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RESEARCH ARTICLE

Investigating the Relationship between Serum Levels of PAPP-A and Free β-hCG in the First Trimester of Pregnancy with Placental Thickness and Percentile of Fetal Weight in Third Trimester Ultrasound

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ABSTRACT

Introduction: **Fetal growth disorder is one of the most important factors in the morbidity and mortality of newborns. Investigating the factors and predicting them can be done through biochemical markers and sonography. The quality of the placenta was measured by measuring PAPP_A and free B_HCG and its quantity by examining the placenta by ultrasound. This study aimed to determine the correlation between fetal growth percentile and these three variables.**

Methods: **This prospective cohort study was conducted on 462 pregnant mothers in Ahvaz. The criteria of this study were singleton pregnancies, accurate knowledge of last menstrual date, non-smoking, no drug or alcohol consumption and consent to participate in the research exclusion criteria were fetal anomaly, chromosomal disorder and lack of ultrasound in the third trimester. PAPP-A and free B-HCG were measured in the 11–13 + 6 weeks of pregnancy, and then in the third trimester fetal placental thickness and fetal weight were measured by two-dimensional sonography. The data was analyzed using SPSS software version 26 as well as Pearson statistical logistic test and the results were analyzed.**

Results: **Out of the 462 fetuses none of them were under the 10% weight percentile. 187 fetuses were between 10%–50% of the weight percentile and 260 fetuses were between 50%–90% weight percentile and 15 fetuses were above the 90% weight percentile. The level of free B-HCG was significantly different in the three weight groups, the uppermost level of B-HCG was in the 90% weight percentile group (p-value = 0.008). The level of PAPP-A also correlated with the fetuses' weight percentiles (p-value = 0.002). There was a positive and significant correlation between placental thickness in the third trimester in the three groups (p-value = 0.004) which means that with the increase in the thickness of the placenta, the fetus's weight increases.**

Conclusion: **Based on this study, the measurement of placental markers and diameter helps predict birth weight and is expected to help in deciding the time and type of pregnancy termination.**

Keywords: FGR, free β-hCG, PAPP-A, placental thickness.

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1. Introduction

Fetal growth disorder is one of the most important factors in the morbidity and mortality of newborns. Investigating the factors and predicting them can be done through biochemical markers and sonography.

FGR is defined as fetal weight of less than the 10th percentile and can be a primary reason for infant mortality and morbidity instigating 60%–80% of neonatal mortality [1]. Low Birth weight can have long-term health effects such as lung disease especially asthma during childhood and adolescence, malnourishment, type 2 diabetes and insulin resistance, low Apgar score, neurodevelopmental delay, cardiovascular disease and long-term metabolic disease [2]–[6]. The placenta is the main source of nutrition for the fetus hence directly affecting the fetal birth weight, the placenta can be the initial organ to exhibit signs of aberrancy in the pregnancy [7]. Placental thickness less than 2 cm or more than 4 cm is considered abnormal, and FGR babies have a smaller weight and capacity as well as thickness than babies with normal birth weight. It has been observed that abnormal placenta can be related to irregular Pregnancy-associated plasma protein (PAPP-A) levels [8], [9].

PPAP-A is secreted by the placenta in the maternal bloodstream and is part of routine prenatal screening for Down syndrome and other chromosomal trisomy. Beta-human chorionic gonadotropin (β-hCG) is also produced in the placenta and can be detected in blood and urine, and it's used to detect pregnancy [10].

In a study done by Sirikunalai *et al.*, it was found that abnormally high or low levels of free β-hCG can be associated with adverse pregnancy outcomes such as intrauterine growth restriction, premature birth, low birth weight and low Apgar score, as well as the risk of premature birth and gestational diabetes in the group with lower β-hCG levels in the first trimester, on the other hand in many other studies, no significant relationship was found between free β-hCG level and adverse pregnancy outcomes, including intrauterine growth restriction and premature birth [11]–[14].

As a result, we need to conduct more studies to identify the exact mechanisms in this field. Considering the high level of adverse pregnancy outcomes and low birth weight babies in Iran and considering that the level of PAPP-A and free β-hCG serum markers are different in different populations and their range should be determined; The present study was conducted to investigate the relationship between serum levels of PAPP-A and free β-hCG in the first trimester with placental thickness and fetal weight percentile in third trimester ultrasound.

