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Increased risk of low infant birth weight in pregnant women with low PAPP-A values measured in the first trimester

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ABSTRACT

Objectives: Testing pregnant women as early as in the first trimester has multiple advantages. Firstly, the first trimester screening combining ultrasound and serum marker testing (PAPP-A and free β-hCG) offers the highest currently possible — except for expensive tests using cell-free DNA biomarkers from the mother's blood (ccf DNA) — detectability of aneuploid fetuses. Secondly, nuchal translucency (NT) measurement helps determine the risk of numerous abnormalities other than aneuoploidies. Lastly, nearly complete ultrasound assessment of fetal anatomy can be performed as early as in the first trimester of pregnancy.

Material and methods: This study is based on prospective analysis. Study subjects were 236 pregnant women. One hundred thirty-one patients with a single pregnancy were qualified into the study group and had a combined ultrasound and biochemical screening for Down's syndrome performed between 11 + 0 and 13 + 6 weeks of gestation, with the measured PAPP-A value at ≤ 0.50 MoM (multiples of the median). The control group comprised 105 pregnant women with PAPP-A value at a similar stage of pregnancy at > 0.5 MoM.

Results: The average observed value of the PAPP-A in the study group was 0.35 MoM while in the control group 1.29 MoM. Moreover, combined observation of infant birth weights in both groups compared to the PAPP-A MoM values has shown a significant relationship between those characteristics (r = 0.15, p = 0.0184).

Conclusions: The results showed that pregnant women with low PAPP-A MoM value measured during the first trimester have a higher risk of giving birth to a low-birth-weight infant (which is the value below 2500 g), than the pregnant women whose PAPP-A MoM value in the first trimester did not meet this criterion.

Keywords: small-for-gestational-age infants; PAPP-A protein; β-hCG; ultrasound scan

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INTRODUCTION

Small-for-gestational-age (SGA) infants are at a higher risk of perinatal mortality and both short-term and long-term morbidity; this risk can, however, be reduced if the condition is diagnosed prior to delivery permitting strict supervision, appropriate delivery date, and immediate post-natal care [1]. Testing pregnant women as early as in the first trimester has multiple advantages. Firstly, the first trimester screening combining ultrasound and serum marker testing (PAPP-A and free ß-hCG) offers the highest currently possible — except for expensive tests using cell-free DNA biomarkers from the mother's blood (ccf DNA) — detectability of aneuploid fetuses [2]. Secondly, nuchal translucency (NT) measurement helps determine the risk of numerous abnormalities other than aneuploidies [2–4]. Lastly, nearly complete ultrasound assessment of fetal anatomy can be performed as early as in the first trimester of pregnancy [2, 3]; moreover, the first trimester ultrasound assessment includes measurement of crown-rump length which is the most reliable method of estimating the actual gestational age. It can be assumed with a high degree of probability that a correctly determined gestational age is one of key pieces of information required to manage normal and high-risk pregnancies [2]. Pregnancy-associated plasma protein A was first identified in 1974 [5]. It is currently used in most screening programs oriented at early detection

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of the Down syndrome as its low serum concentration in maternal blood has been found to be associated with trisomies 21, 18, and 13 [6, 7]. Circulating pregnancy-associated protein A is mainly derived from syncytiotrophoblast [8], and PAPP-A gene is located on human 9q33.1 chromosome. Moreover PAPP-A increases bioavailability of insulin-like growth factors (IGF I and IGF II) by fragmenting their binding proteins (IGFBP-4, -5). IGF is believed to have mitogenic and antiapoptotic effect and to be vital for cellular growth in most human tissues [9]. PAPP-A, involved in control of the insulin-like growth factor system in the first trimester of pregnancy, at low levels, seems to result in a significantly reduced activity of IGF-I and IGF-II, showing an affinity with the early placentation process and, consequently, placental growth and function [10].

