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Original Article

The predictive value of maternal serum screening tests for adverse pregnancy outcomes

Gulten Ozgen, Gultekin Adanas Aydin

Bursa Yuksek Ihtisas Education and Training Hospital, Clinic of Gynaecology and Obstetrics, Bursa, Turkey

Abstract

Aim: Free beta-human chorionic gonadotropin (Fβ-hCG), pregnancy-associated plasma protein-A (PAPP-A), alpha-fetoprotein (AFP), unconjugated estriol (uE3), and inhibin-A have been shown to be useful not only in identifying chromosomal abnormalities in the first and second trimesters, but also in predicting adverse pregnancy outcomes (APOs). In this study, we aimed to investigate the predictive value of maternal serum screening tests for various APOs including preeclampsia, intrauterine growth retardation (IUGR), preterm labor, and gestational diabetes mellitus (GDM).

Material and Methods: The study was carried out at our clinics and included a total of 220 pregnant women who respectively underwent the double and quadruple marker testsduring the 11th to 14th and 15th to 22nd gestational weeksbetween January 2017 and December 2018. Patient data (maternal age, parity/gravidity, gestational age, history of infertility, use of *in vitro* fertilization, maternal/fetal complications, preterm labor, mode of delivery, birth weight, and length of stay in the neonatal intensive care unit) were reviewed retrospectively.

Results: The AFP levels were statistically significantly higher in patients with IUGR (p=0.022),GDM (p=0.036), and preterm labor (p=0.021), compared to the control group with no APO. No significant correlation was found between preeclampsia and the serum markers.

Conclusion: Our results show that elevated maternal serum AFP levels might be associated with various APOs,requiring closer patient follow-up for early diagnosis and treatment.

Keywords: Adverse pregnancy outcomes; pregnancy; serum screening markers

INTRODUCTION

Over the last two decades,non-invasive first- and second-trimester screening tests as well as maternal age and ultrasonographic findings have been widely used for the early detection of chromosomal abnormalities such as fetal aneuploidy, neural tube defect, and trisomy 18 and 21 (1). During the late 1980s, maternal serum alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and unconjugated estriol (uE3) were commonly used as the triplemarker test (2-4). In 1996, inhibin-A was discovered and added to these three markers to form the quadruple test (5), which is often done during the 15th to 22nd gestational weeks. Like the double marker test, which measures nuchal translucency (NT), β-hCG, and pregnancy-associated plasma protein-A (PAPP-A) in the first trimester, the quadruple marker test is a highly sensitive (~83%), early diagnostic test for Down syndrome (6,7).

Previous studies have demonstrated that the first- and second-trimester screening tests have a high predictive value for APOs such as preterm labor, preterm premature rupture of membranes (PPROM), intrauterine growth retardation (IUGR), gestational diabetes mellitus (GDM), and preeclampsia (PE) (8,9). In women with no evidence of chromosomal abnormality or neural tube defects, the presence of at least one abnormal test result is associated with an increased risk of fetal and neonatal mortality (10).

Also, several studies have associated abnormal results from the triple and quadruple tests with APOs and shown that maternal/fetal complications are more frequent than neural tube defects and aneuploidies. Explanations of the underlying mechanisms have been based on abnormal placentation and perfusion. Although in most cases these complications occur in later stages of pregnancy, most of them are related to placental ischemia in the first trimester, which makes them potentially predictable in early pregnancy screening programs (11,12).

In this study, we aimed to investigate the predictive value of maternal serum screening tests for various APOs and

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Corresponding Author: Gultekin Adanas Aydin, Bursa Yuksek Ihtisas Education and Training Hospital, Clinic of Gynaecology and Obstetrics, Bursa, Turkey **E-mail:** gadanas@gmail.com

provide information for early diagnosis strategies and specialized care plans.

