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Biochemical markers in screening for preeclampsia and intrauterine growth restriction

Markery biochemiczne w predykcji stanu przedrzucawkowego i zahamowania wewnątrzmacicznego wzrastania płodu

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Abstract

Objectives: *The aim of the study was to evaluate the relationship between the concentrations of substances released by the placenta: placental growth factor (PlGF), pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotropin (β-hCG) and the risk of early and late preeclampsia (PE) and intrauterine fetal growth restriction (IUGR).*

Material and methods: *A total of 180 pregnant women between 11+0 and 13+6 weeks gestation were recruited for a case-control study. Twenty-two patients suffered from early PE, 29 patients from late PE. Data analyzed during the study included maternal history and concentrations of PAPP-A, PlGF, β-hCG.*

Results: *The multiple of the median (MoM) value of the PAPP-A concentrations was 1.01 in the control group (interquartile range (IQR), 0.65-1.55), 0.67 (IQR, 0.382-0.82) in the group of patients with early preeclampsia and 0.74 (IQR, 0.33-1.09) in the group of patients suffering from late preeclampsia. MoM value of the PlGF concentrations was 1.21 in the control group (IQR, 0.93-1.57), 0.62 (IQR, 0.51-0.96) in the group of patients with early preeclampsia and 0.92 (IQR, 0.63-1.09) in the group of patients suffering from late preeclampsia. MoM value of β-hCG concentrations was 1.14 in the control group (IQR, 0.75-1.49), 1.08(IQR, 0.74-1.23) in the group of patients with early preeclampsia and 1,25(IQR, 1,05-1,49) in the group of patients suffering from late preeclampsia. The performance of screening was determined by the areas under the curve and detection rates, with a fixed false-positive rate of 10%.*

Conclusions: *Decreased levels of PAPP-A and PlGF are related to an increased risk of preeclampsia and its complications.*

Key words: **preeclampsia** / **PAPP-A** / **PlGF** /

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Streszczenie

Cel pracy: *Celem przedstawionego badania była ocena zależności między stężeniami uwalnianych przez łożysko substancji – łożyskowego czynnika wzrostu (PlGF), ciążowego białka A (PAPP-A) oraz podjednostki beta ludzkiej gonadotropiny kosmówkowej (β-hCG) a ryzykiem wystąpienia wczesnej i późnej postaci stanu przedrzucawkowego oraz zahamowania wewnątrzmacicznego wzrastania płodu.*

Materiał i metody: *Badaniem kliniczno-kontrolnym objęto grupę 180 pacjentek ciężarnych w 11+0-13+6 tygodniu ciąży. U 22 pacjentek wystąpiła wczesna postać stanu przedrzucawkowego, u 29 pacjentek rozwinęła się późna postać preeklampsji. Dane analizowane w toku badania obejmowały wywiad ciężarnych oraz stężenia PAPP-A, PlGF, β-hCG.*

Wyniki: *Wartość środkowa wielokrotności mediany stężenia PAPP-A wyniosła 1,01 (przedział międzykwartylowy (IQR), 0,65-1,55) w grupie kontrolnej, 0,67 (IQR, 0,382-0,82) w grupie pacjentek z ciążą powikłaną wczesną postacią preeklampsji i 0,74 (IQR, 0,33-1,09) w grupie pacjentek z ciążą powikłaną późną postacią preeklampsji. Wartość środkowa wielokrotności mediany stężenia PlGF wyniosła 1,21 (IQR, 0,93-1,57) w grupie kontrolnej, 0,62 (IQR, 0,51-0,96) w grupie pacjentek z ciążą powikłaną wczesną postacią preeklampsji i 0,92 (IQR, 0,63-1,09) w grupie pacjentek z ciążą powikłaną późną postacią preeklampsji. Wartość środkowa wielokrotności mediany stężenia β-hCG wyniosła 1,14 (IQR, 0,75-1,49) w grupie kontrolnej, 1,08 (IQR, 0,74-1,23) w grupie pacjentek z ciążą powikłaną wczesną postacią preeklampsji i 1,25(IQR, 1,05-1,49) w grupie pacjentek z ciążą powikłaną późną postacią preeklampsji. Wyniki dopasowania predykcji zastosowanych testów przedstawiono za pomocą pola pod wykresem (AUC) oraz współczynnika wykrywalności dla odsetka wyników fałszywie dodatnich (FPR) na poziomie 10%.*

Wnioski: *Obniżone stężenia PAPP-A i PlGF są związane z podwyższonym ryzykiem rozwoju stanu przedrzucawkowego i jego powikłań.*

Słowa kluczowe: **stan przedrzucawkowy** / **PAPP-A** / **PlGF** /

Introduction

Hypertension in pregnancy remains consistently one of the major problems of contemporary obstetrics. Annually, approximately 3 million pregnant women worldwide are diagnosed with hypertension, and about 50 thousand pregnant women die from the disease and its complications [1-3].