PAPP-A concentration in maternal blood serum is detectable shortly following implantation, with its level growing with gestational age, doubling every 3–4 days during the first trimester. PAPP-A concentration reaches its maximum level at the final stage of pregnancy [11]. Average half-life of pregnancy-associated plasma protein A following a spontaneous childbirth is 53 ± 26 hours [12]. In addition to gestational age, PAPP-A concentration on maternal blood serum is affected by maternal and pregnancy-related characteristics [13]. Some of them, like multiparosity and smoking, are probably associated with the trophoblastic tissue mass since PAPP-A concentration increases with placental volume measured by ultrasound [13]. Other factors, such as the mother's body weight prior to pregnancy, have been correlated with distribution volume, while its association with the fetus' sex, number of previous pregnancies, ethnicity, and assisted reproduction has not found any biological explanation to date. The best documented clinical application of PAPP-A are first trimester screening programs aimed at detecting chromosomal abnormalities characterized by low PAPP-A levels. These programs are aimed at identifying pregnant women who should be offered testing cell-free DNA biomarkers from maternal blood, the so-called non-invasive prenatal test (NIPT), chorionic villus sampling (CVS), or amniocentesis. Since maternal PAPP-A level indirectly reflects placental volume and, probably, trophoblastic tissue mass, it would seem logical that low PAPP-A values are associated with reduced biometric fetal values in the first and the second trimester of pregnancy, as well as adverse pregnancy outcomes, such as IUGR and — consequently — low birth weight, spontaneous abortion, stillbirth, preeclampsia, or premature birth [3]. Clinical utility of the above-mentioned relationships has not been fully explained, however, since detection rates of adverse pregnancy outcomes are, regrettably, relatively low (8–16%) [3].

Definitions of an SGA fetus and severe SGA vary. For the purposes of this paper, we assumed that SGA would refer to a fetus with estimated weight (EFW) or abdominal circumference (AC) values below 10th percentile, while severe SGA would refer to cases with EFW or AC values under 3rd percentile [14]. IUGR indicates that the prenatally presenting pathognomic factor reduced the genetic potential of fetal growth, and fetal growth rate did not reflect gestational age. IUGR is not synonymous to SGA. Some fetuses/infants with IUGR features have low biometric measurement values compared to gestational age, while 50–70% of SGA fetuses are constitutionally smaller because their growth rate depends on the mother's body proportions and ethnicity [15]. Structurally normal SGA fetuses have a higher risk of perinatal complications and deaths, but the most adverse health outcomes apply to IUGR-burdened fetuses with adverse implications for further mental and physical development of such infants [1]. Methods used to assess the risk of SGA fetus development in the first and second trimesters of pregnancy include: general medical and obstetrical history, obstetrical examination, screening for the first trimester Down syndrome markers in maternal blood, and evaluation of uterine arterial flow, and the risk of preeclampsia. SGA detection methods in the second and third trimester of pregnancy allowing an accurate diagnosis include serial ultrasound measurements of fetal AC and assessment of estimated fetal weight using individualized percentile norms performed every 2–3 weeks. The published average AC and EFW growth rates after 30 weeks of gestation are 10mm over 14 days and 200 g over 14 days for EFW likewise, although when the values are lower there is also a greater diversity [reflecting various methods of calculating standard deviation (SD)] [16]. It was also shown that AC value change by less than 5mm over 14 days was indicative of IUGR [17]. There is evidence that statistically best prognoses for SGA are achieved with universal ultrasound biometric screening of fetuses in the third trimester, especially around 36 weeks of gestation [18]. This is related to the fact that 85% of SGA infants with birth weight < 10 percentile are born after 37 weeks of gestation [1]. The most sensitive single biometric measurement in SGA prediction is abdominal circumference of the fetus, reflecting liver size and — thus — the stored glycogen and degree of nutrition. A systemic review of 45 studies describing a total of 70 models for EFW in various combinations of measurements of fetal head circumference (HC), biparietal diameter, femoral length (FL), and abdominal circumference (AC) [19] has showed the model devised by Hadlock et al. [20] to be the most accurate, including measurements of HC, AC, and FL; EFW measured within two days of birth was within 10% of birth weight in 80% of cases.

A lower volume of amniotic fluid may be another one of first signs of IUGR in ultrasound scans. Clinically significant oligohydramnios (*i.e.*, AFI < 5 cm or the largest single fluid

pocket < 2 cm) has a positive predictive value of 86% for IUGR. Bottom threshold values of AFI (5–10cm) were shown to be correlated with a 4-fold increased incidence of fetal growth restriction [21].

Objectives

This study aimed to evaluate the risk of placental dysfunction expressed with intrauterine fetal growth inhibition and low birth weight of the infant related to low PAPP-A levels found in a double test from maternal blood.

MATERIAL AND METHODS

General characteristics

This study is based on prospective analysis which was approved by the Ethics Committee — Medical University of Warsaw (Number AKBE/89/13). Ultrasound scans were performed by physicians holding Certificates of Competence issued by the Fetal Medicine Foundation (FMF) for testing between 11 and 13 + 6 weeks of gestation. Procedures used during this study were performed in accordance with the criteria defined by the Fetal Medicine Foundation (FMF).