2. Methods

This is a prospective cohort study that was conducted on 462 pregnant mothers in Ahvaz. The sampling was done purposefully. Based on this, a pregnancy control and care center under the cover of Ahvaz Jundishapur University of Medical Sciences, which had the highest number of referrals and population diversity, was selected.

To conduct the study, after obtaining written permission from the ethics committee of Ahvaz Jundishapoor University of Medical Sciences and obtaining the necessary permissions from the Research and Technology Vice-Chancellor, visit a selected pregnancy control and care center in Ahvaz City became. All referring pregnant women were examined for having the inclusion criteria, and finally, the research objectives were presented to 462 women who met the inclusion criteria, who agreed to participate in the study.

The criteria for entering the study included: singleton pregnancy, accurate knowledge of the last menstrual date, non-smoking, no drug and alcohol consumption, and consent to participate in the research. Exclusion criteria included: diagnosis of fetal anomaly, chromosomal disorders, and lack of follow-up and ultrasound in the third trimester of pregnancy.

The questionnaire of demographic and obstetric characteristics was completed by the researcher at the first visit in the first trimester, and then the serum level of PAPP-A and free β-hCG based on the results of the screening test that was conducted in the 11th to 14th week of pregnancy for all pregnant women to screen for Down syndrome and disorders Chromosome was done and recorded. Then, in the third trimester of women who performed their pregnancy care regularly and did not meet the exclusion criteria, fetal weight percentile (calculation of fetal weight based on gestational age by ultrasound), placenta thickness (as checked by ultrasound) two-dimensional and assessment of placenta thickness at the junction of the umbilical cord) in the third trimester of pregnancy and other pregnancy outcomes (miscarriage, preeclampsia, diabetes and amniotic fluid volume disorders) were evaluated and recorded in the desired form. It should be noted that in all the participating women, placental thickness and fetal weight percentile were evaluated by a perinatologist using the Mindray Resona 7 ultrasound machine, which was constant throughout the study. In the end, the data were analyzed using SPSS version 26 software, as well as Pearson and Logistic statistical tests, and the results were analyzed.

3. Results

In this study, 500 pregnant women were examined in terms of meeting the inclusion criteria, 38 of these women (35 due to lack of follow-up and ultrasound in the third trimester and 3 due to termination of pregnancy due to chromosomal problems) and anomaly) were excluded from the study and finally 462 women who were eligible for the study were examined.

3.1. Demographic Characteristics, Clinical and Laboratory Variables in the Entire Population

Table I describes the variables studied in the participants based on the mean and median of their repetition in the study, based on which the average level of FBHCG was 1.34 MOM with a range of (0.156–9.858) MOM. The average level of PAPP-A was 1.17 MOM with a range

TABLE I: Demographic Characteristics, Clinical and Laboratory Variables in the Entire Population

Sample characteristics	Mean (range)
Age of mother	28.89 (18–43)
Gravid	2 (1–7)
Maternal BMI	26.128 (16.4–39.4)
Free beta HCG (MOM)	1.345 (0.156–9.858)
PAPP-A (MOM)	1.175 (0.179–3.978)
Gestational age by last menstrual period (wks)	31.9 (28–36.7)
Placenta thickness by trimester 3 Sono (millimeter)	39.93 (20–80)
Weight percentile by trimester 3 Sono (%)	56.97 (10–95)

TABLE II: Patients' Characteristics, Clinical Variables and Thickness

Variables	Level	Placenta thickness		p-value
		Medium (n = 419)	High (n = 43)	
Age of mother		28.88 ± 3.96	28.98 ± 4.03	0.867
Gravida		2 (1, 2)	2 (1, 3)	0.281
BMI		26.02 ± 4.51	26.94 ± 4.69	0.170
Free beta HCG (MOM)		1.36505	1.15988	0.042
PAPP-A (MOM)		1.19472	0.98870	0.039
Fetal sex (male, female)	Male	199 (48.54)	23 (44.23)	0.659
	Female	211 (51.46)	29 (55.77)	
ASA and enoxaparin	No	320 (78.05)	41 (78.85)	1.000
	Yes	90 (21.95)	11 (21.15)	
Hypothyroid	Yes	59 (14.39)	9 (17.31)	0.538
	No	351 (85.61)	43 (82.69)	
Thalassemia minor	Yes	28 (6.83)	2 (3.85)	0.559
	No	382 (93.17)	50 (96.15)	
In vitro fertilization	Yes	6 (1.46)	2 (3.85)	0.224
	No	404 (98.54)	50 (96.15)	

