JOURNAL OF FERTILITY AND REPRODUCTIVE HEALTH
Jan - Jun 2026, VOL. 4, ISSUE 1, pp. 38-44
https://doi.org/10.61577/jfrh.2026.100005

ORIGINAL ARTICLE

The relationship between various types of stress and outcome of in vitro fertilization treatment in infertile women: A prospective study

Pantea Askari[1], Jafar Askari[2], Maryam Eftekhar[3] and Afsaneh Hassanbeigi[3]

[1] Faculty of Medicine, Hormozgan University of Medical Sciences, Iran
[2] Department of Clinical Psychology, Research Center of Addiction and Behavioral Sciences, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] Research and Clinical Center for Infertility, Yazd Reproductive Sciences Institute, Yazd, Iran

ABSTRACT

Objective: The aim of this study is to investigate the relationship between three types of stress, namely experienced acute, chronic, and perceived (appraisal) stress and the outcome of in vitro fertilization treatment in infertile women.

Method: In this study, a sample of 172 infertile women in the age range of 20-40 years of women referred to Yazd reproductive sciences institute was been used. Based on the outcome of treatment, the levels of the three types of stress were compared in two groups of women with successful and unsuccessful pregnancies.

Results: Based on the results, among 172 women participating in the study, 48 (27.9%) had successful and 124 (72.1%) had unsuccessful pregnancies. According to the findings, the differences between the two groups of successful and unsuccessful pregnancies in acute and chronic stress were not significant, but in perceived stress, although the difference was not significant, it was very close to the level of significance ($p = 0.07$).

Conclusion: Considering that only the difference in perceived stress between the two groups of successful and unsuccessful pregnancies was very close to the level of significance ($p = 0.07$), it seems that in future studies using larger samples, this difference may become significant. This means that when patients have a more catastrophic appraisal of their stressful events, the negative consequences of stress may be influential, and it can be mainly related to the negative outcome of pregnancy by in vitro fertilization treatment.

KEYWORDS

Assisted reproductive technology; In vitro fertilization treatment; Coping with stress; Pregnancy rates; Infertility

ARTICLE HISTORY

Received 21 May 2026;
Accepted 11 June 2026;
Published 22 June 2026

Introduction

According to the World Health Organization, infertility is the inability to achieve a successful pregnancy after one year or more of regular sexual intercourse [1]. The prevalence of the disorder in Iran is reported to be 20.2% [2]. It is emphasized that the successful or unsuccessful outcome of infertility treatments including in vitro fertilization (IVF) can be influenced by stress [3–5]. Although, infertile couples suffer more stress than fertile couples, but on the other hand, it has been proven that high levels of psychological distress also increase the risk of infertility [6,7]. Stress can negatively affect various aspects of pregnancy, including sexual desire, sperm quality, ovulation capacity and implantation [8]. The direct effects of stress are related to the autonomic nervous, endocrine and immune systems. In contrast, the indirect effects are related to changes in behaviors affecting health such as inappropriate sexual behaviors and substance use [9]. Accordingly, stress can affect pregnancy in a variety of ways, including HPA axis hyperactivity, hormonal problems, immune system dysfunction, decreased sperm quality, and behavioral disorders such as inappropriate sexual behavior or drug use [10,11]. In this regard, it seems that a distinction should be made between the effects of acute and chronic stress. Acute stress can occur during the treatment process [12,13]. Various studies show that different stages of infertility treatment are also associated with very high stress and anxiety [14,15]. At the Same Time, chronic stress can be affected by past stressful and traumatic events [16]. In addition, the way a person reacts to stress is also important and depends on genetic factors, personality traits, previous experiences, the amount of social support and methods used to cope with stress [17].

In recent decades, the concept of stress in the behavioral and health sciences has become very popular, and to explain it, three general models have been introduced. The first model, stress as a response, was introduced by Hans Selye. In this model, stress is a series of acute psychophysiological reactions to threats, especially following the activation of the sympathetic nervous system, including heart palpitations, rapid breathing, sweating, fear, and emotional arousal [18]. The "stress as a stimulus" model was introduced as the second model in the 1960s. Holmes and Rahe, 1967 believed that stress is an independent variable that includes a series of important life events and changes that one has to adapt to these events and changes [19]. To measure these important life events, these two researchers designed the Social Readjustment Rating Scale (SRRS), which contains 43 life events, including divorce, dismissal, and emotional breakdown. Based on their research, they concluded that there is a correlation between chronic stress caused by significant life changes and stress-related diseases. Finally, Lazarus and Folkman proposed the "stress as an interaction" model as the third one [20]. In this model, it is believed that stress is an interaction between a person's psychophysiological characteristics and environmental expectations of him. Lazarus believes that among the psychophysiological characteristics of the individual, cognitive appraisal is the most important and central factor influencing how stress is experienced [21]. Lazarus and Folkman were the first researchers to introduce the concept of interpretation or cognitive appraisal in their model of stress, which includes primary and secondary appraisal. The primary appraisal involves determining whether the stressors pose a threat or danger to the individual, but the secondary appraisal involves