Study group

All the patients consented in writing to being included in the study. Pregnant women who did not consent and/or had an abnormal fetal karyotype diagnosed were excluded from the study. Information on gestational week of delivery and birth weight were obtained during phone call interviews with the mothers.

The study included 236 pregnant women who in the years 2010–2012 were under perinatal care at NZOZ ARS Medical Specialist Medical Services Centre in Poznan or at the Division of Gynecological Surgery at Poznan University of Medical Sciences. In this research project, data from combined ultrasound and biochemical screening for Down syndrome in the first trimester of pregnancy were used. Abnormal fetal karyotype was an exclusion criterion for the study. In continuation of the research process, the patients were divided into two groups: study group and control group. One hundred thirty-one patients with a single pregnancy were qualified into the study group, and had a combined ultrasound and biochemical screening for Down's syndrome performed between 11 + 0 and 13 + 6 weeks of gestation, with the measured PAPP-A value at ≤ 0.50 MoM (multiples of the median). The control group comprised 105 pregnant women with PAPP-A value measured between 11 + 0 and 13 + 6 weeks of gestation at > 0.5 MoM. In continuation of the research process, descriptive statistics of the study material analyzed gestational week of delivery and infant birth weight. Then, the relationship between maternal serum PAPP-A values measured and the above-mentioned characteristics was evaluated. To evaluate the effect of low PAPP-A values on intrauterine fetal growth and infant birth weight, the population of the study and control groups infants born were divided into two groups: low birth weight (LBW) < 2500 g and birth weight of > 2500 g.

Testing PAPP-A and β-hcg serum levels

Blood for measurement of PAPP-A and β-hCG serum levels in the first trimester of pregnancy was sampled from the patients' antecubital veins. The next step involved measurement of the levels of the analyzed biochemical parameters using DELFIA® Xpress system with PAPP-A and β-hCG measurement kits. The kit has been approved and recommended by the Fetal Medicine Foundation. The measured PAPP-A concentration values were archived in an electronic database created for the purposes of this research project. PAPP-A levels in maternal blood serum were expressed as multiples of the median (MoM) for gestational age, as is conventional for biochemical variables varying depending on gestational week [22]. Individual risk of giving birth to an infant with a chromosomal aberration was calculated using ASTRAIA calculating program, having considered the initial risk associated with the mother's age and gestational age calculated using the date of last menstruation and corrected using crown-rump length (CRL), nuchal translucency (NT), PAPP-A MoM, and β-hCG MoM values.

Statistical analysis

Data from the interval scale were analyzed using Student's t-test. Distribution normality evaluation was performed using the Kolmogorov-Smirnov normality test, and the hypothesis of homogenous variance was validated using Fisher-Snedecor test. Should the data distribution be other than normal or when the data derived from the ordinal scale, they would be analyzed using the Mann-Whitney non-parametric test. Comparisons of more groups at the same time were made using the Kruskal-Wallis test. Where significant differences had been found, the Dunn post-hoc tests were used to identify homogenous groups. The relationship between the parameters was analyzed using Spearman's correlation coefficient. Data from the nominal scale were analyzed using the chi-square test. Statistica 10 PL (StatSoft) software was used to perform statistical analysis. The tests were considered statistically significant at $p < 0.05$.

RESULTS

Descriptive statistics for the PAPP-A parameter

Analysis of the PAPP-A values measured and expressed in MoM values in the study and control groups has shown that the average values of this parameter in both groups are respectively 0.35 MoM, and 1.29 MoM (Tab. 1, Fig. 1).

Table 1. Descriptive statistics of the PAPP-A parameter in prospective analysis

Variable	N valid	Mean	SD
Study group			
PAPP-A [MoM]	131	0.352911	0.103403
Control group			
PAPP-A [MoM]	105	1.285000	1.282284

