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The Relationship of Pregnancy-Associated Plasma Protein A and Human Chorionic Gonadotropin with Adverse Pregnancy Outcomes: A Prospective Study

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Abstract

Purpose This prospective study investigated the relationship between pregnancy-associated plasma protein A (PAPP-A) and human chorionic gonadotropin (hCG) and adverse pregnancy outcomes in the Iranian population.

Materials Overall, 994 singleton pregnant mothers of 18–35-year old were referred for first-trimester screening tests, including PAPP-A and β-hCG, at the age of 6 days and 11–13 weeks, and were followed until the end of their pregnancy. The adverse pregnancy outcomes, PAPP-A, and β-hCG serum levels were recorded and analyzed. The sensitivity and specificity of the test were measured by calculating the area under the curve of receiver operating characteristic curve (ROC).

Results The mean serum level of PAPP-A and β-hCG was 1.10 ± 0.69 and 1.09 ± 0.8 MoM, respectively. Pregnancy-associated plasma protein A, regardless of its percentile, showed a significant relationship with the incidence of preeclampsia, preterm birth, and fetal low birth weight ($p < 0.001$ for each). However, the relationship between PAPP-A and abortion was not significant ($p > 0.05$). According to ROC, the results indicated that PAPP-A had a significant relationship with the incidence of preeclampsia, preterm birth, and fetal low birth weight ($p < 0.001$). However, β-hCG levels showed no significant relationship with adverse pregnancy outcomes.

Conclusions The result of this study revealed that lower level of PAPP-A and β-hCG could be a predictive factor in preterm labor. Also, this study indicated that PAPP-A measurements could be a screening test for adverse pregnancy outcomes, such as preeclampsia, low birth weight and preterm labor.

Keywords PAPP-A · β-hCG · Preeclampsia · Preterm labor · Low birth weight · Abortion

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Introduction

Pregnancy-associated plasma protein A (PAPP-A) is secreted by the placenta and enters directly into maternal circulation. The concentration of PAPP-A increases till the end of pregnancy and is detectable in maternal serum since the blastocyst implantation period. It is one of the principal markers measured in Down syndrome screening and should be performed between 11 and 14 weeks of gestational age. The serum markers for Down syndrome could influence pregnancy outcomes in the first and second trimesters [1]. Human chorionic gonadotropin (hCG) is the first hormone detected in pregnancy. It is produced by placenta, and its rapid rise in material serum or urine is an ideal marker for confirmation of conception [2]. As reported in the literature, maternal serum markers, such as PAPP-A and β-hCG, are related to adverse pregnancy outcomes, such as fetal growth

restriction, preeclampsia, low birth weight, still birth, and preterm labor [3, 4].

Despite vast amount of research, none could prove their high sensitivity in detecting low- or high-risk pregnancy, according to adverse pregnancy outcomes [5, 6]. In spite of the relatively high adverse pregnancy outcomes in Iran, little research has been performed on such markers. On the other hand, the levels of these markers vary in different populations, the range of which should be detected [7]. The current research investigated the relationship between PAPP-A and hCG and adverse pregnancy outcomes in the Iranian population.

Methods and Materials

Study Population

This prospective analytical study was performed on singleton pregnant mothers of 18–35 years of age, whose first obstetrical visit was before 14 weeks of gestational age, at the health care centers of Qazvin province, Central region of Iran, during years 2016–2017. The participants were included in the study after information was provided by the researcher and an informed consent was obtained. The participants were excluded if they had diabetes, heart disease, hypertension, chromosomal abnormality, fetal anomaly, multiple pregnancy, and any other disease or if the tests were performed at any other laboratories, except the reference laboratories.