MATERIAL and METHODS

This retrospective study was carried out at the obstetrics and gynecology outpatient clinics of the Bursa Yuksek Ihtisas Training and Research Hospital between January 2017 and December 2018 and included a total of 220 pregnant women who respectively underwent the double and quadruple marker tests in the 11th to 14th and 15th to 22nd gestational weeks. The inclusion criteria were as follows: pregnancy with live fetus, crown–rump length between 45 and 84 mm during the 11th to 14th gestational weeks, and 15- to 22-week gestation for the quadruple marker test. Women with fetal aneuploidy or neural tube defects and multiple pregnancies were excluded from the study. Additional exclusion criteria were as follows: NT >3.5 mm, suspicious fetal ultrasonographic findings, amniocentesis positivity, and presence of maternal cardiovascular diseases, chronic hypertension, diabetes mellitus, renal failure, thalassemia, hypo- or hyperthyroidism and congenital diseases. Written informed consent was obtained from each participant. The study protocol was approved by the Institutional Ethics Committee (2011-KAEK-25, 2019/02-17). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Medical records of the participants (demographic data, maternal age, parity/gravidity, gestational age, history of infertility, use of *in vitro* fertilization, maternal/fetal complications including GDM, gestational hypertension, IUGR, oligo-polyhydramnios, ablatio placentae, postpartum hemorrhage, preterm labor, mode of delivery, birth weight, and length of stay in the neonatal intensive care unit) were reviewed retrospectively.

The PE diagnosis was based on the systolic blood pressure (≥140 mmHg) or diastolic blood pressure (≥90 mmHg) measurements after the 20th gestational week(performed twice in 4- to 6-hour intervals while the subject was resting) and 300 mg/dL proteinuria in a 24-hour urine sample or >1+ proteinuria in spot urine specimens.

The small for gestational age (SGA) (a birthweight below the 10th percentile for the gestational age)was also electronically computed (https://fetalmedicine.org/research/assess/growth).

The GDM screening was performed in the 24th to 28th gestational weeks. In addition to the double marker test, a 50-g glucose challenge test was performed and first-hour glucose levels exceeding 140 mg/dL were considered to indicatea 100-g 3-h oral glucose tolerance test. The GDM diagnosis was confirmed when two or more measurements were ≥95 mg/dL under fasting conditions, ≥180 mg/dL at 1 h, ≥155 mg/dL at 2 h, and ≥140 mg/dL at 3 h.

Preterm labor was defined as labor before the completion of the 37th week of gestation.

For the double-marker-test PAPP-A measurements during the11th to14th gestational weeks, blood samples were taken from the antecubital vein of the seated subject by using the vacutainer system. The serum was obtained by centrifugation at 4000 rpm for 15 min. The materials obtained were frozen at-80 °C prior to transportation. The IMMULITE immunoassay analyzer (Siemens Healthcare Diagnostics, Inc.) was used for the quantitative measurements of PAPP-A.

Measuring the maternal serum levels of the four biomarkers (AFP, hCG, uE3, inhibin-A), the quadruplemarker test was performed during the 15th to 22nd gestational weeks. The AFP, hCG, and uE3 levels were measured using the KRYPTOR compact PLUS (Thermo Fisher Scientific, Hennigsdorf, Germany) and the inhibin-A levels using the time-resolved amplified cryptate emission(TRACE) technology (Ansh Labs, Webster, TX,USA) and Immunomat (Institut Virion\Serion, Würzburg, Germany).

Statistical analysis

Statistical analysis was performed using the SPSS(v. 23.0) software package (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean±standard deviation (SD), median (min.–max.), and number, and frequency. A binary logistic regression model was used to examine the possible correlations between abnormalities and risk factors. In case of significant correlation between the double and quadruple marker test results and abnormalities, cut-off values were calculated using the receiver operating characteristic (ROC) curve. The sensitivity and specificity values were also calculated. $p<0.05$ was considered statistically significant

RESULTS

The mean participant age was 29.15±6.248 (range 16–42) years. Of the 220 participants, nine (4%) had IUGR, 12 (6.1%) had PE, seven (5.4%) gave birth before the 34th gestational week, 34 (15.4%) gave birth before the 37th gestational week, six (2.7%) had PPROM, two (0.9%) had postpartum hemorrhage, and 19 (8.6%) had GDM. The descriptive data are shown in Table 1.

The clinical and screening data of patients with and without IUGR are presented in Table 2. The mean AFP level was statistically significantly (1.024-fold) higher for the IUGR group ($p=0.022$). In addition, as AFP was the only significant parameter associated with IUGR based on the double and quadruplemarker tests, the optimal cut-off value was calculated as 42.55 ng/mL. The AFP parameter showed 69.9% sensitivity in discriminating patients withIUGR and 51.1% specificity in discriminating the non-IUGR cases.