SD — standard deviation

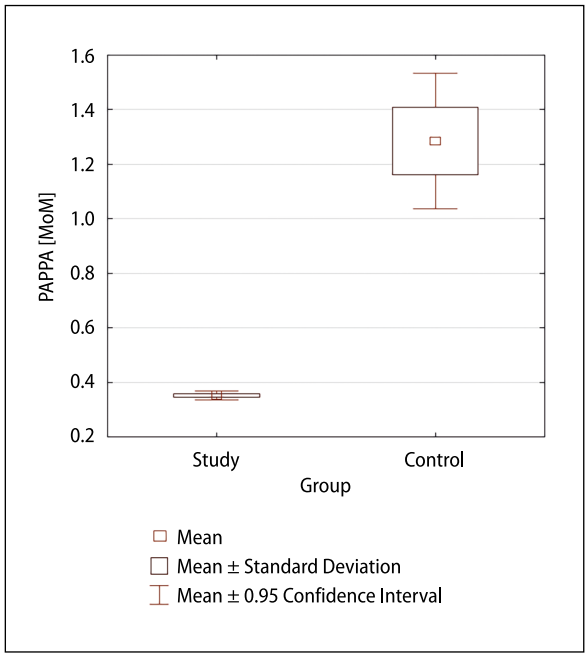

Figure 1. Average and 95% confidence intervals for PAPP-A values in the study and control groups

Relationship between infant birth weight and PAPP-A values measured in blood serum of pregnant women

The correlation between infant birth weights in the study and control groups combined and the measured PAPP-A MoM values were observed ($r = 0.15$, $p = 0.0184$) (Fig. 2).

To evaluate the effect of low PAPP-A values on intrauterine fetal growth and infant birth weight, the population of the study and control groups infants born were divided into two groups: low birth weight (LBW) < 2500 g and birth weight of > 2500 g. There were 10 infants with low birth weight in the study group, while only two such cases were observed in the control group (Fig. 2). Analysis of the correlation between the study groups and the birth weight (< 2500g and ≥ 2500g) has shown that in the group of pregnant women with low PAPP-A values (PAPP-A < 0.5 MoM), a statistically significant increase in the incidence of low infant birth weight was observed — 7.6% vs. 1.9% ($p = 0.0465$) (Fig. 2).

It was found that pregnant women with a low level of PAPP-A MoM value measured between weeks 11 and 13 + 6 have a statistically significantly higher risk of giving birth to a low birth weight infant than the pregnant women whose PAPP-A MoM value measured in that period did not meet this criterion (Fig. 3).

DISCUSSION

Low birth weight is a major cause of infant morbidity and mortality, and intrauterine growth restriction (IUGR) may be a late manifestation of early placental growth disorders [23]. This study has shown that low PAPP-A levels found in an integrated double test have a predictive value for identifying fetuses at risk of intrauterine fetal growth inhibition expressed as an increased risk of low-birth-weight infant. The first references indicating the relationship between low levels of proteins produced by the placenta and pregnancy abnormalities in the form of disturbed fetal growth were published in 1984 by Westergaard et al. [24] and Pledger et al. [25].

Evaluation of material in prospective analysis comprising 236 observations (study group n = 131, control group n = 105) has shown a statistically significant correlation between infant birth weights the measured PAPP-A values ($r = 0.15$, $p = 0.0184$) (Fig. 2). Lower PAPP-A value was correlated with lower infant birth weight value. PAPP-A value < 0.5 MoM in maternal serum was the study group inclusion criterion. Average value of this parameter in the study group was 0.35 MoM, and 1.29 MoM in the control group (Tab. 1, Fig. 1). Division of infants into those with birth weight < 2500 g and those with birth weight ≥ 2500g has shown that low PAPP-A levels found in an integrated double test have a predictive value for identifying fetuses at risk. There were 10 cases of infants with low birth weight in the study group, while in the control group, there were only two such cases (Fig. 3). Relationship analysis has shown that in the group of pregnant women with low PAPP-A level values, 7.6% of infants were born with birth weight > 2500 g, compared to only 1.9% in the control group ($p = 0.0465$) (Fig. 3)

The relationship presented above is analogous to other studies and observations [26]. The quoted experiment involved a prospective clinical trial with 8347 pregnant female subjects. It evaluated the relationship between pregnancy-associated plasma protein A (PAPP-A) in maternal serum in the first trimester of pregnancy and an increased risk of intrauterine growth restriction measured using biometric parameters assessed in ultrasound scan between the first and the second trimester of pregnancy. In addition to this, Salvig et al. [26] found PAPP-A values under 0.30 MoM to be associated with a nearly two times greater risk of reduced fetal growth rate below the 10th percentile than higher PAPP-A values. This study also found that extremely low PAPP-A levels are not only associated with low birth weight but also with a slower

