P R A C E O R Y G I N A L N E

położnictwo

Reference values for placental growth factor (PlGF) concentration and uterine artery Doppler pulsatility index (PI) at 11–13^{+6} weeks of gestation in the Polish population

Wartości referencyjne w polskiej populacji dla łożyskowego czynnika wzrostu (PlGF) oraz współczynnika pulsacji (PI) w tętnicach macicznych między 11–13^{+6} tygodniem ciąży

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Abstract

Objectives: *The aim of the study was to determine placental growth factor (PlGF) concentration and uterine artery (UtA) Doppler pulsatility index (PI) at 11–13^{+6} weeks of gestation in the Polish population.*

Material and methods: *A prospective study was performed in pregnant women who underwent routine ultrasound scan at 11–13^{+6} weeks of gestation. All participants completed a questionnaire about their medical history, demographics and current pregnancy. Mean arterial pressure (MAP) was calculated. Gestational age was confirmed by CRL and mean UtA PI was calculated. Blood samples were taken to measure beta HCG, PAPP-A and PlGF concentrations.*

Results: *Out of the 577 analyzed participants, 60 (10.4%) were found to have abnormal placentation disorders (20 – hypertensive disorders and 40 – IUGR). The patients were subdivided into two groups, depending on pregnancy outcome: unaffected (n=517) and affected (n=60). The study did not confirm the anticipated correlation between maternal BMI and PlGF, but the concentration of PlGF was significantly increased in smokers. UtA PI values were not statistically significantly different depending on maternal age, BMI, method of conception, smoking or parity. The study confirms that both, UtA PI and PlGF concentrations are CRL-dependent. Median MoM values for PlGF and UtA PI were obtained for each set of CRL measurements. Median PlGF MoM was decreased in pregnancies complicated by hypertensive disorders and IUGR as compared to the unaffected group.*

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Conclusions: *The established reference ranges for UtA PI and PlGF at 11–13^{+6} weeks of gestation may be of clinical value in predicting placenta-associated diseases in early stages of pregnancy in the Polish population.*

Key words: **preeclampsia** / **Doppler studies** / **uterine artery pulsatility index** / / **placental growth factor** /

Streszczenie

Cel pracy: *Celem pracy było ustalenie wartości referencyjnych w polskiej populacji dla stężenia łożyskowego czynnika wzrostu (PlGF) oraz wskaźnika pulsacji (UtA PI) przepływu w tętnicach macicznych w 11–13^{+6} tygodniu ciąży.*

Materiał i metody: *Przeprowadzono prospektywne badanie u ciężarnych, które przebyły rutynowe badanie ultrasonograficzne w pierwszym trymestrze. Uzyskano informacje dotyczące wywiadu medycznego, danych demograficznych oraz przebiegu ciąży. Na podstawie pomiarów wyliczono średnie ciśnienie tętnicze (MAP). Wiek ciąży potwierdzono na podstawie długości siedzeniowo ciemieniowej płodu (CRL). Dokonano Dopplerowskiej oceny przepływu w tętnicach macicznych oraz wyliczono średni wskaźnik pulsacji. W pobranych próbkach krwi oznaczono stężenia beta HCG, PAPP-A oraz PlGF.*

Wyniki: *Z pośród badanych 577 ciężarnych u 60 (10,4%) kobiet doszło do rozwoju powikłań związanych z zaburzeniem implantacji: u 20 do nadciśnienia indukowanego ciążą, a u 40 do ciężkiej hipotrofii płodu. W związku z tym analizowaną populację podzielono na grupę niepowikłaną (n-517) oraz z powikłaniami (n-60). Stwierdzono, że z czynników matczynych jedynie palenie papierosów miało wpływ na obniżenie stężenia PlGF. Natomiast zarówno PlGF jak i wartość UtA PI zmieniały się w zależności od wieku ciążowego (CRL). Wyznaczono wartości MoM badanych markerów dla poszczególnych przedziałów CRL. Stwierdzono istotnie niższe wartości średnich MoM PlGF w grupie powikłanej nadciśnieniem i ciężką hipotrofią płodu w porównaniu do grupy niepowikłanej.*

