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. 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. It is of clinical value to identify women...
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 (PIGF) 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-PIGF 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. In other words, early intervention with aspirin may improve the maternal and neonatal outcomes in such high-risk patients.

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. 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 outcome.

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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. 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.17 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 <0.05.

Results
Maternal characteristics and perinatal outcomes are presented in Table 1.

| 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/m²)                      | 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     |
| Smokinae                          | 17 (1)     | 48 (10)     | 14 (7)       | .01     |
| GA at delivery (d)               | 225 (196–222) | 264 (232–281) | 276 (263–292) | <.01   |
| Birthweight (g)                  | 1351 (605–1691) | 2537 (1771–3343) | 2941 (2341–3959) | <.01   |
| SGA                               | 67 (4)     | 1 (2)       | 4 (2)        | <.01   |
| Placental weight (g)             | 352 (166–486) | 550 (350–723) | 520 (430–850) | <.01   |

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.

5 Intergroup significance (EOPE vs normal); Bonferroni-corrected Wilcoxon test (P<.05). 6 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 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-PIGF ratio, respectively. The AUROC curve for the EOPE group determined using the AGESs-to-PIGF ratio was the highest among the 3 variables. The AUROC curve for the AGESs-to-PIGF ratio was significantly higher than that of AGEs (0.925 vs 0.782; P=.03), although the AUROC curve for the AGESs-to-PIGF ratio did not reach statistical significance compared with that for PlGF. The AGESs-to-PIGF ratio could predict EOPE with a detection rate as high as 83% and an FPR of 10% (Table 4).

### 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<sup>a</sup> |
| 19–24 wk     | 80.6 (58.5–119.3) | 86.0 (67.2–135.6) | 76.5 (64.2–94.1) | <.01<sup>a</sup> |
| 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.

<sup>a</sup> Intergroup signiﬁcance (EOPE vs normal), Bonferroni-corrected Wilcoxon test (P<.05).

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### 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<sup>a</sup> |
| 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 (17.12–111.14) | .02<sup>a</sup> |
| 19–24 wk     | 70.70 (10.86–242.23) | 201.51 (57.57–499.73) | 222.56 (47.77–772.24) | .05<sup>a</sup> |
| 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-PIGF ratio (×10<sup>6</sup>) |            |             |               |         |
| 11–13 wk     | 0.78 (0.15–4.86) | 0.10 (0.01–0.34) | 0.10 (0.01–0.75) | <.01<sup>a</sup> |

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.

<sup>a</sup> Intergroup significance (EOPE vs normal), Bonferroni-corrected Wilcoxon test (P<.05).

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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. 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. 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
low-resistance vascular network in the placenta. 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. Given that, relative to GA-matched controls, PlGF levels are abnormally low in women with PE even before PE onset, 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. 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.

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-PIGF ratio at 11 to 13 weeks of gestation was higher than that for AGES or PIGF alone. Moreover, we found that the AGES-to-PIGF 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, 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-PIGF ratio at 11 to 13 weeks of gestation was higher than that for AGES or PIGF alone. Moreover, we found that the AGES-to-PIGF 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, 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 competing FMF risk model, which is composed of MAP, UtA-PI, and PIGF, is a useful tool for predicting PE. However, its clinical utility for predicting EOPE remains to be elucidated. In this study, we found that the combination of the AGES-to-PIGF 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-PIGF 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.

Clinical 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. Accumulating evidence suggested that the interaction of AGES with RAGEs evokes oxidative stress and through various biological pathways.

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. Accumulating evidence suggested that the interaction of AGES with RAGEs evokes oxidative stress and through various biological pathways.
inflammatory reactions in several tissues and organs, including the placenta, which could contribute to trophoblast apoptosis.\textsuperscript{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.\textsuperscript{32–34} These findings suggested that the combination of impaired placental angiogenesis because of insufficient PIGF 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-PIGF 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.\textsuperscript{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-PIGF 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.

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