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REVIEW ARTICLE

Stress and Infertility – An Overview

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ABSTRACT

The present review crucially aims to highlight the relationship between various types of stress and change in male and female reproductive function. Chronic anxiety, depression, psychogenic distress, physical exertion–related stress consistently activates the hypothalamic-pituitary-adrenal axis. Almost each component of this activated axis, such as CRH, ACTH, β-endorphin and glucocorticoids exerts profound inhibitory effects on the hypothalamic-pituitary-gonadal axis and subsequently leads to reproductive failure in males and females. The pulsatile secretion of GnRH and the response of gonadotroph to GnRH stimulation are severely impaired. Increased levels of corticoids inhibit gonadal axis at the hypothalamic, pituitary and ovarian levels and concurrently result in deficient ovarian function. Similarly, the axis inhibits at the testicular levels and severely affects testosterone levels, sperm production and sperm quality. Therefore, it is clear from the present review that activation of stress systems could potentially influence reproduction at any level of the hypothalamo-pituitary- gonadal axis.

Key words: Stress, Male reproduction, Female reproduction.

INTRODUCTION

Any change in insidious and outside environment leads to the change in homeostatic balance in living life, stress as any threat, real or perceived, that compromises homeostasis [1]. Stress is essentially a result of chain reactions of neuroendocrine mechanisms, beginning with an excitation in the brain stem, followed by an increased secretion of hormones from the adrenal gland that keep the whole organism in a state of heightened alertness [2]. Others defined stress as “non-specific result of any demand upon the body” that may be mental or physical. The various physiological changes seen in response to stress are due to increased hypothalamo-pituitary action, activation of pituitary-adrenal system and secretion of various hormones [3, 4]. In fact, long-lasting or recurrent stress situations can be detrimental to health by inducing functional troubles and the effects are psychosomatic disturbances which, in the long run, can turn into organic illnesses [2]. Under the influence of stresses, various adaptive responses occur in the different biological systems, and if these stresses are frequent and intense and override a certain limit, the responses become pathological in nature. It has been well documented that one of the most important stress responses in the biological systems is an alteration in the rate and nature of secretion from classic endocrine glands [5, 6].

The "internal milieu" concept introduced by the French physiologist Claude Bernard analogy of that represent "external milieu" that is internal and external environment, the change in this milieu elicit response so called stress response ensuing change in reproductive function [7]. Experimental data in animal and human suggest that chronic or severe stress cause anovulation and amenorrhea in women [8] and to decrease in sperm count, motility and morphology in men [8, 9].

However, in many instances, stress has a more subtle, less defines influence or is associated with other factors that make the interpretation of observed effects more difficult. In addition, stress affects many endocrines and other regulatory system and thus resulting effects are usually not limited to change in reproductive functions. Nevertheless, there are some well defined syndromes induced or associated with stress that results in abnormal reproductive functions. Moreover, the neuroendocrine mechanism triggering the stress response and their hormonal signals are now better known [8, 9].

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Neuroendocrine mechanism during stress

The hypothalamic-pituitary-adrenal (HPA) axis has been known to be involved in the stress response for many years and a large number of reports have contributed information with animal and human data [10]. The main players in this axis are corticotrophin releasing hormone or factor (CRF), adrenocorticotropic hormone (ACTH) and cortisol. Since the discovery of structure of CRF by Vale and colleagues [11], many advances have been made to enhance our understanding of the mechanism mediating activation of HPA axis by stress and the subsequent changes in reproductive functions. In addition to CRF, several other brain neurotransmitters such as vasopressin, oxytocin, β-endorphin, angiotensin II, epinephrine, norepinephrine and serotonin among others are known to be involved in mediating and integrating the stressful stimuli [12]. Several of these have been called "'stress hormone" to indicate their primary role in stress response. In many instances, secretion or activation of the hormonal system serves as a biochemical marker to measure the stress response and in general, increased CRF secretion is almost always associated with an activation of HPA axis [13].

