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Assessing the Median Serum Placental Growth Factor (PlGF) Levels in the First Trimester of Pregnancy Regarding Gestational Age and Maternal Influencing Factors from a Prospective Observational Trial

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objective: To investigate the association of risk factors, including ethnicity, maternal weight, smoking status, and assisted reproduction technology, with serum placental growth factor (PlGF) levels in the early first trimester of pregnancy.

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Methods: This was a multicenter observational study involving pregnant females in the first trimester between 11+0 and 13+6 weeks of gestation. Serum PlGF concentrations were analyzed in relation to ethnicity, maternal weight, smoking status, and conception through assisted reproduction technology.
Results: A total of 376 patients were included in the study and had their serum PlGF levels measured. The results showed that the serum PlGF level was 4.3% higher in the Asian group compared to the Caucasian group. Smokers had 1.78 times higher levels of serum PlGF compared to non-smokers. Assisted reproduction technology had no impact on levels of serum PlGF compared to spontaneous pregnancies. There was a negative correlation between serum PlGF levels and maternal weight, but is was statistically insignificant.
Conclusion: Maternal weight was negatively correlated with serum PlGF levels, even this association was statistically not significant. High serum PlGF levels were observed in smokers and in non-Caucasians. Further research is needed to establish a concrete analysis of these findings.

Keywords: Maternal impact factors; serum placental growth factor (PlGF); median values.

1. INTRODUCTION

Currently, pre-eclampsia (PE) is a significant risk factor during pregnancy, with an occurrence rate of 3-5% [1-8] and is associated with increased morbidity, including low birth weight [2,9], and HELLP syndrome [10,11], as well as mortality [1-5,12]. PE is a pregnancy-related hypertensive disorder that can occur during the second half of pregnancy and is characterized by high blood pressure and proteinuria [2,9]. It is divided into an early-onset and late-onset form, occurring between 20-34 weeks and after 34 weeks of pregnancy, respectively [3,12]. PE is defined as a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg [2,9] which firstly occurs after week 20 of pregnancy and is accompanied by proteinuria protein ≥ 3g / 24 hours [2,9].

There are several known risks factors for PE [1,2,7], including antiphospholipid-syndrome (relative risk 9.72), diabetes mellitus (relative risk 3.56), twin pregnancy (relative risk 2.93), nulliparity (relative risk 2.91), positive family history (relative risk 2.90), high BMI (relative risk 2.47), advanced maternal age (relative risk 1.96) and a history of PE in previous pregnancies (relative risk 7.19) [13].

Several markers have been proposed as potential predictors of PE [14,15]. The most commonly used is Doppler sonography of the uterine artery [1,16,17], but biochemical parameters such as free beta hCG, PAPP-A, PP-13, sFlt-1, P-selectin, NGAL, and Placenta Growth Factor (PIGF) have also been studied [1,2,11,18-20]. Out of these laboratory parameters, PIGF has shown most promising as a predictor of PE, particularly when used in combination with sFlt-1 in the second trimester [21,22], or as a single parameter in the first trimester of pregnancy [1-3].

PlGF is a member of the vascular endothelial factor family and is produced by the trophoblast cells in the placenta [1]. In normal pregnancies, PIGF concentration increases throughout pregnancy [1,2] and is influenced by a number of maternal factors, such as age, body weight, assisted reproduction technology (ART), racial origin, cigarette smoking, caffeine intake [1,2,6], or diabetes mellitus Type 1 and Type 2 [2]. However, in cases of pathological conditions such as fetal aneuploidy and/or impaired placentation, PIGF concentrations may be reduced, leading to increased risk of PE, HELLP syndrome, or small for gestational age (SGA) [2,11]. Conversely, higher levels of PIGF are associated with reduced risk of PE and SGA [9,23].

1.1 Aim

The Brahms/Kryptor is a novel analysis technique that allows for the measurement of PlGF serum concentration in the first trimester, between 11+0 and 13+6 weeks of pregnancy. In order to establish a screening test for PE based on very early PlGF serum concentration, it is necessary to compare measured concentrations to standard values. However, currently, only unpublished data are available in this regard. The aim of this study is to determine the median PlGF serum concentration values according to pregnancy age between 11+0 and 13+6 weeks and to examine the influence of various factors on these values.

2. MATERIALS AND METHODS

This is a prospective multicenter observational study of pregnant women in the first trimester, conducted at two clinics in Germany: Women's Practice Bahnhofstrasse in Wolfenbüttel and MVZ Dr. Markus Luetge in Salzgitter. The study took place between September 2018 and December 2020 and is registered in the German Clinical Trials Registry (DRKS00014630).

Approval from local ethics boards were obtained and all enrolled patients provided written informed consent. The study population consisted of pregnant women who visited these clinics for routine monitoring and were between 11+0 to 13+6 weeks of pregnancy. Blood samples were taken once per patient to retrieve the PlGF serum concentration.

