

STRESS: AT WHAT POINT IN THE MEDICAL TREATMENT OF INFERTILITY SHOULD IT BE TREATED?

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New techniques help solve infertility. They include hormonal stimulation, intracytoplasmic sperm injection (ICSI), gamete intrafallopian tube transfer (GIFT) and in vitro fertilization (IVF). The psychological disposition of the parents-to-be influences their fertility, and thus the outcome of fertilization techniques. Fertility clinics offer consultation with a psychologist with a view to keeping in check the stress produced by the treatment itself. However, the evidence suggests a need to consider both chronic and acute stress levels, and to provide treatment for their reduction prior to commencing the (actual) fertility treatment. Lower stress levels mean better female and male fertility, though there is as yet no conclusive experimental evidence that lower stress levels result in better fertility treatment outcome. Even so, reduction of stress may reduce the number of treatment cycles needed before pregnancy is obtained and may prepare the couple for an initial failure of treatment; it may even make the more invasive techniques unnecessary. Primary psychological treatment for trait and state stress, being a less invasive method than IVF, ICSI or GIFT, should be applied wherever indicated.

Keywords: Assisted Reproductive Technology (ART); evidence; infertility; fertility; professional ethics; stress.

Técnicas nuevas ayudan a solucionar la infertilidad. Incluyen la estimulación hormonal, la inyección intracitoplasmática de espermatozoides (ICSI), la transferencia intrafalopiana de gametos (TIG) y la fertilización "in vitro" (FIV). La disposición psicológica de los padres aspirantes tiene influencia sobre su fertilidad y, por tanto, sobre el resultado de las técnicas de fertilización. Los centros de fertilidad incorporan la asistencia de un psicólogo con el objetivo de limitar el estrés producido por el mismo tratamiento. Sin embargo, la evidencia pide que se considere tanto niveles de estrés crónico como agudo, y que se traten ambos antes del tratamiento de fertilidad actual. Con niveles de estrés más bajos la fertilidad femenina y masculina mejora, aunque no exista aún evidencia concluyente de que el estrés más bajo resulta en un mejor resultado del tratamiento de fertilidad. Aún así, la reducción del estrés puede reducir el número de ciclos de tratamiento necesarios para conseguir el embarazo, puede preparar a la pareja para un fallo inicial del tratamiento o puede hacer innecesario el uso de técnicas más invasivas. El tratamiento psicológico primario del estrés crónico, además del estrés agudo, es un método menos invasivo que la FIV, ICSI o TIG y, por ende, debe ser aplicado siempre que esté indicado.

Palabras clave: Tecnología reproductiva asistida (TRA); evidencia; infertilidad; fertilidad; ética profesional; estrés.

Assisted reproduction techniques are of a medico-biological nature. Within reproductive medicine it is accepted that in this process psychology can have a significant, though always secondary function. Images of the IVF (in vitro fertilization) process, with microscopes, tiny needles, genetic-biological analyses and the like, widely publicized by the media and well-known among the general public, appear to underline the primacy of technology and laboratory techniques in the struggle to solve the problem of infertility. However, two facts lead us to question this view and ask: Might the role of psychology not be so secondary after all?

Fact number one is the low success rate of assisted reproduction technology (ART). Approximately 2% of all

conceptions in Europe are medically assisted, primarily through IVF (Hunfeld, Passchier, Bolt & Buijsen, 2004). Of these IVF treatments, just 15-20% achieve pregnancy the first time (Verhaak et al., 2005). It is acknowledged that the biological causes identified up to now explain only a part of unsuccessful IVF treatments. Psychological factors such as stress can have a negative influence on IVF outcome, and constitute causal factors of infertility (Lord & Robertson, 2005; Thiering, Beaufepaire, Jones, Saunders & Tennant, 1993).

Fact number two is the scant use that is made of psychological resources, either for the diagnosis or for the actual treatment of infertility. We recently found, in prestigious databases of medico-clinical studies on infertility (www.controlledtrials.com; www.clinicaltrials.gov), 206 studies in progress or recently completed, none of which includes any form of recognized psychological or psychosocial intervention.