Catecholaminergic and serotonergic system is also marker for HPA activation during stress response and the interference with the action of these amines can result in blunted or nullified stress response. A close association also exists between the activation of CRF and central opoid (β endorphin) system. Secretion of CRF, vasopressin and some of the amines into the pituitary portal vasculature leads to an increased activation of the corticotrophins in the anterior pituitary and to an enhanced release of ACTH and β – endorphin [12]. The elevated level of ACTH increases cortisol secretion from adrenal gland which leads to a number of adaptive changes in metabolic activity. In addition to this neurohormonal pathway, there is also direct neural stimulation to the adrenal medulla which results in enhanced secretion of adrenaline. Under chronic stress situation, changes in the steady state of hormone level and in their metabolic clearance may occur and part of the process of adaptation may involve sacrificing certain functions, such as reproduction in order to maintain other vital functions [14].

Recent work has clearly demonstrates that enhanced CRF activity i.e., increased release within the brain into the pituitary circulation, leads to suppression of gonadotropin secretion and thereby decreased gonadal function. The intrinsic mechanism mediating this response is a direct inhibition of the activity of GnRH pulse generator by the CRF in the rhesus monkey [15] and to decrease GnRH in hypophyseal portal system [16]. Direct evidence for an inhibitory effect of CRF on gonadotropin secretion in the human has been provided by Barbarino *et al*. [16]. Authors showed that CRF infusion in normal women reduced plasma level of LH and FSH and this effect is abolished by the administration of naloxone, an opoid receptor blocker, suggesting that opoid peptide are involved in mediating the effect of CRF on GnRH and gonadotropin release both in human [17] and in animal [18]. The accompanying acute increase in cortisol level does not appear to be involved in mediating the inhibitory response [15, 17]. However, recent studies in the rhesus monkey demonstrates that chronic increase in cortisol secretion such as those seen in prolonged stress may lead to inhibition of gonadotropin release [19]. The mechanism appears to be a decreased function or activity of the GnRH pulse generator, which leads to decreased secretion of LH and FSH from gonadotroph of anterior pituitary, thus dysfunction of gonads and hence infertile.

Stress and human reproduction

Physical stress leads to low testosterone level due to a low LH pulse frequency [20]. The effect of surgical stress on the secretions of LH, FSH, testosterone (T) and estradiol (E2) were studied in male patients. Data of this study suggest that secretions of LH were increased during surgery and following surgical stress, T and E2 concentrations were suppressed resulting in a compensatory elevation of LH concentrations [21].

Many infertile couples show marked stress during infertility evaluation and treatment. Most of the investigations 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 [22]. Stress hormones such as catecholamines (adrenalin, noradrenalin and dopamine) and the hypothalamic-pituitary-adrenal axis interact with hormones which are responsible for normal ovulatory cycles: i.e., GnRH, prolactin, LH and FSH. Endogenous opiates and melatonin secretion are altered by stress and interfere with ovulation. Sympathetic innervations of the female reproductive system provide routes by which stress can influence fertility at the sex organs

level. Infertility causes stress which is aggravated as time passes and the couple remains infertile. The IVF program is considered by many as the final step for the evaluation of the couple's fertility potential; hence, couples participating in an IVF program are highly stressed, especially after a failed IVF cycle [22].

Emotional factors may negatively affect fertility in the male. Up to 10% of infertile males have had improvement in their semen analysis after cessation of all treatment for a prolonged period of time. The concept that emotional stress might lead to oligospermia was further supported in a report describing testicular biopsies obtained from men awaiting sentencing after raping and impregnating women. A more obvious effect of the emotional stress infertility places on the male is the occurrence of impotence. It has been estimated that up to 10% of infertility may be partially or completely explained on the basis of male sexual dysfunction [23].

The gradual unraveling of the complexities of neuroendocrinology has permitted increased understanding of the role that stress might play in infertility. Catecholamines, prolactin, adrenal steroids, endorphins, and serotonin all affect ovulation and in turn are all affected by stress [22]. Infertility is frequently perceived by the couple as an enormous emotional stress, and such stress might be result from infertility or habitual abortion. It is also appeared that a small percentage of patients do achieve pregnancy following adoption. Possibly this can be explained by a reduction in stress, and subsequently, alterations in the neuroendocrinologic characteristics of the infertile couple [23].

