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Clinical Importance of Low Level of PAPP-A in First Trimester of Pregnancy - An Obstetrical Dilemma in Chromosomally Normal Fetus

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Abstract

BACKGROUND: A variety of recent evidence exists about the clinical implication of low level of Pregnancy-associated plasma protein A (PAPP-A) in pregnancy. This glycoprotein is a protease, which releases the Insulin-like growth factor from IGFBP 4. Its role is a trophoblastic invasion of decidua, stimulation of cell mitosis and differentiation. It has an immunosuppressive effect in the placenta, inhibition of coagulation and complex role for integration of all these processes in the placenta. Level of PAPP-A (under 0.4 MoM-Multiple of Medians) in first-trimester screening in chromosomally and morphologically normal fetuses, could influence fetal weight, preeclampsia, premature birth and stillbirth. As a result of the complications mentioned above, there is implication on timing, mode of delivery and condition of the newborn.

AIM: The study aims to evaluate the influence of low PAPP-A, measured in the first trimester on the outcome of pregnancy, with accent disorders which are the result of placental insufficiency. Also, gestational week, mode of delivery and condition of newborn secondary underlying conditions will be evaluated.

MATERIAL AND METHODS: After given information and consultation about the expectation from the screening, pregnant women with a singleton pregnancy were tested for First Trimester Screening to estimate the risk for Trisomy 21, 13, 18- the most frequent chromosomopathies. After exclusion of chromosomopathies and congenital malformations, one hundred and fourteen patients enrolled in the study. The target group (n = 64) with PAPP-A below 0.4 MoM and control group (n = 50) with PAPP-A equal and above 0.4 MoM. An assessment of mode and time of delivery and presence of small for gestational age newborns, preeclampsia, premature birth and newborn condition at delivery was made.

RESULTS: The percentage of the patients delivered in term was similar between the target group (n = 64) and the control group (n = 50), 82.81% vs 82.0% respectively. The rate of cesarean section was 29.7 % in the target group vs 32% in the control group. A significant difference was found about elective vs urgent cesarean section in favour of the target group. The difference was present about the complication in pregnancy before delivery, 56% vs 22%, p = 0.023, which were the main indication for cesarean section. The difference in newborn outcome was not significant.

CONCLUSION: There is a difference in frequency of complications, in the cases with PAPP-A under 0.4 MoM, such as premature birth, preeclampsia compound with SGA fetuses versus the control group. The difference for SGA newborn and premature birth among the groups has statistical significance. The patients delivered with cesarean section were with the main indications SGA or elevated blood pressure, often occurred combined with prematurity. Apgar score and birth weight were similar in target and control group, but the newborns with a birth weight under 2500 g. were more frequent in the target group. Because these results did not show another significance among two groups, probably lower cut-off is needed, combining with another test (Doppler of uterine arteries in the first trimester, biochemical test). Presence of other diseases which could hurt placental function should be emphasised.

Introduction

The measurement of Pregnancy-associated plasma protein A in the first trimester of pregnancy (PAPP-A), is a part of the combined screening in the first trimester for chromosomopathies, according to the recommendations of the Fetal Medicine Foundation (FMF) [1], [2]. Since its discovery by Lin in 1974, till now, this glycoprotein remains a dilemma about the interpretation of its concentrations in placenta and blood in pregnant women during

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pregnancy, in the first trimester and use in everyday practice [3]. PAPP-A is a large glycoprotein in complex with eosinophilic pro-Major basic protein (pro-MBP) [4]. It is a highly potent protease for insulin-like growth factor binding protein 4 and 5 (IGFBP 4 and 5). The protein is a powerful inhibitor of IGF in vitro, suggesting that proteolysis acts like a positive regulator of the IGF- availability. PAPP-A in the serum of the pregnant woman has an IGF- dependent protease activity on IGFBP-4 [5]. 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 trophoblastic invasion of decidua and modulates the transport of glucose and amino acids in the placenta [4], [5], [6]. Thus, low PAPP -A might be a cause for inappropriate placental perfusion affecting the fetal growth and leading to placental depended on adverse conditions in pregnancy [7], [8]. PAPP-A is a placental product from syncytiotrophoblast and septal X cells, and its concentration is low in the first trimester. Insufficient _syncytiotrophoblast_ development and function have an important role in the abnormal placental secretion of main placental proteins (beta HCG, PAPP-A, SP1 and HPL) [3], [4], [7], [9]. The median value for PAPP-A increase from 0.4 MoM in a 10th gestational week to approximately 0.7 MoM in the 13th gestational week, so the PAPP-A increases as the pregnancy progresses till term [7], [8], [9]. Does low value of PAPP-A (< 0.4 MoM) could predict an adverse perinatal outcome that includes fetuses with intrauterine growth restriction (IUGR) resulting in SGA infant in most of the cases, preeclampsia and preterm birth is still unclear [10], [11], [12], [13], [14], [15].

