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ORIGINAL RESEARCH

Infertility-related stress, anxiety and ovarian stimulation: can couples be reassured about the effects of psychological factors on biological responses to assisted reproductive technology?

Zaira Donarelli^{a,*}, Gianluca Lo Coco^b, Salvatore Gullo^c, Angelo Marino^d, Aldo Volpes^d, Laura Salerno^a, Adolfo Allegra^d

^a ANDROS Day Surgery Clinic, Psychology Unit, Palermo, Italy; ^b Department of Psychological and Educational Sciences, University of Palermo, Palermo, Italy; ^c ANDROS Day Surgery Clinic, Medical Statistics Unit, Palermo, Italy; ^d ANDROS Day Surgery Clinic, Reproductive Medicine Unit, Palermo, Italy

* Corresponding author. E-mail address: zairadn@gmail.com (Z. Donarelli).



Group analysis psychotherapist Dr. Zaira Donarelli has been a member of the clinical and scientific staff of the ANDROS Day Surgery Clinic in Palermo (Italy) since 2003. Her research and publications involved the psychological aspects of infertility, including couples' dynamics, distress and quality of life. She is a reviewer for the following journals: *Human Reproduction*, *Journal of Reproductive and Infant Psychology*, *International Journal of Women's Health*, *International Journal of Fertility and Sterility*, *Reproductive BioMedicine Online* and *Sage Open*.

Abstract The aim of this prospective, longitudinal study was to examine the association between couples' pre-treatment psychological characteristics (state anxiety and infertility-related stress levels of both partners) and ovarian response during assisted reproductive technology treatment in a well-controlled sample. A total of 217 heterosexual couples (434 patients), suffering from primary infertility and undergoing their first assisted reproductive technology treatment at the Reproductive Medicine Unit of ANDROS Day Surgery Clinic in Palermo (Italy), were recruited. Psychological variables were assessed using the State Scale of State-Trait Anxiety Inventory (STAI-S) and the Fertility Problem Inventory (FPI). The number of follicles ≥ 16 mm in diameter, evaluated by transvaginal ultrasound scan on the eleventh day of the workup, was chosen as the outcome measure. No association between women's level of anxiety and infertility-related stress, and the number of follicles ≥ 16 mm in diameter was found. Moreover, the male partner's infertility stress and anxiety did not influence the relationship between the woman's infertility-related stress, anxiety level and ovarian response. Fertility staff should reassure couples that the woman's biological response to ovarian stimulation is not influenced by either partner's level of psychological distress.

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Introduction

Between 9 and 15% of the childbearing population experience infertility (Boivin et al., 2007) and 55% of infertile couples request treatment using assisted reproductive technology to address the issue (Bunting and Boivin, 2007). According to Boivin et al. (2011), many couples experiencing infertility believe that stress or anxiety contribute to the outcome of fertility treatment. A considerable literature has accumulated regarding the association of psychological distress with assisted reproductive technology outcome, and several hypotheses have also been put forward to account for the reasons why psychosocial factors and an individual's level of distress could be associated with the assisted reproductive technology treatment outcome. One hypothesis is that activation of the hypothalamic–pituitary–adrenal (HPA) axis during stress interferes with the gonadotrophin-releasing hormone (GnRH) pulse generator, the activity of which is required to cause a cascade of other hormonal events that undermine the reproductive function (Ferin, 1999; Lancaster and Boivin, 2005). Other proposals include behavioural effects, for example, that stress might trigger or be associated with behaviour or lifestyle decisions that may then compromise fertility (Boivin and Schmidt, 2005; Waylen et al., 2009).

