Open Access Maced J Med Sci **electronic publication ahead of print,**
published on June 06, 2018 as https://doi.org/10.3889/oamjms.2018.238

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2018.238
eISSN: 1857-9655
Clinical Science

Obstetric Outcome in Pregnant Patients with Low Level of Pregnancy-Associated Plasma Protein A in First Trimester

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Citation: Livrinova V, Petrov I, Samardziski I, Jovanovska V, Simeonova-Krstevska S, Todorovska I, Atanasova-Boshku A, Gjeorgjievska M. Obstetric Outcome in Pregnant Patients with Low Level of Pregnancy-Associated Plasma Protein A in First Trimester. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2018.238

Keywords: Factor screening; First trimester; Pregnancy-associated plasma protein A; the Perinatal outcome

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Received: 13-Apr-2018; **Revised:** 15-May-2018; **Accepted:** 23-May-2018; **Online first:** 06-Jun-2018

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Pregnancy-associated plasma protein A (PAPP-A), is a protease which releases Insulin-like growth factor. The role of this factor is stimulation of cell mitosis, differentiation and trophoblastic invasion of deciduas. Identification of patients with low PAPP-A (under 0.4 MoM in the first trimester has an influence on birth weight, attenuation of fetal growth, preeclampsia, birth and fetal demise.

AIM: The main issue in the study is evaluating an influence of PAPP-A, calculated in the first trimester on the unfavourable outcome of pregnancy.

MATERIAL AND METHODS: Seventy pregnant women with singleton pregnancy underwent first-trimester biochemical screening. The target group were women with PAPP-A below 0.4 MoM, and in control group, PAPP-A were over 0.4 MoM. There was an assessment of the influence on the mode of delivery, gestational week, the presence of intrauterine growth restriction, preeclampsia, temporary birth, intrauterine fetal demise and newborn condition.

RESULTS: In target group, consisted of 35 patients, 16 were delivered at term. From 28 to 37 g.w.- were 7 patient, 22-28 g.w.- 4 and 8 patients were under the 22 g.w (all with fetal demise) there were 19 pretemporary deliveries - 9 with Cesarean Section (SC). In the target group: 5 newborn were with IUGR, 6 women had preeclampsia, 1 had placental abruption. In control group were 35 patients: 28 delivered at term, 9 with SC, 26 vaginal deliveries; with IUGR were 4 newborns. Two newborns were hypertrophic.

CONCLUSION: There is a significant difference in unfavourable outcome in the cases with PAPP-A under 0.4 Mom, particular in the group, with a PAPP-A value under 0.2 MoM. The patients delivered with SC with the main indications in utero hypoxia, growth restriction and elevated blood pressure had PAPP-A between 0.3-0.4 MoM. The patients with intrauterine fetal death and placental abruption in the most of the cases have PAPP-A value under 0.2 MoM. There is a need to be aware in these pregnancies to achieve the preventions of adverse outcome, to decrease perinatal morbidity and mortality.

Introduction

The concentration measurement of Pregnancy-associated plasma protein A in the first trimester of pregnancy (PAPP-A), is one of the combined biochemical screening methods for aneuploidies, according to the recommendations of the Fetal Medicine Foundation (FMF), the combined screening method in the first trimester of pregnancy [1].

PAPP-A is a protease for insulin-like growth factor binding protein 4 (IGFBP 4), which facilitate the degradation of this protein, resulting in the release of insulin growth factor (IGF). IGFBP has a great ability for modification of its structure and function, as a result of proteolytic degradation. The intact IGFBP 4 is a powerful inhibitor of IGF in vitro, suggesting that proteolysis acts as a positive regulator of the IGF-availability. PAPP-A isolated from the serum of the pregnant woman has an IGF-dependent protease activity of IGFBP-4. This protease has an important role in the local proliferative answer, acting by accelerating the cell division. It increases the bioavailability of IGF, which in return mediates the trophoblast invasion of the decidua and modulates the transport of glucose and amino acids in the placenta

[2]. A disorder in the release of IGF might be a cause for inappropriate placental perfusion, which would affect the fetal growth and other adverse conditions in pregnancy [3] [4].

