

Female infertility as a result of stress-related hormonal changes

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ABSTRACT

Introduction: Contemporary civilization provides a number of stress factors, and exposure to these factors disrupts the functioning of many systems of the human body. As a result of stress, organisms activate a complex range of responses involving the endocrine, nervous and immune systems. In normal conditions, when stress decreases, the stress response stops and the body quickly recovers and returns to its balanced state. Chronic stress that breaks homeostatic mechanisms, may lead to many changes, including the hormonal ones, responsible for fertility problems.

Aim: To highlight the influence of hormonal changes observed during chronic stress on the mechanisms engaged in female fertility.

Methods: Literature for this review was obtained from PubMed searches and relevant textbooks.

Main outcome measures: A brief overview of the impact of stress-related hormonal changes on fertility impairment in women.

Results: Stress-related hormonal changes may negatively affect the mechanisms ensuring successful female reproduction.

Conclusions: Hormonal responses observed during chronic stress due to permanent activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, may lead to different disfunctions, especially when homeostatic mechanisms are broken. A better understanding of the mechanisms related to chronic stress may contribute to a more detailed explanation of the causes of many female infertility cases.

KEYWORDS

Female infertility, stress, autonomic nervous system, catecholamines, glucocorticosteroids, thyroid hormones.

Introduction

Infertility, defined as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse, according to World Health Organization's statistics refers to 48 million couples and 186 million individuals globally^[1]. Based on wide cohort-studies performed in recent years in the United States, chronic stress is considered as a potential cause of female infertility^[2,3].

Stress is considered to be the state of real or perceived threat to homeostasis, which may challenge the well-being of the organism^[4]. Under stress conditions, organisms activate a complex range of responses involving the endocrine, nervous and immune systems, collectively known as the stress response^[5]. Studies in psychophysiology have revealed that the most important part of peripheral nervous system involved in stress response is the autonomic nervous system (ANS) which consists of two parts - the sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS). The SNS, for which the neurotransmitters are epinephrine (E) and norepinephrine (NE), causes arousal and physical changes (e.g., an increase in heart rate), while the PSNS maintains homeostasis through the release of acetylcholine (ACh), which essentially exerts the opposite effect. Simultaneous activity of these two nervous systems is mutually exclusive; one cannot be aroused and relaxed

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at the same time. Thus, under stressful conditions, affecting the SNS and preventing PSNS from activity disrupts homeostasis^[6]. Homeostasis is the key feature of any system in which its variables are set in the way that internal states become stable and relatively constant throughout time.

This process is the most important trend of the body to maintain internal stability as a response to changes caused by external factors^[7]. Under normal conditions, when stress decreases, the stress response stops and the body quickly recovers and returns to its balanced state. However, if stressors become chronic, the sympathetic hyperactivity without the normal counteraction of the PSNS in the form of release of stress hormones, could increase the risk of conditions such as obesity, cancer, heart disease, hypertension, diabetes, depression, gastrointestinal problems and infertility^[8].

The presence of psychological distress has been recognized to be the cause of several disorders in reproductive life,

including amenorrhea, oligomenorrhea, and the premenstrual syndrome [9-11].

In response to stress, enhanced secretion of a number of hormones, such as corticotropin-releasing hormone (CRH), glucocorticosteroids, catecholamines, prolactin, as well as the altered release of thyroid hormones are observed. This serves to increase the mobilization of energy sources and the body adaptation to new circumstances. However, the distribution of energetic resources is a trade-off between survival and reproduction [8]. At the physiological level, the division of resources is likely mediated, in part, through the regulation of the stress response by the hypothalamic-pituitary-adrenal (HPA) axis. Elevated levels of glucocorticoids following the activation of the HPA favor energy mobilization, cardiac output and sharpened cognition over growth, cellular immunity, and reproduction. When circulating levels of glucocorticoids exceed levels essential to promote fertility, survival occurs at the expense of reproduction [12]. The stress-related activation of the HPA affects the hypothalamic-pituitary-gonadal axis (HPG) by restraining the release of gonadotropin-releasing hormone (GnRH) from hypothalamus and inhibiting the secretion of luteinizing hormone (LH) from the pituitary [13], as well as the release of estradiol and progesterone from the ovaries [14,15].

High levels of circulating stress hormones can interfere with the timing of ovulation and shorten the luteal phase. During the period between pre-conception and early pregnancy stress hormones may prevent implantation and early pregnancy maintenance by luteal phase defect mechanisms resulting from diminished progesterone availability [16,17]. Additionally, the changed levels of hormones observed during stress could directly influence the quality of egg cells, thickness of the endometrial layer or other structures engaged in the reproductive process [18,19]. Stress could also cause infertility by affecting gamete transport [20] and delaying or inhibiting the LH surge of the menstrual cycle [21] resulting in an increased risk of anovulation [22].

In this review, we will briefly highlight the influence of hormonal changes observed during chronic stress on the mechanisms engaged in female fertility.

Catecholamines

The ANS has a direct role in physical response to stress. As mentioned before, the principal neurotransmitters of ANS are NE, E and ACh [23].

