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Comparison of Pregnancy-Associated Plasma Protein-A Levels in Women with and Without Intrauterine Growth Restriction

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ABSTRACT

Background & Objective: The initial diagnosis of predictive markers is essential for the IUGR. High levels of PAPP-A lead to increased levels of free IGF-1, which in turn reflects the function of the placenta and the fetus in normal growth. The objective of this study was to compare the level of PAPP-A in pregnancy weeks 11-14 in women with and without intrauterine growth restriction and to assess the ability of this marker to predict adverse outcomes in pregnancy.

Materials & Methods: In this Comparative Cross-sectional study, 227 pregnant women were studied during 2017. Mothers were divided into two main groups, with and without intrauterine growth restriction. The relevant data, including birth weight, preeclampsia, gestational diabetes, Apgar score, and PAPP-A, were recorded on special forms. Data analysis was done using SPSS-21 software.

Results: The mean age of participating women in this study was 28.8 ± 5.6 years. The median (IOR) number of gravidity and Gestational weight gain was one (1) and 12 (7) kg, respectively. The difference in median (IOR) PAPP-A in patients with and without IUGR was statistically significant 0.64(0.57) and one (0.57), respectively, P= 0.001. The cut-off point for PAPP-A was 0.73 with a sensitivity=72.2% (95% CI: 64.32-79.16%) and a specificity =60.5% (95% CI: 48.65 -71.56%).

Conclusion: The results of this study confirm the relationship between low levels of PAPP-A and adverse outcomes of pregnancy. In the present study, the optimal cut-off point (0.73) is higher than other studies, which can be due to racial and epidemiological differences.

Keywords: Intrauterine growth restriction, Pregnancy-associated plasma protein-A, Preeclampsia, Gestational diabetes

Introduction

Intrauterine growth restriction (IUGR) is one of the most common reasons of perinatal mortality. IUGR refers to a condition in which fetal weight is less than the tenth percentile of the weight curve for the gestational age. It affects approximately 5 to 10 percent of pregnancies **(1)**. Fetal-placental abnormalities, external factors and genetics together are involved in IUGR and its related disorders **(2)**. Regular pre-natal care focuses on identifying women at high risk, as well as careful monitoring and appropriate intervention. Early diagnosis of predictive markers is essential for IUGR risk probability. Accordingly, non-invasive methods such as uterine arteries doppler examination, the placental volume and vessel status checking, and serum biochemical markers are the main targets of many studies **(3, 4)**. With the advancement of ultrasound technology along with the measurement of serum markers in the first trimester of pregnancy, many adverse effects, especially IUGR, can be evaluated. Numerous maternal serum markers have been reported in association with preeclampsia and IUGR. Some of them are human chorionic gonadotropin (hCG), pregnancy-associated plasma protein-A (PAPP-A), angiogenic factors, insulin resistance markers, adiponectin and inhibin A **(5)**.

PAPP is a macro-globulin glycoprotein with a molecular weight of 800,000 with mobility in the alpha-2 band electrophoresis, which has IGFBP protease activity and leads to the release of IGF-1 **(6)**. Insulin-like growth factors (IGFs) play an important

role in the growth of fetal tissues during pregnancy. There are at least six types of IGF-binding proteins (IGFBPs) that organize IGFs activity by increasing half-life, localization and migration in different tissues **(7)**. PAPP-A is secreted by the cells of Syncytiotrophoblast and maternal decidual. So, the low level of this protein is indirectly reflective of the placental failure, which in turn leads to abnormal growth of the fetus **(3)**.

Several studies show the relationship between maternal PAPP-A levels during pregnancy and birth weight. In fact, low levels of PAPP-A leads to decreasing the release of IGF and subsequently reducing fetal growth and other adverse outcomes of pregnancy such as hypertension during pregnancy, preterm labor, small for gestational age (SGA), spontaneous abortion and fetal aneuploidy **(8, 9)**.

Anisakis stated that maternal PAPP-A levels at 8-14 weeks of pregnancy were a strong predictor of perinatal adverse events. The power of the relationship between PAPP-A and the results before 13 weeks was similar to the relationship after 13 weeks. In fact, these results indicate that in most women, adverse pregnancy outcomes can be detected in the first trimester **(10)**.

