Predictive ability of serum advanced glycation end products at 11 to 13 weeks of gestation for early-onset preeclampsia

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BACKGROUND: Placental hypoxia and resultant oxidative stress have been associated with the development of preeclampsia. Oxidative stress promotes the formation of advanced glycation end products.

OBJECTIVE: This study aimed to assess whether serum levels of advanced glycation end products during the early stage of pregnancy are a predictive biomarker of early-onset and late-onset preeclampsia.

STUDY DESIGN: This was a nested case-control study that included 6 women with early-onset preeclampsia, 21 women with late-onset preeclampsia, and 50 age- and body mass index–matched healthy female control subjects. All women enrolled in the study had a complete medical history, including mean arterial pressure and uterine artery pulsatility index measurements. Furthermore, the women underwent blood chemistry analysis, including circulating levels of advanced glycation end products, soluble fms-like tyrosine kinase-1, and placental growth factor. Clinical measurements and biochemistry were evaluated at 11 to 13 and 19 to 24 weeks of gestation.

RESULTS: The median serum concentrations of advanced glycation end products at 11 to 13 weeks of gestation were significantly higher in patients with early-onset preeclampsia than in those with late-onset preeclampsia and control subjects (6.62 vs 4.10 vs 3.77; $P<.05$), but no significant difference was found in advanced glycation end products at 19 to 24 weeks of gestation among the 3 groups. The advanced glycation end product–to–placental growth factor ratio in the first trimester of pregnancy was significantly higher in patients with early-onset preeclampsia than in those with late-onset preeclampsia or control subjects (0.78 vs 0.10 vs 0.10; $P<.05$). The area under the receiver operating characteristic curve values for patients with early-onset preeclampsia were 0.782 (95% confidence interval, 0.522–0.922), 0.855 (95% confidence interval, 0.433–0.978), and 0.925 (95% confidence interval, 0.724–0.983) for the advanced glycation end product and placental growth factor levels and advanced glycation end product–to–placental growth factor ratios, respectively. This population achieved a 100% detection rate for predicting early-onset preeclampsia at a screen-positive rate of 10% by combining the advanced glycation end product–to–placental growth factor ratio and the mean arterial pressure.

CONCLUSION: The study results suggested that an elevated advanced glycation end product–to–placental growth factor ratio and mean arterial pressure at 11 to 13 weeks of gestation could be a potential biomarker for predicting the future development of early-onset preeclampsia.

Key words: advanced glycation end product, biomarker, early-onset preeclampsia, first-trimester screening, mean arterial pressure, placental growth factor, uterine artery pulsatility index

Introduction

Preeclampsia (PE) is a devastating complication that affects 3% to 10% of pregnant women worldwide and is associated with an increased risk of maternal and fetal or neonatal morbidity and mortality.[1] In recent years, prophylactic use of low-dose aspirin before 16 weeks of gestation has been demonstrated to reduce the risk of PE by half compared with its use after 16 weeks.[1] It is of clinical value to identify women

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Why was this study conducted?

This study aimed to determine the predictive performance of a model that included serum levels of advanced glycation end products (AGEs) at 11 to 13 weeks of gestation for early-onset preeclampsia (EOPE).

Key findings

The advanced glycation end product (AGE)-to-placental growth factor (PlGF) ratio in the first trimester of pregnancy was significantly higher in women who subsequently developed EOPE. The area under the receiver operating characteristic curve for predicting EOPE, calculated using a combination of the AGE-to-PlGF ratio and mean arterial pressure, was higher than those of other models.

What does this add to what is known?

A new risk factor-based model, including serum levels of AGEs at 11 to 13 weeks of gestation, may improve the predictive performance for EOPE.

at high risk of developing PE at the early stage of pregnancy because they could receive the most clinical benefit from aspirin prophylaxis.[2] In other words, early intervention with aspirin may improve the maternal and neonatal outcomes in such high-risk patients.[3] Early-onset PE (EOPE) and late-onset PE (LOPE) are characterized by shared clinical features; however, they are different entities in terms of etiology, pathogenesis, and clinical prognosis.[4,5] Compared with LOPE, EOPE is characterized by poor trophoblast development early in pregnancy, which leads to impaired placentation with a more adverse maternal or neonatal prognosis.[4,5] Therefore, it is desirable to develop a clinical tool for identifying pregnant women at high risk of EOPE at an early stage of pregnancy, which would enable physicians to provide early intervention with aspirin.

