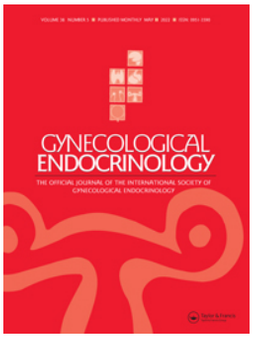

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RESEARCH ARTICLE

Supraphysiological hCG day estradiol levels can predict pregnancy-associated plasma protein A levels in maternal serum in the first trimester

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ABSTRACT

Objective: To investigate the effect of hCG day estradiol (hCG-E2) used in Down Syndrome screening on maternal serum levels of PAPP-A in fresh *in vitro* fertilization (IVF) cycles.

Methods: This study was a retrospective analysis of a cohort that resulted in a single pregnancy after a total of 92 fresh IVF cycles. The primary outcome of this study was to determine the effect of fresh IVF cycle parameters on the PAPP-A level and the cutoff value for hCG-E2 predicting a low PAPP-A level, while the secondary outcome was to determine whether the effect of IVF parameters on the PAPP-A level was significant.

Results: There was a negative correlation between PAPP-A levels and the number of hCG-E2 and grade 1 embryos (respectively, $p = .049$; .047), while a positive correlation was observed between baby weight at birth and the PAPP-A ($p < .05$). At a PAPP-A value of 0.82, the difference between the two groups, in terms of hCG-E2, the number of grade 1 embryos, and pregnancy-related complications was significant ($p = .050$; .029; .033, respectively). The threshold value of hCG-E2 affecting PAPP-A levels was statistically significant (AUC = 0.618; $p = .050$; hCG-E2 = 4869.5 pg/ml). In the model, an increase in the number of grade 1 embryos resulted in higher PAPP-A levels (OR = 2.26; $p = .044$).

Conclusion: The fact that the hCG-E2 cutoff value, which lowers PAPP-A, reflects excessive ovarian stimulation argues for the correction of the dual screening test in a subset of patients with high response to the first-trimester screening test.

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Intracytoplasmic sperm injection; *in vitro* fertilization; estradiol; pregnancy-associated plasma protein-A

Introduction

Pregnancy-associated plasma protein-A (PAPP-A) is a metalloproteinase found in increasing concentrations in human serum during pregnancy. It is produced by placental trophoblasts and decidualized endometrial stromal cells at the placental-endometrial interface and utilizes insulin-like growth factor-binding protein-4 as its main substrate [1,2]. In *in vitro* studies, it has been reported to support the proliferation and adhesion of trophoblast cells via autocrine pathways [3].

The importance of PAPP-A in clinical practice is that it is one of the maternal serum biomarkers used in first-trimester Down Syndrome screening. Serum PAPP-A levels in the first trimester are decreased in pregnant women with Down Syndrome [4]. Measured serum concentrations of PAPP-A are influenced by many factors. Assisted reproductive methods are one of these situations, and there are difficulties in interpreting Down Syndrome screening tests in the first trimester of pregnancies by *in vitro* fertilization/intracytoplasmic sperm injection/embryo transfer (IVF/ICSI-ET). Many studies have shown lower PAPP-A levels in IVF-ICSI pregnancies [5–10]. IVF/ICSI-ET treatments aim to increase the chance of pregnancy by retrieving more eggs and embryos. However, this affects the receptivity of the endometrium by causing hormone levels at supraphysiological levels that interfere with embryo implantation [11] and the placentation process [12]. The concept that high hCG-E2 leads to poorer pregnancy outcomes has increased debate about the safety of fresh embryo transfer and the preference for selectively frozen embryos ET [13].

