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Stress and human reproduction

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Summary

The interaction between emotional stress and infertility has been investigated for many years. Many infertile couples show marked stress during infertility evaluation and treatment. Most of the investigations that were performed during the last two decades show that in the majority of cases stress is the result and not the cause of infertility.

The biological interaction between stress and infertility is the result of the action of stress hormones at the brain level, especially on the hypothalamus-pituitary and on the female reproductive organs. Stress hormones such as catecholamines (adrenalin, nonadrenaline and dopamine) and the hypothalamic-pituitary-adrenal axis interact with hormones which are responsible for normal ovulatory cycles: i.e., gonadotropin releasing hormone (GnRH), prolactin, LH and FSH. Endogenous opiates and melatonin secretion are altered by stress and interfere with ovulation. Sympathetic innervation of the female reproductive system provides routes by which stress can influence fertility at the of the sex organs level.

Infertility causes stress which is aggravated as time passes and the couple remains infertile. Among the causes of stress are the couple's isolation, life with unrealized potential and unborn child, disruption of day-to-day life during infertility evaluation and treatment, and the couple's feeling that they do not have control of their own lives. The IVF program is considered by many as the final step for the evaluation of the couples fertility potential, hence, couples participating in an IVF program are highly stressed, especially after a failed IVF cycle.

Stress; Reproduction

The physiological interaction between stress and infertility

The body's response to stress

The body responds to stressful events – physical or psychological – by releasing 'stress hormones' which prepare its response to increased demands. These hormones regulate each other and, at the same time interact with other hormones which are essential for reproduction, and act directly on the reproductive system.

Stress increases the activity of the sympathetic nervous system and the adrenal medulla, which results in increased release of adrenaline (A) and noradrenaline (NA). With prolonged stress the activity of enzymes that synthesize A and NA is increased which therefore results in increased

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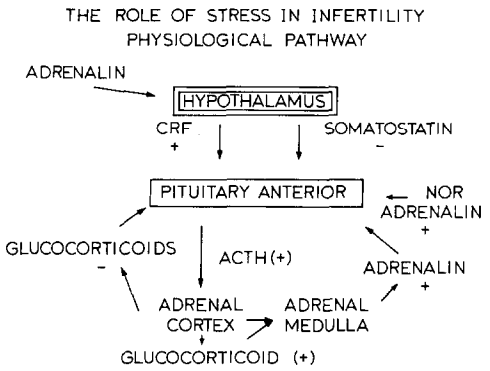

Fig. 1. The role of stress in infertility: physiological pathway.

concentration of A and NA in the blood stream and within the brain.

The hypothalamic pituitary adrenal axis is influenced by a variety of stressful events which cause release of ACTH from the anterior pituitary. Elevation of ACTH concentration causes increased release and biosynthesis of glucocorticoid hormones from the adrenal cortex and enlargement of the cortex. Cortico releasing factor (CRF) which is synthesized in the hypothalamus, is a major factor that positively influences ACTH release [1,2] (Fig. 1).

These stress hormones interact with each other as follows:

(1) Glucocorticoid hormones increase conversion of NA and A in adrenal medulla.

(2) CRF, NA and A increase ACTH secretion from the anterior pituitary. Glucocorticoids and somastatin decrease ACTH secretion.

(3) CRF stimulates central noradrenergic activity.

Central hormonal influence on the menstrual cycle

Catecholamines

Several studies showed that psychological trauma may lead to alterations in catecholamine concentration. NA is synthesized in cell bodies within the mesencephalom and lower brain stem. Its formation is extraordinarily plastic.

Under normal conditions the amount of NA available for release from nerve terminals remains constant despite moderate variations in body activities. NA secretion is regulated by short term mechanisms that involve first enzyme pathway – tyrosine hydroxylase, and occur primarily in nerve terminals. Severe stress results in long-term changes which last many days. These changes occur in cell bodies as a result of enzyme induction and formation of new proteins. Changes in NA secretion are seen in nerve terminals a few days after stress was applied [3].

Normal menstrual cycles are maintained by the pulsatile release of GnRH from the hypothalamus. Catecholaminergic secretions within a critical range of frequency and amplitude mediate GnRH release [4,5]. Medications that interfere with catecholamine metabolism disturb gonadotropin release and result in anovulation (Fig. 2). A common example is reserpine.