***Correspondence:** Dr. Jafar Askari, Department of Clinical Psychology, Research Center of Addiction and Behavioral Sciences, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. e-mail: askarifarr@gmail.com

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assessing the extent and quality of their resources and coping strategies to combat the stressors.

Various studies have been conducted on the relationship between stress and the outcome of infertility treatment. Despite this, in many of them the negative effect of stress on pregnancy outcome has been confirmed but in some studies, such a result has not been obtained [22–30]. On the other hand, Wesselink et al. [31]. Emphasise that some epidemiologic studies of the association between stress and fertility among women report conflicting results. Sominsky emphasizes that it is very difficult to give a definitive answer to the question of whether stress can impede fertility [8]. Trolice also asserts that reaching a definitive conclusion about the relationship between stress and infertility has been the subject of a constant debate between various researchers, and he believes that this conflict is due to the lack of a considerable number of prospective controlled studies [32]. In this regard, Matthiesen et al. point out that the existence or non-existence of a relationship between stress and infertility, as well as the strength of this relationship, is not yet known, so more research in this context is essential [27]. Accordingly, Matthiesen et al. point out that since we do not yet know the exact existence or non-existence of a relationship between stress and infertility, as well as the strength of this relationship, further research is needed. In addition to doing its part to resolve the ambiguity about the relationship between stress and the outcome of infertility treatment, this study also seeks to determine what types of stressors (acute, chronic, or perceived stress) increase the risk for an unsuccessful pregnancy. As far as we know, this is the first study that simultaneously and comparatively examines the relationship between the three models of stress, namely acute (during IVF treatment), chronic (due to current mental pressures caused by unpleasant life events of the past year) and perceived stress (due to the cognitive appraisal of recent life events /changes) and the outcome of IVF treatment.

Materials and Methods

Design and participants

This is a descriptive-analytical prospective study that has been approved to be performed at the Research and Clinical Center for Infertility of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. The study sample is infertile women referred to the Yazd Reproductive Sciences Institute in the age range of 20-40 years from April to September 2020. Participants were selected by using purposeful sampling technique method. The sample size was calculated with regard to the confidence interval of 95%, power of 80%, a standard deviation of 7.1 for the stress score and an expected minimum difference of 3 points in the average stress score of two groups of successful and unsuccessful pregnancies in the Perceived Stress Scale. By using the following formula, to achieve a significant difference, the sample size includes 88 subjects in each of the two groups and 176 in total.

The entry criteria are infertile patients who are candidates for treatment with IVF. Exclusion criteria also include: a history of severe estrotriosis, suffering from severe male factor (azoosperm) and patients in whom embryo transfer is not performed due to Ovarian Hyperstimulation Syndrome (OHSS). Participation in the study is voluntary and with the informed consent of patients. In this study, successful conception after IVF is the criterion for successful pregnancy. To conduct the research, after selecting the sample among those who were referred for IVF, before the last stage of treatment (embryo transfer), the level of three types of stress were measured in all sample subjects. Then, based on the pregnancy test result two weeks after the embryo transfer, the participants were divided into two groups of successful and unsuccessful pregnancy and finally, the scores of the three types of stress in the two groups were statistically compared.

Instruments

Spielberger state-trait anxiety inventory

The State-Trait Anxiety Inventory (STAI) is a tool that is usually used to measure state and trait anxiety and can be used in clinical situations to diagnose anxiety [33]. State anxiety refers to the degree and intensity of a person's perceptible and emotional reactions to a stressful situation, but trait anxiety refers to individual differences in the tendency to perceive different situations as a threat and danger. Scoring is done on a four-point Likert scale, namely never, low, medium and high, with a score of 1 to 4. In the state anxiety scale, questions 1, 2, 5, 8, 10, 11, 15, 16, 19, and 20 and in the trait anxiety scale, questions 1, 3, 6, 7, 10, 13, 14, 16, and 19 are scored in reverse. Test-retest reliability coefficients ranged from 0.65 to 0.75 over a period of 2 months [33]. The reliability and validity of the Persian version of this questionnaire have been declared satisfactory [34]. In this study, the state anxiety scale was used to measure acute experienced stress.

