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Original Article

Psychological stress is related to treatment outcome in women undergoing in-vitro fertilization and Embryo transplantation

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Abstract: Objective: To explore whether psychological stress is related to treatment outcome in women undergoing in-vitro fertilization and embryo transplantation. Methods: A prospective cohort study was conducted in the Reproductive Medicine Center of a university hospital in Henan. 435 infertile women undergoing in-vitro fertilization and embryo transplantation (IVF-ET) participated in the study. The basal sex hormones were measured. Self-reported questionnaire (Fertility Problem Inventory) was used to assess perceived psychological stress. Then, we separated participants into three groups according to their total FPI scores and observed their IVF treatment outcomes. Results: Higher perceived psychological stress was related to a rise of FSH and LH and dosage of GnRha, while a decrease of retrieved oocyte counts, lower high quality embryo rate and clinical pregnancy rate. The results from the logistic regression analysis showed that high psychological stress was a risk factor of pregnancy failure of IVF-ET. Conclusion: Psychological stress was related to basal sex hormones and pregnancy outcome among women undergoing in-vitro fertilization and embryo transplantation.

Keywords: Infertility, psychological stress, hormone, pregnancy outcome

Introduction

Individuals perceive stress differently, and the importance of reducing stress in all aspects of daily living cannot be understated [1]. Increasingly, stress exposure has been proved to be related to pregnancy failure. Stress and reproduction are interrelated. Preconception stress could increase the risk of infertility [2]. In turn, the diagnosis of infertility and the concurrent medical treatment are rather stressful events for the couple, especially for women [3-5].

Psychological stress, behaving anxious and depressed, was negatively associated with a positive pregnancy outcome after IVF [6-8]. Impaired reproductive outcomes may be triggered by stress-inducing events and may be more prevalent in women susceptible to a physiological stress over-response [9]. Evolutionary theory has long been used to explain the relationship between human reproductive failure and stressful events [10, 11]. Therefore, psychological factor is an important factor and cannot be ignored in the process of infertility treatment, which directly or indirectly influence the therapeutic effect [12]. In fact, it is also one of the reasons that make couples drop out from the treatment of infertility prematurely [13, 14]. Conversely, some studies declared that psychological stress examinations could not predict pregnancy outcome in an assisted reproductive technology program (ART) [15, 16]. Outcomes are still unclear.

Oxidative stress may be associated with health outcomes and sex hormones have been shown to have antioxidant properties [17]. Adverse psychological conditions may lead to endocrine disorder. Sex hormone changes are the embodiment of the endocrine disorder. So, there is possible relationship between psychological stress and sex hormones. Sex hormones are closely related to fertility. In the process of IVF-ET, there are also many important laboratory indicators, such as retrieved oocyte counts, fertilization rate, cleavage rate and high quality

embryo rate, which also are greatly related to pregnancy outcome. However, most studies were designed to compare the different stress between pregnant and non-pregnant subjects only but not take individual hormonal variation and many laboratory indicators into account.

In this study, We hypothesize that psychological stress may influence sex hormones retrieved oocyte counts, fertilization rate, cleavage rate and high quality embryo rate, and then affect pregnancy outcome of IVF. In an attempt to further address this critical data gap, we will examine the relation of psychological stress to IVF treatment outcome through a more comprehensive assessment, including sex hormones, some crucial laboratory indicators and pregnancy rate.

Materials and methods

Population and eligibility

This prospective cohort study was conducted in the Reproductive Medicine Center of a university hospital in Henan. The study was approved by clinical ethics committee of the First Affiliated Hospital of Zhengzhou University from October 2014 to July 2015, 435 infertile women, who underwent in-vitro fertilization and embryo transplantation (IVF-ET), were enrolled participated in the study. Eligibility included the following: (1) primary infertility females diagnosed with pure tubal factor; (2) self-reported menstrual cycle length of 21-42 days; (3) females undergoing their first cycle of IVF using the standard long protocol for the controlled ovarian hyperstimulation (COH); (4) females not taking contraceptive, hypertensive and hormonic drugs in the past three months. All respondents were informed about the objectives of the study and the confidentiality of the date before they start to fill out the questionnaires, and signed consent forms as well.

