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To cite this article: Vehbi Yavuz Tokgoz , Yeliz Kaya & Ahmet Basar Tekin (2020): The level of anxiety in infertile women whose ART cycles are postponed due to the COVID-19 outbreak, Journal of Psychosomatic Obstetrics & Gynecology, DOI: [10.1080/0167482X.2020.1806819](https://doi.org/10.1080/0167482X.2020.1806819)

To link to this article: <https://doi.org/10.1080/0167482X.2020.1806819>



Published online: 19 Aug 2020.



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The level of anxiety in infertile women whose ART cycles are postponed due to the COVID-19 outbreak

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ABSTRACT

Aim: This study evaluated the level of fear and anxiety related to the COVID-19 outbreak, in infertile women whose ART cycles were delayed due to the pandemic.

Materials and methods: An online survey was sent to women whose ART cycles were postponed due to the COVID-19 outbreak between April and May 2020. The study population were 101 participants. The main outcome measure is to determine the levels of fear and anxiety in infertile women by using the Spielberger State-Trait Anxiety Inventory (STAI-T and STAI-S) and Fear of COVID-19 scale (FCV-19S). The relationship of the COVID-19 outbreak with the willingness to go ahead with the desire for pregnancy was also assessed.

Results: The state-anxiety levels were significantly higher in women above 35 years (45.0 ± 5.2 vs. 42.2 ± 4.5 , $p = 0.006$). Women with diminished ovarian reserve had a higher state-anxiety compared to other causes, but were not found to be significant (44.7 ± 5.2 vs. 42.5 ± 5.0 , $p = 0.173$). Women who thought that the possibility of not being able to get pregnant was more important than being infected with the COVID-19 had higher anxiety levels than women who thought just the opposite. The diminished ovarian reserve and high duration of infertility were found to be significantly associated with higher anxiety levels (OR = 2.5, $p < 0.05$). The diminished ovarian reserve and previous ART failure significantly predicted the presence of clinical state-anxiety.

Conclusion: The state-anxiety was found to be higher in women whose cycles were postponed due to the outbreak and the presence of diminished ovarian reserve also significantly affected anxiety levels. Further research is needed to assess whether COVID-19 will have any impact on ART treatments in the next few years.

ARTICLE HISTORY

Received 26 May 2020
Revised 2 August 2020
Accepted 3 August 2020

KEYWORDS

COVID-19; anxiety;
postponement; ART;
infertility

Introduction

The Coronavirus disease 2019 (COVID-19) emerged in China between the late 2019 and early 2020, and subsequently spread to other countries within a few months. World Health Organization (WHO) declared this disease as a pandemic on 11 March 2020 [1]. There were almost 4.5 million confirmed cases and 300,000 deaths globally according to WHO reports, at the time of writing the manuscript [2]. In Turkey, there were 146,457 confirmed cases and 4055 deaths by 15 May 2020. Epidemics and pandemics such as Severe Acute Respiratory Syndrome (SARS) and COVID-19 are known to cause some important psychological problems (psychosis, anxiety, depression, and trauma) in individuals [3–5]. The physical health of people who encountered the COVID-19 worsened during this period, and most of the people were observed to

experience significant psychological problems such as anxiety, depression, and panic disorders due to the pandemic of COVID-19 [6]. The COVID-19 outbreak was an unprecedented situation and it put important stress and pressure on individuals and also health-care systems.

Infertility, which is defined as the inability to conceive spontaneously within one year is also known to affect the social and mental health of the couples [7]. The process of diagnosis and treatment of infertility may have an impact on the personal lives of women, which may lead to anxiety, depression, and emotional stress [8]. The emotional response to infertility and especially assisted reproductive technology (ART) are anxiety and depression [9]. Anxiety levels of infertile women may vary with age, cause of infertility, duration of infertility, socioeconomic status and some other unexpected stressors like outbreaks [10–12].

Based on the above evidence and information, we speculated that there may be some changes and affecting factors in the stress and anxiety levels of infertile women whose treatment was delayed during this COVID-19 pandemic especially in diminished ovarian reserve. The present study aimed to evaluate anxiety levels and fear associated with COVID-19 as well to assess the predictors that affect the anxiety levels during the outbreak for women whose ART cycles were postponed due to COVID-19.