The Fetal Medicine Foundation (FMF) has proposed a competing risk model composed of the mean arterial pressure (MAP), mean uterine artery pulsatility index (UtA-PI), and placental growth factor (PlGF) levels at 11 to 13 weeks of gestation.[6] In a Japanese population, this combined prediction model was shown to predict preterm PE with up to 91% accuracy at a false-positive rate (FPR) of 10%.[7] However, it was also demonstrated that including the UtA-PI value does not markedly improve the performance of the algorithm.[7] Moreover, measuring the UtA-PI is a time-consuming procedure, which requires appropriate training of sonographers and adherence to standard operating procedures.[8] In addition, the clinical utility of this model for predicting EOPE remains largely unknown.

Reducing sugars, such as glucose, can react nonenzymatically with free amino groups in proteins, lipids, and nucleic acids, to form advanced glycation end products (AGEs).[9,10] AGE formation and accumulation have been known to progress under conditions of diabetes mellitus and oxidative stress, thereby making AGE levels suitable biomarkers for diabetes mellitus- and age-related disorders, including atherosclerotic cardiovascular and Alzheimer diseases and cancer.[9–13] Furthermore, placental expression of AGEs has been found to be increased in patients with PE than in the control subjects, thus being involved in trophoblast apoptosis after oxidative stress.[14] These observations led us to hypothesize that serum AGE levels during early-stage pregnancy may serve as a predictive biomarker of EOPE. In this study, we tested this hypothesis.

Materials and Methods

Study population

This nested case-control study was conducted at the Showa University Hospital in Tokyo, Japan. The eligibility criteria for this study were maternal age ≥18 years, no serious mental illness and learning disabilities, and singleton pregnancy with a live fetus with no major abnormality identified at 11 to 13 weeks of gestation. Based on these criteria, we invited 1035 women who provided their informed consent. Subsequently, we excluded 122 cases (12%) because there were missing ultrasound measurement data (n=17), biomarker data (n=39), and outcome data (n= 4). In addition, cases in which the pregnancies resulted in miscarriage before 22 weeks of gestation (n=2) and women that underwent pregnancy termination (n=20) were excluded. All 913 enrolled women were followed up and delivered at our hospital between June 2017 and December 2019. The study was approved by the ethics committee of the Showa University Hospital (reference number 2270). The confidentiality of the patients involved was protected, and no personal data were required for this study. All eligible women were provided with written information about the study, and those who agreed to participate provided written informed consent. Therefore, 6 women with EOPE and 21 women with LOPE were included among the 913 women. Moreover, 50 women with matched maternal age and body mass index (BMI) with no pregnancy complication were selected as normal controls. Clinical measurements and biomarkers were determined among 3 groups divided into the EOPE, LOPE, and normal groups. The EOPE group was defined by a diagnosis of PE before 32 weeks of gestation, and the LOPE group was defined by a diagnosis at or after 32 weeks of gestation. The gestational age (GA) was confirmed by ultrasound measurement of the crown-rump length during aneuploidy screening between 11 and 13 weeks of gestation. PE was defined as gestational hypertension accompanied by proteinuria or other maternal organ dysfunctions at or after 20 weeks of gestation, with all symptoms normalized to those at 12 weeks after delivery, according to the Japan Society for the Study of Hypertension in Pregnancy.[15,16] Proteinuria was not considered mandatory for PE diagnosis. However, PE was diagnosed by the presence of de novo hypertension after 20 weeks of

gestation, accompanied by proteinuria and/or evidence of maternal acute kidney injury, liver dysfunction, neurologic features, hemolysis or thrombocytopenia, or fetal growth restriction. A systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg on at least 2 occasions, 4 hours apart, was defined as hypertension. Proteinuria was defined as a protein excretion of ≥300 mg/d in a 24-hour urine collection. Superimposed PE was defined as chronic hypertension diagnosed before 20 weeks of gestation, with proteinuria emerging afterward. Superimposed PE was included as PE in this study. Researchers in this study confirmed the clinical diagnoses made by clinicians to enhance the diagnostic accuracy.