According to the lack of adequate studies on the level of PAPP-A in our race and the controversial studies in relation to PAPP-A and IUGR in other countries, the objective of the present study was to compare the level of PAPP-A in pregnancy 11-14 weeks in women with and without IUGR in the referred population to Al-zahra Hospital. Also, the ability of this marker was evaluation order to predict the outcome of pregnancy.

Methods

This study is a comparative cross-sectional which was conducted on women referring to Alzahra hospital in Rasht during 2017. Sample size to determine sensitivity of PAPPA marker to predict IUGR with confidence interval 95%, deviate 10% basis of Nicolaides (11) paper result (Sen= 0.87%) was 221. The current study was conducted after obtaining the ethical approval from the ethics committee of Guilan University of Medical Sciences (Code: IR.GUMS.REC. 1396.58) and written consents were taken from all participants.

Inclusion criteria were: mothers with a gestational age (GA) above 28 weeks at the time of entering the study, between 11-14 weeks of GA were carrying out the PAPP-A est, singleton pregnancy and alive fetuses, without any fetus structural anomalies, pregnancy without a result of IVF, no smoking, no chronic diseases (including Heart- kidney and liver failure, diabetes mellitus and rheumatology).

Exclusion criteria included the patient's lack of cooperation in providing PAPP-A results, or after seeing the PAPP-A test, it was cleared that the patient did not take the test at the right time of 11-14 weeks.

By drawing the weight of newborns in the "percentile weight based on the gestational age at birth time" curve, the percentile weight of the infants was calculated. Infants with a weight percentile below 10% were referred to as IUGR in the first group. The rest of the infants with a percentile weight greater than 10% were placed in the second group. In order to prevent selection bias, each IUGR infants who were included in the study, one infant from the previous birth and one newborn from the next delivery, who had the inclusion criteria, were considered as the control group.

The following information was collected from patients' medical records: PAPP-A level and its history in screening the first trimester of pregnancy, gestational age based on first trimester ultrasonography or reliable LMP, third trimester ultrasonography, gestational diabetes screening at 24-28 weeks of gestation, maternal blood pressure, Urinary randomization protein or 24-hour urine protein in case of preeclampsia diagnosis, the weight of the beginning and the end of pregnancy, height, delivery mode, weight and APGAR score of the newborn.

Statistical Analysis:

Education, BMI at the early pregnancy, gestational weight gain, gestational age, and history data analysis was done using SPSS-21 software (IBM, USA). According to the Shapiro-Wilk test, Normal probability plot, PAPP-A didn't have a normal distribution.

To compare the main variables of the research (PAPP-A in both groups with and without IUGR), the Mann-Whitney-U test was used. Multivariate logistic regression models were included among the variables that had P <0.1 in univariate analysis with IGUR and PAPPA status. After adjusting the effects of age, of diabetes, preeclampsia, history of hormonal disease and delivery mode, the logistic regression was used to determine the effect of PAPP-A as the predictor marker for IUGR. We use the ROC curve to obtain the cut-off point, where sensitivity and specificity are optimal. The optimal cut-point as the point maximizing the product of sensitivity and specificity (Concordance Probability Method (CZ)). P-value less than 0.05 were considered significant.

Results

In this study, 227 cases were investigated. 151 (66.5%) of them without IUGR and 76 (33.5%) were identified with IUGR. The mean age of pregnant women was 28.8 ± 5.6 years, and the majority was in the age range 20 to 35 years. Regarding the status of education, the majority of the samples (45.8%) had a cycle degree (middle school) up to diploma. The majority of samples (96.5%) had normal amniotic fluid status. The history of stillbirth was reported in 2.2% of the cases, and 70.9% of the cases were cesarean delivery. Regarding the Apgar scores, the most

common scores of the first and fifth minutes were eight and nine (Respectively, with 44.5% and 54.2%).

Table 1 contains information on participants' Pregnancy parameters characteristics. In the study of PAPPA in terms of IUGR, median (Interquartile Range= IQR) PAPPA in individuals with and without IUGR was median= 0.65 (0.57) and median=1(0.57). Therefore, the level of this protein was lower in pregnancies with IUGR. This difference was statistically significant (P < 0.001) (Table 2).

