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Prestimulation parameters predicting the pregnancy outcomes after IVF-ET in patients with unexplained infertility

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ABSTRACT. – OBJECTIVE: Assisted Reproductive Technologies (ART) are considered to be the most effective treatment option for unexplained infertility. This study aims to investigate the pregnancy outcomes of women who received *in-vitro* fertilization-embryo transfer (IVF-ET) treatment for unexplained infertility and the contributing factors affecting these outcomes.

PATIENTS AND METHODS: The present study included 789 consecutive women with unexplained infertility who were treated with IVF-ET at the ART Clinic of the Health Sciences University, Ankara Etlik Zübeyde Hanım Gynecology Training and Research Hospital between January 2007 and December 2019. The contributing factors affecting these outcomes, such as body mass index (BMI), basal follicle-stimulating hormone (FSH), and antimullerian hormone (AMH), were evaluated retrospectively.

RESULTS: Clinical pregnancy per cycle was 19.8% among patients recruited. No statistically significant difference was detected in terms of age, infertility duration, and BMI of the patients who achieved pregnancy and who failed to get pregnant after IVF-ET treatment. The basal FSH level was found to be significantly lower (p=0.001), and the AMH level was significantly higher in patients who had clinical pregnancy (p=0.001). The basal AMH cut-off value was calculated to be 3.34 ng/mL, and the basal FSH cut-off value was calculated as 7.26 IU/L for the prediction of clinical pregnancy.

CONCLUSIONS: IVF-ET treatment can be applied as a successful treatment option in unexplained infertility cases. Although the basal FSH and AMH values are not the cut-off values that have high sensitivity and specificity, they are considered to be associated with pregnancy rates.

Key Words:
Unexplained infertility, *In-vitro* fertilization, Pregnancy.

Introduction

Infertility is defined as the inability to achieve pregnancy despite regular unprotected sexual intercourse for at least one year, and it affects 15% of couples worldwide[1]. Infertility may arise due to dysfunction in the male or female reproductive system. Various factors such as aging, sexual dysfunction, infections, hormonal factors, malnutrition, smoking, alcohol, caffeine consumption, occupational risks, and sexually transmitted diseases are known to impair the fertility potential of women and men[2]. Unexplained infertility is a diagnosis made by the exclusion of the presence of other causes of infertility after routine infertility workups such as semen analysis of the partner, basal serum hormone levels, ovarian reserve tests, evaluation of the uterine cavity and tubal patency, and confirmation of the absence of uterine pathologies. Evaluation of the *in-vitro* fertilization-embryo transfer (IVF-ET) cycles of the women diagnosed with unexplained infertility revealed various defects in follicular development, ovulation, implantation, and luteal phase of the treatment cycles in some of the patients. Implantation failure, cervical factors, and defects in sperm/ovum interaction were proposed to be the causes of infertility in this group of patients.

The aim of our study was to investigate the pregnancy outcome of the patients who underwent IVF-ET for unexplained infertility and the impact of the prestimulating parameters such as demographic data, duration of infertility (DI), body mass index, and basal follicular stimulating hormone and antimullerian hormone levels on the cycle by comparing the women who achieved

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clinical pregnancy with the ones who did not conceive. The secondary outcome was to evaluate the impact of these factors on the oocyte quality, embryo development, and implantation.

Patients and Methods

The present study was conducted retrospectively after obtaining approval from Health Sciences University Etlik Zübeyde Hanım Gynecology Training and Research Hospital Ethics Committee (2020-68, dated 03.06.2020). Written informed consent was provided by the patients for the purpose of receiving therapy and for the publication of this study. The study recruited 789 consecutive patients who received their first IVF-ET treatment for unexplained infertility between January 2007 and December 2019 and met the inclusion criteria. The inclusion criteria specified that patients had to be aged between 18 and 40 and exhibit normal test results during an infertility workup. This included a basal FSH level of less than 10 IU/ml, mid-luteal progesterone greater than three ng/ml, AMH of at least 1.2 ng/ml, a normal uterine cavity, and patent tubes as confirmed by hysterosalpingography, and a normal sperm analysis for the partner according to WHO criteria[3]. The exclusion criteria were as follows: 1. age <18 years, >40 years of age, 2. basal FSH >10 ıu/mL and/or AMH <1.2 ng/mL, 3. hormonal dysfunction including polycystic ovarian syndrome, hypothyroidism, hyperthyroidism, anorexia nervosa, 4. presence of endometriosis, uterine anomalies or tubal obstruction diagnosed *via* hysteroslpingography 5- Having a freeze-thaw cycle.