In science, and hence in medicine and biology, but also in psychology, the goal should be the optimum evidence-based treatment. The effectiveness of treatments and therapies should be verified and published for the information of the professional community, but also –and very importantly– for that of people seeking to solve their problems. Professionals will prefer the evidence to be conclusive, though especially in preventive medicine and in those cases where there are only treatments that are *possibly* effective and without negative side effects, such treatments should not be discarded. It would be less than scientific to embrace high-tech intervention without taking account of relevant psychological factors and incorporating them in both diagnosis and treatment. Time and the evidence, indeed, are showing that this blinkered approach is mistaken.

Medical science demands robust experimental evidence that a particular procedure remedies the condition sooner or better than another, and sooner and better than no procedure or a placebo. In contrast, psychological science seeks experimental evidence that a particular procedure improves the chances of people being able by themselves to prevent or correct factors which, in the medium to long term, would affect quality of life and/or result in pathology. The medical and psychological goals differ not only insofar as the former seeks *certainties* and the latter seeks *probabilities*, but also with regard to the source of change, being either external –through medication or intervention– or internal –through cognitive, behavioural or psychodynamic changes.

The professional person or team involved in our area –fertility– can and should combine these goals and co-ordinate them to increase success rates and improve cost-effectiveness (Campagne, 2006). Preventive and supportive psychological treatments should be applied even when their efficacy has been established only in a provisional way –that is, they should be classified as “evidence-based” at a lower level of evidence than that which would apply to a medical treatment.

I shall continue with an outline of some of the neurobiological pathways through which stress may influence fertility, and review the experimental evidence as to such influence in healthy persons. This will be followed by a brief review of the available evidence in relation to the relevance of some of the “markers” for stress for IVF outcome. Finally, I shall discuss some of the technical and ethical reasons why fertilization techniques should include at least one serious attempt to reduce existing stress levels.

HOW DO STRESS AND FERTILITY INTERACT?

The majority of research on the interaction between emotional stress and infertility from the last 30 years has shown that although infertility causes stress, stress does not necessarily cause infertility. Various factors play a part in this difference, one of the most decisive being the chronicity of stress. Stress can provoke long-term changes in multiple neurochemical systems (Kaufman, Plotsky, Nemeroff & Chamey, 2000).

Stress involves the reciprocal and differential reactions of the hypothalamic-pituitary-adrenal (HPA) axis and of the noradrenergic and adrenergic nerves to different types of “stressor”, with physiological differences between the male and female response. Recent models consider many more interactions with other hormonal and neurobiological systems, such as the hypothalamic-pituitary-gonadal (HPG) axis or the sympathetic-adrenal-medullary system (see Figure 1).

Stress mediators can have both protective and harmful effects, depending on the time course of their secretion. In the long term they produce what has been called “allostatic overload”, meaning a change in the stability of important physiological systems, with negative consequences, affecting fertility (McEwen, 2005).

Stress differs from anxiety, and the biological markers are not conclusive with regard to its harmfulness. High stress is not necessarily perceived psychologically as anxiety, and vice versa. Sanders and Bruce (1999) established a relationship between psychosocial stress and female fertility, independent of stress hormone levels.

The early work by Selye (1950), who observed ovarian atrophy in rats exposed to stress, has been followed by a number of studies confirming the potential of stress to inhibit the HPG axis and affect fertility (Berga, 1966). However, attempts to isolate *single* causal links between stress and infertility have been less successful, which is unsurprising considering the complex nature of this relationship. Stress hormones and the HPA axis interact with hormones which affect fertility directly, such as GnRH, prolactin, LH and FSH, as well as with hormones that may interfere indirectly with fertility, such as cortisol, endogenous opioids and melatonin.

The fact that similar neurotransmitters and nuclei within the hypothalamus control stress and reproduction increases the possibilities for reciprocal interference. Other substances apparently unrelated to the HPA/adrenergic interaction have been seen to exert a

significant influence on fertility, as is the case of activated T cells in peripheral blood, associated with a lower implantation rate in women undergoing IVF (Dobson, Ghuman, Prabhakar & Smith, 2003; Gallinelli et al., 2001; Palter, Tavares, Hourvitz, Veldhuis & Adashi, 2001).