Stress and male infertility

Different studies showed that stress has negative impact on sperm parameters; mainly morphology, motility and density. Similar study evaluates semen profiles and revealed that sperm density, total sperm count, and both quantitative and qualitative sperm motility were significantly lower [24]. Another study provides evidence for a significant decline in semen quality of male IVF patients and demonstrates an inverse relationship between semen quality and specific aspects of psychological stress [25]. Further, in a study apparent association between emotional stress and quality of sperm was correlated negatively [26]. In a prospective study, the relationship between psychological stress and sperm concentration, motility and morphometry were evaluated. Sperm concentration, percent motility, and semen volume were determined in relationship to psychological job stress and life-event stress. The recent death of a close family member was associated with a reduction in straight-line velocity and percent of progressively motile sperm [27]. Although, another prospective study showed that the effect of a man's daily life psychologic stress on his semen quality is small or nonexistent and has effect of stress only on fecundability, and this only among men with low sperm concentration [28].

Psychological stress on male infertility was demonstrated, found to be associated with working in industry and construction as compared with other occupations. These patients also tended to smoke more than the other workers, more often worked in shifts and reported physical exertion in work and were more exposed to noise [29, 30]. Many of the reports indicated certain other disturbances of male infertility, such as impotence, sham ejaculation, retrograde ejaculation and oligospermia which have been associated with psychological factors [31, 32, 33].

Stress and female infertility

Stress on the reproductive axis in women is mostly derived from clinical studies of individual stressors and the cumulative effects of "real life" stress. Cortisol increases in response to a broad variety of individual stressors [34]. The association between daily fluctuations in women's urinary cortisol and reproductive hormones: estrone conjugates, pregnandiol glucuronide, luteinizing hormone, and follicle stimulating hormone were studied [35]. Nonetheless, the predominant impact is on the cortisol levels were associated with significant increases in gonadotropin and progestin levels during the follicular phase. When stress is prolonged, it is likely that secretion of the gonadotropins will be suppressed but the effects of acute stress or repeated acute stress are not clear [36]. Different stressors activate different pathways for varying durations, and the actions of stress vary with sex and are influenced by the predominance of particular sex steroids in the circulation. The mechanisms by which stress influences reproduction are likely to involve complex interactions between a number of central and peripheral pathways and these pathways affect the secretion and actions of GnRH, gonadal steroids and inhibin [37].

Occupational psychological stress is inversely associated with conceiving [38]. Work load, sporting activity is also important in female infertility [39]. Various studies have demonstrated the importance of the mind-body connection and

fertility. The fertility treatments, ranging from medical monitoring, to hormonal remedies and in vitro fertilization (IVF), are both a physical and emotional burden on women's psychological factors and stress-induced changes, and cortisol are predictive of a decreased probability of achieving a viable pregnancy [40]. Anxiety and depression in the in vitro fertilization (IVF)-failed women were significantly higher than the IVF-success women [41]. HPA axis, activated by stress, exerts an inhibitory effect through a stress hormone on the female reproductive system. CRH inhibit pituitary luteinizing hormone and ovarian estrogen and progesterone secretion. These effects are responsible for the "hypothalamic" amenorrhea of stress, which is observed in anxiety, depression and chronic excessive exercise [42].

In addition, corticotrophin-releasing hormone and its receptors have been identified in most female reproductive tissues, including the ovary, uterus, and placenta [43]. Intense exercise clearly can cause amenorrhea in women athletes [44]. Athletic amenorrhea is classified within the general category of chronic anovulation syndrome [45] in which several other exercise associated amenorrhea are present [46]. LH hormone is impaired at rest in normal menstruating athletes, acute exercise has an inhibitory effect on luteinizing hormone pulsatile release at the hypothalamic level in eumenorrheic athletes [47]. Regular strenuous exercise also evokes central pathway notably the opoid systems well as amenirgic and CRF system. During training program, an athlete may be subjected to many factors including loss of weight and fat, low weight and fat, acute and chronic hormonal changes, and physical and emotional stresses. Each of these, alone or in combination, may be associated with menstrual irregularity or amenorrhea [48].

