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ORIGINAL INVESTIGATION / ÖZGÜN ARAŞTIRMA

The Efficacy of First Trimester Maternal PAPP-A and Free ß-hCG Levels in Predicting Adverse Pregnancy Outcomes

İlk Trimester Maternal PAPP-A ve Serbest ß-hCG Düzeylerinin Kötü Gebelik Sonuçlarını Öngörmedeki Etkinliği

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ABSTRACT

Objective: This study aimed to determine the efficacy of first trimester maternal pregnancy associated plasma protein-A (PAPP-A) and free human chorionic gonadotropin (ß-hCG) levels in predicting adverse pregnancy outcomes.

Method: A total of 1104 women (mean±SD age: 29.1±5.7 years) with singleton pregnancies who had antenatal first trimester screening test within 11–14th gestational weeks were included in this retrospective study. Data on obstetric and fetal characteristics and adverse pregnancy outcomes were recorded. PAPP-A and ß-hCG, based on multiples-of-median (MoM) values, were categorized as normal (0.5–2.5 MoM) or abnormal (low: ≤0.49 MoM and high: >2.5 MoM) and they were evaluated by Odds ratio according to obstetric and fetal characteristics and adverse pregnancy outcomes.

Results: While the rates of intrauterine growth restriction (IUGR), preterm premature rupture of the membranes (PPROM), small for gestational age baby (SGA), neonatal death, gestational diabetes and abruptio placentae were found to be higher in pregnant women with PAPP-A level of 0.49 and below, there was no difference in large for gestational age baby (LGA) rates. While the rates of abortion, preeclampsia, IUGR, SGA, preterm labor, abruptio placentae, and gestational hypertension were found to be significantly higher in pregnant women with ß-hCG level of 0.49 and below, no difference was found in terms of abortion, preeclampsia, preterm delivery, gestational hypertension, and LGA rates.

Conclusion: Since first-trimester maternal serum PAPP-A and ß-hCG levels are associated with IUGR, PPROM, SGA, neonatal death, gestational diabetes and abruptio placentae, it may be used to detect pregnant women requiring additional fetal surveillance.

Keywords: Adverse pregnancy outcomes, first trimester, PAPP-A, predictive value, ß-hCG

ÖZ

Amaç: Çalışmanın amacı, ilk trimester maternal serum gebelikle ilişkili plazma protein A (PAPP-A) ve serbest beta-human koryonik gonadotropin (beta-hCG) düzeylerinin kötü gebelik sonuçlarını öngörmedeki etkinliğini saptamaktır.

Yöntem: Bu retrospektif çalışmaya, tekil gebeliği olan ve 11 ila 14. gestasyonel haftalarda antenatal ilk trimester tarama testi yapılan toplam 1104 gebe dahil edildi. Obstetrik ve fetal özellikler ile kötü gebelik sonuçlarına ait veriler kaydedildi. PAPP-A ve beta-hCG medyan katsayıları (MoM) esas alınarak, normal (0,5–2,5 MoM), anormal (düşük: ≤0,49 MoM ve yüksek >2,5 MoM) şeklinde sınıflandırıldı ve bunlar Odds oranı kullanılarak obstetrik ve fetal özellikler ile kötü gebelik sonuçlarına göre değerlendirildi.

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Bulgular: PAPP-A düzeyi 0,49 ve altında olan gebelerde abortus, preeklampsi, intrauterin gelişme geriliği (IUGR), gestasyon haftasına göre küçük (SGA) bebek, preterm eylem, dekolman plasenta, gestasyonel hipertansiyon oranları bakımından normal olgulara göre anlamlı düzeyde yüksek saptandı. Gestasyon haftasına göre büyük (LGA) bebek oranları açısından fark saptanmadı. Beta-hCG düzeyi 0,49 ve altında olan gebelerde IUGR, preterm prematür membran rüptürü (PPROM), SGA, neonatal ölüm, gestasyonel diyabet ve dekolman plasenta oranları normal olgulara göre yüksek saptanırken abortus, preeklampsi, preterm eylem, gestasyonel hipertansiyon ve LGA oranları açısından fark saptanmadı.