Traditionally, cortisol is considered a biological indicator of stress, but in the case of fertility things are not so simple. Serum glucocorticoid levels often, but not always, differ between women who conceive and others who do not, but follicular levels of glucocorticoid hormones, especially lower follicular cortisone and a higher cortisol/cortisone ratio, have been shown to have a significant effect on pregnancy rates in IVF. A link was found between fertility and the activity of the ovarian enzyme 11 β -hydroxysteroid dehydrogenase (11 β -HSD), which catalyzes the interconversion of cortisol and the biologically inactive cortisone (Smith et al., 1997). Other studies found significant differences in estradiol (E₂) and progesterone areas under the curve (AUC) in the luteal phase of women who conceived after IVF and those who did not (Czemczky, Landgren & Collins, 2000). Thus, stress may appear only in other substances or at other sites, or at very low levels, and cannot be determined through the measurement of glucocorticoids alone (Lewicka et al., 2003).

Stress has also been shown to have a negative impact on diverse parameters associated with semen quality, which, similarly, declines in patients undergoing IVF/ICSI (Clarke, Klock, Geoghegan & Travassos, 1999). Loss of glutathione and of free sulfhydryl content of seminal plasma due to stress play their part in influencing the quality and motility of sperm (Eskioçak et al., 2005), which are also affected by inhibition of the conversion of androstenedione to testosterone in Leydig cells on account of higher levels of adrenocorticotrophic hormone (ACTH) and cortisol (Klimek, Pabian, Tomaszewska & Kolodziejczyk, 2005).

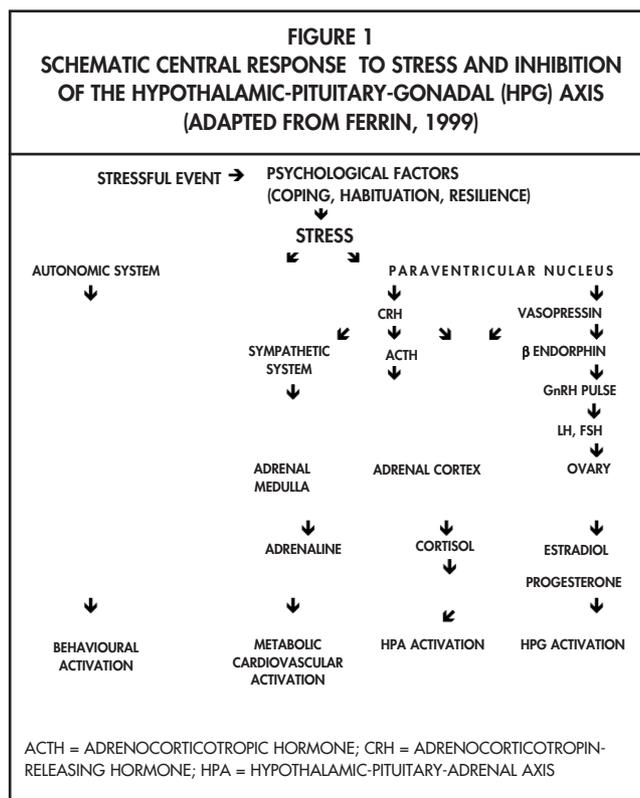
WHICH STRESS MARKERS ARE RELEVANT FOR IVF OUTCOME?

Table 1 provides an overview of the substances related to stress that can affect fertility in different ways. Anticipatory anxiety and high levels of anticipatory cortisol prior to oocyte retrieval (OR) and embryo transfer (ET) result in lower pregnancy rates, as do depression, high active coping, high avoidance and high expression of emotion (Smeenk et al., 2001, 2005). Older studies

used “traditional” biological markers, failing to find the significant links identified by recent work. This makes it essential to select a combination of markers with demonstrated relevance for fertility.