of (0.179–3.978) MOM. The average placental thickness based on third-trimester ultrasound was 39.93 mm with a range of 80–20 mm and the average fetal weight percentile was 56.97 with a range of (10–95) percent.

3.2. Demographic Characteristics, Clinical and Laboratory Variables Based on Placental Thickness in the Third Trimester of Pregnancy

Table II shows the relationship between demographic characteristics and clinical and laboratory variables with placental thickness. A total of 462 cases participated in this study, none of them had low placental thickness (0 to 19 mm), 419 cases had medium placental thickness (20 to 50 mm), and 43 cases had high placental thickness (above 50 mm).

No significant difference was observed in maternal age and BMI between the two groups (28.88 ± 3.96 vs. 28.98 ± 4.03, p = 0.867; 26.02 ± 4.51 vs. 26.94 ± 4.69, p = 0.170, respectively). Similarly, no significant relationship was observed between the number of pregnancies, fetal sex, history of APS, hypothyroidism, thalassemia minor and IVF pregnancies with placental thickness. Among these factors, a significant difference in the level of placental hormones was observed between the groups with medium and high placental thickness, but in the opposite direction in the case of free β-hCG (1.36505 vs. 1.15988, p = 0.042). and PAPP-A (1.19472 vs. 0.98870, p = 0.039).

3.3. Demographic Characteristics, Pregnancy's Laboratory Variables Based on Percentile of Fetal Weight in the Third Trimester of Pregnancy

Table III shows the relationship between demographic characteristics, and clinical and laboratory variables with percentile of fetal weight. A total of 462 people participated in this study, none of the participants had a weight percentile below 10%, but 187 cases had a fetal weight percentile of 10% to 50%, 260 cases had a fetal weight percentile of 50% to 90%, and 15 people had a high fetal weight percentile. They were 90 percent. No significant difference was observed in the mean age of the mother (p = 0.478), the number of pregnancies (p = 0.086) and the mean BMI (p = 0.453) between the three groups with different weight percentiles. Similarly, no significant relationship was observed between fetal sex, history of APS, hypothyroidism, thalassemia minor and IVF pregnancy with the percentile of fetal weight classified into three groups. However, there was a positive and significant difference in the average level of placental hormones in three groups with different weight percentiles, which was in the case of β-hCG (p = 0.008) and PAPP-A (p = 0.002).

In Table IV, a follow-up test was performed to determine precisely which subgroups of fetal weight percentiles had this significant increase in the level of placental hormones. In the percentile of fetal weight above 90%, the Free β-hCG level is significantly higher than the percentile of fetal weight 10%–50% (p = 0.016). It was also found that the PAPP-A level in the fetal weight percentile group above 90% was significantly higher than the group with a fetal weight percentile of 50%–90% (p = 0.036) and higher than the group with a fetal weight percentile of 10%–50% (p = 0.004, p = 0).

3.4. Investigating the Correlation between Fetal Weight Estimation and Placental Thickness in the Last Trimester of Pregnancy

Table V, based on the results of the correlation test between the estimation of the weight of the fetus and the thickness of the placenta in the last trimester of pregnancy, there is a positive and significant correlation (p = 0.004), which means that with the increase in the thickness of the placenta, the weight of the fetus increases. It is equal to r = 0.13

4. Discussion

This study aims to assess the correlation between first-trimester PAPP-A and β-hCG levels and placental thickness, and their association with fetal birth weight in the third trimester of pregnancy. Our outcome indicates that fetuses above the 50 percentile weight have higher values of PAPP-A and β-hCG and that as the placental thickness increases fetal weight percentile will also increase.

