

The role of psychological distress in the outcome of in vitro fertilization

Uloga psiholoških teškoća u ishodu izvantjelesne oplodnje

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Summary

Introduction: Infertility affects a significant proportion of couples worldwide and may be associated with psychological difficulties. Assisted reproductive technologies (ART), including in vitro fertilization (IVF), provide a solution but are associated with emotional challenges such as anxiety, depression, and stress, which may impact treatment outcomes.

Respondents and methods: The study involved 200 women undergoing IVF at the Clinic for Gynecology and Obstetrics. Psychological distress was assessed using the CORE-OM questionnaire before treatment. One year later, respondents were contacted to determine IVF outcomes. Statistical analyses explored the association between psychological factors and treatment success.

Results: Higher levels of depressive symptoms were found to have negative implications for IVF outcomes. Regression analysis confirmed that depression was the only significant negative predictor of treatment success. Self-directed risk behaviors showed a trend toward significance, while anxiety and overall risk behaviors, although correlated with IVF outcomes, did not emerge as significant predictors in the regression model.

Conclusion: The results showed that higher levels of depressive symptoms were associated with less favorable IVF outcomes, while the association with anxiety was not confirmed in the regression analysis. Integrating psychological support into infertility treatment may contribute to improved success rates and enhanced well-being of patients. Future research should include biological factors and longitudinal designs to provide a more comprehensive understanding of the issue.

Keywords: Assisted reproduction, Infertility, IVF, Psychological distress

Sažetak

Uvod: Neplodnost zahvaća značajan dio parova širom svijeta i može biti povezana s psihološkim teškoćama. Metode medicinski potpomognute oplodnje (MPO), uključujući in vitro oplodnju (IVF), nude rješenje, ali su povezane s emocionalnim izazovima poput anksioznosti, depresije i stresa, što može utjecati na ishod liječenja.

Sudionici i metode: U istraživanju je sudjelovalo 200 žena uključenih u IVF postupak na Klinici za ginekologiju i porodništvo. Psihološke teškoće ispitane su pomoću CORE-OM upitnika prije početka liječenja. Godinu dana kasnije, ispitanice su kontaktirane radi utvrđivanja ishoda IVF-a. Statističke analize ispitale su povezanost psiholoških čimbenika s uspješnošću liječenja.

Rezultati: Utvrđeno je da više razine depresivnih simptoma imaju negativne implikacije na ishod IVF-a. Regresijskom analizom potvrđeno je da je depresivnost jedini značajni negativni prediktor uspjeha liječenja. Samousmjereni rizični ponašanja pokazala su trend prema značajnosti, dok se anksioznost i

ukupna razina rizičnih ponašanja, iako su korelirale s ishodom liječenja, nisu potvrdile kao značajni prediktori u regresijskom modelu.

Zaključak: Rezultati su pokazali da su više razine depresivnosti povezane s nepovoljnijim ishodom IVF-a, dok se povezanost anksioznosti nije potvrdila u regresijskoj analizi. Uključivanje psihološke podrške u liječenje neplodnosti može pridonijeti većoj uspješnosti i boljoj dobrobiti ispitanica. Buduća istraživanja trebala bi uključiti biološke čimbenike i longitudinalne dizajne radi sveobuhvatnijeg razumijevanja problema.

Ključne riječi: IVF, medicinski potpomognuta oplodnja, neplodnost, psihološke teškoće