Table 3 presents data based on the PE presence. The mean body mass index (BMI) and hCG values were higher in the PE patients ($p\leq0.10$). The mean E3, E3-multiple of the median (MoM), and AFP levels were also higher in these patients ($p\leq0.10$). However, no significant correlation was found between PE presence and the double and quadruple marker tests results.

Table 1. Descriptive data

Variable	n	Mean	SD	Min	Max	Percentile 25th	Percentile Median
Age, year	220	29.15	6.248	16	42	24.00	29.00
Height, cm	102	161.69	4.70	145.00	173.00	159.00	161.00
Weight, kg	172	67.42	11.86	42.00	120.00	59.00	67.00
BMI, kg/m^2	99	26.40	4.24	17.80	42.52	23.44	26.04
Gravida, n	137	2.50	1.26	1.00	8.00	2.00	2.00
Parity, n	135	1.61	1.12	.00	6.00	1.00	2.00
Abortus, n	134	.25	.57	.00	3.00	.00	.00
Gestational age, week	218	16.28	2.01	11.00	21.00	16.00	17.00
NT, mm	120	1.33	.35	.40	3.00	1.10	1.30
PAPP-A, ng/mL	120	3.54	4.07	.53	40.30	1.45	2.79
PAPP-A-MoM, MoM	105	1.72	6.34	.18	65.80	.67	.92
Double screening, hCG,mIU/mL	120	41.25	31.82	8.67	196.00	19.15	31.00
Double screening, hCG-MoM, MoM	107	1.03	.80	.21	4.31	.51	.73
Quadruple screening, hCG, mIU/mL	220	19009.41	12017.27	1444.00	101007.00	11462.00	16341.50
Quadruple screening, hCG-MoM, MoM	194	.82	.42	.11	2.74	.55	.74
E3, ng/mL	221	.75	.39	.13	2.23	.46	.69
E3-MoM	192	.72	.37	.22	3.59	.52	.66
AFP, ng/mL	218	46.52	20.81	14.60	136.00	32.80	42.75
AFP-MoM	190	1.21	.46	.38	3.09	.86	1.13
Inhibin-A, pg/mL	212	184.45	86.30	45.00	624.00	124.25	173.00
Inhibin-A-MoM, MoM	176	1.05	.51	.21	3.56	.68	.99
Labor week	200	38.26	1.97	28.00	42.00	38.00	39.00
APGAR score	197	9.00	.45	5.70	9.12	9.10	9.10
Birth weight, g	201	3248.46	567.35	930.00	4570.00	2965.00	3280.00

SD, Standard Deviation; min, minimum; max, maximum; BMI, Body Mass Index; NT, Nuchal Translucency; PAPP-A, Pregnancy-Associated Plasma Protein A; MoM, Multiples of Median; hCG, Human Chorionic Gonadotropin; E3, Estriol; AFP, Alpha Fetoprotein; APGAR, Appearance, Pulse, Grimace, Activity, and Respiration

Table 2. Descriptive data of patients with and without IUGR and serum biomarkers

	IUGR						OR	95% CI	
	No			Yes					
Variable	n	Mean	SD	n	Mean	SD		Lower	Upper
Age, year	179	28.93	6.17	17	30.53	7.41	1.042	0.962	1.128
BMI, kg/m^2	86	29.12	24.15	12	25.71	4.55	0.951	0.816	1.108
Gravida, n	119	2.51	1.27	15	2.33	1.11	0.883	0.555	1.406
Parity, n	117	1.66	1.15	15	1.33	0.82	0.748	0.437	1.278
NT,mm	99	1.33	0.35	9	1.27	0.20	0.541	0.062	4.751
PAPP-A, ng/mL	99	3.50	4.41	9	3.83	2.09	1.015	0.886	1.164
PAPP-A-MoM, MoM	86	1.10	0.64	9	1.03	0.63	0.840	0.266	2.653
Double screening, hCG, mIU/mL	99	41.47	32.77	9	48.06	33.13	1.005	0.987	1.024
Double screening, hCG-MoM, MoM	88	1.01	0.78	9	1.33	1.08	1.466	0.733	2.933
Quadruple screening, hCG, mIU/mL	179	18451.9	10523.7	17	24619.2	22866.1	1.000	1.000	1.000
Quadruple screening, hCG-MoM, MoM	158	0.82	0.40	14	0.85	0.49	1.195	0.334	4.274
E3, ng/mL	180	0.75	0.40	17	0.66	0.37	0.504	0.118	2.158
E3-MoM	156	1.05	4.11	14	0.61	0.23	.217	.022	2.150
AFP,ng/mL	178	45.05	19.24	16	57.83	30.04	1.024	1.003	1.045
AFP-MoM	155	1.19	0.45	14	1.36	0.67	1.960	.707	5.432
Inhibin-A, pg/mL	177	187.70	102.14	14	217.20	81.93	1.004	.998	1.009
Inhibin-A-MoM, MoM	147	1.63	7.11	9	1.25	0.58	1.811	.633	5.178
Labor week	182	3330.93	504.97	18	2437.78	541.26	0.997	0.996	0.999

