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ORIGINAL ARTICLE

Psychological stress during in vitro fertilization and embryo transfer is influenced by the patients' background and gender

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Abstract
Purpose This study evaluated the changes in psychological stress during in vitro fertilization and embryo transfer (IVF–ET) and the relationship of such stress to the patients' background and gender.
Methods Sixty couples undergoing IVF–ET were administered the State–Trait Anxiety Inventory-JYZ (STAI) test at six different points during IVF–ET procedures. Anxiety scores at each time point were recorded and analyzed according to gender, fertility status, and duration of treatment.
Results The median state anxiety score for women increased following induction until oocyte collection, after which it temporarily declined and then increased again until the pregnancy test. No such changes were noted in men. Scores for women who had undergone a shorter period of IVF treatments were higher while state and trait anxiety in men increased with a prolonged treatment period. Unsuccessful treatment increased the state and trait anxiety of women.
Conclusions Psychological stress changed periodically depending on the duration of the patients' treatment and fertility status also influenced anxiety levels. These findings will prove helpful in guiding psychological therapy and counseling for couples attempting to conceive by in vitro fertilization.

Keywords Anxiety · ART · Gender · Psychological stress · STAI

Introduction

Some 9–15 % of potential parents worldwide experience infertility [1], a condition that may induce adverse psychological effects on multiple levels [2]. For example, infertile individuals experience anxiety, distress, and depression from their intrinsic condition as well as from societal influence [3–6]. Remarkable advances over the last three decades in assisted reproductive technology (ART) involving in vitro fertilization and embryo transfer (IVF–ET) [7, 8] have not only given these couples hope but have, in fact, resulted in marked numbers of new pregnancies, with IVF–ET success rates (live births) approaching the natural fertility rate [8]. Unfortunately, the IVF–ET process itself causes distress and anxiety [9–11], so much so that some couples abandon treatment [12]. This stressful aspect of IVF–ET deserves as much attention as that given to enhancing ART techniques.

Fertility research, which is designed to help infertile parents produce healthy and happy children, has focused on

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unraveling the complex interactions between psychological and physiological processes [1]. The most common perception that can be gleaned from the literature is that stress and anxiety lower IVF–ET success rates [2, 13], despite early conflicting reports [14, 15]. Although the aforementioned perception may be changing, particularly in light of recent research findings in a large population indicating that successful outcomes are independent of patients' psychological state [1], these findings should not divert attention from alleviating the stress patients experience while they undergo IVF–ET.

In vitro fertilization patients are subjected to treatments that can be physically and psychologically demanding, typically involving up to 2 weeks of ovarian stimulation, oocyte retrieval, and embryo transfer. Stress-inducing aspects of the procedure include the possibility of life-threatening excessive hyperstimulation, and invasive egg harvesting. Furthermore, a patient's hopes for a good outcome can exacerbate feelings of anxiety, thereby potentially resulting in depression if such an outcome is not achieved. Any of these stressors can, therefore, significantly impact the psychological well-being of otherwise normal patients, possibly overwhelming those already burdened by preexisting psychological difficulties associated with their infertility.

This study asked patients to complete a short questionnaire, the State–Trait Anxiety Inventory (STAI) Form JYZ, to better understand patients' stress levels during IVF–ET and to facilitate the design of more effective interventions [16]. The STAI is a simple and effective approach that has been established for examining stress. The STAI measures state (temporary) anxiety and trait (long-term) anxiety within a scoring range of 20–80, where the higher the score indicates greater anxiety [17]. Specifically, the study asked whether one or both partners experienced stress and, if so, when did it occur and to what extent.

