ORIGINAL ARTICLE

First trimester prediction of HELLP syndrome

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ABSTRACT

Objective The aim of this study was to evaluate first-trimester maternal characteristics and biomarkers in pregnancies that subsequently develop HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome.

Method Maternal history, biochemical, and biophysical parameters were compared between women who developed HELLP, preeclampsia (PE) without HELLP and controls. After determination of significant variables through univariate analysis a first-trimester prediction model was obtained by applying logistic regression analysis. Performance of the model was evaluated.

Results Twenty participants with HELLP were compared with 147 patients that developed PE without HELLP and 2810 controls. Women with HELLP were more likely Caucasian, nulliparous and presented a higher mean arterial pressure (MAP) when compared with controls. As opposing to women who developed HELLP, women who developed PE without HELLP were more likely of African–American origin and presented an even higher first-trimester MAP. Enrollment biochemical and biophysical parameters were similar between HELLP and PE or controls. Ethnicity, nulliparity, history of previous PE, history of previous HELLP syndrome, and first-trimester MAP were primary risk factors. A prediction rule for HELLP syndrome had an area under the curve of 0.80, with 75% sensitivity for 79% specificity.

Conclusion The majority of pregnancies that develop HELLP syndrome can be predicted in the first trimester. © 2015 John Wiley & Sons, Ltd.

Funding source: This study was supported by a grant from Diagnostic Technologies Limited and PerkinElmer.
Conflicts of interest: None declared

INTRODUCTION

HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, which is considered to belong to the disease spectrum of preeclampsia (PE) occurs in 0.5–0.9% of all pregnancies and in 10–20% of those with severe PE.[1] It is generally accepted that PE, particularly early onset disease, results from impaired placentation in early gestation, and HELLP syndrome has been shown to share histopathologic, placental morphologic and changes in gene expression with early onset PE.[2–4] First-trimester biochemical and biophysical maternal changes observed in pregnancies that develop PE have been used to develop algorithms to estimate the individualized risk of a woman to develop PE. However, such algorithms fail to predict HELLP syndrome.[5]

The objectives of this study are first, to compare first-trimester maternal characteristics and biomarkers in pregnancies that subsequently develop HELLP syndrome with those in pregnancies that develop PE without HELLP and normal controls and second, to develop a model for first-trimester prediction of HELLP syndrome.

METHODS

Two prospective observational studies enrolled women at 11 to 13 weeks' gestation with the primary aim of developing a first-trimester predictive model for PE.[6,7] Women provided written informed consent to participate in the study, which was approved by the institutional review boards of both hospitals, and they filled a questionnaire on demographic characteristics and medical history. Transabdominal ultrasound examination was carried out to confirm gestational age, measure the fetal crown-rump length and perform uterine artery Doppler to measure the pulsatility index (UTPI).[6–8] Maternal weight (in kilogram) and height (in centimeter) were measured, and body mass index (in kg/m^2) was calculated. Blood pressure (mmHg) was measured on regularly calibrated equipment (Dinamap Pro 1000 V3, GE Medical Systems, Milwaukee, Wi; 3BTO-A2, Microlife). Maternal blood samples obtained by occlusive venipuncture were analyzed for serum concentration of pregnancy-associated protein-A (PAPP-A), free β-human chorionic gonadotropin, and placental growth factor (PLGF), using NTD labs (PerkinElmer, Melville, NY) or the DELFIA

XPRESS analyzer (PerkinElmer Life and Analytic Sciences).[6,7] The biochemistry results were reported as multiples of the median after absolute measurements were compared with reference ranges of a normal population.[6,7] Women who were on aspirin were not excluded from analysis. Aspirin prophylaxis (81 mg/day) was recommend at the time of first-trimester screening for women with a prior PE, prior stillbirth, prior fetal growth restriction, thrombophilia, autoimmune disease, recurrent pregnancy loss (defined as two or more pregnancy losses), bilateral uterine artery notching, or a combination of these on first-trimester ultrasonography.