PAPP-A is a placental secretory product, and its value is low in the first trimester. The syncytiotrophoblastic deficient forming can have a role in the abnormal placental secretion in affected pregnancies. Normally, the media for PAPP-A rises from 0.4 MoM in the 10th gestational week to approximately 0.7 MoM in the 13th gestational week, so the PAPP-A increases as the pregnancy progress.

The low value of PAPP-A (< 0.4 MoM) could predict an adverse perinatal outcome that includes fetuses with intrauterine growth restriction (IUGR), preeclampsia, preterm birth, miscarriage and stillbirths [5] [6] [7].

Material and Methods

This study was submitted and approved by the Ethical Review Committee of the Medical University in Skopje and is in adherence to the laws and regulations of the country in which the research was conducted. Written consent with patient permission was obtained from each patient.

This prospective cohort study was conducted at the University Clinic for Obstetrics and Gynecology in Skopje included 75 successively admitted and delivered patients during the period of one year from January 2017 to December 2017. All delivered neonates were without a sign of congenital infection, malformation and chromosomopathies.

The study was taken at the University Clinic of Gynecology and Obstetrics, Skopje. The analyses were performed at the Biochemical laboratory in the Clinic, till some patients (70 patients) was fulfilled. The selection of the patients was made consecutive from patients in whom a combined biochemical screening in the first trimester was performed. The patients were divided into two groups: *the target group* - 35 patients who delivered with values of PAPP-A below or equal to 0.4 MoM and a *control group* - 35 patients who delivered with values of PAPP-A over 0.4 MoM. All the patients had fetuses without chromosomal abnormalities. The data for the patients was collected by questionnaire that included anamnestic, demographic information, information about present pregnancy, personal, familial and obstetric history.

Inclusion criteria for PE were the presence of proteinuria at least 0.5 g/L/24 hours, increase in systolic pressure for minimum 30 mmHg, and diastolic pressure 15mmHg, measured two times apart for six hours, compared with blood pressure before pregnancy.

Exclusion criteria were underlying presidential morbidity: chronic hypertension, diabetes, renal disease, autoimmune and metabolic disease (NICE guidelines). Inclusion criteria for IUGR were birthweight less than 5th percentile for gestational age and sex, and exclusion criteria were the presence of congenital infection, anomalies and chromosomopathies and mother who took medication, alcohol and with toxicomania. The placental abruption was clinically and histopathological proven, and exclusion criteria were rupture of membrane, uterine fibroid or other operation of the uterus.

Methods

The concentrations of free β-HCG and PAPP-A were measured from 5ml of the peripheral blood sample with vacutainer in a tube without anticoagulant. The samples were delivered to the laboratory at the Clinic. The present device-Siemens Healthier-Immulite 2000 XPi, with a method of chemiluminescence, and the risk was calculated by licensed software PRISCA version 5.2.1, which is integrated into the device and is used at the Clinic.

The results are presented in absolute values and percentages. *The target group* is the one with PAPP-A below 0.4 MoM, and *the control group* is the one with values of PAPP-A over 0.4 MoM. The difference in the incidence of the qualitative parameters was analysed by Chi-squared test. The values of $P < 0.05$ were taken for statistical significance.

SPSS V.20 was used for numeric and attributive parameters. Standard descriptive and analytical bivariant and multivariant methods were used. Statistical significance among attributive parameters was determined wit Chi-square test and numerical parameters with Student T-test.

Results

There is no significant difference in the prevalence of the patients in both groups, i.e. the age is not a risk factor that affects the value of PAPP-A in patients without chromosomopathies.

The percentage of term deliveries in the target group was 47%, compared to the control group in which it was 80%. There was a significant percentage of deliveries before 22nd gestational weeks in the target group - 22% compared to the same parameter in the control group - 0%.