In response to stress, CRH, synthesized in the hypothalamus in the neurons localized in the paraventricular nucleus, is released and acts on the locus coeruleus. From there, the signal reaches the sympathetic and parasympathetic preganglionic neurons, which, by activating adrenoreceptors, increase the sympathetic activity and decrease parasympathetic activity. Simultaneously, the activation of the SNS stimulates the secretion of CRH [24].

The SNS controls catecholamines (E, and to a lesser extent NE) biosynthesis and secretion from the adrenal medulla. The PSNS mainly uses ACh as its neurotransmitter [25,26]. In normal conditions, the PSNS is activated when a stressful situation is

alleviated, due to the SNS and the PSNS being highly coordinated to maintain physiological homeostasis [27]. It is probable that stress increases the activity of SNS and decreases the activity of PSNS (thereby increases the levels of E and NE, and decreases ACh, respectively). During chronic stress the activation of the SNS is continued without parasympathetic counter-activity [28].

Presumably, the ovary function is mainly controlled by the HPA and the direction of ANS action is a result of a balance between cholinergic and noradrenergic activity. A change in this balance to a hyper-noradrenergic state turns the ovary into a polycystic ovary, while a change to a cholinergic predominance result in a healthy condition [29]. It has been reported that changes in the activity of sympathetic nerves result in the increase of androgen secretion, however not stimulating estrogen release from the ovary [30]. It is also possible that the persistent influence of sympathetic nerve hyperactivity on the ovary, may contribute to ovarian failure expressed by anovulation, as a result of ovarian vasoconstriction and reduction of ovarian estradiol secretion [31,32].

Corticotropin-releasing hormone

An activation of the HPA during stress conditions exerts an inhibitory effect on the female reproductive system through the suppression of the hypothalamic GnRH secretion, which is affected by CRH and CRH-induced proopiomelanocortin peptides, such as beta-endorphin [33]. Beta-endorphin is an endogenous neuropeptide, found in the hypothalamus and pituitary gland, playing a significant role in the pathophysiology of hypothalamic amenorrhea.

This effect is based on the disturbed GnRH production and consequently the impaired release of LH. CRH may directly inhibit GnRH secretion and stimulate beta-endorphin production in the case of stress-related amenorrhea [9,34] and finally diminishes the release of ovarian hormones [14]. Moreover, the presence of CRH and CRH-receptors have been found in the ovaries, the endometrial glands, decidualized endometrial stroma, placental trophoblast, syncytiotrophoblast and decidua [35]. Ovarian CRH, identified in several ovarian structures (the theca, stroma, and cytoplasm of the ovum and granulosa cells), can participate in follicular maturation, ovulation, luteolysis and ovarian steroidogenesis. Disruption of CRH expression leads to premature ovarian insufficiency, anovulation, corpus luteum and ovarian dysfunction [36-39].

Corticotropin-releasing-hormone receptors type 1 (CRHR-1) (similar to those of the anterior pituitary) are also detected in both the ovarian stroma and theca and in the cumulus oophorus of the graafian follicle. *In vitro* experiments have shown that CRH exerts a dose dependent inhibitory effect on ovarian steroidogenesis [40]. The expression of the *CRH* gene, demonstrated in the uterus, may indicate that endometrial CRH also participates in physiological events in that organ [41,42], especially in decidualization and blastocyst implantation [36].

Thus, an increase of CRH secretion observed during chronic stress, particularly if homeostatic mechanisms disrupt, may negatively affect reproductive capacity.

Glucocorticosteroids

Adaptive response to stress in the human body is regulated by the activation of the HPA axis that triggers neurons in the paraventricular nucleus of the hypothalamus to secrete CRH and arginine vasopressin (AVP). These hypothalamic hormones induce the anterior pituitary gland to release adrenocorticotropic hormone (ACTH) that stimulates the synthesis and secretion of glucocorticosteroids (cortisol), adrenal androgens and also - to a lesser extent - mineralocorticoids in the adrenal cortex. As part of the physiological adaptation to stress, the HPA axis affects the functions of the HPG axis, which is responsible for reproduction mechanisms ^[144]. High levels of cortisol exert inhibitory effects on the GnRH neurons ^[43,44].

Additionally, as demonstrated in studies on animals, high levels of glucocorticosteroids negatively influence the ability of an oocyte to become fertilized properly by the apoptosis of ovarian epithelial cells, leading to a decline in growth factor levels and estrogen to progesterone ratio and an increase in Fas ligand in the follicular fluid, impairing oocyte developmental potential ^[45,46]. *Ex vivo* studies suggest that stress response causing release of cortisol and aldosterone may impact uterine physiology through independent mechanisms disturbing normal changes in endometrial stromal cells after implantation ^[47]. In other studies, it has been demonstrated that pregnancy begins with successful fertilization and implantation, which depend on endometrial receptivity ^[48]. An endometrial thickness of 10-11 mm has been suggested to be a predictive value for the achievement of pregnancy ^[49]. Higher cortisol levels - observed in women under stress - have coexisted with a thinner endometrium ^[50]. Chronically elevated glucocorticosteroids can lead to many complications that disturb the normal reproductive process and consequently result in infertility.