Down Syndrome screening tests are more complex and difficult to interpret in IVF/ICSI pregnancies. A higher risk of Down Syndrome than in spontaneous pregnancies may lead to an increase in invasive procedures and the risk of complications associated with invasive procedures due to false-positive results. This situation causes unnecessary stress in these patients who have already achieved pregnancy laboriously and late [14]. Because of this problem, we wanted to investigate the effect of stimulation factors on PAPP-A MoM levels in IVF pregnancies and conducted a noninvasive, retrospective observational study on patients in our clinical practice.

Material and methods

This retrospective cohort study was conducted between 2007 and 2018 at the IVF clinic of Etlik Zübeyde Hanım Women's Health Training and Research Hospital. A total of 1348 IVF cycles and only gonadotropin-releasing hormone cycles with long agonist ($n = 46$) and short antagonist ($n = 46$) were included in the study and patient data were analyzed using a computerized database. Exclusion criteria for the study were body mass index (BMI)

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Table 1. Correlation analysis results between PAPP-A and quantitative parameters.

	PAPP-A	
Parameter	*r*	*P*
Total number of antral follicles	−0.133	.206
Basal FSH, IU/l	0.028	.788
Total gonadotrophin dose, IU	0.066	.530
Days of stimulation	0.104	.324
Estradiol on HCG day, pg/ml	−0.206	**.049**
hCG günü > 15 mm folikül sayısı	0.064	.543
Endometrial thickness on hCG day, mm	0.002	.982
Oocytes retrieved	−0.047	.656
Number of mature oocytes	−0.129	.220
Oocyte quality index	−0.030	.776
Number of 2 pronuclei	−0.043	.686
Number of grade 1 embryos	−0.208	**.047**
Number of grade 2 embryos	0.137	.194
Number of grade 3 embryos	0.079	.455
Number of grade 4 embryos	−0.154	.143
Transfer day	0.062	.555
Baby weight	0.310	**.003**

r: Spearman rho correlation coefficient.

>30 and <20 kg/m^2, pregnancies older than 35 years, known endocrine disorders, multiple pregnancies, freeze-thaw cycles, and smoking. After exclusion according to these criteria, a total of 593 IVF/ICSI- ET cycles were included in the study. They were excluded from the study because 212 patients did not have information on the PAPP-A MoM value, 113 patients on baby weight at birth, 61 patients on pregnancy-related complications, and 115 patients on the hCG-E2 value.

The study's Institutional Review Board approved the research project and protocols. All data used in the study were collected from patients who underwent routine and standard IVF/ICSI treatment at an accredited center without additional interventions. All human study methods were performed in accordance with relevant guidelines and regulations.

Combined first-trimester screening tests (11 + 0 and 13 + 6 weeks of gestation/measurement of crown-rump length:45–84 mm), complications during pregnancy, week of birth, and baby weight at birth were obtained from the medical records of our hospital. The PAPP-A and free beta-hCG levels were measured using an Immulite 2000 analyzer. The measured marker values were converted to pregnancy-specific MoM values using Prisca 4.0 software and reciprocal linear regression [A] after adjusting for factors such as gestational age, smoking status, and maternal weight. Invasive testing was recommended for definitive diagnosis when the combined risk index was higher than 1/270.

The primary outcome of this study was to determine the effects of fresh IVF cycle parameters on PAPP-A MoM level and hCG-E2 cutoff value, which predicts a low PAPP-A MoM value. The secondary outcome was whether the model created was significant in the logistic regression analysis for the effect of IVF parameters on the PAPP-A MoM value.

