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REVIEW

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Stress and Anxiety Levels in Couples who Undergo Fertility Treatment: a Review of Systematic Reviews

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ABSTRACT

Background: Infertility is an issue that affects many parameters peoples' lives, as individuals and as couples. Besides the physical and economic impact of infertility on the couples, there is a significant reflection of infertility on their mental health and well-being, which follows them from the moment of the diagnosis up until the end of their treatment.

Objective: The aim of this review was to investigate whether psychological factors such as stress, anxiety or depression have an impact on the assisted reproduction treatment outcome and whether the use of supporting methods may help couples to minimize their fertility related stress, anxiety and depression and improve the treatment outcome.

Methods: After a systematic search of the electronic databases, fourteen studies were included in this umbrella review. The included studies were systematic reviews and meta-analyses published between January 2015 and February 2020. The population of interest was women, men or couples facing infertility and undergoing fertility treatment. The included studies assessed the relationship between stress and anxiety in couples undergoing fertility treatment and the outcome of the treatment, the psychological state and psychological adjustment of the couples after a negative result and the impact of interventional methods for reducing stress, anxiety or depression on the psychological state of the couples undergoing treatment and their pregnancy outcomes.

Results: This review fails to provide a certain answer to our research hypothesis due to conflicting results in the included studies. However, it has been observed that couples who reported better psychological state or have been treated with an interventional method for psychological support, were more likely to adjust better to the treatment procedure and the outcome as well.

Conclusion: Psychological support and consultation

during assisted reproduction treatment is highly recommended by researchers and clinicians.

Keywords: assisted reproduction, IVF, ICSI, stress levels, anxiety levels, psychological support.

1. INTRODUCTION

Throughout the years of development in the field of assisted reproduction treatment techniques, the researchers have focused their interest not only on the medication and treatment improvements, but in the possible involvement of the psychological factor in the In Vitro Fertilization (IVF) outcome, as well. Supporting the couples with various psychosocial interventions and educating them in detail around their situation and treatment options, are procedures which researchers highly recommend to be adopted by assisted reproduction units (1-4).

Infertility is an issue that affects many parameters peoples' lives, as individuals and as couples. Besides the physical and economic impact of infertility on the couples, there is a significant reflection of infertility on their mental health and well-being, which follows them from the moment of the diagnosis up until the end of their treatment (4, 5). Especially in cases of negative result treatment, researchers have found long term maladjustment in relational and social level (6).

The purpose of this review was to highlight the conflicting results that are observed in the relevant literature and answer to the question whether the psychological factors such as anxiety, stress and depression can affect the assisted reproduction treatment outcome. Systematic reviews are described as the most reliable source of evidence to guide clinical practice and its purpose is to deliver a summary of the available pri-

mary research. With the number of systematic reviews increasing daily, the umbrella reviews have a clear role in evidence-based practice and decision making (7). The summary of systematic reviews, or an umbrella review, aims to provide an overall picture of findings when the available information is rapidly increasing, without repeating the searches and assess the risk of bias from the included studies (8).

By creating an umbrella review, we are able to summarize the findings of the available systematic reviews (8), which provide a wide scope on the psychological effects of infertility on the couples and on their pregnancy outcomes (9-12). Some included studies also provide information on the effect of psychosocial interventions on reducing infertility stress. Also, they investigate the possibility of better treatment outcomes as a result of providing a comparison of outcomes between couples who participated in an interventional group and those who did not (1, 3, 4, 5, 13).

2. OBJECTIVE

The aim of this review was to investigate whether psychological factors such as stress, anxiety or depression have an impact on the assisted reproduction treatment outcome and whether the use of supporting methods may help couples to minimize their fertility related stress, anxiety and depression and improve the treatment outcome.

3. METHODS

Search strategy

A systematic search of the electronic databases was undertaken from November 2019 to March 2020 to identify reviews that examined the levels of stress and anxiety in couples undergoing fertility treatment and their possible association to the treatment outcome. Also, this search included reviews that used psychological interventions of reducing stress and anxiety in an attempt of leading to better treatment outcome (higher pregnancy rates, better adjustment to a negative result). The electronic databases that were searched were MedLine, PubMed, Embase, CINAL, Cochrane Database.

For the systematic search of the databases the MeSH terms, PICO and PICO management elements were used, depending on the database, with the following terms: infertility, infertility stress, stress levels, anxiety levels, psychological adaptation, assisted reproduction treatment, in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and psychological interventions.

Other search methods were used, such as hand search in reference lists of the articles that were considered for inclusion, to include more studies that might have not to be identified through the database systematic search.

