Journal of Infertility and Reproductive Biology

J Infertil Reprod Biol, 2021, Volume 9, Issue 3, Pages: 109-116. https://doi.org/10.47277/JIRB/9(3)/109

Emotional Stress Lowers Follicular Output Rate (FORT) of Unexplained Infertile or Poor Responder Women unlike Women with Male Infertility without any Prognostic Effect on Cycle Outcomes during Ovulation Induction for In Vitro Fertilization

Serkan Kahyaoglu[1], Pınar Gulsen[2], Ozge Gurbuz[3], Caner Kose[4]*, Inci Kahyaoglu[4], Hacer Cavidan Gulerman[1], Nafiye Yilmaz[1], Yaprak Ustun[4]

[1] Department of Reproductive Endocrinology, Ankara City Hospital, University of Health Sciences, Ankara, Turkey
[2] Private Ankara IVF Center, Ankara, Turkey
[3] Department of Obstetrics and Gynecology, Sanliurfa Maternity Hospital, Sanliurfa, Turkey
[4] Department of Reproductive Endocrinology, Etlik Zubeyde Hanim Women's Health Hospital, University of Health Sciences, Ankara, Turkey

Received: 12/06/2021 Accepted: 23/08/2021 Published: 20/09/2021

Abstract

A total of 78 patients have accepted to evaluate and answer questions in the Beck depression questionnaire form at the beginning of their controlled ovarian hyperstimulation procedures. Among these patients; 28 (36%), 27 (34%), and 23 (30%) of them were accepted for in vitro fertilization and embryo transfer (IVF-ET) treatment due to male factor, explained infertility and poor ovarian reserve respectively. Based on the Beck depression scale; 9 (12%) patients had mild depression, 31 (39%) patients had moderate depression and 38 (49%) patients had severe depression. IVF-ET cycle outcomes of these three groups of depression levels are statistically similar. A significant negative correlation between Beck depression scores a Follicular Output Rate (FORT) ratios, but not for metaphase II (MII) oocyte numbers, has been detected among unexplained infertile and poor ovarian reserve groups. A significant relationship between increasing Beck depression scores and lower FORT ratios have also been detected for unexplained infertile and poor ovarian reserve groups. FORT ratio which is achieved during the controlled ovarian hyperstimulation (COH) process of IVF-ET procedures seems to be lowered by emotional stress among unexplained or poor responder infertile women despite lack of a clinical effect on other cycle outcomes. Further studies investigating the effect of emotional stress itself and interventions to relieve this stress on IVF-ET cycle outcomes are needed to clarify this uncertainty.

Keywords: in vitro fertilization, Depression, Embryo Transfer, Infertility

Introduction

As psychological distress affects the general health and well-being of people, a similar detrimental impact on reproductive health has previously been proposed (1). Being childlessness, procedures of infertility treatment, the uncertainty of cycle outcomes in terms of achievement of a healthy pregnancy, and social pressure on infertile women are main sources of psychological distress on women during infertility treatment procedures. During the ovulation process, folliculogenesis and steroidogenesis concomitantly take place to generate the most suitable follicle containing mature oocyte. These processes are managed from centrally secreted hormones like a gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormones (LH). Theoretically, psychological distress might affect secretion of these hormones and generation of a healthy oocyte by increased levels of glucocorticoid hormones and lowered levels of endorphin. Psychological distress and depressive mood result with increased secretion of corticotrophin-releasing hormone (CRH) from the hypothalamus. Increased CRH both directly affects the secretion of GnRH secreting neurons in the arcuate nucleus and indirectly by decreased endorphin levels. Serum glucocorticoid level which is also increased by CRH stimulation decreases hypothalamic GnRH secretion, pituitary gonadotropin secretion, ovarian steroidogenesis, and effects of ovarian steroid hormones on receptor containing tissues. However, previous studies have not proven the negative effects of psychological distress on the cycle outcomes of fertility treatment.

Follicular Output Rate (FORT) has been proposed as a measure of the responsiveness of the antral follicle to controlled ovarian stimulation (COS).

This is a primary endpoint ratio between the number of follicles that reach the preovulatory maturation stage (16-22 mm)

***Corresponding author:** Caner Kose, Department of Reproductive Endocrinology, Etlik Zubeyde Hanim Women's Health Hospital, University of Health Sciences, Ankara, Turkey. E-mail: dr.canerkose@gmail.com

J Infertil Reprod Biol, 2021, Volume 9, Issue 3, Pages: 109-116. https://doi.org/10.47277/JIRB/9(3)/109

in response to FSH and the pool of FSH-sensitive antral follicles on cycle day 1-3 which is called as Follicular Output Rate (FORT). In a prospective study, Genro et al. demonstrated that serum AMH levels were positively correlated with the number of small antral follicles at baseline and preovulatory follicles. They concluded that FORT was 47.5+1.4% and failed to be influenced by the woman's age, BMI, basal E2, and FSH level. Besides, the authors also emphasized that FORT was negatively correlated with AMH levels irrespective of duration for COH and total utilized FSH dose which means that AMH inhibits the sensitivity of antral follicles to FSH (2). Currently, intrinsic and extrinsic factors influencing the FORT rate which is achieved during controlled ovarian hyperstimulation are unknown and worth to be investigating. Psychological stress is prevalent among infertile women and we hypothesized that this stress might affect FORT and/ or IVF-ET cycle outcomes. FORT is calculated as the ratio of preovulatory follicles which are detected upon sonography as arbitrarily 16– 22 mm in size on the day of exogenous ovulation trigger with hCG to the number of small antral follicles (3-8 mm) on the day 1-3 of the menstrual cycle (3-5).