Statistical analysis

The distribution of continuous variables was presented as mean and standard deviation (SD), whereas categorical variables were presented as ratios and percentages of the total. Spearman correlation analysis was performed for the relationship between PAPP-A and IVF cycle parameters. Patients were divided into two groups (group 1: ≤0.82, group 2: >0.82) when the PAPP-A MoM value was 0.82 [7]. Between groups 1 and 2, continuous variables were compared using Student's *t*-test or Mann–Whitney *U*-test depending on the normality of the distribution, and a comparison of categorical variables was performed using Pearson's chi-square test or Fisher's exact test. The area under the curve (AUC) was calculated by receiver-operating characteristic analysis (ROC) to evaluate the hCG-E2 cutoff value and predictive accuracy in predicting the probability of a decrease in PAPP-A MoM. Logistic regression analysis, which included variables found to be significant in correlation analysis, was used to examine whether or not the model obtained was significant; sensitivity and specificity analyzes were performed. Statistical analysis was done using Statistical Package for Social Sciences software (SPSS Inc; Chicago, IL, USA) version 20.0. The significance level was $p \leq .005$ for all statistical tests.

Results

Of the 92 patients enrolled in the study whose IVF treatment ($n = 46$ long agonist and $n = 46$ antagonist cycles) resulted in a live birth, 76 (82.6%) had a single term birth and 16 (17.3%) had a single preterm birth. While 61 (66.3%) patients had no complications during pregnancy, 8 (8.7%) patients had a preterm birth, 8 (8.7%) patients had gestational diabetes mellitus, and 3 (3.3%) patients had placenta previa totalis, oligohydramnios was observed in 3 (3.3%) patients, pregnancy-related hypertensive disorder in 1 (1.1%) patient, intrauterine growth retardation in 4 (4.3%) patients, and polyhydramnios in 1 (1.1%) patient. While the maternal serum PAPP-A MoM value measured at the second trimester Down Syndrome screening test was 0.82 and below in 45 (48.9%) patients, it was above 0.82 in 47 (51.1%) patients. Most patients ($n = 56$, 60.9%) were stimulated with rc FSH (follitropin-alpha or follitropin-beta), 34 patients (37%) were stimulated with rc FSH + HMG (human menopausal gonadotropin), and 2 patients (2.2%) were stimulated with HMG only.

The demographic characteristics and IVF cycle characteristics of the included patients were as follows (mean ± SD): age: 27.97 ± 3.98; BMI: 25.12 ± 2.72 (kg/m^2); and baseline FSH: 6.76 ± 2.18 (IU/ml); mean total gonadotropin dose: 1995.38 ± 697.69 (IU); and stimulation duration: 9.63 ± 1.82 days. On the day of hCG administration, ovarian response parameters in patients were as follows (mean ± SD): hCG day E2: 2609.89 ± 1296.57 pg/ml; the number of retrieved oocytes (>15 mm): 12.38 ± 5.48; endometrial thickness: 10.47 ± 1.79 mm; PAPP-A MoM measured by dual screening test during pregnancy: 0.95 ± 0.53; baby weight at birth: 2982.99 ± 692.97 g. When comparing the PAPP-A MoM values depending on the IVF/ICSI treatment cycle parameters, the lower PAPP-A MoM value (mean) was statistically significant only in the group with complications ($p = .03$). The difference between treatment protocol (long agonist/antagonist), type of drug used in treatment (rc FSH/rc FSH + HMG/HMG) and BMI (20–25 and 25–30 kg/m^2) was not significant ($p = .833/.879/.988$, respectively). While there was a significant negative correlation between the PAPP-A MoM value and the number of hCG-E2 and grade 1 embryos (good quality embryos), a significant positive correlation was found between baby weight at birth and the PAPP-A MoM (respectively $r = -0.206/p = .049$; −0.208/.047; 0.310/.003). According to this result, higher hCG-E2 levels were associated with lower PAPP-A MoM values (Table 1, Figure 1). ROC analysis was performed to calculate the hCG cutoff value predicting a lower PAPP-A MoM (≤0.82) [7]; the AUC value was statistically significant [AUC = 0.618 ($p < .050$, 95% confidence interval (CI) 0.501 − 0.735)] and the hCG cutoff value was calculated to be