Clinical measurements

The MAP was measured using a validated automated device (Omron HCR-7101 sphygmomanometer; Omron Healthcare Co Ltd, Kyoto, Japan), according to a standardized protocol used by nurses who had received appropriate training on the use of the device.[17] The left and right UtA-PI values were measured via transabdominal color Doppler ultrasonography, and the average values were recorded. The transabdominal approach used for assessing UtA-PI followed a standardized protocol.[8,18]

Sample collection

Blood samples were taken from the peripheral vein of the arm. Blood samples from all women were collected at 11 to 13 and 19 to 24 weeks of gestation. None of the women developed PE at the time of blood sampling. After collection, the samples were centrifuged at 3000 rpm for 10 minutes at 4°C. The obtained serum and plasma samples were stored at −40°C until analysis.

Biochemical analyses

The concentrations of PlGF and soluble fms-like tyrosine kinase-1 (sFlt-1) were measured using an automated analyzer, the DELFIA Xpress system (PlGF 1-2-3 kits; DELFIA Xpress Random Access Platform; Perkin Elmer, Inc, Waltham, MA), following the manufacturer's instructions. The serum concentrations of AGEs were determined using an enzyme-linked immunosorbent assay, as described previously.[19] The test kits conformed to internationally accepted laboratory accreditation standards.

Statistical analysis

The data were entered into a computerized data analysis program (Statistical Package for Social Science for Windows, version 20.0J; SPSS Inc, Chicago, IL). Continuous variables were presented as the median (range). The Mann-Whitney *U* test was used to compare continuous variables, including maternal weight, MAP, UtA-PI, and concentrations of AGEs, PlGF, and sFlt-1 between the EOPE, LOPE, and normal groups. Categorical variables were reported as counts and percentages and compared using the Fisher exact test or chi-squared test. Multiple comparisons among the EOPE, LOPE, and normal groups were performed using the Mann-Whitney *U* test and chi-squared test with the Bonferroni correction. Discrimination was assessed using the area under the receiver operating characteristic (AUROC) curve. Statistical significance was defined as a *P* value of <.05.

Results

Maternal characteristics and perinatal outcomes are presented in Table 1. We examined 77 women in this study, and their clinical measurements and biomarkers were determined at 11 to 13 and 19 to 24 weeks of gestation. Moreover, 6 women (8%) with EOPE, 21 women (27%) with LOPE, and 50 normal pregnant women (65%) as controls participated in this study. No significant difference was found in age, BMI, and frequency of primipara among the groups, whereas perinatal outcomes (including GA at delivery, birthweight, small for gestational age (SGA), and placental weight) were significantly lower in the EOPE group than in the LOPE and normal groups.

The clinical measurements of the 3 groups, taken at 11 to 13 and 19 to 24 weeks of gestation, are presented in Table 2. MAP in the first and second trimesters of pregnancy were significantly higher in the LOPE group than in the EOPE and normal groups. UtA-PI in the first and second trimesters of