Wnioski: *Określenie wartości referencyjnych wskaźnika pulsacji przepływu w tętnicach macicznych oraz PlGF między 11–13^{+6} tygodniem może stanowić podstawę do wprowadzenia wczesnego skriningu preeklampsji i hipotrofii płodu u ciężarnych w polskiej populacji.*

Słowa kluczowe: **stan przedrzucawkowy** / **badania doplerowskie** / **indeks pulsacji tętnicy macicznej** / **łożyskowy czynnik wzrostu** /

Introduction

The typical medical care for pregnant women was established 80 years ago and assumed that most serious complications occur later in pregnancy. There is strong scientific evidence that at least some of the late pregnancy complications are related to impaired placentation early in gestation. The new concept of medical care for pregnant women is based on the inverted pyramid of care [1]. Nowadays, it is possible to predict complications in early pregnancy with the use of maternal characteristics, as well as ultrasound and biochemical markers. Transabdominal and transvaginal uterine artery (UtA) Doppler ultrasound examination is a valuable technique which allows to assess uteroplacental circulation from the early stages of pregnancy [2]. It has become a useful clinical tool to screen for the development of preeclampsia, fetal growth restriction, placental abruption and stillbirth [3-5]. Hypertensive disorders affect 1 in 10 pregnancies. Preeclampsia – the most severe manifestation of hypertensive disorders in pregnancy – remains to be the major cause of maternal and neonatal morbidity and mortality. Extensive research conducted by the Fetal Medicine Foundation revealed that combination of maternal characteristic and biophysical as well as biochemical tests in the first trimester may identify 90% of pregnancies that will develop preeclampsia before 34 weeks of gestation [1, 6].

The screening process involves the analysis of maternal characteristics, measurements of maternal mean arterial pressure, uterine artery pulsatility index, and placental growth factor (PlGF) concentration in maternal serum. PlGF is expressed at high levels by trophoblast cells in the placenta. Low levels of PlGF in the first trimester are associated with higher risk of preeclampsia in later gestation [7-11]. Roberge et al., in their meta-analysis proved that early administration of low-dose aspirin reduces the risk of preeclampsia [12]. Low-dose aspirin initiated at or before 16 weeks reduces the risk of severe preeclampsia in later stages of pregnancy. Therefore, screening for preeclampsia in the first trimester has a significant clinical value as it decreases maternal and neonatal mortality. The clinical value of PlGF and UtA Doppler ultrasound imaging is based on the reference range. The aim of the study was to obtain reference ranges for the Polish population.

Methods

A prospective study was carried out in a group of pregnant women during a routine ultrasound scan at 11–13^{+6} weeks of gestation at the First Department of Obstetrics and Gynecology, Medical University of Warsaw, and Department of Reproduction and Gynecological Endocrinology, Medical University of

Bialystok. Multiple pregnancy, major fetal anomalies or abnormal karyotype constituted the exclusion criteria. The Local Ethics Committee approved the study and all patients signed an informed consent form. Maternal weight and height were measured on the day of the scan. All patients completed a questionnaire about maternal age, racial origin (Caucasian, African, Asian or mixed), method of conception (spontaneous or assisted reproduction techniques), smoking, and parity. Blood samples for beta HCG, PAPP-A and PlGF were taken on the day of the scan. All biochemical markers were evaluated using automated machines that provide reproducible results (Delfia Xpress® System by Perkin Elmer Life). Arterial pressure measured was measured in all study participants (Microlife BP 3BTO-A) and mean arterial pressure was calculated (MAP). Integrated first-trimester screening based on the Fetal Medicine Foundation Guidelines was performed. All scans were performed transabdominally with ALOKA 10. Pulsed Doppler technique was used to evaluate uterine artery PI. The measurements were performed from the ascending branch of the uterine arteries. First, a sagittal section of the uterus was obtained and the cervical canal was visualized. Ultrasound transducer was gently tilted from side to side and color flow mapping was used to identify each uterine artery. Pulsed wave Doppler was used with the gate set at 2 mm and the insonation angle was less than 30 degrees. Three consecutive uterine artery waveforms were used to calculate the pulsatility index (PI). The measurements were taken in accordance with the Fetal Medicine Foundation Guidelines [3]. Nuchal translucency, nasal bone, ductus venosus blood flow and tricuspid regurgitation were assessed. All ultrasound and Doppler studies were carried out by sonographers who had received the appropriate Certificate of Competence in 11^{+0} to 13^{+6} weeks scan and Doppler of The Fetal Medicine Foundation (www.fetalmedicine.com). Biochemical markers results and patient demographic data were recorded in computer database. The patients were informed about their adjusted individual risk for trisomy 21, 18 and 13 and those with high risk were offered invasive testing for fetal karyotyping. Data on pregnancy outcome were collected from the hospital maternity records or directly from the patients.