Pituitary functions are affected through changes in catecholamines concentrations that influence the pulsatile release of GnRH. NA measurements in human plasma during preovulatory period showed a marked rise in NA preceding or simultaneous with the LH surge [6]. Changes in NA levels are found in anorexia nervosa and may be responsible for the low basal gonadotropins in these patients [7]. Animal studies [5,8] conclude that NA stimulates GnRH by permissive mechanism, probably by affecting the membranes of the GnRH neurons. NA causes phasic discharge of GnRH, but synchronous release of GnRH neurons is not mediated via the NA mechanism.

γ-Aminobutiric acid (GABA) release impairs GnRH secretion. Rapid decline of the GABA tonus in the preoptic nucleous causes syn-

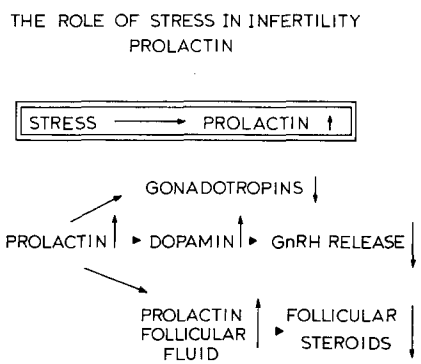

Fig. 2. The role of stress in infertility: physical or psychogenic.

chronous secretion of GnRH and secretion of pulsatile LH from the anterior pituitary [5,9].

Dopamine, which is the immediate precursor of NA, functions as a key neurotransmitter in the hypothalamus and pituitary gland. Dopamine concentration in the central nervous system is influenced by stress. Axo-axonic interactions exist between dopamine and the GnRH nerve terminals, and dopamin has a inhibitury effect on GnRH secretion. Increased dopamine secretion can be measured in patients with hypothalamic hypogonadotropic amenorrhea and in patients with anorexia nervosa. Blockade of dopaminergic receptors causes elevation of LH levels, which suggests that LH inhibition was due to increased dopamin activity [10–14].

Prolactin

Prolactin hormone levels are raised during chronic and acute stress [15]. A rise in prolactin exists even after administration of dopamine (dopamine is considered to be the prolactin-inhibiting factor). Administration of β-adrenergic blockade (propranolol) prevents the stress-induced increase in prolactin levels. This suggests another mechanism by which elevation of catecholamines concentration influences fertility during stress [12,15,16] (Fig. 3).

Elevated prolactin levels may cause infertility by three possible mechanisms:

(1) Women with high prolactin levels have elevated dopamine levels which supress GnRH release.

(2) High prolactin levels supress gonadotropins.

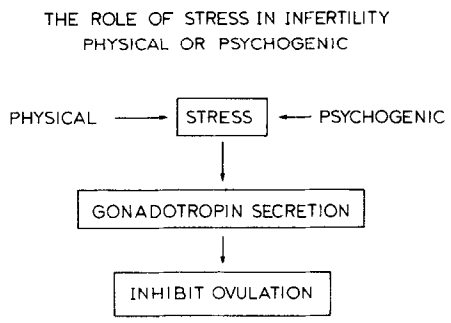

Fig. 3. The role of stress in infertility: prolactin.

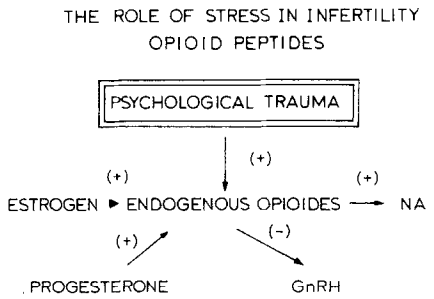

Fig. 4. The role of stress in infertility: opioid peptides.

(3) Elevated prolactin levels in follicular fluid suppress normal follicular steroidogenesis [17].

CRF, which is released during stress, acts within the brain in such a way that it inhibits LH release. The most probable hypothesis is that CRF release inhibits the secretion of GnRH [1].

Few data exist about the role of serontin in infertility. But, serontin levels are increased during stress, and may be responsible for the increasing levels of prolactin [18]. Serotonin may act by direct inhibition of GnRH secretion [10].

Endogenous opiates (Fig. 4)

Endogenous opiates are a group of polypeptides that are synthesized in the hypothalamus hypophysis, in different sites of the central nervous system and autonomic nervous system and in other tissues, such as the ovary, gastrointestinal tract and lungs. β-Lipoprotein was first discovered in 1964. Proopiomelantonin from the hypophysis is broken into ACTH precursor and β-lipoprotein. β-Lipoprotein has no opiate activity but is further broken into enkephalins, α-, β- and γ-endorphins and -dynorphins. Endogenous optiate levels are raised during stress and intense exercise [12,19].