TABLE 1
Participant characteristics

Variable	EOPE (n=6)	LOPE (n=21)	Normal (n=50)	*P* value
Maternal age (y)	40 (30−47)	35 (27−41)	36 (26−44)	.14
Maternal weight (kg)	56 (50−70)	53 (40−75)	54 (39−70)	.71
Maternal height (cm)	159 (155−167)	160 (147−170)	159 (148−180)	.95
BMI (kg/m^2)	22.2 (19.8−25.1)	20.8 (17.3−30.8)	21.2 (16.4−30.4)	.59
Primipara	67 (4)	76 (16)	48 (24)	.08
In vitro fertilization	17 (1)	48 (10)	14 (7)	.01
Smoking	17 (1)	0 (0)	6 (3)	.25
GA at delivery (d)	225 (196−222)	264 (232−281)	276 (263−292)	<.01[a,b]
Birthweight (g)	1351 (605−1691)	2637 (1771−3343)	2941 (2341−3959)	<.01[a,b]
SGA	67 (4)	1 (2)	4 (2)	<.01
Placental weight (g)	352 (166−486)	550 (350−723)	520 (430−850)	<.01[a]

Data are presented as median (interquartile range) or percentage (number), unless otherwise indicated.

BMI, body mass index; *EOPE*, early-onset preeclampsia; *GA*, gestational age; *SGA*, small for gestational age.

[a] Intergroup significance (EOPE vs normal), Bonferroni-corrected Wilcoxon test (*P*<.05); [b] Intergroup significance (LOPE vs normal), Bonferroni-corrected Wilcoxon test (*P*<.05).

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TABLE 2
Comparison of maternal measurements in each group

Variable	EOPE (n=6)	LOPE (n=21)	Normal (n=50)	*P* value
Maternal weight (g)				
11–13 wk	55.6 (46.5–68.0)	53.2 (42.0–82.9)	53.9 (38.5–70.3)	.76
19–24 wk	57.2 (48.2–68.3)	55.8 (43.5–83.8)	56.4 (42.2–72)	.96
MAP (mm Hg)				
11–13 wk	88.7 (78.1–124.9)	94.1 (79.2–115.1)	79.1 (66.2–91.7)	<.01[a]
19–24 wk	80.6 (58.5–119.3)	86.0 (67.2–135.6)	76.5 (64.2–94.1)	<.01[a]
Mean UtA-PI				
11–13 wk	2.31 (1.05–3.16)	1.32 (0.55–3.00)	1.67 (0.71–3.14)	.03
19–24 wk	2.10 (0.89–2.56)	1.04 (0.42–2.22)	1.13 (0.60–2.37)	.02

Data are presented as median (interquartile range), unless otherwise indicated.

EOPE, early-onset preeclampsia; *LOPE*, late-onset preeclampsia; *MAP*, mean arterial pressure; *PlGF*, placental growth factor; *UtA-PI*, uterine artery pulsatility index.

[a] Intergroup significance (LOPE vs normal), Bonferroni-corrected Wilcoxon test ($P<.05$).

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pregnancy were significantly higher in the EOPE group than in the LOPE and normal groups.

The maternal biochemical measurements of the 3 groups, taken at 11 to 13 and 19 to 24 weeks of gestation, are presented in Table 3. The median serum concentrations of AGEs in the first trimester of pregnancy were significantly higher in the EOPE group than in the LOPE and normal groups (Figure 1, A). The median serum concentration of AGEs in the second trimester of pregnancy did not differ among the 3 groups. The median serum concentrations of PlGF in the first and second trimesters of pregnancy were significantly lower in the EOPE group than in the LOPE and normal groups, whereas the sFlt-1 levels were not significantly different among the 3 groups in both the first and second trimesters of pregnancy. The AGEs-to-PlGF ratio in the first trimester of pregnancy was significantly higher in women in the EOPE group than women in the LOPE and normal groups (Figure 1, B).

The results of the receiver operating characteristic analysis for predicting EOPE in the first trimester of pregnancy using several biomarkers are shown in Figure 2. The AUROC curve values for EOPE were 0.782 (95% confidence interval [CI], 0.522–0.922), 0.855 (95% CI, 0.433–0.978), and 0.925 (95% CI, 0.724–0.983) for the AGEs, PlGF, and AGEs-to-PlGF ratio, respectively. The AUROC curve for the EOPE group determined using the AGEs-to-PlGF ratio was the highest among the 3 variables. The AUROC curve for the AGEs-to-PlGF ratio was significantly higher than that of AGEs (0.925 vs 0.782; $P=.03$), although the AUROC curve for the AGEs-to-PlGF ratio did not reach statistical significance compared with that for PlGF. The AGEs-to-PlGF ratio could predict EOPE with a detection rate as high as 83% and an FPR of 10% (Table 4).

