (Table 1).

Because preeclampsia represents a dynamic state of interactions between systemic endothelial dysfunction, maternal immune status, and perhaps aberrant angiogenic factors in the circulation, the severity of preeclampsia can be highly variable depending on the timing and the degree of placental function reduction. As a result, it is not easy to classify the severity of preeclampsia properly. Subclassification of patients based on gestational age at disease onset is relatively simple and meaningful given that patients with preeclampsia who deliver prior to 37 weeks' gestation have a 7.1- to 8.1-fold higher risk for death from cardiovascular disease than those deliver at term.[13,14] Also, there is compelling epidemiologic evidence that preeclampsia with IUGR is associated with greater risk for later maternal cardiovascular disease and death compared with preeclampsia in which IUGR is not present.[4,15,16] Our results further show that the severity of preeclampsia, according to the time of onset and the presence or absence of IUGR, is associated with some of the cardiovascular risk factors tested during the first trimester of the pregnancy.

The value of hsCRP and homocysteine as early predictors of preeclampsia has been the subject of several reports.[17–22] An increase of hsCRP and homocysteine suggests an enhanced cardiovascular inflammatory response. Earlier studies have provided conflicting data on levels of hsCRP and homocysteine at different stages of pregnancy prior to the onset of preeclampsia. Our results are in agreement with several studies showing that an exaggerated maternal inflammatory response is associated with preeclampsia during the first trimester of pregnancy.[17,18] However, 2 recent studies have reported no significant difference in second trimester hsCRP levels between women who subsequently develop preeclampsia and normotensive pregnancies.[19,20] In contrast, elevated CRP levels were detected during the third trimester in pregnancies with preeclampsia in other studies.[21,22] Although there is no definitive explanation for this biphasic exaggerated inflammatory response in preeclampsia, it has been hypothesized that the maternal inflammatory response may be activated during the early phase of placentation, followed by adaptation during midgestation, and then a third trimester reactivation. Obviously, further investigations are needed to explore the exact mechanism of this observation.

In this study, we also identified plasma homocysteine level as a marker of the presence and severity of preeclampsia independent of maternal age, body weight, and lipid parameters.

This finding is partly consistent with the finding of a meta-analysis of 25 relevant primary studies, which concluded that homocysteine concentrations are increased in normotensive pregnancies that later develop preeclampsia, and are significantly elevated once preeclampsia is established.[23] However, due to the lack of a dose-dependent relationship, the prognostic value of homocysteine level on the severity of preeclampsia cannot be established from the collected literature. Consequently, whether high concentrations of circulating homocysteine represent a cause or a secondary response reflecting metabolic alterations in preeclampsia remains unclear. If a high homocysteine level indeed participates in the pathogenesis of preeclampsia, it could be related to direct injury to vascular endothelial cells or increased oxidative stress.[24]

Notably, current studies have shown a distinct pattern of dyslipidemia during the first trimester in pregnancies classified based on the time of preeclampsia onset and the presence of IUGR. We found that pregnancies with late-onset preeclampsia or preeclampsia without IUGR had a more dyslipidemic profile. On the other hand, pregnancies with early-onset preeclampsia or preeclampsia with IUGR had significantly lower LDL-C and a less dyslipidemic profile as compared to those without IUGR. Our findings are consistent with the observation of Baker et al[25] that midgestation dyslipidemia is associated with mild, but not severe preeclampsia. In addition, in a prospective study by Llurba et al,[26] it was shown that women with preeclampsia who had normal triglyceride levels delivered at a much earlier gestational age and had a higher incidence of IUGR than women with preeclampsia who had elevated triglycerides. These findings suggest that early-onset preeclampsia associated with IUGR might originate from placental underperfusion, and that altered maternal metabolism, such as occurs with dyslipidemia syndrome, contributes a greater degree to the pathogenesis of some preeclamptic features with less placental dysfunction, and therefore normal fetal weight. The main difference between our study and that of Llurba et al[26] was that blood samples analyzed in our study were obtained in the first trimester (ie, 11–13 weeks' gestation), far before the onset of clinic manifestations of preeclampsia. Importantly, our results confirm the idea that there may be variant forms of preeclampsia that can be identified by differences in lipid profiles.