Study Design

Basic demographic data, including age, weight, height, parity, and gestational age, were recorded at the time of performing the screening tests. All the participants were referred to the reference laboratories for screening tests and reference radiology for nuchal translucency (NT) ultrasound scan, at the age of 11–13 weeks and 6 days. The method for measuring these markers in serum was the enzyme-linked immunosorbent assay (ELISA), which was the same in all the reference laboratories [8]. In order to compare the assessments, maternal age, weight and gestational age were used for standardizing PAPP-A results to multiple of the median (MOM) at the mentioned reference laboratories [9]. The results were recorded and all the pregnant mothers were followed up for prenatal care, according to the schedule released by the Iranian Ministry of Health.

Study Outcome

The participants were divided to three categories, based on their PAPP-A serum levels: (1) 5%; (2) between 5 and 95%,

and (3) more than 95%. In each case, pregnancy outcome was followed up and fetal birth weight was recorded. Abortion before 22 weeks of gestational age, preeclampsia, preterm birth, and fetal weight (g) were charted in the questionnaire. Abortion was defined as unexpected pregnancy loss before 22 weeks of gestation. Preterm birth was defined as termination before 37 weeks. Preeclampsia was confirmed by systolic blood pressure of ≥ 140 mmHg and diastolic blood pressure of ≥ 90 mmHg plus proteinuria, as an objective criterion, presenting massive endothelial injury, defined as more than 300 mg proteinuria in the 24 h of urine collection or the ratio of urinary protein to creatinine equal or more than 0.3 or the detection of more than 30 mg protein in a random urine sample [10]. Postpartum follow-ups were performed by a resident midwife at each health care center.

Statistical Analysis

Data were evaluated with independent T test and Mann–Whitney in two-variable groups and analysis of variance (ANOVA) or Kruskal–Wallis in multivariate groups. Quantitative data were compared by Chi-square or Fisher's exact test. The significance level was defined by $p < 0.05$. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the test were measured by calculating the area under the curve (AUC) of receiver operating characteristic curve (ROC) [10].

Result

At first, 1200 pregnant females were evaluated, out of whom 206 cases were excluded using exclusion criteria, and finally, 994 pregnant females participated in this research. Their age ranged from 14 to 44 years with 27.73 ± 6.12 as the average. Mean body mass index (BMI) was calculated as 25.73 ± 4.22 kg/m^2. Overall, 539 (54.2%) participants were primiparous, whereas 455 (45. 7%) were multiparous. The range of fetal birth weight was 1.1–4.5 kg with average of 3.2 ± 0.46 kilograms (kg), out of which 60 (6.14%) fetuses had low birth weight. PAPP-A ranged from 0.05 to 4.99, and the mean was 1.1 ± 0.69 MoM. Mean β-hCG was 1.09 ± 0.8 with a range of 0.06–11.12 MoM. Finally, we recorded 899 (90.44%) term birth, 18 (1.81%) abortions, and 77 (7.74%) preterm births. Preeclampsia occurred in 73 (7.34%) cases. Age was the only demographic variable, which had a significant relationship with preterm birth and abortion ($p = 0.017$ and $p < 0.001$, respectively). Pregnancy-associated plasma protein A, regardless of its percentile, had a significant relationship with the incidence of preeclampsia, preterm birth, and fetal low birth weight ($p < 0.001$ for each). However, this relationship with abortion was not significant ($p > 0.05$) and

β-hCG indicated no relationship with the mentioned adverse pregnancy outcomes ($p > 0.05$) (Table 1).