Patients with pre-existing hypertension, those taking acetylsalicylic acid, or those pregnant with multiple births were excluded from participation.

Patients who did not meet the required time window in pregnancy, had miscarriages, or had incomplete data sets were also excluded from analysis.

In total, 432 cases were recruited for this prospective study. After excluding cases with missing data, such as those with missing smoking status (n=1), no status on ART (n=3), no maternal weight status (n=6), no PIGF status (n=13), missing pregnancy week (n=1), no delivery weight status, or those who had an abortion or miscarriage (n=32), 376 cases remained for further analysis.

The study population's serum PlGF values were analyzed according to maternal weight, smoking status (yes or no), method of conception (spontaneous /assisted reproduction) and ethnic origin (Caucasian, Afro-Caribbean, Asian and Oriental).

Age depending median values were computed using various computed regression analysis methods, including linear, exponential, logarithmic, polynomial, potential, and hyperbolic regression analysis, with the use of the the Regression App for Mac (by Kevin Silmore v1.1) and OpenOffice software package (The Apache Software Foundation, v4.1.9).

To compare the measured PlGF values in relation to unpublished data from the test kit manufacturer (Brahms/Kryptor, Thermo-Fisher Scientific, Heringsdorf, Germany), a Student´s t-test for connected samples was performed using JASP, (JASP team, Amsterdam, v0.8.1.1).

Additionally, the PlGF concentrations were transformed from raw data to multiples of median (MoM) according to the previously calculated gestational age-dependent reference values.

The PlGF-MoMs were compared between different ethnic origins (Caucasian vs. Oriental, Caucasian vs. Asian, Caucasian vs. Afro-Caribbean), smokers vs. non-smokers, and assisted reproduction technique (ART) vs. non-ART. After confirming the existence of a normal distribution using the Kolmogorov-Smirnov test, consistency among samples was checked using the Student´s t-test for unconnected samples (WinSTAT, R. Fitch Software, v 2005.1). Statistical significance was assumed for a p-value <0.05.

As maternal weight is a metric scale factor, the correlation between maternal weight and PlGF concentration was analyzed using the Pearson correlation coefficient and a regression analysis (WinSTAT, R. Fitch Software, v 2005.1) after normal distribution was demonstrated again by the Kolmogorov-Smirnov test.

3. RESULTS

When comparing our data to the values considered as normal and provided by the manufacturer, we found a significant correlation between the data sets, with $p<0.001$.

The mean PlGF serum concentration in correlation to pregnancy age was given as f(x)=(9.3328019641 • X) -77.6187630387 (R^2=0.1265, refer to Fig. 1). The numeric median values according to gestational age are listed in Table 1. Other regression analyses using logarithmic (R^2=0.1246), exponential (R^2=0.1238), logarithmic (R^2=0.1240), power (R^2=0.1221), and hyperbolic (R^2=0.1221) regression yielded in worser R-values or were not computable (potential, differend types of hyperbolic regression).

In our study group 26 cases belonged to the Oriental ethnic origin, 3 cases to the Asian ethnic origin, and 3 cases to the Afro-Caribbean ethnic origin. We observed that in the Oriental population, the serum PlGF was 4.34% higher (p=0.63) and in the Asian group, the serum PlGF

values were 29.91% higher than in the Caucasians. Afro-Caribbean women had 26.01% higher PlGF levels (p=0.32) compared to Caucasian women.

Sixteen cases were smokers, who had 1.78-fold higher levels of PIGF (p=0.0003).

Thirteen cases had ART. No differences could be detected between both groups.

The weight range of the study population was between 52.3 kg and 118 kg, with an average weight of 74.6 kg. We found a small but measurable impact of maternal weight on PlGF levels, as demonstrated by a Pearson correlation of r = -0.01 (R^2 = 0.0009) for the regression formula f(x)=x / (6.908462154 + 0.979081743 · x).

The correction factors are listed in Tables 2 and 3.

Table 1. Median PlGF value in pg/ml depending on the week of pregnancy. Double standard deviation in brackets

Gestational age (week + day)	Median PlGF concentration [pg/ml] (-2 std. dev / +2 std. dev)
11+0	25.042 (13.825 – 36.259)
11+1	26.375 (15.158 – 37.592)
11+2	27.709 (16.492 – 38.925)
11+3	29.042 (17.825 – 40.259)
11+4	30.375 (19.158 – 41.592)
11+5	31.708 (20.492 – 42.925)
11+6	33.042 (21.825 – 44.258)
12+0	34.375 (23.158 – 45.592)
12+1	35.708 (24.491 – 46.925)
12+2	37.041 (25.825 – 48.258)
12+3	38.375 (27.158 – 49.591)
12+4	39.708 (28.491 – 50.925)
12+5	41.041 (29.824 – 52.258)
12+6	42.374 (31.158 – 53.591)
13+0	43.708 (32.491 – 54.924)
13+1	45.041 (33.824 – 56.258)
13+2	46.374 (35.157 – 57.591)
13+3	47.707 (36.491 – 58.924)
13+4	49.041 (37.824 – 60.258)
13+5	50.374 (39.157 – 61.591)
13+6	51.707 (40.490 – 62.924)