TABLE 3
Comparison of maternal biochemical measurements in each group

Variable	EOPE (n=6)	LOPE (n=21)	Normal (n=50)	*P* value
AGEs (μg/mL)				
11–13 wk	6.62 (2.80–12.75)	4.10 (0.30–11.99)	3.77 (0.87–23.12)	.03[a]
19–24 wk	4.60 (2.36–13.78)	2.80 (0.28–12.53)	3.02 (0.72–25.66)	.13
PlGF (pg/mL)				
11–13 wk	11.49 (1.11–45.76)	35.63 (9.66–134.79)	34.73 (17.32–111.14)	.02[a]
19–24 wk	70.70 (10.86–242.23)	201.51 (57.57–499.73)	222.56 (47.77–772.24)	.05[a]
sFlt-1 (pg/mL)				
11–13 wk	533.99 (359.78–1000.99)	580.82 (18.27–1134.03)	621.25 (246.87–2577.92)	.38
19–24 wk	741.11 (543.77–1887.17)	635.03 (14.84–1508.14)	656.07 (211.63–2599.31)	.22
AGEs-to-PlGF ratio ($\times 10^6$)				
11–13 wk	0.78 (0.15–4.86)	0.10 (0.01–0.34)	0.10 (0.01–0.75)	<.01[a]

Data are presented as median (interquartile range), unless otherwise indicated.

EOPE, early-onset preeclampsia; *LOPE*, late-onset preeclampsia; *MAP*, mean arterial pressure; *PlGF*, placental growth factor; *sFlt-1*, soluble fms-like tyrosine kinase-1.

[a] Intergroup significance (EOPE vs normal), Bonferroni-corrected Wilcoxon test ($P<.05$)

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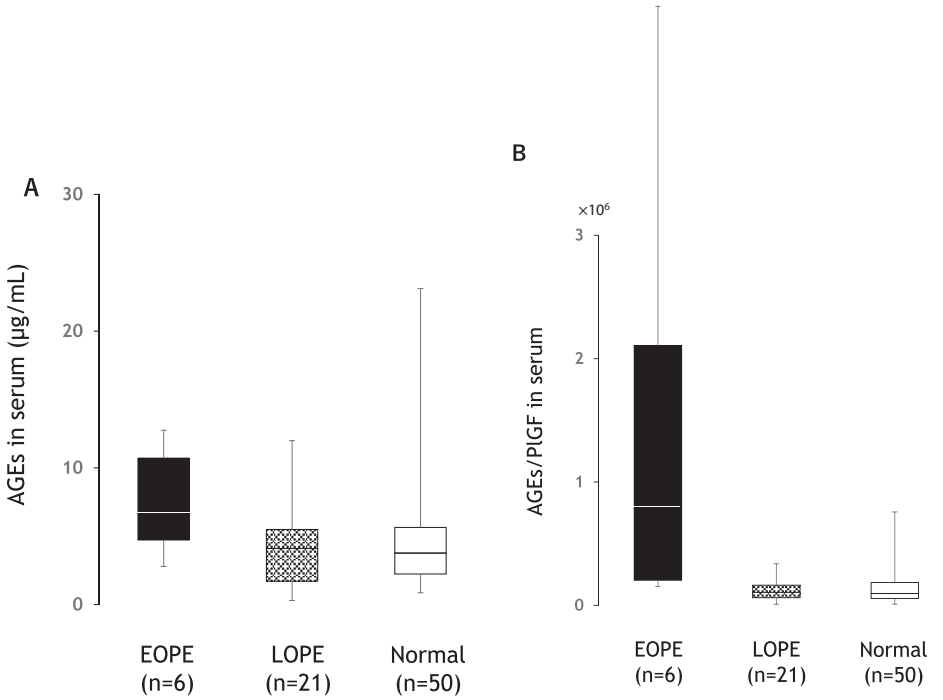
FIGURE 1
Box plots of AGEs concentrations and AGEs-to-PlGF ratio



A, Median value of AGEs. **B,** Median value AGEs-to-PlGF ratio. The *closed box* indicates the EOPE group. The *hatched box* indicates the LOPE group. The *clear box* indicates the normal group.