In this cross-sectional study, we evaluated the cycle outcomes of infertile women with unexplained infertility, diminished ovarian reserve, and male factor infertility based on their psychological distress levels which were measured by using the Beck depression scale at the beginning of the ovulation induction cycle.

Material and Methods

This study has been performed in the University of Health Sciences Turkey, Ankara Dr. Zekai Tahir Burak Women's Health, Health Application, and Research Center. The study group has been voluntarily selected from the infertile women aged 24-40 years old who have been appointed for in vitro fertilization and embryo transfer (IVF-ET) treatment for unexplained infertility, diminished ovarian reserve, and male factor infertility between December 2018 and December 2019.

Patient selection, evaluation of depression, and data collection

Women with clinical conditions like polycystic ovary syndrome, hypogonadotropic hypogonadism, and endometriosis which might affect ovulatory processes have been excluded. Women with systemic illnesses and hormonal disorders like thyroid disease have also been excluded. All women have been seen by a psychologist before the treatment cycles and there was no psychiatric disease precluding them from proceeding with the IVF-ET treatment cycle. Seventy-eight patients have been selected from three etiological groups including male factor, poor ovarian reserve, and unexplained infertility who have received GnRH antagonist IVF-ET treatment procedures during the study period. Beck depression II (BDI-II) scale which includes 21 questions with multiple choices has been asked to each patient at the beginning of the ovarian stimulation procedures (6). The results of the test have been evaluated by the authors at the end of the treatment cycle without any expression to the patients regarding the test results for preventing patient bias. However, patients with test results reflecting moderate or severe depression have been referred to a psychiatry specialist following the treatment cycle. Age, gravidity, parity, body mass index, infertility etiology, Beck depression score, antral follicle count, preovulatory follicle count, cycle length, FORT ratios of the preovulatory follicle to antral follicle count, serum estradiol level on hCG day, number of harvested oocytes during pick-up procedure, number of M2 oocytes, embryo number, high-quality embryo number, transferred embryo number, and clinical pregnancy rate have retrospectively been evaluated from the medical records of our institution's IVF center. All patients provided written informed consent.

Ovulation induction protocol

GnRH antagonist controlled ovarian stimulation protocol has been started subcutaneously on cycle day 2 or 3 with 150-300 IU/day hMG (Menogon, Ferring; Merional, IBSA; İstanbul, Turkey) and/or 150-300 IU/day recombinant FSH until two or more follicles reached 18 mm in diameter until ovulation triggering. The doses of hMG and recombinant FSH have been adjusted according to the women's baseline ovarian reserve and ovarian response during ovarian stimulation. Premature LH surge has been suppressed by using subcutaneous 0.25 mg cetrorelix (Gonal-F, Cetrotide; Merck Serono; İstanbul, Turkey) which has been started on day 6 of stimulation or detection of serum E2 levels of >300 pg/mL or generation of >14 mm follicles. The first visit for transvaginal ultrasonographic folliculometry procedure has been performed on the fifth day of ovarian stimulation and every other day until ovulation triggering. Recombinant human chorionic gonadotropin (hCG) (250 micrograms sc., Ovitrelle, Merck Serono, Istanbul, Turkey) was administered when at least two leading follicles reached a mean diameter of 18 mm. Oocyte retrieval procedure has been performed by using transvaginal ultrasonography guidance after 36 hours following hCG injection. Intracytoplasmic sperm injection (ICSI) procedure has been performed for all oocytes and metaphase II (MII) oocytes were reviewed after 16 hours following ICSI. Embryo grading was recorded according to the published criteria (7). Grade 1 embryos have been considered as good quality embryos and 1or 2 best quality embryos have been transferred under ultrasonographic guidance on days 3-5 for all patients based on the woman's age and IVF cycle number (2 embryos have been transferred to women who are older than 35 years and/or when current IVF-ET cycle number is third or higher). Following the embryo transfer (ET), all patients received vaginal progesterone (Crinone 8% gel, Serono) supplementation twice a day or vaginal micronized progesterone (600mg/day given at 8h intervals) starting on the day of oocyte pick up and continuing either up to menstruation or up to 7. weeks of gestation pregnancy in case of pregnancy achievement. Clinical pregnancy was defined as the presence of a gestational sac with accompanying fetal heartbeat on ultrasonography at least 3-4 weeks after ET (8).

Statistical analysis

Statistical analysis was performed by using SPSS 22.0 version. The normal distribution of data was evaluated by using the Kolmogorov-Smirnov test. The continuous variables were presented by means ± standard deviation and compared by using the independent samples t test. The nonparametric variables and data without normal distribution were tested by using Kruskal Wallis test and Mann-Whitney U test. Correlation analyses were performed by using Pearson and Spearman's correlation tests. Receiver operating curve (ROC) analyses have been performed for determining the predictive value of Beck depression scores on

J Infertil Reprod Biol, 2021, Volume 9, Issue 3, Pages: 109-116. https://doi.org/10.47277/JIRB/9(3)/109

FORT and IVF-ET cycle outcomes among patients' depression levels and IVF-ET indications. The comparison of categoric values was performed by using Fisher's exact test, or the Chi-square test. All p values <0.05 were considered statistically significant.