Pregnancy outcome was ascertained by study personnel at the moment of delivery and verified by source documentation. Preeclampsia was defined as new-onset or worsening proteinuria and systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on two occasions ≥6 h apart after 20 weeks' gestation; PE superimposed on chronic hypertension was defined as worsening blood pressure and increasing proteinuria after 20 weeks' gestation.[9] The diagnosis of HELLP syndrome was established when at least one of the three parameters was present: platelet count < 100.000/dL, elevated plasma level of transaminases (AST and ALT > 70 IU/l), and lactic dehydrogenase enzyme > 600 IU/mL. When an incomplete HELLP syndrome form was considered (in the absence of all the three parameters), hypertension was present at the moment of diagnosis and the analytic changes could not be explained by any other differential diagnosis.

Statistical analysis

Maternal characteristics and biomarkers in cases of HELLP syndrome were compared with those of PE without HELLP and normal controls. The Mann–Whitney *U*-test, Pearson χ^2, or Fisher's exact test were performed to compare continuous and categorical variables, respectively. By performing comparison analysis we obtained candidate variables for prediction of HELLP syndrome. A binary logistic regression analysis was performed using the obtained candidate variables, and the log odds was used to construct a predictive model. Receiver operating characteristic curve, the area under the curve, 95% confidence interval (CI), and detection and false positive rates were obtained. The statistical software package SPSS 14.0 (SPSS Inc. Chicago, IL, USA) was used for all data analyzes and a *p*-value of <0.05 was considered significant.

RESULTS

The study population of 2969 pregnancies was recruited from Johns Hopkins School of Medicine and included 12 (0.4%) that developed HELLP syndrome and 147 (5%) that developed PE without HELLP. Eight patients that presented first-trimester characteristics that matched our first-trimester variables, from King's College Hospital (London, UK) first-trimester prospective database, were added to the HELLP syndrome group. Median gestational age at delivery in those with HELLP syndrome (36.5 weeks) and PE without HELLP (36.7 weeks) was significantly lower than in the controls (39.1 weeks, $p < 0.001$). Median birth weight percentile in those with HELLP syndrome (3.7%) and PE without HELLP (28.1%) was significantly lower than in the controls (43.7%, $p < 0.001$).

Maternal characteristics and biomarker levels of the three groups are presented in Table 1 and Figure 1 and compared in Table 2. In women with HELLP syndrome, compared with controls, the incidence of African racial origin was lower, nulliparity was higher and median MAP was higher. In women with HELLP syndrome, compared with those of PE without HELLP, the incidence of Caucasians was higher and those of African origin lower and median MAP was lower. In the group of PE without HELLP syndrome, compared with controls, there was a higher incidence of African origin, chronic hypertension, diabetes mellitus, renal disease, nulliparity, and previous PE, and the median UTPI and MAP were higher and median PAPP-A and PLGF were lower.

Logistic regression analysis demonstrated that prediction for HELLP syndrome was provided by racial origin, nuliparity, prior history of HELLP syndrome and PE (Table 3). The obtained first-trimester algorithm for HELLP syndrome prediction was Y = −8.909 + (−0.493*Caucasian) + (−1.984*African) + (1.655*nulliparous) + (2.078*prior PE) + (3.739*Prior HELLP) + (0.042*MAP). The receiver operating characteristic curve for prediction of HELLP syndrome by the algorithm for HELLP syndrome is compared with our previously published one on prediction of PE[6] in Figure 2. The area under the curve obtained for the HELLP syndrome algorithm was 0.80 (CI 95%, 0.70–0.91) and for the PE algorithm was 0.67 (CI 95%, 0.54–0.79). The HELLP syndrome algorithm, at the optimal cutoff of 1/95, predicted 75% of affected cases at false positive rate of 21%; at false positive rate to 10%, the detection rate was 55% (Table 4).

DISCUSSION

The findings of this first-trimester study confirm the results of previous reports that in pregnancies that develop PE, compared with normal controls, UTPI, and MAP are increased and serum PAPP-A and PLGF are decreased. The study has also demonstrated that in pregnancies that develop HELLP syndrome, compared with those that develop PE without HELLP syndrome, women are more likely to be Caucasian and nulliparous and have less marked blood pressure elevation. Consideration of these differences in the construction of a prediction model specific for HELLP syndrome improves identification of women at risk compared with an algorithm that is geared towards prediction of PE.

