The Effect of Depression and Anxiety on the Outcome of Assisted Reproductive Technology (ART)

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تاثیر افسردگی و اضطراب بر پیامد درمان کمک باروری

خلاصه

مقدمه: موفقیت درمان کمک باروری می تواند وابسته به عوامل متغیری مثل سطح اضطراب زن در زمان درمان باشد. این مطالعه برای ارزیابی تاثیر افسردگی و اضطراب زنان بارور بر پیامد درمان کمک باروری طراحی شده است.

روش کار: این مطالعه موردی شاهدی بر ۳۰۰ زن نابارور داوطلب روش کمک باروری در مرکز ناباروری منتصریه دانشگاه علوم پزشکی مشهد انجام شد. بیماران با آگاهی و رضایت در مطالعه شرکت نمودند. پیش از استفاده از آنالوگهای هورمونهای آزاد کننده گنادوتروپین، از بیماران خواسته شد که پرسشنامه بررسی، اضطراب سرشتی و حالتی و نیز پرسشنامه بررسی افسردگی و نیز پرسشنامه مربوط به خصوصیات فردی آزمونهای حاملگی پانزده روز بعد از انجام IUI و IVF انجالم شد.

نتایج: هیچگونه ارتباط آماری قابل توجهی بین سطوح متفاوت افسردگی و پیامد درمان ناباروری وجود نداشت (P=۰/۱۹). این ارتباط بین سطوح متفاوت اضطراب و درمان ناباروری چشمگیر بود (P=۰/۰۱۶ و P=۰/۱۹). با افزایش اضطراب سرشتی و حالتی نتایج مثبت آزمون حاملگی کمتر محتمل بود.

نتیجه گیری: ارزیابی دقیق زنان با استفاده از یک گروه متخصصین شامل یک روانپزشک بالینی، یک روانشناس و یک متخصص زنان و زایمان برای کاهش اضطراب و حصول پیامد بهتر مورد نیاز می باشد.

کلمات کلیدی: روش کمک باروری، اضطراب، افسردگی، ناباروری

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Introduction

Infertility is failure to achieve pregnancy after a year of regular sexual intercourse without birth control. This problem is faced by 10-15 % of the couples (1).

Infertility has various causes which include: a problem in the woman (in 40-55 % of cases) or in the man (in 25-40 % of cases) or in both. In some cases no reason is found, which includes 10 % of the cases.

In the past few decades, new and more efficient techniques by the name of Assisted Reproductive Technologies (ART) have become widely available throughout the world to solve fertility problems. These techniques include hormonal stimulation, ICSI, gamete intra-Fallopian transfer (GIFT), IUI[1] and IVF[2], and their cost is, on average, considerable (1). There is substantial initial evidence that the psychological disposition of the parents-to-be influences their fertility and thus the outcome of fertilization techniques (2). IVF and IUI are among the common methods in this technology. Women undergoing IVF treatment are often anxious and depressed because of their infertility and the uncertainties of the treatment with which they have to deal (3). Indeed, epidemiological and anecdotal data suggest a relationship between psychological factors and infertility (4,5). However, a systematic review of controlled studies before 1990 presented contradicting results (6). More recently, one review (7) indicated the influence of psychological factors on the outcome of ART. The role of psychological factors in ART outcome has still to be established. As this knowledge is a prerequisite for adjuvant psychological interventions, the question has a major clinical relevance. Several statistical models have been published using combinations of biomedical factors in relation with ART outcome. The model of Templeton is well known: it is based on a large database and includes the factors age, duration of infertility, number of previous unsuccessful ART attempts, tubal indication for fertility treatment, and number of previous pregnancies as independent predictors (8). Others (9) identified two factors, i.e. at least two preceding gestations and age, to be significant in predicting ART outcome. It was also demonstrated that both models have limited external validity (9,10). A possible reason for the limited validity of the presented models is that they are based only on stable variables. Some studies, however, indicate that the success of assisted reproductive treatment may also be dependent on variable factors, such as a woman's distress level at the time of treatment (11, 12,13). The main objective of the current study, was to clarify the additional role of pre-existing anxiety and depression on ART results, controlling for known predictors.

Meanwhile, many factors affect reproduction strength, which can be named as follows: sports, smoking and alcoholic drinks, drugs, age, weight, and psycho-emotional problems (14).

Psychological stresses cause infertility through various mechanisms. In women, occupational and psychological stresses reduce reproduction. Such effects take place in the form of incidents leading to restraint of ovulation, change in oviducts movements, and lengthening of cycles.

