Pregnancy Hypertension 12 (2018) 124–128

Contents lists available at ScienceDirect

Pregnancy Hypertension

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

Predictive value of sFlt-1, PlGF, sFlt-1/PlGF ratio and PAPP-A for late-onset preeclampsia and IUGR between 32 and 37 weeks of pregnancy

C. Birdir[a,b,*], L. Droste[a], L. Fox[a], M. Frank[c], J. Fryze[a,b], A. Enekwe[a], A. Köninger[a], R. Kimmig[a], B. Schmidt[c,1], A. Gellhaus[a,1]

[a] Department of Obstetrics and Gynecology, University Hospital of Essen, Essen, Germany
[b] Department of Obstetrics and Gynecology, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[c] Institute for Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany

ARTICLE INFO

Keywords:
Preeclampsia
sFlt-1
PlGF
PAPP-A
Third trimester
Screening

ABSTRACT

Objectives: The aim of this study was to investigate, whether maternal serum levels of sFlt-1, PlGF and PAPP-A at third trimester of pregnancy are associated with late-onset PE and intrauterine growth retardation (IUGR) after 34 weeks of pregnancy.

Methods: This was a prospective study measuring the maternal serum levels of soluble tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A) at 32–37 weeks of pregnancy: 730 patients were enrolled and 676 had neither intrauterine growth restriction (IUGR) nor preeclampsia (PE) or pregnancy induced hypertension (PIH) throughout the pregnancy. 22 patients developed IUGR, 32 PE and 24 PIH.

Results: Linear regression analyses after adjusting for maternal age, gestational age at the blood sampling and maternal BMI showed associations between PE and serum sFlt-1 levels (Exp(ß) = 3.29; 95% CI: 2.69–4.04), serum PlGF levels (Exp(ß) = 0.18; 95% CI: 0.13–0.24), sFlt-1/PlGF ratio (Exp(ß) = 15.59; 95% CI: 10.64–22.84) and serum PAPP-A (Exp(ß) = 1.48; 95% CI 1.15–1.89). sFlt-1, PlGF and sFlt-1/PlGF-Ratio showed comparable area under the curve (AUC) estimates with a predictive ability to discriminate pregnancies developing PE and IUGR from controls. The predictive ability of PAPP-A for PE was only slightly better than chance.

Conclusions: This study supported the ability of a single measurement of sFlt-1/PlGF ratio at third trimester to predict PE and IUGR occurring after 34 weeks of pregnancy. However, larger multicentre studies are needed to replicate our results.

1. Introduction

Preeclampsia (PE) is one of the most common pregnancy complications with high morbidity and mortality throughout the world. A new prediction model at first trimester can detect 100% of pregnancies with PE that occur before 32 weeks of pregnancy [1]. This model allows to detect high-risk pregnancies to offer a prophylactic therapy with acetylsalicylic acid (Aspirin) before 16 weeks of pregnancy, which may prevent early-onset preeclampsia or intrauterine growth restriction (IUGR) [2]. Neither this prediction model nor the prophylactic therapy with Aspirin is effective to predict or prevent late-onset PE after 37 weeks of pregnancy.

Various clinical studies in the last years demonstrated that there is a strong correlation between PE and maternal serum levels of soluble tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) [3–5]. It has been proven that using a ratio between these two parameters (sFlt-1/PlGF ratio) can exclude PE at second and third trimester of pregnancy for 1 week from the day of blood sample testing [6]. Another study group developed a prediction model combining the maternal serum levels of sFlt-1 and PlGF with maternal history and biophysical markers to predict PE in various time intervals at third trimester [7–9].

Effective screening for fetal trisomies 21, 18 and 13 can be provided at 11–13 weeks' gestation by combination of maternal age, fetal nuchal translucency thickness (NT), fetal heart rate (FHR) and maternal serum free β-human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein-A (PAPP-A) [10]. The assessment of PAPP-A showed significant results when used for the screening for PE at 11–13 weeks [1]. But the performance of PAPP-A has not been assessed thoroughly

* Corresponding author at: Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Carl Gustav Carus, an der Technischen Universität Dresden, Fetscherstraße 74, 01307 Dresden, Germany.
E-mail address: cbirdir@gmail.com (C. Birdir).
[1] Equally contributed.

https://doi.org/10.1016/j.preghy.2018.04.010
Received 5 February 2018; Received in revised form 25 March 2018; Accepted 11 April 2018
Available online 11 April 2018

yet at third trimester for the screening of PE.

The aim of this study was to investigate, whether maternal serum levels of sFlt-1, PlGF and PAPP-A at third trimester of pregnancy are associated with late-onset PE and intrauterine growth retardation (IUGR) after 34 weeks of pregnancy.

2. Materials and methods

2.1. Study population

The present prospective study of consecutively enrolled women consisted of 730 pregnant women who received routine examination during pregnancy at 32–37 weeks' gestation between 2014 and 2016, at the University Hospital Essen, Department for Obstetrics and Gynecology, Essen, Germany. All of the enrolled patients had no signs or symptoms of PE, IUGR or pregnancy induced hypertension (PIH) at the time of examination and blood draw. Data, ultrasound examination including the measurement of pulsaltility indices (PI) of umbilical artery and blood samples were derived from all participants with a control group (N = 676) which are defined as those individuals having neither IUGR nor PE or PIH throughout the pregnancy. Patients suffering from IUGR (N = 22), PE (N = 32) and PIH (N = 24) were also examined, which did not show any signs or symptoms at the time of enrollment. PE was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy (ISSHP) [11]. IUGR was defined as the pregnancies ending with a newborn with a birthweight below the 5th centile and a pathological PI of umbilical artery over the 95th centile. There were also other subgroups with pregnancies with a newborn with birthweight below the 10th centile (N = 93) and below the 5th centile (N = 57) only, without pathological Doppler measurements. Statistical analysis of these subgroups of patients can be found in Supplementary Tables I and II.

