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ARTICLE

Combination of serum histidine-rich glycoprotein and uterine artery Doppler to predict preeclampsia

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Abstract

The primary aim of this study is to determine the value of using a combination of serum histidine-rich glycoprotein (HRG) level and uterine artery pulsatility index (PI) in pregnant women at 11–13^{+6} weeks' gestation to predict preeclampsia. The secondary aim is to determine the association between other pregnancy complications with the use of these combined tests. Transabdominal uterine artery PI and serum HRG level were measured at the time of first-trimester aneuploidy screening at 11–13^{+6} weeks' gestation in 327 pregnant women. The primary outcome was preeclampsia. The predictive values of this combination test were calculated. Eighteen cases developed preeclampsia (5.5%) and four of these preeclamptic cases were early-onset preeclampsia (1.2%). The sensitivity, specificity, positive predictive value, and negative predictive value of uterine artery PI combined with serum HRG level to predict preeclampsia were 11.1%, 96.8%, 16.7%, and 94.9%, respectively. For the prediction of early-onset preeclampsia, the sensitivity, specificity, positive predictive value, and negative predictive value were 25%, 97.1%, 10%, and 99%, respectively. An abnormal uterine artery PI and abnormal serum HRG level were associated with preterm delivery and intrauterine growth restriction. Our findings reveal that the combination of uterine artery PI and serum HRG level at 11–13^{+6} weeks of gestation is not an effective method for predicting preeclampsia at the time of first-trimester screening.

Introduction

Preeclampsia is a common obstetric complication that causes both maternal and fetal morbidity and mortality [1]. Preeclampsia also increases the long-term risk of cardiovascular and cerebrovascular disease [2]. The incidence of preeclampsia is 3–5% depending on the population and diagnostic criteria [3]. Early detection of preeclampsia can reduce the severity of complications and improve clinical outcomes, either by early and frequent surveillance or the ability to use aspirin in the first trimester [4, 5].

The exact pathogenesis of preeclampsia is still unknown. A two-stage model has been proposed [6]. The first stage is impaired trophoblastic invasion into spiral arteries, which can result in a small lumen and high resistance. This model can be evaluated by uterine artery Doppler assessment [7]. Many uterine artery Doppler studies have found that preeclamptic patients have more abnormal uterine artery Doppler results than normal patients. Previous studies in our population showed that a uterine artery PI above the 95th percentile and/or bilateral diastolic notches had a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for prediction of preeclampsia of 20–75%, 52.5–95.8%, 9.1–14.3%, and 97.1–97.2%, respectively [8, 9].

Another model proposes angiogenic imbalance. The process of placental development, the coordination of vascular changes, and the regulation of trophoblast growth are mediated by several locally acting angiogenic and anti-angiogenic factors and their receptors [10]. When these processes are suboptimal, the results may be placental dysfunction, which can cause preeclampsia. This can be evaluated by measuring angiogenic factors. Examples of these angiogenic factors include soluble fms-like tyrosine kinase 1, placental growth factor, histidine-rich glycoprotein (HRG), and anandamide [11].

HRG is an abundant multi-domain plasma glycoprotein that has a variety of ligands that can interact with other

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substances. HRG has many functions in pro-angiogenesis, anti-angiogenesis, and coagulation pathways that affect female reproductive system functions. HRG has effects on ovarian function, embryonic implantation, placentation, and changes during pregnancy, especially in preeclampsia [12, 13]. HRG can be detected throughout pregnancy, but lower serum HRG levels are observed in preeclampsia [14, 15]. HRG affects the balance of angiogenesis and is associated with preeclampsia [14–16]. The mechanism is the binding between HRG and anti-angiogenic thrombospondin (TSP-1). The binding between HRG and TSP-1 can inhibit the interaction between TSP-1 and CD36. Thus, the anti-angiogenic signal from the CD36–TSP-1 complex is decreased [17, 18]. CD36 signaling has been studied and is associated with many diseases, e.g., glucose intolerance, atherosclerosis, arterial hypertension, diabetes, cardiomyopathy, and Alzheimer's disease [19]. HRG also has effects on fibrinogen and platelet levels, and coagulation, which may affect preeclampsia [13, 17, 18]. Combinations of uterine artery Doppler with biochemical markers have a higher predictive value for preeclampsia compared with either single test [20, 21]. Because of limitations relating to the heterogeneity of study populations and the fact that most tests can better detect early-onset preeclampsia, the best predictive test for preeclampsia is still questionable [22–24]. At present, the best predictive test is a combination of uterine artery Doppler and the sFlt/PlGF ratio, which is mostly performed in the second trimester [20, 21]. There has been only one study of a combination test comprising uterine artery Doppler and serum HRG level to predict preeclampsia in pregnant women at 14 weeks' gestation [15]. A sensitivity of 91% and a specificity of 62% for predicting preterm preeclampsia were demonstrated.

