# Mini review: Stress and how it affects reproduction

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## Abstract

Chronic anxiety, depression or physical exertion-associated stress consistently activates the hypothalamic-pituitary-adrenal (HPA) axis. Each individual component of the HPA axis, such as CRH, ACTH, β-endorphin or glucocorticoid exerts deleterious effect on the hypo-thalamic-pituitary-gonadal (HPG) axis and subsequently leads to reproductive failure. Gonadotropin-releasing hormone (GnRH) secretion and the response of gonadotrophs to GnRH stimulation are severely impaired. Moreover, failure of gonadal response to gonad-otropin concurrently results in deficient steroidogenesis, anovulation, defective endometrial decidualization and implantation, abnormal fetal outcome and delayed parturition.

In male, a consistent testosterone deficiency due to stress-linked altered functioning of the HPG axis has also been documented.

Stress-associated growth hormone (GH) deficiency with a corresponding deficiency of insulin-like growth factor-1 (IGF-1) at the level of the hypothalamus, pituitary, ovary, and uter-ine endometrium leads to defective reproductive outcome and lactation.

GH or IGF-1 deficiency also impairs testosterone biosynthesis, spermatogenesis, sperm maturation and erectile process.

## Introduction

Activation of the HPA axis concurrently inhibits HPG axis in stress

Individuals frequently encounter stressful conditions. In vertebrates, a major mechanism of physiological response to stress is hyperactivation of the hypothalamic-pituitary-

adrenal (HPA) axis. HPA axis hyperactivation is evident in major depressive [1,2] and anxiety [3] disorders. The occurrence of persistent increase in serum concentration of glucocorticoid in physical and psychological stress in primates [4,5], rodents [6] and domestic species [7] is well documented.

Chronic hyperactivation of glucocorticoids, however, re-sults in the development of diabetes, hypertension and even cancer [8]. The principal regulator of the HPA axis, corticotrophin-releasing hormone (CRH) and its receptors are located in the ovaries, decidual endometrial stroma, placental trophoblast and even in the Leydig cells of the testis [9-12].

Although the inhibitory effect of CRH in decreased LH and FSH secretion [13], ovarian steroidogenesis [14] and testosterone biosynthesis [15] has been documented, yet the locally produced CRH is found to be essential in promoting endometrial decidualization and implantation [16]. CRH may moreover act as the placental clock to trigger the onset of parturition [17]. On the other hand, CRH-activated β-endorphin [18] or corticotropin (ACTH) [19] is known to suppress the gonadotropin-releasing hormone (GnRH) pulses [18,20] with a corresponding attenuation of pulsatile release of luteinizing hormone (LH) [21,22] which subsequently leads to anovulation [23], interruption of endometrial decidualization [24] and pregnancy wastage [25].

The essential rhythmic pattern of GnRH secretion from the hypothalamus leads to an increased pulsatile release of LH [26]. Moreover, in concert with follicle stimulating hormone (FSH), LH dictates preovulatory follicular growth and estrogen production which subsequently trig-gers LH surge and ovulation [27]. Daley et al [28] have shown that stress-like concentration of glucocorticoid blocks estrogen-dependent increase in pituitary tissue concentration of GnRH and GnRH receptor mRNA. Therefore, the concept of glucocorticoid-linked reduced responsiveness of the gonadotrophs to GnRH [29] with a corresponding attenuation of gonadotropin secretion [30] seems to be logical. An excess of glucocorticoid has been found to suppress GnRH secretion [31].

Experimental results of the effectiveness of excessive glucocorticoid on gonadotropin secretion, however, re-main conflicting. When animal studies have linked increased CRH to decreased gonadotropin secretion [32], human studies using short-term infusion of CRH [33], conversely presented contradictory data. Since glucocorti-coid receptors have been demonstrated in rat ovaries [34] and ovarian granulosa cell cytosol [35], the direct effect of glucocorticoids [34] could possibly result in follicular atresia [36] by suppressing the action of LH/hCG at the receptor level [37]. Glucocorticoid-induced suppression of granulosa cell aromatase enzyme activity finally re-sults in estrogen deficiency [38]. Estrogen deficiency has also been recorded in anxiety and depression-related stress [39].