Social readjustment rating scale

The Social Readjustment Rating Scale (SRRS) contains 43 stressful events and was created in order to show the impact of stress caused by major life changes [19]. Regarding the scale, the amount of stress caused by each event is graded from zero to 100. In general, a total score of 150 or less is a sign of a favorable situation, while receiving a total score between 150 and 300 is associated with a 50% probability of suffering from stress-related diseases in the next two years and receiving a total score of 300 and above is associated with an 80% probability of suffering from stress-related diseases in the next two years. Gerst, Grant, Yager and Sweetwood reported the reliability of this scale in healthy and sick people as 0.96 and 0.91, respectively [35]. In the study by Masoudniya, the reliability of the Persian version of this scale was reported as 0.83 [36].

Perceived stress scale

Perceived Stress Scale (PSS), including 10 questions, was used to measure the level of perceived stress. This test has high quality and has been widely used in clinical research [37]. The questions of the test measure the way and intensity of the cognitive evaluation and perceptions (thoughts and feelings) of the subject about the degree of predictability, controllability and emotional load of life events during the past month. The answers to the questions of this test are based on a 5-point Likert scale from never, with a score of 0, to most of the time, with a score of 4, and the answers to questions 4, 5, 7 and 8 are scored inversely. The total score will be between 0 and 40. Scores of 0 to 7 are classified as very low, 8 to 11 as low, 12 to 15 as moderate, 16 to 20 as high, and 21 and above as very high. The Persian version of this scale to measure the level of perceived stress in infertile women has been reported to have satisfactory validity and reliability [38].

Statistical Analysis

In this study, an independent samples t-test and a chi-square test were used to compare demographic variables in the

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studied groups, and independent t-tests were also used to compare the level of stress in the two studied groups. Based on the type of study (prospective) and the desired outcome (pregnancy), the binomial logistic regression method was also used to investigate the effect of three types of stress on pregnancy. Based on this, two relative risk analysis or RRCrude analysis and adjusted relative risks or RRadj analysis with 95% confidence interval have been performed. The collected data were exposed to SPSS version 24 software. Study data are available upon request from the corresponding author.

Results

Comparison of demographic variables in the study groups

Due to the lack of access to the necessary information to determine the outcome of the treatment of 4 patients, the statistical analysis was done using 172 subjects. Based on the results of the study, 48 patients (27.9%) were included in the successful pregnancy group and 124 patients (72.1%) were included in the unsuccessful pregnancy group. In Table 1, demographic variables are compared in both successful and unsuccessful pregnancy groups. As can be seen in this table, there is no significant difference between all demographic variables in the successful and unsuccessful pregnancy groups. This finding shows that the demographic features of both groups are similar.

Comparison of three types stress scores in the study groups

In Table 2, the intensity of the three types of acute, chronic and perceived or appraisal stress in the two groups of successful and unsuccessful pregnancies has been compared. As can be seen, in the two groups of successful and unsuccessful pregnancies, the differences in the three types of acute ($p = 0.29$), chronic ($p = 0.94$) and perceived ($p = 0.07$) stress are not statistically significant.

Table 1. Comparison of demographic variables in the two groups of successful and unsuccessful pregnancies.

		Unsuccessful pregnancy (n = 124)		Successful pregnancy (n = 48)		Demographic variables	
p	t	SD	M	SD	M		
0.9	-0.122	4.87	31.45	4.12	31.35	Age (year)	
0.71	0.364	7.65	13.02	2.9	13.43	Education (year)	
0.43	0.776	3.95	6.87	3.32	7.37	Infertility period (year)	
p	χ^2	%	n	%	n		
0.69	0.154	24.2	30	27.1	13	Feminine	Cause of infertility
		75.8	94	72.9	35	Masculine or undefined	
		100	124	100	48	Total	
0.74	0.107	66.1	82	68.8	33	Without history	History of unsuccessful planting
		33.9	42	31.2	15	With history	
		100	124	100	48	Total	
0.92	0.008	80.6	100	81.2	39	Without history	History of abortion
		19.4	24	18.8	9	With history	
		100	124	100	48	Total	
0.36	0.811	96.8	120	93.8	45	Without history	History of mental illness
		3.2	4	6.2	3	With history	
		100	124	100	48	Total	
0.67	0.181	71.8	89	75	36	Without history	History of thyroid problems and diabetes
		28.2	35	25	12	With history	
		100	124	100	48	Total	

Table 2. Comparison of the three types of stress in the two groups of successful and unsuccessful pregnancies.

