Review Article

Effects of Stress-Induced Glucocorticoids on Reproductive Dysfunction in Men Stress-Induced Glucocorticoids and Male Infertility

Nateghian Z[1], Aliabadi A[2], Aliabadi E[1*]

1. Department of Anatomy, Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
2. Faculty of Veterinary Medicine, Kazeroun Branch, Islamic Azad University, Kazeroun, Iran

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Abstract

There are different factors affecting the reproductive fitness of organisms, such as the ecological and environmental factors, resource availability, and stress within their habitat. The challenging incidents in the organism's environment result in activation of the response system of central stress mediated with the hypothalamic-pituitary-adrenal (HPA) axis. This axis's regulatory function controls such items as immune and cardiovascular functions, metabolisms, and reproductive system. Its activation shows reproductive function through various stressors. Through up-regulating glucocorticoids, stress can adversely influence fertility. Clinical studies and experimental data have demonstrated that stress signaling can have a mediatory effect during direct actions in gonads and reproductive system. The focus of this review is on the stress mechanisms via up-regulating glucocorticoids on male reproductive dysfunction. The individuals with abnormal Hospital Anxiety and Depression Scale (HADS) had higher serum FSH and LH and lower serum total testosterone compared to those with normal HADS. Besides, it was observed that in individuals with abnormal HADS, morphologically normal spermatozoa, sperm count, and motility are lower. For infertility of male cases, stress management is needed.

Keywords: Male hormones, Male infertility, Enviromental stress, Sperm parameters, Men

Introduction

A state of perceived or real threat to homeostasis is mostly named stress, which might lead to an organism (1). To repair homeostatic conditions, various responses are activated, including nervous system, endocrine system, and finally, immune system, which are known as the response of stress (2). The stress response is useful to set survival priorities over physiological activities with less vitality, such as reproduction and growth. The HPA axis (or HTPA axis) consists of the pituitary gland, hypothalamus, as well as adrenal glands, which control the adaptive response of body to stress (1). Stress, which is assessed by elevated glucocorticoid secretion,

*** Corresponding Author: Aliabadi Elham**, Department of Anatomy, Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
Email: aliabade@sums.ac.ir
https://orcid.org/0000-0002-5756-6166

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is known to result in strong reproductive dysfunction. Glucocorticoids (GCs) and stress both show peripheral and central inhibitory effect on the reproductive hormonal axis. GCs and other hormones in the HPA axis (and those contributing to sympathetic system) have the ability to modulate the hypothalamic-pituitary-gonadal (HPG) axis at any level—GCs have an inhibitory effect on GnRH release from the hypothalamus. Moreover, GCs constrain synthesizing and releasing gonadotropin in pituitary, release and synthesis of testosterone from the gonads, and affect sexual behavior and gametogenesis (3).

A stimulatory effect has been found for serotonin(5-HT) on the HPA axis in rodents and humans, which is mediated by 5-HT1A receptor, only male rodents show a response to 5-HT1A antagonism to indicate elevated corticosterone responses to stress (4).When the HPA axis is activated, a low amount of arginine vasopressin (AVP) and oxytocin and corticotropin-releasing hormone (CRH) are released by neurons in the paraventricular nucleus (PVN) of the hypothalamus, which stimulates the secretion of the adrenocorticotropic hormone (ACTH) and anterior pituitary gland (5). ACTH causes the secretion and synthesis of GCs (corticosterone in rodents and cortisol in humans), adrenal androgens, mineralocorticoids (aldosterone), freed from the adrenal cortex into the circulatory system (5, 6). Incremental cortisol inhibition levels lead to secretion of ACTH and CRH in a negative feedback loop of classic endocrine, enabling the return of the HPA axis to a physiological mode, which follows an intense activation.

The functions of hypothalamic-pituitary-gonadal axis (HPG axis) (Figure 1), which is in charge of maturation of reproductive organs as well as the organism's reproductive competency, are mediated by the HPA axis as a section of the physiological adaptation to stress. The reproductive system is controlled by the HPG axis during endocrine signaling, derived from gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus. The pituitary's gonadotroph cells are simulated by GnRH to release and synthesize luteinizing hormone (LH) and follicle stimulating hormone (FSH) (7). Steroid hormones (progesterone and estradiol) respond to control the gonadotrophins secretion (8). Stress signaling has an effect on all the HPG axis levels (9). For instance, as GCs are at high levels, they can inhibit the pituitary gonadotrophs, the GnRH neurons, and finally, the gonads (9, 10). This review aims to present the impacts of stress on the fertility of males and sperm parameters.