Results

A total of 78 patients have accepted to evaluate and answer questions in the Beck depression questionnaire form at the beginning of their controlled ovarian hyperstimulation procedures. Among these patients; 28 (36%), 27 (34%), and 23 (30%) of them were accepted for IVF-ET treatment due to male factors, unexplained infertility, and poor ovarian reserve respectively. IVF-ET cycle parameters and Beck depression questionnaire results of these three groups of patients have been demonstrated in Table 1. When IVF-ET cycle outcomes have been evaluıated; woman age, day 3 FSH levels, antimüllerian hormone levels, day 3 antral follicle count, total utilized gonadotropin amount, estradiol (E2) levels on hCG day, progesterone (P) levels on hCG day, harvested M2 oocytes, 2PN embryos, and total embryo numbers are significantly different among these three groups of IVF-ET indications. Based on the Beck depression scale; 9 (12%) patients had mild depression, 31 (39%) patients had moderate depression and 38 (49%) patients had severe depression. IVF-ET cycle outcomes of these three groups of depression levels are statistically insignificant except for Beck depression scores (Table 2). Similarly, when cycle outcomes of the patients with mild/ moderate depression have been compared with patients with severe depression, IVF-ET cycle outcomes of these two groups of depression levels are statistically insignificant either (Table 3). When Spearman correlation analyses have been performed to evaluate any positive or negative correlation between Beck depression scores and FORT ratios separately for three IVF-ET indications of male factor, unexplained infertility, and poor ovarian reserve; correlation coefficient r values and p values were as follows respectively: 0.26 and p=0.12, -0.44 and p=0.02, -0.67 and p<0.001. When Spearman correlation analyses have been performed to evaluate any positive or negative correlation between Beck depression scores and MII oocyte numbers separately for three IVF-ET indications of male factor, unexplained infertility, and poor ovarian reserve; correlation coefficient r values and p values were as follows respectively: 0.18 and p=0.34, 0.12 and p=0.55, -0.12 and p=0.57. Following stratification of patients based on FORT rates of <33%, 34-66%, and >67%, ROC (Receiver Operating Characteristic) analyses have been performed to evaluate the relationship between increasing Beck depression scores and lower FORT ratio (<33%) results. A statistically significant positive relationship has been found between increasing Beck depression scores and lower percentile (<33%) FORT ratios of the whole study group (AUC:0.63; 95% CI: 0.50-0.76; P=0.049; Cut-off value=26.5; Sensitivity: 71%, Specificity:45%) (Figure 1). When ROC analyses to evaluate a relationship between increasing Beck depression scores and lower FORT ratios have been performed separately for male factor, unexplained infertility, and poor ovarian reserve groups; a statistically significant and positive relationship has been found between increasing Beck depression scores and lower FORT ratios for unexplained infertile and poor ovarian reserve groups but not for male factor group (Male factor= AUC:0.40; 95% CI: 0.18-0.62; P=0.41/ Unexplained infertility= AUC:0.73; 95% CI: 0.55-0.92; P=0.036/ Poor ovarian reserve= AUC:0.85; 95% CI: 0.68-1.00; P=0.006) (Figures 2-4).

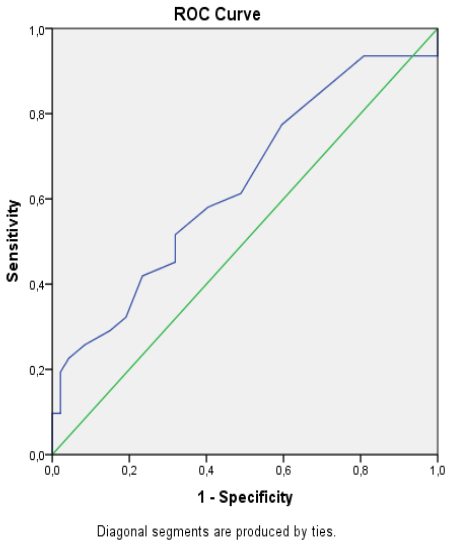

Figure 1. Receiver operating characteristic (ROC) analysis of increasing Beck depression scores and lower percentile (<33%) FORT ratios of the whole study group (AUC:0.63; 95% CI: 0.50-0.76; P=0.049; Cut-off value=26.5; Sensitivity: 71%, Specificity:45%).