Diagnosis of Unexplained Infertility

Unexplained infertility diagnosis was based on normal semen analysis defined by WHO criteria[3], normal basal hormonal test results and a normal uterine cavity with bilateral patent tubes [basal FSH value of <10 IU/L, E2 of <60 pg/mL (Advia Centaur, Siemens, Germany) and AFC of >7 or AMH levels of >1.2 ng/mL, documentation of ovulation by normal mid-luteal serum progesterone levels >3 ng/mL)] and documentation of normal uterine cavity and bilateral or unilateral tubal patency by hysterosalpingography. All the patients had their demographic characteristics, body mass index, and infertility workup test results recorded electronically. The ovulation hyperstimulation protocols (OH), routine follicular growth, total oocyte count, number of mature oocytes collected during oocyte pick-up (OPU), quality of the embryos, number of embryos transferred, the day of the embryo transfer (ET), endometrial thickness at the day of ET and the results of the treatment cycle were also recorded.

IVF-ET Protocol

Conventional protocols, including the GnRH agonist protocol, flexible GnRH antagonist protocol, or the microdose flare-up agonist protocol, were used for controlled ovarian stimulation and were applied to the recruited women at the Assisted Reproductive Techniques Clinic.

Recombinant FSH (Gonal-F, Merck Serono, Darmstadt, Germany; Puregon, Organon, Amsterdam, the Netherlands) with or without human menopausal gonadotropin (Menogon, Ferring Pharmaceuticals, Kiel, Germany; Merional, IBSA, Lugano, Switzerland) was used at doses ranging from 150 IU/day to 450 IU/day, in accordance with the patient's age, body mass index, and the number of antral follicles in conventional protocols.

The long protocol with a GnRH agonist (Lucrin, Abbott, Rungis Cedex, France) or the GnRH antagonist protocol (Cetrotide, 0.25 mg/day, Serono, Darmstadt, Germany) was used for pituitary down-regulation. The microdose flare-up protocol was used by the application of GnRH agonist (Lucrin, Abbott, Rungis Cedex, France). Cycle monitorization with serial transvaginal ultrasonography (TVS) (General Electric Logiq A5, Milwaukee, WI, USA) was performed by a physician, starting on day 5 of the ovarian hyperstimulation and also serum luteinizing hormone (LH), progesterone (P), and estradiol (E2) were measured until the day of human chorionic gonadotropin (hCG) injection. The dose of gonadotropin was adjusted according to the ovarian response. When the mean diameter of at least three follicles reached 18 mm, recombinant HCG (Ovitrelle 250 mg, Sereno, Istanbul, Turkey) was administered for final oocyte maturation. Oocyte pick-up (OPU) was performed using transvaginal ultrasound-guided aspiration 34 to 36 h after the hCG injection. The oocytes were inseminated by using intracytoplasmic sperm injection.

Embryo transfer was performed 3 or 5 days after the retrieval of the oocytes under transabdominal ultrasonographic guidance. All of the subjects received luteal phase support starting on the day of oocyte retrieval until the day of the β-hCG test. A daily dose of 100 mg of progesterone in oil (Progestan, Koçak, Istanbul, Turkey) or vaginal progesterone (Crinone 8% gel, Merck, Darmstadt,

Germany) was used for luteal support. Serum β hCG levels were measured 14 days after OPU, and in cases of pregnancy, luteal phase support was continued up to 10-12 weeks of gestation. Patients with positive fetal heartbeat at ultrasonography were defined as clinical pregnancy-positive in our study.