Therapeutic methods

Patients were treated by a short-acting gonadotropin-releasing hormone induced dynamic agent (GnRHa, Diphereline, supplied by Ferring GmbH, Germany) for pituitary regulation, and used long luteal phase. One to three embryos were transplanted after 48 to 72 hours of oocyte retrieval. The standard number of embryo transplant was one or two embryos for females under 35 years old, and two or three embryos for females above 35 years old. Fourteen or eighteen days after transplantation, the concentration of women's HCG in their blood was measured. If the concentration of women's HCG was above 50 IU/L, it indicated biochemical pregnancy. Thirty-five days after transplantation, abdominal ultrasound was employed to examine the gestation sac. If gestation sac was found in or outside the womb t or villi was found through uterine curettage, it indicated clinical pregnancy; if gestation sac was not be found in the womb and mixed echo was found outside the womb, it indicated ectopic pregnancy.

Data collection

The socio-demographic and clinical data were collected by a questionnaire, which included age, height, weight, residence, duration of infertility, educational level, employment status, and net family monthly income and so on.

Exposure assessment

To assess perceived psychological stress, females completed a self-reported questionnaire before they drew blood on the morning of day 3 (follicular phase) of the menstrual cycle. The Fertility Problem Inventory (FPI), a 46-item self-administrated and multidimensional measure, is reliable and valid in assessing perceived psychological stress including social concern, sexual concern, relationship concern, need for parenthood and rejection of childfree lifestyle [18]. Each item was rated on a six-point scale from strongly disagreement (1) to strongly agreement (6). Responses were summed for a total score. Higher scores mean higher psychological stress. The Mandarin version of FPI got satisfactory psychometric properties and was used effectively to assess infertile Chinese couples [19]. In the present study, Cronbach's α was 0.77 for women.

Outcomes assessment

To assess the basal hormones, three milliliters of fasting venous blood samples were collected aseptically from each subject on the morning of day 3 (follicular phase) of the menstrual cycle. After centrifugation, serum was analyzed by Roche e411 electrochemical luminescence analyzer and its auxiliary reagents for detection

Table 1. FPI scores for three groups

FPI scores	Lowest (n=118)	Middle (n=199)	Highest (n=118)
Social	28.41±5.34	36.40±6.24	41.35±6.84
Sex	17.10±6.31	23.30±6.13	29.70±6.24
Relationship	29.24±6.27	35.34±6.12	42.94±8.06
Need for parenthood	31.39±7.02	36.39±6.93	41.61±7.75
Rejection of childfree lifestyle	18.12±6.65	25.42±6.18	29.29±7.34
Total	124.16±19.21	157.15±20.02	183.15±21.25

of sex hormones, including Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Prolactin (PRL), Estradiol (E2), Progesterone (P), Testosterone (T).

Laboratory indicators, which included duration of GnRha, dosage of GnRha, retrieved oocyte counts, fertilization rate, cleavage rate and high quality embryo rate were also examined.

Pregnancy outcome, including embryo transfer rate, biochemical pregnancy rate, clinical pregnancy rate and ectopic pregnancy rate were also recorded.

Statistical analysis

The socio-demographic and clinical variables were expressed through descriptive statistics. Comparisons of means and proportions were run by single factor variance analysis and x^2 tests, respectively. Means and SDs were computed for all FPI scores. Based on the 27% demarcation principle, females were separated into three groups according to their total FPI scores. Single factor variance analysis were used to find significant differences of hormone levels and some laboratory indicators and x^2 tests were used to compare the differences of proportions among different level of psychological stress of infertile women. Logistic regression analysis was carried out to explore whether (and to what extent) psychological stress contributed to the pregnancy outcome of IVF with case-mix adjustment. All statistical analyses were conducted using PASW Statistical version 17.0 (SPSS Inc., Chicago, IL, USA). Significance for all multilevel analyses was set at $P<0.05$.

