Experimental
&
Clinical Article

Evaluation of Psychological Distress in Infertile Women who Underwent ART Cycle During the COVID-19 Pandemic

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ABSTRACT

OBJECTIVE: We aimed to determine the frequency of psychological distress and related factors in infertile women who underwent assisted reproductive technologies during the COVID-19 pandemic and to develop health policies accordingly.

STUDY DESIGN: This cross-sectional study was carried out with 352 infertile women who applied to the in vitro fertilization clinic between December 2020-February 2021. In the face-to-face survey study, five questionnaires were given to all participants: (1) a Questionnaire regarding the socio-demographic/general health characteristics of the patient, (2) Impact of Event Scale-Revised, (3) Beck's Depression Inventory, (4) State-Trait Anxiety Inventory -1, (5) State-Trait Anxiety Inventory-2.

RESULTS: Post-traumatic stress disorder was detected in 129 (36.6%) infertile women. In cases of diminished ovarian reserve and oocyte freezing; a significantly higher incidence of post-traumatic stress disorder was found compared to patients with unexplained infertility, polycystic ovary syndrome, and male factor infertility (p=0.004). Minimal-mild depression level was detected in 295 (83.8%) participants, and moderate-severe depression level was found in 57 (16.2%) participants. The mean State-Trait Anxiety Inventory-1 and State-Trait Anxiety Inventory-2 scores of infertile women were 43.5±6.7 and 46.6±6.3, respectively. A statistically significant relationship was found between the duration of infertility and moderate-severe anxiety according to State-Trait Anxiety Inventory-1 (p=0.046).

CONCLUSION: Our findings show that women with long-term infertility and undergoing oocyte freezing are the most affected patients by the pandemic. It would be appropriate for in vitro fertilization centers to provide psychological support to patients that have a mentally high risk of distress.

Keywords: Anxiety, Assisted reproductive technologies, COVID-19, Depression, Infertility, Pandemic

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Introduction

Previous studies have shown that increased risk of psychological problems during such pandemics. Studies conducted one month after (1,2), one year later (3), and 30 months after (4) the severe acute respiratory syndrome (SARS) pandemic reported an increase in psychiatric problems such as anxiety, depression, and post-traumatic stress disorder (PTSD). In a study that studied 3200 women during the 2019 coronavirus disease (COVID-19) pandemic period, it was reported that by April 2020, the rates of depression and anxiety reached 29%, and traumatic stress symptoms were detected in 17% of women (5).

There are opinions that early diagnosis and treatment of psychologically affected patients may improve fertility outcomes. A study by Hoff et al investigated whether reproductive specialists screen patients for depression or anxiety and the effect of mental health disorders on fertility. The authors

argued that an easily evaluable rapid screening for anxiety and depression could be performed by reproductive specialists and that the affected patients could be treated earlier and fertility outcomes could be improved (6).

Unfortunately, COVID-19 continues to make headlines with new mutations and increasing deaths. The uncertainty of the long-term consequences of COVID-19 on pregnancy and infertility can be a source of further panic, stress, and anxiety in already vulnerable infertile patients. It was reported that the COVID-19 pandemic caused the postponement of pregnancy in many women, affecting pregnancy planning behavior (7). For this reason, it is very important for health professionals dealing with the COVID-19 pandemic to identify appropriate and correct strategies when providing healthcare to infertile couples, to minimize the mental and physical health of women planning an imminent pregnancy, such as diminished ovarian reserve (DOR) and oncofertility.

We aimed to determine the frequency of psychological distress and related factors in infertile women who underwent assisted reproductive technologies (ART) during the COVID-19 pandemic and to develop new policies for psychological support for the high-risk infertile group.