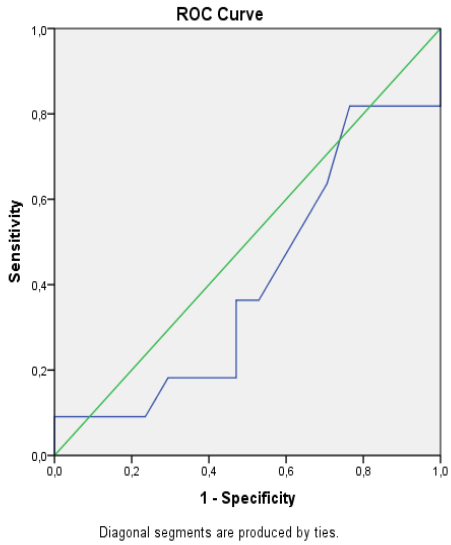

Figure 2. Receiver operating characteristic (ROC) analysis of increasing Beck depression scores and lower percentile (<33%) FORT ratios of the male factor group (AUC:0.40; 95% CI: 0.18-0.62; P=0.41)

Journal of Infertility and Reproductive Biology
J Infertil Reprod Biol, 2021, Volume 9, Issue 3, Pages: 109-116. https://doi.org/10.47277/JIRB/9(3)/109

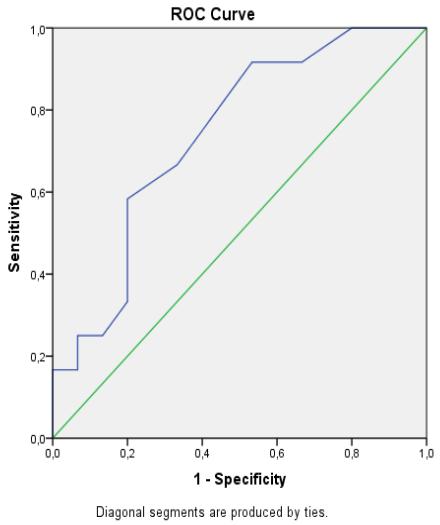

Figure 3. Receiver operating characteristic (ROC) analysis of increasing Beck depression scores and lower percentile (<33%) FORT ratios of the unexplained infertile group (AUC:0.73; 95% CI: 0.55-0.92; P=0.036).

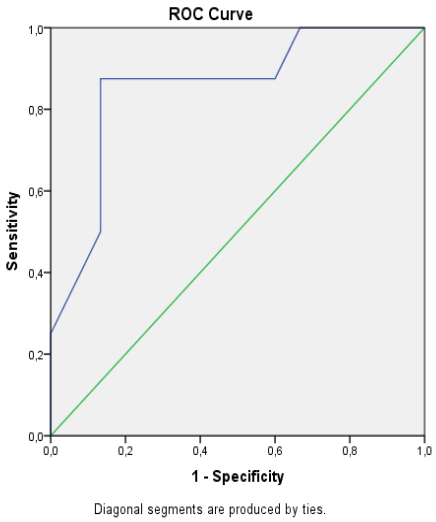

Figure 4. Receiver operating characteristic (ROC) analysis of increasing Beck depression scores and lower percentile (<33%) FORT ratios of the poor ovarian reserve group (AUC:0.85; 95% CI: 0.68-1.00; P=0.006).

Table 1. The comparison of patients' IVF-ET cycle parameters according to IVF-ET indication

Parameter	Male factor (N=28) Mean±SD	Unexplained infertility (N=27) Mean±SD	Poor ovarian reserve (N= 23) Mean±SD	P-value
Age (years)	28.6±4.8	31.8±4.4	33.8±4.7	<0.001**
Body mass index (BMI) (kg/m^2)	24.4±3.8	25.4±4.6	24.7±4.3	0.70*
Cycle number (n)	1.4±0.7	1.6±0.7	1.7±1.1	0.41**
Day 3 FSH level (mIU/mL)	6.71±1.49	6.45±1.65	10.04±1.04	0.002*
Day 3 LH level (mIU/mL)	8.37±13.36	5.74±2.20	6.00±2.87	0.68**
Antimüllerian hormone level (ng/ml)	2.76±2.13	3.05±1.99	0.73±0.70	<0.001**
Beck depression score (points)	27.46±7.51	30.63±12.13	30.22±5.46	0.23**
Total antral follicle count (n)	10.24±2.86	12.48±3.65	6.00±2.66	<0.001**
Stimulation days (n)	9.82±1.36	9.78±1.25	9.30±1.46	0.34*
Total gonadotropins used (IU)	2096±674	2291±717	3130±714	<0.001*
Follicle Output Rate (%)	48.9±26.8	39.8±19.5	45.8±23.0	0.47**
E2 level on hCG day (pg/mL)	2272±898	2308±1204	1072±750	<0.001**
P level on hCG day (ng/mL)	0.64±0.38	0.75±0.32	0.46±0.24	0.011**
Endo thickness on hCG day (mm)	10.49±2.25	10.07±1.71	10.08±1.96	0.80**
M2 oocyte number (n)	9.39±3.74	8.11±3.45	4.47±3.66	<0.001**
2PN number (n)	7.46±3.12	5.70±2.92	2.83±1.85	<0.001**
Embryo number (n)	3.89±2.75	3.62±2.00	1.74±1.57	0.001**
Good quality embryo number (n,%)	12 (44.4%)	15 (55.6%)	7 (30.4%)	0.20***
Fertilization rate (%)	80±13	70±21	67±26	0.13**
Transferred embryo number (n)	1.22±0.42	1.35±0.48	1.43±0.87	0.51***
Clinical pregnancy rate (n,%)	13 (46.4%)	10 (37.0%)	7 (30.4%)	0.49***