The study aims to evaluate the influence of low PAPP-A, measured in the first trimester on the outcome of pregnancy, with accent disorders which are the result of placental insufficiency. Also, gestational week, mode of delivery and condition of newborn secondary underlying conditions will be evaluated.

Material and Methods

This study was submitted and approved by the Ethical Review Committee of the Medical Faculty 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. A prospective longitudinal study was conducted at the University Clinic of Gynecology and Obstetrics, Skopje. Analyses for PAPP –A were performed at the Biochemical, clinical laboratory. chromosomopathies were excluded at Cytogenetic laboratory. The pregnant women were followed up during the pregnancy and delivered 2017 and 2018. After First Trimester screening, if the risk

was < 1:250, prenatal genetic testing to exclude chromosomopathies was offered. A total of 114 patients without chromosomopathies and congenital malformations enrolled in the study. Depend on the level of PAPP-A; there were 64 patients in the target group with values of PAPP-A below of 0.4 MoM and 50 patients in the control group with values of PAPP-A ≥ 0.4 MoM. The data for the patients was collected by a questionnaire that included demographic information, information about the current pregnancy, personal and obstetric history. In both groups, the presence of obstetrical complications such as preeclampsia, small for gestational age, premature deliveries, fetal distress, mode of delivery and indications for caesarean section were evaluated. The definition of hypertensive disorders, small for gestational age and preterm delivery was by relevant obstetric guidelines. The newborn's condition at delivery was evaluated.

The concentrations of free β HCG and PAPP-A were measured from 5 ml of peripheral vein blood. The sample was taken with vacutainer in a test tube without anticoagulant. Siemens Healthinner Immulite 2000 XPi device, with a method of chemiluminescence immunoassay, was used, and the risk was calculated (Siemens Corporation).

Statistical method

SPSS for Windows V.23.0 was used. Average and standard deviation were used for numeric variables with symmetrical distribution and median for numerical variables with asymmetrical distribution. Categorical parameters are presented with distribution of frequencies. Statistical significance among attributive parameters was determined with the Chi-square test and independent numerical parameters with Student T-test and Mann-Whitney U test.

The values of p < 0.05 were taken for statistically significant. The results are presented in absolute values and percentages.

Results

A total of 114 patients were enrolled. The patients were divided into two groups: target group-64 patients and control- 50 patients.

Maternal age - the average age in the target group was 28.8 ± 4.8 years and the control 30.6 ± 5.3 years, p = 0.057 (Table 1).

Table 1: Maternal age

Group	Descriptive Statistics			P - level
	N	Mean ± SD Maternal age	Range	
Target group	64	28.8 ± 4.8	18– 41	P = 0.057 ns
Control group	50	30.6 ± 5.3	17– 41	

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Gestational age of delivery was similar between two groups, p = 0.87 (Table 2).

Table 2: Gestational week of delivery

Group	Descriptive statistics			P - level
	N	Mean ± sd	Range	
Gestational week of delivery				
Target group	64	38.35 ± 2.6	30.5-41.5	T = 0.16
Control group	50	38.42 ± 2.2	30.2-41.5	P = 0.87

The mode of delivery – vaginal vs caesarean section wasn't significantly different between the groups (p = 0.79). Delivery by caesarean section occurred in 29.7% target group vs 32% of the control group (Table 3).

Table 3: Mode of delivery and type of indication

Variable	Group			P - level
	N	Target N (%)	Control N (%)	
Mode of delivery				
Vaginal	79	45 (70.31)	34 (68)	χ^2 = 0.07
Cesarean section	35	19 (29.69)	16 (32)	P = 0.79
Type of indication for cesarean section				
Elective	13	8 (12.5)	5 (10)	χ^2 = 0.44
Urgent	22	11(17.19)	11(22)	P = 0.51

We didn't find a difference between delivery by elective vs urgent caesarean section, (p = 0.51).

The results show a significant difference in _complications in pregnancy_ before delivery, among the groups (p = 0.023) (Table 4).

Table 4: Complications before delivery

Variable	Group			P - level
	N	Target N (%)	Control N (%)	
Complications before delivery				
Yes	38	27 (42.19)	11 (22)	P = 0.023 sig
No	76	37 (57.81)	39 (78)	

Distribution of complications is present in Table 5. The most frequent complications were premature birth and SGA newborn in the target group.