Material and Method

Patient population: This cross-sectional study was carried out using a face-to-face questionnaire methodology in the IVF Clinic of the University of the Health Sciences, Zeynep Kamil Women and Children's Disease Research and Training Hospital in Istanbul between December 2020 - February 2021. Ethical approval for the study was taken from the University of Health Sciences Ethics Committee (decision number 188, dated December 9, 2020). Written informed consent was obtained from all patients. All study procedures were carried out in accordance with the 1964 declaration of Helsinki and subsequent amendments. The population of the study consisted of 357 infertile women between 23 and 45 years of age who underwent controlled ovarian hyperstimulation during the research period. Eligibility criteria included the following: being literate, having no physical or psychological conditions impairing communication skills, and provision of informed consent for the study procedures. Individuals with a history of psychiatric conditions whether using medicine or not were excluded. In addition, the study was conducted with 352 participants, since two tubal factor infertility and three combined factor cases were excluded due to the small group size.

The sample size was calculated using OpenEpi (v.3) software. When unpredicted and 50% predicted anxiety rates were taken into consideration, a total of 317 patients were required to represent with 99.99% power and an alpha error level of 5% approximately 200 infertile women attending our ART unit for the first time within one month.

Data on socio-demographic and general health characteristics (age, gender, occupational experience, marital status, employment status, economic status, infertility type, infertility duration, presence of chronic disease, smoking, personal, and family history of COVID-19 infection), general awareness of COVID-19, expectations from the in vitro fertilization process, changes in lifestyle during the pandemic, general attitudes, and mental health were obtained using a face-to-face questionnaire methodology. For the latter assessments, the impact of event scale (revised) (IES-R), beck depression inventory (BDI), and state-trait anxiety inventory (STAI)-1 (state anxiety)-STAI-2 (trait anxiety) was used.

Impact of event scale (revised) (IES-R): IES was originally developed by Horowitz et al. in 1979 (8) and was subsequently revised by Weiss and Marmar (i.e. IES-R) in 1997 (9) for use in patients with PTSD. This tool includes 22-items and 3 subdomains: re-experiencing (items 1-3, 6, 9, 14, 16, and 20), avoidance (5, 7, 8, 11-13, 17, and 22), and arousal (4, 10, 15, 18, 19, 21). Each symptom is scored on a 5-point Likert type scale from "none" to "very much". The perception of the stressful condition was extended to 30 days rather than the originally proposed 7-day period, to better reflect the events' impact during the COVID-19 pandemic where restrictions were placed. The total score is between 0 and 88, with higher scores indicating more severe post-traumatic stress disorder. The cut-off value was reported to be >33 (9). The Turkish version was adapted by Corapcioglu et al. in 2006 (10).

*Beck depression inventory (*BDI): Was developed by beck in 1961 (11) to measure the behavioral signs of depression. In the present study, the 1989 version of the beck depression scale adapted by Hisli (12) was used. In this 21-item scale, for each item, subjects select the sentence that best expresses their condition out of four sentences. Higher scores indicate more severe depression. A total score of 0 to 9, 10 to 16, 17 to 23, and ≥24 is considered "minimal depression", "mild depression", "moderate depression", and "severe depression", respectively. During the development of the Turkish version, a cut-off score of 17 was found to be able to distinguish between depression requiring treatment from other depressive states with an accuracy of > 90%. For study purposes, minimal and mild depression, as well as moderate and severe depression were combined.

State-trait anxiety inventory (STAI)*:* Was developed by Spielberger et al. in 1970 (13) to detect anxiety and differentiate it from depressive symptoms in the clinical setting. The adaptation studies for the Turkish populations were carried out by Oner and Le Compte in 1985 (14). STAI-1 (state anxiety) may be described as the fear, nervousness, and irritability caused by different situations that are perceived as dangerous by the individual. On the other hand, STAI-2 (trait anxiety) may be defined as stress, anxiety, and discomfort experienced

on a day-to-day basis. This is generally a measure of how an individual feel in situations typically experienced by everyone on a day-to-day basis. Each questionnaire consists of 20 items, with responses rated between 1 and 4. Direct expressions describe negative emotions, while inverted expressions describe positive emotions. The lowest score reflects the low anxiety levels and the highest score reveals the severe anxiety of the participant. While a score of < 20 points out to absent or minimal anxiety, scores of 21-40, 41-60, and > 61 indicate mild, moderate, and severe anxiety, respectively. In the present study, cases with minimal and mild anxiety as well as moderate and severe anxiety were combined.