Inclusion and exclusion criteria

The included studies were systematic reviews and meta-analyses, published from January 2015 to March 2020, in the English language. The population of the included stud-

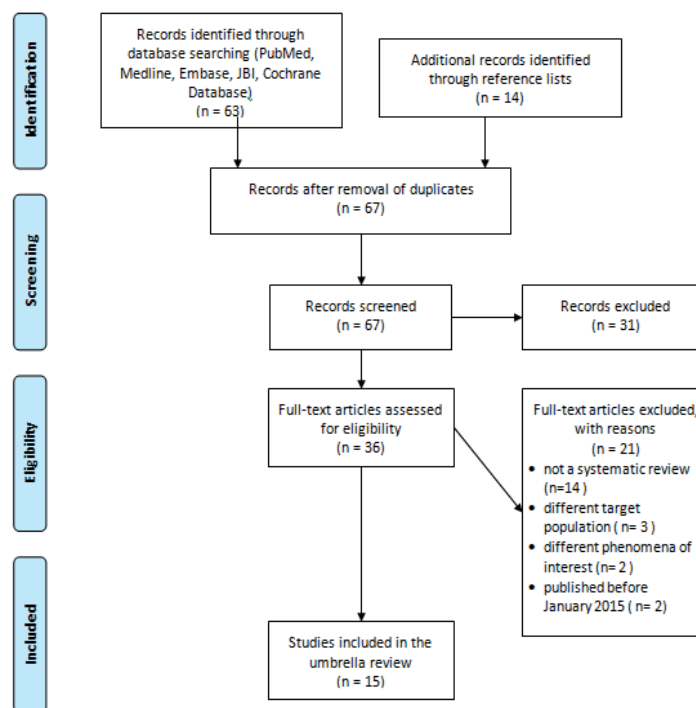


Figure 1. Selection of studies flow diagram.

ies were couples facing infertility that were observed from the moment of their consultation until the end of their treatment. The included studies assessed the relationship between stress and anxiety in couples undergoing fertility treatment and the outcome of the treatment. The research question was whether higher levels of stress, anxiety or depression were leading to lower pregnancy rates. Studies that provided information on the psychological state and psychological adjustment after negative result were also included. Additionally, studies that assessed the impact of psychological interventions reducing stress, anxiety or depression on women's psychological status and on pregnancy outcome were also included.

Study screening and study selection

For this review a total of 63 studies were extracted from the database systematic search and another 14 studied from manual search of literature. The study selection flow diagram can be found in Figure 1. The screening and selection of studies was performed in March and April 2020 using the ROBIS checklist for umbrella reviews (7). After the removal of duplicate articles, 67 articles remained for screening. At this point 31 studies were excluded based on the title or abstract examination. The remaining 36 studies were assessed for eligibility and 21 studies were excluded for the following reasons: 14 studies were excluded because the research method was not a systematic review of the literature, 3 studies developed their research around different target population, 2 studies observed different phenomena of interest and 2 studies were published before January 2015.

Assessment of methodological quality/critical appraisal

The 14 studies that met the inclusion criteria were evaluated for methodological quality, using the ROBIS criteria. The tool is completed in three phases, covering questions that are related to the effectiveness of interventions, etiology, diagnosis and prognosis of the systematic reviews and

meta-analyses (7).

Data collection and summary

From each study the reviewer extracted the maximum available information following the JBI data extraction tool for Systematic Reviews and research synthesis (14). This tool provides consistency in extraction of accurate data across the included studies. After all three phases of the tool are completed, the risk of bias in the review should be determined. The methodological quality and the extraction of data were performed by first and last author.

4. RESULTS

Methodological quality

All the included studies in this review have raised low concerns on the second phase of the ROBIS tool, regarding the specification of the eligibility criteria, the methods of identification and selection of studies, the appraisal for data collection assessment and the description of synthesis and findings. The risk of bias was also characterized as low, according to the third phase of the ROBIS criteria.

The results of the included studies will be presented in two categories. The first category will present the findings of the studies who investigate the relationship between psychological factors and the outcome of fertility treatment, and the second category will present the findings of the studies that investigated the efficacy of an interventional method for psychological support on both reducing distress and improving treatment outcomes.

Association between psychological disorders associated with infertility and the ART outcome.