Materials and methods

The study was conducted in a reproductive endocrinology and infertility unit of a university-based hospital. This cross-sectional study was performed through an online survey to prevent the spread of the COVID-19. The necessary information and aim of this study were explained at the beginning of the survey. The web-based questionnaire was sent to the participants *via* an online global platform. The survey was completely voluntary and anonymously. The Directorate-General for Health Services of the Ministry of Health and Local Ethics Committee of our university approved the study (Ref. No: E.46253-2020/3). The online survey was sent to a total of 187 participants who had records at the center during this period and it was answered on the internet within 12 days by 101 participants. The women who recruited for the study were determined according to the records in the fertility center. These participants were only women whose ART treatment process was delayed due to the COVID-19 outbreak. Women who had other reasons not performing the ART process were not recruited for the study population. The inclusion criteria of the study were; being able to understand Turkish, aged between 20 and 41 years, and the delay of the ART procedures during the outbreak. Exclusion criteria were data and participants who did not complete the questionnaire and those who refused to take the survey. Demographic variables including age, education level, employment status, duration of infertility, and the cause of infertility were questioned and recorded.

We aimed to determine the relationship of the COVID-19 outbreak with the willingness to go ahead with the desire for pregnancy. We asked some specific questions such as “Do you think COVID-19 can have a negative effect on pregnancy?” and “Would you consider postponing your pregnancy plans because of the COVID-19 outbreak?” These questions were assessed with a 5-point Likert-scale from “strongly disagree” to “strongly agree”. Moreover, some questions such as

“What is your anxiety caused by the postponing of the treatment process due to the COVID-19 outbreak?” and “Do you feel anxiety that the possibility of the pregnancy may be negatively affected due to postponing of the treatment during COVID-19 outbreak?” were asked to observe the effect of the postponement of the treatment process on the anxiety status. We also assessed the anxiety level by using standardized and validated “Spielberger State-Trait Anxiety Inventory (STAI-T)” and “Spielberger State-State Anxiety Inventory (STAI-S)” [13]. We used the validated Turkish version of these inventories [14]. The inventories were assessed with a 4-point Likert-scale from “never” to “almost always”. The lowest and highest scores were 20 and 80, respectively. The lowest score reflects the low anxiety levels and the highest score reveals the severe anxiety for the participant. The Cronbach alpha scores of these questionnaires were 0.82 and 0.90 in our study, respectively. The fear of COVID-19 was also evaluated with a scale that was developed recently in the Iranian population [15]. The Fear of COVID-19 scale (FCV-19S) was used to present psychometric properties associated with COVID-19 among infertile women in the study population, and was examined with a 5-point Likert-scale from “strongly disagree” to “strongly agree”. We used the FCV19-S to determine the fear of COVID-19 by reason of a positive correlation with the anxiety levels [15]. The total score ranges from 7 to 35 and the higher scores indicate greater fear of COVID-19. The Cronbach alpha score of this scale was established as 0.85 in our study.

The power analysis was performed based on an expected prevalence of anxiety as 36.17% in infertile women [16]. The calculation showed that at least 92 participants would need to be enrolled with an alpha-error level of 0.05 and a power of 80% to detect an increase of the prevalence from 36.17% to 50% according to the literature findings of the COVID-19. The online survey was conveyed to 187 women to get enough participants because the response rate of online surveys is approximately 45–50% in the literature [17].

The Statistical Package for Social Sciences (SPSS) Version 20.0 (SPSS Inc., Chicago, IL) was used to analyze the data. Descriptive parameters were evaluated with mean \pm SD (standard deviation) and median (interquartile range) values. The Student’s *t*-test, ANOVA test, Mann–Whitney *U* test, and Kruskal–Wallis tests were performed whether the data were parametric or non-parametric. Frequency and percentages values were expressed and showed in the figures. We also used multivariate linear regression and logistic

Table 1. The Comparison of the STAI scores of participants according to some socio-demographic and clinical parameters.