Statistical Analysis

The patients who achieved pregnancy during the treatment cycle were compared in terms of age, BMI, basal hormone values, duration of stimulation, total oocyte count, number of recruited mature oocytes, and pregnancy results were compared. The analyses of the data were made by using the SPSS Statistics 22 Package Program (IBM Corp., Armonk, NY, USA). The descriptive statistics and continuous variables were given as mean, standard deviation, maximum, and minimum values, and the categorical variables were shown as the number of cases (n) and (%). The distribution of the variables and normality analyses were made by using the Kolmogorov-Smirnov test. The Independent Sample *t*-test and the Chi-square were used to compare statistically significant differences between the study groups. The Pearson and Spearman's Correlation tests were used to evaluate the quantitative data. The predictive values of the investigated parameters were compared with the Receiver Operating Characteristic Curve (ROC). The risk factors that affected the binary independent variables were graded and evaluated by using the Binary Logistic Regression Analysis. The 95% confidence interval was calculated for each variable, and the results were considered to be statistically significant at $p<0.05$.

Results

A total of 789 women who were treated during the study period and met the inclusion criteria were included in the study. The mean age of the women was 31.2±4.9 years, and the mean BMI was 26.1±4.6 kg/m^2. The mean duration of infertility was 65±46 months. The clinical pregnancy

Table I. Baseline and cycle characteristics of patients with unexplained infertility.

	Clinical pregnancy (-) n=633 (80.2%) mean±SD	Clinical pregnancy (+) n=156 (19.8%) mean±SD	*p*
Age, (years)	31.6±5.2	31.1±4.4	0.868
BMI, (kg/m²)	26.2±4.7	25.9±4.6	0.505
Infertilityduration, (months)	66±48	63±48	0.493
Basal FSH, (IU/L)	9±5.1	7.6±3.3	0.001*
Basal LH, (IU/L)	5.3±3.3	4.8±2.8	0.069
Basal E2, (ng/L)	49.8±33	55.3±53	0.232
AMH, (ng/mL)	3.3±2.1	5.1±3.6	0.001*
Antral follicle count	10±6.8	11.2±6.9	0.053
Stimulation duration, days	11.7±7.8	13.3±8.3	0.031*
Total gonadotropin dose, (IU)	2,262±924	2,377±862	0.714
Estradiol on hCG day, ng/L	2,102±1,364	2,310±1,403	0.109
Progesterone on hCG day, (ng/mL)	0.7±0.6	0.7±0.2	0.485
Number of follicles 15-17 mm at hCG day	3±2.6	3.6±2.8	0.025*
Number of follicles >17 mm at hCG day	2.7±2.3	3.3±2.7	0.014*
Total oocyte count	12.64±8.21	12.08±6.62	0.676
Number of mature oocytes	9.52±5.94	8.66±4.05	0.284
Number of inseminated oocytes	3.71±0.73	3.93±0.58	0.001*
Estradiol on transfer day, (ng/L)	1,385±789	1,487±1,114	0.272
Progesterone on transfer day, (ng/mL)	2.13±0.28	2.21±0.4	0.031*
Number of 2PN	5.4±3.98	6±4.18	0.364
Stimulation protocols	n (%)	n (%)	0.005*
Long agonist	216 (74.5)	74 (25.5)	
Antagonist	382 (84.1)	72 (15.9)	
Micro dose flare-up	35 (77.2)	10 (22.8)	

Results are given as mean (n). FSH: follicle stimulating hormone, LH: luteinizing hormone, E2: estradiol, AMH: anti-Müllerian hormone, GnRH: gonadotropin-releasing hormone, HCG: human chorionic gonadotropin, E2: estradiol, LH: luteinizing hormone, OPU: oocyte collection, ICSI: intracytoplasmic sperm injection, ET: embryo transfer, 2PN: pronuclear stage. **p*-values with statistical significance ($p<0.05$).