AGEs, advanced glycation end products; *EOPE*, early-onset preeclampsia; *LOPE*, late-onset preeclampsia; *PlGF*, placental growth factor.

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The AUROC curve for EOPE determined on the basis of a combination of the AGEs-to-PlGF ratio and MAP was the highest compared with the other models, although the AUROC curve for the AGEs-to-PlGF ratio and MAP did not reach statistical significance compared with that determined on the basis of the AGEs-to-PlGF ratio alone. The risk of EOPE using the AGEs-to-PlGF ratio had a detection rate of 83% (95% CI, 43.7−97.0) with a fixed FPR of 10%. The risk of EOPE using the combination of the AGEs-to-PlGF ratio and MAP had a detection rate of 100% (95% CI, 61.0−100.0) with a fixed FPR of 10% (Table 4).

Comment

Principal findings

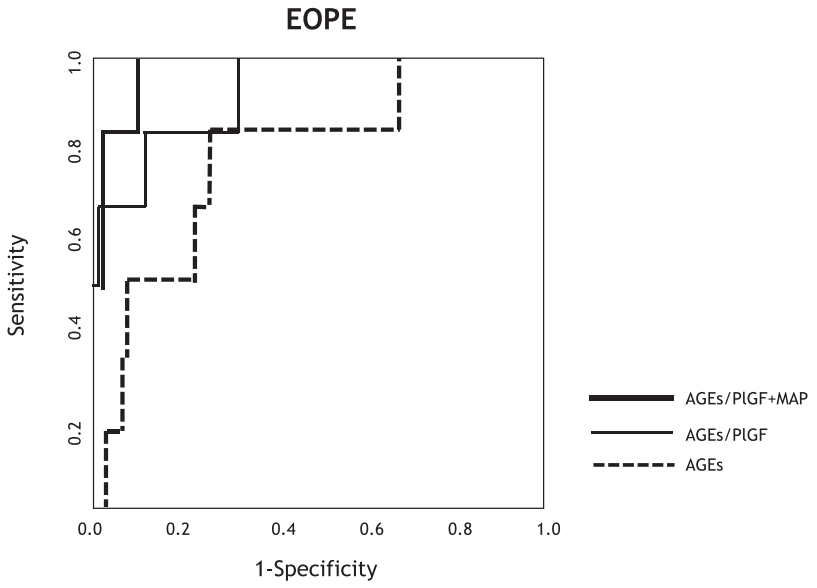
We demonstrated that maternal serum AGEs levels in the first trimester of pregnancy were significantly higher in women in the EOPE group than in women in the LOPE and normal groups. In particular, the AGEs-to-PlGF ratio in the first trimester of pregnancy was significantly higher in women who subsequently developed EOPE. Furthermore, the AUROC curve for predicting EOPE calculated using a combination of the AGEs-to-PlGF ratio and MAP was higher than those of the other models. Our findings suggested that combining the AGEs-to-PlGF ratio and MAP at 11 to 13 weeks of gestation could serve as a novel and sensitive biomarker for predicting EOPE in Japanese women.