The researchers categorized the participants to three groups based on their PAPP-A level as follows: first group PAPP-A $\leq$ 34 MOM (under 5th percentile), second group $0.35 \leq$ PAPP-A ≤ 2.45 (among 5th–95th percentile), and the third group PAPP-A ≥ 2.46 or more than 95th percentile. None of the demographic variables had a significant relationship with PAPP-A in pregnant mothers ($p > 0.05$). The researchers observed a significant relationship between different PAPP-A percentiles and preeclampsia, preterm birth, and fetal low birth weight incidences ($p < 0.001$, $p = 0.003$, and $p < 0.001$, respectively). With regard to the β-hCG level, the researchers categorized the data to three groups as follows: The first β-hCG ≤ 0.34 MOM or under the 5th percentile; the second $0.35 \leq$ β-hCG ≤ 2.49 MOM or between the 5th and 95th percentile; and the last group with β-hCG ≥ 2.5 MOM or over the 95th percentile. None of the demographic variables presented a significant relationship with β-hCG level in pregnant mothers ($p > 0.05$). The researchers observed a significant relationship between these categories and preterm birth and abortion incidence ($p = 0.001$ for each) (Table 2).

According to ROC, data analysis proved PAPP-A significance in preeclampsia predication with 81% sensitivity, 74% specificity, 23.6% PPV, and 97.5% NPV (AUC = 0.797, $p < 0.001$); however, the research showed no significant relationship between β-hCG level and preeclampsia prediction (AUC = 0.507, $p = 0.839$) (Fig. 1) (Table 3) with 0.674 sensitivity, 0.675 specificity, 84.92% PPV, and 95.88% NPV (AUC: 0.712, $p < 0.001$). However, β-hCG levels showed no significant relationship with preterm labor (AUC: 0.546, $p < 0.181$) (Fig. 2; Table 3).

Data analysis indicated that PAPP-A could predict low birth weight with 0.711 sensitivity, 0.70 specificity, 13.4% PPV, and 97.1% NPV (AUC: 0.717, $p < 0.001$), whereas β-hCG showed no significant difference associated with low birth weight (AUC: 0.488, $p < 0.764$) (Fig. 3; Table 3).

Neither PAPP-A nor β-hCG had a significant relationship with abortion ($p = 0.492$, $p = 0.112$, AUC = 0.456, AUC = 0.388, respectively).

Discussion

This study was performed for the assessment of the relationship of first trimester, PAPP-A, and β-hCG with adverse pregnancy outcomes in Iran. The results indicated no significant relationship between demographic variables and material PAPP-A and β-hCG levels. In contrast, Sung et al. [11] only demonstrated a significant relationship between PAPP-A and maternal age, not with other demographic variables. In this study, 7.34% of the conceptions resulted

Table 1 The relationship of demographic characteristics and β-hCG and PAPP-A with adverse pregnancy outcomes

	Preeclampsia			Preterm labor			Abortion			Low birth weight		
	Yes (n=73)	No (n=921)	p value	Yes (n=77)	No (n=899)	p value	Yes (n=18)	No (n=976)	p value	Yes (n=60)	No (n=916)	p value
Age	28.89±6.71	27.64±6.07	0.209	28.51±7.07	27.59±5.94	0.017	31.94±9.33	27.66±6.03	0.000	28.78±6.56	27.6±5.99	0.568
Parity			0.321			0.373			0.091			0.314
Primiparous	42 (7.8%)	497 (92.2%)		44 (8.2%)	495 (91.8%)		6 (1.1%)	533 (98.9%)		35 (6.6%)	496 (93.4%)	
Multiparous	31 (6.8%)	424 (93.2%)		33 (7.3%)	422 (92.7%)		11 (2.4%)	444 (97.6%)		25 (5.6%)	419 (94.4%)	
BMI	27.74±4.92	25.57±4.12	0.061	26.08±4.60	25.69±4.19	0.714	26.29±4.01	25.72±4.23	0.92	26.47±4.38	25.68±4.21	0.514
PAPP-A	0.61±0.46	1.14±0.69	0.000	0.77±0.59	1.13±0.69	0.000	0.96±0.65	1.10±0.69	0.491	0.78±0.64	1.12±0.69	0.000
β-hCG	1.18±1.35	1.09±0.74	0.839	1.17±1.39	1.09±0.73	0.156	0.92±0.86	1.10±0.80	0.112	1.32±1.53	1.08±0.72	0.764