IUGR, Intrauterine Growth Retardation; OR, Odds Ratio; CI, Confidence Interval; SD, Standard Deviation; BMI, Body Mass Index; NT, Nuchal Translucency; PAPP-A, Pregnancy-Associated Plasma Protein A; MoM, Multiples of Median; hCG, Human Chorionic Gonadotropin; E3, Estriol; AFP, Alpha Fetoprotein

Table 3. Descriptive data of patients with and without PE and serum biomarkers

	PE								
	No			Yes			OR	95% CI	
Variable	n	Mean	SD	n	Mean	SD		Lower	Upper
Age, year	180	28.75	6.14	12	34.75	5.94	1.188	1.059	1.332
BMI, kg/m^2	87	28.72	24.08	11	28.56	2.59	1.124	.983	1.286
Gravida, n	122	2.39	1.15	12	3.50	1.83	1.716	1.149	2.562
Parity, n	120	1.55	1.05	12	2.33	1.50	1.732	1.066	2.812
Gestational age, week	180	16.39	1.96	11	17.09	.70	1.243	.865	1.787
NT,mm	98	1.31	.35	7	1.47	.18	3.108	.477	20.251
PAPP-A, ng/mL	98	3.64	4.42	7	1.98	1.47	.657	.366	1.179
PAPP-A-MoM, MoM	86	1.10	.65	6	.87	.46	.481	.089	2.596
Double screening, hCG, mIU/mL	98	39.79	29.13	7	63.81	63.31	1.016	.998	1.034
Double screening, hCG-MoM, MoM	88	1.01	.82	6	1.26	.78	1.367	.593	3.154
Quadruple screening, hCG, mIU/mL	182	19015.24	12428.96	11	19926.45	7532.90	1.000	1.000	1.000
Quadruple screening, hCG-MoM, MoM	159	.81	.39	10	1.01	.65	2.475	.717	8.539
E3,n g/mL	183	.75	.40	11	.54	.20	.121	.011	1.288
E3-MoM	157	1.04	4.10	10	.56	.17	.079	.004	1.720
AFP, ng/mL	180	46.61	20.69	11	35.23	17.00	.958	.915	1.004
AFP-MoM	156	1.21	.47	10	1.11	.53	.619	.134	2.858
Inhibin-A, pg/mL	177	188.89	89.82	11	226.16	218.43	.995	.986	1.004
Inhibin-A-MoM, MoM	147	1.66	7.11	6	.85	.46	.320	.036	2.816
Labor week	183	38.33	1.89	12	36.83	2.89	.790	.648	.964

IUGR, Intrauterine Growth Retardation; OR, Odds Ratio; CI, Confidence Interval; SD, Standard Deviation; BMI, Body Mass Index; NT, Nuchal Translucency; PAPP-A, Pregnancy-Associated Plasma Protein A; MoM, Multiples Of Median; hCG, Human Chorionic Gonadotropin; E3, Estriol; AFP, Alpha Fetoprotein

Table 4. Descriptive data of patients with and without preterm labor and serum biomarkers