Materials and methods

Sixty couples were recruited in the study. Any individuals that were undergoing psychiatric care or who had a history of psychiatric illness were excluded from the study. The protocols for ovarian stimulation have been described previously [18, 19]. Briefly, ovarian stimulation was performed with the initial dose of urinary FSH (Gonapure; ASKA Pharmaceutical Company Ltd., Tokyo, Japan) or recombinant FSH (Follistim; Schering-Plough Corporation, Kenilworth, NJ, USA) at 150-300 IU per day for the first 2 days, after which doses were adjusted individually based on the follicular response. An injection of 10,000 IU of human chorionic gonadotropin (Gonatropin; ASKA Pharmaceutical Company Ltd.) was administered when at least two follicles reached 16 mm or more in mean diameter, and oocyte retrieval was performed 35.5 h later. The procedures used for oocyte retrieval, sperm and oocyte preparation, IVF and ICSI have been described previously [20, 21]. A maximum of two embryos were transferred. Clinical pregnancies were defined as the presence of fetal cardiac activity following increased serum human chorionic gonadotropin (hCG) levels.

The STAI form JYZ [16] were administered during IVF–ET as: (1) the day the ovulation-inducing drugs were first given, (2) the day before and (3) the day of oocyte collection, (4) the day of ET, (5) 1 week after ET, and (6) the day of the pregnancy test using the serum hCG levels or when menstruation commenced. Patients were asked to evaluate their state and trait anxieties at night before going to bed on each indicated day. They were also questioned about their age, fertility status, treatment history, lifestyles, and other characteristics. Informed consent was obtained from each of the subjects, and Nagoya University Graduate School of Medicine's Ethics Committee approved the study. Data were analyzed by Wilcoxon *t* test and Kruskal–Wallis *H* test using the SigmaPlot 11 software package (Systat Software Inc., San Jose, CA, USA) program.

Results

Patients

Table 1 summarizes the pertinent characteristics of the 60 couples included in the study. The subjects were placed

Table 1 Characteristics of the patients

	Average age (years)
Gender	
Men ($n = 60$)	36.9 ± 5.2
Women ($n = 60$)	35.5 ± 3.7
Duration of treatment (years)	
Average ($n = 60$)	3.9 ± 3.0
Intervals	**Couples (*n*)**
<3 years	20
≥3 but <5 years	21
≥5 years	19
Infertility factors	***n***
Women	12
Men	18
Women and men	14
Not identified	16

into three distinct groups of nearly the same size based on the length of their infertility treatment. All of the patients were assigned to four groups based on the main cause of infertility: tubal factor, endometriosis, male factor or unexplained infertility. Tubal factor and endometriosis were defined as female factors of infertility. These are known infertility factors; however, they had no discernible effect on STAI scores (data not shown). Twenty-two couples conceived. Five out of these 22 and nine out of 38 women had habitual alcohol intake in the pregnant and non-pregnant group, respectively. Four out of 22 and five out of 38 women had smoking habits in the pregnant and non-pregnant group, respectively. There were no significant differences in the STAI scores between the smoking and no smoking groups, or the habitual alcohol intake and no habitual alcohol intake groups (data not shown).

STAI scores

The total average state and trait anxiety scores for the 60 couples studied were 48.0 ± 15.7 and 42.5 ± 11.9 (women), and 43.7 ± 11.5 and 41.9 ± 11.1 (men), respectively. Scores greater than 44 are highly suggestive of anxiety [22], thus the scores for women in the present study suggested that they experienced state anxiety to a greater extent than did the men. However, the trait scores for women and men do not suggest any significantly increased trait anxiety. An analysis of subgroups divided by the woman's age (≥35 vs. <35 years) showed no significant differences in the mean of state and trait anxiety scores (45.6 ± 8.7 vs. 43.8 ± 6.4 in the state anxiety and 43.9 ± 10.3 vs. 44.4 ± 7.5 in the trait anxiety). There was no significant correlation between the men's and women's scores of state or trait anxiety, either ($r^2 = 0.0475$ in the state anxiety, $r^2 = 0.0293$ in the trait anxiety).

Figure 1 shows that scores for women for both state and trait anxiety changed over the course of treatment. State anxiety (Fig. 1a) and trait anxiety (Fig. 1b) were highest, respectively, on the day of ET (stage 5) and when the pregnancy test result was received (stage 6). However, these differences, while obvious when displayed graphically, were not statistically significant. Furthermore, there were no significant trends in the men's scores at any stage (Fig. 1a, b).