Introduction

Infertility or reduced fertility is defined as the inability to conceive after one year of sexual intercourse without the use of contraceptive methods¹, or after six months in women older than 35 years². It occurs in 8 to 15% of couples^{3,4}. Medically assisted reproduction methods increase the possibility of achieving biological parenthood, with a long-term cumulative pregnancy rate close to 70%⁵. Even though in vitro fertilization (IVF) is one of the most challenging and stressful methods of infertility treatment⁶, meeting the criteria for inclusion in treatment increases optimism and hope in achieving biological parenting⁷. The implications of infertility treatment for emotional experiences and social relationships including coping with a certain probability of failure, physically and mentally demanding IVF, expectations of loved ones, feeling of guilt over the inability to fulfill a partner's desire for parenthood are just some of the potential causes of high anxiety levels⁸. Stress has been identified as the most common reason for giving up further treatment after failure in women already involved in infertility treatment methods⁹. In addition, there may be a negative impact of treatment failure on the relationship with the partner and anxiety caused by the thought of repeated medical interventions¹⁰. The nature of the procedure alone – the time and in some cases the financial complexity of IVF¹¹ can contribute to negative emotional reactions, increased stress levels and withdrawal¹². Intense psychological demands, especially if they are out of the ordinary, in people with a predisposition to psychosomatic reactions more often lead to anxiety and various mental and physical manifestations¹³. Although treatment failure results in feelings of disappointment, the risk of treatment is most often accepted as inevitable, and disappointment as an incentive for a new attempt¹⁴. It is likely that patients would try to explain the high level of anxiety related to assisted reproduction procedures by accompanying challenges – financial, time, family or business, and that it is actually a fear of medical interventions in the conception process that should be natural, or fear of challenges and demands of a parenting role with

which they have no experience yet¹⁵.

The failure of assisted reproduction methods is associated with feelings of loss, intense anger, high levels of anxiety^{16,17}, guilt, helplessness and hopelessness¹⁸⁻²⁰, and according to one study, 35.7% of women reported experiencing suicidal thoughts after unsuccessful medically assisted reproduction²¹. In a study that analyzed anxiety levels in women who conceived naturally compared to women who conceived using assisted reproduction methods, the results showed that there was no difference in the level of general anxiety, but anxiety related to the risk of complications in pregnancy or during childbirth and anxiety associated with separation from the child after childbirth were significantly higher in women who conceived using assisted reproduction methods²². Studies have confirmed the expected association between high levels of anxiety and negative infertility treatment outcomes, even more often than depression²³. This relationship is complex and two-way – the failure of assisted reproduction methods has been accompanied by a significant increase in anxiety levels²⁴.

Psychological stressors associated with infertility include negative self-image, feelings of guilt and shame²⁵⁻²⁹, as well as elevated levels of psychophysical stress and depression³⁰, anxiety, and somatization³¹. Women diagnosed with infertility often feel responsible for the inability to conceive, experience frustration, anger, and sadness, and question their sense of femininity and overall identity¹². Studies have also found that increased levels of anxiety and depression correlate with a lower rate of positive outcomes of IVF and pregnancy^{23,32}. Symptoms of depression can significantly predict the outcome of IVF²³. Infertility treatment may be associated with the development of depressive symptoms³³, and in women with a history of psychological disorders, worsening of symptoms may occur during infertility treatment³⁴. Symptoms of depression may also affect a patient's willingness to continue infertility treatment, according to a study of more than 39,000 women in assisted reproduction, which found that the average number of started cycles was significantly lower in women with depressive symptoms³⁵. Despite the association of lower IVF

positive outcome rates with depressive symptoms, a clear relationship between depression and conception failure has not been established due to the challenge of assessing depressive symptoms in patients and the difficulty in establishing a cause-and-effect relationship. However, identifying patients with depression at the beginning of the procedure could contribute to a better infertility treatment outcome. Additional counseling or psychotherapy should be provided to high-risk patients³⁶.

The aim of this study was to examine the level of psychopathological difficulties in women undergoing assisted reproduction and their role in treatment outcomes. It was hypothesized that the biopsychosocial model would be applicable in predicting the success of assisted reproduction, and that higher levels of psychopathological symptoms would be significantly negatively associated with treatment outcome.

Respondents and methods

Respondents

The study included 200 women referred to in vitro fertilization. The respondents' ages ranged from 25 to 45 years ($M = 33.9$; $SD = 4.3$). All respondents were diagnosed with infertility, and individual testing was performed at the beginning of treatment, prior to hormonal induction. The criteria for inclusion in the study were a diagnosis of infertility and signed informed consent. Exclusion criteria were diagnosis of mental illness or current psychopharmacotherapy. Most respondents (80.5%) were married, while others were in an extramarital union (15.5%) or not in a relationship at the time of the study (3.0%, including both single and divorced women). These categories reflect the respondents' self-reported relationship status and do not imply specific legal or medical circumstances. The majority (86.5%) had no children, 13.0% had one child, and 0.5% had two children. A high proportion of respondents (70.5%) had a higher education level, exceeding the average for women in the general population in Croatia. Most were employed (94.0%), while 6.0% were unemployed. The majority of respondents (83.5%) had no additional diagnosis besides infertility. Among those with a second diagnosis (16.5%), the most common were endometriosis and polycystic ovary syndrome (3.5% each), followed by hypothyroidism (3.0%), asthma (1.5%), and Hashimoto's syndrome (1.0%). Individual cases included type 1 diabetes, epilepsy, lupus, uterine fibroids, pituitary microadenoma, scoliosis, Crohn's disease, and spondyloarthropathy.

