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Unsuccessful Infertility Treatment and Psychological Outcomes: A Prospective Cohort Study

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ABSTRACT

Background and Aim: To quantitatively examine the association between the negative outcome of infertility treatment and psychological disorders in infertile women and to determine any difference in their post- treatment mental health compared to those who had a successful cycle.

Methods: This study included sixty- one infertile women who underwent infertility treatment between December 2022 and July 2023. Their mental health status was assessed with three self- reported measurement tools before the treatment and again after identifying the pregnancy test result.

Results: Women who had a positive test result were recruited into the successful group (n= 13), and those with a negative test were included in the unsuccessful group (n= 48). Women who had an unsuccessful treatment showed a significant increase in their levels of depression, anxiety, stress, hopelessness, and grief (P-value < 0.001). In comparison between women with successful and unsuccessful treatment, infertile women in the unsuccessful group showed higher levels of depression, anxiety, stress, hopelessness, and grief after the treatment (P-value < 0.001).

Conclusion: An unsuccessful treatment may potentially increase infertile women's psychological disorders. This suggests that addressing the psychological aspect alongside infertility treatments for infertile women may help achieve a comprehensive treatment approach.

INTRODUCTION

Infertility is a significant concern in the field of reproductive health (1, 2). Despite recent progress in Assisted Reproductive Technology (ART), the global infertility rate continues to rise annually (3), and the rate of successful treatment is still low (4).

Psychological factors, including high levels of stress, anxiety, and depression, are among the identified predictors of treatment failure in infertile women (5-8).

A large percentage of infertile women experience one or more unsuccessful treatment processes. A qualitative study in 2019 reported that infertile individuals encountered stressors following unsuccessful treatment cycles. They described feeling exhausted from the treatment process, frustrated, fearful of failure of subsequent treatment, and stressed due to their relationship with their spouses (9).

However, few studies have quantitatively examined the impact of these experiences on their mental health, mainly addressing one aspect of psychological issues (10-12).

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If an unsuccessful result leads to psychological problems, it could affect the patient's lifestyle and subsequent infertility treatments (13).

Given the importance of the issue and the absence of comprehensive evidence, this study aimed to examine the effect of unsuccessful infertility treatment on the levels of stress, anxiety, depression, feelings of hopelessness, and grief in infertile women.

MATERIALS and METHODS

This prospective cohort study was conducted at the Ibn Sina Infertility Treatment Center in Kamali Hospital, a tertiary care center specializing in reproductive medicine.

Study Design and Participants

After obtaining approval from the Ethics Committee, this cohort study recruited women who had undergone IVF/ICSI infertility treatment at the Ibn Sina Infertility Treatment Center from December 2022 to July 2023. The inclusion criteria for the study were as follows:

Women with a history of primary or secondary infertility seeking IVF (In Vitro Fertilization) treatment for the first time. No prior history of undergoing IVF or other assisted reproductive treatments (e.g., microinjection).

No specific etiology for infertility was required; meaning women with various causes such as male-factor, female-factor, or unexplained infertility were included.

Additionally, participants had to meet the following criteria: Be a candidate for infertility treatment during the recruitment period. Be older than 18 years. Provide informed consent to participate in the study.

The exclusion criteria were as follows

History of neurological or psychiatric problems or use of psychotropic medications.

Any problems in various aspects of the patient's life during the interval between two phases of data collection, such as the death of relatives, new challenges in personal life, or marital relationships.

Women who met the inclusion and exclusion criteria received counseling about study enrollment through both oral and written information and then signed a written informed consent after counseling. A comprehensive checklist covering sociodemographic information, medical information, and reproductive history was obtained from each participant via structured interview at the first visit to the clinic. The checklist consisted of the participant's age, education levels, employment and economic status, duration of marriage and infertility, history of puncture, number of live children and pregnancies, and the demographic information of their spouses (i.e., age, education, and occupation). Additionally, the participants filled out the data collection tools in the interview room located at the IVF unit of the clinic. Researchers clarified questions that were not fully understood. The questionnaires were completed by participants at the beginning of the treatment and again after identifying the pregnancy test results. Every woman underwent Human Chorionic Gonadotropin (HCG) pregnancy blood testing 14 days after Intra- cytoplasmic sperm injection (ICSI). A positive pregnancy was determined by a serum HCG level exceeding 10 IU/L.