In the current review, seven (7) studies provided data regarding the association between psychological factors and the assisted reproduction treatment outcome. Of the 7 included studies, 5 were meta-analyses and 2 were systematic reviews of the literature. The results were conflicting regarding the effect of stress, anxiety and depression on the treatment outcome (2, 9, 10, 11, 15). The mixed findings could be attributed to the small sample sizes of the aforementioned studies. A positive correlation of the psychological state of the participants with the treatment outcome was observed in cases of trait anxiety (2) and severe depression with an increased risk of residual symptoms in later life (9). However, in these cases it was not clear whether these measures varied from baseline to period during treatment or period after the end of the treatment. In 2018, Nicoloro¹⁰ and colleagues assessed the anxiety, depression and stress measure at baseline and during the treatment. The results revealed that these variables do not affect treatment outcomes, while moderators such as age and duration of infertility did not affect the levels of stress, anxiety or depression that was measured in the couples (10). Furthermore, Purewal¹¹ and colleagues found that increased depression and anxiety levels at baseline were associated with negative treatment outcomes. However, changes in these levels during treatment were not observed to affect the outcome (11).

Association between the negative ART outcome and the psychological adaptation.

Regarding the effect of assisted reproduction techniques on anxiety or depression levels, the results are mixed. In

the studies that investigated the psychological adaptation of the couples on a negative treatment outcome, the levels of depression and anxiety on both women and men were elevated after a negative result, the levels of marital stress and negative emotions were found elevated in women (15), couples also reported worse mental health and well being, with the period right after the negative result being one of intense grief and emotional pain (6). In these studies there was an improvement in their overall psychological state over time (6, 15). However, in the study of Gdańska⁹ and colleagues which measured the impact of fertility treatment on anxiety and depression, the researchers did not find an impact of the treatment on the psychological state of the couples. They found increased anxiety after multiple attempts without a risk of developing psychological or psychiatric disorders in later life due to ART (9).

In most studies the population that was participating was infertile women or couples undergoing fertility treatment, with the male population being underrepresented by the majority of studies. In one study that focused on gender differences in the psychological adaptation after a negative treatment outcome, men were identified having a poorer look on their relationship, as well as reporting lower marital satisfaction and interest in sexual relations (15). Another systematic review which focused only on the male psychological adaptation throughout the fertility treatment process, revealed that men felt less supported and involved in the process, reported worse mental health and sexual function after a negative outcome, with increased fertility related stress and depressive symptoms (16).

Association between interventional methods for psychological support, improvement of psychological parameters and fertility treatment outcomes.

In this review, six studies included that investigate the efficacy of interventional methods on improving the psychological state of the participants and measure the effect on the assisted reproduction treatment outcome. One of the included studies was a systematic review and a meta-analysis (13) and the rest were systematic reviews of the literature (1, 3, 4, 5, 12). The results are promising regarding both counseling and self-administered interventions (4,5,12). However, the researchers report small groups of participants and suggest the conduction of larger studies with higher methodological quality (3, 13), more strict time points in which the measures are undertaken, including the two weeks period of waiting between the embryo transfer and the test result (5). The interventions had positive effect on reducing fertility stress (4), distress, anxiety (1, 5, 13), improved fertility quality of life (1) and marital function (5). In these studies the interventional methods proved to have a beneficial effect on psychological factors and to the overall treatment experience as secondary results. The couples adjusted better to the treatment, were more likely to continue the treatment (1, 4, 12), supported their partner through the changes that the treatment and the outcome brought to their lives and reported better marital function as well (4, 5). Regarding the effect of psychological interventions on the pregnancy outcome the results were not consistent with some studies reporting similar pregnancy results between the intervention groups and control groups

(1,4), while other reported higher pregnancy rates in the intervention group (5, 12), with participants being twice as likely to become pregnant comparing to the control group (13). However, one review failed to provide certain results for any psychological pregnancy outcome in a primary or secondary level due to the level of heterogeneity between the studies and the reported biases by the researchers (3).

All of the studies included group and private counseling interventions, with group interventions providing better outcomes in a socioeconomic level with the participants reporting feeling less isolated and being able to afford continuing therapy for longer periods of time (4, 13). The types of counseling methods of which efficacy was investigated were mainly mind and body interventions and cognitive behavioral therapy, but other methods we mentioned as well, such as supportive interventions through telephone support and coaching methods (4), relaxation methods including yoga, meditation (1, 3, 4, 12), acupuncture (1) and hypnotherapy (3). There were some educational methods used as well, aiming to provide information for the cause of infertility and their treatment procedure (3), support changes in their lifestyle (12) and even help them reevaluate parenthood goals, make future plans and cope with a negative treatment outcome (5).