Sonuç: İlk trimester maternal serum PAPP-A ve beta-hCG düşüklüğü IUGR, PPROM, SGA, neonatal ölüm, gestasyonel diyabet ve dekolman plasenta ile ilişkili bulunması nedeniyle ek fetal izlem gerektiren gebelerin tespitinde kullanılabilir.

Anahtar kelimeler: İlk trimester, olumsuz gebelik sonuçları, PAPP-A, prediktif değer, beta-hCG

INTRODUCTION

The first trimester maternal serum pregnancy-associated plasma protein-A (PAPP-A) and free β-human chorionic gonadotropin (β-hCG) testing is widely used in prenatal screening for detection of pregnancies with fetal trisomies 21, 18, and 13.[1–5] However, data from follow-up studies have also revealed their utility in estimating adverse pregnancy outcomes in the presence of confirmed normal fetal karyotype, which resulted in concerns regarding the fetal well-being in these 'high-risk' pregnancies.[3–6]

Therefore, low maternal serum levels of PAPP-A and/or β-hCG in the first trimester have been reported to be associated with increased risk of low birth weight, preterm delivery, miscarriage, intrauterine growth restriction (IUGR), small for gestational age (SGA).[3–5,7–9] However, while some studies have indicated low levels of serum PAPP-A are associated with early-onset placental dysfunction and thus adverse obstetric and neonatal outcome in euploid fetuses, low sensitivity and week-to-moderate association has also been emphasized as major drawbacks.[3,4,7–11] In addition, the association between pregnancy complications and low levels of β-hCG is considered to be less clear.[4,7,11–13] Particularly, the association between these maternal serum analytes and adverse outcomes remains controversial with no current guidelines available for optimal surveillance of the suggested high-risk pregnancies.[3,4,11,14–17]

The aim of this study was to determine the utility of first trimester maternal PAPP-A and ß-hCG levels in predicting adverse pregnancy outcomes in singleton pregnancies.

METHOD

Study Population

A total of 1104 women (mean±SD age: 29.1±5.7 years) with singleton pregnancies who had antenatal first trimester screening test (PAPP-A and ß-hCG) within 11–14th gestational weeks of antenatal follow up and then regularly followed until delivery at İstanbul Kanuni Sultan Süleyman Health Training and Research Hospital were included in this retrospective study between July 2012 and February 2014.

This study was conducted in accordance with the ethics principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee (date of approval: 25/04/2014; protocol no: KAEK/2014/1/5).

Study Parameters

Data on maternal age, height, weight, body mass index (BMI), hypertension, insulin dependent diabetes, smoking, obstetric (gravidity, parity, abortion and delivery type) and fetal characteristics, adverse pregnancy outcomes including gestational diabetes, gestational hypertension, preeclampsia, preterm premature rupture of the membranes (PPROM), placental abruption, abortion, IUGR, SGA, large for gestational age (LGA), preterm delivery and neonatal mortality were recorded.

PAPP-A and ß-hCG, based on multiples of median (MoM) values, were categorized as normal (0.5–2.5 MoM) or abnormal (low: ≤0.49 MoM and high: >2.5 MoM) and were evaluated according to obstetric and fetal characteristics, the pregnancy complications and fetal adverse outcomes. The odds ratios (OR) of adverse outcomes were analyzed for combined risk incorporating both biochemical parameters and then separately for each parameter.

Adverse Outcomes

Abortus was defined as pregnancy loss prior to 20 completed weeks' gestation. Gestational hypertension was considered as increase in systolic blood pressure by >30 mmHg and increase in diastolic blood pressure by >15 mmHg compared to pre-pregnancy or first trimester values along with a recorded blood pressure of >140/90 mmHg at two consecutive measurement. Preeclampsia was considered in case of hypertension accompanied with edema and proteinuria emerging after 20 completed weeks of gestation. Placental abruption was considered as the early separation

Table 1. Maternal characteristics, obstetric history and first trimester screening for ß-hCG plus PAPP-A