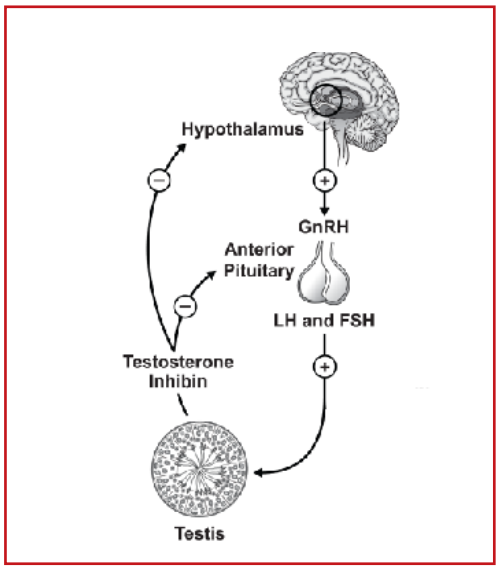

Figure 1. The Hypothalamo-Pituitary-Gonadal Axis includes the effects of the hypothalamus, pituitary, and gonads as a feed forward/back entity. The hypothalamus produces gonadotropin-releasing hormone, which signals through the anterior portion of the pituitary gland to produce luteinizing hormone (LH) and folliclestimulating

hormone (FSH). In males, LH stimulates the Leydig cells of the testes to produce testosterone and FSH signals through the Sertoli cells to support spermatogenesis.

2. Action of Stress-induced Glucocorticoids in the HPG Axis

First, stress leads to inhibiting reproductive behavior in addition to physiology to preserve itself. The stress-induced increase in glucocorticoids decreases secretion of GnRH, resulting in hypogonadotropichypogonadism. In Cushing's disease, which is a kind of disorder of hypercortisolemia, hypogonadism seems common. The feedback to GnRH is not paired. In addition, in men, levels of testosterone are also low. In the brain, the special areas and cell types containing glucocorticoid receptor GR causes the feedback to glucocorticoids to be directed. The hippocampus, which is a plentiful GR expression site in the brain, not only mediates different behavioral responses to glucocorticoids but also causes inhibitory responses, which are indirect, to the hypothalamus (11,12). Moreover, GR, which is in hypothalamic neurons, directly contributes to glucocorticoid that settles the HPG axis regulation. Current research on GR in GnRH-containing hypothalamic cell lines, which function as ligand-activated transcription regulators, support the conclusions drawn from this review (13). Endogenous GnRH mRNA as well as the transcriptional activity of vectors of transfected GnRH promoter-reporter gene is repressed by glucocorticoid treatment in hypothalamic cell lines (14). Furthermore, not only GnRH synthesis is suppressed, but also the GnRH pulse-generating center activity is decreased by glucocorticoids (15). Based on this, it is suggested that the main site for the inhibitory actions of glucocorticoids on gonadotropin secretion inhabit at a suprapituitary level, likely during an intervention of hypothalamic GnRH free.

Recently, a new negative regulator of the HPG axis, which is known as gonadotropin-inhibitory hormone (GnIH), has been discovered.

In addition, orthologous neuropeptides, which are known as RFamide-related peptides (RFRPs), have been recognized in primates and rodents (16,17). Chronic and acute stress stimulates RFRP expression in the hypothalamus of adult male rat, in which RFRP and GR expressions have an overlap (18). In mammals and birds, RFRP has a key effect on suppressing HPG function in vivo. The release of LH and sexual behavior are suppressed by stress and systemic administration of RFRP. Adrenalectomy causes stress induction of increased expression of RFRP in the hypothalamus and prevents LH suppression.