Besides the disagreement on the efficacy of psychological interventions on the treatment outcome, the included studies support the positive effect of interventions on psychological status of infertile couples. The uses of counseling, supportive and self-administered interventions during the procedure are encouraged by the researchers. Although the European Society of Human Reproduction (ESHRE) have format requirements for psychological counseling for infertility patients (12), it would be beneficial for the couples to be provided with a psychological support method delivered by fertility and health care practitioners (4, 5) even as a secondary outcome, meaning better adjustment in the lifestyle changes that assisted reproduction treatment implies. Couples with less anxiety are more likely to continue with their treatment, have a better overall experience regardless the result (12) feel supported by each other and make optimistic plans for their future after a negative result (5).

5. DISCUSSION

In this umbrella review the hypothesis that was investigated was whether psychological factors such as stress, anxiety or depression have an impact on the assisted reproduction treatment outcome. Even though the researchers did not agree on the degree that psychological factors impact on the outcome of the treatment (2, 9, 10, 11, 15), it has been observed that couples who reported lower levels of anxiety, stress and depression, or had received interventions with aspects of psychological support were more likely to adjust better to the treatment procedure, to the lifestyle changes that treatment implies, feel less isolated in their social cycle, function better into their marriage and accept their cause of infertility, the severity of their situation and the outcome as well (4, 5, 12). Therefore, even if neither stress or anxiety nor psychological intervention methods that are used to treat these psychological disorders have a proven impact on the treatment outcome, lower levels of

stress and anxiety and higher use of psychological interventions are beneficial as a secondary result in assisted reproduction treatments. The adaptation of methods for psychological support of the couples before, during and after their treatment by psychologists, healthcare practitioners and fertility clinics is strongly recommended by the majority of the included studies (2, 4, 5, 6, 11, 12, 15).

Some of the included studies investigated the emotional adaptation to a negative treatment result (6, 15, 16). After a negative treatment outcome researchers reported deterioration of mental health and well being, with elevated levels of depression and anxiety, which gradually improved over time, as they accepted the outcome, felt that they explored the available options and stated pursuing new life goals (6). Mind and body interventions as well as cognitive behavioral therapy are proven to be beneficial for coping with these emotions as well as reevaluating parenthood goals and making plans for the future (4, 5).

In a study focusing on the effect of depression and anxiety on ART outcome and the effect of ART in general on anxiety and depression levels revealed that anxiety levels were only elevated after multiple attempts and ART. Furthermore, increased anxiety levels caused by the treatment were not associated with higher risk of developing a psychological disorder in later life. However, the same study reported lower pregnancy rates in cases of severe depression with an increased risk of depression levels remaining elevated later in life. This study highlighted the need for early diagnosis of psychological and psychiatric disorders related to fertility stress and further investigation on the two way relationship between stress, anxiety and depression with ART (9). The results were optimistic once they did not reveal a permanent impact of assisted reproduction treatment on the emotional state of the couples but there is a need of further research in order to fully understand the long term impact of infertility and the experience of the couples with fertility treatments.

The limitations and weaknesses of the included studies that were commonly mentioned by the researchers were that the available information and measurements came from studies with a small number of participants (10, 11). Plus, the time points in which the measurements were undertaken varied between the studies (5) and the target populations did not provide variety in order to represent the majority of the people (1). Due to these limitations the results were conflicting regarding the effect of stress and anxiety levels on the treatment outcome. Nevertheless, it was proved that psychological interventions have a positive impact on fertility treatment as a secondary result. Group counseling is more effective than private counseling (13) and the most efficient interventional methods are cognitive behavioral therapy and Mind and Body interventions (1, 5, 12).

6. CONCLUSION

In this review the positive effect of psychological interventions on the couples undergoing assisted reproduction treatment has been proven as a secondary outcome. Psychological support improves women's or couples' emotional state, well being, adjustment to the treatment outcome and

their overall fertility treatment experience (1, 5, 7, 12, 13).

Recommendations for future research should be the development of tools that are able to detect fertility related stress for couples, regarding their gender, and single parent families. By limiting the participants to female and male couples, or female only, we will be missing information from a growing part of the population. Furthermore, it would be beneficial to conduct larger population studies which investigate the emotional and adaptation differences between partners who undergo fertility treatment, in order to find the most efficient method that helps them not feel emotionally separated, but to fully support each other throughout such an emotionally difficult period which is the assisted reproduction treatment period.

- **Authors' contribution:** PL initiated the research, conducted the field work, analyzed the data, and wrote the manuscript. KG gave a substantial contribution to the conception and design of the work, analyzed the data with PL and contributed in the discussion, interpretation of data and drafting the manuscript. AS contributed the discussion. All the authors have read and approved the final manuscript.
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