Results

Based on the 27% demarcation principle, totally 435 females were separated into three groups according to their total FPI scores (the 27% lowest group, n=118; the 46% middle group, n=199; the 27% highest group, n=118). **Table 1** shows the FPI scores for three groups. The total FPI scores of the lowest group were 124.16±19.21, ranging from 102 to 138. The total FPI scores of the middle group were 157.15±20.12, ranging from 139 to 178. The total FPI scores of the highest group were 183.15±21.25, ranging from 179 to 238.

Table 2 describes the socio-demographic and clinical variables of three groups. The results showed that there were no significant difference in age, BMI, duration of marriage, residence, duration of infertility, educational level and employment status ($P>0.05$). However, the percent of higher net family monthly income in lowest group were significantly higher than middle and highest groups ($P<0.05$).

Table 3 presented the comparison of basal sex hormone levels, some laboratory indicators and pregnancy outcome in three groups. The level of FSH and LH, dosage of GnRha, retrieved oocyte counts, high quality embryo rate and clinical pregnancy rate were significantly different in three groups. The highest group had a higher level of FSH and LH, dosage of GnRha, but a less retrieved oocyte counts, lower high quality embryo rate and clinical pregnancy rate. The results of the logistic regression analysis were presented in **Table 4**. Psychological stress and age were significant factors related to pregnancy outcome (clinical pregnancy). After case-mix adjustment, high psychological stress was a risk factor of pregnancy failure of IVF-ET [odd ratio (OR)=-0.537; 95% confidence interval (CI): 1.009-1.028; $P=0.000$].

Discussion

The present study aimed to explore the relation of psychological stress and IVF treatment outcome. A more comprehensive assessment, including sex hormones, some crucial laboratory indicators and pregnancy outcome was examined in this study. We found that higher perceived psychological stress, measured by FPI in women undergoing their first cycle of IVF,

Table 2. Socio-demographic and clinical variables of three groups

	Lowest (n=118)	Middle (n=199)	Highest (n=118)	F/X^2	*P*-value
Age	30.29±4.88	30.02±5.42	31.06±5.15	1.511	0.222
BMI	22.51±3.04	22.16±2.95	23.08±4.77	2.482	0.085
Duration of marriage	7.06±5.23	6.03±4.912	6.53±4.856	1.621	0.199
Residence				2.477	0.290
Urban	65 (55.1%)	119 (59.8%)	60 (50.8%)		
Rural	53 (44.9%)	80 (40.2%)	58 (49.2%)		
Duration of infertility				4.695	0.320
<2 years	30 (25.4%)	58 (29.1%)	32 (27.1%)		
2~5 years	54 (45.8%)	96 (48.2%)	47 (39.8%)		
>5 years	34 (28.8%)	45 (22.6%)	39 (33.1%)		
Educational level				4.311	0.366
High school degree or below	51 (43.2%)	67 (33.7%)	44 (37.3%)		
Junior college degree	36 (30.5%)	59 (29.6%)	36 (30.5%)		
University degree or above	31 (26.3%)	73 (36.7%)	38 (32.2%)		
Employment status				0.823	0.663
Unemployed	19 (16.1%)	34 (17.1%)	24 (20.3%)		
Employed	99 (83.9%)	165 (82.9%)	94 (79.7%)		
Net family monthly income				9.916	0.042
<5000 RMB	44 (40.7%)	88 (44.2%)	55 (46.6%)		
5000~8000 RMB	30 (27.8%)	76 (38.2%)	42 (35.6%)		
>8000 RMB	34 (31.5%)	35 (17.6%)	21 (17.8%)		

was related to a rise of FSH and LH and dosage of GnRha, while a decrease of retrieved oocyte counts, lower high quality embryo rate and clinical pregnancy rate. From the logistic regression analysis results, we found that high psychological stress was a risk factor of pregnancy failure of IVF-ET.