The objective of this study is to determine the predictive value of the combination of serum HRG level and uterine artery Doppler to predict preeclampsia in women at 11–13 $^{+6}$ weeks' gestation and to identify associations between other pregnancy complications with the use of these combined tests.

Methods

This prospective observational study was performed at the Faculty of Medicine, Department of Obstetrics and Gynecology, Chulalongkorn University, and King Chulalongkorn Memorial Hospital, Bangkok, Thailand, between 1 November 2014 and 31 October 2015. The study was approved by the Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University. Written informed consent was obtained from all subjects.

Singleton pregnant women with a gestational age 11–13^{+6} weeks were invited to participate in the study. Gestational age was calculated from the last menstrual period and confirmed by first-trimester ultrasound. Exclusion criteria included underlying medical diseases that may affect serum HRG level (advanced liver cirrhosis, HIV infection, renal disease, asthma, pulmonary disease, and thrombotic disorders), aspirin usage, and fetal abnormalities (structural or chromosomal).

The sample size calculation was based on the sensitivity for predicting preeclampsia from Bolin et al. [15]. Accordingly, 320 women were required for this study.

The primary outcome was the diagnosis of preeclampsia. Secondary outcomes included preterm delivery, intrauterine growth restriction (IUGR), gestational diabetes, neonatal respiratory distress syndrome (RDS), and perinatal death. Preeclampsia was defined as a blood pressure of at least 140/90 mm Hg, measured on two occasions at least 6 h apart, with proteinuria of at least 300 mg/24 h or at least 1 + on urine dipstick test, or urine protein-creatinine ratio (UPCI) > 0.3. Both the elevated blood pressure and

Table 1 Basic characteristic data, maternal, and neonatal outcomes

	Control (n = 309)	Preeclampsia (n = 18)	P-value
Maternal age (years)	32.4 ± 4.1	32.2 ± 5.9	0.86
Parity			0.932
0	203 (65.7)	12 (66.7)	
≥1	106 (34.3)	6 (33.3)	
Pre – pregnancy BMI (kg/m^2)	22.1 ± 4.0	24.9 ± 7.2	0.005
Obesity (BMI ≥ 30 kg/m^2)	13 (4.2)	5 (27.8)	<0.001
Total weight gain (kg)	14.0 ± 4.8	12.9 ± 7.5	0.40
GA at delivery (weeks)	37.9 ± 2.1	36 ± 3.1	<0.001
Preterm delivery (< 37 weeks)	31 (10)	7 (38.9)	<0.001
IUGR	12 (3.9)	2 (11.1)	0.176
Gestational diabetes	18 (5.8)	2 (11.1)	0.303
Mode of delivery			0.012
Vaginal route	171 (55.3)	4 (22.2)	
Cesarean section	138 (44.7)	14 (77.8)	
Birth weight (g)	3043.8 ± 515.2	2652 ± 781.7	0.003
Apgar scores			
< 5 at 1 min	9 (2.9%)	1 (5.6%)	0.436
< 5 at 5 min	5 (1.6%)	1 (5.6%)	0.289
RDS	11 (3.6)	4 (22.2)	0.006
Perinatal death	0 (0)	0 (0)	NA

Data are presented in mean ± SD or n (%)

BMI, body mass index; GA, gestational age; IUGR, intrauterine growth restriction; NA, not applicable; RDS, respiratory distress syndrome

proteinuria occurred for the first time after 20 weeks' gestation [25]. Early-onset preeclampsia was defined as preeclampsia that occurred before 34 weeks' gestation. Late-onset preeclampsia was defined as preeclampsia that occurred at 34 weeks' gestation or later [26].

The maternal demographic data, uterine artery Doppler PI, serum HRG level, and maternal and neonatal outcomes were recorded.

