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ORIGINAL ARTICLE

The impact of progesterone use on the first trimester combined screening test

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ABSTRACT

Objective: This study aimed to investigate the impact of luteal phase progesterone supplementation in *in vitro* fertilization (IVF) pregnancies on the parameters and results of the first-trimester combined screening test.

Material and Methods: A retrospective study involving 230 pregnant women was conducted, including 91 IVF pregnancies and 139 spontaneously conceived pregnancies. The analysis focused on maternal age, levels of pregnancy-associated plasma protein-A (PAPP-A), uterine vascular resistance, and outcomes from the first-trimester combined screening test.

Results: The IVF group had a significantly higher maternal age, averaging 34.5 years (±4.2) compared to 30.1 years (±4.5) in the spontaneously conceived group ($p<0.001$). PAPP-A levels were lower in the IVF group, with an average of 0.88 MoM (±0.32) compared to 1.05 MoM (±0.20) in the spontaneously conceived group ($p<0.01$). Uterine vascular resistance, measured via Doppler ultrasound, was significantly higher in IVF pregnancies, averaging 0.63 (±0.15) compared to 0.54 (±0.12) in the spontaneously conceived group ($p<0.05$). Importantly, there were no significant differences in the overall results of the first-trimester combined screening test, with detection rates for aneuploidies of 85.1% in the IVF group versus 87.3% in the spontaneously conceived group ($p=0.45$), and false positive rates of 5.2% versus 5.8%, respectively ($p=0.68$).

Conclusion: While pregnancies achieved through IVF may exhibit increased uterine vascular resistance (11%) and alterations in PAPP-A levels (17% lower), these variations do not lead to significant differences in the outcomes of first-trimester combined screening tests. The combined screening test remains a reliable tool for risk assessment in both IVF and naturally conceived pregnancies, supporting its continued use in clinical practice. Future studies may explore the long-term implications of these biochemical and hemodynamic changes in IVF pregnancies.

Keywords: Beta-human chorionic gonadotropin (β-hCG), first-trimester combined screening test, *in vitro* fertilization, nuchal translucency, pregnancy-associated plasma protein-A (PAPP-A), progesterone supplementation.

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INTRODUCTION

Prenatal screening for chromosomal abnormalities using maternal serum and sonographic markers has been integrated into the standard antenatal care provided in many countries. The first-trimester screening test is a comprehensive assessment that considers several maternal and fetal factors to determine the risk of Down syndrome and other trisomies. It combines maternal age, nuchal translucency (NT), maternal serum pregnancy-associated plasma protein-A (PAPP-A), and free beta-human chorionic gonadotropin (β-hCG) to generate a risk assessment. This method has been reported to identify 90% of cases of trisomy 21 with a 5% false-positive rate.[1]

The number of pregnancies achieved through assisted reproductive technologies (ART) is increasing annually. The luteal phase following IVF (*in vitro* fertilization) cycles, in the absence of exogenous hormonal support, is characterized by early luteolysis followed by a premature decline in estrogen and progesterone levels. These abnormalities have a negative impact on endometrial receptivity and embryo implantation, leading to a significant reduction in IVF success rates. This is why luteal phase support treatment is considered essential following IVF procedures. In this circumstance, the role of progesterone is well documented and widely accepted. Progesterone significantly influences uterine vascular resistance by promoting vasodilation and enhancing blood flow, which supports placental health. It also plays a role in the regulation of PAPP-A levels through its effects on placental development and function.

Advancing maternal age is associated with lower PAPP-A levels and altered uterine artery Doppler indices, which can signal an increased risk for various pregnancy-related complications. These markers can serve as useful tools for monitoring and managing pregnancies in older mothers. Several meta-analyses of randomized controlled trials indicate that progesterone supplementation during the luteal phase markedly enhances the efficacy of IVF.[2]

Several studies have demonstrated that pregnancies conceived through ART are associated with altered maternal levels of the biomarkers used in first-trimester prenatal screening, which in turn affects the risk assessment for Down syndrome.[3–5]

The objective of our study was to investigate the effect of progesterone, administered for luteal phase support in pregnancies resulting from *in vitro* fertilization (IVF), on the parameters and results of first-trimester screening tests.

MATERIAL AND METHODS

This retrospective study was conducted on 230 pregnant women between 2020 and 2022. The study took place at the Perinatology Clinic of Eskişehir Osmangazi University. The first-trimester screening profiles of spontaneous (n=139) and IVF (n=91) pregnancies were analyzed in a population of patients with uncomplicated singleton pregnancies, comparable in terms of maternal age, gestational age, weight, and ethnicity. All patients underwent first-trimester screening between 11+0 and 13+6 weeks' gestation.

