Pregnancy Hypertension 13 (2018) 148–153

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

Association of increased cord blood soluble endoglin with the development of bronchopulmonary dysplasia in preterm infants with maternal preeclampsia

Do-Hyun Kim[a], Seung Han Shin[b], Ee-Kyung Kim[b], Han-Suk Kim[b,*]

[a] Department of Pediatrics, Dongguk University Ilsan Hospital, Goyang, Republic of Korea
[b] Department of Pediatrics, Seoul National University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Bronchopulmonary dysplasia
Preeclampsia
sFlt-1
Soluble endoglin
PlGF

ABSTRACT

Objectives: To investigate whether the levels of angiogenic factors in cord blood are associated with the development of bronchopulmonary dysplasia (BPD) in preterm infants with maternal preeclampsia.
Study design: This retrospective cohort study included 199 singleton infants (gestational age < 32 weeks), including the preeclampsia group (59 infants) with severe/moderate BPD (24 infants) or no/mild BPD (35 infants) and the no preeclampsia group (140 infants).
Main outcomes measures: The levels of soluble fms-like tyrosine kinase-1 (sFlt-1), soluble endoglin, and placental growth factor (PlGF) in cord blood were measured and compared among the study groups.
Results: The soluble endoglin level and the ratio of (sFlt-1 + soluble endoglin) to PlGF were significantly higher in the preeclampsia group than in the no preeclampsia group ($P < .05$). Among preterm infants with maternal preeclampsia, both of these parameters were also significantly higher in the severe/moderate BPD group than the no/mild BPD group ($P < .05$). Receiver operator curve analysis revealed that increased cord blood soluble endoglin was predictive of severe or moderate BPD in preterm infants with maternal preeclampsia (area under the curve 0.73). Gestational age (adjusted odds ratio [OR] 0.25; $P < .001$) and high soluble endoglin level in cord blood (> 3420 pg/mL) (adjusted OR 11.9; $P = .006$) were significant risk factors for the development of severe or moderate BPD in the preeclampsia group according to multivariate logistic regression analysis.
Conclusion: Increased cord blood soluble endoglin is associated with the development of severe or moderate BPD in preterm infants with maternal preeclampsia.

1. Introduction

Preeclampsia is the most common medical complication of pregnancy worldwide, resulting in substantial perinatal and neonatal morbidity and mortality [1]. Alterations in angiogenic state appear to be involved in the pathogenesis of preeclampsia. Increased levels of anti-angiogenic factors, such as soluble vascular endothelial growth factor (VEGF) receptor-1 (soluble fms-like tyrosine kinase-1, also known as sFlt-1) and soluble endoglin, and decreased levels of proangiogenic factors, including free VEGF and placental growth factor (PlGF), play a central role in the pathogenesis of preeclampsia [2–5]. This anti-angiogenic state is shared by the fetus, resulting with increased cord blood sFlt-1 but decreased VEGF and PlGF levels in infants with maternal preeclampsia [6].

Bronchopulmonary dysplasia (BPD) is a chronic lung disease in preterm infants that is characterized by arrested lung development due to early lung injury [7]. Similar to the pathogenesis of preeclampsia, the development of BPD is also associated with dysregulation of angiogenesis in the pulmonary vasculature of the developing lung (the 'vascular hypothesis') [8–12]. In other words, alterations in angiogenic state appear to be involved in the pathogenesis of both preeclampsia and BPD. The relationship between preeclampsia and increased risk of BPD has been increasingly examined. Exposure to excess sFlt-1 in amniotic fluid during late gestation caused sustained reductions in alveolarization and pulmonary vascular growth in rats, leading to the development of BPD [13]. In many epidemiologic studies, preeclampsia was shown to be independently associated with a high risk of BPD, although little is known about the underlying mechanism [14–18].

To investigate the underlying mechanism that may link preeclampsia with a high risk for BPD under conditions of impaired angiogenesis, we hypothesized that the levels of sFlt-1 and soluble endoglin (as antiangiogenic factors) and PlGF (as a proangiogenic factor)

* Corresponding author at: Department of Pediatrics, Seoul National University Children's Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea.
E-mail address: kimhans@snu.ac.kr (H.-S. Kim).

https://doi.org/10.1016/j.preghy.2018.06.002
Received 16 November 2017; Received in revised form 6 March 2018; Accepted 9 June 2018
Available online 09 June 2018

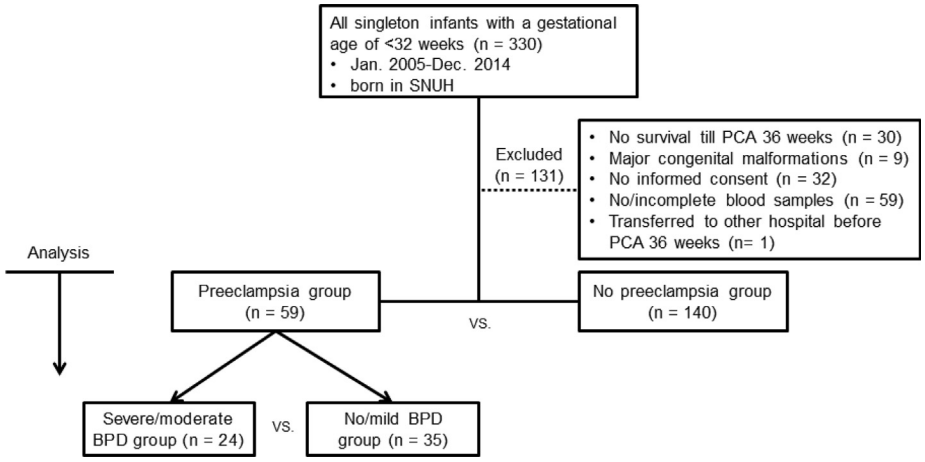

Fig. 1. Flow diagram showing the study design involving the 330 infants screened in this study. *SNUH,* Seoul National University Hospital; *PCA,* postconceptional age.