The subjects were divided into three distinct groups based on the length of IVT–ET treatment. It is reasonable to assume that the rigors of IVT–ET would be increasingly stressful over time. In fact, male state and trait anxiety scores were found to be higher in the couples treated for five or more years (Fig. 2a, b). Interestingly, there were gender differences regarding the fact that women treated

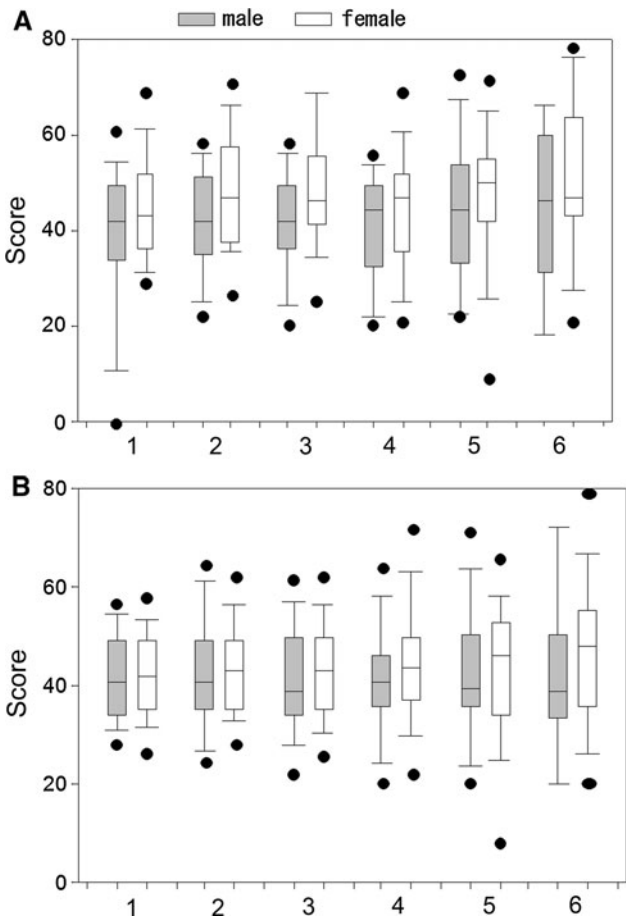

Fig. 1 *Box plots* of the STAI scores according to the gender and IVF treatment cycle. **a** State anxiety. **b** Trait anxiety. Scores for men and women are indicated by *filled and unfilled rectangles*, respectively. The *horizontal line in each box* represents the median value. The *boundary of the box* closest to zero indicates the 25th percentile and the *boundary of the box* farthest from zero indicates 75th percentile. The *ends of the lines* (*whiskers*) above and below the hinges (*tops and bottoms of boxes*) indicate the 90th and 10th percentile, respectively. The *filled circles* above and below the upper and lower hinges indicate the 95th and 5th percentile, respectively. The *numbers* on the *x*-axis correspond to the stages of treatment as follows: (1) the day the ovulation-inducing drugs were first given, (2) the day before and (3) the day oocytes were collected, (4) the day of ET, (5) 1 week after ET, and (6) the day of the pregnancy test or when menstruation commenced

for 5 years or more demonstrated lower scores in both anxiety categories than men whose state and trait anxieties tended to increase with longer treatment (Fig. 2c, d).

Figure 3 shows that women whose pregnancy tests were negative were more acutely anxious, thus suggesting that there may be a marginal effect of anxiety on IVF–ET success. This result is reflected by the combined scores for couples (negative pregnancy test: state = 48.9 ± 11.9, trait = 45.7 ± 10.1; positive pregnancy test: state = 44.4 ± 8.9, trait = 41.8 ± 11.0).