Uterine artery doppler measurement

Uterine artery flow velocity waveforms were obtained by using ultrasonographic machines (GE Voluson E8, GE Medical Systems, Zipf, Austria) with a convex abdominal probe AB 2–7 MHz by a single operator. Each subject was examined once in the semi-recumbent position after 5 min of bed rest. The measurement of the uterine artery Doppler was performed by placing a transducer along the inguinal canal. Then, color Doppler was used to identify the external iliac and uterine vessels just lateral to the uterus. Flow velocity waveforms were obtained from each uterine artery at the crossing of the external iliac artery. A pulsed wave Doppler gate was then placed over the uterine artery with an angle of insonation $< 30°$. Three consecutive waveforms were obtained. The mean PI was calculated and the presence or absence of an early diastolic notch was noted. An abnormal uterine artery Doppler pattern was defined as the presence of a mean PI > 95th percentile for the given gestational age. The mean intra-observer coefficient of variation for the PI was 0.91.

Serum HRG collection and measurement

After Doppler examination, venipuncture was performed and blood was collected into non-heparinized tubes. Blood samples were centrifuged at 2,500 r.p.m. for 10 min and stored at − 80 °C until assayed. Serum HRG level was measured by means of an enzyme-linked immunosorbent assay (Cloud-Clone Corp., TX, USA) according to the manufacturer's recommendations. The kit used was a sandwich enzyme immunoassay. The degree of enzymatic turnover of the substrate was determined using a wavelength absorbance measurement at 450 nm using a microplate reader. The minimum detectable HRG concentration in the assays, as reported by the manufacturer, was 0.21 ng/ml. The inter-assay and intra-assay coefficients of variation were < 10%.

Statistical analysis

Data were analyzed with the SPSS software package version 17.0 for Windows (SPSS Inc., Chicago, USA). Data were expressed in terms of mean, SD, sensitivity, specificity, PPV, NPV, and relative risk with a 95% confidence interval. The optimal cutoff levels for HRG were calculated using the receiver operator characteristic (ROC) curve. The χ^2-test and Fisher's exact test for categorical variables and independent *t*-test for continuous variables were used when appropriate. A *P*-value of < 0.05 was considered statistically significant.

Table 2 Serum histidine-rich glycoprotein level and uterine artery Doppler study

	Control (n = 309)	Preeclampsia (n = 18)	Early-onset preeclampsia (n = 4)	*P*-value
HRG (μg/ml)	6.2 ± 2.6	6.0 ± 1.3		0.46
			5.5 ± 2.0	0.568
UA PI	1.6 ± 0.5	1.9 ± 0.8		0.021
			1.8 ± 0.8	0.329
Notching				
Unilateral	94 (30.4)	8 (44.4)		0.212
			3 (75)	0.09
Bilateral	51 (16.5)	4 (22.2)		0.519
			1 (25)	0.518

Data are presented in mean ± SD or n (%)

HRG, histidine-rich glycoprotein; PI, pulsatility index; UA, uterine artery

Results

A total of 340 pregnant women were enrolled in this study. Thirteen cases were excluded (1 case of trisomy 13, 6 cases of abortion, and 6 cases lost to follow-up). Data from 327 pregnant women were analyzed. Eighteen cases developed preeclampsia (5.5%) and four of these preeclamptic cases were early-onset preeclampsia (1.2%).

The basic characteristic data of the pregnant women, and the maternal and neonatal outcomes in this study are shown in Table 1. There were no statistically significant differences in age, parity, and total weight gain between pregnant women with and without preeclampsia. Pregnant women with preeclampsia had a higher body mass index than controls. Pregnant women with preeclampsia also had a lower gestation age at delivery and a lower birth weight than controls. Pregnant women with preeclampsia had higher rates of preterm delivery, cesarean section, and neonatal RDS than controls.

Table 2 shows that pregnant women with preeclampsia did not have significantly lower serum HRG levels than the controls (6.0 ± 1.3 μg/ml vs 6.2 ± 2.6 μg/ml, $p = 0.46$). In addition, pregnant women with early-onset preeclampsia also did not have significantly lower serum HRG levels than

Table 3 Predictive value of abnormal serum HRG level and uterine artery PI for preeclampsia

