Significance of pregnancy-associated plasma protein A (PAPP-A) concentration determination in the assessment of final outcome of pregnancy

Značaj određivanja koncentracije plazma proteina trudnoće A (PAPP-A) u proceni konačnog ishoda trudnoće

Dragan Lončar, Mirjana Varjačić, Slobodan Arsenijević
Gynecology and Obstetrics Clinic, Clinical Centre Kragujevac, Kragujevac, Serbia

Abstract

Background/Aim. Pregnancy-associated plasma protein A (PAPP-A) is high molecular matrix metalloproteinase originally isolated in the serum of pregnant women. The aim of this study was to analyze the values of concentration of PAPP-A in assessment of progress and outcome of pregnancy in pregnant women diagnosed with threatening preterm delivery, pre eclampsia and fetal growth restriction in relation to physiological pregnancy of the same gestational age. Methods. The study included 60 pregnant women that were divided into three groups according to gestational age and the diagnosis of imminent premature birth upon reception, pre eclampsia and fetal growth restriction as follows: the group I from 28 to 32 weeks of gestation, a total of 25 pregnant women, the group II from 33 to 36 weeks of gestation, a total of 23 pregnant women, and the group III from 37 to 41 weeks of gestation, a total of 12 pregnant women. The control group consisted of 60 pregnant women without complications of pregnancy that were identically divided into three groups according to gestational age as in the sample. We performed quantitative determination of PAPP-A from the venous blood of patients by using commercial tests of the company Diagnostics Product Corporation (DPC), Los Angeles, California, USA. Results. There was a statistically significant difference in PAPP-A values in the examined groups in all gestational ages (p < 0.01). The value of the PAPP-A concentration in different gestational ages with equal statistical significance indicated the possibility of complications, which was examined during pregnancy in relation to the control group of pregnant women with physiological pregnancies. This study confirmed that there was a statistically significant difference in fetal body weight at birth (p < 0.05), Apgar score in 5 min after birth (p < 0.05), and gestational age at birth (p < 0.05), as parameters of the outcome of pregnancy course, between the examined groups of pregnant women in relation to the value of PAPP-A concentration. The age of pregnant women was not statistically different in the examined groups (p > 0.05). Conclusion. Differences in PAPP-A concentration should point out to the obstetrician the need for more intensive antepartum fetal surveillance in order to increase the chances of favorable perinatal outcome, regardless gestational age.

Key words: pregnancy outcome; premature birth; pregnancy-associated plasma protein A; pre-eclampsia; fetal growth retardation; apgar score; gestational age.

Apstrakt

Uvod/Cilj. Plazma protein A povezan sa trudnoćom pregnancy-associated plasma protein A (PAPP-A) je visokomolekularna matriks metaloproteinaza koja je prvobitno izolovana iz seruma trudnih žena. Cilj istraživanja bio je analiza vrednosti koncentracije PAPP-A u proceni toka i ishoda trudnoće kod trudnica sa dijagnozom pretečeg prevremenog porođaja, preeklampsije i zastoja u rastu ploda u odnosu na fiziološku trudnoću iste gestacijske starosti. Metode. U studiju je bilo uključeno 60 trudnica koje su bile podeljene u tri grupe prema gestacijskoj starosti i prijeđnoj dijagnozi pretečeg prevremenog porođaja, preeklampsije i zastoja u rastu ploda: grupa I od 28 do 32 nedelje gestacije imala je ukupno 25 trudnica, grupa II od 33 do 36 nedelja gestacije, ukupno 23 trudnice, i grupa III od 37 do 41 nedelje gestacije, ukupno 12 trudnica. Kontrolnu grupu činilo je 60 trudnica bez ispitivanih komplikacija podeljenih prema gestacijskoj starosti identično kao i u eksperimentalnoj grupi. Kvantitativno određivanje PAPP-A vršeno je iz venske krvi bolesnice primenom komercijalnih testova firme Diagnostics Product Corporation (DPC), Los Anđeles, Kalifornija, USA. Rezultati. Postojala je statistički značajna razlika u koncentraciji PAPP-A u izvršenim grupama za sve gestacijske starosti (p < 0.01). Vrednost koncentracije PAPP-A u različitim gestacijskim starostima s jednako statističkom značajnom indikirala je mogućnost komplikacija, koje je istraživano tokom gravitacije u odnosu na kontrolnu grupu bolesnica sa fiziološkim gravitacijama. Ovaj istraživački rad potvrdio je da postoji statistički značajna razlika u težini beba u porodu (p < 0.05), Apgar score u 5 minuta nakon poroda (p < 0.05), i gestacijskom starom na porodu (p < 0.05), kao parametara procesa gravitacije, između izvršenih grupa bolesnica u odnosu na vrednost koncentracije PAPP-A. Starost bolesnica nije statistički bila različita u izvršenim grupama (p > 0.05). Zaključak. Razlike u koncentraciji PAPP-A trebalo bi poštovati obitelj za potrebu daljeg antepartum fetalnog obilježavanja kako bi se povećale pravljice slične perinatalne dobiti, prema svakoj gestacijskoj starosti. Ključne riječi: rezultati gravitacije; ranje porođaje; PAPP-A; pre-eclampsija; pretečeg porođaja; Apgar score; gestacijska starost.
Introduction