Measurement Tools

Beck Hopelessness Scale (BHS)

The Beck Hopelessness Scale (BHS) is a 20-question questionnaire developed by Beck et al. to measure hopelessness (14). Specific questions earn points for "yes" or "no" responses, with total scores ranging from 0 to 20. Higher scores indicate greater levels of hopelessness. The Persian version of BHS, translated and validated by Kaviani H et al., was utilized (15).

Depression Anxiety Stress Scales (DASS-21)

The DASS-21 is a shorter version of DASS-42, measuring Depression, Anxiety, and Stress. Scores range from 0 to 4, with each subscale score multiplied by two for comparability (16). Higher scores indicate higher levels of each condition. The Persian DASS-21 version was used in this study to evaluate participants' mental health (17).

Grief Experience Questionnaire (GEQ)

Barrett and Scott created the Grief Experience Questionnaire (GEQ) in 1989 with 55 items using a 5-point Likert scale. It evaluates various grief aspects like guilt, responsibility, and reactions to death (18). Mehdi-Poor et al. adapted the questionnaire for an Iranian study, resulting in a 34-item version with seven subscales. Responses are on a 5-point Likert scale, generating subscale scores from 5 to 25. Total scores of 34-68, 68-102, and over 102 indicate low, moderate, and high grief levels (19).

Statistical Assessment

Continuous variables are presented as mean ± SD or median (interquartile range). Categorical variables are presented as percentages. Chi-squared or Fisher's exact test was used to compare categorical variables. The t-test was used for normally distributed continuous variables, and the Mann-Whitney U test was used for non-parametric variables. ANCOVA was used to adjust for covariates to assess the effects of infertility treatment on psychological factors. A P-value of < 0.05 was considered statistically significant for all analyses. Analysis was performed using IBM SPSS v22.

RESULTS

A total of 61 women were included in the current study, and all completed two weeks of follow-up (loss to follow-up: 0%). The median ages of included participants and their spouses were 34 (28, 38) and 37 (33, 42), respectively. Participants were categorized into two groups based on the outcome of the treatment: successful (women who achieved pregnancy) and unsuccessful (women who did not). Of the participants, 48 were in the unsuccessful group, while 13 were in the successful group.

As presented in Table 1, the baseline characteristics of participants achieving successful pregnancy were comparable to those with unsuccessful ICSI (P-value > 0.05).

The comparison of DASS-21 after infertility treatment demonstrated that patients in the unsuccessful group exhibited higher scores of depression, anxiety, and stress compared to the successful group (mean difference (95% CI): 20.00 (14.00, 26.00), 16.00 (10.00, 22.00), and 20.00 (14.00, 22.00), respectively). Furthermore, women with unsuccessful pregnancies experienced higher levels of hopelessness (mean difference (95% CI): 14 (12.27, 15.00)) and grief (mean difference (95% CI): 37.36 (27, 57)) after the treatment in comparison with those who achieved pregnancy (Table 2). Changes in the psychological status of all patients are summarized in Figures 1-2.

After adjusting for confounding variables, including the baseline psychological scores, age, occupation, and education levels of women and their spouses, number of abortions, live children, and stillbirth, duration of infertility and marriage, history of puncture, and their socioeconomic status, mean differences in all three subscales of DASS-21, Beck hopelessness, and GEQ-34 scores remained statistically significant (Table 2).

The evaluation of the median of three subscales of DASS-21, BHS, and GEQ-34 scores before and after the treatment in the successful and unsuccessful groups revealed the following: In the unsuccessful group, the median depression score increased from 5.50 to 27, anxiety from 5 to 21, stress from 11 to 26.85, BHS from 2.72 to 15.72, and GEQ-34 from 61.84 to 83.39. Conversely, for women in the successful group, the median depression score remained unchanged, anxiety and stress decreased from 8 to 6 and 12 to 8, respectively, and GEQ-34 decreased from 48.35 to 46.00 (Table 2).