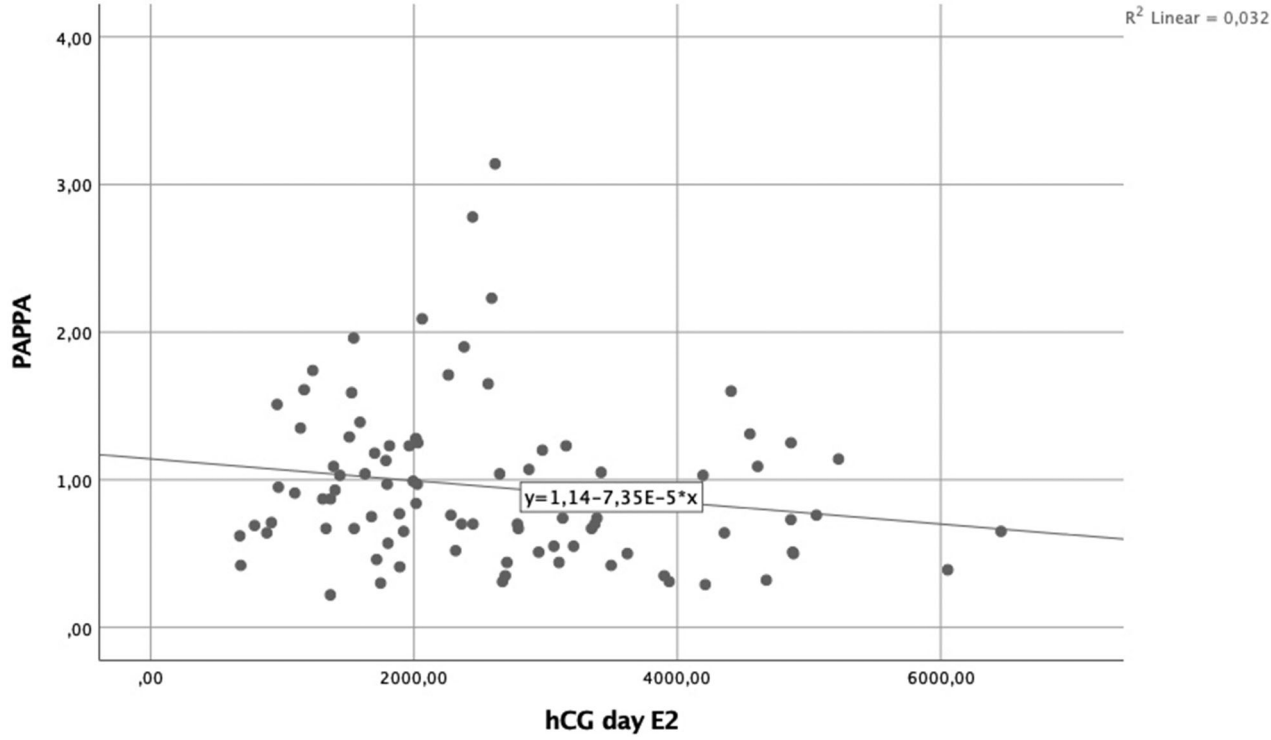

Figure 1. Correlation chart between hCG day estradiol and PAPP-A MoM (Spearman correlation coefficiant: −0.206, $p = .049$).