Table 2 The relationship of different levels of β-hCG and PAPP-A with adverse pregnancy outcomes

Conceptional outcomes	PAPP-A				β-hCG			
	≥ 2.46 (n = 50)	0.35–2.45 (n = 893)	≤ 0.34 (n = 51)	p value	≥ 2.5 (n = 50)	0.35–2.49 (n = 892)	≤ 0.34 (n = 52)	p value
Preeclampsia								
Yes (n = 73)	2 (2.7%)	54 (74.0%)	17 (23.3%)	<0.001	5 (6.8%)	64 (87.7%)	4 (5.5%)	0.755
No (n = 921)	48 (5.2%)	839 (91.1%)	34 (3.7%)		45 (4.88%)	828 (89.9%)	48 (5.21%)	
Preterm labor								
Yes (n = 77)	4 (5.2%)	62 (80.5%)	11 (14.3%)	0.003	4 (5.19%)	65 (85.71%)	8 (10.38%)	0.001
No (n = 899)	45 (5%)	816 (90.8%)	38 (4.2%)		44 (4.9%)	815 (90.7%)	40 (4.4%)	
Abortion								
Yes (n = 18)	1 (5.5%)	15 (83.3%)	2 (11.1%)	0.446	2 (11.1%)	12 (66.7%)	4 (22.2%)	0.001
No (n = 976)	49 (5.02%)	878 (89.86%)	49 (5.02%)		48 (4.9%)	880 (90.2%)	48 (4.9%)	
Low birth weight								
Yes (n = 60)	4 (6.7%)	46 (76.7%)	10 (16.7%)	<0.001	5 (8.33%)	54 (90%)	1 (1.66%)	0.23
No (n = 915)	45 (4.9%)	831 (90.8%)	39 (4.3%)		43 (4.7%)	825 (90.2%)	47 (5.1%)	

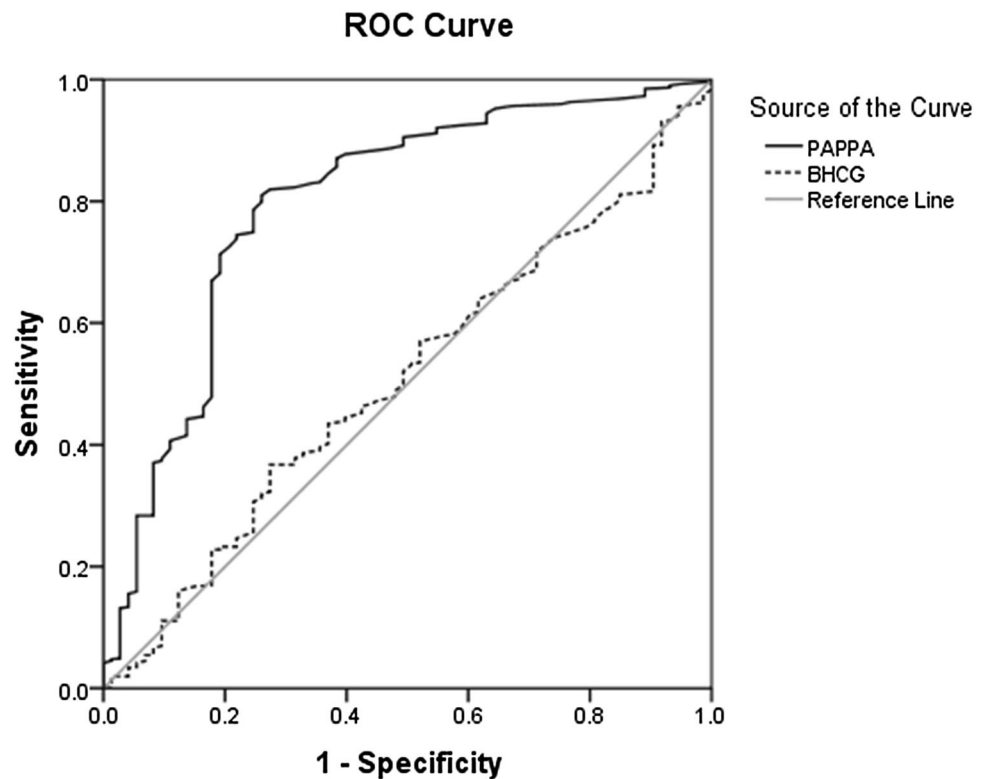**Fig. 1** Diagnostic value of PAPP-A for detecting of preeclampsia according to ROC