Not only were the mean scores of DASS-21, BHS, and GEQ-34 significantly higher in women with unsuccessful ICSI, but all the aforementioned expected scores also had a predominantly increasing trend in non-pregnant patients. In contrast, they had a decreasing trend in pregnant patients (Figures 1-2).

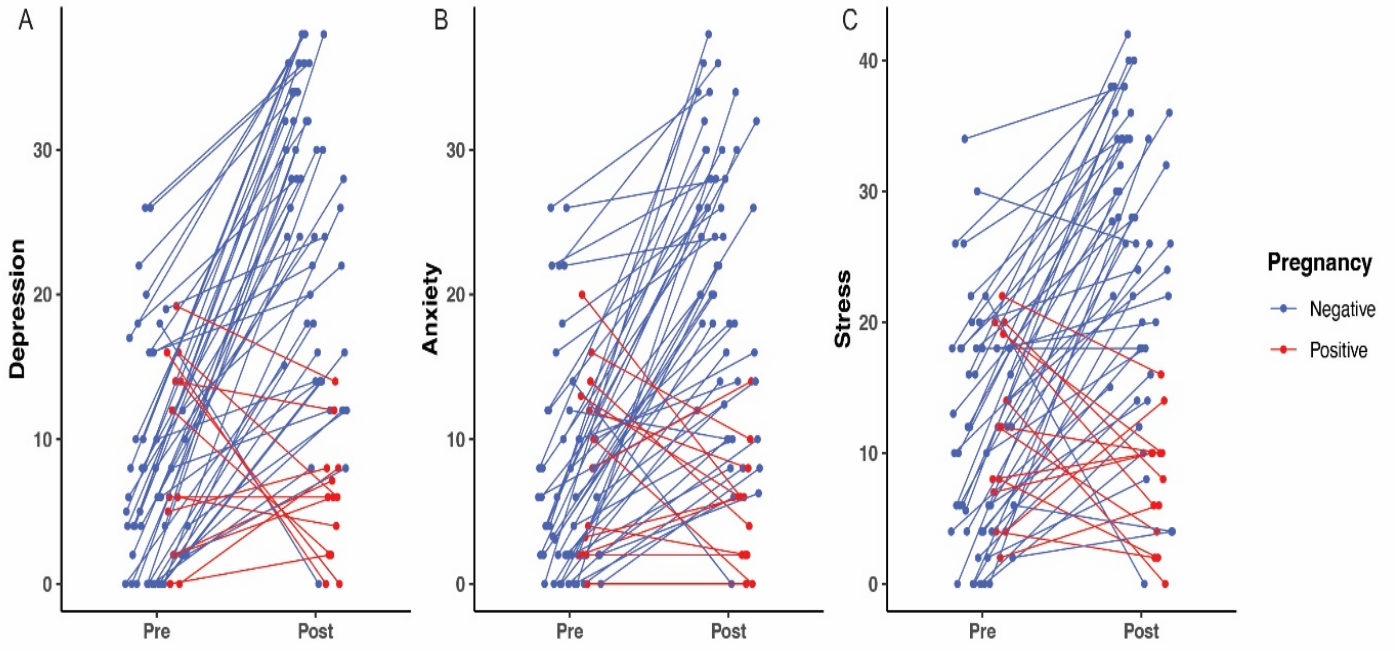

FIGURE 1. A, B, C: Changes in levels of depression, anxiety, and stress according to DASS-21 for each participant.

