Observational Study

Medicine

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Diagnostic efficacy of aneuploidy markers correlated with early onset preeclampsia

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Abstract

Low-dose aspirin administration before 16 weeks of gestation can prevent preeclampsia (PE) more effectively. In order to determine if aspirin should be administered, this study aimed to investigate the predictive value of pregnancy-associated plasma protein A (PAPP-A) and aneuploidy markers for the onset period of PE. 1053 singleton pregnant women were included in the study, and serum PAPPA-A and aneuploidy markers were analyzed between 3 group (normotensive, late-onset PE, and early-onset PE). The utility of these markers for predicting early-onset preeclampsia (EOPE) was compared using each marker and their combination. Alpha-fetoprotein (AFP)/PAPP-A > 6.89 and human chorionic gonadotropin (hCG)/PAPP-A > 7.94 were associated with EOPE with a positive likelihood ratio (LR) (6.52, 95% confidence interval [CI] 4.9–7.1), and (5.77, 95% CI 3.9–6.4). The combination of markers could predict EOPE more accurately compared to the single markers. AFP/PAPP-A > 6.89 and hCG/PAPP-A > 7.94had a predictive ability for EOPE, and these cutoff values can help determine the use of aspirin at an earlier gestational age (GA).

Abbreviations: AFP = alpha-fetoprotein, AUC = area under curve, GA = gestational age, hCG = human chorionic gonadotropin, LOPE = late-onset preeclampsia, LR = likelihood ratio, PAPP-A = pregnancy-associated plasma protein-A, PE = preeclampsia, QUAD = quadruple screen test, uE3 = unconjugated estriol.

Keywords: alpha-fetoprotein, aspirin, human chorionic gonadotropin, preeclampsia, pregnancy-associated plasma protein A

1. Introduction

Hypertensive disorders of pregnancy (HDP) are among the leading causes of maternal and neonatal morbidity and mortality worldwide. The incidence of HDP increased by approximately 10.92% from 1990 to 2019.[1] Preeclampsia (PE) is the most severe disease among the HDPs, and a multi-organ progressive disorder which clinically manifests in the form of new onset of hypertension and proteinuria or end-organ dysfunction with or without proteinuria. It is a major pregnancy complication in Korea, with an annual incidence increase of 11%.[2] PE can be divided into early and late stages according to the onset period based on the 34th week of gestation.[3] Although their clinical features are somewhat similar, maternal and perinatal outcomes are more severe in early onset preeclampsia (EOPE).[4,5] These differences are due to the fact that the 2 subtypes have different etiologies and maternal hemodynamics.[6] EOPE is associated with abnormal placental invasion, failure of the spiral artery remodeling, and highly altered levels of immunological factors, while late-onset preeclampsia (LOPE) is mediated by the underlying maternal constitutional disorder or oxidatively stress in syncytiotrophoblasts.[7,8]

Although the mechanism of PE pathogenesis has not been fully elucidated, several investigators have attempted early prediction and diagnosis of PE. Vascular endothelial growth factor antagonist and the placental growth factor ratio is known as a promising method for to prediction of PE. However, it is limited in their ability for detection since the development of PE can only be predicted approximately 1 to 4 weeks in advance.[9] Abnormal placentation and hypoxia cause placental hypoperfusion, which can lead to changes in uterine artery Doppler index. Thus, PE could be predicted by an increased pulsatility index with notching in the second trimester with 19% sensitivity and 99% specificity.[10] However, this method is limited by an accuracy of less than 50% as a single predictive test.[11]

PAPP-A is a syncytiotrophoblast-derived protease for insulin-like growth factor binding protein-4, a regulator of glucose and amino acid uptake, and a mediator of trophoblast invasion into the decidua.[12] Therefore, it is consistent to speculate that low PAPPA is associated with placental dysfunction disorder, besides, several studies investigating the association between abnormal values of aneuploidy markers and the risk of PE have been conducted.[13,14] The US Preventive Services Task Force recommends the use of low-dose aspirin for prevention of PE after 12 weeks of gestation in individuals at high risk for PE.[15] The optimal timing of aspirin administration to prevent PE is before 16 weeks of gestation.[16]

Therefore, the purpose of this study was to investigate the usefulness of aneuploidy markers for predicting PE before 16 weeks of pregnancy and determine a relationship between aneuploidy and EOPE.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Pyeon SY, Kwon BS, Kim YS, Lee YJ. Diagnostic efficacy of aneuploidy markers correlated with early onset preeclampsia. Medicine 2022;101:50(e32319).