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Positive LR	Negative LR
For preeclampsia						
UA PI > 95th percentile	16.7	94.8	15.8	95.1	3.2	0.9
HRG level < 6.12 μg/ml	33.3	37.2	3	90.6	0.5	1.8
Abnormal HRG level and UA PI	11.1	96.8	16.7	94.9	3.4	0.9
For early-onset preeclampsia						
UA PI > 95th percentile	25	95.2	6.3	98.9	5.2	0.8
HRG level < 6.12 μg/ml	50	37.2	1	98.3	0.8	1.3
Abnormal HRG level and UA PI	25	97.1	10	99	8.6	0.8

HRG, histidine-rich glycoprotein; UA, uterine artery; PI, pulsatility index; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio

the controls (5.5 ± 2.0 μg/ml vs 6.2 ± 2.6 μg/ml, $p = 0.568$). The cutoff value for serum HRG level was established using the ROC curve and the value was 6.12 μg/ml. When using a serum HRG level below 6.12 μg/ml, the sensitivity, specificity, PPV, and NPV for predicting preeclampsia were 33.3%, 37.2%, 3%, and 90.6%, respectively. For predicting early-onset preeclampsia, the sensitivity, specificity, PPV, and NPV were 50%, 37.2%, 1%, and 98.3%, respectively (Table 3).

The uterine artery PIs in women with preeclampsia were higher than the controls (1.9 vs 1.6, $p = 0.021$). The uterine artery PIs in early-onset preeclampsia were not significantly higher than the controls (1.8 vs 1.6, $p = 0.329$) (Table 2). The presence of unilateral and bilateral notching was not different between women with preeclampsia and controls. The 95th percentile for the mean uterine artery PI was calculated. The 95th percentiles for the mean PI at 11–11^{+6}, 12–12^{+6}, and 13–13^{+6} weeks' gestation were 2.73, 2.47, and 2.19, respectively. When using a uterine artery PI above the 95th percentile, the sensitivity, specificity, PPV, and NPV for predicting preeclampsia were 16.7%, 94.8%, 15.8%, and 95.1%, respectively (Table 3). For predicting early-onset preeclampsia, the sensitivity, specificity, PPV, and NPV were 25%, 95.2%, 6.3%, and 98.9%, respectively (Table 3).

When using a uterine artery PI above the 95th percentile combined with a serum HRG level cutoff value below 6.12 μg/ml, the sensitivity, specificity, PPV, and NPV for predicting preeclampsia were 11.1%, 96.8%, 16.7%, and 94.9%, respectively (Table 3). For predicting early-onset preeclampsia, the sensitivity, specificity, PPV, and NPV were 25%, 97.1%, 10%, and 99%, respectively (Table 3).

Using a combination of serum HRG level and uterine artery PI, there was a statistically significant increase in the risk of preterm delivery and IUGR between pregnant women with abnormal and normal combination testing (Table 4).

Table 4 Abnormal serum HRG level and uterine artery PI for other obstetric outcomes

	Relative risk (95% CI)
Preterm delivery (GA < 37 weeks)	3.1 (1.3–7.3)
IUGR	4.4 (1.1–17.4)
Gestational diabetes	1.4 (0.2–9.5)
Neonatal RDS	1.9 (0.3–13.1)

CI, confidence interval; IUGR, intrauterine growth restriction; PI, pulsatility index; RDS, respiratory distress syndrome

Discussion

This study demonstrates that the combination of uterine artery Doppler and serum HRG level is not an effective method for predicting preeclampsia as a first-trimester screening test.

The combination of uterine artery Doppler and serum HRG level was not effective as a first-trimester screening test for predicting preeclampsia in this study. The reason may be due to the complexity and multiple mechanisms in the development of preeclampsia [27]. Uterine artery Doppler and serum HRG level may act independently and in a different manner. Thus, when these tests are used in combination for the purpose of predicting preeclampsia, they may not complement each other, resulting in reduced effectiveness [28]. This finding was consistent with previous studies on combined uterine artery Doppler and angiogenic factor testing in that the combination test did not improve the predictability of preeclampsia [23, 28–30] but was different from other studies [31, 32]. Most markers for prediction preeclampsia in the first trimester had poor sensitivity and specificity, and could only predict early-onset preeclampsia [20, 21].