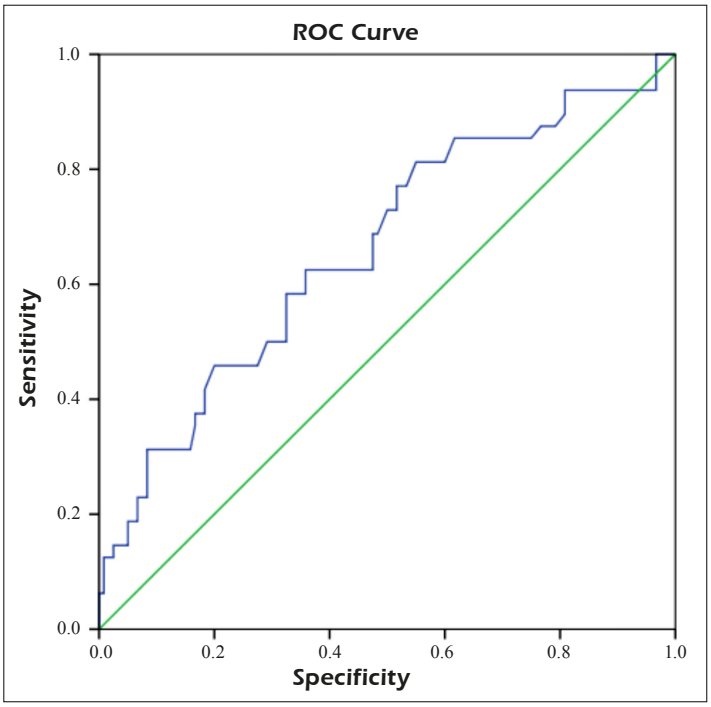

Figure 1. ROC curve of serum AMH levels to predict clinical pregnancy. The receiver-operator characteristic curve used to identify the significant cut-off point (3.34 ng/mL) for the ability of serum AMH levels to predict clinical pregnancy with a sensitivity of 62.5%, and a specificity of 37.5%. The area under the curve for the prediction of a positive value was 0.661, p=0.05.

rate was 19.8% per cycle. The distribution of the demographic data of the patients with and without clinical pregnancy is shown in Table I.

It was found that female age, BMI, male age, antral follicle count, sperm count, and sperm morphology did not have a significant effect on clinical pregnancy. Basal serum FSH level was found to be significantly lower in patients with clinical pregnancy than in the patients without pregnancy (7.6±3.3 *vs.* 9±5.1 IU/L, p=0.001). The mean serum AMH level was found to be significantly higher in the group with clinical pregnancy when compared to the group without clinical pregnancy (5.1±3.6 *vs.* 3.3±2.1 ng/mL, p=0.001). Basal serum LH and E2 levels were similar in both groups (p=0.050) (Table I). Low basal FSH (OR: 1.007, p=0.042) and high AMH (OR: 1.245, p=0.024) were found to be factors positively affecting the development of clinical pregnancy (Table II).

ROC curve analyses were performed to identify the significant cut-off point for the ability of AMH and basal serum FSH to predict clinical pregnancy, with an average accuracy of the area under the ROC curve (AUC: 0.661, 95% CI, 0.568-0.754, p=0.001 and AUC: 0.571, 95% CI, 0.520-0.621, p=0.008, respectively) (Figures 1 and 2). The AMH cut-off value for predicting clinical pregnancy was determined as 3.34 ng/mL with 62.5% sensitivity and 37.5%

Table II. Logistic regression analysis of the factors that are effective in clinical pregnancy.

	Odds ratio Exp (B)	95% CI	*p*
Age, years	0.99	0.96-1.03	0.868
BMI, kg/m^2	0.99	0.95-1.02	0.633
AMH ≥3.34, ng/mL	1.24	1.01-1.52	0.024*
FSH ≤7.26, IU	1.07	0.78-1.10	0.042*
Antral follicle count	0.99	0.96-1.01	0.611
Male's age, years	1.00	0.96-1.04	0.810
Sperm count, million	0.99	0.99-1.00	0.657
Sperm motility, %	1.00	0.99-1.01	0.313
Total progressive motil sperm count, %	1.00	1.00-1.00	0.431
Sperm morphology Kruger %	0.96	0.93-0.99	0.012

*p-values with statistical significance (p<0.05). BMI: body mass index, AMH: anti-Müllerian hormone, FSH: follicle-stimulating hormone.