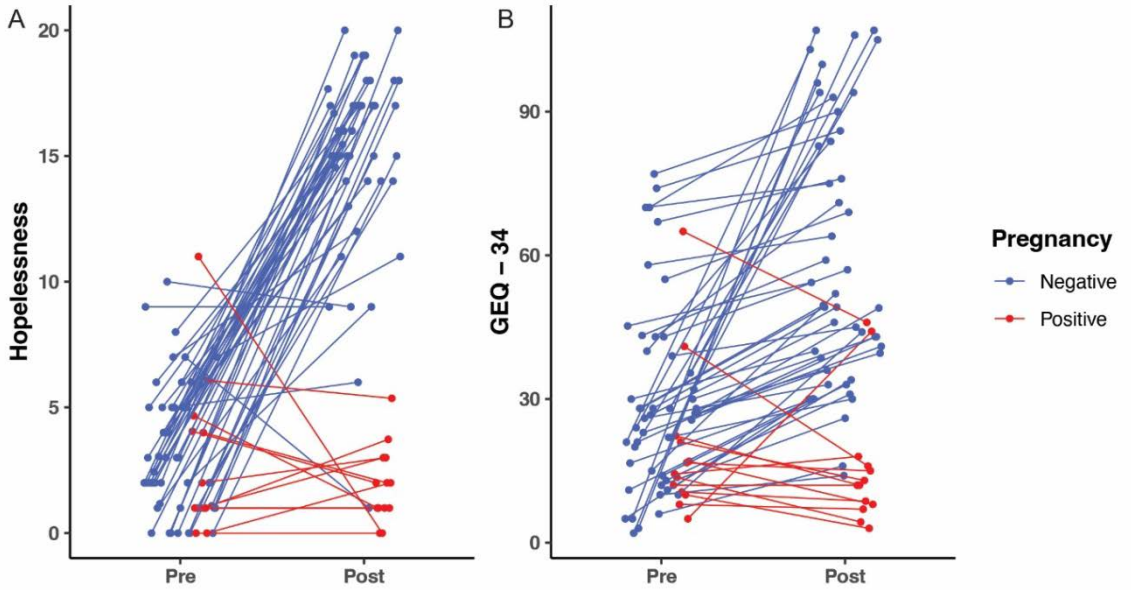

FIGURE 2. A: Changes in levels of hopelessness according to BHS for each participant. B: Changes in levels of grief (all items) according to GEQ-34 for each participant.

Table 1. Characteristics

Descriptive characteristics		Successful group N = 13	Unsuccessful group N = 48	Total N = 61	P-value
Age (years) ***Median (IQR]***		33 (27, 38)	34.5 (28, 39)	34 (28, 38)	0.432
Education ***n (%)***	**Below diploma**	23.1 (3)	29.2 (14)	27.9 (17)	0.791
	Highschool diploma	30.8 (4)	35.4 (17)	34.4 (21)	
	Academic	46.2 (6)	35.4 (17)	37.7 (23)	
Employment status ***n (%)***	**House Wife**	84.6 (11)	85.4 (41)	85.2 (52)	0.780
	Employee	15.4 (2)	10.4 (5)	11.5 (7)	
	Self-Employed	0.0 (0)	4.2 (2)	3.3 (2)	
Socio-economic status ***n (%)***	**Very low**	7.7 (1)	0.0 (0)	1.6 (1)	0.367
	Low	0.0 (0)	6.2 (3)	4.9 (3)	
	Moderate	92.3 (12)	81.2 (39)	83.6 (51)	
	High	0.0 (0)	8.3 (4)	6.6 (4)	
	Very high	0.0 (0)	4.2 (2)	3.3 (2)	
Infertility ***n (%)***	**Primary**	69.2 (9)	69.8 (30)	69.6 (39)	> 0.99
	Secondary	30.8 (4)	30.2 (13)	30.4 (17)	
Infertility Duration ***Median (IQR]***		3 (2,4)	4 (2,6)	4 (2,6)	0.295
Years of Marriage ***Median (IQR]***		6 (3.75, 10.5)	7 (3.75, 10.25)	6.5 (3.75, 10.25)	0.952
History of puncture ***n (%)***	**Yes**	30.8 (4)	25.0 (12)	26.2 (16)	0.728
	No	69.2 (9)	75.0 (36)	73.8 (45)	
Number of Pregnancy ***Median (IQR)***		1 (0, 1.25)	1 (0, 1.5)	1 (0, 1.5)	0.811
Live Children ***Median (IQR)***		0 (0, 0.25)	0 (0, 1)	0 (0, 1)	0.708
Abortion ***Median (IQR)***		0.5 (0, 1)	0 (0, 0.75)	0 (0, 1)	0.281
Still Birth ***Median (IQR)***		0 (0, 0)	0 (0, 0)	0 (0, 0)	0.359
Characteristics of spouses					
Age (years) ***mean ±SD***		35 (32, 37)	39 (33, 45.25)	37 (33, 42)	0.069
Education ***n (%)***	**Below diploma**	38.5 (5)	37.5 (18)	37.7 (23)	> 0.99
	Highschool diploma	30.8 (4)	35.5 (17)	34.4 (21)	
	Academic	30.8 (4)	27.1 (13)	27.9 (17)	
Employment status ***n (%)***	**Employee**	30.8 (4)	50.0 (24)	45.9 (28)	0.357
	Self-Employed	69.2 (9)	50.0 (24)	54.1 (33)	