Maternal characteristics	n	%	Mean±SD	Min-max
Age (year)			29.1±5.7	16–46
Height (cm)			159.0±6.0	151–171
Weight (kg)			64.1±11.3	40–123
BMI (kg/m^2)			25.3±4.8	15.43–53.95
Hypertension	58	5.3		
Insulin dependent diabetes mellitus	38	3.4		
Smoking	85	7.7		
Test week			12.2±0.7	10–14
Obstetric history				
Gravidity			2	1–11
Parity			1	0–10
Abortion			0	0–8
ß-hCG (MoM)			1.36±1.14	0.11–7.55
PAPP-A (MoM)			1.11±1.08	0.08–10.37

Test categories	Normal (0.5-2.5 MoM)		Low (≤0.49 MoM)		High (>2.5 MoM)	
	n	%	n	%	n	%
ß-hCG (MoM)	612	55.4	301	27.3	191	17.3
PAPP-A (MoM)	585	53.0	396	35.9	123	11.1

ß-hCG: Beta-human chorionic gonadotropin; PAPP-A: Pregnancy-associated plasma protein-A; BMI: Body mass index

of a normally placed placenta from the lining of the uterus before completion of the second stage of labor. PPROM referred to rupture of fetal membranes prior to labor before 37 weeks of gestation.

SGA and LGA were considered for a fetal birthweight being less than expected for the gestational age (<10. percentile) and more than expected for the gestational age (>90. percentile), respectively. Fetal, perinatal, and neonatal mortality were considered for intrauterine death of a fetus >500 g, death of a fetus at ≥28. gestational week and death within the first seven days postpartum, respectively. IUGR was considered as fetal weight <10. percentile of the gestational week accompanied with oligohydramnios and pathologic fetal Doppler findings. Preterm delivery was defined as a spontaneous delivery before 37 completed weeks of gestation.

Statistical Analysis

Statistical analysis was made using NCSS 2007 statistical Software (Utah, USA). Chi-square (χ^2) test and OR were used for the comparison of categorical data. Independent sample t-test was used for parametric variables. Data were expressed as mean±standard deviation (SD), 95% confidence interval (CI) and percent (%) where appropriate. A p-value less than 0.05 was considered statistically significant.

RESULTS

Maternal Characteristics, Obstetric History and Screening for ß-hCG and PAPP-A

Maternal characteristics, obstetric history and screening for ß-hCG and PAPP-A are shown in Table 1. ß-hCG levels per se were normal in 612 (55.4%) pregnancies, low in 301 (27.3%) and high in 191 (17.3%) pregnancies, while the PAPP-A-levels per se were normal in 585 (53.0%) pregnancies, low in 396 (35.9%) and high in 123 (11.1%) pregnancies (Table 1).

Maternal and Obstetric Characteristics with Respect to ß-hCG and PAPP-A

No significant difference was noted between pregnant women with low vs. normal findings on combined PAPP-A and

Table 2. Maternal characteristics according to normal and abnormal ß-hCG and PAPP-A groups

	ß-hCG and PAPP-A				p
	Abnormal (≤0.49 MoM) (n=250)		Normal (0.5-2.5 MoM) (n=516)		
	n	%	n	%	
Maternal characteristics					
Age (year), mean±SD	28.62±5.39		29.16±5.85		0.216
Height (cm), mean±SD	160±6		159±6		0.240
Weight (kg), mean±SD	64.4±11.15		63.83±11.79		0.522
Body mass index (kg/m^2), mean±SD	25.28±4.8		25.19±4.87		0.818
Hypertension	18	7.2	40	4.7	0.117
Insulin dependent diabetes	7	2.8	31	3.6	0.527
Smoking	18	7.2	67	7.9	0.736
Delivery type					
Cesarean section	127	50.8	448	52.5	0.644
Vaginal delivery	123	49.2	406	47.5	
Fetal sex					
Female	121	48.4	414	48.5	0.983
Male	129	51.6	440	51.5	

PAPP-A: Pregnancy-associated plasma protein-A; ß-hCG: Beta-human chorionic gonadotropin

ß-hCG testing in terms of maternal characteristics, delivery type or fetal sex (Table 2).