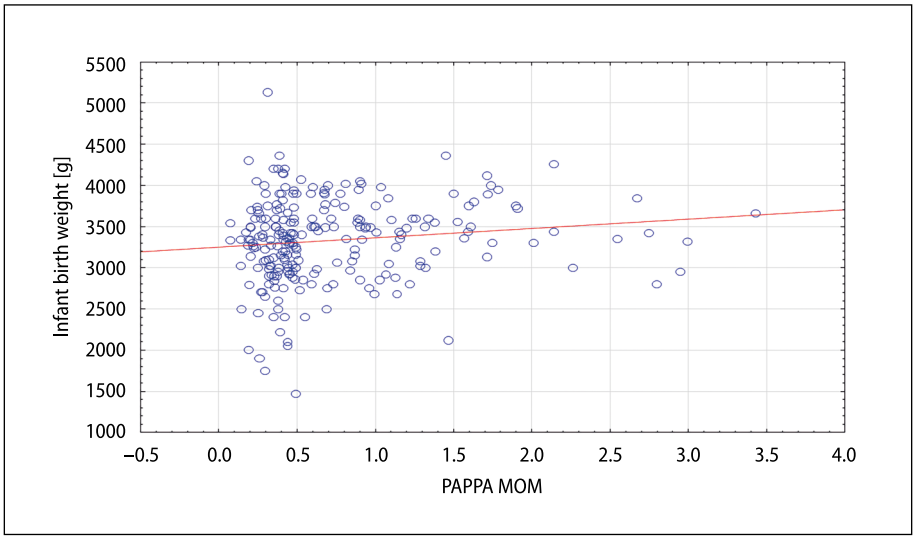

Figure 2. Relationship between infant birth weight in the study and control groups combined and the PAPP-A MoM values measured (p = 0.0184)

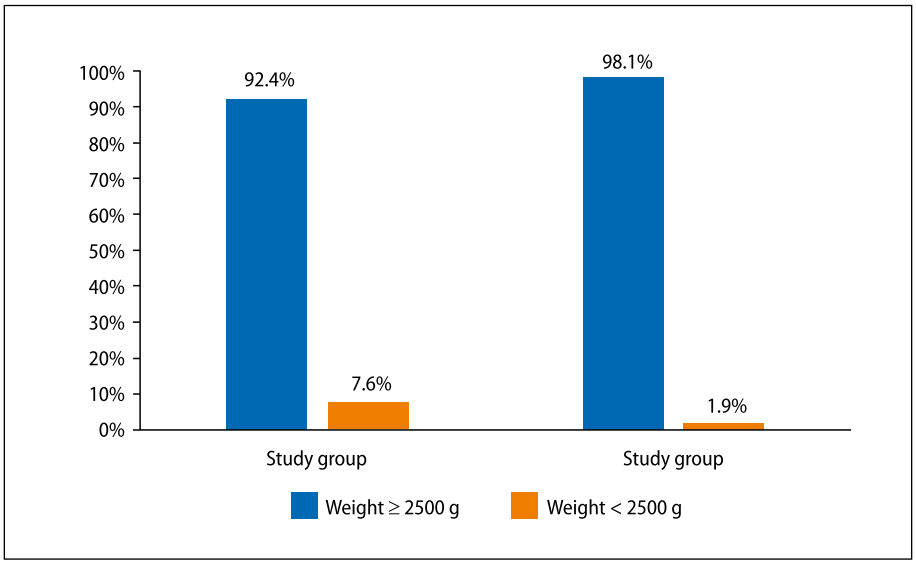

Figure 3. Incidence of low infant birth weight in the study and control groups (p = 0.0465)

fetal growth rate prior to 20 weeks of gestation. Moreover, these researchers found high PAPP-A values (≥ 3.0 MoM) to be associated with fetal growth rate above the 90th percentile. Other available references indicate that taking into consideration both the results of fetal size assessment at 18–20 weeks of gestation or its growth between 11–14 and 18–20 weeks of gestation, as well as the results of testing for first trimester placental function markers in maternal serum improves prognostic value for small-for-gestational age (SGA) fetuses [27]. Another study of a series of cases involving a large number (49,801) women in 11 + 0 to 13 + 6 weeks of gestation found that low PAPP-A values also showed a reversely proportional association with the risk of SGA fetal growth. [28]. Other authors have also shown low PAPP-A levels to be associated with low birth weight or SGA [27–29]. According to Smith GC et al. [30], checks of insulin-like growth factor (IGF) system, directly affected by PAPP-A in the first and early in the second trimester of pregnancy, may have a vital role in determination of further course of the pregnancy. In the analysis by Scott et al. [31], the risk of fetal growth disorders with PAPP-A MoM values < 0.2 was twice as high as in the general population. According to Krantz et al. [32], PAPP-A MoM value below the 1st percentile was associated with a 24.1% incidence of SGA infants, while values below the 5th percentile with 14.1% incidence of SGA infants in that group. Peterson et al. [33] in 2008 published their study results presenting a positive correlation between PAPP-A values and infant birth weight. PAPP-A values < the 10th, 5th, and 1st percentile increased the