Instruments

Clinical Outcomes in Routine Evaluation – Outcome Measure (CORE-OM)

The CORE-OM is a comprehensive tool for measuring general psychological distress, consisting of 34 self-assessment items across four dimensions: subjective well-being, problems/symptoms, functioning, and risk behaviors³⁷. Items are rated on a 5-point Likert scale ($0 = not\ at\ all$, $4 = most\ or\ all\ of\ the\ time$), with higher scores indicating greater levels of distress. The problems/symptoms dimension includes four clusters: depression, anxiety, physical problems, and trauma-related symptoms. The functioning dimension is divided into two clusters: general functioning (e.g., ability to manage everyday tasks) and close and social relationships. The subjective well-being subscale assesses general emotional state and life satisfaction, without further clustering. The risk behaviors dimension includes two clusters: risk to self (e.g., self-harm, suicidal ideation) and risk to others (e.g., aggression). The questionnaire has good reliability and validity, with high sensitivity to change and significant differences between clinical and non-clinical samples. It is widely used in psychological care to monitor treatment effects and is sensitive to the presence and intensity of psychopathological issues. A critical value of 1 is proposed for identifying significant distress. The total score is calculated as the mean of all 34 items. Subscale scores are similarly computed as the mean of items within each domain: subjective well-being (4 items), problems/symptoms (12 items), functioning (12 items), and risk behaviors (6 items). Higher scores indicate greater psychological distress, and a mean score of ≥ 1 suggests clinically significant distress.

Socio-demographic questionnaire

A questionnaire of participant's sociodemographic and general characteristics was constructed for the purposes of this research. It contains questions about age, level of education, psychiatric diseases in personal anamnesis, other chronic diseases in personal anamnesis, duration of relationship with partner, number of children, duration of infertility, current number of IVF and the question of former use of psychological help.

Procedure

The research was approved by the Ethics Committees of the Clinical Hospital Center Zagreb

and the University of Zagreb, School of Medicine. All respondents were tested by the same person, ensuring standardization. The first part of the study was conducted from April 2018 to June 2019 at the outpatient clinic of the Division of Human Reproduction, Department of Obstetrics and Gynecology, Clinical Hospital Center Zagreb. Participation was voluntary with a high response rate (>90%). The respondents were informed about the study's purpose, data usage (for research only), anonymity, and signed informed consent. Personal phone numbers were collected solely for the second part of the study. The second part of the study, aimed at evaluating treatment outcomes, was conducted one year later via telephone. Respondents were contacted to self-report on the outcome of IVF treatment (e.g., pregnancy, delivery), the date of delivery if applicable, and whether they had required psychological support during the IVF process. Due to the study's design and the guaranteed anonymity of the respondents, medical documentation was not accessed or verified.

Statistical methods

Statistical analyses included: 1) frequency analyses and descriptive statistics for all variables; 2) multiple regression analysis to determine the contribution of individual predictors to the variance of the criterion variable (in this study, the criterion variable is the outcome of IVF, with predictor clusters and dimensions from the psychopathological difficulties questionnaire); 3) appropriate statistical procedures to determine differences between the arithmetic means of the observed variables. The normality of the distribution of continuous variables was tested using the Kolmogorov-Smirnov test, and the homogeneity of variance between two or more groups was tested using Levene's test.