Adverse Pregnancy Outcomes with Respect to ß-hCG results

Low vs. normal ß-hCG levels were associated with higher likelihood of certain adverse pregnancy outcomes, and the strongest associations were noted for neonatal mortality placental abruption, gestational diabetes and SGA (Table 3, Fig. 1).

High vs. normal ß-hCG levels were only associated with lower likelihood of gestational hypertension and higher likelihood of gestational diabetes (Table 3, Fig. 1).

Adverse Pregnancy Outcomes with Respect to PAPP-A levels

Low vs. normal PAPP-A levels were associated with higher likelihood of several adverse pregnancy outcomes, and the strongest associations were noted for placental abruption, SGA, IUGR, abortion, gestational diabetes, neonatal mortality, preeclampsia and PPROM (Table 4, Fig. 1).

High vs. normal PAPP-A levels were also associated with higher likelihood of certain adverse pregnancy outcomes such as placental abruption, abortion and neonatal mortality (Table 4, Fig. 1).

DISCUSSION

Consistent with some literature, our findings revealed significant association of abnormal first trimester maternal PAPP-A and ß-hCG levels with increased likelihood of certain pregnancy adverse outcomes, such as PPROM, placental abruption, SGA, IUGR, preterm birth, preeclampsia, abortion, stillbirth and gestational hypertensive disorders.[4,7,8,13,18–23]

In addition, our findings indicated poorer performance of first trimester maternal ß-hCG testing than PAPP-A testing in predicting the risk for placental abruption, gestational diabetes, PPROM, neonatal mortality, SGA and IUGR. Moreover, no significant association of ß-hCG values was noted with the risk of developing preeclampsia, abortion or preterm birth, despite all were strongly predicted by PAPP-A (Table 3). These findings seem consistent with the consideration of the association between low levels of β-hCG and pregnancy complications to be obscure and less clear than low PAPP-A levels, as reported to be associated only with some adverse pregnancy outcomes such as fetal loss, IUGR, and low birth weight.[4,7,12,13]

In the present study, low PAPP-A values were most strongly predictive for increased risk of placental abruption and IUGR amongst the adverse outcomes, while predictive value of low

Table 3. Pregnancy complications and fetal adverse outcomes with respect to ß-hCG results

	ß-hCG											
	Normal (0.5–2.5 MoM) (n=612)		Abnormal Low (≤0.49 MoM) (n=301)		Abnormal High (>2.5 MoM) (n=191)		OR	Low vs. normal %95 CI (LL-UL)	p	OR	High vs. normal %95 CI (LB-UB)	p
	n	%	n	%	n	%						
Pregnancy complications												
Abortion	73	11.9	45	14.9	25	13.1	1.29	0.87–1.94	0.240	1.11	0.68–1.80	0.736
Gestational hypertension	51	8.3	23	7.6	7	3.7	0.91	0.54–1.52	0.817	0.41	0.19–0.94	**0.044**
Gestational diabetes	67	10.9	77	25.6	33	17.3	2.79	1.94–4.02	**<0.001**	1.69	1.08–2.67	**0.028**
Preeclampsia	41	6.7	18	5.9	14	7.3	0.89	0.50–1.57	0.785	1.1	0.59–2.06	0.891
Placental abruption	10	1.6	15	4.9	4	2.1	3.15	1.4–7.11	**0.007**	1.29	0.4–4.15	0.914
PPROM	40	6.5	45	14.9	17	8.9	2.51	1.6–3.95	**<0.001**	1.39	0.77–2.53	0.342
Fetal adverse outcomes												
IUGR	46	7.5	43	14.3	21	10.9	2.05	1.32–3.19	**0.002**	1.52	0.88–2.62	0.171
SGA	44	7.2	52	17.3	14	7.3	2.69	1.76–4.13	**<0.001**	1.02	0.54–1.91	0.948
LGA	11	1.8	8	2.7	4	2.1	1.49	0.59–3.74	0.542	1.17	0.37–3.71	0.791
Preterm birth	44	7.2	25	8.3	17	8.9	1.17	0.7–1.95	0.641	1.27	0.71–2.28	0.518
Neonatal mortality	7	1.1	17	5.7	4	2.1	5.17	2.12–12.62	**0.002**	1.85	0.53–6.38	0.528