Information related to the PAPP-A comparison in both groups with and without IUGR based on various parameters presented in (Table 3). PAPP-A levels in mothers with normal BMI (18.5-24.99) and overweight (25.0-29.99) in IUGR group were significantly lower than those without IUGR (P = 0.001 and P= 0.049, respectively). In all three gestational weight gain (GWG) categories(less weight gain than expected, normal and higher than expected), the PAPP-A level in women with IUGR was significantly lower than women without IUGR. PAPP-A levels in women aged 20-35 years and also in all three grades of education (middle school, high school and higher diploma) in IUGR group was significantly lower than the group without IUGR (Respectively: P= 0.001, = 0.006, P= 0.034, P= 0.11). In women with a history of diabetes as well as in cesarean delivery, PAPPA levels were significantly lower in IUGR positive group than negative IUGR (P<0.001, P = 0.001 and P = 0.015, respectively). In pregnant women who did not have preeclampsia, PAPP-A levels in the IUGR group were significantly lower than those without IUGR, but in mothers with preeclampsia, this difference was not significant. The amount of PAPP-A in women with preterm and term labor, in IUGR group was significantly lower than the without IUGR (P = 0.046, P = 0.001, respectively).

In this study, after adjusting confounding variables such as GWG, BMI, gestational age, diabetes history, preeclampsia and delivery mode, backward logistic regression multiple analysis model (backward LR) was used to determine the effects of PAPP-A on the incidence of IUGR. Regression analysis results showed that PAPP-A was a significant predictor of IUGR (Odds ratio =0.306, P= 0.001) (Table 4).

Table 1. The frequency distribution of maternal characteristics

characteristics	Mean±SD	Median	Percentile 25	Percentile 75
Age (Year)	28.8±5.6	28	25	33
Gravidity (No)	1.70±0.93	1.00	1.00	2.00
Parity (No)	0.49±0.66	0.00	0.00	1.00
Abortion (No)	0.22±0.54	0.00	0.00	0.00
BMI(kg/m2)	25.81±5.43	24.92	22.19	28.89
Number of kids alive	0.47±0.63	0.00	0.00	1.00
Diastolic blood pressure (Cm.hg)	7.09±1.12	7.00	6.00	8.00
Systolic blood pressure (Cm.hg)	11.63±1.43	11.00	11.00	12.00
Mother's weight at the Early pregnancy(Kg)	66.80±14.52	65.00	57.00	74.00
Maternal weight in late pregnancy(Kg)	79.42±14.69	78.00	70.00	87.00
Gestational weight gain(Kg)	12.63±4.95	12.00	9.00	16.00
mean neonatal weight(g)	2646.83±641.96	2550.00	2200.00	3150.00
Gestational age(week)	37.42±2.34	37.85	36.30	39.15

Table 2. Investigating the level of PAPPA in terms of IUGR

PAPPA	without IUGR	IUGR	Total	*P-Value
Standard Deviation	0.48	0.49	0.49	
Median	1.00	0.64	0.88	**<0.001
IQR	0.57	0.57	0.63	

***Mann-Whitney Test**
****P-value<0.05**

Table 3. Comparison of PAPP-A in both groups with and without IUGR based on different parameters

		PAPPA						P-value
		without IUGR*			IUGR			
		Median	P25	P75	Median	P25	P75	
BMI (kg/m2) at the Early pregnancy	<18.5	0.97	0.57	1.02	1.02	0.58	1.59	0.724
	18.5-24.99	1.02	0.71	1.22	0.56	0.44	0.98	*0.001
	25-29.99	0.96	0.63	1.32	0.60	0.42	1.03	*0.049
	>30	1.07	0.75	1.25	0.68	0.61	0.98	0.071
Gestational weight gain(Kg)	Low weight gain	1.09	0.86	1.58	0.62	0.45	1.07	*0.006
	Normal weight gain	0.91	0.61	1.25	0.56	0.48	1.03	*0.023
	High weight gain	1.03	0.69	1.21	0.68	0.44	0.98	*0.012
Age(year)	<20 years	0.75	0.27	1.33	1.02	0.41	1.45	0.769
	20-35	1.01	0.71	1.24	0.61	0.44	0.98	*0.001
	>35	1.00	0.68	1.33	0.72	0.59	0.94	0.124
education	Under middle school	1.03	0.75	1.24	0.74	0.49	1.03	*0.006
	middle school-diploma	0.96	0.60	1.25	0.63	0.45	1.04	*0.034
	diploma up to higher	0.88	0.62	1.29	0.53	0.45	0.64	*0.011
Delivery mode	Normal	0.93	0.53	1.10	0.81	0.58	1.16	0.924
	cesarean	1.04	0.74	1.29	0.60	0.41	0.92	*0.001
History of diabetes	does not have	1.02	0.68	1.25	0.66	0.45	1.02	*0.001
	has	0.88	0.65	1.14	0.54	0.41	0.60	*0.015
Preeclampsia	does not have	1.00	0.69	1.25	0.64	0.45	1.02	*0.001
	has	0.98	0.56	1.18	0.59	0.48	0.98	0.323
Preterm	No	1.03	0.80	1.25	0.66	0.47	0.98	*0.046
	Yes	0.79	0.56	1.20	0.61	0.41	1.03	*0.001