TABLE III: Patients' Characteristics, Clinical Variables and Laboratory Factors by Weight Percentile by Trimester 3 Sono (%)

Variables	Level	Weight percentile by trimester 3 Sono (%)			p-value
		10–50 (n = 187)	50–90 (n = 260)	≥90 (n = 15)	
Age of mother		28.61 ± 4.09	28.96 ± 3.92	29.40 ± 3.87	0.478
Gravida		2 (1, 2)	2 (1, 2)	2 (1, 2)	0.086
BMI		26.00 ± 4.93	26.06 ± 4.33	26.95 ± 4.51	0.453
Free beta HCG (MOM)		1.20880	1.40710	1.99607	0.008
PAPP-A (MOM)		1.08849	1.21223	1.62493	0.002
Fetal sex (male, female) by trimester 3 Sono	Male	64 (13.85)	132 (28.57)	26 (5.63)	0.209
	Female	78 (16.88)	145 (31.39)	17 (3.68)	
ASA and enoxaparin	No	117 (25.32)	206 (44.59)	38 (8.23)	0.040
	Yes	25 (5.41)	71 (15.37)	5 (1.08)	
Hypothyroid	Yes	20 (4.33)	42 (9.09)	6 (1.30)	0.979
	No	122 (26.41)	235 (50.87)	37 (8.01)	
Thalassemia minor	Yes	9 (1.95)	20 (4.33)	1 (0.22)	0.576
	No	133 (28.79)	257 (55.63)	42 (9.09)	
In vitro fertilization	Yes	1 (0.22)	6 (1.30)	1 (0.22)	0.454
	No	141 (30.52)	271 (58.66)	42 (9.09)	

TABLE IV: Correlations between Biochemical Markers and Weight Percentile

Multiple comparisons							
Hochberg							
Dependent variable	(I) wp2	(J) wp2	Mean difference (I-J)	Std. error	Sig.	95% Confidence interval	
						Lower bound	Upper bound
Free beta HCG (MOM)	10–50 percentile	3.00	−0.198299	0.100706	0.141	−0.43961	0.04301
		4.00	−0.787270*	0.281850	0.016	−1.46263	−0.11190
	59–90 percentile	2.00	0.198299	0.100706	0.141	−0.04301	0.43961
		4.00	−0.588971	0.278896	0.102	−1.25726	0.07932
	>90 percentile	2.00	0.787270*	0.281850	0.016	0.11190	1.46263
		3.00	0.588971	0.278896	0.102	−0.07932	1.25726
PAPP-A (MOM)	10–50 percentile	3.00	−0.123743	0.059199	0.107	−0.26560	0.01811
		4.00	−0.536441*	0.165683	0.004	−0.93345	−0.13943
	50–90 percentile	2.00	0.123743	0.059199	0.107	−0.01811	0.26560
		4.00	−0.412699*	0.163947	0.036	−0.80555	−0.01985
	>90 percentile	2.00	0.536441*	0.165683	0.004	0.13943	0.93345
		3.00	0.412699*	0.163947	0.036	0.01985	0.80555

Note: *The mean difference is significant at the 0.05 level.

TABLE V: Correlation between Fetal Weight Estimation and Placental Thickness in the Last Trimester of Pregnancy

		Placenta thickness by trimester 3 Sono (mm)	Estimate of fetal weight by trimester 3 Sono (gr)
Placenta thickness by trimester 3 Sono (millimeter)	Pearson correlation	1	0.132**
	Sig. (2-tailed)		0.004
	N	462	462
Estimate of fetal weight by trimester 3 Sono (gr)	Pearson correlation	0.132**	1
	Sig. (2-tailed)	0.004	
	N	462	462

Note: **Correlation is significant at the 0.01 level (2-tailed).

Pakinat *et al*. suggested that PAPP-A could predict low birth weight however β-hCG was not significant for fetal weight this is also agreeable in the study done by Kavak *et al*. that β-hCG had no predictive value for fetal birth weight, however, a study done by Sirikunalai *et al*. showed that low β-hCG levels showed significant relations to low birth weight and IUGR which in our study both PAPP-A and β-hCG in the first trimester of the pregnancy were lower in fetuses with lower weight percentile [10], [11], [15].