Multiple regression analysis was used for describing correlation factors which have an effect on logarithmic-transformed UtA PI and PlGF variables. Mann-Whitney test was used to determine the significance of differences in the median MoM between the affected and unaffected groups. Data were calculated using STATISTICA (v.10).

Results

A total of 620 singleton pregnancies were examined during the study period, i.e. from June 2011 to June 2013. Forty-three patients were excluded due to miscarriages (n=6) or because it was impossible to collect information about the pregnancy outcome (n=37). Among 577 analyzed patients, there were 60 (10.4%) cases with abnormal placentation disorders – 20 with the hypertensive disorders and 40 with intrauterine growth retardation (IUGR). The patients were subdivided into two groups depending on the pregnancy outcome: unaffected (n=517) and affected (n=60). Patient demographics are presented in Table I. Statistical analyses for PlGF concentration and UtA PI were performed in both, the unaffected and affected groups. The distribution of both markers was made Gaussian after a logarithmic transformation.

Table I. Characteristics of the studied groups.

	Unaffected (n=517)	Affected (n=60)
Mean maternal age (years)	28 ± 4	28 ± 4
BMI	23.1 ± 3.67	24.5 ± 4.59
Parity: Nulliparous	292 (56,5%)	24 (40%)
Conception: IVF	18 (3.5%)	1 (1.7%)
Smokers	39 (7.5%)	7 (11.7%)
MAP	89 ± 7.1	91.9 ± 7.8

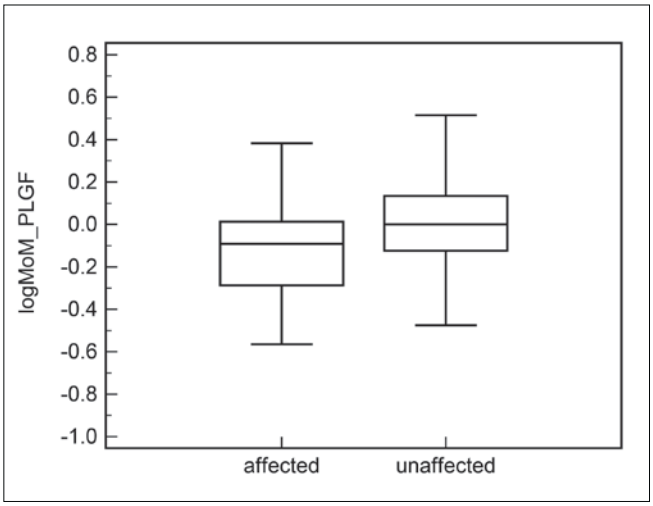

Figure 1. Distribution of log PlGF concentration expressed as multiples of the median in the affected and unaffected groups.