	Preterm									
	Normal			≤37th GW			OR	95% CI		p
Variable	n	Mean	SD	n	Mean	SD		Lower	Upper	
Age, year	164	28.64	6.21	33	31.24	6.18	1.070	1.006	1.138	0.032
BMI, kg/m^2	79	29.12	25.20	19	26.96	4.27	1.036	.924	1.162	0.545
Gravida, n	108	2.46	1.31	26	2.62	1.02	1.098	.790	1.525	0.578
Parity, n	106	1.60	1.17	26	1.69	.88	1.073	.734	1.568	0.716
Abortus, n	106	.24	.59	25	.28	.46	1.138	.551	2.351	0.727
Gestational age, week	162	16.35	1.92	34	16.85	1.96	1.158	.939	1.428	0.170
NT, mm	89	1.33	.34	19	1.32	.33	.960	.222	4.154	0.957
PAPP-A, ng/mL	89	3.77	4.61	19	2.38	1.59	.778	.576	1.050	0.100
PAPP-A-MoM, MoM	79	1.13	.64	16	.90	.58	.497	.173	1.427	0.194
Double screening, hCG, mIU/mL	89	42.08	33.09	19	41.76	31.63	1.000	.985	1.015	0.969
Double screening, hCG-MoM, MoM	80	1.05	.81	17	.98	.87	.889	.446	1.772	0.739
Quadruple screening, hCG, mIU/mL	164	18341.01	10609.96	33	21841.64	17783.72	1.000	1.000	1.000	0.144
Quadruple screening, hCG-MoM, MoM	148	.81	.40	25	.87	.46	1.406	.535	3.694	0.489
E3, ng/mL	165	.76	.41	33	.67	.30	.517	.177	1.508	0.227
E3-MoM	146	1.07	4.25	25	.66	.24	.507	.108	2.380	0.389
AFP, ng/mL	163	44.71	18.16	32	53.45	28.99	1.018	1.002	1.036	0.032
AFP-MoM	145	1.17	.43	25	1.42	.65	2.635	1.160	5.985	0.021
Inhibin-A, pg/mL	161	189.43	102.61	31	193.91	91.75	1.000	.997	1.004	0.820
Inhibin-A-MoM, MoM	134	1.68	7.44	23	1.16	1.001	.997	1.005	1.001	0.599
Labor week	166	38.92	.87	34	35.00	2.53	1.465	.679	3.162	0.330
APGAR score	163	9.07	.29	34	8.70	.81	.263	.112	.620	0.002
Birth weight, g	167	3377.46	429.857	34	2614.85	723.540	.997	.996	.998	0.001

OR, Odds Ratio; CI, Confidence Interval; SD, Standard Deviation; GW, Gestational Week; BMI, Body Mass Index; NT, Nuchal Translucency; PAPP-A, Pregnancy-Associated Plasma Protein A; MoM, Multiples Of Median; hCG, Human Chorionic Gonadotropin; E3, Estriol; AFP, Alpha Fetoprotein; APGAR, Appearance, Pulse, Grimace, Activity, and Respiration

Table 4 presents data based on the pregnancy length. The mean AFP (p=0.035) and AFP-MoM (p=0.014) levels were significantly higher for the women who had an early preterm birthbefore the 34th gestational week. The optimal cut-off value for AFP-MoM levels was 1.5 MoM,showing 66.7% sensitivity in discriminating cases of early preterm labor and 81.6% specificity in discriminating cases of non-early preterm labor.

Similarly, the mean AFP (p=0.032) and AFP-MoM (p=0.021) values were significantly higher for the women who had a preterm birth during the 34th to 37th gestational weeks. The mean PAPP-A levels were also significantly lower in these patients (p≤0.10). The optimal cut-off value forAFP-MoM levels was 1.24 MoM, showing56.0% sensitivity in discriminating cases of preterm labor and 62.1% specificity in discriminating cases of non-preterm labor. There was no statistically significant correlation between the serum markers and PPROM.

Table 5 presents data based on the GDM presence. The meanAFP (p=0.016) and AFP-MoM (p=0.036) values were statistically significantly higher for the patients with GDM. In addition, there was a significant correlation between the hCG-MoM levels and GDM presence (p≤0.10). The optimal cut-off value for AFP-MoM levels was 0.855 MoM, showing 77.8% sensitivity in discriminating patients withGDM and 25.3% specificity in discriminating the non-GDM cases.