*P values were calculated by using One Way ANOVAtest
** P values were calculated by using Kruskal Wallis test and Mann Whitney U test was used for post hoc analyses for statistically significant p values
*** P values were calculated by using Pearson Chi-square test
(The distribution of continuous variables is tested by using Kolmogorov Smirnov test)

J Infertil Reprod Biol, 2021, Volume 9, Issue 3, Pages: 109-116. https://doi.org/10.47277/JIRB/9(3)/109

Table 2. The comparison of patients' IVF-ET cycle parameters according to the severity of depression

Parameter	Mild depression (N=9) Mean±SD	Moderate depression (N=31) Mean±SD	Severe depression (N= 38) Mean±SD	P-value
Age (years)	32.5±5.6	29.6±4.8	32.3±4.9	0.06**
Body mass index (BMI) (kg/m^2)	23.3±3.4	25.2±4.8	24.9±3.8	0.49**
Cycle number (n)	2.0±1.0	1.42±0.6	1.66±0.9	0.21**
Day 3 FSH level (mIU/mL)	8.21±3.72	7.03±2.03	7.92±3.78	0.79*
Day 3 LH level (mIU/mL)	5.91±1.99	7.81±12.74	6.10±2.73	0.93**
Antimüllerian hormone level (ng/ml)	2.85±2.05	1.98±1.35	2.33±2.42	0.46**
Beck depression score (points)	18.2±0.8	25.4±1.5	35.1±9.3	<0.001**
Total antral follicle count (n)	9.00±4.33	10.48±4.60	8.69±3.46	0.18**
Stimulation days (n)	9.56±1.66	9.77±1.33	9.58±1.32	0.82**
Total gonadotropins used (IU)	2214±839	2515±867	2491±785	0.61**
Follicle Output Rate (%)	43.3±14.0	48.9±26.8	41.8±22.1	0.54**
E2 level on hCG day (pg/mL)	2535±1292	1962±1077	1762±1082	0.15**
P level on hCG day (ng/mL)	0.58±0.36	0.62±0.30	0.63±0.37	0.93**
Endo thickness on hCG day (mm)	10.22±2.59	10.37±2.14	10.11±1.71	0.98**
M2 oocyte number (n)	8.22±4.86	7.54±3.65	7.28±4.37	0.81**
2PN number (n)	6.67±3.35	5.42±3.24	5.26±3.34	0.50**
Embryo number (n)	2.78±2.10	3.23±2.14	3.18±2.62	0.85**
Good quality embryo number(n,%)	2 (25%)	16 (51.6%)	16 (42.1%)	0.37***
Fertilization rate (%)	86.7±12.0	69.8±20.9	72.9±22.6	0.09*
Transferred embryo number (n)	1.38±0.51	1.31±0.66	1.32±0.58	0.72**
Clinical pregnancy rate (n,%)	5 (55%)	9 (29%)	16 (42%)	0.28***

*P values were calculated by using One Way ANOVA test, ** P values were calculated by using Kruskal Wallis test and Mann Whitney U test was used for post hoc analyses for statistically significant p values, *** P values were calculated by using Pearson Chi-square test (The distribution of continuous variables is tested by using Kolmogorov Smirnov test)

Table 3. The comparison of IVF-ET cycle parameters of patients with severe depression and patients with mild/ moderate depression

Parameter	Mild/Moderate depression (N=40) Mean±SD	Severe depression (N=38) Mean±SD	P-value
Age (years)	30.2±5.0	32.3±4.9	0.07**
Body mass index (BMI) (kg/m^2)	24.8±4.6	24.9±3.8	0.98**
Cycle number (n)	1.5±0.7	1.6±0.9	0.93**
Day 3 FSH level (mIU/mL)	7,3±2.5	7.9±3.7	0.76*
Day 3 LH level (mIU/mL)	7.4±11.2	6.1±2.7	0.18**
Day 3 E2 level (pg/mL)	54.84±33.19	49.35±19.80	0.27*
Antimüllerian hormone level (ng/ml)	2.18±1.55	2.33±2.42	0.50**
Beck depression score (points)	23.8±3.3	35.1±9.3	<0.001**
Total antral follicle count (n)	10.2±4.5	8.6±3.4	0.07**
Stimulation days (n)	9.7±1.4	9.6±1.3	0.64**
Total gonadotropins used (IU)	2447±859	2491±785	0.54**
Cancellation rate (n,%)	28/76 (36.8%)	1/56 (1.8%)	<0.001
Follicle Output Rate (%)	47.7±24.5	41.8±22.1	0.27**
E2 level on hCG day (pg/mL)	2091±1137	1762±1082	0.15**
P level on hCG day (ng/mL)	0.61±0.31	0.63±0.37	0.95**
Endo thickness on hCG day (mm)	10.3±2.2	10.1±1.7	0.90**
M2 oocyte number (n)	7.7±3.9	7.2±4.3	0.53**
2PN number (n)	5.7±3.2	5.2±3.3	0.51**
Embryo number (n)	3.1±2.1	3.1±2.6	0.78**
Good quality embryo number (n,%)	18 (46.2%)	16 (42.1%)	0.72***
Fertilization rate (%)	73.6±20.4	72.9±22.6	0.98*
Transferred embryo number (n)	1.32±0.6	1.32±0.58	0.60**
Clinical pregnancy rate (n,%)	14 (35%)	16 (42%)	0.51***