Pregnancy-associated plasma protein A (PAPP-A) is high molecular matrix metalloproteinase originally isolated in serum of pregnant women. PAPP-A is a glycoprotein, macroglobulin, of molecular weight of 800,000 with alpha 2-electrophoretic mobility, and it is produced in syncytiotrophoblast cells of the placenta. Determination of PAPP-A is performed by radioimmunoassay method (immune test with isotope). The first radioimmunoassay determination of PAPP-A was carried out in 1980. Using RIA method it is possible to determine its presence already 3–4 weeks after conception and no later than the 6th week of gestation. The maximum level PAPP-A has at the term delivery. PAPP-A exerts an inhibitory effect on the enzyme elastase, a protease located in the granules of neutrophils granulocytes and participates in processes that lead to the destruction of proteins. By direct immunofluorescence, the presence of PAPP-A in spermatozoid’s heads is determined at about 2%. PAPP-A exerts an inhibitory effect on fixation of both complements and coagulation system, as well as on the affinity to heparin. It is assumed that suppressed level of PAPP-A reduces the zinc ion that is required in the fetal organogenesis, which represents one of the factors for the occurrence of congenital malformations. During pregnancy, PAPP-A concentration in maternal blood increases. Decreased concentration is related to increased incidence of chromosomal abnormalities in early gestation and in later pregnancy course because of the associated placental insufficiency. It is characterized by the appearance of fetal growth restriction, preeclampsia, preterm delivery and stillbirth. PAPP-A is a regulator of bioactivity of insulin-like growth factor. Testing of the role of PAPP-A in other tissues of the organism has started recently. Increased values of PAPP-A were found in patients with acute coronary syndrom in contrast to healthy population and those with a diagnosis of stable angina pectoris. It is important to mention that PAPP-A, which is in circulation of patients with coronary disease is circulating in free form, whereas in pregnant women a complex of PAPP-A and the proform of eosinophil major basic protein is present. This brings into question the adequacy of the used substrates that were synthesized for the detection of complex form of PAPP-A. PAPP-A represents a useful biomarker in clinical monitoring of pregnancy course. However, new prospective studies are needed by using appropriate substrates for the detection of PAPP-A in order to assess the proper role of metalloproteinase in clinical practice. The aim of this study was to analyze the value of PAPP-A concentration in assessing the final outcome of pregnancy in pregnant women diagnosed with threatening preterm delivery, preeclampsia and the fetal growth restriction in relation to physiological pregnancies of the same gestational age.