The association between the risk of developing preeclampsia and impaired glucose metabolism during pregnancy is a widely accepted concept. In the present study, we found that dysglycemic factors, including fasting insulin and insulin resistance (HOMA score), were higher in preeclamptic pregnancies than in normal pregnancies. On the other hand, fasting glucose and HbA_{1c} were not significantly different between the 2 groups. Our results are mostly in agreement with a prior nested case-controlled study by Emery et al[27] in which early hyperinsulinemia, a marker of insulin resistance, was shown to be a predisposing factor for mild preeclampsia. Our current study extends those results by showing that markers of insulin resistance were similar between early-onset and late-onset preeclampsia, however, significantly different between preeclampsia with and without IUGR.

The underlying mechanism of preeclampsia is thought to be impaired remodeling of the spiral arteries, leading to disturbed placental function in early pregnancy. A 2-stage model of preeclampsia had been proposed to address its pathophysiology.[28,29] The 1st stage is reduced placental perfusion that leads to the 2nd stage in which clinical manifestations occur. Several potential factors have been suggested as possible links between placental changes and maternal-fetal diseases originating from preeclampsia.[6,29–31] Results from our study demonstrate that maternal cardiovascular disease risk markers detected during the first trimester, including oxidative factors (hsCRP, homocysteine), dysglycemia factors, and dyslipidemia factors, might play an important role as the link between reduced placental perfusion and the preeclampsia syndrome.

Interestingly, these factors showed widely discrepant patterns among different types of preeclampsia. Oxidative factors are an important link of abnormal placentation in early-onset preeclampsia and preeclampsia with IUGR. Although in late-onset preeclampsia and preeclampsia without IUGR, dysglycemia and dyslipidemia may play this role (Table 5). These data enforced the idea that preeclampsia is likely composed of 2 distinct disorders, early-onset preeclampsia and late-onset preeclampsia, which are associated with different biochemical markers.[6,31] Early-onset preeclampsia is considered a fetal disease that is typically associated with IUGR.[6] Our results, based on early trimester risk factor analysis, support this hypothesis. We thus further extend the original model and propose a 2-stage different disease model of preeclampsia pathophysiology (Figure 3). The modification supports the existence of subtypes of preeclampsia that might be identified by different linkage markers. Multiple linkages also raise the possibility of early prediction, prevention, and preparation for preeclampsia according to its disease phenotype.

Several potential limitations inherent to the interpretation of these study results should be considered. First, the results of this nested control study should be regarded as hypothesis generating because of the relatively small number of cases, and caution should be exerted while inferring causation. Second, this single tertiary center study needs validation in future prospective investigations involving a large number of pregnancies undergoing prenatal screening at a large number of hospitals. Third, we could not correct for confounding factors such as family history predisposition to preeclampsia, personal nutritional habits, and socioeconomic status, as this information was not available in our dataset. Fourth, our measurements were performed only from 11 to 13 weeks' gestation, and thus do not know the levels of the measured analytes prior to pregnancy. Therefore, our findings could only provide indirect evidence for a causal relationship between the maternal cardiovascular disease risk factors and the severity of preeclampsia.

Important strengths of this study included the fact that the maternal age was similar among the study groups, and that all groups had a similar gestation age during which the plasma was collected, given that plasma levels of many metabolic factors are dependent on the gestational stage of pregnancy. Also, we excluded women with chronic medical illnesses such as chronic hypertension and diabetes, as these diseases could have a measurable impact on cardiovascular disease risk factors. Thus, our study has provided an ideal setting to assess the effects of risk variables that can be incorporated into the first-trimester serum screening, thereby allowing the prediction of those at a great risk for developing preeclampsia and evaluating disease severity.

Our data suggests that early-onset preeclampsia and/or preeclampsia with IUGR might originate from reduced placental perfusion due to abnormal implantation, and that homocysteine-related endothelial dysfunction could be a contributor to these disorders. However, dyslipidemic syndrome that alters maternal metabolism contributes a greater degree to the pathogenesis of some preeclampsia features with less placental dysfunction that develops later in the pregnancy, and therefore is associated with a normal fetal weight. It is noteworthy that

TABLE 5. Differences in Maternal Cardiovascular Risk Factors Between Uncomplicated Pregnancies and Those Complicated by Preeclampsia, Early-Onset Preeclampsia, Late-Onset Preeclampsia, Preeclampsia With IUGR, and Preeclampsia Without IUGR