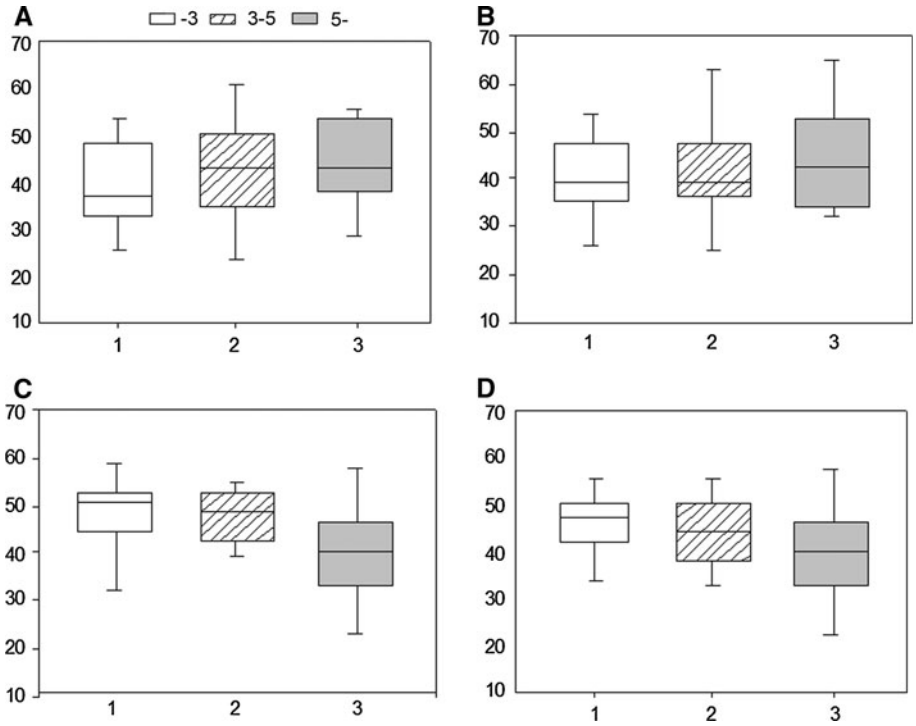

Fig. 2 *Box plots* of the STAI scores according to the length of infertility treatment. **a**, **b** show male state and trait anxiety scores, respectively, while **c** and **d** show female state and trait anxiety values, respectively. *Unfilled, crosshatched, and filled boxes* indicate treatment duration of <3, 3–5, and >5 years, respectively. The *box plots* were constructed as described in the legend for Fig. 1

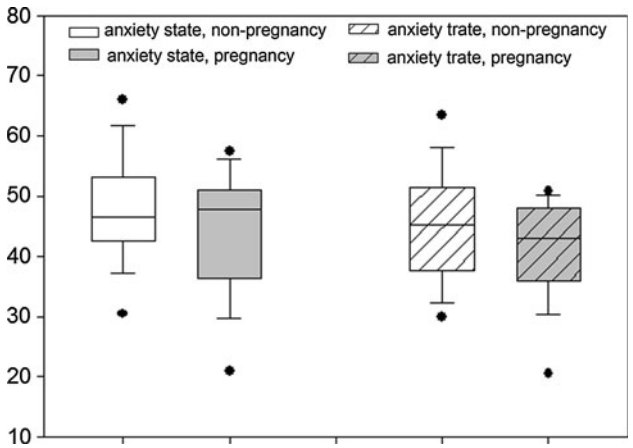

Fig. 3 STAI scores based on the results of the pregnancy status. State anxiety scores for non-pregnant and pregnant subjects are represented by *unfilled and filled rectangles*, respectively. Trait anxiety scores for non-pregnant and pregnant women are represented by *unfilled crosshatched and filled crosshatched rectangles*, respectively. The *box plots* were constructed as described in the legend for Fig. 1

Discussion

The primary goal of this study was to determine whether couples experienced stress during the complex and demanding process of IVF–ET. The major findings were that women experienced both general and stage-specific state and trait anxiety, whereas men did not; however, men were subject to stress when involved in a prolonged period of IVF–ET treatments. In addition, unsuccessful treatment increased anxiety in women.