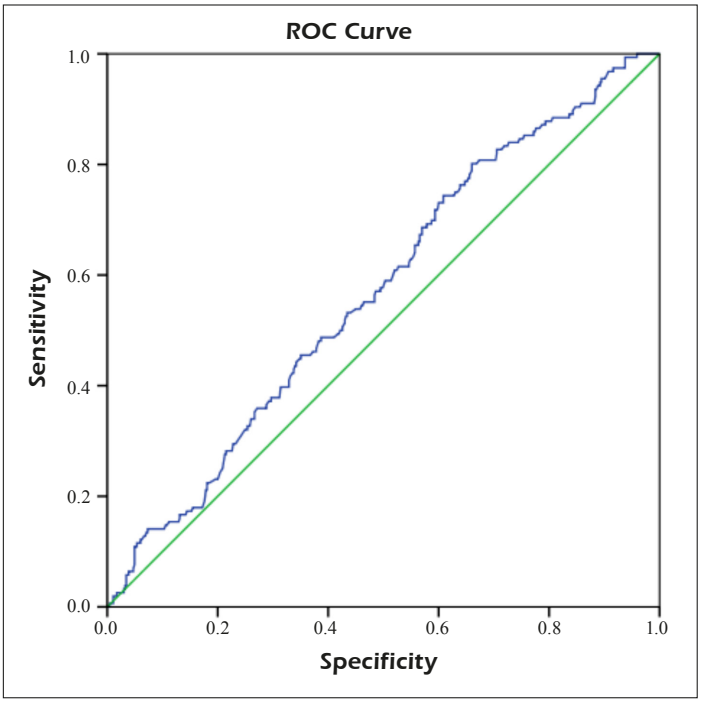

Figure 2. ROC curve of serum basal FSH levels to predict clinical pregnancy. The receiver-operator characteristic curve used to identify the significant cut-off point (7.26 IU/l) for the ability of day-3 follicle-stimulating hormone to predict clinical pregnancy with a sensitivity of 53.8% and specificity of 45.8%. The area under the curve for the prediction of a positive value was 0.571, p=0.05.

specificity. The serum basal FSH cut-off value for clinical pregnancy prediction was determined as 7.26 IU/L (sensitivity 53.8%, specificity 45.8%). In correlation analysis, a weak and positive correlation was observed between the age of the patients and total oocyte count, number of mature oocytes retrieved, basal serum FSH levels (r=0.209, p=0.001; r=0.249, p=0.001; r=0.215, p=0.001, respectively). The age of the patients was negatively correlated with AMH levels and the number of antral follicles (r=-0.292, p=0.001; r=-0.331, p=0.001, respectively). The correlation analysis of the fertilization-related factors is shown in Table III.

The mean duration of ovulation stimulation was found to be 13.3±8.3 days in patients with clinical pregnancy and 11.7±7.8 days in patients without pregnancy, and the difference was statistically significant (p=0.031). On the hCG injection day, the follicle count of the follicles with a diameter of 15-17 mm and ≥17 mm was significantly higher in the group that achieved clinical pregnancy (p=0.025 and p=0.014). The gonadotropin doses that were administered in both groups were similar (p=0.701). No significant difference was detected in terms of the number of oocytes collected and the mature oocyte count in patients with and without pregnancy (p=0.676 and p=0.284).

The antagonist protocol was applied to 57.6% of the 789 patients, while 36.7% received the GnRH agonist protocol, and the flare-up protocol was applied to 5.7%. Clinical pregnancy was achieved in 25.5% of the patients who underwent the long luteal protocol, 22.2% of patients who underwent the flare-up protocol, and 15.9% of the patients who underwent the antagonist protocol. Clinical parameters of the ovulation induction and ovarian response of the patients with and without clinical pregnancy are given in Table I.

No statistically significant difference was detected in terms of partners' age, sperm count, sperm motility, total progressive sperm count, and sperm morphology between the two groups in which clinical pregnancy developed and did not develop as a result of IVF-ET treatment (Table IV).