Table 5: Distribution of complications

Complication Before delivery	Group		
	N	Target N	Control N
No	76	37 (57.81%)	39 (78 %)
Yes	38	27 (42.19%)	11 (22%)
Distribution of complications			
Premature delivery due to uterine contractions	11	3	8
Sga	15	11	4
Sga, pe	4	4	0
Sga, fetal distress	1	1	0
Pe, fetal distress	1	1	0
Sga, pe, fetal distress	1	1	0
Pe	6	4	2
Fetal distress	1	1	0
Stillbirth	1	1	0
Abruption	1	1	0
Lga	3	3	0
Total number	45	31	14

There are a discrepancy in the total number (n = 45) and patients with (noted as main) complications (n = 38) because more than one complication is present in the same patient. The frequency of SGA newborn has significant statistical difference p = 0.023 (Table 6).

Table 6: Distribution of SGA newborn

Sga	Group			P - level
	N	Target N (%)	Control N (%)	
Yes	21	17 (26.56)	4 (8)	P = 0.023 sig
No	93	47 (73.44)	46 (92)	

In the target group, the duration of pregnancy till 37 g. w. or less was significantly more frequent than in control-32.8% (21) vs.16% (8), p = 0.04 (Table 7).

Table 7: Duration of pregnancy (g. w.)

Gestational week	Group			P - level
	N	Target N (%)	Control N (%)	
> 37 week	85	43 (67.19)	42 (84)	P = 0.04 sig
≤ 37 week	29	21 (32.81)	8 (16)	

Outcome of newborn

Average birth weight was (in grams) 3028.9 ± 743.4 vs. 3175.4 ± 677.9. p = 0.13 Very similar results were for birth height (in cm) 48.94 ± 3.1 vs. 49.36 ± 3.5, p = 0.21.

Viability of newborn

The value of Apgar score in the first and fifth minute, didn't show statistical significance (p = 0.43, p = 0.19) respectively, although they were lower in the target group at the fifth minute (Table 8).

Table 8: Apgar score at first and fifth minute

Apgar score	Group	Descriptive Statistics				P = level
		N	Mean ± SD	Range	Median	
First minute	Target	64	7.68 ± 0.8	4 - 9	8 (8– 8)	Z = 0.78
	Control	50	7.82 ± 0.7	5 – 9	8 (8– 8)	P = 0.43 ns
Fifth minute	Target	64	8.6 ± 0.8	6– 10	8 (8– 9)	Z = 1.3
	Control	50	8.82 ± 0.6	6– 10	9 (9– 9)	P = 0.19 ns

Discussion

Level of PAPP-A (under 0.4 MoM) in first-trimester screening in chromosomally and morphologically healthy fetuses, could contribute to the placental mediated complication, such as preeclampsia, premature birth, SGA, stillbirth, miscarriages [15], [16]. This implies on time and mode of delivery and newborn outcome.

In the study, there were no significant differences in maternal age. The total premature deliveries were due to uterine contractions and iatrogenic termination because of complications in pregnancy. The frequency of pregnancy up to 37 g.w. in target group was higher with statistical significance (p = 0.04) [15], [17]. We didn't find a difference for preeclampsia compare to other studies [16], [17].

There are studies for positive association between complications and low level of PAPP-A under 0.3 MoM [12], [13], [18], [19].

In our study urgent cesarean sections rate is almost 20% and is similar in both groups. Other studies present higher once in target group-30% [14].

Preeclampsia was present around 10% in the target group, similar to unselected pregnant women (6-8%). Almost 17% of a newborn in the target group were small for gestational age below the 10th percentile, higher than in Thompson study-7.44% [20].

Some studies show a significant difference in an adverse outcome in a group with PAPP-A below 0.4 MoM, probably because of different statistical power [21], [22].

There are a lot of studies with a different outcome. They included patients with different characteristics (race origin, body weight, previous poor obstetric history). Also, the presence of underlying disorders such as hypertension, diabetes, hypothyreosis, autoimmune disease etc. was included. In our study, the patients didn't have these conditions as they were exclusion criteria in the study. The number of patients enrolled in the studies is different; from national level study to trial study. Our study was with a relatively lower number of patients according to other studies. Better predictive results have studies which involve other tests (doppler of uterine arteries and fetal dopplers, different biochemical tests) [21], [23], [24].

In conclusion, there is a difference in unfavourable outcome in the cases with PAPP-A under 0.4 MoM, particular in the group of patients with premature birth, and SGA as a result of placental insufficiency. These factors lead to fetal distress or compromised fetal oxygenation. The patients delivered with cesarean section were with the main contributing factor- preterm fetus. Compare with the control group, these complications in pregnancy were rare. In the control group, the main indications was previous one or more cesarean section, disproportion, transverse lie or breech presentation of the fetus. Birth weight, average gestational age and Apgar score were similar in target and control group. The detection rates could be improved with appropriate intervention before complications arise.

In term of fact, there are national recommendations for follow up of patients with low values of PAPP-A, we should attempt other countries. The main aim will be improving the perinatal outcome for mothers and the newborns. It is necessary to assess the cost-benefit if recommendations are going to be implemented in our circumstances.

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