Results

Descriptive statistics (mean, standard deviation) and Kolmogorov-Smirnov test results for all CORE-OM domains (Subjective Well-being, Problems/Symptoms, Functioning, and Risk Behaviors) are presented below in order to examine departures from normality. Kolmogorov-Smirnov test showed that the distributions of results on applied questionnaire were statistically significantly different from normal ($p < 0.01$; Table 1). deviation of the distribution from normality was expected for the distribution of results on the CORE-OM questionnaire. This result is in line with previous research that found that the

distributions of results on the CORE-OM questionnaire on the nonclinical sample were positively asymmetric and significantly deviated from the normal distribution, which was expected because the results represent a relatively rare occurrence of psychopathology in the general population. The respondents in this study in the context of psychopathological symptoms were a non-clinical sample. Given the above and the fact that deviations from the normal distribution were not extreme, as well as evidence that the application of parametric tests gives valid results on data that are not distributed according to the normal distribution, further procedures were performed by parametric statistical methods.

Table 1 Means, standard deviations and significance of the Kolmogorov-Smirnov test (CORE-OM; N = 200)

Tablica 1. Aritmetičke sredine, standardne devijacije i značajnost Kolmogorov-Smirnovljevog testa (CORE-OM; N = 200)

| | M | SD | p from K-S |
|--|------|------|------------|
| Subjective well-being <i>Subjektivna dobrobit</i> | 1.27 | 0.90 | 0.00 |
| Problems/symptoms <i>Problemi/simptomi</i> | 1.25 | 0.88 | 0.00 |
| Functioning <i>Funkcioniranje</i> | 3.15 | 0.61 | 0.00 |
| Risk behaviors <i>Rizična ponašanja</i> | 0.14 | 0.45 | 0.00 |

Table 2 shows the descriptive statistics based on the answers in the CORE-OM questionnaire. All values of risk dimensions and clusters were below the critical values for the female population in Croatia³⁸. However, if the value of 1 is determined less strictly as a common critical value, the results in the dimensions of subjective well-being (M = 1.26, SD = 0.89) and problems / symptoms (M = 1.20, SD = 0.87), and the clusters of anxiety (M = 1.54, SD = 0.95), physical problems (M = 1.43, SD = 1.06), depression (M = 1.03, SD = 0.92) and traumatization (M = 1.01, SD = 1.03) were relatively high.

One year after the initial testing, the respondents were contacted by phone to inquire about the IVF outcomes. Of the 200 respondents, 170 (85%) responded, 29 (14.5%) did not answer despite multiple attempts, and 1 participant (0.5%) had changed their phone number, making the contact information from the initial testing invalid. Among the 170 respondents, 76 (45%) were still undergoing assisted reproduction, 28 (16%) were pregnant, and 66 (39%) had given birth (Table 3).

Table 2 Descriptive statistics on CORE-OM questionnaire

Tablica 2. Deskriptivna statistika upitnika CORE-OM

| Dimensions and subdimensions of the CORE-OM questionnaire <i>Dimenzije i poddimenzije upitnika CORE-OM</i> | Min | Max | M | SD |
|---|------|------|------|------|
| Subjective well-being <i>Subjektivna dobrobit</i> | 0.00 | 3.75 | 1.26 | 0.89 |
| Problems/symptoms <i>Problemi/simptomi</i> | 0.00 | 3.58 | 1.20 | 0.87 |
| Depression <i>Depresivnost</i> | 0.00 | 3.75 | 1.03 | 0.92 |
| Anxiety <i>Anksioznost</i> | 0.00 | 4.00 | 1.54 | 0.95 |
| Physical problems <i>Tjelesni problemi</i> | 0.00 | 4.00 | 1.43 | 1.06 |
| Traumatization <i>Traumatizacija</i> | 0.00 | 4.00 | 1.01 | 1.03 |
| Functioning <i>Funkcioniranje</i> | 0.00 | 2.42 | 0.82 | 0.60 |
| General functioning <i>Opće funkcioniranje</i> | 0.00 | 3.00 | 0.92 | .66 |
| Social relations <i>Socijalno funkcioniranje</i> | 0.00 | 3.75 | 0.99 | 0.84 |
| Close relations <i>Bliskost</i> | 0.00 | 2.50 | 0.56 | 0.61 |
| Risk behaviors <i>Rizična ponašanja</i> | 0.00 | 4.00 | 0.12 | 0.38 |
| Risk to Self <i>Ponašanja rizična za pojedinca</i> | 0.00 | 4.00 | 0.12 | 0.39 |
| Risk to Others <i>Ponašanja rizična za druge</i> | 0.00 | 4.00 | 0.11 | 0.46 |