In the control group, the number of patients who delivered by Caesarean section was 9, and the number who delivered spontaneously was 26.

Table 1: Prevalence of complication in the patients

PAPP-A value (MoM)	0.0 -0.10	0.11-0.20	0.21-0.30	0.31-0.40	Total	> 0.4 Control group
Fetal loss	2	3	2	1	8	0
Hypertension			1	5	6	2
IUGR			3	2	5	4
Placental abruption		1			1	0
Preterm delivery (total= iatrogenic+ contractions)					11	7
Fetal hypoxia			5	4	9	4

In the target group, there were 8 pregnancies terminated with artificial abortion because of an intrauterine death of the fetus, 1 patient delivered a death fetus spontaneously, in the 31st gestational week with preterm placental abruption. Although there is no significant difference in the delivery with Caesarean section, it should be noted that in the control group there were 7 preterm deliveries, 4 of them were delivered by Caesarean section, and 3 were spontaneously delivered.

Table 2: Complication and PAPP-A value

Complication number (%)	Fetal loss	Hypertension with or without proteinuria	IUGR	Placental abruption	Fetal hypoxia	Without complication	Total
Target group	8 (22.8)	6 (17.1)	5 (14.3)	1 (2.8)	9 (25.8)	6 (17.2)	35 (100)
Control group	0 (0)	2 (5.7)	4 (11.4)	0 (0)	4 (11.4)	25 (71.5)	35 (100)
p value	< 0.05	< 0.05	> 0.05	> 0.05	< 0.05	1.00	

Discussion

The values of PAPP-A between 0.05 and 0.20 MoM are associated with adverse outcomes, such as stillbirths and preterm placental abruption [8]. The received results correlate with the study from 2010 [9]. There is a significant difference in the adverse outcome of life born with PAPP-A values between 0.3 and 0.4 MoM, compared to the control group. This group involves the patients who delivered a live-born infant by Caesarean section because of IUGR, fetal hypoxia and elevated blood pressure [10] [11]. There are many studies that prove the correlation between low values of PAPP-A below 0.4 MoM and the birth weight and fetal growth. In one retrospective cohort study, it is found positive predictive values for SGA of 2.97 (95% CI from 1.1 to 6.4) [12].

There is a significant difference in the adverse outcome in patients with values of PAPP-A below 0.4 MoM, especially with values below 0.2 MoM. In the patients, who delivered by Caesarean section with a life born because of a fetal growth restriction, fetal hypoxia and elevated blood pressure in the pregnancy, the value of PAPP-A is 0.3 to 0.4 MoM. Patients with intrauterine fetal death and preterm placental abruption, have a value of PAPP-A below 0.2 MoM, but having only 2 patients with this result, we can not interpret its statistical significance. The PAPP-A values interval between 0.3 and 0.4 MoM, showed more fetuses with growth restriction and preeclampsia, and iatrogenic preterm delivery because of the complications mentioned above. There is no significant difference in the number of spontaneous preterm delivery among the patients with a PAPP-A value below 0.4 MoM. The most of premature deliveries in control group are due a premature rupture of membrane and premature contractions.

To make an algorithm for following of these pregnancies, a huge series of a pregnant woman should be included, and more precise definition of the values of this protein should be done, that has a significant impact of the pregnancy outcome. In term of the fact that there is a national recommendation for follow up on patients with low values of PAPP-A in some countries, an attempt for its implementation in our country could be done [13]. The listed Australian recommendations for follow up of patients with low PAPP-A values (below 0.37 MoM - 5th percentile), can be applied for the beginning as it is national approved and it covers a big group of patients. Caution should be taken about the obtained results, with a purpose of prevention of an adverse pregnancy outcome and decreasing the perinatal mortality and morbidity. It is necessary to assess the cost-benefit if these recommendations are going to be implemented in our circumstances.

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