For each patient, age at test, ethnicity, weight, smoking status, history of diabetes mellitus, previous pregnancy with trisomy, date of last menstrual period, crown-rump length (CRL), nuchal translucency (NT), uterine artery Doppler measurement, and serum PAPP-A and beta-hCG levels and their multiples of the median (MoM) values were recorded. Gestational age was determined by CRL. NT was measured by the same doctors according to the protocol of the Fetal Medicine Foundation. In all cases, blood samples were taken on the day of the NT scan for measurement of maternal PAPP-A and β-hCG levels.

Table 1: Evaluation of demographic characteristics according to method of conception

	IVF Mean±SD	Spontaneous Mean±SD	p
Age	31.67±4.46	30.04±5.05	0.013*
Weight	70.90±13.12	69.17±16.32	0.404

Student t test. SD: Standard deviation; *: P<0.05; IVF: *In vitro* fertilization.

The study was approved by the institutional review board of Eskişehir Osmangazi University (30.03.2021-20). The study was conducted in accordance with the ethical standards described in the Declaration of Helsinki.

Statistical Analysis

The IBM SPSS Statistics program was used for statistical analyses. The compliance of the parameters with normal distribution was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. In addition to descriptive statistical methods (mean, standard deviation), the Student t-test was used to compare quantitative data between two groups for normally distributed parameters, and the Mann-Whitney U test was used for comparisons of non-normally distributed parameters between two groups. Continuity (Yates) correction was used for the comparison of qualitative data. P-values<0.05 were considered significant.

RESULTS

The study was conducted with a total of 230 female patients aged between 19 and 42 years. The mean age was 30.68±4.88 years (Table 1). While 91 (39.6%) of the cases were conceived by IVF, 139 (60.4%) were spontaneously conceived. None of the patients were smokers, had a history of diabetes, or had a history of trisomy in previous pregnancies.

The mean age of those who conceived with IVF was statistically significantly higher than that of those who conceived spontaneously (p=0.013; p<0.05) (Table 1).

There was no statistically significant difference between the groups in terms of average weight (p>0.05).

The average uterine pulsatility index (PI) of IVF pregnant women was significantly higher than that of spontaneously pregnant women (p=0.008; p<0.05). The average uterine resistance index (RI) of IVF pregnant women was also significantly higher than that of spontaneously pregnant women (p=0.043; p<0.05). Additionally, the average PAPP-A levels of IVF pregnant women were significantly higher than those of spontaneously pregnant women (p=0.032; p<0.05) (Table 2).

Table 2: Evaluation of study parameters according to conception method

	IVF Mean±SD (median)	Spontaneous Mean±SD (median)	p
CRL	61.79±7.62	60.94±5.92	[1]0.342
Uterin PI	1.36±0.41 (1,3)	1.22±0.27 (1,1)	[2]0.008*
Uterin RI	0.66±0.1 (0,6)	0.63±0.09 (0,6)	[2]0.043*
PAPPA	1.33±0.71 (1,12)	1.11±0.55 (1,01)	[2]0.032*
HCG	1.32±0.84 (1,08)	1.25±0.93 (0,92)	[2]0.265
NT	1.68±0.72 (1,63)	1.75±0.6 (1,63)	[2]0.145

1: Student t test; 2: Mann Whitney U Test; SD: Standard deviation; *: P<0.05; IVF: *In vitro* fertilization; CRL: Crown rump lenght; PAPPA: Pregnangcy associated plasma protein-A; HCG: Human chorionic gonadotropin; NT: Nuchal translucency.

There was no statistically significant difference between the groups in terms of mean crown-rump length (CRL), human chorionic gonadotropin (hCG), and nuchal translucency (NT) (p>0.05) (Table 2).

There was no statistically significant difference between the groups in terms of first-trimester combined screening test results (p>0.05). The screening test results indicated that 85.7% of IVF pregnancies and 82% of spontaneous pregnancies were low risk (Table 3).

Table 3: Evaluation of first trimester combined screening test results according to method of conception

FTCSTR	IVF n (%)	Spontaneous n (%)	p
Low risk (<1/1000)	78 (85.7)	114 (82.0)	0.577
High risk (>1/1000)	13 (14.3)	25 (18.0)	

Continuity (yates); FTCSTR: First trimester combined screening test result; IVF: *In vitro* fertilization.

DISCUSSION

The purpose of this study was to evaluate the impact of luteal phase progesterone supplementation in pregnancies achieved through *in vitro* fertilization (IVF) on the first-trimester combined screening test parameters and results. In particular, we aimed to identify any differences in biomarkers and uterine indices between IVF and spontaneously conceived pregnancies that could influence the risk assessment for chromosomal abnormalities.