Variables	Preeclampsia	Early-Onset Preeclampsia	Late-Onset Preeclampsia	Preeclampsia With IUGR	Preeclampsia Without IUGR
Oxidative factors					
hsCRP, mg/L	↑	↑↑	↑	↑↑	↑
Homocystine, μmol/L	↑	↑↑	—	↑↑	—
Dysglycemia factors					
Fasting glucose, mg/dL	↑	—	↑	—	↑
HbA_{1c}, %	—	—	—	—	—
Fasting insulin, mU/L	↑	↑	↑	—	↑
HOMA	↑	↑	—	—	↑
Dyslipidemia factors					
Total cholesterol, mg/dL	—	—	↑	↓	↑
Triglycerides, mg/dL	↑	↑	↑	↓	↑↑
HDL-C, mg/dL	—	—	—	↓	—
LDL-C, mg/dL	—	↓	↑	↓	↑
VLDL-C, mg/dL	↑	—	↑	—	↑
Body mass index, kg/m^2	—	—	—	—	—

HbA_{1c} = glycatedhemoglobin, hsCRP = high-sensitive C-reactive protein, HDL-C = high-density lipoprotein cholesterol, HOMA = homeostasis model assessment index, IUGR = intrauterine growth restriction, LDL-C = low-density lipoprotein cholesterol, VLDL-C = very low density lipoprotein cholesterol.

maternal glycemic status was not significantly different between these groups, suggesting similar degree of inert oxidative insulin dysfunction regardless of the existence of different pathologic lines.

CONCLUSION

In summary, this study provides evidence that patients with preeclampsia can be subdivided into 2 different pathogenic groups according to the time of onset and fetal weight. A series of reproducible parameters distinguished a subgroup of these patients that presented specific patterns of maternal serum marker profiles. These findings support the idea that preeclampsia may be a heterogeneous syndrome with multiple etiologic factors. Future prospective studies measuring these maternal serum analytes throughout pregnancy and the postpartum period are needed for further understanding of the importance of the oxidative, dysglycemia, and dyslipidemia risk factors in preeclampsia, and their long-term impact on the cardiovascular health of women. The pathogenic implications of this finding involving both variants of preeclampsia can be of great help in the design and development of predictive and preventive interventions for preeclampsia and its complications.

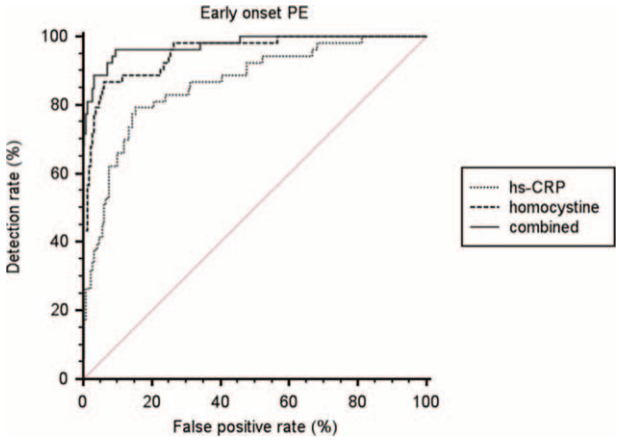

FIGURE 3. Two-stage different-disease model of the pathogenesis of preeclampsia. The model emphasizes that abnormal placental perfusion (stage I) interacts with different maternal constitutional factors (oxidative, inflammatory, and dysmetabolic processes) to result in diseases with different severities in stage II.

REFERENCES

1. Steegers EA, von Dadelszen P, Duvekot JJ, et al. Pre-eclampsia. *Lancet.* 2010;376:631–644.
2. Bell MJ. A historical overview of preeclampsia-eclampsia. *J Obstet Gynecol Neonatal Nurs.* 2010;39:510–518.
3. von Dadelszen P, Magee LA, Roberts JM. Subclassification of preeclampsia. *Hypertens Pregnancy.* 2003;22:143–148.
4. Rasmussen S, Irgens LM. History of fetal growth restriction is more strongly associated with severe rather than milder pregnancy-induced hypertension. *Hypertension.* 2008;51:1231–1238.
5. Valensise H, Vasapollo B, Gagliardi G, et al. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension.* 2008;52:873–880.
6. Raymond D, Peterson E. A critical review of early-onset and late-onset preeclampsia. *Obstet Gynecol Surv.* 2011;66:497–506.
7. Magnussen EB, Vatten LJ, Lund-Nilsen TI, et al. Prepregnancy cardiovascular risk factors as predictors of pre-eclampsia: population based cohort study. *BMJ.* 2007;335:978–981.
8. Hedderson MM, Darbinian JA, Sridhar SB, et al. Prepregnancy cardiometabolic and inflammatory risk factors and subsequent risk of hypertensive disorders of pregnancy. *Am J Obstet Gynecol.* 2012;207:68.e1–68.e9.