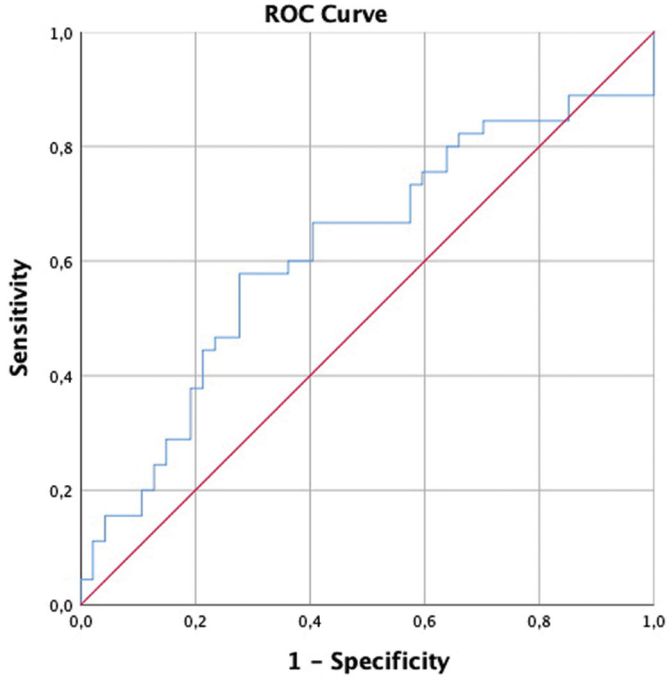

Figure 2. Receiver operating characteristic curve for estradiol on the day of hCG for prediction of low PAPP-A MoM (AUC: 0.618, $p = .050$). (hCG day estradiol: 4869.5).

4869.5 pg/ml (Figure 2). For the PAPP-A MoM value of 0.82 [7], the comparison of the two groups (group 1: ≤0.82; group 2: >0.82) in terms of IVF treatment cycle parameters (BMI, age, baseline FSH at day 3, type of drug used in the stimulation, IVF treatment protocol, initial gonadotropin dose of stimulation at day 3, total number of antral follicles, IVF stimulation duration, total dose of gonadotropin used during IVF, follicle number >15 mm per day hCG, hCG-E2, hCG day endometrial thickness, total number of retrieved oocytes, number of mature oocytes, oocyte quality index, number of 2 pronuclei, embryo score on the second day, number of grade 1, grade 2, grade 3, and grade 4 embryos, and ET day) and pregnancy parameters (pregnancy-related complications, ongoing pregnancy outcome, and baby weight at birth), the development of pregnancy-related complications (group 1: 44.4%; group 2: 23.4%; $p = .033$), hCG-E2 (group 1: 2885.24 ± 1418.46; group 2: 2346.27 ± 1120.67; $p = .05$) and the number of grade 1 embryos ($p = .029$) showed statistically significant difference. The difference in baby weight at birth was not significant; however, the p-value was .053 (Tables 2 and 3). Logistic regression analysis was performed to investigate the effect of IVF/ICSI parameters on the PAPP-A MoM value used in the first-trimester screening of patients who became pregnant after an IVF/ICSI cycle and had a live birth. The model established with the number of grade 1 embryos, IVF treatment protocol, and hCG-E2 parameters proved to be significant ($p = .036$). In the model, an increase in the number of grade 1 embryos resulted in a higher PAPP-A MoM value (OR = 2.259; 95%CI = 1.022–4.995, $p = .044$). The model predicting PAPP-A MoM had a sensitivity of 66%, a specificity of 60%, and an overall rate of 63.0% (Table 4).

Discussion

In our study, the cutoff value of hCG-E2 for PAPP-A ≤ 0.82 in ROC analysis was 4869.5 pg/ml (AUC = 0.618, $p = .050$). This value was higher than that found by Giorgetti et al. [15]. In their study investigating the relationship between treatment parameters and PAPP-A in IVF/ICSI pregnancies, Giorgetti et al. emphasized that an hCG-E2 level of 1300 pg/ml was strongly correlated with low PAPP-A values. In the same study, although PAPP-A MoM levels were significantly lower in IVF/ICSI

Table 2. Comparison of IVF cycle results for groups 1 and 2.