Investigators have recorded that glucocorticoid could greatly diminish the tissue uptake of estrogen [40] and estrogen-stimulated synthesis of DNA in the uterus [41]. Moreover, the number of estrogen receptors [42], blood flow [43], protein synthesis [44], prostaglandin synthesis [45] and insulin-like growth factor-1 (IGF-1) mRNA ex-pression

[46] in the uterus are found to be inhibited by glucocorticoids. Most of these estrogen-induced uterine profiles are essentially important for blastocyst implanta-tion [47], endometrial decidualization [48], pregnancy maintenance [49] and parturition [50]. It is, however, im-portant to note that glucocorticoid receptors in the uterus remain unaltered under the condition of chronic stress or even after prolonged glucocorticoid administration [51]. Estrogen deficiency not only impairs luteal steroidogene-sis in pregnant rats [52], it also jeopardizes receptor ex-pression of estrogen and progesterone in uteri [53], which subsequently results in pregnancy wastage [54] and parturition failure [50]. Moreover, the parental stress-associa-ted shorter gestation, complicated delivery, smaller birth weight in humans [55,56] could possibly be linked to the free access of excess glucocorticoid through placental barrier [57]. Excess glucocorticoid is also found to cause delayed parturition and still birth in rats [50]. Highly anx-ious women have similarly been shown to have a signifi-cant reduction of uterine blood flow in the third trimester of pregnancy, as compared to less anxious women [58]. In rats, chronic stress during pregnancy exerts profound long-term influences on the offspring [59].

Although females are known to be more vulnerable to stress and exhibits hyperactivity of the HPA axis function in comparison to male animals [60,61], yet the site of chronic stress-associated lesion of the hypothalamic-pituitary-testicular axis has been identified to be at the level of the hypothalamus [62]. Exogenous glucocorticoid is also found to attenuate plasma testosterone concentra-tion in men by inhibiting GnRH secretion [29,63]. The suppressive effect of ACTH on gonadotropin secretion [64] has been recorded in male patients with Cushing's syndrome [65]. Moreover, the suppressive effect of ACTH on gonadotropin secretion has never been recorded in patients with adrenocortical insufficiency [66].

Glucocorticoid receptors have been located in the rat Leydig cells [67]. The restraint stress-induced reduction in plasma concentration of testosterone, however, is claimed to be LH-independent [68], but appears to be related to the inhibition of the activities of steroidogenic enzymes [69]. β-endorphin blocker, such as naloxone or naltrexone has been shown to counteract the inhibitory effect of restraint stress on plasma testosterone levels by maintaining the normal functioning of the testicular ster-oidogenic enzymes [70]. In stressed rats, a concomitant rise in testicular nitric oxide (NO) concurrently with down regulated testosterone production has also been documented [71].

**HPA axis activation and suppression of the GH-IGF-1 axis**

The HPA axis activation and growth hormone (GH) blunting have in fact been linked in a primate study [72]. A blunted GH response to clonidine has however, been experienced in both anxiety and depression [73]. Attenuated release of GH in response to stress has been recognized long ago in experimental animals [74]. Experimental evidences suggest that GH may function as a cogonadotropin [75]. GH receptor mRNA expression and GH binding protein (GHBP) have been detected in the ovary of humans [76] and in several animal species [77-79]. A number of in vitro studies have shown that GH can influence oocyte maturation, increase receptors to gonad-otropin, thereby aiding folliculogenesis [80].

It is known that sexual maturation is delayed in Laron dwarfism [81] and growth hormone insensitivity also impairs the ability of young adult female mice to form functional corpora lutea of pregnancy [82]. However, a full

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reproductive potential requires actions of GH and adequ-ate levels of insulin-like growth factor-1 (IGF-1) in peripheral circulation [83]. Therefore, to induce ovulation in Laron dwarfism, IGF-1 treatment is often preferred [84]. GH-receptor gene knockout mice are found to be IGF-1 deficient [85]. IGF-1 receptors were detected in the pituitary, gonads and reproductive tract [86] and the influence of IGF-1 on the release of GnRH [87] and gonadotropin [83], follicular steroidogenesis, ovarian follicular growth, and ovulation [see 88] have also been documented.

IGF-1 mRNA was identified in the adult testis [89]. In the human testis, IGF-1 was also identified in Leydig cells, Sertoli cells and primary spermatocytes [90]. A vital role of IGF-1 in testicular steroidogenesis [91] has also been suggested. GH treatment to adult GH/IGF-1-deficient Ames dwarf mice increased plasma IGF-1 level and concurrently increased androstenedione and testosterone release from the isolated testes [92]. In hypophysectomized rats, GH administration resulted in an increase in the LH receptor content of the testis [93] and GH has been shown to enhance the testicular responsiveness to gonadotropin treatment [94].

Although, an enormous amount of experimental and clini-cal data are available, the absolute pathway between the stress-induced hyperactivation of the HPA axis and corresponding attenuation of the HPG axis has yet to be deter-mined

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