in cord blood are associated with the development of severe or moderate BPD in preterm infants with maternal preeclampsia.

2. Methods

2.1. Patients

All singleton infants with a gestational age of < 32 weeks born in Seoul National University Hospital during a 10-year period from January 2005 to December 2014 were screened. Infants with major congenital malformations and infants without a cord blood sample were excluded. Infants who were transferred to other hospitals or died before reaching a postconceptional age (PCA) of 36 weeks were also excluded (Fig. 1).

Data on the patients' clinical characteristics were collected and analyzed retrospectively. Clinical characteristics were directly evaluated by a single reviewer using medical records. Maternal preeclampsia was defined as new-onset hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg on at least two occasions at least 4 h apart) after 20 weeks' gestation in a formerly normotensive patient, accompanied by proteinuria ≥ 300 mg per 24-hour urine collection [19]. BPD and its severity were defined using the criteria of the National Institute of Child Health Workshop definition for BPD [20], i.e., treatment with oxygen for at least 28 days with division into the following 3 subgroups at 36-week PCA: (1) mild (breathing room air); (2) moderate (need for a < 30% fraction of inspired oxygen), and (3) severe (need for ≥30% fraction of inspired oxygen and/or positive pressure support). BPD-associated pulmonary hypertension (PH) was diagnosed based on echocardiograms demonstrating elevated right ventricle pressure using the following criteria in preterm infants with BPD: (1) velocity of tricuspid valve regurgitation of ≥3 m/s in the absence of pulmonary stenosis, and (2) flat or leftward deviated interventricular septal configuration and right ventricular hypertrophy with chamber dilation. Patients with one or both of these findings beyond 2 months of age were characterized as having PH. The diagnosis of respiratory distress syndrome required the presence of respiratory distress, increased oxygen requirement and a radiological finding consistent with respiratory distress syndrome in the absence of other causes of respiratory distress. Patent ductus arteriosus was diagnosed by echocardiography, and only cases treated with prostaglandin inhibitor or surgical ligation were included. The presence of proven sepsis was defined as at least a single blood culture and clinical signs of infection. Other clinical characteristics studied included preterm premature rupture of membrane, histologic chorioamnionitis (HCAM; presence of acute inflammatory changes on a membrane roll and the placental chorionic plate), and oligohydramnios (defined as amniotic fluid index < 5 cm by ultrasound performed just before delivery).

2.2. Umbilical cord blood samples and assays

Umbilical cord blood was collected in ethylenediaminetetraacetic acid-containing blood collection tubes by arteriopuncture of the umbilical artery at birth. The samples were then centrifuged at 3000*g* for 5 min at 4 °C, and the supernatants were stored in polypropylene tubes at −70 °C. The sFlt-1, soluble endoglin, and PlGF levels in cord blood were measured using human ELISA kits (MyBioSource, Inc., San Diego, CA., USA; Cusabio Biotech Co., Baltimore, MD., USA; R&D Systems, Minneapolis, Minn., USA, respectively) according to the manufacturer's protocols. The ratio of (sFlt-1 + soluble endoglin) to PlGF for each patient was calculated to assess the balance between the anti- and proangiogenic factors in the infants' serum.

2.3. Statistical analyses

First, we performed univariate analyses to investigate demographic and clinical characteristics in the study subjects by groups. Categorical variables were analyzed by the χ^2 test and Fisher's exact test. Differences in continuous variables were assessed by Student's *t* test. The sFlt-1, soluble endoglin, PlGF levels and the ratio of (sFlt-1 + soluble endoglin) to PlGF in cord blood were adjusted for gestational age by analysis of covariance (ANCOVA). For cord blood soluble endoglin, we calculated receiver operating characteristic (ROC) curve and performed a sensitivity analysis to determine the cut-off value for predicting the development of severe or moderate BPD in preterm infants born to mothers with preeclampsia. Next, to determine independent risk factors for the development of severe or moderate BPD in the preeclampsia group, we performed a multivariate logistic regression analysis. Variables that were significant in the previous univariate analysis were included in the logistic regression model. We calculated the adjusted odds ratio (OR) for the development of severe or moderate BPD and the 95% confidence interval (CI) of the selected variables. Data are presented as the mean ± standard deviation or frequency, and a *P*-value of < .05 was considered statistically significant. The statistical analyses were performed using SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Classification of the study subjects

A total of 199 infants fulfilled the study criteria, and this group accounted for 60% of all singleton infants with a gestational age <