9. Romundstad PR, Magnussen EB, Smith GD, et al. Hypertension in pregnancy and later cardiovascular risk: common antecedents? *Circulation.* 2010;122:579–584.
10. Melchiorre K, Sutherland GR, Liberati M, et al. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension.* 2011;58:709–715.
11. Cheng PJ, Huang SY, Shaw SW, et al. Maternal homocysteine level and markers used in first-trimester screening for fetal Down syndrome. *Reprod Sci.* 2010;17:1130–1134.
12. Cheng PJ, Huang SY, Shaw SW, et al. Effect of maternal hepatitis B carrier status on first-trimester markers of Down syndrome. *Reprod Sci.* 2010;17:564–567.
13. Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet.* 2001;357:2002–2006.
14. Irgens HU, Reisaeter L, Irgens LM, et al. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ.* 2001;323:1213–1217.
15. Manten GT, Sikkema MJ, Voorbij HA, et al. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. *Hypertens Pregnancy.* 2007;26:39–50.
16. Yinon Y, Kingdom JC, Odutayo A, et al. Vascular dysfunction in women with a history of preeclampsia and intrauterine growth restriction: insights into future vascular risk. *Circulation.* 2010;122:1846–1853.
17. Sacks GP, Studena K, Sargent K, et al. Normal pregnancy and preeclampsia both produce inflammatory changes in peripheral blood leukocytes akin to those of sepsis. *Am J Obstet Gynecol.* 1998;179:80–86.
18. Redman CW, Sargent IL. Pre-eclampsia, the placenta and the maternal systemic inflammatory response – a review. *Placenta.* 2003;24(Suppl A):S21–S27.
19. Savvidou MD, Lees CC, Parra M, et al. Levels of C-reactive protein in pregnant women who subsequently develop pre-eclampsia. *BJOG.* 2002;109:297–301.
20. Djurovic S, Clausen T, Wergeland R, et al. Absence of enhanced systemic inflammatory response at 18 weeks of gestation in women with subsequent pre-eclampsia. *BJOG.* 2002;109:759–764.
21. Teran E, Escudero C, Calle A. C-reactive protein during normal pregnancy and preeclampsia. *Int J Gynaecol Obstet.* 2005;89:299–300.
22. Kumru S, Godekmerdan A, Kutlu S, et al. Correlation of maternal serum high-sensitive C-reactive protein levels with biochemical and clinical parameters in preeclampsia. *Eur J Obstet Gynecol Reprod Biol.* 2006;124:164–167.
23. Mignini LE, Latthe PM, Villar J, et al. Mapping the theories of preeclampsia: the role of homocysteine. *Obstet Gynecol.* 2005;105:411–425.
24. Mao D, Che J, Li K, et al. Association of homocysteine, asymmetric dimethyl arginine, and nitric oxide with preeclampsia. *Arch Gynecol Obstet.* 2010;282:371–375.
25. Baker AM, Klein RL, Moss KL, et al. Maternal serum dyslipidemia occurs early in pregnancy in women with mild but not severe preeclampsia. *Am J Obstet Gynecol.* 2009;201:293.e1–293.e4.
26. Llurba E, Casals E, Domínguez C, et al. Atherogenic lipoprotein subfraction profile in preeclamptic women with and without high triglycerides: different pathophysiologic subsets in preeclampsia. *Metabolism.* 2005;54:1504–1509.
27. Emery SP, Levine RJ, Qian C, et al. Twenty-four-hour urine insulin as a measure of hyperinsulinaemia/insulin resistance before onset of pre-eclampsia and gestational hypertension. *BJOG.* 2005;112:1479–1485.
28. Redman CW, Sargent IL. Latest advances in understanding pre-eclampsia. *Science.* 2005;308:1592–1594.
29. Roberts JM, Gammill HS. Preeclampsia: recent insights. *Hypertension.* 2005;46:1243–1249.
30. George EM, Granger JP. Recent insights into the pathophysiology of preeclampsia. *Expert Rev Obstet Gynecol.* 2010;5:557–566.
31. Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. *Placenta.* 2009;30(Suppl A):S32–S37.