Discussion

In line with previous studies, we found that IVF-ET treatment is an option with a high rate of pregnancy in couples who have unexplained infertility[4]. In our study, the pregnancy rate was found to be 19.8% per patient per cycle during IVF-ET treatment. Previous studies[5,6] reported that 2-13% of pregnancies can develop spontaneously per cycle in couples with a diagnosis of unexplained infertility. IVF-ET treatment is considered to be an option in couples who can not achieve spontaneous pregnancy, and recent studies reported that pregnancy is achieved with IVF-ET treatment at a rate of 16.5-39.5% in couples with unexplained infertility[7,8]. The pregnan-

Table III. Correlation analysis of the fertilization-related factors.

	Age, years		AFC		Greater than 17 mm Follicle number		hCGday estradiol, ng/L		Total oocyte number		Mature oocyte number	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
Age, years			-0.404	0.011*	-0.219	0.042*	-0.083	0.019*	-0.086	0.025*	-0.450	0.043*
AMH, ng/mL	-0.292	0.001*	0.209	0.045*	0.341	0.013*	0.352	0.017*	0.232	0.012*	0.249	0.027*
AFC	-0.404	0.011*			0.361	0.018*	0.361	0.046*	0.654	0.040*	0.454	0.025*
FSH, IU	-0.315	0.005*	-0.331	0.001*	-0.180	0.035*	-0.250	0.032*	-0.211	0.016*	-0.111	0.038*
BMI, kg/m^2	0.212	0.124	0.003	0.324	-0.089	0.046*	- 0.095	0.049*	-0.250	0.050*	-0.311	0.029*

BMI: body mass index, AMH: anti-Müllerian hormone, FSH: follicle stimulating hormone, AFC: antral follicle count. **p*-values with statistical significance ($p<0.05$).

Table IV. Evaluation on male factor in patients who received IVF-ET treatment because of unexplained infertility.

	Odds ratio Exp (B)	95% CI	p
Male's age (years)	34.2±5.4	34.1±4.6	0.745
Sperm count (10^6)	60.1±35.7	62.9±37	0.661
Total progressive sperm count (10^3)	45.2±59.6	47.8±69.7	0.791
Sperm motility (A+B %)	71±22.6	73.4±19.6	0.223
Sperm morphology (% normal morphology)	11.8±6.4	14.1±6.2	0.251

The results are given as mean (n).

cy rate of the presented series (19.8%) during IVF-ET treatment is in accordance with the literature. The patients' first IVF-ET cycle results were evaluated in the present study. It is possible that the pregnancy rate per patient per cycle increases even more with the pregnancies that will be achieved in the repetitive cycle trials, and thus, cumulative pregnancy rates will be higher. Türkyılmaz and Api[7] found that the pregnancy rate was 16.6% per cycle, and the pregnancy rate was 21.7% per patient in 132 treatment cycles. These findings are similar to the findings of the presented study. When IVF-ET was compared with other treatment modalities in terms of efficacy in couples with unexplained infertility, the live birth rates were found to be significantly higher in IVF-ET than the expectant management (45.8% *vs*. 3.7%)[9]. In a recent meta-analysis[10], the success rates of IVF-ET in unexplained infertility cases were higher than controlled ovarian stimulation and intrauterine insemination (COH + IUI) relative risk ratio (RR) 1.53, (95% CI, 1.01-2.32) and (RR) increased to 2.15 (95% CI, 1.16-4.0) in women who were over 38 years of age.

When the demographic data and clinical characteristics of the patients who achieved pregnancy during IVF-ET treatment were compared with the ones who failed to get pregnant, we did not find a significant relationship between the duration of infertility and achieving pregnancy in patients with unexplained infertility[11]. Duration of infertility is reported to be an important predictor of pregnancy outcome, especially in the unexplained infertility group. Although the etiology of unexplained infertility is multifactorial, couples with a longer duration of infertility are likely to be affected with more severe fertility problems than those with a shorter duration of infertility. Pettersson et al[12] found that women with a shorter duration of infertility had better outcomes following IVF treatment.

Obesity was associated with ovulatory dysfunction in women by various authors, and it was reported that infertility, because of ovulation disorder, increased as BMI increased[13]. There are studies reporting that BMI has effects on the success of pregnancy after IVF-ET treatment[6], as well as several other studies reporting that there are no significant relations between BMI and fertilization rates after IVF-ET treatment[14,15]. In the presented study, BMI had no significant effects on pregnancy rate after IVF-ET treatment in women with unexplained infertility. This result might be speculated to be related to the presence of spontaneous ovulation in the unexplained infertility group.