From the clinical point of view, the most important form of hypertension in pregnancy is preeclampsia. The incidence of preeclampsia in primiparas is estimated at around 2 to 7% [4, 5]. It is a systemic disease associated with high maternal mortality (15% - 46%), which increases the perinatal mortality rate: it is estimated to represent over 65% of perinatal deaths [6, 7]. Complications of preeclampsia, in the form of intrauterine growth restriction and preterm labor, are not only the most significant causes of neonatal morbidity and mortality, but also have a long-term impact on child development, generating high health care costs [8-10].

Screening for the most common chromosomal abnormalities, i.e. trisomy of chromosomes 21, 18 and 13, is based on a combined analysis of clinical data of pregnant, nuchal translucency assessment (NT), and concentrations of pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotropin (β-HCG) between 11 + 0 and 13 + 6 weeks of gestation. Numerous reports on the pathogenesis of preeclampsia indicate abnormal placentation as the cause [11]. The placental function can be evaluated by analyzing such peptides as PAPP-A, β-HCG and placental growth factor (PlGF), which are produced by the placenta and released into the maternal circulation.

The aim of this study was to identify the relationship between the concentrations of substances released by the placenta, i.e. placental growth factor, pregnancy-associated plasma protein A and free beta-human chorionic gonadotropin, and the risk of early and late preeclampsia and intrauterine fetal growth restriction.

Materials and methods

The research was carried out in the Perinatology and Gynecology Department, Polish Mother's Memorial Research Institute tertiary care centre and in the private practices NZOZ Medyk W. Litwinski and NZOZ Sonomedica in the years 2013 and 2014. Approval for the study was given by the local bioethics committee. The study group consisted of 80 pregnant women at gestational age between 11+0 and 13+6 weeks of gestation who displayed the risk factors of developing preeclampsia given in the literature: PE in the previous pregnancy/pregnancies, high blood pressure before pregnancy, diabetes, obesity, kidney diseases and systemic diseases. In addition, 100 pregnant woman without risk factors in their medical history were also included in the study. Written consent was obtained from each patient.

All patients fulfilled the inclusion criteria. Patients in multiple pregnancies, with fetal anomalies, abortion or termination of pregnancy were excluded from the study. The presence of risk factors was not strictly associated with the development preeclampsia in all cases.

The patients were divided into three groups according to the development of preeclampsia: 1. A control group comprising patients without preeclampsia (n=129); 2. Patients with early-onset preeclampsia (n=22); 3. Patients with late-onset preeclampsia (n=29). The subjects in the above mentioned groups were analysed for the presence of potential markers for the development of preeclampsia and its complications.

At the first visit, at a gestational age between 11+0 – 13+6 weeks, a detailed maternal history was taken from each patient, a blood sample was collected and an ultrasound examination was performed. In the ultrasound examination, crown-rump length and nuchal translucency were measured according to the guidelines of the Fetal Medicine Foundation. The anatomy of the fetus was initially evaluated.

Table I. Maternal characteristics.

	Control (n=129)	Early preeclampsia (n=22)	Late preeclampsia (n=29)	IUGR (n=43)
Age	28 (25-31)	29.5 (26-34)	30 (27-33)	29 (26-34)
BMI	23.9 (22-27.6)	30.6 (23.1-32.3)	26.5 (23.6-29.7)	28.7 (23.6-32.4)
Smoking	10 (8%)	2 (9%)	6 (21%)	6 (14%)
Parity				
Primiparous	74 (41%)	14 (64%)	6 (21%)	22 (51%)
Preterm delivery	7 (5%)	5 (23%)	14 (48%)	11 (26%)
History of preeclampsia	13 (10%)	7 (31%)	18(62%)	13 (30%)
Diabetes	7 (5%)	5 (23%)	1 (3.45)	8 (18%)
Chronic hypertension	14 (11%)	12 (55%)	9 (31%)	25 (58%)
Kidney disease	3 (2%)	6 (27%)	2 (7%)	9 (21%)
Preeclampsia in mother	9 (7%)	2 (9%)	3 (10%)	5 (12%)

Table II. Data for each marker in the four outcome groups.