Different types of stress	Successful pregnancy (n=48)		Unsuccessful pregnancy (n=124)			
	M	SD	M	SD	t	p

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Table 2 (continued)

Different types of stress	Successful pregnancy (n=48)		Unsuccessful pregnancy (n=124)			
	M	SD	M	SD	t	p
Acute stress (Feeling stress during the IVF procedure)	143.93	93.76	**145.17**	114.90	-.067	0.94
Chronic stress (Life events in the past year)	37.68	**9.28**	**39.34**	**9.28**	-1.04	0.29
Perceived or appraised stress (Stress caused by negative evaluation of events)	13.35	**6.**96	**15.41**	**6.**77	-1.77	0.07

Table 3. Simple and multiple analysis of the relationship between stress and demographic variables with pregnancy outcome.

Variables	Simple analysis			Multiple analysis		
	RRCrude	95% CI	p	RRAdj	95% CI	p
Acute stress	1	**0.99**-1	**0.**94	1	0.99-**1**	0.93
Chronic stress	1.01	0.98-1.05	**0.**29	**0.99**	0.94-**1.04**	0.83
Perceived or appraised stress	1.04	0.99-1.07	**0.**08	1.06	0.99-1.13	0.07
Age	1	**0.9**3-1.0**7**	**0.**90	1.01	**0.9**4-1.10	0.64
Education	**0.**99	**0.94**-1.03	**0.**71	**0.**97	**0.9**2-1.02	0.32
Infertility period	**0.**96	0.88-1.05	**0.**47	**0.**94	0.85-1.04	0.23
Cause of infertility	1.16	0.54-2.48	**0.**69	1.22	0.55-2.27	0.61
History of unsuccessful planting	1.12	0.55-2.30	**0.**74	1.29	0.57-2.92	0.53
History of abortion	1.04	**0.**44-2.43	**0.**92	1.05	**0.**40-2.75	0.91
History of mental illnesses	**0.50**	0.10-2.32	**0.37**	**0.**28	0.05-1.53	0.14
History of thyroid problems and diabetes	1.18	0.55-2.52	0.67	1.11	0.50-2.46	0.78

Based on the analysis using binomial logistic regression (relative risk analysis) (Table 3), the findings also show that there is no significant relationship between pregnancy outcome and the use of IVF treatment method in the three types of stress, namely acute stress (RR=1.01, 95% CI 0.98-1.05), chronic stress (RR=1.00, 95 % CI 1-0.99), and perceived stress (RR=1.01, 95% CI 1.05-0.98). Regarding perceived stress, p value is very close to the significance level (p = 0.08). By controlling the demographic variables of age, education, duration of infertility, cause of infertility, history of unsuccessful implantation, history of abortion, history of mental illness, and history of thyroid problems and diabetes in multiple analysis, no significant relationship has been found between pregnancy outcome and acute (RR=0.99, 95% CI 1.04-0.94), chronic (RR=1.00, 95% CI 1-0.99), and perceived stress (RR=1.06, 95% CI 1.13-0.99). Regarding perceived stress, here again, the p value is very close to the significance level (p = 0.07).

Discussion

The aim of this study was to investigate the relationship between experienced acute, chronic and perceived or appraisal stress with the outcome of IVF treatment in infertile women. According to the research results, successful pregnancy was achieved in 48 (27.9%) of the women participating in this study. This finding is very close to the results obtained in the studies by Gourounti, Anagnostopoulos, and Vaslamatzis, Azmoudeh et al., and especially Maroufizadeh, Navid, Omani-Samani, and Amini [22,39,40]. In the study by Gourounti et al., among the 160 patients participating in their research, 41 (26%) succeeded in pregnancy. in the study by Azmoudeh et al., on 160 infertile women under treatment, 20.6% succeeded in pregnancy, and in the study by Maroufizadeh et al., on 142 patients, 26.8% of the participants succeeded in getting pregnant [22,39,40].