*P values were calculated by using Independent Samples t-test, ** P values were calculated by using Mann Whitney U test, *** P values were calculated by using Pearson Chi-square test (The distribution of continuous variables is tested by using Kolmogorov Smirnov test)

J Infertil Reprod Biol, 2021, Volume 9, Issue 3, Pages: 109-116. https://doi.org/10.47277/JIRB/9(3)/109

Discussion

The homeostasis all vital physiologic systems of the body is constantly challenged by adverse real or even perceived intrinsic/ extrinsic stressors. Complex and interconnected neuroendocrine, cellular and molecular infrastructures play roles for the stress response which is located in both the central nervous system (CNS) and the periphery (1). Genetic, environmental, and developmental factors determine the adaptive responses to potential stressors. Inability to effectively respond to these stressors may lead to the establishment of disease states which can potentially result in detrimental effects on physiological functions like growth, reproduction, metabolism, and immunocompetence. Potent stressors result in adaptive changes in the body which improve the chances of survival and maintenance of homeostasis. When the human body is exposed to potent stressors; vegetative functions like feeding and reproduction are inhibited and behavioral adaptation mechanisms including enhanced arousal, alertness, vigilance, cognition, focused attention and analgesia become prominent. Strong interdependent links exist between neurobehavioral and psychoemotional stress and certain disease states related to autoimmunity, inflammation, malignancy, metabolic, growth, and reproductive disorders. Understanding the pathophysiological pathways and neurochemical networks may clarify the pathogenesis of stress-related complications. Based on these facts, the potential clinical effects of stress on reproductive function have not been evaluated rigorously. Infertility itself may be a potent stressor due to the inability to conceive independently of the cause. Fertility treatment procedures including assisted reproductive techniques (ART) can also induce anxiety and depression among infertile women. Previously, various studies have been performed to evaluate the relationship between the psychological health of infertile women and fertility treatment outcomes. Despite most of the studies around this area have not shown any relationship between depression and Assisted Reproductive Techniques treatment outcomes, in some studies pregnancy rates seem to be lower among infertile women with these mood disturbances (9). A meta-analysis including prospective studies has been conducted by Boivin et al. evaluating the relationship between emotional distress in infertile women and failure of assisted reproductive technologies. They concluded that emotional distress caused by fertility problems or other life events co-occurring with treatment does not compromise the chance of becoming pregnant (10). In another meta-analysis, Purewal et al. have evaluated 11 studies on whether initial anxiety and depression scores during assisted reproductive technology (ART) treatment and changes in anxiety and depression scores between baseline and during ART treatment are associated with ART treatment outcome (11). They concluded that women who achieved pregnancy had significantly lower depression and anxiety scores during treatment than women who did not become pregnant. They also stated that changes in the anxiety and depression scores from baseline to treatment period were not associated with ART outcome. In a recently performed cross-sectional study, beliefs of 1460 infertile women regarding whether a relationship between emotional stress and poor fertility treatment outcomes exactly exists or not. Among these women, 28.9% were believing that emotional stress could cause infertility, 69.0% were believing that emotional stress could reduce success with fertility treatment, and 31.3% were believing that emotional stress could cause a miscarriage (12). In a review of systematic reviews investigating the effect of stress/ anxiety levels and interventions to ameliorate these mood disorders in couples who undergo fertility treatment on cycle outcomes; despite an observation has detected upon couples who reported better psychological state or have been treated with an interventional method for psychological support were more likely have better adjustments to the treatment procedure and the cycle outcomes, the authors have stated that a certain answer to these questions could not be provided due to conflicting results in the studies included to the systematic reviews (13).

In 2011; Genro et al. have performed a study investigating a relationship between AMH levels and FORT ratios. They concluded that the percentage of follicles that effectively respond to FSH treatment during COH by reaching pre-ovulatory maturation is negatively related to serum AMH levels independent of the duration of COH and total administered FSH dose during IVF-ET treatment procedure (2, 14). In a prospective cohort study; the authors concluded that FORT was an independent variable affecting the clinical pregnancy rate in IVF/ICSI cycles. They determined low, intermediate, and high FORT percentages for <33%, 34-67%, and >67% respectively. They emphasized that higher FORT values were reflected with higher oocyte yield and top-quality embryos and clinical pregnancy rates in women with unexplained infertility undergoing IVF/ICSI when they compared the clinical pregnancy rates among pregnant and nonpregnant women, FORT ratios of 60.9% and 53.1% have been detected respectively (15). The cut-off values of FORT to define poor responders have not been determined yet. Based on the Bologna criteria; poor responders have been defined as those who had three or fewer oocytes with a conventional protocol. Calculation of the FORT ratio may provide a more accurate definition of ovarian response to ovulation induction by taking into account baseline antral follicle count. Gallot et al. have investigated the predictive value of low, moderate, and high FORT ratios for determining clinical pregnancy rates per oocyte retrieval. They emphasize that clinical pregnancy rates per oocyte retrieval have increased significantly from low to high FORT groups which were independent of the confounding covariates like women's ages, AFC, and preovulatory follicle count (16). In 2013; Zhang et al. have evaluated 1503 IVF-ET cycle outcomes of non-PCOS patients and they concluded that numbers of retrieved oocytes and of all embryos that could be transferred, as well as rates of good-quality embryos, embryo implantations, and clinical pregnancies, progressively increased with FORT. Paradoxically; they also mentioned that fertilization and good-quality embryo rates were significantly higher for patients with medium FORT ratios than low and high FORT ratios. These contradictory results precluded to make any clinical advice for ovulation induction strategy regarding a targeted FORT ratio to improve IVF-ET cycle outcomes (17). Bessow et al. have demonstrated that <6 mm antral follicles were less sensitive to ovulation induction based on the FORT ratios which were achieved by administration of exogenous FSH unlike antral follicles >6 mm in size (18). In a retrospective study; Yang et al. have evaluated the predictive value of the FORT ratio on the pregnancy outcome of 1541 patients with PCOS undergoing IVF-ET treatment procedure. They concluded that from the low to high FORT ratio groups; the