Table 3 Diagnostic value of PAPP-A for detecting of adverse pregnancy outcomes according to ROC

	Cut off	y	D	Sensitivity	Specificity	PPV (%)	NPV (%)	AUC	p value
Preeclampsia	0.585	0.55	0.103	0.81	0.74	23.6	97.5	0.797	<0.001
Preterm labor	0.745	0.349	0.211	0.674	0.675	84.92	95.88	0.712	<0.001
Low birth weight	0.705	0.406	0.176	0.711	0.70	13.4	97.1	0.717	<0.001

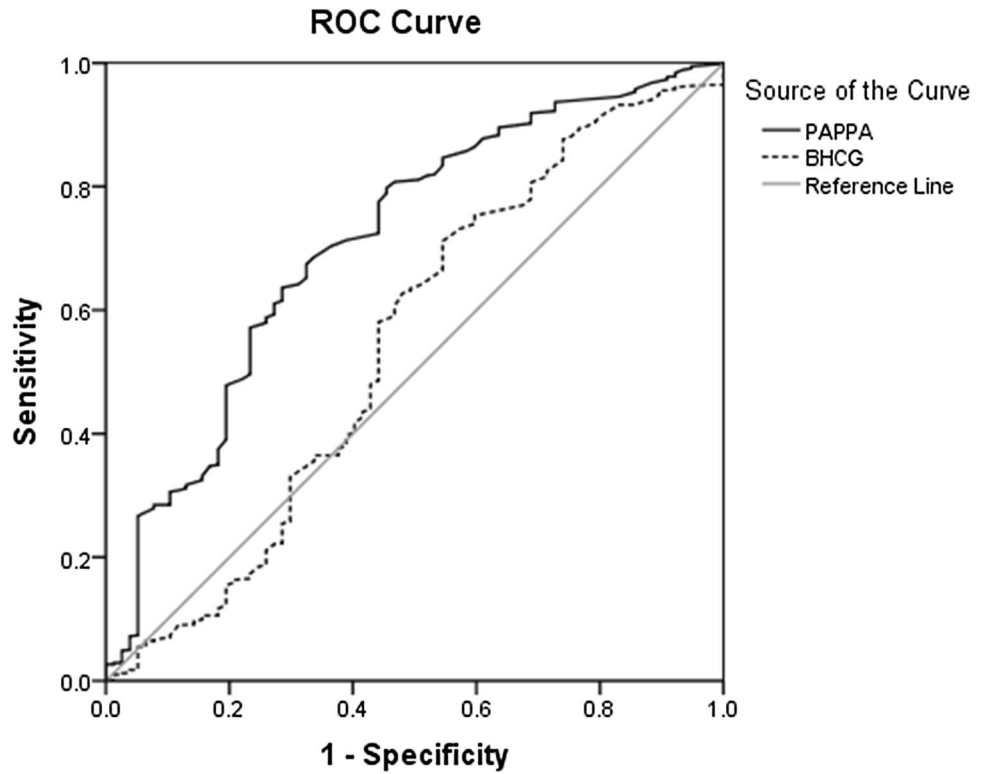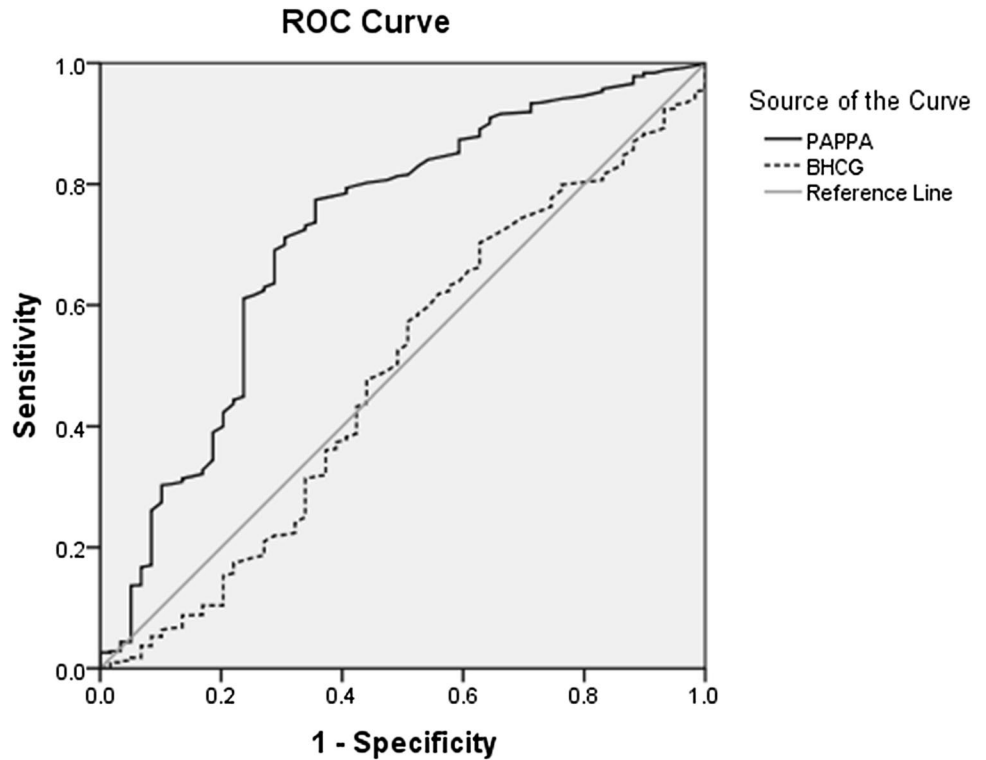**Fig. 2** Diagnostic value of PAPP-A for detecting preterm labor according to ROC