Prolactin

The physiologic response to stress is complex. Besides NE release from the central nervous system, secretion of E from the adrenal medulla and the activation of the HPA axis, the release of prolactin is observed as evidence of the significant role of this hormone in the development of stress-induced pathology.

Functional hyperprolactinemia that occurs during stress may be caused by stress-related neuroendocrine changes of dopamine and serotonin, thus affecting prolactin secretion ^[51]. Hyperprolactinemia increases the secretion of ACTH, which induces adrenal hypertrophy and increases the adrenal cortex sensitivity to ACTH ^[52]. In addition, prolactin has a direct synergistic effect with ACTH on adrenocortical cells to increase adrenal androgen ^[53], cortisol and aldosterone ^[54] release and stimulates catecholamine synthesis in the adrenal medulla ^[55].

Stress affects individuals in different ways, so those more sensitive to stress, present symptoms of hyperprolactinemia which in turn may particularly impact fertility. Besides the effects mentioned above, which are directly correlated with hormonal changes resulting from the stress-related hyperprolactinemia, increased levels of prolactin in the reproductive system cause abnormal frequency and amplitude of female LH

pulsations, inhibit gonadotropin release and directly inhibit basal and gonadotropin-stimulated ovarian secretion of estradiol and progesterone ^[52]. Ovulation disorders related to increased secretion of prolactin may be one of the causes of female infertility induced by stress ^[50]. Considering far-ranging direct and indirect effects of prolactin, it appears evident that hyperprolactinemia caused by chronic stress may significantly reduce female reproductive capacity.

Thyroid hormones

As mentioned above, stress increases SNS activity while decreasing simultaneously PSNS activity. The thyroid gland is supplied with adrenergic nerves and the cholinergic axons deriving from the vagus nerve. Blood vessels of the thyroid gland are densely innervated by autonomic nerves and also their axon terminals are found around thyroid follicles ^[56]. In conditions of increased SNS activity, stimulatory effects of the thyroid stimulating hormone (TSH) on thyroid cells are inhibited by NE and the secretion of thyroid hormones (THs: thyroxine - T_4 and triiodothyronine - T_3) is decreased ^[57,58]. Elevated cortisol levels, observed during chronic stress, exert an inhibitory action on the hypothalamic-pituitary-thyroid axis ^[59] by suppression of the secretion of thyrotropin-releasing hormone (TRH), TSH and THs ^[60]. Chronic stress may also induce changes in thyroid hormone activity that contribute to hypothyroidism. Stress may contribute through altering the function of important thyroid hormone transporters and the enzymes - iodothyronine deiodinases. It is generally accepted that glucocorticoids increase type 2 deiodinase (D2) activity that converts T_4 to T_3 in the central nervous system and decrease type 1 deiodinase (D1), responsible for the conversion of serum T_4 to T_3 ^[60]. All listed mechanisms lead directly or indirectly to the impairment of the actions of THs.

THs are essential for the normal reproductive function of humans and animals. T_3 acts directly on ovarian, uterine, and placental tissues via specific nuclear receptors that modulate the development and metabolism of these organs ^[61-65]. The hormones in question synergize with follicle-stimulating hormone (FSH) and stimulate granulosa cell differentiation, followed by normal follicle development which is necessary for ovulation and corpus luteum formation ^[63]. T_4 and T_3 stimulate epithelial and stromal cells and uterine musculature proliferation through estrogen sensitized uterine cells ^[66]. Deficiency of THs leads to the significant reduction of endometrial thickness and the smaller number of endometrial glands ^[67,68] that may result in lowered endometrial receptivity. The hormones produced by the thyroid are also involved in the proliferation, differentiation, survival, and invasive and endocrine functions of trophoblastic cells ^[69], hence, their low levels may be co-responsible for a pathological pregnancy course. Additionally, THs act indirectly through multiple interactions with other hormones and growth factors, such as estrogens, prolactin, and insulin-like growth factor, and by influencing the release of GnRH in the HPG axis ^[70]. Therefore, changes in the serum levels of THs, observed during chronic stress, may result in female fertility disorders ^[71,72].

Conclusions

Stress affects individuals in different ways, therefore the reaction to stressors may vary depending on individual sensitivity to stress or the character of stressors. However, stress response serves to prioritize survival over less essential physiological functions, including growth and reproduction. The hormonal changes caused by the permanent activation of the HPA and the SNS (e.g., increased levels of CRH, cortisol, prolactin), in addition to changes in serum levels of THs observed during chronic stress, disrupt homeostatic mechanisms and may result in female fertility disorders. The involvement of chronic stress in the pathogenesis of a variety of diseases has been well documented. It may also negatively affect the mechanisms assuring successful female reproduction such as ovulation, ovarian steroidogenesis, endometrial development, follicular maturation or implantation. Better understanding the stress related hormonal changes and their impact on reproduction mechanisms may shed new light on a still underestimated role of chronic stress in female infertility.

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