Methods

A prospective, observational study was conducted at the Gynecology and Obstetrics Clinic, Clinical Center Kragujevac, Kragujevac, Serbia, in 2010. During examination the clinical–experimental model of study was used. Quantitative measurements of PAPP-A levels were determined from venous blood of patients using the commercial tests of the company Diagnostic Product Corporation (DPC), Los Angeles, California, USA (DPC-USA). The tests, based on an analytical principle of immunochemiluminescence, were implemented using the automated analyzer Immulite 2000. The manufacturer of the analyzer is also DPC-USA.

The study included 60 pregnant women that were divided into three groups according to gestational age and the diagnosis of imminent premature birth upon reception, preeclampsia and fetal growth restriction as follows: the group I, from 28 to 32 weeks of gestation, a total of 25 pregnant women; the group II, from 33 to 36 weeks of gestation, a total of 23 pregnant women; the group III, from 37 to 41 weeks of gestation, a total of 12 pregnant women.

The criterion for inclusion of pregnant women in the study included the previously established all three diagnoses that were listed as complications of pregnancy course according to the following standards: preterm delivery before the end of 37th week of pregnancy; the diagnosis of preeclampsia based upon the blood pressure above 140/90 mmHg, proteinuria in 24 hour urine of ≥ 0.3 g / per day; intrauterine growth restriction (IUGR) of fetus was diagnosed on the basis of ultrasonographic growth parameters: biparietal diameter (BPD), transverse trunk diameter (TTD), head circumference (HC), abdominal circumference (AC), femur length (FL) and differences in the measured parameters below the 10th percentile than expected for gestational age.

The control group consisted of 60 pregnant women without complications of pregnancy that were identically divided into three groups according to gestational age as in the sample. All the obtained results of research were entered into a single database with valid logic control. Statistical analysis included calculating the average values and standard deviations (SD) for each numerical parameter and analysis of the obtained value in relation to the subgroups (t-test, Mann-Whitney) by using the statistical software SPSS 17.

**Results**

There was a statistically significant difference of PAPP-A values in the examined groups in all gestational ages \(p < 0.01\) (Table 1 and 2 and Figure 1). The mean values and standard deviations of PAPP-A concentration (mU/mL) in a total sample of pregnant women diagnosed with threatening preterm delivery, preeclampsia and intrauterine growth restriction were shown in Table 3.

It is found that pregnant women of 28–32 gestational weeks diagnosed with threatening preterm delivery and preeclampsia, showed significantly lower values PAPP-A than in healthy pregnant women \(p = 0.001\).

Pregnant women of 33–36 gestational weeks diagnosed with threatening preterm delivery and preeclampsia, showed significantly lower values of PAPP-A than in healthy pregnant women \(p = 0.01\) (Table 3 and 4).

Pregnant women at term and the diagnosis of preeclampsia, show significantly lower values of PAPP-A than healthy pregnant women \(p = 0.01\). Healthy pregnant women at 28–32 gestational weeks, showed significantly higher values than pregnant women diagnosed with pre eclampsia and intrauterine growth restriction in the same gestational age. The same comment goes for the t-test in pregnant women of 33–36 gestational weeks and for a group of pregnant women with normal term pregnancies (Tables 3 and 4).

### Table 1

<table>
<thead>
<tr>
<th>Weeks of gestation (wg)</th>
<th>Number of women</th>
<th>PAPP-A concentration (mU/mL)</th>
<th>(\bar{X} \pm SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28–32</td>
<td>25</td>
<td>9,353</td>
<td>304,789</td>
</tr>
<tr>
<td>33–37</td>
<td>23</td>
<td>424</td>
<td>357,207</td>
</tr>
<tr>
<td>&gt; 37</td>
<td>12</td>
<td>37,352</td>
<td>276,849</td>
</tr>
</tbody>
</table>

\(p < 0.01\) vs group 28–32 wg

### Table 2

The mean values and standard deviations of the concentration of pregnancy-associated plasma protein (PAPP-A) (mU/mL) in the total sample of pregnant women