Table 3 Outcome of IVF one year after the first test
Tablica 3. Ishod IVF postupka godinu dana nakon prvog testiranja

| Outcome/Ishod | N | Percentage Postotak |
|--|-----|---------------------|
| Still in the IVF process <i>Još uvijek u postupku</i> | 76 | 45% |
| Pregnant/ <i>Trudna</i> | 28 | 16% |
| Gave birth/ <i>Rodila</i> | 66 | 39% |
| Total/ <i>Ukupno</i> | 170 | 100% |

The variable 'IVF outcome' was coded as an ordinal variable reflecting reproductive success: 0 = still undergoing treatment, 1 = pregnant, and 2 = gave birth. The table of correlations between the CORE-OM dimensions and clusters and IVF outcome shows a statistically significant negative correlation of the depression cluster ($r = -0.22, p < 0.05$), anxiety

cluster ($r = -0.15, p < 0.05$), the risk behaviors dimension ($r = -0.18^*, p < 0.05$), and the cluster of risk behaviors directed toward self ($r = -0.20^{**}, p < 0.01$) with the outcome of assisted reproduction (Table 4). Other dimensions and clusters of the CORE-OM were not significantly associated with IVF outcome.

Table 4 Correlation of dimensions and clusters of dimensions of the CORE-OM questionnaire with the outcome of IVF

Tablica 4. Korelacija dimenzija i klastera dimenzija upitnika CORE-OM s ishodom MPO postupka

| Dimensions and subdimensions of the CORE-OM questionnaire <i>Dimenzije i poddimenzije upitnika CORE-OM</i> | r |
|---|--------|
| Subjective well-being <i>Subjektivna dobrobit</i> | -0.07 |
| Problems/symptoms <i>Problemi/simptomi</i> | -0.15 |
| Depression <i>Depresivnost</i> | -0.22* |
| Anxiety <i>Anksioznost</i> | -0.15* |
| Physical problems <i>Tjelesni problemi</i> | -0.10 |
| Traumatization <i>Traumatizacija</i> | -0.15 |
| Functioning <i>Funkcioniranje</i> | -0.1 |
| General functioning <i>Opće funkcioniranje</i> | -0.14 |
| Social relations <i>Socijalno funkcioniranje</i> | -0.08 |
| Close relations <i>Bliskost</i> | -0.03 |
| Risk behaviors <i>Rizična ponašanja</i> | -0.18* |
| Risk to Self <i>Ponašanja rizična za pojedinca</i> | 0.20** |
| Risk to Others <i>Ponašanja rizična za druge</i> | 0.02 |

Note: $p < 0.05^*$; $p < 0.01^{**}$

Considering the observed correlations with the IVF outcome, significant beta coefficients were expected for some of the predictors. This was partially confirmed in the regression analysis (Table 5), where depressive symptoms ($\beta = -0.30, p = 0.04$) emerged as a significant negative predictor of IVF outcome. Self-directed risk behaviors ($\beta = -0.32, p = 0.05$) showed a trend toward significance. Although anxiety and the overall dimension of risk behaviors were correlated with IVF outcome, they did not prove to be significant predictors in the multivariate model. These results suggest that depressive symptoms are particularly associated with reduced IVF success,

while the role of self-directed risk behaviors warrants further investigation.

Table 5 Standardized and non-standardized coefficients of analyzed predictors and significance
 Tablica 5. Standardizirani i nestandardizirani koeficijenti analiziranih prediktora i značajnost

| Model | Unstandardized coefficients <i>Nestandardizirani koeficijenti</i> | | Standardized coefficients <i>Standardizirani koeficijenti</i> | t | p |
|---|--|--|--|-------|------|
| | B | Standard error <i>Standardna pogreška</i> | β | | |
| Constant <i>Konstanta</i> | 1.04 | 0.13 | | 7.89 | 0.00 |
| Risk behaviors <i>Rizična ponašanja</i> | 0.85 | 0.60 | 0.23 | 1.41 | 0.16 |
| Depression <i>Depresivnost</i> | -0.29 | 0.14 | -0.30 | -2.04 | 0.04 |
| Anxiety <i>Anksioznost</i> | 0.15 | 0.13 | 0.15 | 1.14 | 0.26 |
| Risk to Self <i>Ponašanja rizična za pojedinca</i> | -1.04 | 0.53 | -0.32 | -1.96 | 0.05 |

Discussion

This study examined the association between psychopathological difficulties and the outcome of assisted reproduction. The respondents were infertility patients undergoing assisted reproduction at the Clinic for Gynecology and Obstetrics, without diagnosed psychiatric disorders at the time. Most were highly educated, employed, and motivated to participate.