Sociodemographic and clinical variables	n (%)	Trait-anxiety (STAI-T)		State-anxiety (STAI-S)	
		Mean ± SD or Median (IQR)	p	Mean ± SD or Median (IQR)	p
Age					
<35 years	63 (62.4)	49.0 (6.0)	0.135 ^a	42.2 ± 4.5	0.006 ^b
≥35 years	38 (37.6)	47.5 (5.0)		45.0 ± 5.2	
Education Level					
Literate-Primary School	5 (5.0)	53.4 ± 5.9	0.005 ^c	49.0 (6.00)	0.128 ^d
Secondary-High School	52 (51.5)	49.4 ± 4.8		44.0 (7.75)	
University and above	44 (43.6)	47.4 ± 4.7		42.0 (6.75)	
Employment Status					
Employed	47 (46.5)	48.0 (4.00)	0.575 ^a	43.7 ± 5.0	0.389 ^b
Unemployed	54 (53.5)	48.5 (6.50)		42.9 ± 4.9	
Duration of infertility					
1–3 years	42 (41.6)	47.5 (6.00)	0.662 ^d	43.3 ± 4.4	0.930 ^c
4–7 years	32 (31.7)	47.5 (6.75)		43.0 ± 5.4	
>7 years	27 (26.7)	49.0 (5.00)		43.5 ± 5.3	
Cause of infertility					
DOR	36 (35.6)	49.0 (6.75)	0.134 ^d	44.7 ± 5.2	0.173 ^c
Unexplained	28 (27.7)	46.5 (6.00)		42.5 ± 5.0	
Male Factor	22 (21.8)	47.0 (4.50)		42.6 ± 4.1	
Others	15 (14.9)	49.0 (6.00)		42.1 ± 4.7	
Previous ART failure					
Yes	57 (56.4)	48.0 (6.50)	0.773 ^a	42.5 ± 4.9	0.094 ^c
No	44 (43.6)	48.0 (5.75)		44.2 ± 4.9	
Postponed treatment due to COVID-19					
Cycle postponement	84 (83.2)	49.0 (6.00)	0.100 ^a	43.7 ± 4.8	0.032 ^b
Suspension of preparation	17 (16.8)	47.0 (3.50)		40.9 ± 4.9	
Desire to continue treatment					
Yes	33 (32.7)	49.2 ± 4.2	0.703 ^c	45.0 (6.50)	0.221 ^d
No	40 (39.6)	48.7 ± 4.6		42.5 (7.00)	
Not sure	28 (27.7)	48.2 ± 4.7		42.5 (8.50)	
Which one is more worried?					
The possibility of becoming infected the COVID-19	25 (24.8)	49.0 (8.50)	0.656 ^a	41.0 (4.50)	0.027 ^a
The possibility of not being pregnant	76 (75.2)	48.0 (5.00)		44.5 (6.00)	

SD: standard deviation; IQR: interquartile range; STAI-T: Spielberger State-Trait Anxiety Inventory; STAI-S: Spielberger State-State Anxiety Inventory.

^aMann–Whitney *U*-test; ^b*t*-Test; ^cANOVA test; ^dKruskal–Wallis test.

regression analysis to determine the effect of potential confounders on anxiety outcomes. Odds ratio (OR) with a 95% confidence interval (CI) expressed the effects of covariates. A *p*-value of <0.05 was considered statistically significant.

Results

In this cross-sectional study, the online survey was initially sent to 187 women according to the database of our fertility center. Of these women, five stated that they would not continue with the fertility treatment process while 71 of them declined to participate in the questionnaire. Eventually, 101 women fully completed the online survey, and their data were collected for analysis. All of the participants experienced the postponement of their ART cycle which was about to start or suspension of the preparation process of their ART procedures, due to the COVID-19 outbreak. The mean age of the study population was 33.3 ± 4.3 years and the mean duration of infertility was 5.7 ± 4.1 years. The causes of infertility among the participants were diminished ovarian reserve (*n* = 36, 35.6%),

unexplained infertility (*n* = 28, 27.7%), male factor infertility (*n* = 22, 21.8%) and others (*n* = 15, 14.9%). The distribution of education level of the women were literate or primary school (5%, *n* = 5), secondary or high school (51.5%, *n* = 52) and university and above (43.6%, *n* = 44). More than half of the participants were unemployed (53.5%, *n* = 54).