In previous studies, the characteristics of patients with HELLP syndrome were primarily gathered at the time of diagnosis and have yielded inconclusive findings that are most likely because of ascertainment bias; our patient group originated from prospectively enrolled cohorts in the first-trimester and therefore may be less prone to such bias. Some studies highlighted nulliparity as a risk factor,[10–12] while others have not confirmed this finding.[13–15,3] There is also contradictory evidence concerning the association between HELLP syndrome and racial origin with one study reporting a higher incidence in Caucasian women[12] and another in women of African origin.[13] In our study women with subsequent HELLP syndrome had MAP that was higher than normal controls but lower than in women that developed PE without HELLP syndrome. A previous study reported that development of HELLP syndrome in a

Table 1 First-trimester maternal characteristics between groups

Parameters	HELLP $n=20$	PE $n=147$	Controls $n=2810$
Age (median)	31 (18–45)	27 (18–45)	30 (18–55)
Racial origin, *n* (%)			
Caucasian	13 (65)	44 (29.9)	1225 (43.6)
African	4 (20)	95 (64.6)	1399 (49.8)
South Asia	1 (5)	2 (1.4)	90 (3.2)
Chinese/Japanese	—	1 (0.7)	15 (0.5)
Indian/Pakistani	—	2 (1.4)	38 (1.4)
South American	1 (5)	3 (2)	30 (1.1)
Mixed	1 (5)	—	7 (0.2)
Other	—	—	6 (0.2)
Ovulation induction, *n* (%)	—	3 (2)	27 (1)
Smoker, *n* (%)	—	15 (10.2)	266 (9.5)
History of chronic hypertension, *n* (%)	2 (10)	42 (28.6)	206 (7.3)
History of diabetes mellitus, *n* (%)	2 (10)	22 (15.0)	96 (3.4)
Renal disease, *n* (%)	—	4 (2.7)	4 (0.1)
Thrombophilia, *n* (%)	—	3 (2)	60 (2.1)
Obstetric history, *n* (%)			
Nulliparous	14 (70)	82 (55.8)	1187 (42.2)
Previous preeclampsia	3 (15)	26 (17.7)	118 (4.2)
Previous HELLP syndrome	1 (5)	1 (0.7)	6 (0.2)
Previous preterm birth	—	2 (1.4)	50 (1.8)
Aspirin < 16 weeks, *n* (16%)	3 (15)	53 (30.6)	469 (16.7)
Body mass index, median (IQR)	25.20 (19.90–43.24)	29.45 (15.92–61.14)	26.63 (15.47–73.11)
Mean arterial pressure, median (IQR)	87.67 (73–101.8)	93 (66.33–135.67)	82.67 (48.33–138.0)
Mean UTPI, median (IQR)	1.57 (0.54–2.22)	1.53 (0.32–3.04)	1.38 (0.28–3.70)
PAPP-A MoM, median (IQR)	0.78 (0.28–2.99)	0.81 (0.09–4.29)	1.04 (0.08–5.13)
PLGF MoM, median (IQR)	0.82 (0.16–1.98)	0.82 (0.10–2.78)	1.00 (0.03–4.09)

IQR, interquartile range; HELLP, hemolysis, elevated enzymes, low platelets; UTPI, uterine artery pulsatility index; PAPP-A, pregnancy-associated protein; MoM, multiples of the median; PLGF, placental growth factor.