Statistical analyses

Statistical analysis was done using the Statistical Package for Social Sciences version 17 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed as number (%), mean ± standard deviation, median value, minimum and maximum, as appropriate. Kolmogorov-Smirnov test was used to test the distribution of continuous data. Statistical analyses were performed by the Student t-test for normal distribution data, the Mann-Whitney U test, and the Kruskal-Wallis test for abnormal distribution data. Categorical variables were analyzed by χ^2 test (with Fisher exact test for groups with less than five expected frequencies in a cell). For multivariate analysis, logistic regression was used. Statistical significance was set at $p \leq 0.05$.

Results

The mean age of patients was 31.2±5.8 years. The mean duration of marriage and infertility were 5.23±3.46 and 4.25± 3.12 years, respectively. Overall, 254 patients (72.2%) had received their first infertility treatment. Table I shows the details of the socio-demographic data and general health characteristics of the participants. Intracytoplasmic sperm injection (ICSI) was planned for 340 patients, while 12 underwent oocyte freezing. Oocyte freezing was performed in 7 of 12 patients due to diminished ovarian reserve (DOR) and 5 due to oncofertility. The etiological distribution among 340 patients included unexplained infertility in 219 (62.2%), DOR in 67(19%), male factor in 42 (11.9%), and polycystic ovary syndrome (PCOS) in 12 (3.4%). The mean body mass index (BMI) was 26.1±5.06, and 69 (19.6%) were current smokers with a 5.4±4.9 pack/year history. Chronic diseases were present in 63 (17.9%), the most frequent being diabetes mellitus (4.5%), followed by goiter (4.3%) (Table I).

From the answers given to the survey, it was understood that the most stressful source before the pandemic in infertile women was the inability to conceive 74.4%. One year after the outbreak, this rate was found to be 70.7% (Table II). In the first three months of pandemics, the concern of the inability to conceive as one of the main stress sources was %41.5. The most common change in women's lifestyles was a decrease in their daily activities (49.1%) (Table II).

The mean IES-R score of the participants was 29.8±13.2. A total of 129 (36.6%) women were found to have PTSD, while 223 women did not have this condition. Significantly more frequent PTSD was found in patients with a higher number of abortions (p=0.049). When the patients are compared according to their infertility etiology, a significantly higher incidence of PTSD was found in patients with DOR and undergoing oocyte freezing compared to patients with other etiologies (p=0.004). The rate of treatment cessation in cases with PTSD was higher than in those without PTSD (p=0.005). Also, excessive sleep or insomnia was significantly more common in cases with PTSD (p=0.044). PTSD was more common among women whose relatives or loved ones died due to COVID-19 (24.8%) than those who had no COVID-19-related deaths in the family or among loved ones (p=0.01).

Impact of event scale (revised) scores were higher among cases with DOR, oocyte freezing, or unexplained infertility as compared to those with a male factor or PCOS (p<0.001) (Table III). A logistic regression analysis was performed, using male-factor infertility as a reference with the lowest IES-R scores. Accordingly, unexplained infertility, DOR, and oocyte freezing were associated with a 3.46-fold (95% CI 1.393-8.623; p=0.008), 3.78-fold (95% CI 1.394-10.244; p=0.009), and 10.79-fold (95% CI 2.436-47.838; p=0.002) increased risk for PTSD, respectively (Table IV).

The mean BDI score was 9.6±9.7. A comparison of BDI scores according to etiology of infertility showed significantly higher BDI scores only in those undergoing oocyte freezing (p=0.022) (Table III). Although not statistically significant, it was observed that oocyte freezing cases (33.3%) were more moderate to severe depressive than women with other infertility etiologies (p<0.087). According to the multivariate logistic regression analysis, in which we evaluated the independent effect of variables associated with moderate-severe depression level, 10.0 times more (95% CI 1.558-64.198; p=0.015) moderate-severe depression was found in those who underwent oocyte freezing (Table IV). Patients with moderate to severe depression had significantly higher packs/years of smoking as compared to those with minimal/mild depression (p=0.012).