Stress or its negative associated mood state, anxiety, represents a threat to IVF/ICSI treatment outcome, but so does depression (Smeenk et al., 2001). Subclinical levels of depressive symptoms can have major health implications (Gold, Zakowski, Valdimarsdottir & Bovbjerg, 2004).

Different types of appropriate response to stress, or degree of “resilience”, determine its ultimate effects (Demyttenaere, Nijs, Ever-Kiebooms & Koninckx, 1991, 1992). Previous exposure to a chronic stressor significantly increases neuroendocrine reactivity to a novel acute stressor, though it is not necessarily reflected in the trait-stress questionnaires widely used in research (Gold, Zakowski, Valdimarsdottir & Bovbjerg, 2003). As mentioned above, neither do “traditional” biological stress markers necessarily reflect perceived stress. For example, anxiogenic norepinephrene impact is counteracted by the neuropeptide Y, whilst the impact of cortisol is counteracted by dehydroepiandrosterone (DHEA) (Rosenbaum & Covino, 2005).



These findings make it essential to measure stress before and during the fertility treatment, using a combination of biological and psychological means.

Moreover, there are differences in habituation underlying the chronicity of the impact of stress (Schommer, Hellhammer & Kirschbaum, 2003), which thus influence fertility in the long term.

REDUCING STRESS BEFORE FERTILITY TREATMENT COMMENCES

Personality dimensions, coping modes, susceptibility to stress and resilience correlate with IVF outcome (Klonoff-Cohen, 2005). These influences may contribute to infertility from well before the problem manifests itself. Hence, the acute stress caused by the fertility problem needs to be distinguished from chronic stress not causally related to infertility (Eugster, Vingerhoets, van Heck & Merkus, 2004).

Those studies of the influence of stress on fertility treatment outcome that measured both chronic (or "trait") and procedural (or "state") stress/anxiety did so with a measure in serum at the first consultation at the fertility clinic. However, the chronic stress score obtained then necessarily includes accumulated anticipatory stress, brought on by previous stages of the "infertility experience" that commenced the day the couple started

suspecting that something could be amiss. Moreover, it includes chronic stress due to other factors. Baseline acute and chronic stress affects biological end-points, that is, the number of oocytes retrieved and fertilized, but it also affects pregnancy, live birth delivery, birth weight and multiple gestations, whilst procedural stress only influences biological end-points (Klonoff-Cohen, Chu, Natarajan & Sieber, 2001). Stress itself increases treatment drop-out rates (Rajkhowa, McConnell & Thomas, 2006). Therefore, managing baseline stress is even more important than managing the stress brought on by the fertility treatment.

In order to protect the early embryo, the acute stress produced by or during the fertility treatment should be treated exclusively with psychological techniques or treatments, possibly complemented by dietary adjustments and changes in procedure. Chronic stress, however, would benefit more from treatment *prior to the fertility treatment* (Cwikel, Gidron & Sheiner, 2004). In either case, the approach should be tailored differentially to men and to women. The female response to marital stress, for example, differs significantly from the male response, and results in greater and more persistent hormonal and immunological changes (Kiecolt-Glaser et al., 1997, 1998).

The psychological treatments should be those that have been validated for *the particular situation of infertility treatment*, since many traditional remedies do not function in this context, or indeed make things worse. Efficacy is *male/female factor dependent*.

For both women and men, the short-term goal should be to reduce the patient's feelings of helplessness (see also Table 2).

With a view to structuring the application of the psychological measures, I propose the algorithm in Figure 2, which is based on the following premises:

1. It is not a specialist at the fertility clinic who makes the preliminary infertility diagnosis, but rather another physician, commonly the gynaecologist or the family doctor.
2. This physician should establish stress levels with the aid of validated questionnaires or refer to a psychologist to verify whether chronic stress plays a significant role. These measurements do not include the stress induced by visits to the fertility clinic.
3. Where indicated, stress reduction techniques are applied, and after 3 (?) months stress levels are mea-