The mean levels of the STAI-T, STAI-S, and FCV-19S were 48.7 ± 4.5, 43.3 ± 4.9, and 16.7 ± 5.3 respectively. We categorized age, education level, employment status, duration, and cause of infertility to assess the anxiety levels for the participants (Table 1). Age and education level seem to affect the status of anxiety among infertile women. Women who did not have any previous ART failure had higher state-anxiety levels than women with previous ART failure, albeit not significantly. In Table 1, we demonstrated that worry about the possibility of not being able to get pregnant seems to be a significantly important parameter that affected the state-anxiety levels among infertile women. The postponement of treatment was found to significantly affect especially the state-anxiety levels. We observed the evaluation of the women's idea

about whether COVID-19 has an impact on the pregnancy outcomes and consideration of postponing the pregnancy plan due to the COVID-19 outbreak. Almost half of the participants (42.6%, $n = 43$) did not think that COVID-19 may affect pregnancy outcomes, while some of the participants (37.6%, $n = 38$) felt some anxiety about the delay of the treatment process. Almost half of the women (44.6%, $n = 45$) agreed to postpone their pregnancy plan due to COVID-19. Majority of the participants (86.1%, $n = 87$) felt anxiety about the possibility of the pregnancy may be negatively affected due to delaying of the treatment process during COVID-19 outbreak. The total score of FCV-19S was found to be significantly higher in the group of women who desired to postpone the process compared to women who desired to continue the treatment (17.7 ± 4.7 vs. 14.3 ± 5.7 , $p = 0.013$, respectively). The questions and distribution of the answers for FCV19-S were shown in Table 2. Although most of the patients did not express significant somatic symptoms, nearly half of the women thought that COVID-19 created discomfort and fear in their life.

We performed linear regression analyses to identify the potential confounders that may affect STAI-T and STAI-S separately (Table 3). All independent variables such as age, education level, employment, duration of infertility, the anxiety of desire to have a child,

postponement of the ART procedure and the worry about COVID-19 were added to the analysis; we then performed a backward stepwise model and determined the most significant predictors of anxiety levels (Table 3). The cause of infertility was divided into two groups as diminished ovarian reserve (DOR) and other than DOR, before performing the regression analysis. We established that DOR and postponement of the cycle had a significant impact on STAI-S levels because most of the women who had DOR thought that they had limited time to conceive. The state-anxiety was stated as clinically significant anxiety with a suggested cut-off of 40 and higher according to the literature [18]. We demonstrated the prevalence of clinical state-anxiety according to the clinical cutoff value as 71.3%. The multivariate stepwise logistic regression analysis was performed to indicate the potential confounders in the prediction of clinical significant anxiety (Table 4).

Discussion

Our web-based cross-sectional study showed that the prevalence of state-anxiety was high in women whose ART cycles were postponed due to COVID-19 according to literature findings regarding the prevalence of anxiety in infertile women. The levels of anxiety,

Table 2. The questions and distribution of the answers of FCV-19S.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
I am most afraid of coronavirus-19	10 (9.9)	30 (29.7)	15 (14.9)	36 (35.6)	10 (9.9)
It makes me uncomfortable to think about coronavirus-19	11 (10.9)	28 (27.7)	13 (12.9)	46 (45.5)	3 (3.0)
My hands become clammy when I think about coronavirus-19	43 (42.6)	46 (45.5)	7 (6.9)	3 (3.0)	2 (2.0)
I am afraid of losing my life because of coronavirus-19	24 (23.8)	32 (31.7)	20 (19.8)	18 (17.8)	7 (6.9)
When watching news and stories about coronavirus-19 on social media, I become nervous or anxious	12 (11.9)	30 (29.7)	18 (17.8)	33 (32.7)	8 (7.9)
I cannot sleep because I'm worrying about getting coronavirus-19	45 (44.6)	45 (44.6)	5 (5.0)	5 (5.0)	1 (1.0)
My heart races or palpitates when I think about getting coronavirus-19	50 (49.5)	41 (40.6)	6 (5.9)	4 (4.0)	0 (0.0)

FCV-19S: Fear of COVID-19 scale.

Data were given as n (%).

Table 3. The multivariable linear regression analysis for predictors of trait and state anxiety.

Independent variables	Trait-anxiety (STAI-T)			State-anxiety (STAI-S)		
	<i>B</i>	Standardized Beta	<i>p</i>	<i>B</i>	Standardized Beta	<i>p</i>
Age	-0.312	-0.301	0.002	0.137	0.119	0.220
Education level (University and above vs. High school and below)	-2.452	-0.318	0.001	-1.193	-0.140	0.153
Cause of infertility (DOR vs. Others)	2.563	0.275	0.005	2.526	0.245	0.008
Duration of infertility	0.077	0.071	0.461	0.348	0.292	0.020
Postponed treatment due to COVID-19 (Cycle postponement vs. Suspension of preparation)	-1.270	-0.106	0.256	-3.113	-0.236	0.011

STAI-T: Spielberger State-Trait Anxiety Inventory; STAI-S: Spielberger State-State Anxiety Inventory.