The mean STAI-1 and STAI-2 scores of the participants were 43.5±6.7 and 46.6±6.3, respectively (Table III). According to multivariate logistic regression analysis, a significant relationship was found between anxiety and duration of infertility and BMI. State anxiety score was found to be significantly higher in patients with long-term infertility (p=0.046). Also, trait anxiety was found to be associated with BMI (OR: 0.9 %95 CI 0.990-0.988; p<0.016) (Table IV).

Table I: *Socio-demographic and infertility characteristics of the participants (n = 352)*

Characteristic		mean ± SD	median (min-max)
Age (years)		31.2±5.8	30 (20-48)
Gravida		0.5±0.0	0 (0-7)
Parity		0.1±0.4	0 (0-3)
Abortus		0.3±0.8	0 (0-7)
BMI (kg/m2)		26.1±5.1	26.6 (16.4-43.2)
Spouse age (years)		34.2±5.8	34 (20-53)
Duration of marriage (years)		5.2± 3.5	4 (1-20)
Duration of infertility (years)		4.3± 3.1	3 (1-20)
Smoking (pack/year)		5.4± 4.9	3.8 (0.2-20)
		n	%
Educational status	Primary school	55	15.6
	Secondary school	75	21.3
	High school	82	23.3
	University	140	39.8
Occupation	Officer	17	4.8
	Worker	50	14.2
	Self-employed	75	21.3
	Housewife	210	59.7
Smoking habit	Smoker	69	19.6
	Not smoking	283	80.4
Chronic diseases	Yes	63	17.9
	No	289	82.1
Family income	Low	35	9.9
	Medium	289	82.1
	High	28	8
Social security status	Yes	324	92
	No	28	8
Etiology of infertility	Male factor	42	11.9
	PCOS	12	3.4
	Unexplained infertility	219	62.2
	DOR	67	19
	Oocyte freezing	12	3.4
History of COVID-19 diagnosis	Yes	44	12.5
	No	308	87.5
History of COVID-19-related death among relatives/loved-ones	Yes	63	17.9
	No	289	82.1

Table II: *Distribution of lifestyle changes and stress factors during the COVID-19 pandemic*

Characteristics	n	%	
Sleep time during the pandemic	Increased	68	19.3
	Decreased	48	13.6
	Not changed	236	67
Daily activity changes during the pandemic	Increased	30	8.5
	Decreased	173	49.1
	Not changed	149	42.3
Frequency of eating/drinking	Increased	81	23
	Decreased	20	5.7
	Not changed	251	71.3
Main cause of stress (before pandemic)	Infertility	262	74.4
	Occupational problems	37	10.5
	Financial problems	53	15.1
Main cause of stress (first three months of the pandemic)	Coronavirus	136	38.6
	Infertility	146	41.5
	Occupational problems	16	4.5
	Financial problems	54	15.3
Main cause of stress (after one year of the pandemic)	Coronavirus	62	17.6
	Infertility	149	70.7
	Occupational problems	13	3.7
	Financial problems	28	8

Table III: *Questionnaires that were used for the mental state evaluation of the participants and scale scores according to infertility etiology*

		mean ± SD	median (min-max)
IES-R		29.8±13.2	28.5 (2-70)
STAI 1 (State Anxiety)		43.5± 6.7	44 (26-69)
STAI 2 (Trait Anxiety)		46.6± 6.3	46(30-69)
BDI		9.6±9.7	6 (1-53)
		n	%
BDI	Minimal depression	229	(65.1%)
	Mild depression	66	(18.7%)
	Moderate depression	21	(6.0%)
	Severe depression	36	(10.2%)
IES-R	PTSD present	129	(36.6%)
	PTSD absent	223	(63.4%)
STAI 1	Minimal anxiety	-	
	Mild anxiety	113	(32.1%)
	Moderate anxiety	234	(66.5%)
	Severe anxiety	5	(1.4%)
STAI 2	Minimal anxiety	-	
	Mild anxiety	58	(16.5%)
	Moderate anxiety	284	(80.7%)
	Severe anxiety	10	(2.8%)