Written informed consent was obtained from these women, and the study was approved by the Ethics Committee of the medical faculty of the University of Duisburg-Essen (No. 06-2969, 03-2157).

2.2. Data assessment

Maternal serum sFlt-1, PlGF, sFlt-1/PLGF ratio and PAPP-A levels were measured in the selected serum samples. The maternal data collected during routine visits were as follows: Maternal age, weight of the newborn, gestational week at time of blood sampling and gestational week at birth as well as cigarette smoking during pregnancy. The maternal weight and height were measured and converted to body mass index (BMI; kg/m^2). Twin pregnancies and pregnancies with major maternal diseases were excluded. An ultrasound scan was performed to calculate the estimated weight and to assess the fetal wellbeing. Doppler measurement of the umbilical artery was done to analyse the blood flow. The gestational age was confirmed by measurement of fetal crown-rump length (CRL) at first trimester of pregnancy [12]. Major fetal abnormalities were excluded.

2.3. Sampling of blood serum

Blood (9 ml) was collected from each woman between week 32 + 0 and 37 + 0 of pregnancy using a S-Monovette (Sarstedt AG and Co.), was stored at 4 °C and processed within 4 h to avoid blood cell lysis. Blood fractionation was carried out by centrifugation at 10 min for 2500 × *g*. Subsequently, 3–4 ml of the upper phase, containing blood serum, were removed, stored at −80 °C and subjected to the determination of sFlt-1, PlGF and PAPP-A.

2.4. Determination of sFlt-1, PlGF and PAPP-A

50 µl of the pre-diluted sample plus 150 µl of dead volume was used to measure concentration of sFlt-1 (BRAHMS sFlt-1 KRYPTOR), PlGF-Plus (BRAHMS PlGF plus KRYPTOR), and PAPP-A (BRAHMS PAPP-A KRYPTOR); all from Thermo Fisher Scientific, using BRAHMS KRYPTOR compact PLUS machine based on TRACE® Technology (Time-Resolved Amplified Cryptate Emission) (Thermo Fischer Scientific, BRAHMS GmbH, Hennigsdorf, Germany), according to the protocol.

The detection limit was assessed as being 22 pg/mL for sFlt-1, 3.6 pg/mL for PlGF and 0.004 IU/L for PAPP-A. The functional assay sensitivity, detected by inter-assay precision of 20% coefficient of variability (CV), has been assessed as being lower than 29 pg/mL for sFlt-1, 6.7 pg/mL for PlGF and 0.01 IU/L for PAPP-A respectively.

2.5. Statistical analysis

Descriptive statistics of the study population were computed stratified by pregnancy outcomes. A control group of patients having none of the pregnancy outcomes under investigation was also identified for further analyses. Continuous variables were reported as mean and standard deviation (± SD) and medians with interquartile range (IQR), discrete variables are given in frequency and percent (n%). Group differences were also presented as boxplots.

Linear regression models were fitted to examine the association between pregnancy outcomes and the biomarkers under investigation. Pregnancy outcomes were included separately into the model as independent variables with controls as reference for each biomarker as dependent variable. Effect size estimates, corresponding 95% confidence intervals (95%-CI) and respective *p* values were calculated separately for each pregnancy outcome adjusted for age of the mother, gestational week at time of blood sampling and BMI of the mother. To address the skewed distribution of the respective biomarkers they were log-transformed prior to analysis. To the sFlt-1: PlGF ratio a log (sFlt-1: PlGF ratio + 1) transformation was applied to address numerical errors. The respective effect size estimates were presented back-transformed as exponentiated regression coefficients (exp[ß]). They can be interpreted as multiples of the average biomarker value per pregnancy outcome group compared to controls.

Receiver operating characteristic (ROC) analysis was performed separately for each biomarker to test their ability to discriminate between controls and cases. The area under the curve (AUC) with corresponding 95% confidence intervals was estimated to describe the probability of accurately discriminating between cases and controls. In addition, the threshold that maximizes the sum of sensitivity and specificity was calculated according to Youden (1950) for each parameter [13].

All statistical analyses were carried out with the statistical computing software R v3.1.1 [14] (R 2011). The package pROC was used for the receiver operating characteristic curve analysis [15].

3. Results

Table 1 represents the characteristics of the study population. The maternal age was similar in all groups. Compared to controls, the maternal BMI was higher in patients who later developed PE and lower in patients who developed IUGR. The week of gestation was lower at birth in cases of IUGR and PE. The Supplementary Table I represents the characteristics of the study population with all subgroups of patients (Supplementary Table I). The median level of sFlt-1 was substantially higher in PE and IUGR groups compared to controls; whereas the median levels of PlGF were lower. Higher median levels of PAPP-A in PE were detected (Fig. 1).

Results of the linear regression analyses after adjusting for maternal age, gestational age at the blood sampling and maternal BMI showed associations between PE and serum sFlt-1 levels (Exp(ß) = 3.29; 95% CI: 2.69–4.04), serum PlGF levels (Exp(ß) = 0.18; 95% CI: 0.13–0.24), sFlt-1/PlGF ratio (Exp(ß) = 15.59; 95% CI: 10.64–22.84) and serum PAPP-A (Exp(ß) = 1.48; 95% CI 1.15–1.89) (Table 2).