Table 4. Multivariate logistic regression analysis of the presence of clinical anxiety.

Independent Variables	aOR	95% CI	<i>p</i>
Diminished ovarian reserve	4.176	1.387–12.575	0.011
Previous ART failure	0.326	0.123–0.866	0.024

especially the state-anxiety were higher in women who experienced a postponement of the ART cycle compared to the suspension of the preparation process. We suggest that the disappointment about postponement might influence the anxiety levels for infertile women during the period of the outbreak. Moreover, DOR as a cause of infertility significantly affected the women leading to more anxiety than the other causes. The concern for delaying the pregnancy may negatively affect the possibility of maternity.

Infertile women make up a vulnerable population and they also have a low self-esteem because of the low fecundability. Anxiety is a normal adaptive response of humans in stressful situations [19]. The prevalence of anxiety was observed as 39.6% for high levels of trait-anxiety in infertile women compared to fertile controls as 17.6% [20]. In a very recent meta-analysis, the authors established the prevalence of anxiety as 36.17% in infertile women and also stated that this proportion increased from a high-income population (25.05%) to low-middle income population (54.24%) [16]. We observed the prevalence of trait- and state-anxiety according to the clinical cutoff values as 29.7% and 71.3%, respectively. The prevalence of state-anxiety was higher than recent literature findings. Conversely, Maroufizadeh et al. showed that anxiety, depression, and distress were similar between pregnant and non-pregnant women with in-vitro fertilization (IVF) treatment [21].

Several studies were performed to determine the effect of anxiety and depression in the COVID-19 outbreak. Most of the studies were carried out using online surveys, especially in China where the first case emerged. One-fifth of the Iranian general population who attended a cross-sectional study had severe or very severe anxiety [22]. The present study is the first study that evaluated the psychological effects of COVID-19 among infertile women. We observed the clinical anxiety as the prevalence of 71.3%. In Turkey, Durankus and Aksu performed a recent preliminary study to evaluate the effect of the COVID-19 pandemic on anxiety and depression among pregnant women [23]. They found the prevalence of anxiety as 35.4% in the study population, besides it was demonstrated that the Beck anxiety inventory (BAI) and the Beck

depression inventory (BDI) significantly correlated with the effects of COVID-19 on psychology. Another study from Turkey reported the proportion of anxiety as 45.1% in the general population [24]. The authors also emphasized that women were most psychologically affected by the COVID-19 outbreak than men. Our study demonstrated that nearly half of women felt uncomfortable about COVID-19. We followed national regulations, as well regulations of international reproductive health societies such as American Society for Reproductive Medicine (ASRM), European Society of Human Reproduction and Embryology (ESHRE), and International Federation of Fertility Societies (IFFS) to identify plans for fertility treatments. All societies suggested deferring treatment and pregnancy plans for infertile patients at the beginning of the pandemic [25–27]. The Italian Society of Fertility and Sterility and Reproductive Medicine (SIFES-MR) published a commentary about the COVID-19 and ART and they concluded that pregnancies should be postponed until reliable evidence shows the association between COVID-19 and pregnancy [28]. However, almost all of these societies neglected the psychological consequences of COVID-19 on the fertility outcomes. We emphasized the effect of this outbreak on anxiety levels specifically in women whose ART cycles were delayed in this period.

On the other hand, women who are in the borderline for conceiving like advanced maternal age and DOR have some concerns about the decreasing possibility of pregnancy [29]. Infertility is a disease and ‘time variable’ treatments such as advanced maternal age have a significant impact on the outcomes [30]. In a recent study, Yilmaz et al. found that fertility distress does not have any relation with the age of infertile women [31]. Age was also stated as a positive factor related to high anxiety levels during the COVID-19 outbreak in China [32]. Anxiety and depressive symptoms were found to be more likely in those below 35 years of age in the study by Huang et al. [32]. Similarly, we also found that the trait-anxiety was higher in women younger 35 years old but, the state-anxiety was significantly lower in this age group. The risk of COVID-19 is higher in older people although anxiety levels are high in young cases, which can be explained by concerns about the future and the economic impacts of the outbreak on the affected group.