Although much research has been conducted into the influence on outcome of psychological factors related to IVF and intracytoplasmic sperm injection (ICSI), the results are still inconclusive. For example, Smeenk et al. (2001) found a significant relationship between a composite baseline score of state anxiety and depression and a woman's chance of pregnancy in IVF/ICSI treatment (controlling for age and number of previous pregnancies). Also, Gourounti et al. (2011) found that, having controlled for biomedical factors, infertility-specific stress and anxiety were negatively associated with the chance of pregnancy after IVF in a sample of 160 infertile women. However, two recent meta-analyses do not support these findings. The first meta-analysis (Boivin et al., 2011) included 14 prospective studies, which examined the relationship between pretreatment emotional distress (evaluated through self-report measuring of anxiety, depression and psychological wellbeing) and pregnancy (operationally defined as clinical/preclinical pregnancy or live birth rate) in infertile women undergoing fertility treatment. The findings from this study supported the hypothesis that emotional distress, caused by fertility problems or other life events co-occurring with treatment, does not compromise the possibility of becoming pregnant. However, the authors affirm that definitive research on this link is still lacking. The meta-analysis by Matthiesen et al. (2011) also showed no significant association between depression and clinical pregnancy, and only a slight negative association between stress and clinical pregnancy, and between state or trait anxiety and clinical pregnancy.

The contradictory results from previous research regarding this topic may be due to several methodological shortcomings, in addition to the study design. For example, despite the majority of studies including patients who were undergoing their first IVF/ICSI treatment, as a group the participants are mostly heterogeneous in terms of causes and type of infertility.

In Boivin's et al. meta-analysis (2011), the main methodological limitations of the studies were the use of

convenience samples (non-consecutive or selected samples), failure to fully demonstrate the equivalence of pregnant and non-pregnant groups on prognostic indicators before treatment and the assessment of outcome after a single cycle of treatment with assisted reproductive technology.

It is also worth mentioning that the majority of studies regarding the association between psychological variables and the outcome of IVF/ICSI treatment used the realization of pregnancy as an outcome measure. Pregnancy after IVF/ICSI treatment is the final step in a chain of component events, such as the woman's response to pharmacological stimulation, the number of follicles obtained, the number and quality of oocytes retrieved, the quality of the sperm, the quality of the embryos and the embryo-transfer procedure. Assessments provided by medical staff, with regard to the quality of oocytes, the development of embryos or the skill of the oocyte retrieval and embryo-transfer operators, may also impact on the ultimate outcome of IVF (Angelini et al., 2006; Karande et al., 1999).

Despite the very early phases of IVF being critical for the outcome, no meta-analyses were conducted (due to the few studies available) to investigate the impact of depression, anxiety and stress on the initial measures (e.g. the number of follicles or oocytes) related to pregnancy outcome (Matthiesen et al., 2011). Several previous studies suggested that a woman's age, body mass index (BMI), FSH dosage, duration and cause of infertility and number/type of attempts (Broekmans et al., 2014; Rittenberg et al., 2011; Shen et al., 2003) may have an influence on the number of follicles observed during hormonal stimulation. Regarding the influence of a woman's psychosocial state, a study by Klonoff-Cohen et al. (2001) showed that the number of oocytes retrieved and fertilized, and embryos transferred, decreased with each increase in a woman's negative affect score on the Positive and Negative Affect Scale (PANAS) and Profile of Mood States (POMS) scales. Conversely, in the study by Smeenk et al. (2001) there was no relationship between baseline state anxiety (as measured by the State-Trait Anxiety Inventory [STAI]) and the number of follicles or oocytes in 291 women undergoing IVF/ICSI treatment. Ebbesen et al. (2009) found that negative life events experienced within the previous 12 months had a bearing on the number of oocytes obtained during oocyte retrieval, whereas there was no effect from perceived current stress, measured by the Perceived Stress Scale, in a sample of 887 Danish women undergoing their first IVF treatment cycle. Moreover, in the Nouri et al. study (2011), women's stress as measured by saliva and by the Fertility Problem Inventory (FPI; Newton et al., 1999) was not prospectively associated with a reduced number of oocytes in a sample of 83 patients undergoing their first IVF cycle. Interestingly, Lancaster and Boivin (2005) tested a model with a latent psychological factor (whose indicators were dispositional optimism, escapist coping and trait anxiety) to predict the ovarian response dimension (women's peak oestradiol level, number of follicles and number of oocytes) in a sample of 97 women who were about to begin IVF treatment; this provided evidence for shared variance among the three psychosocial variables and their correlation with women's ovarian response to stimulation. Taken together, the results from these previous studies do seem inconclusive, and again, several methodological flaws, as well as the clinical

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