ß-hCG: Beta-human chorionic gonadotropin; OR: Odds ratio; CI: Confidence interval; LL: Lower limit; UL: Upper limit; LB: Lower bound; UB: Upper bound; PPROM: Preterm premature rupture of the membranes; IUGR: Intrauterine growth retardation; SGA: Small for gestational age; LGA: Large for gestational age

β-hCG was much lower for these outcomes. This supports the growing evidence that decreased PAPP-A is associated with a delivery of a SGA baby at the end of pregnancy.[24–28]

In a study with 8012 pregnant women on the association between first-trimester trisomy 21 screening markers with adverse pregnancy outcome, the authors have reported that PAPP-A <1. percentile (OR 5.4) and PAPP-A <5. percentile (OR 2.7) and ß-hCG <1. percentile (OR 2.7) were associated with increased risk of IUGR with positive predictive values of 24.1%, 14.1%, and 14.3%, respectively, while PAPP-A <5. percentile (OR 2.3) was also associated with increased risk of preterm delivery before 34 weeks of gestation.[7] The authors have also noted that the especially high predictive power of PAPP-A levels for IUGR suggests the likelihood of patients in this group to benefit from increased surveillance for this condition.[7]

Especially in the present study, not only abortion but also placenta-related complications (preeclampsia, placental abruption) and fetal adverse outcomes (preterm delivery, SGA, IUGR and neonatal mortality) had strong relationships particularly with low PAPP-A levels, suggesting that the potential benefit increased surveillance in patients at risk of these conditions. Indeed, the strong predictive role of low PAPP-A for several pregnancy complications and fetal adverse outcomes in the present study seems consistent with the association of decreased production of PAPP-A with lower placental size, decreased placental perfusion and lower umbilical artery pH as well as the increased risk for intrapartum fetal distress development and preterm delivery.[13,18,29,30]

The differences in PAPP-A levels, especially the extremely low PAPP-A levels enabling higher predictivity for adverse neonatal outcomes, is suggested to emphasize the likelihood of more careful and delicate antepartum surveillance to be required for avoiding adverse perinatal outcomes in that selected group of patients.[30,31] Therefore, our findings emphasize the likelihood of a high-risk maternal serum screen, the abnormal-low PAPP-A in particular, to be useful clinical biomarker to identify the women requiring additional fetal surveillance for increased risk of early pregnancy complications as well as adverse fetal outcomes.[3,32]

Nonetheless, it should be noted that the association between these maternal serum makers and abnormal pregnancy outcomes remains controversial mostly due to overall low sensitivity and high false-positive rates.[3,14–17] Hence, despite presence of a number of associations with adverse outcomes,