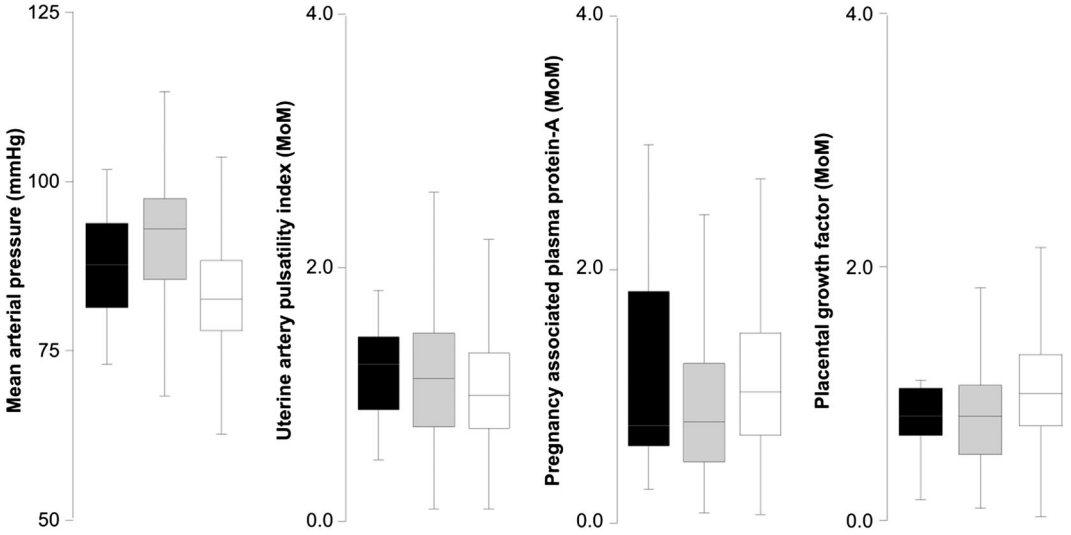

Figure 1 Box plot of first-trimester biophysical and biochemical variables in pregnancies that developed HELLP syndrome (black box), preeclampsia (grey box), and normal controls (white box)

Table 2 p-value between groups

Parameters	HELLP versus PE	HELLP versus Controls	PE versus Controls
Age	0.101	0.356	0.026*
Racial origin			
Caucasian	0.002*	0.054	0.001*
African	<0.001**	0.008*	<0.001**
South Asia	0.320	0.481	0.325
Chinese/Japanese	1.0	1.0	0.559
Indian/Pakistani	1.0	1.0	1.0
South American	0.403	0.198	0.224
Mixed	0.120	0.055	1.0
Other	—	1.0	1.0
Ovulation induction	1.0	1.0	0.185
Smoker	0.220	0.249	0.766
History of chronic hypertension	0.077	0.655	<0.001**
History of diabetes mellitus	0.742	0.151	<0.001**
Renal disease	1.0	1.0	<0.001**
Thrombophilia	1.0	1.0	1.0
Obstetric history			
Nulliparous	0.228	0.012*	0.001*
Previous preeclampsia	1.0	0.051	<0.001**
Previous HELLP syndrome	0.226	0.048	0.300
Previous preterm birth	1.0	1.0	1.0
Aspirin < 16 weeks	0.148	0.843	<0.001**
Body mass index	0.089	0.570	<0.001**
Mean arterial pressure	0.022*	0.014*	<0.001**
Mean UTPI	0.563	0.125	<0.025*
PAPP-A MoM	0.209	0.780	<0.001**
PLGF MoM	0.567	0.242	<0.001**

HELLP, hemolysis, elevated enzymes, low platelets; UTPI, uterine artery pulsatility index; PAPP-A, pregnancy-associated protein; MoM, multiples of the median; PLGF, placental growth factor.
*$p < 0.05$.
**$p < 0.01$.

Table 3 Logistic regression analysis for HELLP syndrome

	Odds	CI 95%	*p*-value
White	2.470	0.983–6.210	0.055
African	0.245	0.082–0.734	0.012*
Nulliparous	5.236	1.659–16.526	0.005*
Prior preeclampsia	7.989	1.756–36.346	0.007*
Prior HELLP syndrome	42.069	4.206–420.721	0.001*
Mean arterial pressure	1.043	0.994–1.095	0.085

*p-value < 0.05.

previous pregnancy was associated with 14–24% risk of recurrence.[14] In our study, a history of PE or HELLP syndrome were both risk factors for development of HELLP syndrome.