Psychological distress and infertility

Psychological distress describes anxiety, depression and underlying psychopathology which are related to success or failure in conceiving, and proposed neurophysiological mechanisms that relate psychological status and fertility [49]. Psychological consequences of infertility presents infertility as a devastating experience, and shows overwhelmingly distressing effect for women than it is for men [50]. In a study of patients starting IVF-treatment correlates the variability in psychological distress and infertility-specific concerns and raise important questions for infertility counseling [51]. Psychological distress is high in a women suffering from abuse and are associated with infertility and female infertility expressed higher distress to infertility than their husbands. Although no differences in psychosocial responses were found among husbands, regardless of the diagnosis [52]. A couple that is trying to conceive will undoubtedly experience feelings of frustration and disappointment if a pregnancy is not easily achieved. The differences in psychological distress, marital satisfaction, and sexual satisfaction between Chinese infertile husbands and wives were evaluated and the study revealed that husbands expressed significantly less distress than that of the wives [53].

Psychological factors to infertility in women are depression, anxiety and stress-dependent changes [54]. Changes in diurnal excretion patterns of cortisol have been shown to accompany mental stress and to mediate the down-regulation of the hypothalamo-pituitary-gonadal (HPG) axis [55]. This impact could possibly involve inhibitory mechanisms at the pituitary level, by reducing the release of FSH and LH by GnRH [56]. Furthermore, research has shown that the effect of cortisol on the HPG axis is dependent on the endocrine status of the ovary in its different stages within the menstrual cycle [57]. Psychological distress significantly increases norepinephrine and cortisol concentrations and a lower concentration of norepinephrine and cortisol, both in serum and follicular fluid, were found in fertile women [58]. Concentrations of steroid in serum positively associated with the anxiety [59]. Norepinephrine and cortisol concentrations may negatively influence the clinical pregnancy. These biological stress markers could be one of the links in the complex relationship between psychosocial stress and infertility [60].

Gender differences in psychosocial responses were evaluated in a study and it revealed that infertile women showed higher distress than their partners on a global measure of psychiatric symptoms and subscales of anxiety, depression, hostility, and cognitive disturbances as well as on measures of stress and self-esteem [61]. Infertile men and women have negative emotional responses, such as stress, anxiety and depressions are both a physical and emotional burden on women and their partners [62]. Psychological factors such as depression, state-anxiety, and stress-induced changes in heart rate and cortisol

are predictive of a decreased probability of achieving a viable pregnancy [63].

Stress, adaptation and infertility

Stress can affect many aspects of physiology, and levels of stress, emotional status, and means of coping with stress can influence health and disease [64]. The stress system consists of brain elements, of which the main components are the corticotropin-releasing hormone (CRH) and locus ceruleus (LC)-norepinephrine (NE)/autonomic systems, as well as their peripheral effectors, the pituitary-adrenal axis and the autonomic system, which function to coordinate the stress response [65]. Activation of the stress system results in behavioral and physical changes which allow the organism to adapt. Adaptability leads to increased levels of glucocorticoids that promote gluconeogenesis, mobilization of amino acids, and stimulation of fat breakdown to maintain circulating levels of glucose necessary to mount a stress response. In addition to profound changes in the physiology and function of multiple tissues, stress and elevated glucocorticoids can also inhibit reproduction, a logical effect for the survival of self. Precise levels of glucocorticoids are required for proper gonadal function; where the balance is disrupted, so is infertility [66].

CONCLUSION

In many cultures, the social and familial issues regarding reproduction are of great importance. Hence it seems only logical to conclude that a couple failing to achieve the expected goal of reproduction will experience feelings of frustration and disappointment. It remains unclear whether stress and infertility are closely related, or that other parameters that affect stress are the important predictors of fertility. The majority of the studies rejected the theory of stress as a lone factor in the etiology of infertility. However, there is growing evidence that stress stands as an additional risk factor for infertility. It seems by the emerging evidence that more intervention studies should be conducted in order to assess whether reducing stress during fertility treatments can alter fertility treatment results. Meanwhile, collecting data regarding the couples stress level seems an appropriate approach, especially since many couples feel that health care systems do little to ease the psychological burden they experience during treatment. Despite extensive research, the mechanisms by which stress affects reproduction are unknown. But it is clear from the data that activation of stress systems could potentially influence reproduction at any level of the hypothalamo-pituitary- gonadal axis.

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