Ovarian reserve decreases with age, and thus the pregnancy outcomes worsen. We also found that women with DOR had higher anxiety levels. Pastore et al. found that women with DOR were more nervous and sorehead in comparison with others [33]. In a

cross-sectional study, higher infertility-related distress was found in the DOR group than in those with anatomical problems [11]. They claimed that strong feelings about social isolation, decreased sexual desire, and taking parenthood as an essential goal might contribute to the great distress for DOR patients in their life. It is recommended not to suspend the fertility treatments in POSEIDON patients especially group 3 during the COVID-19 outbreak because some physical and psychological health problems may occur in these patients if a postponement is made [34]. We also found that DOR significantly predicted the clinically significant state-anxiety. Another important issue is that postponement of fertility treatments will have an impact on the potential of pregnancy especially in these groups of women. In a case-control study, the postponement of the orthopedic surgical operations was found to increase the anxiety levels in patients [35]. There are no studies that assess the effect of anxiety about deferring the pregnancy plan in ART cycles. Over half of our study population had anxiety about delaying fertility treatments.

It was suggested that fertility treatments may have negative effects on the mental health of infertile women [10]. We do not have the exact information about whether psychological distress is a reason or result for infertile women. Failure of ART may be itself an important reason of anxiety for infertile women. Maroufizadeh et al. showed that patients with infertility experienced more anxiety and depression after at least one ART failure compared to patients without a history of ART [36]. On the contrary, Reis et al. found that couples had higher state-anxiety levels during the first ART cycles than in multiple cycles [37]. Similar to this study, we demonstrated that women who were to undergo the first ART cycle had more state-anxiety compared to cases with at least one previous ART failure. However, previous ART failure significantly decreased the probability of clinical anxiety in our study population.

Mental health interventions should not be neglected in the vulnerable population such as infertile couples and pregnant women during the public health problems such as COVID-19 outbreak. The uncertainty and unpredictability of the outbreaks threaten the mental health of the people, with physical consequences. There are several studies evaluating prevention and treatment options for the COVID-19, nevertheless, limited data is available about psychological outcomes of the COVID-19 outbreak [6,22,32,38]. To the best of our knowledge, the present study is the first to evaluate the anxiety status of

infertile women during the COVID-19 outbreak. Additionally, there is no study in the literature about the concern of women whose cycles were postponed for any reason. After updates of the recommendations of ESHRE and ASRM, most of the fertility centers started performing ART cycles [39,40]. The psychological health of infertile women is an unnoticed situation especially among public health problems, so it should not be ignored for vulnerable populations. Alviggi et al. also proposed that psychological support should be an alternative for infertile women prior to commencing ART treatments [34]. Further studies are required to explore the effect of COVID-19 because the effect of COVID-19 may remain a few years and it may have serious impact on the important health situations such as ART treatments by restricting to the treatment options.

One of the strengths of the present study is that it measured the psychological state of infertile women during the outbreak. Another important aspect of our study is that it is the first one assessing the anxiety of infertile women whose ART cycles delayed due to any reason. Limitations of the current study are the relatively small sample size and single-center cross-sectional design. We performed the survey via a web-based questionnaire, so it might make a selection bias. We could not ensure a control group to compare the outcomes of the infertile women. The absence of a control group to compare the differences may be another critical limitation, but the pandemic is an extraordinary situation for all of us, so it is difficult to determine the suitable control group in a study.

In conclusion, the COVID-19 outbreak is still an unexpected global problem and has been affecting the physical health of the people. It was observed that anxiety and depression were high during the pandemic. The COVID-19 outbreak should not cause, even temporarily, neglect of appropriate treatment options for women who need urgent therapy in ART. We concluded that infertile women whose ART cycles were delayed due to the COVID-19 outbreak had significant anxiety. Moreover, women with DOR reported higher anxiety levels during this period. The concern of not being able to conceive caused more anxiety than becoming infected with the coronavirus. There is a lack of data concerning the psychological problems of the public, so support and interventions should be focused on the vulnerable population such as infertile and pregnant women in order to improve negative emotional factors. Future

studies are required to confirm and eliminate unclear data.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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