<table>
<thead>
<tr>
<th>Weeks of gestation</th>
<th>Number of women</th>
<th>(\bar{X} \pm SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28–32</td>
<td>25</td>
<td>91,432 ± 48,121</td>
</tr>
<tr>
<td>33–36</td>
<td>23</td>
<td>135,061 ± 65,089</td>
</tr>
<tr>
<td>&gt; 37</td>
<td>12</td>
<td>154,287 ± 43,458</td>
</tr>
</tbody>
</table>

### Table 3

Obstetrics parameters and age in the group of pregnant women with preterm delivery, preeclampsia and intrauterine growth restriction (n = 60)

<table>
<thead>
<tr>
<th>Weeks of gestation (number of women)</th>
<th>Fetal body weight (g) (\bar{X} \pm SD)</th>
<th>Apgar score/after 5 min (\bar{X} \pm SD)</th>
<th>Gestational fetal age at birth (ng) (\bar{X} \pm SD)</th>
<th>Age of the pregnant woman (year) (\bar{X} \pm SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28–32 (n = 25)</td>
<td>2,640 ± 110</td>
<td>7.2 ± 0.9</td>
<td>36.0 ± 2.2</td>
<td>26.4 ± 3.1</td>
</tr>
<tr>
<td>33–36 (n = 23)</td>
<td>2,750 ± 205</td>
<td>8.0 ± 1.8</td>
<td>38.3 ± 1.8</td>
<td>25.0 ± 2.8</td>
</tr>
<tr>
<td>&gt; 37 (n = 12)</td>
<td>3,040 ± 180</td>
<td>8.3 ± 1.4</td>
<td>39.2 ± 3.0</td>
<td>28.2 ± 3.3</td>
</tr>
</tbody>
</table>
vascularization of the placenta 10, 11. These early events in the
phoblast invasion and hence in the early development and
that insulin-like growth factor plays an important role in tro-
sulin-like growth factor from these proteins so that they can
4 and 5. This means that it has the ability to help release in-
and mortality morbidity of mother as well as fetus. PAPP-A
pregnancy and therefore significantly reduce the incidence
women who will be suggested an intensive surveillance of
preeclampsia and growth restriction for selection of
MoM levels we consider useful in advising women with low
the control group of pregnant women with normal pregnan-
ties examined during pregnancy course in relation to
in physiological pregnancy 7. Correlation between the level
of this enzyme and the incidence of preeclampsia was esti-
mated by comparing the relative concentration of PAPP-A at
different gestation.

In the preeclampsia group, the median PAPP-A MoM
was significantly reduced (0.772 MoM, \( p < 0.0001 \)). With
decreasing level of PAPP-A, a probability ratio for pre-
eclampsia was growing. At the 5th percentile of the normal
(PAPP-A MoM 0.415), the probability rate was increased 4
times \(^7\). In our sample there was a statistically significant
difference in values of PAPP-A in the examined groups at all
gestational ages (\( p < 0.01 \)). We showed that the value of
PAPP-A concentration in different gestational ages with
equal statistical significance indicates the possibility of com-
plications examined during pregnancy course in relation to
the control group of pregnant women with normal pregnan-
cies. A probability factor of preeclampsia on any of PAPP-A
MoM levels we consider useful in advising women with low
levels of PAPP-A. The use of low PAPP-A in the prediction
of preeclampsia and growth restriction for selection of
women who will be suggested an intensive surveillance of
pregnancy and therefore significantly reduce the incidence
and mortality morbidity of mother as well as fetus. PAPP-A
is a “protease” for insulin-like growth factor binding proteins
4 and 5. This means that it has the ability to help release in-
sulin-like growth factor from these proteins so that they can
freely interact with their cellular receptors. It is considered
that insulin-like growth factor plays an important role in tro-
phoblast invasion and hence in the early development and
vascularization of the placenta \(^10, 11\). These early events in
the formation of the placenta are extremely important for
the outcome of pregnancy, and when abnormal, they are associ-
ated with miscarriage, fetal growth restriction, hypertensive
disorders induced by pregnancy (preeclampsia), fetal death
or preterm delivery. It is assumed that low levels of PAPP-A,
leading to reduced release of insulin-like growth factor,
could be a path to placentation abnormalities, culminating in
the adverse outcomes of pregnancy. Spencer et al \(^8\) in their
study on 54,722 normal singleton pregnancies examined the
role of PAPP-A in the course of pregnancy. At the 5th per-
centile of PAPP-A (0.415 MoM), the probability rate for the
fetus loss before 24 weeks was increased 3.3 times and above
24 weeks 2.8 times. In other words, there was three times in-
creased risk of fetal loss with low levels of PAPP-A. Cowans
and Spencer \(^9\) have recently confirmed a link between low
PAPP-A and low fetal weight at birth in relation to the ex-
pected for gestational age. In their research they found a linear
association of fetal growth restriction and reduced level of
PAPP-A, in other words, the lower level of PAPP-A, the lower
level of fetal birth weight of any gestational age \(^10\).