Age has been identified as a significant predictor of clinical pregnancy in IVF treatment cycles. Ovarian function decreases in women with increasing age, and the number of quality oocytes decreases after the age of 35[16]. The decreasing number of oocytes with advancing age has a negative effect on IVF-ET success rate in women, and pregnancy rates decrease in accordance with the decrease in the number of oocytes collected per cycle[17]. Low implantation rates were reported after the transfer of the embryos obtained from the oocytes of older women[18]. Hansen et al[11] found that age has a small impact on clinical outcomes in the unexplained group and reported an odds ratio of 0.93 for the outcome of live birth. In our study, there was no significant difference in terms of age between those who achieved pregnancy with IVF-ET and those who did not. Female age was not correlated with the pregnancy rate after IVF-ET in our study group, and logistic regression analysis showed that the odds ratio appears not to reflect an impact on clinical outcomes (0.99; 95% CI, 0.96-1.33). Fang et al[19] reported that age, along with FSH levels, is a more accurate predictor for IVF-ET treatment response in women with normal ovarian reserve.

Basal hormone levels and ovarian reserve parameters of patients diagnosed with unexplained infertility are within normal limits, so women

with diminished ovarian reserve were not recruited for the presented study. In our study, a cut-off value <7.26 IU/L was calculated for FSH in predicting clinical pregnancy development after IVF-ET. The present study showed that basal FSH and AMH levels may be predictors of pregnancy outcomes in unexplained infertility groups following IVF treatment. Toner[20] reported that basal FSH was effective on IVF-ET performance. Onagawa et al[21], examined 72 IVF cycles of 59 infertile patients, and the day 3 FSH threshold value during the pituitary suppression was determined to be 5.25 IU/L, as the number of oocytes collected was low when FSH basal was above this value and *vice versa*. A well-documented association exists between ovarian reserve and basal serum FSH levels. In the presented study, low basal FSH and high AMH levels were found to be two parameters associated with increased pregnancy rates and had a diagnostic value in predicting pregnancy, while no relation was detected between basal E2 and LH levels and pregnancy success.

Although AMH levels are more predictive of ovarian response, several studies also showed that serum levels of AMH at the initiation of the stimulation protocol were predictive of live birth rates[11]. Brodin et al[22] demonstrated that AMH is positively associated with pregnancy and live birth rate and may serve as a prognostic factor for IVF-ICSI treatment success. Ebner et al[23], reported that oocyte quality was lower in patients with AMH levels below 1.66 ng/mL and above 4.52 ng/mL when compared to those between these two values. In the presented study, an AMH cut-off value of <3.34 IU/L was calculated for predicting clinical pregnancy development after IVF-ET with a sensitivity of 62.5% and a specificity of 37.5%.

It was reported that when the number of oocytes collected in one cycle is up to 15 oocytes, the live birth rates increase; a plateau occurs between an oocyte number of 15 to 20, and pregnancy success begins to decrease when the number of oocytes is over 20[17]. No significant differences were detected in the number of oocytes collected or the number of mature oocytes between the study grou F-ET treatment cycles, but a relationship was found between the AMH, FSH levels, and the clinical pregnancy rates in the unexplained infertility group. The positive association between AMH and clinical pregnancy rates after IVF cycles might reflect the presence of a higher number of oocytes. AMH and FSH cut-off levels may predict pregnancy outcomes with low sensitivity and specificity.

Conflict of Interest
The authors declare that they have no conflict of interest to disclose.

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Ethics Approval
Ethics approval was granted by the Ethics Committee of the Health Sciences University Etlik Zübeyde Hanım Gynecology Training and Research Hospital (No. 2020-68, dated 03.06.2020).

Informed Consent
Written informed consent was provided by the patients to receive therapy and for the publication of this study.

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Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions
A.C.O and B.D. conceived of the presented idea. A.C.O., B.D, R.O., and S.D. contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. All authors discussed the results and contributed to the final manuscript.

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