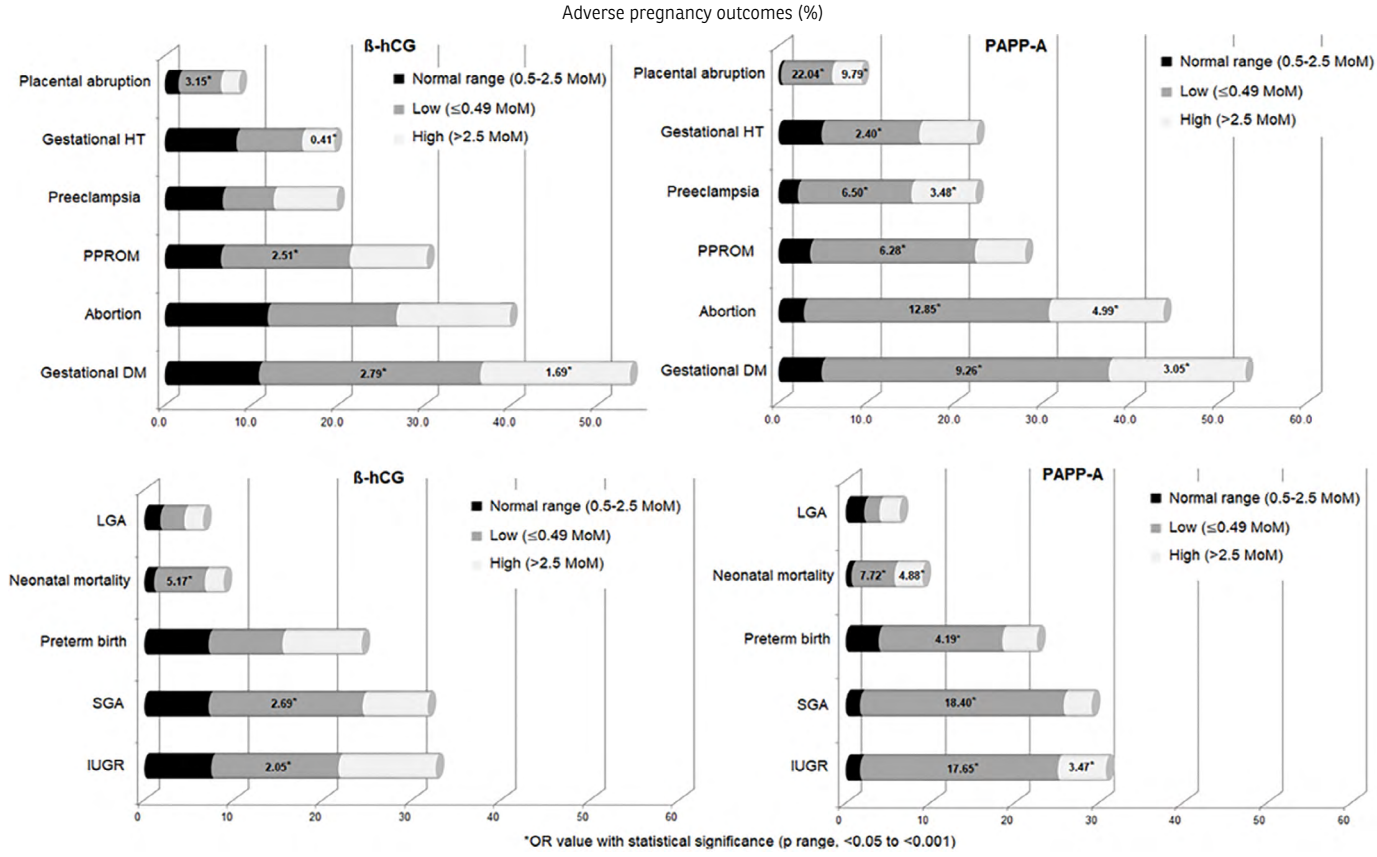

Figure 1. Adverse pregnancy outcomes according to PAPP-A and ß-hCG results

PAPP-A: Pregnancy-associated plasma protein-A; ß-hCG: Beta-human chorionic gonadotropin

especially in case of PAPP-A, some studies have indicated that neither of these tests have appropriate performance characteristics to be considered as screening tests, limiting their utility as effective surveillance tools in chromosomally normal pregnancies.[3,4,23,27]

Both low and high abnormal levels of β-hCG and PAPP-A were associated with increased likelihood of gestational diabetes in our cohort. Likewise, previous studies have reported that first-trimester β-hCG could predict second-trimester gestational diabetes diagnosis,[12,21,33] while high β-hCG levels have also been reported to be an independent risk factor for the development of gestational diabetes.[34] In addition, low PAPP-A has also been reported to predict gestational diabetes development with a sensitivity of 73.3–81.4%, specificity of 50.5–57.3% and an area under curve of 0.61–0.70.[35,36] Thus, PAPP-A is considered useful as the first-trimester of pregnancy predictor for gestational diabetes development but with limited utility in gestational diabetes diagnosis in the second-trimester of pregnancy.[33,35–37]

Major strength of the current study seems to the close similarity between groups in most of the potentially confounding variables such as obstetric and fetal characteristics, and the comprehensive analysis of low and high levels for ß-hCG and PAPP-A as compared with normal-range in several subgroups of pregnancy complications and fetal adverse outcomes. However, certain limitations to this study should be considered. First, due to the retrospective single center design, a small sample size as well as potential bias during validation of data retrieved from hospital records could not be excluded. Second, lack of data on a longer-term follow-up and combined analysis of other potential predictor factors (i.e., maternal age, weight, smoking) is another limitation which otherwise would extend the knowledge achieved in the current study.