Received: 3 August 2022 / Received in final form: 29 November 2022 / Accepted: 29 November 2022

http://dx.doi.org/10.1097/MD.0000000000032319

2. Materials and Methods

Between 2014 and 2021, a total of 1567 singleton pregnant women who underwent aneuploidy testing were retrospectively analyzed at the obstetrics clinic of KyungHee University Medical Center. A total of 514 pregnant women were excluded due to underlying disease (diabetes, thyroid dysfunction, thrombophilia, autoimmune disease), prior placental dysfunction disorder (PE, intrauterine growth restriction, oligohydramnios), morbid obesity, dissenting patients, and other reasons. The flow diagram of the study is presented in Figure 1. PE was diagnosed based on new onset hypertension (systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg) with proteinuria (at least 300 mg per 24-hour urine collection, protein-to-creatinine ratio of at least 0.3 mg/dL, or urine dipstick test result of 2+) or end-organ dysfunction with or without proteinuria after 20 weeks of pregnancy.[17] EOPE and LOPE were defined as patients diagnosed before 34 + 0 weeks and ≥ 34 + 0 weeks, respectively.[6] Serum PAPP-A was measured at 10 to 13 + 6 weeks of gestation, and QUAD markers, alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), inhibin-A, and unconjugated estriol (uE3) were analyzed between 14 and 16 weeks of gestation by chemiluminescent immunoassays using UniCel DxI 800 (Beckman Coulter Inc., Fullerton, CA). The blood samples were allowed to clot between 15°C and 22°C for 30 to 90 minutes, and then centrifuged for 15 minutes at 300 g. The serum was collected and stored at –20°C for up to 4 days and then stored at –70°C. Serum analytes were adjusted to the MoM for gestational age (GA), maternal age, and weight. The research project has been approved by a suitably constituted Ethics Committee of Kyung Hee university (No. 2022-08-004) within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2004).

The data were analyzed using the statistical software R version 4.0.0 and verified by a second independent person. The statistical analyses involved maternal characteristics, GA at the time of blood sampling and delivery, and median levels, which were presented as median and interquartile range. Statistical analysis between groups was performed with the Kruskal–Wallis test, and the Wilcoxon rank-sum test for multiple comparisons with Bonferroni correction as post hoc analysis. The aneuploidy values were assessed with a multivariable logistic regression analysis after adjustments for GA and body mass index. Cutoff values were estimated using a receiver operating characteristic curve and Youden index to investigate the correlation of each marker with the prevalence and onset period of PE. A log transformation was used for non-normal distribution. Statistical significance was set at P value < .05.

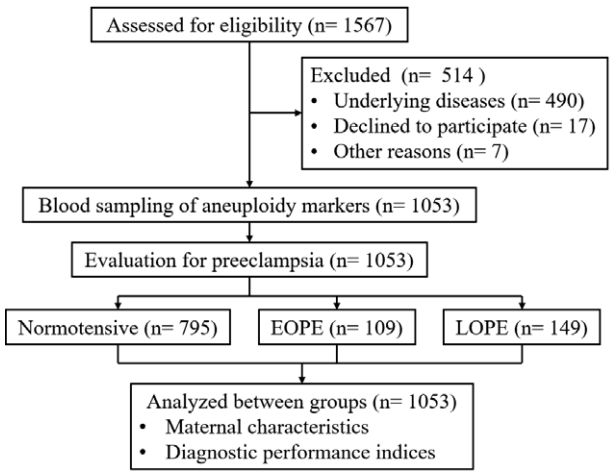

Figure 1. Flow diagram of patient's selection. EOPE = early-onset preeclampsia, LOPE = late-onset preeclmapsia.

3. Results

No statistical significance were observed in maternal age, gravidity, parity, and GA between the PAPP-A and QUAD markers among the normotensive, LOPE, and EOPE groups (Table 1). The GA at delivery in the EOPE group was significantly lesser than that in the LOPE and normotensive groups (P < .001) and it is strongly associated with severe adverse neonatal outcomes.[18] Body mass index during early pregnancy and at < 14 completed gestational weeks was significantly higher in the PE group than in the normotensive group, especially in the LOPE group (P < .01). This finding suggests that LOPE is related to maternal factors.

The estimated cutoff values of each aneuploidy marker, along with the area under the curve (AUC) based on the presence of EOPE, are shown in Table 2. Initially, we analyzed the relationship between the cutoff value of each parameter and the development of EOPE. The PAPP-A ≤ 0.56 had the highest AUC (0.725) and positive likelihood ratio (LR, 4.79[2.9–5.7]). However, these parameters showed a positive LR of less than 5 or a negative LR of 0.2 or more; hence, there was insufficient evidence to predict EOPE with these cutoff values. Tancrède et al demonstrated that elevated serum AFP or hCG was associated with placenta-mediated adverse pregnancy outcomes.[19] Therefore, we calculated the combined ratio of decreased PAPP-A and increased AFP or hCG levels to determine whether a more accurate prediction is possible. AFP/PAPP-A > 6.89, hCG/PAPP-A > 7.94, and LR + (6.52) had the highest AUC (0.783) and LR + (5.77), second highest AUC (0.766), respectively, than those of the single parameter. Based on each LR, it was seen that the increase in the probability of EOPE using the cutoff value increases by at least 38% for AFP/PAPP-A, 34.6% for hCG/PAPP-A, and 29.8% for PAPP-A.[20]

Table 1

Maternal characteristics between 3 groups.