Some studies showed that psychological stress was negatively associated with a positive pregnancy outcome after IVF. Conversely, other studies declared that psychological stress examinations could not predict pregnancy outcome in an assisted reproductive technology program (ART). So, the relation of stress and IVF outcome are inconsistent [6-8, 14, 15, 20-22]. However, most of these studies focused on anxiety and depression of infertile women, which was different from the present study focusing on perceived infertility-related stress as measured by FPI. Some studies even demonstrated an increase in pregnancy rate with psychological interventions [23, 24]. The present results were incompatible with the view of the effectiveness of the initial IVF cycle for any couple may be enhanced by moderate infertility-related stress as measured by FPI as well [25]. However, we found that moderate infertility-related stress was scored at 123.3±3.1, which was somewhat similar to our results of total FPI scores of 124.16±19.21. There is a saying goes 'of all who lack filial piety, the worst is who has no children', so procreation is very important in the traditional culture of China. Therefore, we might explain this difference by that women experienced more infertility-related stress in China than American, due to the deep-rooted traditional concepts about fertility.

All the activities of human body are regulated by neuroendocrine system. Stress significantly reduced the probability of conception each day during the fertile window, possibly exerting its effect through the sympathetic medullar pathway [26]. Chronic stress might affect the hypothalamic-pituitary-adrenal (HPA) axis [27, 28], while the HPA axis exert profound, multilevel inhibitory effects on the female reproductive system [29]. The normality of the hypothalamus-pituitary-ovarian (HPO) axis is a prerequisite for women's reproductive function. When an individual experiences psychological stress, HPO axis might be restrained by activated HPA axisdue to the chain reaction.

Table 3. Comparison of basal sex hormone levels, some laboratory indicators and pregnancy outcome in three groups

	Lowest (n=118)	Middle (n=199)	Highest (n=118)	*P*-value
Basal sex hormones				
FSH	7.10±10.55	7.18±3.96	9.85±10.12	0.008
LH	6.67±5.20	7.36±4.44	10.89±6.84	0.000
E2	63.56±54.63	61.69±70.92	55.56±50.80	0.572
PRL	15.73±8.80	19.93±31.76	23.30±47.60	0.214
P	1.11±1.09	1.13±1.44	0.88±0.65	0.145
T	0.61±2.21	0.40±0.38	1.26±6.66	0.125
Laboratory indicators				
Duration of GnRha (d)	11.08±1.71	11.26±2.65	11.23±1.99	0.790
Dosage of GnRha (IU)	1892.80±883.52	2052.43±1169.67	2246.02±836.42	0.028
Retrieved oocyte counts (n)	13.10±6.77	11.52±8.35	9.42±7.36	0.001
Fertilization rate (%)	66.93 (1016/1518)	66.22 (1537/2321)	65.32 (842/1289)	0.668
Cleavage rate (%)	82.38 (837/1016)	81.46 (1252/1537)	80.2 (681/849)	0.486
High quality embryo rate (%)	69.41 (581/837)	63.74 (798/1252)	59.18 (403/681)	0.000
Pregnancy outcome				
Embryo transfer rate (%)	78.81 (93/118)	78.39 (156/199)	73.73 (87/118)	0.564
Biochemical pregnancy rate (%)	61.2 (57/93)	60.25 (94/156)	50.57 (44/87)	0.258
Clinical pregnancy rate (%)	55.9 (53/93)	51.2 (80/156)	37.93 (33/87)	0.031
Ectopic pregnancy rate (%)	3.77 (2/53)	5.00 (4/80)	3.03 (1/33)	0.877

Table 4. Logistic regression analysis; whether (and to what extent) psychological stress contributes to the pregnancy outcome of IVF with case-mix adjustment