preovulatory follicle count and serum estradiol at the day of hCG, the number of retrieved oocytes, MII oocytes, the total number of embryos, and the number of high-quality embryos were significantly increased unlike AFC, gonadotropin stimulation duration in days and total gonadotropin consumption which were significantly decreased with increasing FORT ratios (19).

In our study, we performed the Beck depression questionnaire to volunteer infertile women who have been in a COH process for the IVF-ET treatment cycle due to male factors, unexplained infertility, and poor ovarian reserve. We have previously consulted these women to the psychologist of our institution and they are eligible for IVF-ET treatment due to the absence of major psychological disorders. Surprisingly, we detected that mild, moderate and even severe depression signs were prevalently present among these women during the COH process based on this questionnaire regardless of the IVF-ET indication. Although, cycle outcomes like total gonadotropin consumption, E2/P levels on hCG day, M2 oocyte numbers, and embryo numbers are statistically different; Beck depression scores, FORT percents, good quality embryo number, and clinical pregnancy rates were similar between three IVF-ET indication groups (Table 1). Based on these results, despite emotional stress seems to be prevalent among infertile women regardless of a specific IVF-ET indication, this clinical entity does not affect pregnancy rates. When we stratified the whole study group according to their depression levels, we did not observe any statistically significant relationship between the severity of depression and ART cycle outcomes (Table 2,3). However, we detected a statistically significant negative relationship between Beck depression score and FORT percent among the whole study group (Figure 1). We detected a cut-off Beck depression score of 26.5 with 71% sensitivity and 45% specificity to predict lower percentile (<33%) FORT percent during IVF-ET procedures. When we performed the same ROC analysis, this statistical significance was relevant for the unexplained infertile and poor ovarian reserve group but not for the male factor group (Figures 2-4). The fact that since the cause of infertility is related to the male partner, this information might psychologically relieve female partners and spare them from FORT percent decrease. Due to the absence of a statistically significant relationship between the higher Beck depression scores and retrieved M2 oocyte numbers/ clinical pregnancy rates regardless of the IVF-ET indication, emotional stress does not seem to affect cycle outcomes except FORT percent for unexplained infertile and poor responder women. Psychological support is still recommended to infertile women because of the lack of high-quality studies and contradictory opinions of the authors who have published their researches around this area. However, the clinical useful effect of tender loving care to infertile women in terms of improved IVF-ET cycle outcomes could not be proven before with good quality studies.

Despite the demonstration of the detrimental effect of increased Beck depression scores on FORT ratios, limitations of our study should be kept in mind. First, oocyte pick-up (OPU) and embryo transfer procedures have been performed by different clinicians. The second limitation is the probability of recall bias for the participants of the study. We have given plenty of time to evaluate and answer the questions in the questionnaire but we could not control the subjectivity problem stemming from patients' own decisions during replying to the questions in the questionnaire. However, previous studies have demonstrated an increased prevalence of mood disorders like emotional stress and depression among infertile women.

In conclusion; the FORT ratio which is achieved during the COH process of IVF-ET procedure seems to be lowered by emotional stress among unexplained or poor responder infertile women despite lack of a clinical effect on other cycle outcomes. Further studies investigating the effect of emotional stress itself and interventions to relieve this stress on IVF-ET cycle outcomes are needed to clarify this uncertainty.

Acknowledgments
None

Funding sources
Not applicable

Conflict of interests
The authors declare that there is no conflict of interest.

Authors contributions
Surgical and Medical Practices: Hacer Cavidan Gulerman, Nafiye Yilmaz, Inci Kahyaoglu, Concept: Serkan Kahyaoglu, Yaprak Ustun; Design: Serkan Kahyaoglu; Data Collection or Processing: Serkan Kahyaoglu, Pınar Gulsen, Caner Kose, Ozge Gurbuz; Analysis or Interpretation: Serkan Kahyaoglu, Pınar Gulsen, Caner Kose, Ozge Gurbuz, Inci Kahyaoglu, Hacer Cavidan Gulerman, Nafiye Yilmaz, Yaprak Ustun; Literature Search: Serkan Kahyaoglu; Writing: Serkan Kahyaoglu

Ethical issue
This retrospective study was conducted in a tertiary health center after obtaining permission for the research from the hospital's institutional review board. The ethics committee of the "Ankara Dr. Zekai Tahir Burak Women's Health Education and Research Hospital, University of Health Sciences" has approved our study on 13/12/2018 with an approval number of 89/2018. This cross-sectional study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent has been taken from all patients who have participated in this study.