Studies show that pregnancy happens in the cycles in which low-level stress and anxiety tests are indicated. Similarly, stress in men causes reduction of libido, reduction in the number of sexual contacts, impotency, disorder in spermatogenesis, reduction in the sperm quality, and consequently reduction in reproduction (15).

The prevalence of psychiatric morbidity specially depression and/or anxiety in the infertile people has been assessed by several authors (16,17). Ramezanzadeh et al (2004) found that in the total sample of 370 Iranian women with infertility,151(%40.8) had depression and 321 (%86.6) had anxiety (18).

Emotional reactions to infertility are not the same in women and men; the latter express it less often than the former, so that it may be interpreted as their indifferent to infertility; whereas, women react to it with stronger emotions and talk about it more frequently.

1- Intra Uterine Insemination
2- In Vitro Fertilization

In general, in every phase of infertility treatment such as acceptance of infertility or rejection of treatment, agreement to adopt a child, etc., a series of reactions emerge in the patient whose encounter and treatment require special psychological interventions (11).

Since successful treatment is declared to be 20% and, besides, such treatments are costly and time-consuming and accompanied by physical problems and contraindications, and with reference to the contradictory results from various studies concerning the effects of psychological problems on ART treatment outcomes and the high prevalence of psychological problems in Iranian patients, the present study aimed at determining the effect of depression and anxiety on Assisted Reproductive Technology.

Material and Methods

The research included a descriptive cross-sectional study performed on 300 infertile women who consecutively invited and agreed to participate. Before down-regulation by means of gonadotrophin-releasing hormone (GnRH) analogues, patients were asked to complete the State and Trait Anxiety Inventory (19). To measure anxiety, and the Beck Depression Inventory (BDI) (20, 21) to measure depression, individual specifications' questionnaires. All the infertile women referring to Montasariya Infertility Center of Mashhad University of Medical Sciences who were ART candidates filled out the personal specification form including: age of the man and the woman, the couple's education, their job status, and the number of children.

The cause and the length of infertility were also inquired from the patients' files. Furthermore, Spielberger's questionnaire was completed to control state and trait anxiety in the patient. The state anxiety refers to the person's anxiety level at a certain time and the trait anxiety denotes an innate tendency of the person to be anxious. Both criteria include 20 questions rating from 1 to 4 in which the highest rate indicates the highest anxiety level. Beck questionnaire was also completed for determining levels of depression. This questionnaire includes 21 questions grading from 0 (mild) to 3 (intense); thus its grading extends from 0 to 63. In this scale, numbers 0 to 9 indicates normality, numbers 10 to 19 shows mild depression, and numbers 20 to 29 denotes average depression, while 30 and over suggest intense depression.

Then, 15 days after ART, the treatment outcome (positive or negative pregnancy test) was determined through βHCG and the relation between the tests and the treatment outcome was examined by SPSS computerized statistic software on Windows XP and the relations between the dependent variable (successful and failed pregnancy) and independent variables (personal specifications of the respondent and the score of Beck and Spiegel Burger tests) were statistically analyzed by ANOVA statistic, logistic regression, and Ki-Square tests.

Results

Among a total of 300 questionnaires, 11 were eliminated due to incomplete response by the respondents and 289 were evaluated, out of which 61 had volunteered for IVF and 228 for IUI. No meaningful statistic relation was found between the education of the man or the woman and the treatment out come. The average age of the infertile women with positive pregnancy test was 27.59 and that of the group with negative pregnancy test was 29.02. No significant statistic relation was found between the age of these women and infertility treatment outcome, either ($p = 0.067$). The average age in the husbands of the women with positive pregnancy test was 32.69 and in those with negative pregnancy tests was 34.29 and there was no statistic relation between the age of these women's husbands with and treatment outcome ($p = 0.425$). Assessments indicated that simply the mother's age was effective in the treatment outcome and the other variables (the personal specification of the subjects) were of no effect ($p>0.03$ & $p = 0.23$). There was no significant statistic relation between the woman's occupation and infertility

treatment outcome (p = 0.058) and between the number of embryos and the pregnancy test result (p = 0.78).

Table 1, shows that 53.2% of the infertile women suffered from some kind of depression in different degrees. As it is noted, the percentage of positive infertility treatment outcome decreases with increase in depression intensity. Of course, there was no significant statistic relationship in this respect (sig = 0.19 & sig > 0.05) according to Manwithney test.