IQR: Interquartile Range; SD: Standard Deviation

Table 2. Physiological status

Instrument		Successful Median (IQR)	Unsuccessful Median (IQR)	P-value (crude)	P-value (Adjusted model) *
Depression	**Pre**	6.00 (2.00, 14.00)	5.50 (2.00, 10.50)	0.582	
	Post	6.00 (2.00, 8.00)	27.00 (16.00, 32.50)	**< 0.001**	**0.001**
	Post-Pre (MD (95%CI)	-2.85 (-7.47, -7.47)	18.00 (15.00, 15.00)		
	(P-Value)	0.203	**< 0.001**		
Stress	**Pre**	12 (7.00, 19.10)	11 (4.00, 18.00)	0.627	
	Post	8.00 (4.00, 10.00)	26.85 (18.00, 34.00)	**< 0.001**	**0.001**
	Post-Pre (MD (95%CI))	-4.16 (-8.67, -8.67)	15.00 (12.00, 12.00)		
	(P-Value)	0.067	**< 0.001**		
Anxiety	**Pre**	8.00 (2.00, 13.00)	5.00 (2.00, 10.50)	0.456	
	Post	6.00 (2.00, 6.00)	21.00 (13.60, 28.50)	**< 0.001**	**0.019**
	Post-Pre (MD (95%CI))	-3.09 (-6.74, -6.74)	13.00 (11.00, 11.00)		
	(P-Value)	0.089	**< 0.001**		
Hopelessness	Pre	1.00 (1.00, 4.05)	2.72 (1.06, 5.00)	0.338	
	Post	2.00 (1.00, 3.00)	15.72 (14.00, 17.00)	**< 0.001**	**<0.001**
	Post-Pre (MD (95%CI))	-0.53 (-5.00, -5.00)	12.83 (11.50, 11.50)		
	(P-Value)	0.552	**< 0.001**		
Guilt	**Pre**	13.00 (10.00, 14.00)	12.00 (9.75, 15.00)	0.965	
	Post	11.00 (10.33, 13.00)	19.22 (14.75, 28.25)	**< 0.001**	0.053
	Post-Pre (MD (95%CI))	-1.00 (-3.34, -3.34)	6.34 (4.61, 4.61)		
	(P-Value)	0.683	**< 0.001**		
Search for explanation	**Pre**	9.00 (8.00, 11.00)	13.00 (10.75, 17.00)	**0.023**	
	Post	9.00 (7.00, 9.00)	17.00 (14.75, 22.25)	**< 0.001**	**0.040**
	Post-Pre (MD (95%CI))	-1.50 (-3.67, -3.67)	4.34 (2.88, 2.88)		
	(P-Value)	0.099	**< 0.001**		
Somatic reaction	**Pre**	6.00 (5.00, 10.00)	9.48 (7.00, 12.00)	0.08	
	Post	7.00 (6.00, 10.00)	12.79 (10.00, 18.00)	**< 0.001**	**0.036**
	Post-Pre (MD (95%CI))	-0.50 (-3.72, -3.72)	3.72 (2.50,2.50)		
	(P-Value)	0.798	**< 0.001**		
Loss of social support	**Pre**	6.00 (4.00, 7.00)	7.09 (5.00, 9.00)	0.13	
	Post	5.00 (4.00, 6.00)	10.00 (8.00, 14.00)	**< 0.001**	0.052
	Post-Pre (MD (95%CI))	-1.35 (-2.50, -2.50)	3.41 (2.50, 2.50)		
	(P-Value)	0.065	**< 0.001**		
Stigmatization	**Pre**	4.00 (3.00, 4.00)	4.71 (3.00, 7.00)	**0.036**	
	Post	3.00 (3.00, 4.00)	7.00 (6.00, 10.25)	**< 0.001**	0.293
	Post-Pre (MD (95%CI))	0.11 (-2.00, -2.00)	3.50 (2.00, 2.00)		
	(P-Value)	0.888	**< 0.001**		