β-Endorphin is 5–10-times more potent than the other opiates listed above. The hypothalamus produces β-endorphin as a major product with little ACTH secretion. The role of β-endorphin in body homeostasis is through cardiovascular and respiratory regulation, temperature homeostasis, pain perception and mood. β-Endorphins regulate hormones which are responsible for normal menstrual cycles and β-endorphin secretion per se is regulated by sex hormones. Opiod secre-

tion is raised after estradiol supplement and even higher levels of secretions are reached after estradiol and progesterone replacement [20]. Increased endorphin release causes decrease in LH levels [14]. The fall in LH levels is the result of GnRH suppression in the hypothalamus. β-Endorphins and dynorphins are the most potent opiates affecting GnRH secretion. This effect is by direct influence on GnRH release and also by elevation of the concentration of NA, which modulates GnRH secretion [10,12,14,21].

In conclusion, psychological trauma leads to elevation of central catecholamines and endorphines, which results in anovulation.

Melatonin

This hormone is secreted from the pineal gland. Reproductive performance in a variety of species is influenced by this hormone [22], especially in seasonal breaders. During day light hours the secretion of melatonin is minimal. With the onset of darkness the sympathetic central nervous system becomes active and releases NA into the pineal parenchymal cells, and thereby initiates melatonin synthesis and release [23]. The nocturnal release of melatonin can be suppressed by intense light [24]. Stress such as sustained excersice [25] and fasting [26] results in an acute elevation of melatonin.

Prolonged increase in melatonin secretion may cause amenorrhea [27]. The frequency of LH pulses is altered; however, this effect requires about 50 days to become evident [28]. The mechanism and site of action of melatonin are still uncertain, and, in fact, the negative correlation between the secretion of melatonin and the antigondal effects in humans could merely be a coincident [23]. However, most studies suggest that the effect of melatonin within the central nervous system is caused either by suppressing pituitary response to GnRH [29] or by inhibiting pulsatile GnRH secretion [30]. Preovalutory ovarian follicular fluid showes increased concentration of melatonin, which may cause direct modulation of ovarian steroidogenesis [31] (Fig. 5).

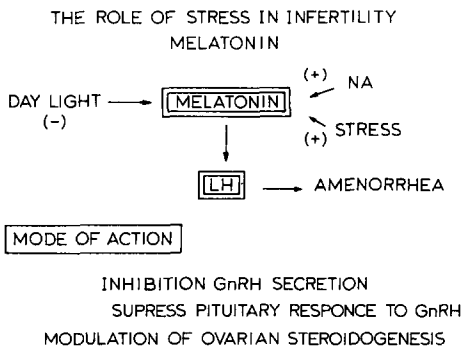

Fig. 5. The role of stress in infertility: melatonin.

Antononic innervation of the female reproductive organs

The pelvic viscera is rich in autonomic innervation – sympathetic and para-sympathetic. Emotional strain might influence reproduction through modulation of the autonomic nervous system. Within the ovary autonomic nerve terminals reach the perivascular interstitial areas and surround the follicles. Hence, autonomic innervation controls ovarian blood supply, ovarian contractility, follicular size and ovulation [32]. All secretory compartments within the ovary contain β-adrenergic receptors [33,34]. Activation of those β-receptors influence follicular development and hormone secretion. Those receptors are down regulated by epinephrine and corticosteroids and up regulated by LH and prolactin [32]. The ampuloisthmic junction and the uterotubal junctions within the oviduct are rich in autonomic nerve terminals. Changes in autonomic strain might influence the transport of ova through the oviduct. Autonomic nerve terminals in the uterus may change implantation rates [35].

The impact of infertility upon stress

In many cases stress and infertility co-exist. However, in most of these cases stress in the result of infertility and in only 5% of the cases stress is the sole cause of infertility [36,37]. Infertility causes stress in several ways, and the couple as a unit, the male and the female react in different ways to those stress stimulators.

The couple

Most infertile couples experience marked isolation. The social unacceptability of childlessness

may result in real stress exerted by the close surroundings, such as family and friends. This kind of pressure is especially strong among religious families. As years pass, social isolation increases because the couple does not participate in activities within the community that involve parents and children, and their psychological state deteriorates [38].

Menning [39] described the infertile couples as being in a mourning process about an unrealized potential and unborn child. This process bears all the known stages of any mourning process, e.g., state of shock, denial, anger and isolation, and at the end acknowledgement.

No empathy or support towards the infertile couple is shown by society because the problem of infertility is not understood. It is hard to sympathize, support and understand a mourning about something that never existed. Hence, the infertile couple has to deal with this problem on its own, and isolation and anger are aggrevated [36,37,40,41].