		mean±sd	p-value
IES-R score	Male factor	23.9±11.5	<0.001*
	PCOS	24.8±8.1	
	Unexplained infertility	29.9±13.6	
	DOR	32.2±12.8	
	Oocyte freezing	39.1±8,9	
BDI score	Male factor	6.1±7.4	0.022*
	PCOS	9.8±12.4	
	Unexplained infertility	10.0±9.8	
	DOR	9.3±8.9	
	Oocyte freezing	15.1±14.4	
STAI-1 score	Male factor	45.8±6.6	0.383
	PCOS	48.7±5.3	
	Unexplained infertility	47.2±6.2	
	DOR	45.0±6.0	
	Oocyte freezing	45.0±7.1	
STAI-2 score	Male factor	45.8±6.6	0.0540.054
	PCOS	48.7±5.3	
	Unexplained infertility	47.2±6.2	
	DOR	45.0±6.0	
	Oocyte freezing	45.0±7.1	

Table IV: *Variables significantly related to the degree of severity of stress, depression, and anxiety in infertile patients according to multivariate logistic regression analysis*

		PTSD[a]		Depression (minimal-mild/moderate-severe)[b]		State anxiety (minimal-mild/moderate-severe)[c]		Trait anxiety (minimal-mild/moderate-severe)[d]	
Variables		AOR (95% CI)	*p*	AOR (95% CI)	*p*	AOR (95% CI)	*p*	AOR (95% CI)	*p*
BMI (kg/m^2)		-	NS	-	NS	-	NS	0.94 (0.89-0.99)	0.016*
Duration of infertility (years)		-	NS	-	NS	1.09 (1.01-64.20)	0.046*	-	NS
Infertility etiology**	Unexplained infertility	3.47 (1.39-8.62)	0.008*	-	NS	-	NS	-	NS
	DOR	3.78 (1.39-10.24)	0.009*	-	NS	-	NS	-	NS
	Oocyte freezing	10.80 (2.44-47.84)	0.002*	10.00(1.56-64.20)	0.015*	-	NS	-	NS

[a]: According to impact of event scale-revised, [b]: According to beck's depression inventory, [c]: According to the state-trait anxiety inventory- 1, [d]: According to the state-trait anxiety inventory- 2, Adjusted odds ratio: Multiple imputation model adjusted for age, gravida, parity, abortion, BMI, income level, education status, infertility etiology, duration of infertility, smoking status, history of COVID-19, COVID-19-related death among close relatives or loved ones.
**: The bold font in the column of "p-value" indicates a significant difference (p < 0.05), ** Male-factor infertility as a reference, NS: Not significant.*

Discussion

The COVID-19 pandemic has impaired the mental health of populations regardless of gender, group (citizens, healthcare workers), or geographical region (15). Health authorities should plan appropriate and correct strategies for infertile couples, and special patient groups such as pregnant women while providing health services to the public. Changes in healthcare services due to the COVID-19 pandemic can cause disruptions or delays in the follow-up and treatment of infertile patients. While canceling treatment cycles of ART patients for ordinary reasons negatively affects the patient's quality of life; with the SARS-CoV-2 pandemic, patients face a great emotional burden of cycle cancellation (16).

In a study investigating the perception and psychological distress of infertility patients after the suspension of fertility treatments during the COVID-19 pandemic (17); it has been reported that most patients, regardless of their background characteristics, prefer to continue treatment when given the chance. Researchers reported that higher self-esteem and more

perceived social support were associated with lower psychological distress while feeling helpless led to higher stress.

Patients with DOR and undergoing oocyte freezing were more likely to have PTSD as compared to those with unexplained infertility, male factor, and PCOS. Women with relatives or relatives who died of COVID-19 had a higher rate of PTSD than those without such a history. In a study conducted by Esposito et al. with 627 infertile patients at Italian ART centers, the deaths of the participants' relatives or friends did not increase any points in the questionnaire (18). However, significantly higher IES-R scores were reported in participants with at least one relative who was infected with SARS-CoV-2, compared to patients with families who were not infected with SARS-CoV-2. Our patients had a significant increase in STAI-1 anxiety scores (mean score 43). This high rate of anxiety among infertile women even one year after the start of the global pandemic is an important finding. It appears that an urgent action plan for maintaining the mental health of infertile women is required, particularly when one considers the severity of anxiety. Accordingly, Esposito et al. (18) also reported a similarly elevated STAI-1 score (51 points) in their sample. In contrast with our study, data were collected via online questionnaires, males were also included, and anxiety was assessed with STAI-1 only with an anxiety cut-off score of > 36 in that Italian study. In that study, 588 participants (93.8%) were female, and 39 (6.2%) were male. The authors also found an increased STAI-1 score when all participants were taken into consideration (the mean score was 45).