	B	SE	wald	OR	P	95% CI
Normal	-5.431	1.470	13.651	1.000	0.000	
psychological stress	0.018	0.005	15.096	-0.537	0.000	[1.009, 1.028]
Age	0.053	0.021	6.416	-0.406	0.011	[1.012, 1.099]
BMI	0.019	0.031	0.369	-0.340	0.544	[0.959, 1.083]
Residence	0.201	0.272	0.548	-0.348	0.459	[0.718, 2.083]
Duration of marriage	0.004	0.025	0.027	0.006	0.871	[0.956, 1.054]
Duration of infertility	0.163	0.168	0.948	-0.246	0.330	[0.847, 1.636]
Educational level	0.082	0.155	0.271	-0.279	0.602	[0.792, 1.487]
Employment status	-0.070	0.272	0.067	-0.373	0.795	[0.547, 1.588]
Net family monthly income	0.081	0.155	0.271	-0.221	0.602	[0.800, 1.469]

The present results showed that women with higher psychological stress had a higher level of basal FSH and LH in follicular phase, indicating psychological stress may affect endocrine function. Sex hormones produced by the HPO axis can promote the maturation of follicle cells. Clinicians might determine the ovarian reserve due to the lowest level of FSH on day 2 or 3 of the menstrual cycle. High level of FSH might predict poor prognosis of pregnancy. Scott *et al*. declared that females whose basal FSH was above 18 IU/L could not live birth babies [30]. LYU *et al*. suggested that the higher ratio of FSH/LH on day 2 or 3 of the menstrual cycle had the lower ovarian reserve and IVF pregnancy rate [31]. We t also found that with the rise of psychological stress, dosage of GnRha increased. However, there was no difference in duration of GnRha, possibly because of the decreased sensitivity of ovarian to the stimulation of GnRha caused by stress. Women with higher psychological stress had less retrieved oocyte counts, as stress may contribute to reproductive failure in critical windows of

gestational time [32] via anovulation. There was a decrease of high quality embryo rate in women with high psychological stress, which indicated that psychological stress had a negative effect on the embryo quality. High quality embryo is the key to IVF-ET, while high psychological stress might lead to impaired embryos. More recently a stress-compromised blighted fetal environment in utero has been proposed [33-35]. Stress was also associated with implantation failure [36] and dysregulation of placentation [37]. As a result, women with higher psychological stress had a lower clinical pregnancy rate. Besides, the logistic regression analysis results showed psychological stress and age were significant factors related to pregnancy outcome (clinical pregnancy). So we should take age into consideration together with psychological stress for predicting pregnancy outcome or providing psychological interventions.

The present study has several strengths. In the first place, the prospective cohort design allows us to detect more indicators in the process of IVF treatment, which presents a more comprehensive assessment in exploring the relation of psychological stress to IVF treatment outcome. In addition, we focused on chronic stress. Based on the view of infertility as a negative event, chronic stress is existed all the time during the process of IVF treatment. This is the reason why we focused on the FPI questionnaire, a widely validated disease-specific questionnaire for measuring chronic stress as a result of fertility problems [38], which enables the reliability of the present findings.

However, this study also has some limitations. For one thing, it has important limitations in observational design. For another thing, although we focused on chronic stress, stress might change to some extent. However, we didn't collect repeated questionnaires in the process of IVF treatment, so we were unable to examine the changes of psychological stress levels affected by treatment and other reasons. Therefore, a longitudinal research is recommended in the future. Furthermore, we only measured women's basal sex hormones. As sex hormones may change during the course of the menstrual cycle and treatment, we recommend further research a repeated detection to explore the relation of psychological stress and sex hormones.

In conclusion, the results of this study provide a further look at the perceptive association between psychological stress and infertility in a cohort of women undergoing their first cycle of IVF. High psychological stress was a risk factor of pregnancy failure of IVF-ET. To Taking effective psychological interventions to reduce the psychological stress may help patients pregnant successfully.

Disclosure of conflict of interest

None.

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