Table 5. Descriptive data of patients with and without GDM and serum biomarkers

	GDM								
	No			Yes			OR	95% CI	
Variable	n	Mean	SD	n	Mean	SD		Lower	Upper
Age, year	176	28.98	6.36	19	30.68	5.56	1.044	.968	1.127
BMI, kg/m^2	89	28.59	23.77	10	29.13	5.44	1.156	1.006	1.329
Gravida, n	121	2.48	1.26	14	2.71	1.27	1.147	.764	1.722
Parity, n	119	1.61	1.13	14	1.79	1.05	1.142	.709	1.841
Abortus, n	118	.23	.55	14	.36	.74	1.392	.614	3.157
Gestational age, week	175	16.42	1.93	19	16.63	1.67	1.064	.821	1.378
NT, mm	97	1.32	.35	9	1.35	.26	1.297	.187	8.986
PAPP-A, ng/mL	97	3.57	4.40	9	2.87	2.78	.930	.690	1.254
PAPP-A-MoM, MoM	84	1.11	.64	9	.95	.62	.634	.180	2.237
Double screening, hCG, mIU/mL	97	40.82	32.10	9	54.74	41.45	1.010	.993	1.028
Double screening, hCG-MoM, MoM	86	.99	.75	9	1.48	1.27	1.730	.897	3.335
Quadruple screening, hCG, mIU/mL	176	19342.13	12486.78	19	16793.68	8660.40	1.000	1.000	1.000
Quadruple screening, hCG-MoM, MoM	153	.83	.43	18	.77	.27	.658	.177	2.449
E3, ng/mL	177	.73	.40	19	.75	.35	1.138	.352	3.678
E3-MoM	151	1.05	4.18	18	.71	.21	1.075	.224	5.155
AFP, ng/mL	175	47.14	20.99	18	34.89	10.35	.954	.918	.991
AFP-MoM	150	1.23	.49	18	.98	.23	.210	.049	.904
Inhibin-A, pg/mL	170	193.88	103.16	19	160.15	76.58	.995	.989	1.002
Inhibin-A-MoM, MoM	?	?	?	?	?	?	?	?	?
Labor week	?	?	?	?	?	?	?	?	?
APGAR score	?	?	?	?	?	?	?	?	?
Birth weight, g	?	?	?	?	?	?	?	?	?

GDM, Gestational Diabetes Mellitus; OR, Odds Ratio; CI, Confidence Interval; SD, Standard Deviation; BMI, Body Mass Index; NT, Nuchal Translucency; PAPP-A, Pregnancy-Associated Plasma Protein A; MoM, Multiples Of Median; hCG, Human Chorionic Gonadotropin; E3, Estriol; AFP, Alpha Fetoprotein

DISCUSSION

APOs, most notably GDM, preeclampsia, intrauterine growth restriction, preterm labor, perinatal mortality, placenta accreta, fetal macrosomia and shoulder dystocia, still constitute important public health problems, particularly in developing countries. The maternal serum screening tests based on measurements of PAPP-A, AFP, hCG, E3, inhibin, and inhibin-A are useful tools in the early diagnosis and management of such conditions. Abnormal, predictive test results can help determine the need for hospitalization in the neonatal intensive care unit and the appropriate mode of delivery(13-15).

Inhibin-A is a glycoprotein that is synthesized by the syncytiotrophoblast and plays a key role in the cellular development and immune response. It also serves as a useful biomarker in evaluating placental functions and abnormalities of the fetoplacental unit and, when considered together with other risk factors, predicting adverse pregnancy outcomes (16).

Several studies (16–18) have shown a correlation between increased levels of inhibin-A and mild to severe PE. For example, in their study with 5,080 pregnant women, Singnoi et al. (16) reported a higher frequency of preterm labor (12% vs 8.3%), PE (7.3% vs 2.0%), IUGR (10.2% vs 3.3%), and low birth weight (15.1% vs 9.5%) in women with increased levels of inhibin-A (>2.0 MoM) than in those with normal levels (0.5 to 2.0 MoM). However, they found no significant difference between the two groups in terms of the appearance, pulse, grimace, activity, and respiration (APGAR) scores, antepartum hemorrhage, postpartum hemorrhage, and mode of delivery.

Yazdani et al. (19) found a higher frequency of PE (18.8% vs 2.6%), IUGR (12.5% vs 1.3%), and PROM (11.3% vs 2%) in women with positive quadruple-marker-test results than in those with negative results. In comparison to the control group, they associated the higher levels of inhibin-A and AFP with IUGR and the higher levels of AFP and hCG with PROM.