Parameter[a]	Group 1 PAPP-A MoM≤ 0.82	Group 2 PAPP-A MoM > 0.82	p^b-Value
Baby weight	2887.22 ± 737.86	3074.68 ± 641.59	.053
BMI	25.36 ± 2.92	24.89 ± 2.52	.377
Age	28.38 ± 3.80	27.57 ± 4.15	.390
Basal FSH, IU/l	6.63 ± 2.05	6.88 ± 2.31	.540
İnitial stimulation dose at day 3	208.33 ± 66.84	209.04 ± 67.55	.839
Total number of antral follicles	17.31 ± 7.99	14.36 ± 7.49	.057
Days of stimulation	9.47 ± 1.70	9.79 ± 1.94	.650
Total gonadotrophin dose, IU	1945.83 ± 706.79	2042.82 ± 693.14	.506
>15 mm follicle number on hCG day	3.87 ± 2.51	4.30 ± 2.55	.478
Estradiol on HCG day, pg/ml	2885.24 ± 1418.46	2346. 27 ± 1120.67	**.050**
Endometrial thickness on hCG day, mm	10.42 ± 1.77	10.52 ± 1.83	.737
Oocytes retrieved	12.91 ± 5.74	11.87 ± 5.23	.521
Number of mature oocytes	10.29 ± 4.51	8.72 ± 4.50	.094
Oocyte quality index	5.16 ± 0.67	5.13 ± 0.74	.975
Number of 2 pronuclei	6.04 ± 4.00	5.17 ± 3.33	.337
Embryo score on day 2	3.51 ± 0.98	3.94 ± 0.69	.058
Number of grade 1 embryos	0.89 ± 0.65	0.60 ± 0.50	**.029**
Number of grade 2 embryos	0.22 ± 0.42	0.38 ± 0.49	.096
Number of grade 4 embryos	0.02 ± 0.15	0.00 ± 0.00	.307

[a]All values are presented as mean (SD).
[b]Student's *t*-test or Mann–Whitney *U*-Test for differences between normal and elevated progesterone groups.
hCG-P: human chorionic gonadotropin day progesterone; BMI: body mass index ET: embryo transfer; IVF: *in vitro* fertilization; E2: estradiol; ICSI: intracytoplasmic sperm injection; PN: Pronucleus; FSH: follicular phase follicle-stimulating hormone; PAPP-A: Pregnancy Associated Plasma Protein-A; MoM: Multiples of Median.

Table 3. Comparison of IVF cycle results for groups 1 and 2.

Parameter[a]		Group 1 PAPP-A MoM ≤ 0.82	Group 2 PAPP-A MoM > 0.82	*p*-Value
Type of drug used during induction	rcFSH + HMG	16 (35.6%)	18 (38.3%)	.914[c]
	rcFSH	28 (62.2%)	28 (59.6%)	
	HMG	1 (2.2%)	1 (2.1%)	
Ovarian stimulation protocol	Agonist protokol	23 (51.1%)	23 (48.9%)	.835[b]
	Antagonist protokol	22 (48.9%)	24 (51.1%)	
Complication associated with pregnancy	yok	25 (55.6%)	36 (76.6%)	**.033**[b]
	var	20 (44.4%)	11 (23.4%)	
Embryo transfer day	2	3 (6.7%)	1 (2.1%)	.640[c]
	3	21 (46.7%)	22 (46.8%)	
	5	21 (46.7%)	24 (51.1%)	
The result of ongoing pregnancy	Ongoing one pregnancy	8 (17.8%)	5 (10.6%)	.230[b]
	One term birth	27 (60.0%)	36 (76.6%)	
	One preterm birth	10 (22.2%)	6 (12.8%)	

[a]Data are presented as mean ± SD, median [interquartile range] or number (percentage).
[b]Pearson's Chi-Square test.
[c]Fisher's Exact test.
rcFSH: recombinant follicle-stimulating hormone; HMG: human menopausal gonadotropin; IVF: *in vitro* fertilization; ET: embryo transfer; Pregnancy Associated Plasma Protein-A (PAPP-A); MoM: Multiples of Median.

Table 4. Predictive effect of IVF parameters on PAPP-A MoM (omnibüs tests of model coefficients: $p = .036$).