	Normotensive	EOPE	LOPE	*P* value
Age	32.00 [30.00, 34.00]	34.00 [32.00, 37.00]	33.00 [31.00, 35.50]	.375
Gravidity	2.00 [1.00, 3.00]	1.00 [1.00, 2.00]	2.00 [1.00, 2.50]	.651
Parity	1.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	.558
GA at delivery, wks	38.13 [37.11, 39.33]	30.64 [29.15, 33.00]	35.11 [33.45, 37.22]	<.001
BMI, kg/m^2	26.11 [24.55, 29.34]	27.88 [24.82, 30.77]	28.47 [26.22, 31.25]	<.01
GA at PAPPA	12.14 [10.93, 13.77]	11.59 [10.66, 12.87]	11.69 [11.00, 12.35]	.774
GA at QUAD markers	15.25 [14.17, 16.55]	14.75 [14.01, 16.13]	14.91 [14.32, 15.99]	.689

Data are presented as median (25th–75th interquartile range).

BMI = body mass index, EOPE = early-onset preeclampsia, GA = gestational age, LOPE = late-onset preeclampsia, PAPP-A = pregnancy-associated plasma protein-A, QUAD = quadruple screen test.

Table 2

Diagnostic performance indices of aneuploidy markers for EOPE.

Criterion (MoM)	AUC	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
PAPP-A ≤ 0.56	0.725	60.08 [59.82– 82.54]	90.75 [79.53–94.79]	4.79 [2.9–5.7]	0.50 [0.6–0.8]
hCG > 2.99	0.711	59.31 [56.15–77.43]	82.56 [66.25–89.78]	2.88 [1.8–4.0]	0.58 [0.5–0.9]
Inhibin-A > 1.67	0.657	68.23 [53.64–77.18]	75.45 [68.55–87.64]	2.45 [1.9–3.0]	0.48 [0.4–0.7]
AFP > 2.57	0.708	55.21 [49.08–62.84]	85.77 [75.24–92.08]	2.84 [1.9–3.3]	0.77 [0.4–0.9]
uE3 ≤ 0.68	0.628	68.57 [53.22–78.14]	53.12 [43.99–60.17]	1.21 [1.1–1.6]	0.51 [0.4–0.8]
AFP/PAPP-A > 6.89	0.783	70.25 [58.12–75.24]	91.37 [77.42–95.19]	6.52 [4.9–7.1]	0.42 [0.3–0.6]
hCG/PAPP-A > 7.94	0.766	71.42 [59.32–79.13]	89.97 [74.04–93.87]	5.77 [3.9–6.4]	0.46 [0.3–0.6]

The correlation of each marker with EOPE was analyzed by Youden index.

AFP = alpha-fetoprotein, AUC = area under curve, hCG = human chorionic gonadotropin, LR = likelihood ratio, PAPP-A = pregnancy associated plasma protein-A, uE3 = unconjugated estriol.

4. Discussion and conclusions

Several studies have reported the efficacy of aspirin administration in high-risk pregnant women for prevention of placental dysfunction disorders.[16,21] However, the definition of a high-risk pregnant woman has not yet been established, with several complications being encountered while assessing the risk of a pregnant woman with no prior history of PE or fetal growth restriction and other associated medical conditions, such as diabetes, thyroid dysfunction, and connective tissue disorders. An accurate prediction of EOPE is crucial to improve maternal and fetal outcomes before 16 weeks of gestation considering the severity of PE-related complications.

This study suggests that PAPP-A could predict EOPE in the first trimester of pregnancy with more accuracy. It can help identify pregnant women with PAPP-A levels below the cut-off value for detection and analysis of risk factors at an earlier stage. Although not universally accepted, some professional experts have recommended that women with a low PAPP-A value detected during early pregnancy should be considered to be at increased risk for PE and thus, receive low-dose aspirin to reduce the risk of subsequent PE, preterm birth, or fetal growth restriction.[22,23] However, a single marker is not sufficient to determine aspirin administration. Therefore, we analyzed the markers together and confirmed that they could predict EOPE more accurately than single markers. Among the combined markers, AFP/PAPP-A showed highest AUC, specificity, positive LR, and negative LR, and these 2 values can be measured in early pregnancy to help determine the initiation of aspirin administration.

The strength of this study was that we analyzed pregnant women with no risk factors of EOPE, and these results may translate into useful screening tests for low-risk singleton pregnant women. In addition, by analyzing maternal serum marker in pregnant women up to 16 weeks, we could present a rationale for initiating aspirin at an earlier GA. Since the analysis is based on the integrated test most commonly performed in Korea, it is cost-effective, as no additional tests are required to predict EOPE.

The limitations of our study are as follows: AFP and hCG could be affected after assisted reproduction, and we did not exclude such pregnancies.[24] There was no significant difference in the GA between the 3 groups for any aneuploidy marker. However, after 15 weeks of pregnancy, maternal serum levels of AFP and uE3 increased while hCG levels decreased according to the GA, and these effects could not be rule out completely.[25]

In conclusion, low PAPP-A ≤ 0.56 is associated with a higher risk of EOPE, and the combination of AFP/PAPP-A > 6.89 and hCG/PAPP-A > 7.94, is more reliable in predicting EOPE compared to single markers.

Acknowledgments

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors. We would like to thank Editage (www.editage.co.kr) for the English language editing.

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