***P-value<0.05**

Table 4. Determining the effects of PAPP-A on IUGR

Variable	OR	P-Value	95% CI.for OR	
			Lower	Upper
PAPP-A	0.306	*0.001	0.148	0.633
Education	1.545	0.057	0.987	2.421
GWG	0.618	*0.018	0.415	0.921
Gestational age	1.211	*0.010	1.048	1.399
Preeclampsia	3.366	*0.008	1.371	8.264
Constant	0.001	*0.012		

***P-value<0.05**

The results of the ROC curve indicated PAPP-A prediction level is statistically significant in order to determine the neonatal IUGR. (Area under curve = 0.675 with 95% CI: [0.60,0.75]). Therefore, the optimal Cut-off point was 0.73 with a sensitivity of 72.19% with 95% CI: [64.32%, 79.16%] and a specify of 60.53% with 95% CI: [48.65%, 71.56%] (Figure 1). According to Yeden Index, J=Max Value (Sen_{max}+Spe_{Max}-1), Cut off of PAPPA is equal 0.8 (Sen =0.56%, Spe =63%)

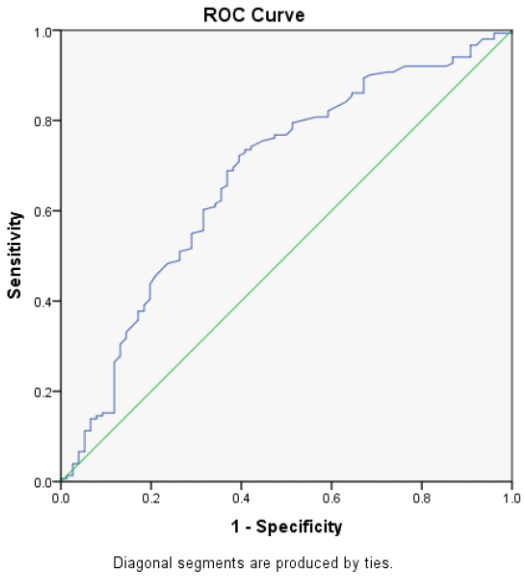

Figure 1. **ROC curve**

Discussion

The result of the current study showed that there is a significant relationship between adverse pregnancy outcomes (especially IUGR) and low levels of PAPP-A in blood serum of pregnant women. Therefore, PAPP-A acts as a valuable element in predicting the risk of adverse pregnancy outcomes. Ong (2000) evaluated 5584 singleton pregnancies at the 10-14 weeks of gestational age and measured the levels of β-hCG and PAPP-A **(12)**. They concluded that low levels of PAPP-A or β-hCG are associated with the subsequent development of pregnancy complications. In another study on 4390 women with singleton pregnancies, it was shown that low levels of PAPP-A at 11-13 weeks of pregnancy were associated with adverse pregnancy outcome **(13)**. In 2009, Goetzinger and Poon **(14, 15)**, in two separate groups, identified low levels of PAPP-A as the predictor of IUGR. Similarly, in the present study, the mean difference of PAPP-A in women with and without IUGR was statistically significant. So, the amount of this protein was significantly lower in pregnant women with IUGR. A high level of PAPP-A leads to IGFBP4 proteolysis and increases IGF-1 levels. Therefore, the level of this protein indirectly reflects the function of the placenta and the normal growth of the fetus **(3)**.

Grill, Rusterholz **(16)** reported that the reduced serum levels of PAPP-A during pregnancy was considered as a risk factor for preeclampsia and IUGR **(16)**. However, some researchers showed increased levels in the last trimester in pre eclamptic pregnancies **(17)**. Kuc and colleagues showed that the low level of PAPP-A was significantly associated with the development of preeclampsia **(18)**. In the present study, in women with preeclampsia, PAPP-A levels in the IUGR group were lower than those without IUGR, but this difference was not statistically significant.