Instrument		Successful Median (IQR)	Unsuccessful Median (IQR)	P-value (crude)	P-value (Adjusted model) *
Shame	**Pre**	6.00 (5.00, 7.00)	7.00 (4.75, 8.25)	0.594	
	Post	4.00 (4.00, 7.00)	9.00 (8.00, 14.00)	**< 0.001**	0.159
	Post-Pre (MD (95%CI))	-1.00 (-3.00, -3.00)	3.00 (2.25, 2.25)		
	(P-Value)	0.138	**< 0.001**		
Judgment	**Pre**	5.00 (5.00, 6.00)	6.56 (4.00, 7.00)	0.375	
	Post	5.00 (4.00, 6.00)	10.00 (8.00, 14.25)	**< 0.001**	0.202
	Post-Pre (MD (95%CI))	-1.00 (-3.50, -3.50)	4.00 (2.50, 2.50)		
	(P-Value)	0.598	**< 0.001**		
Total GEQ-34	**Pre**	48.35 (44.58, 55.00)	60.84 (48.75, 73.25)	**0.043**	
	Post	46.00 (42.00, 50.00)	83.39 (71.91, 118.35)	**< 0.001**	**0.045**
	Post-Pre (MD (95%CI))	-5.65 (-13.35, -13.35)	21.14 (16.16, 16.16)		
	(P-Value)	0.078	**< 0.001**		

***For the P-value (adjusted model), we used ANCOVA to adjust covariates, including the age of women, education of women, women's jobs, number of pregnancies, live children, abortions, stillbirths, infertility type, and infertility duration, years of marriage, history of puncture, successful puncture, socioeconomic status, spouses' age, education, and jobs, and patients' psychological scores before treatment. IQR: Interquartile Range; MD: Mean Difference; Pre: before treatment; Post: after treatment; 95% CI: 95% Confidence Interval; GEQ-34: Grief Experience Questionnaire 34.**

DISCUSSION

The present cohort study aimed to identify if unsuccessful infertility treatment outcomes could predict psychological distress in infertile women. Our findings revealed a significant association between unsuccessful treatment and increased levels of depression, anxiety, stress, feelings of hopelessness, and grief in infertile individuals, considering pre-ICSI mental health status.

These findings were similar to Pasch et al. and Verhaak et al., both of whom observed a significant increase in levels of depression (from 12.39 to 15.85 and 1.3 to 3.9, respectively) and anxiety (from 41.41 to 43.33 and 36.9 to 39.8, respectively) in their participants following a failed IVF cycle (10, 12). Additionally, Pasch et al. argued that levels of depression following unsuccessful treatment were comparable to those experienced by parents who had lost a child and even higher than those reported for cancer patients undergoing treatment (10). Although in these two studies, unsuccessful treatment led to a significant increase in psychological problems in infertile women, the initial increase in psychological problems of unsuccessful women in our study was greater than theirs. In the context of feelings of hopelessness and grief, the median score of BHS in the unsuccessful group after the failed treatment was even higher than breast cancer patients and vulnerable prisoners (mean: 13.3, 10.13, respectively) (14, 15). These women also showed a higher median score of grief than Iranian individuals who experienced the death of relatives during the COVID-19 pandemic (mean: 80.27) (16).