**TABLE 1
MARKERS FOR STRESS**

Substance/Method	Relevance for acute /chronic stress	Relevance as stress marker for IVF outcome
Adrenaline	High	High (at OR*, ET**)
Noradrenaline	High	High (at ET only)
Adrenocorticotrophic hormone (ACTH)	High	High
Amylase	Variable	Questioned
Dehydroepiandrosterone	High	?
Cortisol	Variable	Site-dependent
Estrogen	Variable	?
Prolactin	Probable	Probable
Progesterone/Allopregnanolone	Variable	Questioned
LH	Probable	Probable
Vasopressin	High	?
Natural Killer cells (NK)	High	High
Cardiovascular reaction to provoked stress	High	High
Depression (even subclinical)	High	High
High active coping	High	Probable
High avoidance	High	Probable
High expression of emotion	High	High
State-anxiety	High	High
Self-reported state-anxiety	Questioned	Questioned
Trait-anxiety	Some	Some
Self-reported trait-anxiety	Questioned	Questioned

*OC = OOCYTE RETRIEVAL; **ET = EMBRYO TRANSFER

sured again with the same questionnaires. With these results the couple are referred to fertility treatment.

4. The fertility clinic verifies the stress levels again, this time both psychological and biological (see Table 1, for a selection) and compares the findings with the previous measures to determine the sensitivity to stress treatment.
5. If levels are still over established individual thresholds, another 3 (?) months of stress reduction is attempted.
6. When an acceptable stress reduction is obtained, fertility treatment is initiated with concurrent stress management for both.
7. If baseline stress remains above maximum thresholds, the couple are advised about the increased probability of a negative outcome of the fertility treatment and are recommended to continue with therapy until lower stress levels are attained. If despite the warning they insist, an informed consent sheet is signed and the fertility treatment proceeds.

Several studies present promising results of psychological interventions that yielded higher pregnancy rates (Domar et al., 2000). As mentioned, it is not clear which markers should be measured to assess stress levels. We cannot rely exclusively on objective thresholds of common biological stress markers such as adrenaline or cortisol, since there is considerable overlap of their levels between successfully and unsuccessfully treated women (Smeenk et al., 2005). To initially establish stress levels, a prospective trait-anxiety and state-anxiety questionnaire could provide screening data. The Questionnaire on Emotional Maladjustment and Adaptive Resources in infertility (*Cuestionario de Desajuste Emocional y Recursos Adaptativos en infertilidad*, DERA; Moreno, Antequera & Jenaro, 2008), designed and validated in Spanish population, assesses emotional maladjustment possibly caused by infertility or by the assisted reproduction process, and provides useful data for psychological intervention.

Further research is needed to determine the efficacy of additional or alternative interventions. In the meantime, treatment protocol should include closer monitoring of stress and its effects, together with early interventions to reduce stress (for more information, see the work by Ávila and Moreno-Rosset in this special issue). These interventions would benefit from closer physician-psychologist cooperation (see Table 3).

ETHICAL AND TECHNICAL REASONS SUPPORT THE MANAGEMENT OF STRESS PRIOR TO INITIATING FERTILITY TREATMENTS

The evidence currently available supports the following three assertions:

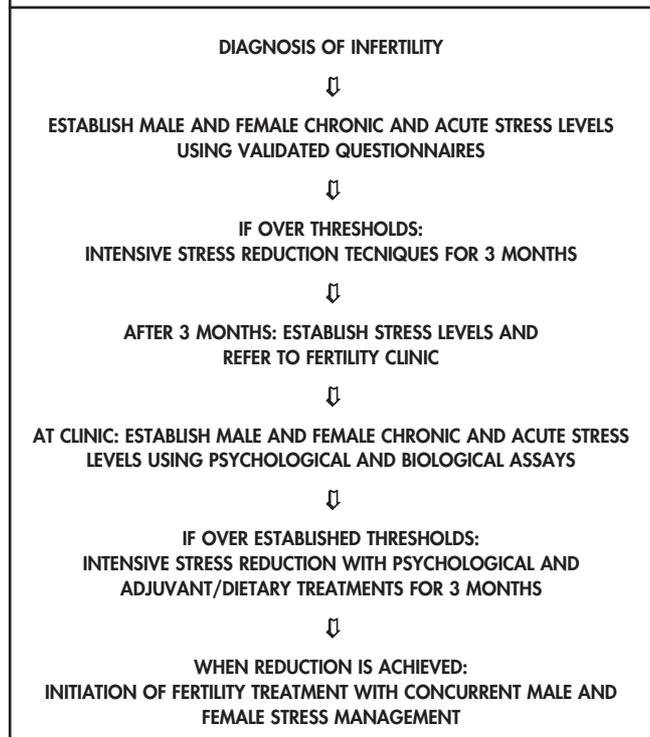
1. Infertility causes stress in the couple involved
2. Fertility treatments cause stress in the couple involved
3. Stress may be a primary or secondary cause of infertility