In conclusion, our findings indicate the utility of high-risk first-trimester screening, particularly low PAPP-A levels, in predicting adverse pregnancy and fetal outcomes in singleton pregnancies, and thus in identifying women requir-

Table 4. Pregnancy complications and fetal adverse outcomes with respect to PAPP-A results

	PAPP-A											
	Normal (0.5–2.5 MoM) (n=585)		Abnormal Low (≤0.49 MoM) (n=396)		Abnormal High (>2.5 MoM) (n=123)		OR	Low vs. normal %95 CI (LL-UL)	p	OR	High vs. normal %95 CI (LB-UB)	p
	n	%	n	%	n	%						
Pregnancy complications												
Abortion	17	2.9	110	27.8	16	13.0	12.85	7.56–21.84	**<0.001**	4.99	2.45–10.2	**<0.001**
Gestational hypertension	29	4.9	44	11.1	8	6.5	2.4	1.47–3.9	**0.005**	1.33	0.59–2.99	0.633
Gestational diabetes	29	4.9	129	32.6	19	15.5	9.26	6.03–14.21	**<0.001**	3.5	1.89–6.48	**<0.001**
Preeclampsia	13	2.2	51	12.9	9	7.3	6.5	3.49–12.13	**<0.001**	3.48	1.45–8.32	**0.007**
Placental abruption	2	0.3	23	5.8	4	3.3	22.04	5.16–94.15	**<0.001**	9.79	1.77–54.13	**0.008**
PPROM	21	3.6	74	18.7	7	5.7	6.28	3.8–10.39	**<0.001**	1.62	0.67–3.9	0.405
Fetal adverse outcomes												
IUGR	10	1.7	93	23.5	7	5.7	17.65	9.06–34.39	**0.001**	3.47	1.29–9.31	**0.022**
SGA	10	1.7	96	24.2	4	3.3	18.4	9.45–35.82	**<0.001**	1.93	0.59–6.27	0.447
LGA	13	2.2	7	1.8	3	2.4	0.79	0.31–2	0.719	1.11	0.31–3.92	0.883
Preterm birth	23	3.9	58	14.7	5	4.1	4.19	2.53–6.92	**<0.001**	1.03	0.38–2.78	0.945
Neonatal mortality	4	0.7	20	5.1	4	3.3	7.72	2.62–22.79	**<0.001**	4.88	1.2–19.8	**0.048**

PAPP-A: Pregnancy-associated plasma protein-A; OR: Odds Ratio; CI: Confidence interval; LL: Lower limit; UL: Upper limit; LB: Lower bound; UB: Upper bound; PPROM: Preterm premature rupture of the membranes; IUGR: Intrauterine growth retardation; SGA: Small for gestational age; LGA: Large for gestational age

ing additional fetal surveillance. Low PAPP-A levels seem to be most strongly predictive for placental abruption, SGA and IUGR, followed by abortion, gestational diabetes, preeclampsia, neonatal mortality, PPROM, preterm birth and gestational hypertension, suggesting that pregnant women at risk of these conditions may benefit from increased surveillance. Low ß-hCG levels seem to be a less powerful indicator of adverse outcomes related to placental abruption, gestational diabetes, PPROM, neonatal mortality, SGA and IUGR along with no significant role in predicting the risk of developing preeclampsia, abortion or preterm birth. Nonetheless, the predictive efficacy of PAPP-A and ß-hCG should be further evaluated in larger scale, longer-term and combined marker analysis studies in terms of their clinical utility and performance characteristics as screening tests to justify their clinical utility as effective tools for closer surveillance of adverse pregnancy outcomes.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul Kanuni Sultan Suleyman Health Training and Research Hospital Clinical Research Ethics Committee (No: KAEK/2014/1/5, Date: 25/04/2014).

Informed Consent: Written informed consent was obtained from all patients.

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