İndependent variable	*p*	OR	95%CI
Ovarian stimulation protocol [1]	.886	1.066	0.445–2.554
Estradiol on hCG day, pg/ml	.117	1.000	1.000–1.001
Number of grade 1 embryos	**.044**	2.259	1.022–4.995

In the model, the increase of grade 1 embryos has resulted in higher PAPP-A MOM value (OR: 2.259, 95%CI: 1.022–4.995).

pregnancies compared with controls, no difference was observed between intrauterine insemination pregnancies and spontaneous pregnancies [15]. In contrast, another similar study found no association between supraphysiological hCG-E2 and low PAPP-A MoM levels and pregnancy outcome [16]. However, in this study by Dunn et al., the lower cutoff for low PAPP-A MoM was 0.4 MoM. Perhaps there are other factors besides IVF treatment that lower PAPP-A so much. Our study used the mean MoM value of 0.82 [7], which is commonly found in IVF pregnancies. While the expression profile and local effects of PAPP-A in folliculogenesis and its role in trophoblastic invasion continue to be investigated, the role and effects of other maternal hormones, such as estradiol, on trophoblast functions are also being further investigated. This interaction raises many questions regarding both the implantation stage and the ongoing pregnancy process in IVF/ICSI-ET pregnancies in which significant hormonal changes, such as high serum estradiol levels, are observed. In studies seeking answers to these questions, deviations from normal PAPP-A MoM levels have been associated with adverse pregnancy outcomes such as pregnancy-induced hypertension and low birth weight [17].

In our study, both hCG-E2 and pregnancy complications were significantly higher in the low PAPP-A group ($p < .05$). There was also a positive correlation between PAPP-A MoM and baby weight at birth ($r = 0.310$; $p < .05$). In their meta-analysis, Cavoretto et al. found that PAPP-A MoM values were lower in pregnancies after IVF/ICSI, IVF, and ICSI compared with spontaneous pregnancies (PAPP-A MoM: 0.85/0.82 and 0.83, respectively) and reported that this change could be due to alterations

in placentation [18]. Tul et al. suggested that the main reason for the decrease in PAPP-A in IVF or ICSI pregnancies was due to exogenous hormone therapy [8,14,19,20].

Study results with fresh and freeze-thaw cycles are inconsistent in the literature. Hunt et al. also found low first-trimester PAPP-A levels in women who conceived after fresh and freeze-thaw cycles [21]. In another study, PAPP-A levels were concluded to be higher in women who became pregnant with frozen ET than in women who became pregnant with fresh ET [22]. This result is consistent with the results of the study, which found that placental volume and PAPP-A levels were higher in patients with frozen ET than in patients with fresh ET [23]. Although the PAPP-A MoM value was lower in the ICSI group ($n = 176$; PAPP-A = 0.82) than in the control group ($n = 24{,}783$; PAPP-A = 0.94) of Matilainen et al., the false-positive rate in ICSI pregnancies was not statistically significant. In our study, we used only fresh cycles.

In another study, a negative correlation was shown between PAPP-A values measured in the first-trimester screening test and the number of aspirated oocytes [8]. In our study, no significant correlation was found between PAPP-A and the total number of antral follicles, the number of oocytes retrieved, the number of mature oocytes, and the number of 2 PN. However, the negative correlation between PAPP-A MoM and the number of hCG-E2, and the number of grade 1 embryos was significant. Also, in the model we created using logistic regression, an increase in the number of good quality (grade 1) embryos resulted in higher PAPP-A MoM levels. Further studies with a larger number of patients are needed to explain this situation. In a very recent study, Pérennec et al. found no significant association between blastocyst morphology and PAPP-A and free beta-hCG in ongoing pregnancy and concluded that blastocyst morphology does not affect placentation [24]. Kavoussi et al. also demonstrated PAPP-A mRNA expression (56.3%) in human blastocoel fluid-conditioned media [25].