Several other studies confirm the association of other
“complications of pregnancy” listed above with low levels of
PAPP-A \(^13-15\). For example, as additional results of risk as-
seessment in the first and second trimester (FASTER) study, it
was found that women with concentration of PAPP-A below
the 5th percentile” were significantly more likely to experi-
en fetal loss before or at the 24th week, low fetal weight at
birth, preeclampsia, gestational hypertension, preterm deliv-
ery \(( p < 0.001)\), stillbirth, preterm premature rupture of fetal
membranes and placental abruption \(( p < 0.02)\) \(^16\).

Our research confirmed the allegations of these studies
since we found statistically significant difference in body
weight of the fetus at birth \(( p < 0.05)\), Apgar score 5 minutes
after birth \(( p < 0.05)\), and gestational age at the time of deliv-
ery \(( p < 0.05)\), as parameters of the final pregnancy outcome
between these groups of pregnant women in relation to the
value of the concentration of PAPP-A The age of pregnant
women in our study was not statistically different in the ex-
amined groups \(( p > 0.05)\). Despite this association, the posi-
tive predictive value of low level of PAPP-A for one of these
outcomes is still relatively low.

Table 4
Obstetrics parameters and age in the group of pregnant women with normal pregnancies

<table>
<thead>
<tr>
<th>Weeks of gestation (number of women)</th>
<th>Fetal body weight (g) $\overline{x} \pm SD$</th>
<th>Apgar score/after 5 min $\overline{x} \pm SD$</th>
<th>Gestational fetal age at birth (ng) $\overline{x} \pm SD$</th>
<th>Age of the pregnant woman (year) $\overline{x} \pm SD$</th>
</tr>
</thead>
<tbody>
<tr>
<td>28–32 (n = 20)</td>
<td>3,640 ± 210</td>
<td>9.2 ± 0.8</td>
<td>39.1 ± 2.6</td>
<td>27.1 ± 4.4</td>
</tr>
<tr>
<td>33–36 (n = 20)</td>
<td>3,550 ± 305</td>
<td>9.0 ± 1.0</td>
<td>38.8 ± 2.9</td>
<td>26.2 ± 1.7</td>
</tr>
<tr>
<td>&gt; 37 (n = 20)</td>
<td>3,660 ± 290</td>
<td>9.3 ± 0.7</td>
<td>39.4 ± 2.7</td>
<td>27.3 ± 4.5</td>
</tr>
</tbody>
</table>
with preeclampsia and intrauterine growth restriction, of the same gestation age. PAPP-A concentration was significantly higher in physiological pregnancies term gestation in relation to the concentration in pregnant women diagnosed with pre-eclampsia and intrauterine growth restriction, of the same gestation age.

PAPP-A concentration in the examined groups of our sample had normal distribution due to inhomogeneity of samples and physiological differences in secretion of enzymes in different periods of pregnancy. The pathologic conditions that we examined additionally influenced the irregularity of PAPP-A distribution.

Considering these limiting parameters, the results of PAPP-A levels in serum of pregnant women can only have the screening value, and on the basis of these results, intensive antenatal care should be undertaken.

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REFERENCES