Professional ethics provides reasons of its own for accepting as valid all three assertions and for the physician to act in consequence. If psychology can help to solve infertility, then psychology should be applied as a

TABLE 2
SHORT-TERM GOALS FOR MALE AND FEMALE PATIENTS
(POOK 1999)

- ✓ Reduction of feelings of helplessness, through “coping” with infertility
- ✓ Changes in sexual behaviour
- ✓ Modification of negative cognitions as to infertility
- ✓ Overcoming deficiencies in knowledge about fertility
- ✓ Improving marital communication skills

FIGURE 2
ALGORITHM FOR ESTABLISHING STRESS LEVELS
PRIOR TO FERTILITY TREATMENT



first option before taking more invasive steps. The professional will apply less invasive treatments first. In this context, treatment protocol should consider stress as both a cause and a consequence of infertility.

The economic cost of infertility treatment is high. If better fertility is achieved through a primary reduction of acute and/or chronic stress, then this should be the guideline for private and public institutions alike.

For the biologist and laboratory technician, being in control of a fertility treatment requires that the number of biological variables be as low as possible. As we have seen, stress results in changes in a number of variables that are difficult to foresee and to control. The treatment cycle and its individual components will be under better control if the exogenous influences of chronic and acute stress are reduced or eliminated before the commencement of the treatment cycle.

CONCLUSION

Infertility is a relative matter, and depends on changes brought about by the human being, by nature or by chance. Acute and chronic stress may cause infertility, or reduce the success rate of fertility treatments. Stress acts through different mechanisms, and its levels cannot be determined by measuring only glucocorticoids or just state-anxiety. What is needed is cooperation between gynaecology, biology and psychology.

**TABLE 3
INTERVENTIONS FOR STRESS CONTROL AND
FERTILITY TREATMENT**

Procedural means:	<ul style="list-style-type: none"> - Protocols to include patient selection according to existing chronic stress levels and response to acute stressors - Preliminary treatments to reduce anxiety and depression before fertilization cycles are initiated
Psychological means:	<ul style="list-style-type: none"> - Cognitive-behavioural therapy - Relaxation training - Differential orientation as to infertility - Fertility sabbatical permit
Technical means:	<ul style="list-style-type: none"> - Frozen back-up semen samples taken at low stress moments outside the fertilization cycle - Further refinement of fertilization techniques (removal of the acrosome prior to ICSI (Morozumi 2005))
Neurobiological means:	<ul style="list-style-type: none"> - Establishing individual baselines and specific stress markers - Setting thresholds for referral - Monitoring for stress before and during fertility treatment

Acute stress should be distinguished from chronic stress. The evidence available suggests that fertility treatment protocol should include stress management and stress reduction as factors of major importance. Consensus should be reached on a protocol that establishes:

1. (very) early measurement of stress in the assisted reproduction procedure.
2. which absolute or relative thresholds should be considered threats to the success of the fertility treatment, indicating a need for pre-treatment to reduce levels of acute and chronic stress, and
3. which evidence-based treatments for this purpose can be recommended.

Stress reduction is a non-invasive, less expensive and ethically acceptable way of improving fertility. The professional in reproductive medicine should always verify stress levels before initiating fertility treatment, and adjust the selection and treatment protocol accordingly.

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