The results of this study also show that the two independent variables of acute stress during IVF treatment and chronic stress due to current mental pressures caused by unpleasant life events in the past year are not correlated with the outcome of pregnancy with the help of IVF treatment. This finding, too, is consistent with the results of some other studies, such as Anderheim et al., Boivin et al., Donarelli et al., Maroufizadeh et al., and Nouri et al. [10,25,40–42].

Considering the variable of perceived stress measured using the Perceived Stress Scale, however, the issue is somewhat different. Perceived Stress Scale measures the quality of a person's cognitive evaluation of stressful events [37]. The questions of this scale are designed in such a way to measure the person's perception of unpredictable, uncontrollable and higher than the individual's tolerance stresses [37,43]. It has also been pointed out that the stress perception scale can determine whether a person's cognitive evaluation of stress has an effect on the formation of his/her disease or not [44]. Based on this, in this study, although the amount of perceived stress caused by cognitive evaluation of negative life events was not significant in two groups of successful and unsuccessful pregnancies at the confidence level of 0.05, the p value obtained from the difference between the two groups was very close to the level of significance (p = 0.07). Considering this, it seems that in future studies using larger samples, the difference may become significant. This can indicate that although the difference in acute and chronic stress between the two groups was not significant, these two

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types of stress do not have a significant correlation with the outcome of pregnancy with the help of IVF treatment. However, what makes the same negative events harmless for one group but pathogenic and harmful for another group, can be the quality of the cognitive appraisal of the events and the different perception of stress in one group as compared to another group. This means that the distress caused by stress can cause a reduction in successful pregnancy with the help of IVF treatment, especially when a person has an excessively catastrophic and irrational evaluation of the events.

In general, it should be emphasized that the role of cognitive evaluation in physical reactions to stress is undeniable. According to the psychological model of stress and disease, cognitive evaluation of life events causes emotional reactions, and emotional reactions, in turn, trigger physiological reactions and increase the risk of disease [45–47].

In addition, many of the reactions that initially occur automatically in response to life events take place following a series of complex cognitive evaluations that are not only useful but also increase the risk of various diseases. In this regard, it should be noted that the intensity of the neuro-endocrine response to stress depends on whether the stressor is evaluated as a threat or a challenge (an opportunity for growth) [48]. Accordingly, when, after cognitive evaluation, the stressor is considered a challenge, a mild fight or flight reaction is observed, while if, after cognitive evaluation, the stressor is considered a threat, the body will react strongly by activating the HPA axis and releasing cortisol. Following stressful events, hormones secreted by the HPA axis can cause a series of abnormal neuroendocrine changes and a negative effect on female fertility [49–51].

Conclusion

Based on the findings of this research, in two groups of successful and unsuccessful pregnancies, the differences in the three types of acute ($p = 0.29$), chronic ($p = 0.94$) and perceived or appraisal ($p = 0.07$) stress were not significant, although this difference in the latter type of stress (perceived stress) was very close to the level of significance. Therefore, considering that the difference in perceived stress between the two groups was very close to the level of significance ($p = 0.07$), it seems that in future studies using larger samples, this difference may become significant. This means that when patients have a more catastrophic appraisal of their stressful events, the negative consequences of stress will be more effective, and it can be mainly related to the negative outcome of pregnancy by in vitro fertilization treatment.

In summary, according to the findings of this research, it should be emphasized that among the three models of acute, chronic, and perceived or appraisal stress, it seems that a negative and catastrophic appraisal of life events can be mainly associated with serious damage to the ability for successful pregnancy with the use of assisted reproductive technologies, including IVF treatment. Accordingly, it seems that adding cognitive training in stress coping methods to IVF treatment can be beneficial for the success of this treatment.

Declarations

Acknowledgements

We would like to thank all those who helped us in implementing this project, especially the esteemed staff of the Yazd Reproductive Sciences Institute.

Conflict of interest

The authors declare no conflict of interest.

Ethical considerations

This study is approved by the Ethics Committee of the Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran. Participation in the study is voluntary and with the informed consent of patients.

Code of ethics

IR.SSU.RSI.REC.1393.313

Funding

This study is funded by the research Committee of the Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran.

Authors' contributions

The first, second, and fourth authors contributed substantially in the conception and design of the study. The fourth and third authors carried out the data collection. First to third authors analyzed and interpreted the data and drafted the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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