There is a negative relationship between maternal age and PAPP-A level **(19)**. Also, it has been demonstrated the relationship between maternal age and the adverse pregnancy outcomes, especially the complications caused by placental dysfunction such as stillbirth, fetal growth restriction, and preeclampsia **(20)**. In the present study, in pregnant women over 35 years, PAPP-A level was lower in the group with IUGR than without IUGR group, but this difference was not statistically significant.

Lončar, Varjačić and Arsenijević **(21)** according to PAPP-A concentration, there was a statistically significant difference between the groups in pregnancy outcomes such as birth weight, fifth minute Apgar, and gestational age at birth time. They concluded that the differences in PAPP-A concentrations suggested the need for more pre-natal care to increase the chances of desirable prenatal outcomes regardless of gestational age **(21)**.

BMI is one of the important factors affecting IUGR, so that very high and very low BMI can lead to IUGR **(22)**. Considering the PAPP-A predictive role for adverse effects of pregnancy, it can be concluded that abnormal BMI can affect PAPP-A levels. In the present study, in the normal and overweight BMI groups (BMI=18.5-30), PAPP-A levels in pregnant women with IUGR were significantly lower than women without IUGR. However, PAPP-A levels in pregnant women with BMI in two-span (BMI > 30 and BMI <5/18) did not show significant differences between the two groups. Also, according to the present study, weight gain during pregnancy had no effect on the results, and in any degree of weight gain, PAPP-A in the IUGR group was less than the without IUGR group.

Other factors affecting IUGR are maternal health and behavioral habits **(23)**, which can be influenced by the level of mother's knowledge and awareness. In the present study, education was detected as a predictor associated with IUGR.

Some studies indicated a relationship between reduced levels of PAPP-A in the early stages of pregnancy and the development of gestational diabetes **(10, 24)**. In fact, the reduced concentration of PAPP-A and gestational hypertension or pre-eclampsia in the final stages of pregnancy is a condition commonly associated with gestational diabetes **(25)**. In this study, 7.5% of the participants in the study and 7.8% of pregnant women with IUGR had gestational diabetes. PAPP-A levels in pregnant women with IUGR in both GDM and non-GDM were significantly lower than women without IUGR. Also, PAPP-A level in the IUGR group was significantly less than women without IUGR. After adjusting for confounding variables in multivariate analysis, similar results were obtained. Education, gestational weight gain and preeclampsia were introduced as other predictors of IUGR.

Based on the results of this study, PAPP-A marker predictor level was statistically significant for the determination of IUGR in newborns. With regard to the sensitivity and specificity of the ROC curve at different points, the best cut-off point was determined 0.73 (sensitivity=72.2%, specificity=60.5%). In two different studies, the cut-off point for PAPP-A was 0.4 and 0.35 respectively **(26, 27)**. Regarding the effect of ethnic and racial factors on the incidence of IUGR **(23)** and the predictive role of PAPP-A on adverse pregnancy outcomes, it seems that differences in cut-off points can be attributed to racial and epidemiological factors.

Conclusion

The results of this study confirmed the association between low levels of PAPP-A and adverse pregnancy outcomes .PAPP-A is one of the three components of routine screening tests for aneuploidy including Down syndrome in the first trimester of pregnancy. By identifying an appropriate cut-off point, it is possible to identify patients at risk and have a better monitoring of their pregnancy care. According to the results of this study, a decrease in serum PAPPA levels during the first trimester of pregnancy is associated with IUGR. Therefore, this marker can be used to predict high-risk pregnancies.

One of the limitations of this study was the inadequacy of the medical records of some patients and their lack of cooperation in the presentation of the PAPP-A result, which had to be excluded from the study. In addition, the retrospective nature of the study, and the small sample size were other limitations of this research. Finally, PAPP-A levels were not measured in a single laboratory which was another limitation of the present study.

Ethical Statement

This study was approved by the ethics committee of Guilan University of Medical Sciences (Code: IR.GUMS.REC. 1396.58) and performed after submission of written signed informed consent form by each patient.

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Conflict of Interest

There are no conflicts of interest.

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