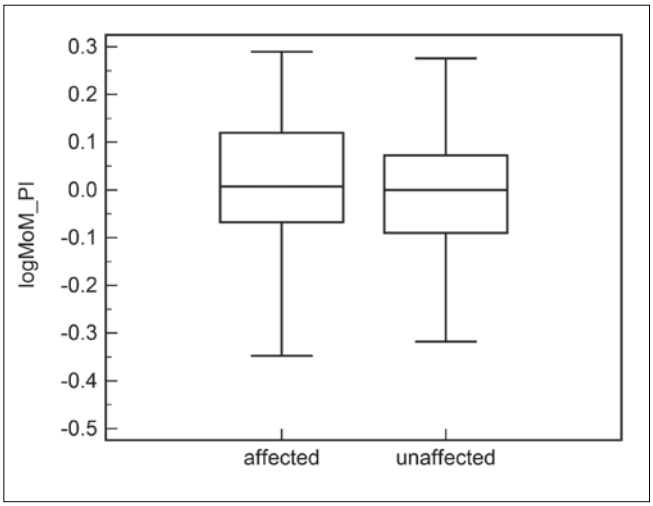

Figure 2. Distribution of log uterine artery pulsatility index expressed as multiples of the median in the affected and unaffected groups.

Multiple regression analyses of log-transformed values were carried out to determine maternal and pregnancy characteristics that provide a significant contribution to the measured concentration of PlGF. Maternal serum PlGF concentration was

Table II. Multiple regression for PlGF with maternal characteristics and gestation in the unaffected group.

Variable	Coefficient	Std. Error	r	t	p
BMI	-0.0005475	0.001012	-0.03009	-0.541	0.5889
CRL	0.006040	0.001248	0.2600	4.840	<0.0001
Smoking	0.08941	0.03336	0.1475	2.680	0.0077

BMI – body mass index; CRL – crown-rump length

Table III. Multiple regression for mean uterine pulsatility index with maternal characteristics and gestation in the unaffected group.

Variable	Coefficient	Std. Error	r	t	p
BMI	0.0007578	0.0006620	0.05665	1.145	0.2530
CRL	-0.001687	0.0007187	-0.1156	-2.348	0.0194
Smoking	0.03528	0.02281	0.07644	1.547	0.1227

BMI – body mass index; CRL – crown-rump length

Table IV. Median, MoM, mean, standard deviation, 95% Confidence Interval for PLGF between 11-13^{+6} weeks weeks in the unaffected group .

CRL (mm)	45.0 – 55.9	56.0 – 65.9	66.0 – 75.9	76.0 – 84.0
n	114	243	129	31
Median **Median MoM**	23.17 0.90	24.83 0.96	28.63 1.11	34.55 1.34
Mean **SD** **95% Confidence Interval**	24.39 9.55 22.30-26.47	26.66 10.69 25.16-28.16	32.08 13.52 29.54-34.62	40.14 25.47 29.39-50.90

Table V. Median, Multiple of Median (MoM), mean, standard deviation (SD), 95% Confidence Interval for mean uterine PI between 11-13^{+6} weeks weeks in the unaffected group.

CRL (mm)	45.0 – 55.9	56.0 – 65.9	66.0 – 75.9	76.0 – 84.0
n	114	243	129	31
Median **Median MoM**	1.80 1.04	1.75 1.01	1.65 0.95	1.63 0.94
Mean **SD** **95% Confidence Interval**	1.84 0.48 1.74 – 1.93	1.78 0.45 1.72 – 1.84	1.74 0.48 1.65 – 1.83	1.67 0.60 1.44 – 1.90

independent of maternal age and weight, parity, in vitro fertilization or mean arterial pressure (MAP), but it was increased in smokers (Table II). In the multiple regression model for log uterine artery PI in the unaffected group, UtA PI was not dependent on any of the maternal characteristics, including BMI (Table III). Both analyzed parameters were related to CRL (crown rump length) measurement. Thus, the unaffected group was subdivided into four sets based on the CRL values: 45mm – 55.9mm (n=114), 56mm – 65.9mm (n=243), 66 mm – 75.9mm (n=129), and 76mm – 84mm (n=31). The median values for PlGF and UtA PI were obtained for each set (Tables IV-V). Subsequently, each measured value in the unaffected and affected pregnancies was expressed as a *MoM (multiple of median)* after adjustment for smoking status and CRL. Median PlGF MoM was decreased in pregnancies complicated by hypertensive disorders and IUGR as compared to the unaffected group (logMoM PlGF affected group=0.0016, logMoM unaffected group=-0.1179; p=0.000024) (Figure 1). Based on statistical analysis, there were no statistically significant differences in the UtA PI MoM between normal pregnancy and impaired placentation groups (Figure 2).