Fig. 3 Diagnostic value of PAPP-A for detecting low birth weight according to ROC

in preeclampsia, whereas this was higher than the prevalence in Iran. Kharaghani et al. [12] estimated preeclampsia prevalence in Iran as 5% in a systematized meta-analysis of the literatures, until year 2014. This is variable in different countries around the world, such as 3.4% in the USA [13] and 3.2–12% in the Asia–pacific [14–16].

Preeclamptic Asian parturients suffer the worst outcome compared with other countries, as it has been reported that 10% of the Asian maternal mortalities are due to preeclampsia [12, 17]. This discloses the importance of searching for predictive factors of preeclampsia. The lower mean PAPP-A in preeclamptic parturients (0.61 ± 0.46) in comparison with non-preeclamptic (1.14 ± 0.69) revealed a significant relationship between the lower first-trimester PAPP-A and preeclampsia incidence. The results of studies conducted in the recent years in Iran, Canada, India, the USA, Finland, Turkey, and England indicate the same relationship as the current study [18–25]. However, Karahasanovic et al. [26] from Denmark and Gupta et al. [27] from India reported that although the PAPP-A level in preeclamptic parturients was lower than non-preeclamptics, this difference was not significant; this could be related to the research method, which was a case–control study. Furthermore, Morris et al. [4] planned a meta-analysis on 175,000 pregnancies and proved that lower level of PAPP-A has a relationship with preeclampsia (1.94 odds ratio). Allen et al. also estimated preeclampsia odds ratio in relation with lower PAPP-A levels, as 2.1, 2.6, and 1.6 with 95% CI in a meta-analysis on more than 65,000 parturients. They determined PAPP-A cutoff of 0.585 with 81% sensitivity and 74% specificity [28]. Compared to Yücel et al. [24] from Turkey, the current study indicated a higher sensitivity for this variable (81% vs. 63.41%). The former study in Iran suggested PAPP-A cutoff of 1.65 and AUC 0.793 with 60% sensitivity and 78% specificity [18].