probability of infant being SGA by 2.0, 2.4, and 9.3 times, respectively, while PAPP-A values > the 90th percentile increased the probability of the infant having birth weight > 4500 g by 2.9 times [33]. Similar conclusions were also reached in the paper by Canini et al. [34]. PAPP-A values in the group of women who had SGA infants were significantly statistically lower, while in the group of women who had LGA infants PAPP-A values were significantly statistically higher. Interesting conclusions were put forward following data analysis by Barret et al. [35]. The risk of having a low-birth-weight infant increased by 4.1 times if PAPP-A MoM values were < 0.3, the risk of premature birth by 2.9 times, and the risk of losing the pregnancy — 5 times. These results corroborate with those previously presented by Kabili et al. [36] in 2004. Fox et al. [27] have shown in their study that PAPP-A concentration is a reliable marker of intrauterine fetal growth inhibition in the second trimester of pregnancy. They presented results of tests on 1098 pregnant women diagnosed with intrauterine growth inhibition in the second trimester of pregnancy. PAPP-A value below the 15th percentile was correlated with an increased incidence of SGA in the second trimester and a lower birth rate, premature birth, and intrauterine death of the fetus. The association between PAPP-A and early fetal growth rate is logical considering PAPP-A's biological function. Pregnancy-associated plasma protein A is of trophoblastic origin and was identified as a protease specific to insulin-like growth factor binding proteins (IGFBPs), specifically IGFBP-4 [37] and IGFBP-5 [38]. These proteins bind IGF-I and IGF-II, thus inhibiting their interaction with cell surface receptors [9]. Low concentration of PAPP-A is associated with a low concentration of bioactive insulin-like growth factors. IGF-I and IGF-II are believed to play a key role in early implantation and regulation of intrauterine fetal growth [10]. According to the available knowledge, the present paper is one of the first of such scientific reports in Poland to have found that placental biomarkers, such as PAPP-A, may affect intrauterine fetal growth rate evaluated between the first trimester of pregnancy (confirmed crown-rump length measurement) and giving birth and, subsequently, evaluation of infant birth weight. In the conducted experiment, the first trimester was confirmed using a precise measurement of crown-rump length compliant with FMF criteria which is a separate and objectively measurable parameter, thus excluding the effect of a potential late ovulation or uncertainty in estimating the date of last menstruation on the results obtained. Pregnant women were selected for the program randomly, and the adopted clinical experiment schema proved to be a reliable and universal tool for population-based studies. One of its possible limitations is that there are fetuses with retarded intrauterine growth prior to the first trimester ultrasound scan, and normal intrauterine growth afterwards. Such retardation of intrauterine growth prior to 12 weeks of gestation is, however, rare and was not an object of focus in this paper [26]. Another potential factor which might adversely affect the quality of study results presented herein is tobacco smoking by pregnant mothers. It has been proven that smoking adversely affects intrauterine fetal growth during pregnancy and contributes to low birth weight [39], and that PAPP-A in the first trimester of pregnancy is lower in smokers than in non-smokers [40]. According to other authors, however, there is a small statistically significant relationship between smoking and fetal growth rate [26]. Relationship between pregnant mother's smoking and fetal growth rate was not included in the scope of this paper and this aspect has not been studied herein.

CONCLUSIONS

This paper has proven that low PAPP-A levels found in a double test have a predictive value for identifying intrauterine fetal growth inhibition of the fetuses and associated low birth weight. Clinical utility of the presented association between low PAPP-A values measured in maternal serum in the first trimester of pregnancy and an increased risk of pregnancy complications expressed as intrauterine growth inhibition and, subsequently, an increased risk of low infant birth weight requires further research. Owing to the better understanding of the biological role of pregnancy-associated plasma protein A, this paper contributes important answers to the detailed questions about the status of the network of interactions between proteins, including PAPP-A, and its importance for the pregnant mother and the fetus. Additional studies may in the future improve our understanding of PAPP-A's function in early pregnancy as well as perinatal care programs for pregnant women.

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Conflict of interests

The authors declare that they have no conflict of interest.

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