Results

EOPE is associated with increased risks of maternal and fetal complications, including prematurity and impaired fetal growth with a globally worse perinatal outcome.[20] Therefore, it is essential to identify women at high risk of EOPE to provide early intervention for these patients. Although the etiologies of EOPE are not fully understood, recent experimental and clinical findings have suggested the involvement of impaired angiogenesis in the placenta of women with EOPE, which could cause uteroplacental hypoxia resulting in oxidative stress, thereby leading to trophoblast apoptosis.[21,22] In our study, we found that birthweight, SGA, and placental weight were more associated with EOPE, whereas MAP was associated with LOPE, thus supporting the concept that placental dysfunction and hypoperfusion may play a role in EOPE. In the case of LOPE, high blood pressure −associated maternal endothelial dysfunction may be involved in this type of PE. UtA-PI in the first (11−13 weeks of gestation) and second (19−24 weeks of gestation) trimesters of pregnancy were significantly higher in the EOPE group than that in the LOPE and normal groups.

PlGF is a placenta-derived angiogenic factor that promotes nonbranching angiogenesis and the formation of a

FIGURE 2
ROC curves for the prediction of EOPE



AGEs, advanced glycation end products; *EOPE*, early-onset preeclampsia; *MAP*, mean arterial pressure; *PlGF*, placental growth factor; *ROC*, Receiver operating characteristics.

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low-resistance vascular network in the placenta.[23] PlGF levels in the maternal circulation have been known to increase during gestation, with concentrations peaking at 26 to 30 weeks of gestation and declining toward term during normal pregnancy.[23] Given that, relative to GA-matched controls, PlGF levels are abnormally low in women with PE even before PE onset,[24] reduced PlGF production and impaired angiogenesis in the placenta may play pathogenic roles in PE. However, there are some controversies regarding the clinical utility of measuring maternal PlGF levels for predicting EOPE.[24,25] Data from several studies exploring PlGF as a predictor of PE showed a wide variation in its diagnostic accuracy, and the predictive odds ratio of PE did not necessarily increase when PlGF measurements were performed before 14 weeks of gestation.[26]

In our study, we showed that serum levels of AGEs at 11 to 13 weeks of gestation were increased in patients with EOPE. The AUROC curve for EOPE calculated from the AGEs-to-PlGF ratio at 11 to 13 weeks of gestation was higher than that for AGEs or PlGF alone. Moreover, we found that the AGEs-to-PlGF ratio in the first trimester of pregnancy was significantly higher in women in the EOPE group than in women in the LOPE and normal groups. Although previous studies have reported that maternal serum AGEs levels are increased in patients with PE,[4,27] the clinical significance of measurements of AGEs before PE onset remains unknown. Our study suggested that a risk factor−based model, including the AGEs levels, could improve the predictive performance for EOPE.

The study results showed that the AUROC curve for EOPE calculated from the AGEs-to-PlGF ratio at 11 to 13 weeks of gestation was higher than that for AGEs or PlGF alone. Moreover, we found that the additional information from MAP significantly improved the predictive performance. O'Gorman et al[6] developed an effective first-trimester screening model for PE using values for the maternal factors UtA-PI, MAP, pregnancy-associated plasma protein-A, and PlGF. Their algorithms detected 89% of EOPE cases with an FPR of 10%. In contrast, our model using the combination of the AGEs-to-PlGF ratio and MAP had a predictive performance for EOPE with a detection rate of 100% at a fixed FPR of 10%. However, it should be noted that our prediction models were not necessarily superior to the FMF model because the higher accuracy of the prediction probability may be attributed to the characteristics of the observed population because of the relatively small number of cases. Although current studies have demonstrated that the best model for PE screening is a combination of a multiplicity of maternal characteristics, such as MAP, UtA-PI, and PlGF, our study demonstrated that the combination of AGEs, PlGF, and MAP is sufficient for predicting EOPE. Previous studies have demonstrated that UtA-PI has a limited effect on predicting EOPE in a Japanese population compared with other parameters.[7] In other words, compared with UtA-PI, AGEs measurements may easily preserve interrater reliability.

Clinical implications

The competing FMF risk model, which is composed of MAP, UtA-PI, and PlGF, is a useful tool for predicting PE.[6] However, its clinical utility for predicting EOPE remains to be elucidated. In this study, we found that the combination of the AGEs-to-PlGF ratio and MAP could predict EOPE at a rate as high as 100% with an FPR of 10%. Therefore, the combination of an elevated AGEs-to-PlGF ratio and MAP at 11 to 13 weeks of gestation may be a useful predictive biomarker for the future development of EOPE. These findings could enable us to identify high-risk patients who would benefit considerably from early aspirin intervention.