In modern society, life styles and career postpone the childbearing age and many couples encounter infertility problems in their late thirties. The feeling of shortness of time as the biological clock is approaching the end of reproductive age adds stress and guilt, and may strain the intercouple relationship. Psychological investigations of infertile couples, before they start the long exhausting way of infertility investigation and treatment, do not show any aberration from normal society. No higher percent psychopathology can be found in this group compared to the general population [10,42].

Infertility investigation itself contributes much stress. The couple meets the infertility team – nurse, physician etc. – which examine the couple and question their most intimate relations [43,44]. Investigation and treatment are demanding – endless bloodtests, repeated appointments, frequent ultrasound examinations, scheduled intercourse and afterwards appointments for post coital test (PCT). Painful procedures, such as hysterosalpingography (HSG), laparoscopy, hysteroscopy etc. are all time consuming and affect other aspects of life such as work and social activities.

In our IVF patients the main cause of stress is disturbance in day-to-day functioning [45]. In most countries all these treatments involve a lot of money.

The effect on the male

The psychological implications of infertility on the male partner were not intensely studied until lately. During infertility treatments, male performance is tested by repeated PCT and semen evaluation which markedly increase anxiety. Masturbation for semen collection is embarrasing and is performed, in many instances, in the clinic or the laboratory. The need for scheduled intercourse times or abstinence, and then during ovulation pressure to perform sexual intercourse, may lead to sexual dysfunction and increase stress. A common example is a periodic impotence when ovulation is expected without any sexual disturbances during other periods of the menstrual cycle [46,47]. A period of impotence has been described in more than 60% of male partners in couples who had recently been informed about the male's infertility [48].

Semen quality has been assessed during stressful conditions on the IVF program. Some reduction in semen quality has been found by means of total sperm count, grade of motility and fertility index. Though inherent variability in semen quality exists, repeated semen samples showed that the fertility index deteriorated 8 times more than it improved. Severe deterioration has been found in 8% of those couples which doubled the incidence of total fertilization failure [48,49].

Male infertility treatments are disappointing and very few modes of treatments are available. The success rate is low, which strongly aggravates the feeling of helplessness in these couples.

The woman

The question whether feminine psychological infertility exists is a controversial subject that has led to many research programs with inconclusive or even contradictory results. On the other hand, it is obvious that many infertile women who come to the infertility clinic are stressed.

In a recent investigation [42] significant emotional maladjustment was no more prevalent in

women coping with infertility than in the general population of women. A review of more than 30 articles, dealing with the effect of stress upon infertility, failed to show whether psychological problems trigger infertility, infertility triggers psychological distress, or that a casual relationship exists between infertility and psychological stress [50].

The effect of stress on infertility is shown during artificial insemination by donor (AID) treatment. Up to 25% fo women who were ovulating regularly and started treatment with AID turned to an anovulatory state for few months, and the only reason for this anovulatory period was stress [51].

An investigation for infertility is considered by many women to be the most stressful experience of their life, which affects every aspect of life. This painful experience was not something infertile women had learned to live with; many women felt controlled by the drive to achieve conception and were unable to concentrate on long-term goals [52]. Infertility investigations and treatment (physicians appointments, blood tests, scheduled intercourse etc.) may cause loss of control, which is described by most patients as the most stressful dimension of the infertility [52].

Infertile couples and especially the women revealed a profile of infertility strain reflecting tension, depressive symptoms, worry and interpersonal alienation [36].

Women in IVF treatment manifest high levels of emotional distress, especially anxiety, depression and hostility [45]. This sub-population of infertile women is one that experiences many years of infertility treatments, reach IVF program with high expectations and regard this treatment as the last chance to conceive.

The psychological impact of treatment failure

Many couples who undergo infertility treatment will eventually come to realize that they will never become parents of a biological child. This is described as 'the crisis of infertility'. At this point many couples experience a mourning response. Patients in IVF experience immediate psychological impact of a failed cycle. After a cycle failure both partners show a significant increase in anxiety and depression symptoms. The prevalence of mild to moderate depression is increased particularly among women [53].

In conclusion, stress and infertility coexist. In some cases infertility is the result of stress or stress aggravates infertility problems.

Stressed infertile couples suffer and find it difficult to cope with their infertility. It is most important that psychological counseling and support should be offered to couples suffering from prolonged infertility, especially to those couples treated by assisted reproductive technology. Therefore, a psychologist and social worker should be an integral part of an infertility team.

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