	Control (n=129)	Early preeclampsia (n=22)	Late preeclampsia (n=29)	IUGR (n=43)
Gestational age CRL (hbd)	12.5 (12.2-13)	12.3 (12-13)	12.6 (12.4-13)	12.4 (12.1-13)
CRL (mm)	63.6 (59.1-68.3)	63.1 (59.0-67.9)	64.7 (61.2-67.1)	61.5 (56.2-67.1)
PlGF	27.4 (19.6-34)	15.55 (11.1-19)	21 (16.7-25.6)	20.5 (14.6-26.2)
PlGF MoM	1.21 (0.93-1.57)	0.62 (0.51-0.96)	0.92 (0.63-1.09)	0.97 (0.59-1.12)
PAPP-A	1.6 (1-2.6)	0.84 (0.67-1.13)	1.03 (0.6-1.8)	0.90 (0.6-1.2)
PAPP-A MoM	1.01 (0.65-1.55)	0.67 (0.382-0.82)	0.74 (0.33-1.09)	0.49 (0.37-1.06)
β-hCG	42.1 (31.2-58)	41.65 (25.7-47)	42 (34.1-55.8)	40.3 (32.4-44.4)
β-hCG MoM	1.14 (0.75-1.49)	1.08 (0.74-1.23)	1.25 (1.05-1.49)	1.12 (0.91-1.25)
Age at delivery (hbd)	39 (37-40)	30 (29-32)	37 (35-37)	32 (29-34)
Birth weight (g)	3450 (3050-3780)	1015 (850-1200)	2920 (2450-3120)	1297 (890-1760)

The following information was included in the patient anamnesis: age, height and weight (to calculate Body Mass Index), parity, type of conception (spontaneous or with assisted conception techniques requiring stimulation of ovulation), smoking during pregnancy, presence of chronic hypertension and diabetes, systemic diseases, antiphospholipid syndrome, kidney diseases and preeclampsia in the previous pregnancy. In the family history, the presence of preeclampsia in mother was taken into consideration.

The concentrations of PlGF, PAPP-A and β-hCG were measured using a DELFIA XPRESS analyzer.

The findings were archived in the View Point system to calculate the risk of developing preeclampsia. The calculation programme was constructed according to the guidelines of Fetal Medicine Foundation.

Results

The characteristics of the study groups are shown in Table I. The group of patients with early PE was characterised by a higher BMI, higher incidence of chronic HA, diabetes and kidney disease in comparison to the control group. The late PE group was characterised by a higher prevalence of smokers, women with history of preeclampsia and chronic hypertension. The IUGR group was characterised by a higher BMI, and higher incidence of diabetes, chronic hypertension and kidney disease.

The impact of the following factors on the prediction of the early, late preeclampsia and intrauterine growth restriction was analysed: PlGF concentration, PlGF MoM, PAPP-A concentration, PAPP-A MoM, β-hCG, β-hCG MoM. The data for each parameter is presented in Table II.

The performance of screening was determined by the areas under the curve (AUC) and detection rates, with a fixed false-positive rate of 10% (Table III, IV).

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Table III. Comparison of screening tests evaluation for early and late preeclampsia and IUGR based on specific factors, maternal risk factors + additional marker.

	Area under the curve (AUC)		
	Early preeclampsia	Late preeclampsia	IUGR
PAPP-A MoM	0.74 (0.04)	0.62 (0.07)	0.69 (0.05)
PlGF MoM	0.79 (0.04)	0.66 (0.05)	0.68 (0.04)
β-hCG MoM	0.59 (0.06)	0.61 (0.05)	0.55 (0.05)
Maternal risk factors +			
PAPP-A MoM	0.85 (0.03)	0.84 (0.03)	0.85 (0.03)
PlGF MoM	0.91 (0.02)	0.86 (0.03)	0.84 (0.03)
β-hCG MoM	---	---	---

Table IV. Comparison of detection rates with fixed false- positive rate of 10% in the early, late preeclampsia and IUGR group.

	Detection rate (%) with fixed false- positive rate of 10% (FPR)		
	Early preeclampsia	Late preeclampsia	IUGR
	FPR 10%	FPR 10%	FPR 10%
PAPP-A MoM	48.3	25.9	33.6
PlGF MoM	57	34.4	46.7
β-hCG MoM	20.3	6.9	21.9
Risk factor +			
PAPP-A MoM	36.4	27.6	55.8
PlGF MoM	81.8	58.6	30.2
β-hCG MoM	---	---	---