Discussion

To the best of our knowledge, our study has been the first to describe reference ranges for UtA Pulsatility Index and PlGF concentration in the Polish population. It presents new mean UtA-PI charts derived from 517 women between 11–13^{+6} weeks of gestation. Both, PlGF concentration and uterine artery pulsatility indices were described by the Fetal Medicine Foundation based

on a study conducted in a large group of women of various ethnic origins. In turn, our study describes reference ranges of PlGF and UtA PI in a group consisting only of Caucasian women and confirms that concentration of both, UtA PI and PlGF is CRL-dependent. As a result, MoM values for different CRL were established for the Polish population. Our study did not confirm the previously described relation between maternal BMI and PlGF, but the concentration of PlGF was significantly increased in smokers. Pandya et al., showed that PlGF concentration decreases with maternal weight, IVF conception, pre-existing diabetes mellitus and in nulliparous women, but increases in smokers, whereas UtA PI was not statistically significantly correlated with maternal age, BMI, method of conception (spontaneous or assisted reproduction techniques), smoking, or parity. The absence of a relation between maternal BMI and UtA PI in our study group is consistent with findings of Alves et al. [13] On the other hand, data published by the Nicolaides team demonstrated UtA PI to decrease with maternal BMI. PlGF is implicated in angiogenesis and trophoblastic invasion of the maternal spiral arteries. [14] Maternal serum PlGF concentration is reduced in pregnancies with impaired placentation, resulting in preeclampsia later in gestation. It is also decreased in pregnancies with small for gestational age infants. Inclusion of the PlGF marker to the combined test (nuchal translucency, PAPP-A and free beta HCG) significantly decreases the false positive rate [15, 16], thus reducing the number of unnecessary invasive procedures and fetal loss. Placental Growth Factor (PlGF) has also been shown to be the most discriminating biochemical marker for preeclampsia [6]. Preeclampsia is responsible for the majority of maternal and neonatal deaths. A recent meta-analysis has shown that the initiation of low-dose aspirin prophylaxis at or before 16 weeks gestation resulted in over 50% reduction of early onset preeclampsia [12]. First-trimester screening for preeclampsia with MAP (mean arterial pressure), UtA PI and PlGF is possible and has a major clinical value. Nowadays, much emphasis is put on early screening for chromosomal abnormalities such as trisomy 21, 18 and 13. Also, a new screening tool, which assesses the risk for those trisomies based on cell free fetal DNA in maternal serum, has been created. This new non-invasive prenatal screening test (NIPT) has the detection rate of >99% for trisomy 21, with false positive rate of <0.1% [17, 18]. Based on the prevalence of the most frequent trisomies and preeclampsia, it seems reasonable to increase screening efforts towards preeclampsia in early gestation. One of the most important arguments supporting this idea is the possibility of prophylaxis with low-dose aspirin treatment in patients with high-risk of preeclampsia. Screening for preeclampsia by means of maternal history may detect only about 30% of women who will develop PET for a false positive rate of 10% [19]. The predicted detection rate of preeclampsia requiring delivery before 34 weeks is 82% [20]. A more effective screening method is provided by the evaluation of uterine artery pulsatility index combined with patient medical history, mean arterial pressure and demographic data, with detection up to 90% for a false positive rate of 10%. In our study, the median PlGF MoM was decreased in pregnancies complicated by hypertensive disorders and IUGR as compared to the unaffected group. On the other hand, there was no significant difference in the UtA PI MoM between normal pregnancy and impaired placentation groups. Thus, the predictive value of those results in the affected group is difficult to determine due to a relatively small sample size. Our study has been the first to determine reference values for uterine artery pulsatility index and placental growth factor in a homogenous group of Polish pregnant women.

Conclusion

The established reference ranges for uterine artery pulsatility index and PlGF at 11–13^{+6} weeks in unaffected pregnancies need further evaluation in predicting placenta-associated diseases in early-stage pregnancy in the Polish population.

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