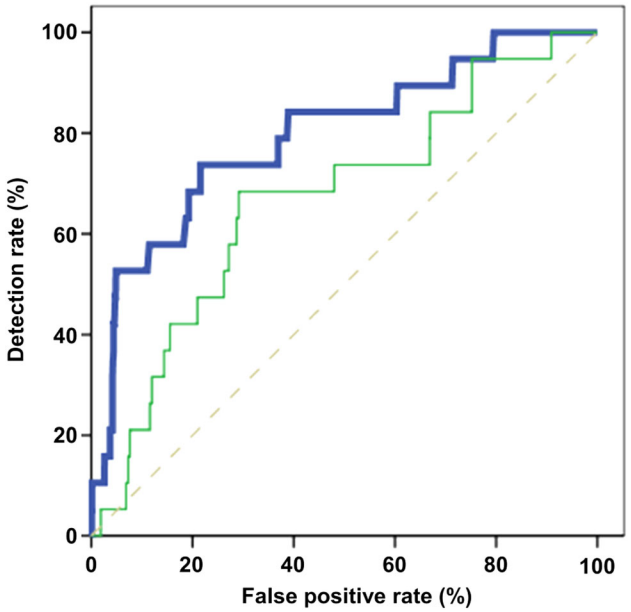

Figure 2 Receiver operating characteristic curve derived from the prediction rule for HELLP syndrome (thick line) and preeclampsia without HELLP syndrome (thin line)

Table 4 Diagnostic performance for HELLP syndrome

Cutoff	Sensitivity	Specificity	+ LR	- LR
1/61	55%	90%	5.53	0.50
1/95	75%	79%	3.51	0.32

LR, likelihood ratio.

In our study, the cohort of women that developed PE had the classic first-trimester risk features, including high UTPI and MAP and low PLGF and PAPP-A.[16–18] Patients with subsequent HELLP syndrome had the highest UTPI and lowest PAPP-A and PlGF, even though not reaching a statistical significance probably because of small sample size – a finding that has not been previously reported in a first-trimester cohort. These findings suggest that the clinical differences between HELLP syndrome and PE without HELLP at the time of diagnosis are also associated with differences in phenotype of women in the first trimester. This requires consideration in the context of first-trimester screening for PE.

We demonstrated that consideration of the first-trimester risk factors that are specific to HELLP syndrome produces a prediction algorithm that performs better than algorithms geared at prediction of PE. This is most likely because of the fact that cardiovascular, metabolic, thrombotic, and personal risk modifiers are most prevalent in women that subsequently develop PE and accordingly are overemphasized in algorithms that are geared toward a phenotype where hypertension is the lead diagnostic sign.[5,19] On the other hand, personal risk factors, such as a previous history of PE or HELLP syndrome, and not metabolic or cardiovascular risk factors, may predispose women to a higher risk of HELLP syndrome development. The first-trimester phenotypic differences between HELLP syndrome

and PE without HELLP may also have implications on pathophysiology and clinical management.

The predominance of placental dysfunction with restriction of fetal growth in patients with subsequent HELLP syndrome suggests that the placental involvement may not be identical to hypertensive PE. Accordingly, patients may benefit from serial monitoring for fetal growth and formal assessment for fetal growth disorders when the diagnosis of HELLP syndrome is made. Similarly, it may be worthwhile examining the efficiency of preventive therapies such as aspirin in this subset of high risk patients.[20,21] To date no studies have specifically evaluated the ability of aspirin to prevent HELLP syndrome. Even though HELLP syndrome has a low incidence and there is no treatment or proved prophylaxis available, the associated morbidity and mortality is high. Therefore, application of first-trimester algorithms specific for HELLP syndrome and evaluation of preventive measures could have an impact because high grade maternal and fetal morbidity may be averted.

The overall low incidence of HELLP syndrome required us to pool patients from two cohorts and the small case size may have influenced the statistical comparisons. Nevertheless, our data suggest that exclusive reliance on traditional PE first trimester screening algorithms is likely to miss women that develop HELLP phenotype PE. In this context we present a multivariable first-trimester algorithm that can predict HELLP syndrome in a high proportion of patients.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- The findings of this first-trimester study confirm the results of previous reports that in pregnancies that develop PE, compared with normal controls, UTPI and MAP are increased and serum PAPP-A and PLGF are decreased.

WHAT DOES THIS STUDY ADD?

- This study demonstrates that in pregnancies that develop HELLP syndrome, compared with those that develop Preeclampsia without HELLP syndrome, women are more likely to be Caucasian and nulliparous and have less marked blood pressure elevation. Consideration of these differences in the construction of a prediction model specific for HELLP syndrome improves identification of women at risk compared with an algorithm that is geared towards prediction of PE.

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