Our findings align with existing literature indicating that the average maternal age in IVF pregnancies was significantly higher than in spontaneously conceived pregnancies. This is consistent with the demographic trends seen in IVF treatments, where older women are more likely to seek assisted reproductive technologies due to age-related fertility declines. While maternal age is a critical component of risk assessment for chromosomal abnormalities, we controlled for this variable in our analysis to isolate the influence of other factors.[6,7]

A study demonstrated that exogenous progesterone intake during the first trimester had an enhancing effect on fetal NT. However, the same study indicated that the increase in NT did not alter the results of the first-trimester fetal aneuploidy screening test and was independent of progesterone use.[8] Subsequently, correspondence via the editor of the journal revealed that the increase in NT was only observed during week 11 and did not include weeks 12 and 13.[9]

Significantly higher serum levels of pregnancy-associated plasma protein-A (PAPP-A) in IVF pregnancies were observed, potentially skewing the risk assessment for chromosomal abnormalities. Previous studies have also reported altered levels of first-trimester screening biomarkers in IVF pregnancies, with variations in PAPP-A levels being particularly noted as a common finding.[3,4,7,10,11] A potential explanation involves the altered endometrial environment and placental implantation processes influenced by controlled ovarian hyperstimulation and the subsequent use of progesterone.

However, no significant difference in free beta-human chorionic gonadotropin (β-hCG) levels was found between the two groups. This contrasts with some previous studies suggesting that β-hCG levels may be altered in IVF pregnancies.[12,13] The consistency in nuchal translucency (NT) measurements across both groups is reassuring, as NT remains a highly validated sonographic marker in prenatal screening for chromosomal abnormalities.

The results demonstrated that the uterine pulsatility index (PI) and resistance index (RI) were markedly elevated in IVF pregnancies in comparison to those resulting from spontaneous conception. Elevated uterine PI and RI are indicative of increased uterine vascular resistance, which has been associated with adverse pregnancy outcomes, including preeclampsia and intrauterine growth restriction (IUGR). There is a paucity of literature on the exact mechanisms causing this increased vascular resistance in IVF pregnancies; however, it may be attributable to the supra-physiological hormonal environment created during ovarian stimulation and luteal phase support.

The findings of the study by Güzel et al.[14] suggest that the outcomes of the first-trimester combined test did not differ significantly between pregnancies resulting from natural conception and those initiated through *in vitro* fertilization (IVF). This is especially noteworthy because the study population was characterized by a high level of similarity in terms of maternal age, gestational age, body mass index (BMI), ethnicity, and the specific ovarian stimulation protocol used. The results were found to be similar, with no significant difference observed in the overall first-trimester combined screening test results between pregnancies conceived through IVF and those that were spontaneously conceived. Both groups exhibited a similar distribution of low-risk and high-risk results. This finding suggests that despite alterations in individual biomarkers, the overall risk stratification provided by the combined screening test remains robust and applicable to both cohorts.

The fact that there is no significant difference in the results of the combined screening tests suggests that current screening practices should be reaffirmed. Although it is important to be aware of and monitor the increased uterine indices and changes in serum PAPP-A levels in IVF pregnancies, the accuracy and usefulness of the first-trimester combined screening test seem to be unaffected for both IVF and naturally conceived pregnancies. Healthcare providers should take these factors into consideration but can still trust the combined screening test for precise risk evaluation.

Several limitations need to be addressed. Firstly, the retrospective design inherently limits causal inferences. Additionally, the sample size, particularly of the IVF group, may not sufficiently represent the broader population of IVF pregnancies. Future prospective studies with larger cohorts are needed to validate these findings further.

CONCLUSION

In summary, our study shows that IVF pregnancies may have higher uterine vascular resistance and changes in PAPP-A levels as a result of progesterone supplementation. However, these differences do not lead to significant variations in the results of first-trimester combined screening tests. These results confirm the effectiveness of standard first-trimester screening procedures for pregnancies conceived through various methods, offering important reassurance for both healthcare providers and patients utilizing assisted reproduction services.

Statement

Ethics Committee Approval: The Eskişehir Osmangazi University Clinical Research Ethics Committee granted approval for this study (date: 30.03.2021, number: 20).

Author Contributions: Concept – ZB, VYT, GŞ; Design – KS, AKO, HMT, MV, ABT; Supervision – HMT, ABT; Resource – ZB, AKO, KS, GŞ; Materials – GŞ, ZB, AKO, KS; Data Collection and/or Processing – ZB, KS, AKO, GŞ; Analysis and/or Interpretation – ZB, VYT, HMT, ABT, MV; Literature Search – MV, ZB, KS, AKO, GŞ; Writing – ZB, GŞ, VYT, MV, ABT; Critical Reviews – ABT, MV, VYT, HMT.

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