Research implications

The expression levels of AGEs and the receptor of AGEs (RAGEs) have been shown to increase in the placentas of patients with PE than in control subjects.[28] Accumulating evidence suggested that the interaction of AGEs with RAGEs evokes oxidative stress and

TABLE 4
Area under the receiver operating characteristic curves for predicting early-onset preeclampsia on the basis of AGE, PlGF, MAP, and AGE-to-PlGF ratio at 11 to 13 weeks of gestation

Variable	FPR of 10%(%)	AUROC curve (95% CI)	*P* value[a]	*P* value[b]
AGE	50	0.782 (0.522–0.922)	.08	—
PlGF	83	0.855 (0.433–0.978)	.27	.70
MAP	33	0.698 (0.415–0.883)	.04	.68
AGE + PlGF	83	0.883 (0.554–0.979)	.23	.50
PlGF + MAP	83	0.879 (0.498–0.981)	.28	.58
AGE + PlGF + MAP	83	0.921 (0.614–0.989)	.33	.33
AGEs-to-PlGF ratio	83	0.925 (0.724–0.983)	.36	.03
AGE-to-PlGF ratio + MAP	100	0.974 (0.867–0.995)	—	.08

AGE, advanced glycation end product; *AUROC*, area under the receiver operating characteristic; *CI*, confidence interval; *FPR*, false-positive rate; *PlGF*, placental growth factor; *MAP*, mean arterial pressure.

[a] "*P* value" refers to the comparison of the AUROC curves of AGE-to-PlGF ratio + MAP with other parameters; [b] "*P* value" refers to the comparison of the AUROC curves of AGEs with other parameters.

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inflammatory reactions in several tissues and organs, including the placenta, which could contribute to trophoblast apotosis.[9,10,29–31] Furthermore, oxidative stress and hypoxia have been reported to further promote the formation of AGEs and sustained activation of RAGEs in endothelial cells.[32–34] These findings suggested that the combination of impaired placental angiogenesis because of insufficient PlGF production, along with activation of the AGEs-RAGE axis in the placenta, may play a crucial role in the pathogenesis of EOPE, in part, via oxidative stress, inflammation, and trophoblast apoptosis.

Strengths and limitations

The study strength was to evaluate the predictive performance of a risk factor–based model, which included measuring the serum levels of AGEs before the onset of PE for EOPE. Our study suggested that the AGEs-to-PlGF ratio and MAP at 11 to 13 weeks of gestation may be a marker for predicting EOPE and could help identify women at high risk of EOPE who would benefit from early intervention. Furthermore, in this study, we measured glyceraldehyde-derived AGEs because this type of AGEs correlates with oxidative stress and inflammatory reactions in patients with metabolic syndrome, diabetes mellitus, nonalcoholic steatohepatitis, and coronary risk factors.[12,32–35]

Our study has some limitations. First, the number of patients with EOPE was too low to draw adequate conclusions. In addition, the small sample size might result in potential confounding effects, and thus, accurate estimates of statistical difference might not be possible. Furthermore, the small sample size may affect the association between elevated AGEs and EOPE development. Moreover, it might be affected by factors, such as racial differences and genetic factors. Thus, studies with larger sample sizes are required to overcome these limitations. Second, MAP was higher in the LOPE group than in the EOPE and normal groups (Table 2). Therefore, MAP may be a more sensitive marker for LOPE. Further longitudinal studies with a large number of pregnant women are needed to clarify whether the AGEs-to-PlGF ratio and MAP at 11 to 13 weeks of gestation is an informative biomarker for predicting EOPE and a therapeutic target for this devastating disorder.

Conclusion

The study results suggested that an elevated AGE-to-PlGF ratio and MAP at 11 to 13 weeks of gestation could be a potential biomarker for predicting the future development of EOPE. ■

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