Table 2. Comparison of the PlGF medians regarding influencing factors with indication of the level of significance

	Average MoM group 1	Average MoM group 2	Factor	p
Smoker/ non-smoker	2.04 (n=16)	1.14 (n=398)	1.78	<0.0001
Asian/Caucasian	1.47 (n=3)	1.13 (n=350)	1.3	0.25
Oriental/ Caucasian	1.18 (n=26)	1.13 (n=350)	1.04	0.63
Afro-Caribbean/ Caucasian	1.43 (n=3)	1.13 (n=350)	1.26	0.32
ART/non-ART	0.99 (n=13)	1.18 (n=398)	0.83	0.20

Table 3. Specification of the correction factor for the maternal weight with the zero point for the correction being 74.1 kg (1.0 average correction factor)

Maternal weight [kg]	Regressionanalysis	Correction factor
50	0.895	1.042
60	0.914	1.020
70	0.928	1.005
74.12 *	0.933	1.000
80	0.939	0.994
90	0.947	0.985
100	0.954	0.978
110	0.960	0.972
120	0.967	0.967
130	0.963	0.963

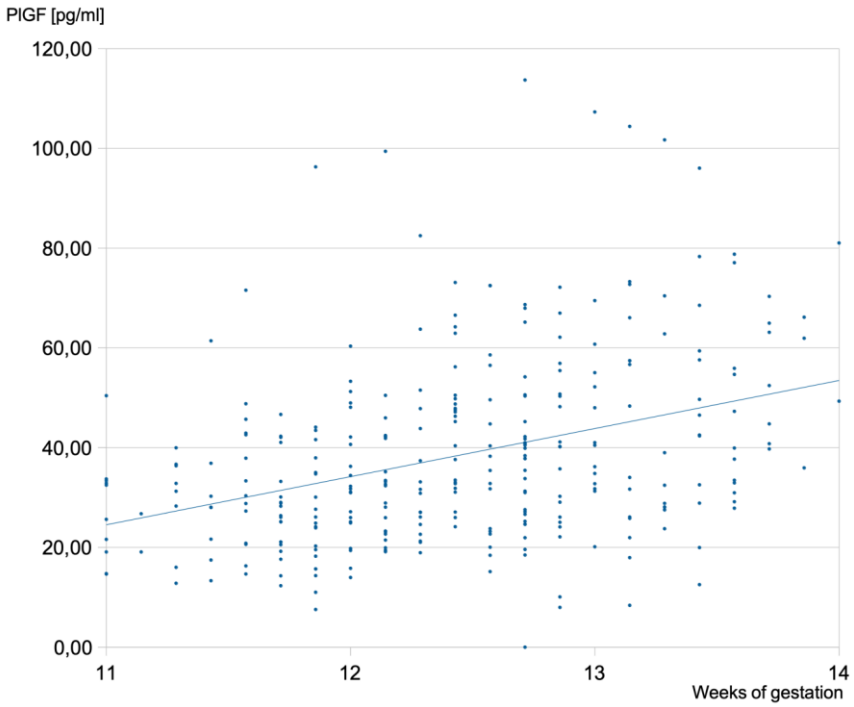

Fig. 1. PGIF levels in ng/dl according to maternal gestational age in weeks, compared with median values from Brams/Kryptor

4. DISCUSSION

Our values were consistent with those of the test kit manufacturer.

We also observed an linear increase in serum PlGF levels with advancing gestational age between 11+0 and 13+6 weeks, which is in line with published data [1,2].

Kasdaglis et al. did not find a significant correlation between serum PlGF values and ethnical origin [1], unlike previous studies, that have shown higher levels in certain ethnic groups [2].

In our study population, subjects of African-Caribbean, Asian, and Oriental origin made up 8.8% of the total study population and had higher PlGF levels, similar to the findings of Tsiakkas et al. [2]. Furthermore, we found that non-Caucasian ethnic groups had higher levels of PlGF than Caucasians; however, these results were not statistically significant due to the small sample size.

Additionally, we found that smokers had a 1.78-fold higher PlGF serum concentration compared to non-smokers, in line with previous studies [2,6,24].

We also found that assisted reproduction had no statistically significant impact on PlGF values similar to the findings of Coté [18].

Furthermore, we found a slightly negative correlation between BMI and PIGF levels, in line with previous studies [1,2,7].

5. CONCLUSION

Overall, our study found that several factors, including ethnic origin, nicotine consumption, and maternal weight were related to PGlF levels, but the results were mostly not significant due to small sample sizes in these subgroups.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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