The current approach involved administering the Japanese version (STAI-JYZ) of the STAI questionnaire, which is considered the definitive instrument for measuring anxiety in adults. The STAI helps differentiate temporary anxiety (state) from a person's steady state, or long-term, anxiety (trait). Researchers expert in interpreting STAI data can distinguish anxiety from confounding depression. The STAI was administered at six stages that were judged to be key stress-inducing events in IVF–ET; (1) the day when ovulation-inducing drugs were first given, (2) the day before and (3) the day of oocyte collection, (4) the day of embryo transplantation and (5) 1 week later, and (6) the day of the pregnancy test. The test results led to several conclusions: (1) While both men and women experienced anxiety under some circumstances, women scored higher than men in general. (2) Women's anxiety levels fluctuated during the IVF–ET process. (3) Men's state and trait anxiety scores tended to be higher after being treated for five or more years. (4) Women indicated that they experienced anxiety when treated for less than 3 years, whereas men did not tend to exhibit such anxiety for this period. (5) Anxiety was higher in couples with negative outcomes (negative pregnancy test). However, our research might have been somewhat biased due to the lack of specifying whether clinicians inform the patients in detail about such laboratory data as the semen analyses and embryo quality or not.

The current research shows that couples experience differences in anxiety during IVF–ET, and that this discrepancy should be addressed with appropriate pharmacological or psychological interventions or both. It is

impractical to provide interventions such as psychological counseling to all patients. A multi-disciplinary approach to this problem that includes both psychological and pharmacological treatment is clearly required. In addition, more research on the effects of psychological stress on the endocrine system is clearly warranted [23]. Further study will be required to explore the correlation between the STAI results and the laboratory data of the endocrine system. Furthermore, a study with a larger number of patients will allow for the analysis of any correlations between the STAI scores and the outcomes of IVF, such as ovarian response and fertilization rate, and to also make subgroup analyses such as educational and economic conditions.

The present study provides a basis for focusing intervention on the most suitable patients during the appropriate stages in IVF–ET and acknowledges that further studies should be conducted involving greater numbers of couples to overcome the relatively small sample size, particularly since the clear differences observed here could not be found to be statistically significant. In addition, patients' psychological characteristics and lifestyles must be carefully considered when drawing conclusions and the analysis should be expanded to include controls for age-matched controls from the general population, from couples with children, and from couples who choose not to have children but are fertile. Administering the STAI to single fertile or infertile men and women who have decided not to have children or intend to undergo IVF–ET once they find a suitable partner may also provide interesting results for purposes of comparison.

The current results are consistent with those obtained in previous studies, particularly with regard to the elevated anxiety experienced by women in comparison to men [24]. IVF is more disruptive to women's work and leisure activities than it is for men. In addition, the effects of hormone stimulation for women may affect the gender difference in anxiety. The current unique characterization of anxiety in men during treatment revealed that anxiety in this group can be as significant as in women under some of the circumstances described above. These results are also generally consistent with previous research demonstrating that women are more adversely affected by negative anxiety states and traits than men, but that male stress does play a role in treatment failure [2]. However, anxiety is not the only adverse psychological factor at work during IVF–ET [25] as women also suffer from depression [26] and other emotional impacts [9, 11, 27]. The current research suggests that more studies on men may be useful in mitigating the impact of these factors on IVF–ET.

The variations in stress levels exhibited by men and women according to their differing circumstances in the present study indicate that tailored psychological intervention will be increasingly valuable. A number of studies address this issue, and informing patients about a 10-year cohort study of patients being treated for the first time by ART may significantly relieve their stress [8]. This study of 3011 women showed the cumulative live birth rates reached 94 % after 18 treatment cycles, arguing strongly that patients should continue their treatments rather than giving up. Patients should also understand that the majority of infertile people are eventually able to overcome the problems associated with infertility to varying extents [28]. Patients can take advantage of convincing new findings demonstrating that social support from their partner and family can directly reduce infertility-related stress in some circumstances [29].

The use of Internet resources has been proposed for those who may not have ready or affordable access to care providers [30]. The results supported "the hypothesis that WCWI (web-based intervention) would lead to a reduction in global stress symptoms." However, the short-term changes (assessed using Symptom Checklist 90-Revised scores) did not support the conclusion that subjects were non-stressed and that infertility-specific stress was reduced. These authors maintain, nevertheless, that their results differentiated general and infertility-specific stresses. Despite WCWI's promise for reducing general stress, more traditional counseling and therapy will continue to play a crucial role in alleviating infertility-specific stress. The present study indicates that these efforts to reduce stress must focus on each stage of the IVF–ET process.

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