PAPP-A is a metalloproteinase produced by placental trophoblasts and endometrial stromal cells [2] and is involved in the stimulation of intracellular mitosis, cell differentiation, and trophoblastic invasion [26]. PAPP-A has also been detected in follicular fluid, and studies in humans and animals suggest that it is a marker for follicular selection and corpus luteum formation. In most mammalian species, regulation of its expression is largely dependent on gonadotropins, FSH, or hCG/LH [27]. Progesterone and estradiol are also found at high concentrations at the maternal-fetal interface during pregnancy, during remodeling, and thus may contribute to the regulation of trophoblast functions [28].

In IVF/ICSI pregnancies, the effect of high hCG-E2 on PAPP-A levels may be due to autocrine and/or paracrine effects of the placenta and ovarian complex. In addition, PAPP-A has been detected in follicular fluid and may contribute to folliculogenesis and the formation of the corpus luteum [27]. It has also been shown that high local estradiol concentrations in the placenta may lead to downregulation of estradiol receptor expression [29]. In animal studies, high estradiol levels have been determined to reduce mRNA expression of vascular endothelial growth factors in extravillous trophoblasts and prevent invasion of extravillous trophoblasts into the uterine spiral arteries [30]. This situation weakens the endometrial function of hCG-E2 and its potent vasodilatory effect on uterine arterioles [31]. As a result, optimal placental trophoblast function cannot be achieved, leading to lower PAPP-A levels [15]. In their pathogenesis, preeclampsia and intrauterine growth retardation, in which abnormal trophoblast function and remodeling of spiral arterioles are observed, are also frequently observed in IVF/ICSI pregnancies [32], and interactions between abnormal hormone levels in PAPP-A and IVF pregnancies and the effects of elevated hCG-E2 on trophoblast function and vascular angiogenesis may contribute to this situation.

The high cutoff hCG-E2 for PAPP-A MoM in our study raises the question of whether there are lower PAPP-A MoM values that are specific only to high-responders in IVF/ICSI pregnancies. Therefore, further studies are needed to determine whether such subgroup correction is necessary for interpreting the test result in IVF/ICSI pregnancies with first-trimester Down Syndrome screening.

Our study is a retrospective study. The main limitation is the lack of data on the dual screening test and the babies' birth weights because some of the patients who became pregnant in the IVF clinic continued their pregnancy follow-ups in other centers and other cities.

Conclusion

In our study, only fresh cycles, long agonist, and antagonist cycles were analyzed. The cutoff value of hCG-E2 that affected the PAPP-A MoM value we used in the first-trimester Down Syndrome screening was quite high. The multivariate logistic regression model established with other stimulation parameters was significant for predicting a low PAPP-A MoM value. In IVF/ICSI protocols, patients with high hCG-E2 may need to be counseled to avoid unnecessary invasive prenatal diagnostic applications because of lower PAPP-A MoM and increased likelihood of false-positive results. This could also have implications for counseling this group of patients with high-stress levels. However, this requires further study and evidence in larger populations. In addition, studies are needed to interpret the effect of high hCG-E2 on PAPP-A and the interpretation of the dual screening test in a subgroup of patients with a high ovarian response and pregnancy after the development of ovarian hyperstimulation syndrome.

Author contributions

Conceptualization: Özlem Kayacık Günday; Data Curation: Oya Aldemir; Formal Analysis: Özlem Kayacık Günday; Investigation: Özlem Kayacık Günday; Methodology: Özlem Kayacık Günday; Project Administration: Özlem Moraloğlu Tekin; Resources: Oya Aldemir; Software: Runa Özelçi; Supervision: Serdar Dilbaz; Validation: Emre Başer; Visualization: Özlem Kayacık Günday; Writing – Original Draft Preparation: Özlem Kayacık Günday; Writing – Review & Editing: Özlem Kayacık Günday, Oya Aldemir, Runa Özelçi, Serdar Dilbaz.

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