AFP is a glycoprotein produced mainly by the fetal liver and partially by the yolk sac. It is found elevated in maternal blood during pregnancy and decreases after delivery. It plays a key role in the reproductive, hematopoietic, placental, hepatic, inflammatory and lymphatic cell growth and regulation (20). After fetal chromosomal and structural abnormalities are ruled out, unexplained elevated levels of maternal serum AFP (>2.5 MoM) often suggest placental abnormalities, multiple pregnancies, fetal death, ovarian tumors, or choriocarcinomas (14). A retrospective study by Wang et al. (21) included medical data of a total of 64,999 pregnant women and serum samples collected from 13,828 women in the second trimester. The maternal serum AFP and β-hCG levels were measured using the enzyme immunoassay method. The researchers reported that the second-trimester mean AFP and hCG levels were respectively 1.09±0.42 MoM and 1.36±1.09 MoMin women who had a preterm birth. Tancrède et al. (22) found that the risk of preterm labor was significantly increased in women with AFP and hCG levels>2.0 MoM, and reported that the mean AFP and hCG values were significantly higher for the preterm-labor group (with APOs including PE, IUGR, and fetal death) than for the control group. However, no significant difference was observed between the full-term labor and control groups in terms of rates of APOs.Moreover, in their study with 5,520 pregnant women, Barkute et al. (23) reported significantly lower newborn weight and length values for mothers with elevated levels ofserum AFP (>2.5 MoM) in the second trimester, and found that the frequency of APOs(such as SGA newborns andfetal malformation and death)was 26.1% in the elevated maternal serum AFP group while only 5.6% in the normal AFP group (0.5 to 2.0 MoM) and 7.3% in the low AFP group (<0.5 MoM).

In our study, the mean maternal serum AFP level was statistically significantly (1.024-fold) higher for the patients with IUGR, although we found no significant difference in terms of PAPP-A, uE3, hCG, and inhibin-A levels. Also, the mean AFP-MoM level was significantly higher (1.5 MoM) for the patients who had an early preterm labor and was 1.24 MoM for the patients who had a preterm labor. The mean PAPP-A level was lower only in the preterm labor group (p≤0.10). For the PE patients, the mean hCG level was higher while the mean uE3 and AFP levels were lower. There was no significant correlation between the PAPP-A and inhibin-A levels.

In their study (24) on the predictive value of biochemical markers for hypertensive disorders in pregnancy,Belovic et al. found no significant differencebetween women with and without gestational hypertension/PE in terms of biochemical marker concentrations. However, the PAPP-A levels in the first and hCG levels in the second trimester were found to be associated with early- and late-onset gestational hypertension/PE. The PAPP-A and hCG levels were found to be higher in patients with PE, though statistically insignificantly.

Compared to healthy controls, Long et al. (25) found lower levels of serum uE3 and uE3-MoM and higher levels of AFP-MoM in patients with PE in the second trimester. However, no significant difference was found between the two groups in terms of AFP, FβhCG, and FβhCG-MoM levels. The researchers concluded that increased levels of uE3 might be associated with a lower risk of PE. Furthermore, Puntachai et al. (26) investigated the relationship between APOs and maternal serum AFP levels in a total of 5,486 women, and found that the preterm labor, gestational hypertension, IUGR, fetal death, andlow birth weight rates and APGAR scores were significantly higher in women with higher AFP levels, while the preterm labor, IUGR, and low birth weight rates were significantly lower in women with low AFP levels.

Another study (27) investigated the maternal mid-trimester Fβ-hCG and AFP levels in spontaneous singleton pregnancies complicated by GDM, gestational hypertension, or intrahepatic cholestasis of pregnancy, and found that the Fβ-hCG and AFP-MoM levels were significantly lower in the GDM group than in the controls, suggesting that GDM might affect the serum Fβ-hCG and AFP levels and Down syndrome screening results. However, we found significantly higher levels of serum AFP (p=0.016) and AFP-MoM (p=0.036) in patients with GDM. For the discrimination of patients with and without GDM, the optimal cut-off valuefor AFP-MoM levels was 0.855 MoM.

CONCLUSION

Finally, it should be noted that our study has several limitations, including its retrospective design and the small sample size involved. In conclusion, we observed that the AFP parameter was significantly associated with IUGR, preterm labor, and GDM. However, there was no significant correlation between the other biomarkers and APOs. These results suggest that elevated maternal

serum AFP levels might indicate a need for closer patient follow-up for the early diagnosis and management of various APOs.

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Gulten Ozgen ORCID: 0000-0002-7888-7583

Gultekin Adanas Aydin ORCID: 0000-0002-9113-9846

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