Dugoff *et al*. assessed 34,271 pregnancies to evaluate the predictive value of PAPP-A and β-hCG levels on adverse pregnancy outcomes and the evaluation results show that PAPP-A below 0.4 MoM is related to low birth weight and other pregnancy adverse outcomes [16] but Kavak *et al*.'s findings show that PAPP-A might have a high negative predictive value but It does not have positive predictive value [15]. Krantz *et al*. found that β-hCG and PAPP-A have positive predictive value for IUGR [17]. The research

which has been done by Springer *et al*. indicates that PAPP-A can be reliable in predicting FGR $<3^{rd}$ percentile [18].

In a study conducted by Papamichail *et al*., the level of PAPP-A below 0.4 MoM is significantly associated with an increased chance of IUGR and adverse pregnancy outcomes [19]. The results of the study conducted by Ozdemir *et al*. reveal that first and second-trimester PAPP-A can prognosticate for IUGR which has a positive correlation with our results [20].

A study which has been done by Gasiorowska *et al*. indicated that newborn birth weight negative association with the age of the mother, and β-hCG protein levels. Furthermore, birth weight directly correlated with PAPPA-A protein levels, and maternal early-pregnancy BMI [21]. However, we did not find any correlation between maternal BMI and fetal weight percentile and PAPP-A and β-hCG both correlated with fetal weight percentile.

Kim *et al*. studied twin pregnancies to demonstrate that although twin pregnancy fetuses are in the lower weight percentiles, PAPP-A can still be a predictive factor in predicting FGR and another biochemical marker Inhibin-A is more valuable in twin pregnancies [22].

In the article published by Turrado Sánchez *et al*., it was found that as the level of PAPP-A decreases, the birth weight also decreases [23].

The study which was published by Honarjoo *et al*. reveals that low levels of PAPP-A would cause a 3.213 times rise in the chance of developing SGA and no correlation between high levels of β-hCG >3 with SGA. As an outcome, a low level of the PAPP-A is a warning indicator for SGA [24].

The study conducted by Dukhovny *et al*. indicated that the majority of women with abnormal analytes did not exhibit risk factors for SGA. Eliminating PAPP-A and β-hCG may present missed opportunities to recognize women at risk for SGA [25].

In women without identifiable risk factors, low PAPP-A levels emerged as a significant indicator of SGA. When PAPP-A levels were below 0.4 MoM and combined with an early fetal growth index below the 10^{th} percentile, the risk of SGA substantially increased (odds ratio (OR) = 5.8; 95% CI, 2.7–12.7). Furthermore, low PAPP-A levels diminished free β-hCG levels, and sluggish early fetal growth were each independently and statistically associated with SGA. Notably, the association between free β-hCG levels below 0.3 MoM and SGA exhibited comparable strength to that of PAPP-A levels below 0.3 MoM and SGA (OR = 3.1 and 3.0, respectively) [26].

Research published by Cohen *et al*. shows that the combination of biomarkers currently utilized in Down syndrome screening may also serve to predict additional adverse pregnancy outcomes [27].

A study done by Ciginni *et al*. that PAPP-A and β-hCG have a positive correlation with fetal weight percentile and high PAPP-A and β-hCG can even predict large for gestational age fetuses [28]. Some study reveals that Since the first trimester of pregnancy, specific values of PAPP-A and free β-hCG could affect the risk of low or high birth weight [28].

During the first trimester, placental thickness shows discrepancies in pregnancies susceptible to preeclampsia (elevated) or SGA (reduced), while remaining within typical parameters in pregnancies vulnerable to both conditions. This implies that the underlying pathologies exert contrasting influences on early placental development. These findings warrant validation in a larger study cohort [29].

In a study done by Barati *et al*. placental pathology and weight were evaluated in 60 pregnancies and compared SGA and AGA fetuses and they concluded that placental weight was significantly different in the two groups (p-value = 0.001) [30].

Liu *et al*. measured placenta and fetal weights within 2 hours after giving birth and found no significant difference in placental thickness between FGR fetuses and control cases (p = 0.450) [31].

5. Conclusion

Predicting the possibility of fetal growth disorder is one of the important goals of prenatal care, the use of free beta, Papp and sonography in the third trimester and examination of the placenta can play this role. It may be possible to predict fetal growth disorders by using software in the future and using these variables.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

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