The combination of uterine artery Doppler and serum HRG level at gestational age 11–13^{+6} weeks for the prediction of preeclampsia had lower sensitivity and specificity when compared with previous studies of combination tests of uterine artery Doppler and other angiogenic factors [23,

28, 31, 32]. This difference may be explained by the different gestational age, population, and angiogenic factor measured. Previous studies of combination tests of uterine artery Doppler and other angiogenic factors (soluble fms-like tyrosine kinase 1, angiopoietin-2) in the second trimester had higher sensitivity than the present study [23, 28]. There has been no study of HRG level in the second trimester for the prediction of preeclampsia. However, previous systematic reviews and meta-analyses demonstrated that the presence of uterine artery notching or increased uterine artery PI in the second trimester are better than in the first trimester for predicting preeclampsia [33].

However, there has been no previous study of the combination of uterine artery Doppler and serum HRG level for the prediction of preeclampsia in pregnant women between 11 and 13^{+6} weeks of gestation. This study found that there was a higher sensitivity for the prediction of early-onset preeclampsia than for the prediction of overall preeclampsia when using the combination of uterine artery Doppler and serum HRG level. This finding was similar to previous studies that found that the combination of uterine artery Doppler and biochemical markers can predict early-onset preeclampsia better than overall preeclampsia [23, 28, 34, 35]. Specifically, biochemical markers and uterine artery Doppler results changed more in cases of early-onset preeclampsia than in cases of late-onset preeclampsia [23, 28, 35].

Serum HRG levels in the present study were not significantly lower in pregnant women with preeclampsia than controls at a gestational age of 11–13^{+6} weeks. This result was contrary to the study from Bolin et al. (2011) [14]. They demonstrated that plasma HRG levels were significantly lower in pregnant women with preeclampsia than controls at gestational ages of 10, 25, and 28 weeks. However, the result of this study was similar to the study from Bolin et al. (2012) [15]. Serum HRG levels in pregnant women with preeclampsia were not different from controls. Serum HRG levels in the present study were not significantly lower in pregnant women with early-onset preeclampsia compared with controls. However, Bolin et al. [15] found that serum HRG levels were significantly lower in pregnant women with early-onset preeclampsia than controls. Mean serum HRG levels in this study were also lower than in the studies from Bolin et al. [14, 15]. This difference might be explained by differences in study populations.

HRG has many functions in pro-angiogenesis and anti-angiogenesis and the balance of coagulation [13, 17, 18]. Decreased serum HRG levels will promote CD36-TSP-1 anti-angiogenic signaling. The interaction between HRG and TSP-1, which inhibits the formation of the CD36-TSP-1 complex, is hypothesized to be the mechanism that may lower the risk of preeclampsia [14, 15]. Thus, low serum HRG levels should increase the risk of preeclampsia. However, in this present study, serum HRG levels were not significantly lower in pregnant women with preeclampsia. This might be explained by the fact that HRG has different expression levels in different populations and may have other mechanisms that affect the inhibition or promotion of preeclampsia. There are a variety of functions for HRG and it has been found to interact with tumor-associated macrophages type M1 and M2 [18]. HRG promotes the function of M1 macrophages and inhibits the pro-angiogenic function of PlGF, as well as the function of M2 macrophages [18]. M1 and M2 macrophages are important in many physiologic changes in pregnancy [36]. The combination of increased function of M1 macrophages and decreased function of pro-M2 macrophages has negative effects on spiral artery remodeling by trophoblasts. Abnormal vascular remodeling has been shown to be related to many obstetric complications (preeclampsia, IUGR, preterm birth, abortion, and placental abruption) [36]. The interaction between HRG and M1/M2 macrophages has been found to occur in the decidual stroma [36]. This interaction may have an association with the result from the study of Kårehed et al. [16] The study showed increased HRG levels in the endothelial and stromal cells in the placentas of pregnant women with preelampsia [16].

Our unique study uses a combination test of uterine artery Doppler and serum HRG level to predict preeclampsia at the time of the first trimester ultrasonographic examination for aneuploidy screening. This test was more convenient for patients as two screenings were performed in one single visit. It should be noted that if these combination tests were performed in the first trimester, aspirin might have been used before 16 weeks of gestation to prevent preeclampsia. Conversely, if these tests were performed later (such as late in the second trimester), the prediction might be more accurate [23, 28]. Further prospective study of these combination tests at a different time of measurement should be conducted to evaluate test usefulness and efficacy. A notable limitation of this study was the small number of early-onset preeclampsia cases.

In conclusion, the combination of uterine artery Doppler and serum HRG level at 11–13^{+6} weeks of gestation was not effective as a first-trimester screening for the prediction of preeclampsia in this study.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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