Compared to a previously published sample of women undergoing medically assisted reproduction in Croatia³⁹, the present study had a significantly higher proportion of university-educated women (70.5%). This difference was statistically confirmed using a chi-square test ($\chi^2(1) = 8.87, p = .003$). Furthermore, when compared to the general female population of similar age (25–34 years), where 51% hold a university degree⁴⁰, the difference remained substantial and statistically significant ($\chi^2(1) = 15.14, p < .001$). The average duration of infertility among the respondents was nearly four years ($M = 3.9, SD = 2.1$). This duration was significantly longer than the average reported in a previous Croatian study ($M = 2.02 \text{ years}$)³⁹, as confirmed by a one-sample t-test ($t(199) = 12.65, p < .001$).

CORE-OM results showed higher scores on non-risk than risk items, indicating distress levels more similar to the general than clinical population. Using a critical value of 1, elevated scores appeared in subjective well-being, symptoms/problems, and clusters of anxiety, physical issues, depression, and

trauma. Anxiety showed the highest average score, consistent with expectations regarding infertility-related distress^{17, 41, 42}. Clinically, at least one participant reached maximum symptom severity in risk behaviors, anxiety, physical problems, and trauma, suggesting the need for psychological support in such cases.

The anticipated association between psychological distress and assisted reproduction outcomes was only partially confirmed. Statistically significant negative correlations were observed with overall risk behaviors, symptoms/problems, and the clusters of depression and anxiety. However, in the regression analysis, only depressive symptoms emerged as a significant predictor of IVF outcome.

Several methodological limitations should be noted. The sample primarily consisted of women residing in highly urbanized areas, which typically offer better access to healthcare services, potentially limiting the generalizability of findings to broader populations. Additionally, the sample may have been affected by self-selection bias, as women experiencing more pronounced emotional difficulties may have been more motivated to participate in the study. Future research could consider alternative recruitment strategies, such as anonymous online surveys, to enhance accessibility, reduce potential bias, and reach a more diverse participant pool.

Future research should include biological factors and compare outcomes between women who conceive naturally and via assisted reproduction. Longitudinal studies would offer valuable insights

into emotional adjustment before, during, and after treatment, helping to identify couples at risk of severe emotional difficulties for early intervention⁴³.

Previous studies confirm that assisted reproduction significantly impacts emotional well-being and is more complex than its somatic aspects⁷. Women often associate infertility treatment with negative emotions such as frustration, shame, and feelings of inadequacy but rarely adopt constructive coping strategies¹¹. Given its global impact on well-being, infertility should remain a focus of social science research. Although this study did not directly examine patient education, the identified psychological distress among respondents suggests that providing timely and accurate information about assisted reproduction procedures might contribute to reducing emotional burden.

Conclusion

This study provided insight into the psychological functioning of women undergoing assisted reproduction, indicating elevated levels of distress, particularly in the domains of depression and anxiety. While the average scores on anxiety and depression were within the lower range of the scale, they still indicate the presence of emotional symptoms in a subset of respondents, suggesting the relevance of ongoing psychosocial support during treatment. The regression analysis partially confirmed the expected associations between psychological variables and the outcome of in vitro fertilization (IVF). Specifically, depressive symptoms emerged as a significant negative predictor of treatment success. Anxiety and risk behaviors, although correlated with IVF outcome, did not prove to be significant predictors in the multivariate model. These findings highlight the complex and multifactorial nature of emotional adjustment in the context of infertility treatment. While this study did not assess the effects of psychological interventions or educational efforts, the observed psychological distress underscores the importance of integrating routine mental health screening and support into fertility treatment protocols. Future research should build on these findings by employing longitudinal designs, including biological markers, and comparing outcomes with naturally conceiving populations to better understand the emotional trajectories and predictors of success in assisted reproduction.

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