This search indicated that mean β-hCG level was higher in preeclampsia parturient. Although the relationship was not significant, the results were similar to those of the current study [9]. However, Yliniemi, Karahasanovic, Keikkala, and their colleagues suggested lower β-hCG levels in preeclamptic mothers [22, 26, 29], which requires more studies in this field. The current research indicated that β-hCG is not a useful factor for predicting preeclampsia, which differs from the results of Keikkala et al.'s study [29], yet is related to Ozdamar's study from Turkey [23]. This study revealed that lower PAPP-A and β-hCG levels had a relationship with preterm labor, which corresponds with Kirkegaard's study from Denmark [30]. Researches carried out in India [27, 31], Thailand [7], the USA [32], and England [33] confirm the same results, whereas in studies from Turkey [34], PAPP-A level had a relationship with preterm labor, yet β-hCG did not. A meta-analysis on 175,000 conceptions revealed lower PAPP-A levels in relationship with preterm labor (0.2, 2.09) [4]. It was determined that PAPP-A cutoff of 0.745 (AUC: 0.712) had 67.4% sensitivity and 67.5% specificity for preterm birth predication; however, β-hCG was not useful for this prediction. The current results are similar to studies of Dane et al. [34] from Turkey and Cohen et al. [5] from the USA.

In this research, no relationship was detected among PAPP-A and β-hCG levels with abortion incidence, although incidence was higher with lower β-hCG. Therefore, PAPP-A and β-hCG are not useful indicators for abortion prediction. The results of Quattrocchi et al. [35] from Italia and Kaitu'u-Lino et al. [36] from Australia were in discordance with the current study and revealed significant lower PAPP-A and β-hCG levels in abortions.

According to the current study, lower PAPP-A levels correlated with lower birth weight, whereas β-hCG did not. The current results correspond with studies from Denmark [8], India [27], Thailand [7], Korea [11], Finland [37], Turkey [34], Germany [38], and England [33]. However, Karagiannis et al. [39] from England indicated that lower β-hCG also correlates with lower birth weight. This discordance could probably be due to the lower sample size of the current study.

The role of low levels of PAAPA for low birth weight prediction is so prominent that Baer et al. [40] proved that lower PAPP-A levels in all gestational weeks could predict low birth weight. The results of Morris et al.'s meta-analysis in 2017 detected that lower PAPP-A predicts low birth weight with 2.83 odds ratio [4]. Cutoff was 0.705 with AUC = 0.717, 70.1% sensitivity, and 71% specificity. In spite of β-hCG, PAPP-A seems appropriate for low birth weight prediction. This corresponded with the researches of Gundu et al. [31] from India and Cohen et al. [5] from the United States.

The limitation of this study was lack of a cohort or case–control format. Another weakness was lack of measurement of other markers as predictive factors. The current researchers suggest more meta-analyses in this field regarding the variable results around the world.

Conclusions

The result of this study revealed that lower PAPP-A and β-hCG levels could be predictive factors in preterm labor and lower PAPP-A levels would be useful in low birth weight and preeclampsia prediction. Also, this study indicated that PAPP-A measurements could be a screening test for adverse pregnancy outcomes, such as preeclampsia, low birth weight, and preterm labor.

Compliance with Ethical Standards

Conflict of interest The authors declared no conflict of interest.

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