Table 1: Causality and treatment variables for pregnant and non-pregnant women in patients receiving ART

Positive Pregnancy Test	N(%)	**Negative pregnancy test**	
(by Causality of Infertility)		**(by Causality of Infertility)**	
Female	23 (29/9)	Female	54 (70/1)
Male	12 (14/6)	Male	70 (85/4)
Both	4 (13/2)	Both	32 (86/8)
undifferentiated	11 (11/3)	Undifferentiated	84 (88/7)
(by number of treatment)		**(by number of treatment)**	
No treatment record	20 (7/36)	No treatment record	103 (83/7)
One-time treatment record	20 (18)	One-time treatment record	91 (82)
two-time treatment record	6 (20)	two-time treatment record	24 (80)
at least 3time treatment record	4 (20)	at least 3time treatment record	21 (80)

The results of state and trait anxiety based on infertility treatment outcome are shown in Table 2. There were no positive pregnancy test results in the women with intense trait anxiety. According to Manwithney test, a significant relation was found between the intensity of trait anxiety and infertility treatment outcome (p= 0.014), and anxiety had a stronger relation with infertility treatment outcome than depression (Table 2).

The cause of infertility is shown in (Table 1). A significant statistic relation was found between the cause of infertility and the treatment outcome (p = 0.008). There were better pregnancy results in case of infertility cause for female reasons.

In order to examine the number of treatments and their effect on the treatment outcome, the people under study were divided into four groups: without previous treatment record one-time treatment record, two-times treatment record, and the group with at least three-time infertility treatment record both (Table 2).

Table 2: Psychological variables for pregnant and non-pregnant women in patients receiving ART

	Positive pregnancy test(%)	Negative pregnancy test(%)	Statistic X^2=pv	OR(95%Cl)
Intensity of State anxiety				
Mild	14(36/6)	29(67/4)	0/004	(1/36,5/84)
Low Average	16(18/4)	7(81/6)	0/000	(5/98,40/67)
High Average	12(10/5)	102(89/5)	0/014	(0/211,0/852)
Relatively Intense	6(16/7)	30(83/3)	0/92	(0/4,2/67)
Intense	2(20)	8(80)	0/08	(0/0671,1/23)
intensity of Depression				
Natural (0-9)	26(19/5)	108(80/5)	0/38	(0/71,2/4)
Mild (10-18)	19(19/8)4(10)	78(80/2)	0/46	(0/67,2/4)
Average (19-29)	1(5/9)	37(90)	0/168	(0/16,4/1)
Intense(30-63)		16(94/1)	0/172	(0/048,2/23)
Intensity of trate anxiety				
Mild	8(34/4)	15(65/2)	0/024	(1/13,7/13)
Low Average	21(19/1)	89(80/2)	0/528	(0/066,2/27)
High Average	16(14/2)	97(85/8)	0/138	(0/86,2/92)
Relatively Intense	5(14/3)	30(85/7)	0/615	(0/285,2/104)
Intense	0(0)	8(100)	0/24	incalculable

With the increase of treatment times the percentage of pregnancy was to some extent increased. However, no significant statistical relation was found in this respect (sig = 0.945 & sig > 0.05).

In the survey of the relation between infertility length and treatment outcome no meaningful statistic relation was found. However, there was a meaningful statistic relation between starting time of treatment and the infertility treatment outcome (p = 0.019). In other words, the sooner the treatment started the more probable was the satisfactory result in pregnancy. According to bimodal logistic regression test (with dependant variable of pregnancy test result, and independent variables of the number of follicles 13, 13-17, and above 17) there was a significant statistic relation between the number of follicles above 17 and the pregnancy result (p = 0.000); whereas this relation was not meaningful regarding the number of follicles 13-17 (p = 0.067).

In this study, out of 61 women candidates of IVF one embryo was transferred in 2.7% of the infertile women, two in 3.4%, three in 7.5%, four in 5.8%, and five in 1.4%. No meaningful statistic relation was found between the number of transferred embryos and pregnancy treatment outcome according to Manwhitney test (p = 0.78).

Discussion

The study results of Wiked and colleagues (2004) indicated that there are three types of relations between the psychological factors and infertility:

1. Psychological factors are risk factors for infertility.
2. Mental disorders can accure following the experience of diagnosis and treatment of infertility.
3. There is a relation between mental disorders such as anxiety and depression and infertility (14).

Different studies indicated that psychological factors may have an effect on treatment outcome. In our study, with an increase in anxiety, the infertility treatment outcome turned to be unsatisfactory. This result is consistent with the previous studies that found an association between anxiety and the results of *in vitro* fertilization. In these studies, the dependent variable was the outcome of IVF, either as pregnancies or births and the independent variable was anxiety (13,22-24).