References
1. Chrousos GP. Stress and disorders of the stress system. Nature Reviews. Endocrinology. 2009; 5(7):374-381.
2. Genro VK, Grynbery M, Scheffer JB, et al. Serum anti-müllerian hormone levels are negatively related to Follicular Output Rate (FORT) in normo-cycling women undergoing controlled ovarian hyperstimulation. Human Reproduction. 2011;26:671-677.
3. Hassan A, Kotb M, AwadAllah A, et al. Follicular output rate can predict clinical pregnancy in women with unexplained infertility undergoing IVF/ICSI: a prospective cohort study. Reproductive Biomedicine Online. 2017;34(6):598-604. doi: 10.1016/j.rbmo.2017.03.004.
4. Yang H, Lin J, Jin C, et al. The Predictive Value of the Follicular Output Rate on Pregnancy Outcome of Patients with Polycystic Ovary Syndrome Undergoing In Vitro

Fertilization and Embryo Transfer. Medical Science Monitor. 2020;26:e916175. doi: 10.12659/MSM.916175.
5. Grynberg M, Labrosse J. Understanding Follicular Output Rate (FORT) and its Implications for POSEIDON Criteria. Frontiers in Endocrinology (Lausanne). 2019;10:246. doi: 10.3389/fendo.2019.00246.
6. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. Journal of Personality Assessment. 1996;67(3):588-597. doi: 10.1207/s15327752jpa6703_13.
7. Veeck LL. An atlas of human gametes and conceptuses: an illustrated reference for assisted reproductive technology. Boca Raton: CRC Press; 1999. https://doi.org/10.1201/9780367803001.
8. Parsanezhad ME, Jahromi BN, Rezaee S, Kooshesh L, Alaee S.The effect of four different gonadotropin protocols on oocyte and embryo quality and pregnancy outcomes in IVF/ICSI cycles; a randomized controlled trial. Iranian journal of medical sciences. 2017; 42 (1), 57.
9. Terzioglu F, Turk R, Yucel C, et al. The effect of anxiety and depression scores of couples who underwent assisted reproductive techniques on the pregnancy outcomes. African Health Sciences. 2016;16(2):441-450. doi: 10.4314/ahs.v16i2.12.
10. Boivin J, Griffiths E, Venetis CA. Emotional distress in infertile women and failure of assisted reproductive technologies: meta-analysis of prospective psychosocial studies. British Medical Journal. 2011;342:d223. doi: 10.1136/bmj.d223.
11. Purewal S, Chapman SCE, van den Akker OBA. Depression and state anxiety scores during assisted reproductive treatment are associated with outcome: a meta-analysis. Reproductive Biomedicine Online. 2018;36(6):646-657. doi: 10.1016/j.rbmo.2018.03.010.
12. Negris O, Lawson A, Brown D, et al. Emotional stress and reproduction: what do fertility patients believe? Journal of Assisted Reproduction and Genetics. 2021;38(4):877-887. doi: 10.1007/s10815-021-02079-3.
13. Paraskevi L, Antigoni S, Kleanthi G. Stress and Anxiety Levels in Couples who Undergo Fertility Treatment: a Review of Systematic Reviews. Materia Socio-Medica. 2021;33(1):60-64. doi: 10.5455/msm.2021.33.60-64.
14. Fatima S, Naqvi Q, Tauseef A, et al. Correlation of Serum Anti-Mullerian Hormone with Ovarian Follicle Output Rate in Infertile Females: A Clomiphene Citrate Challenge Test. Cureus. 2020;12(5):e8032. doi: 10.7759/cureus.8032.
15. Hassan A, Kotb M, AwadAllah A, et al. Follicular output rate can predict clinical pregnancy in women with unexplained infertility undergoing IVF/ICSI: a prospective cohort study. Reproductive Biomedicine Online. 2017;34(6):598-604. doi: 10.1016/j.rbmo.2017.03.004.
16. Gallot V, Berwanger da Silva AL, Genro V, et al. Antral follicle responsiveness to follicle-stimulating hormone administration assessed by the Follicular Output RaTe (FORT) may predict in vitro fertilization-embryo transfer outcome. Human Reproduction. 2012;27(4):1066-1072. doi: 10.1093/humrep/der479.
17. Zhang N, Hao CF, Zhuang LL, et al. Prediction of IVF/ICSI outcome based on the follicular output rate. Reproductive Biomedicine Online. 2013;27(2):147-153. doi: 10.1016/j.rbmo.2013.04.012.
18. Bessow C, Donato R, de Souza T, et al. Antral follicle responsiveness assessed by follicular output rate (FORT) correlates with follicles diameter. Journal of Ovarian Research. 2019;12(1):48. doi: 10.1186/s13048-019-0522-4.
19. Yang H, Lin J, Jin C, et al. The Predictive Value of the Follicular Output Rate on Pregnancy Outcome of Patients with Polycystic Ovary Syndrome Undergoing In Vitro Fertilization and Embryo Transfer. Medical Science Monitor. 2020;26:e916175. doi: 10.12659/MSM.916175.