Discussion

The understanding of the pathophysiology of preeclampsia has enabled biochemical markers to be identified among the factors which play a role in early angiogenesis and placentation. Two of the substances analysed in the present study, i.e. pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotropin (β-hCG) have an integral place in screening for chromosomal abnormalities, while the third, placental growth factor (PlGF), is one of the growth factors involved in the placentation. The findings confirm the previously published results indicating that, after excluding pregnancies with chromosomal abnormalities, low PAPP-A levels at 11+0–13+6 weeks are correlated with a high risk of developing preeclampsia [12-14]. Additionally, the level of PAPP-A is significantly lower in the case of early-onset preeclampsia. Calculated detection rates for early PE, late PE and intrauterine growth restriction based on PAPP-A level alone were only 48%, 26%, and 34% respectively, with a false positive rate of 10%. The detection rate of intrauterine growth, after taking into account the risk factor in medical history and multiples of median of PAPP-A, was 56% with a false positive rate of 10%. A significant correlation between PAPP-A level and age of pregnancy complicated by preeclampsia at the time of delivery was found. These results are consistent with those identified by Poon et al. and Spencer et al., who demonstrated the value of identifying the PAPP-A level in the prediction of early preeclampsia [15-17]. The level of PAPP-A was less decreased in patients who suffered from late preeclampsia than in patients with early preeclampsia. This finding confirms data published by D'Anna et al., who indicate the necessity to distinguish early and late onset preeclampsia [18]. PAPP-A is a substance produced by the syncytiotrophoblast and may be used as a sensitive marker of early preeclampsia, which is a consequence of impaired placentation. In late preeclampsia, the influence of placental factors is less significant, and as a result, the role of PAPP-A is also less significant. As also noted by Cowans et al. and Spencer et al., a relationship was identified in the present study between low PAPP-A level in the first trimester of pregnancy and the incidence of intrauterine growth restriction [19, 20].

In patients with preeclampsia, lower levels of placental growth factor, a marker and mediator of endothelial cell dysfunction, was noted. Similarly to the analysis conducted by Akolekar et al. and Erez et al. and analogical relationship between the level of PlGF and the risk of developing preeclampsia especially its early form was stated [21, 22]. The calculated detection rates for early and late preeclampsia, as well as intrauterine growth restriction, based only on PlGF concentration were 57%, 34% and 47% respectively. The false positive rate was 10%. The detection rates of preeclampsia after taking into account the risk factor in medical history and multiples of median of PlGF were 81% for early preeclampsia and 58% for late preeclampsia. The false positive rate was 10%. However, a retrospective comparative analysis of 131 pregnancies complicated by preeclampsia and 400 uncomplicated pregnancies conducted by Ong et al. found no statistical differences in PlGF concentration between the two groups [23]. In the present study, a significant relationship was found between PlGF level and severity of preeclampsia defined by gestational age in which the iatrogenic premature delivery occurred and the weight of newborn. These results are

consistent with those of previous studies, in which lower levels of PlGF were identified in the presence of symptomatic disease, as well as in the first and second trimester of pregnancy [24-27]. However, differences in PlGF level in pregnancies complicated by intrauterine growth restriction are controversial. In the presented study, significant decreases in PlGF level were noted in the group of pregnancies complicated by intrauterine growth restriction. These results are consistent with those published by Cowans et al., who showed the value of measuring PlGF concentration, not only in the prediction of preeclampsia but also other complications of pregnancy like SGA and IUGR [28]. A different opinion was presented by Vandenberghe et al. who found no statistical differences from controls in a retrospective review of the concentration of PlGF in patients with pregnancies complicated by preeclampsia [29].

According to Akolekar et al., a group of patients with uncomplicated pregnancies demonstrated a rise in PlGF and PAPP-A levels with gestational age (crown-rump length). In the present study, the relationship between cigarette smoking and PAPP-A and PlGF level was not evaluated, as the group of smokers was not large enough. Akolekar et al. recorded an increase in PlGF level and decrease in PAPP-A level in group of patients with uncomplicated pregnancies [22]. Based on these relationships, personal differences should be taken into consideration when evaluating these biochemical markers.

In the present study, no relationship between the level of β-hCG and the incidence of preeclampsia and its complications was observed. These results are consistent with those of other research works conducted on large groups of patients [13, 19]. However, in contrast, Di Lorenzo et al. report the presence a statistically significant relationship between higher β-hCG levels and the incidence of preeclampsia in a prospective study including 2118 patients [30].

Conclusion

The biochemical exponent of abnormal placentation, and consequently, placental function, is a decreased secretion of substances of placental origin. The reveals a significant correlation between reduced levels of placental growth factor and pregnancy-associated plasma protein A in the group of patients with preeclampsia compared to the control group.

The identification of a group of patients at higher risk during routine first trimester examination, despite the lack of commonly recognized preventive methods, will allow intensified obstetric supervision and adequate response in the case of complications.

Oświadczenie autorów

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