In a study by Marom Haham et al., in which 181 infertile women were included and male infertile subjects were excluded, the Mental Health Inventory Approved Scale was used for mental health examination, unlike our study (19). Researchers have reported that suspending infertility treatments at the first stage of the COVID-19 outbreak caused negative emotional reactions in participants. Similar to our study, the authors reported that COVID-19-associated anxiety was significantly associated with psychological distress. As a result of the study, the authors reported that the mental health of patients receiving infertility treatment should be monitored and psychological support may be required if their treatment is suspended again.

It has been repeatedly shown in the literature that prolonged infertility is associated with an increased risk of psychological distress (20). Psychological distress also affects the treatment decision-making process of infertile patients (21). That is why treatment cessation due to the recommendations of the world's leading reproductive associations on COVID-19 (22), as well as restrictions imposed by governments, are likely to increase the risk of depression and anxiety in infertile patients and affect patients' decision-making strategy (23). As a matter of fact, in our study, we showed that state anxiety levels increase as the duration of infertility increases. Moreover, women who wanted to give up on treatment were more likely to have moderate to severe depression. The higher rate of giving up on treatment among women with PTSD in the present study compared to non-affected patients also supports the above-mentioned opinion.

In the study conducted by Barra et al. using an electronic survey, the rate of anxiety and/or depression was reported to be significantly higher in patients over the age of 35 and those who had previous IVF experience (24). In the same study, unlike us, the authors associated the likelihood of psychological symptoms with the presence of myoma uteri, endometriosis, and poor ovarian reserve.

In a study conducted by Cirillo et al. with 140 infertile women who were referred to an ART center using a web-based survey, 30% of anxiety and sadness were reported (25). In Cirillo's study, emotional state including anxiety, sadness, anger, boredom, and optimism was evaluated using a numerical and verbal rating scale (1=not at all, 2=slightly, 3=moderately, 4=very much, 5=extremely). However, in our study, we objectively evaluated psychological distress such as depression, anxiety, and post-traumatic stress disorder using a scale.

Strengths of the present study include prospective design, utilization of a face-to-face questionnaire methodology, the inclusion of infertile women with low/intermediate levels of education and low-income level who represent a more challenging group in terms of access to the internet, and also the participation of patients undergoing oocyte freezing, albeit low in number due to short duration of the study. The studies conducted so far reflect the general prevalence and that almost all of the studies were conducted in the first 6 months of the pandemic. We would like to report that our study was a long-term effect assessment of COVID-19, conducted with infertile patients 1 year after the outbreak. On the other hand, some limitations should also be mentioned. Although this study reflects a single-center experience, another limitation is related to the cross-sectional nature of the questionnaire methodology. The fact that infertile men were not included in the study can be considered another limitation.

In conclusion, it has been observed that a year after the COVID-19 pandemic, infertile women are quite vulnerable to psychological problems such as anxiety and depression. Our findings show that women with long-term infertility and undergoing oocyte freezing are the most affected patients by the pandemic. It would be appropriate for IVF centers to provide psychological support to patients that have a mentally high risk of stress without wasting time.

Declarations

Written informed consent was obtained from all patients. All study procedures were carried out in accordance with the 1964 Declaration of Helsinki and subsequent amendments.

Availability of data and materials: The data supporting this

study is available through the corresponding author upon reasonable request.

Competing interests: All authors declare that they have no competing interests.

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Authors' Contributions: EC: Planned and conducted the study, and participated in the interpretation of the results and writing process. PK: Participated in the conduction of the study, interpretation of the results, and writing process, SS: Participated in the interpretation of the results and writing process, EO: Participated in the interpretation of the results and writing process and edition, BD: Participated to the interpretation of the results and writing process ET: Participated to the interpretation of the results and writing process, IS: Contributed to the edition of the study.

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