As such, and the infertile women who applied earlier for treatment achieved better results. In this respect, our study results were similar to the results achieved in the above/study. In these studies, occupation and high age caused reduced reproduction and undesirable infertility treatment outcome. Stress and occupational pressures in women caused restrains in ovulation and thereby infertility. Similarly, psychological stress caused prolongation of treatment period of the infertile couples (1); whereas in our study such relation was not found.

The results of the study performed by Smeenk and his colleagues in order to determine the effect of anxiety and depression on IVF outcome on 291 infertile women indicated that there was a relation between psychological factors and the likelihood of pregnancy. Similarly, evident anxiety ($p = 0.01$) had a stronger relation with the treatment outcome than depression ($p = 0.03$); whereas in our study no significant statistic relation was found between depression and treatment outcome. However, with the increase of depression intensity the number of positive pregnancy had reduced and this relation was significant regarding state anxiety ($p = 0.019$) and trait anxiety ($p = 0.06$).

The study by Demyttenae and colleagues (1992) and Thiering and colleagues (1993) (23,24) indicated a relation between the increase of intensity in trait anxiety and depression and reduction in likelihood of pregnancy. The results of their study showed that it was more probable that with the increase in the intensity of psychological factors the infertile women would give up seeking for alternative treatments (10, 11); whereas, Boivin and colleagues and Merari and colleagues found no relation between stress levels and treatment outcomes (11, 25).

In a study that Demytienaere performed in 1998 to determine the effect of coping mechanisms and depression levels on IVF outcome, he examined the relation of factors such as infertile women's occupation, the length of their infertility, number of treatments, and number of transferred embryos to treatment outcome and found no significant statistic relation between these variables and treatment outcome (13). Similarly, no significant statistical relation was found between the length of infertility ($p = 0.145$), previous number of treatments ($p = 0.944$), number of embryos ($p = 0.78$), and treatment outcome in our study. Although, there were better pregnancy results in case of infertility cause for female reasons.

In view of the results attained about the effect of psychological disorders on infertility treatment outcome, it is advisable that such people undergo psychological and psychiatric counseling before starting of Assisted Reproductive treatments. So that, suitable solutions would be administered and better treatment outcomes achieved.

Limitations

In the present study the patients undergoing IUI and IVF have been studied together because of the small number of people in the IVF group. Our recommendation would be to re-evalute the findings in a larger patient group and separately for patients with IUI and IVF and also in multiple centers. Moreover, with the number of co-variables being limited to those found in the Templeton model, and the fact that logistic regression cannot establish the exact relationship among variables, causal inference should be made with caution. Finally, the possibility of selection bias cannot be excluded, as some patients indicated `stress' as a reason not to participate.

Conclusions

In conclusion, the current study shows that, in addition to some well-known biomedical

variables, state anxiety may have an independent contribution to explaining the variability in pregnancy rates using Assisted Reproductive Technologies. This effect is probably strongest in the implantation phase of the cycle. These findings are particularly important because in contrast to, for example, the factor of age, psychological factors may well be sensitive to interventions, thus increasing the chance of improving treatment results. If further studies supported this evidence, it would be possible to decide, more accurately, which couples should be the target of psychological counseling (26) improving the accessibility to these interventions, that are still used by only a few infertile couples (27).

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Abstract

Introduction: Success of assisted reproductive treatment may be dependent a variable factors such as the woman's distress level at the term of the treatment. This study was designed to evaluate the effect of anxiety and depression of infertile women on the outcome of ART.

Material and Methods: This case-control study was performed on 300 infertile women who volunteered to undergo ART in Montasariya Infertility Center of Mashhad University of Medical Sciences. They consecutively invited and agreed to participate. Before down-regulation by means of gonadotrophin-releasing hormone (GnRH) analogues patients were asked to complete the State and Trait Anxiety Inventory to measure anxiety, and the Beck Depression Inventory (BDI) to measure depression and individual specifications' questionnaires. Pregnancy tests were done 15 days after performing IUI and IVF.

Results: There were no significant statistical relation between different levels of depression and the infertility treatment outcome ($p = 0.19$). This relationship was significant between different levels of state and trait anxiety and treatment outcome ($p = 0.019$ & $p = 0.016$). With the increase of anxiety the positive result of pregnancy test was less probable.

Conclusion: An accurate assessment of the infertile women by a team of specialists consisting of a clinical psychologist, a psychiatrist, and a gynecologist is needed so that their anxiety would be reduced and better outcome achieved.

Keywords: Assisted Reproductive Technology (ART), Anxiety, Depression, Infertility

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