The higher increases in psychological scores following a failed infertility treatment in our study compared to similar studies in other communities may stem from cultural distinctions among different populations. Iran, as a Middle Eastern country, places a strong emphasis on a woman's social standing, dignity, and self-worth concerning her ability to conceive (32). A recent study showed the high level of anxiety disorders, which are mainly linked to economic hardships in Iran (17). Given the high cost of infertility treatment, the stress and fear of a negative outcome and the cost of the next treatment could explain the significant psychological pressure on infertile individuals in such countries.

The increased psychological problems following unsuccessful infertility treatments may negatively affect the motivation for subsequent treatments and the overall lifestyle of infertile individuals (18). In this regard, Verhaak et al. showed that unsuccessful treatment not only increased levels of psychological distress in infertile women but also served as a less favorable starting point for the next treatment cycle (13). Also, based on recent evidence, these induced mental health problems could negatively impact the results of subsequent treatment (19-21). The mechanism by which mental disorders can lead to unsuccessful infertility treatment remains unclear. However, it has been suggested that mental disorders may influence the function of endocrine glands, the

immune system, and oocyte retrieval outcomes, all of which are associated with reduced fertility and decreased chances of successful treatment (20, 22).

It is established that a high level of depression shortly after a stressful event is a significant risk factor for the development of a depressive disorder (23). Although limited longitudinal studies with constraints such as high drop- out rates showed a decreasing trend over time for levels of psychological disorders following a failed treatment, a significant percentage of women, nearly twenty percent, remain depressed even six months after the last failure (24).

On the other hand, while the levels of psychological issues in our study decreased after treatment in the successful group, a positive result did not alleviate psychological disorders in all infertile women, as some still experienced significant levels of depression, stress, anxiety, as well as feelings of hopelessness and grief (Table 2). This is in line with earlier studies and is supported by research suggesting that the fear of miscarriage may persist even after receiving a positive pregnancy, which could explain the persistence of psychological issues (13, 25).

Healthcare providers need to understand that treatment procedures and their failure can exacerbate the trauma experienced by infertile women. Therefore, taking an approach that encompasses the emotional and psychological well-being of patients, such as counseling during infertility treatment, may be helpful as part of the treatment procedure for women undergoing infertility treatment, especially in societies where motherhood holds significant social influence for women.

CONCLUSION

Infertility, often perceived through the narrow lens of biomedical failure, exacts a far deeper toll—one etched into the psyche of those who endure its uncertainties. This prospective cohort study elucidates the profound psychological ramifications of unsuccessful IVF/ICSI treatment, revealing a stark dichotomy: while successful conception alleviates distress, treatment failure precipitates a surge in depression, anxiety, stress, hopelessness, and grief. The magnitude of this deterioration is not merely statistically significant but clinically alarming, with post-treatment psychological scores in the unsuccessful cohort eclipsing those observed in populations grappling with severe illness or bereavement.

The implications extend beyond transient emotional distress. In cultures where fertility is inextricably linked to identity and social capital—such as Iran, the setting of this study—the psychological burden is compounded by existential and societal pressures. The data suggest that infertility treatment, when unsuccessful, does not merely fail to achieve pregnancy; it risks destabilizing mental health in ways that may undermine future treatment adherence, marital dynamics, and overall well-being. Notably, even "success" does not universally confer psychological relief, as residual anxiety persists in some women, likely fueled by the fragility of early pregnancy after prolonged infertility.

These findings demand a paradigm shift in reproductive care. The current model, which prioritizes biochemical success over holistic well-being, is insufficient. Integrating evidence-based mental health support—such as preemptive counseling, mindfulness-based stress reduction, or structured grief interventions—into standard infertility protocols could mitigate the collateral damage of treatment failure. Moreover, fostering cross-disciplinary collaboration between reproductive endocrinologists and mental health professionals is imperative to address the bidirectional relationship between psychological distress and treatment outcomes.

Future research should investigate longitudinal mental health trajectories post-treatment and the efficacy of targeted psychosocial interventions. For now, this study serves as a clarion call: infertility is not solely a disorder of the body but a crisis of the self. Medicine must respond with equal rigor to both dimensions.

ETHICAL CONSIDERATION

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, registered by the approval number IR.ABZUMS.REC.1400.129.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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