In different species, the preventing effects on LH secretion via acute and chronic treatment with glucocorticoids have been well reported. Although it has been reported that the secretion of gonadotropins may be protected by endogenous glucocorticoids, endogenous glucocorticoids are released in response to acute stress (19), which is called a special mechanism involving prostaglandins (PGs) regulation in the brain, and mediating the suppressive impacts on LH pulsatility, which is common to hypoglycemic, infectious as well as restraint stress. In response to contagious stress, treatment with tumor necrosis factor-α (TNF-α), adrenalectomy improves preventing impacts of TNF-α on pulsatile LH secretion (20). Pretreatment with glucocorticoids reduced suppression of TNF-α-induced of LH secretion in intact rats, shows that levels of threshold glucocorticoid are vital to maintain LH secretion and reproductive function through inflammatory stress (21). Pretreatment with indomethacin, which is a PGs synthesis inhibitor, can block many inhibitory impacts of TNF-α on the LH surge. Synthesis of PGs can be forbidden by glucocorticoids during the induction suppression of the cyclooxygenase inhibitor 2 (COX-2). In the brain, COX-2 expression in blood vessels is improved by restraint stress and hypoglycemia, which support an effect for PGs as acute stresses mediators (22). Incremental release of glucocorticoids in feedback to stress may serve a counter to the

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impacts of stress-induced PGs synthesis so as to maintain in comparison with suppressing reproductive function in condition of acute stress.

In the pituitary, mechanisms have been found to regulate glucocorticoid of transcription of the GnRH receptor (GnRHR) gene (23). Based on reporter as well as tests of chromatin immunoprecipitation, treatment of dexamethasone, which is a synthetic glucocorticoid clinically utilized, can make an increase in GnRHR transcription via nuclear translocation and the GR interaction with the activating protein-1 (AP-1) region of the mGnRHR gene. Besides, dexamethasone along with GnRH performs synergistically at the GnRHR promoter during steroid receptor coactivator-1 recruitment to the AP-1 region, which shows other mechanisms in condition that glucocorticoids are able to regulate the activity of GnRH. However, pituitary cells have also been the main target of glucocorticoid action, feedback has been divergent for FSH and LH here, as well (24).

In addition, there are sex differences for regulating glucocorticoid of LH secretion from the pituitary. Gonadectomized rams have been more irritated compared to gonadectomized ewes to the preventing effects of glucocorticoids on LH secretion (25). The sex differences are special to

glucocorticoids impact on LH pulses indicating sex differences in the action mechanisms of glucocorticoids in order to stop LH in sheep.

Stress-associated reproductive disorders are correlated with decreased pulsatile secretion of LH and FSH from the pituitary gland, attendant with declined expression and GnRH release from the hypothalamus. Therefore, exposure of supraphysiologic glucocorticoid can directly have an effect on the HPG axis via central actions on the pituitary as well as hypothalamus. A different mechanism is suggested by studies that in condition of acute stress glucocorticoids mostly protect than inhibit secretion of LH. This can be special to PGs-mediated suppression of the HPG axis. However, it is necessary to carry out more studies in the brain to clarify the role of glucocorticoids special levels on HPG axis (Figure 2).

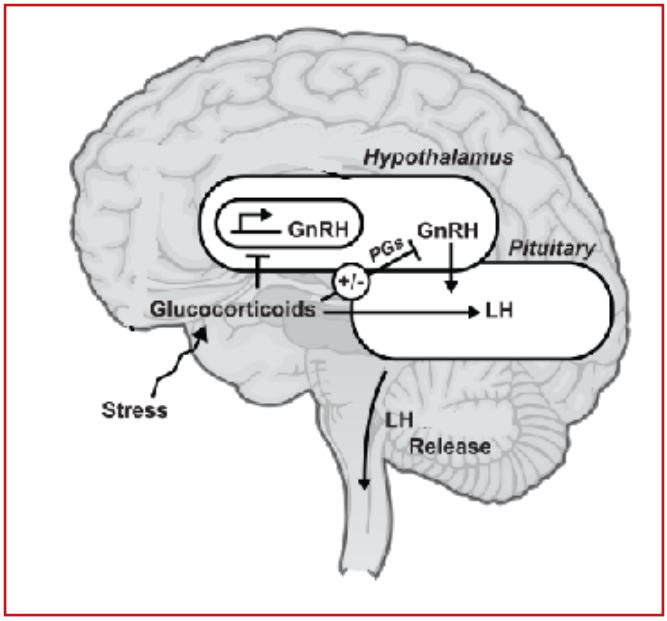

Figure 2. Glucocorticoid Action in the Brain. Stress induces elevated circulating levels of glucocorticoids, which act directly on the hypothalamus to suppress GnRH production as well as to directly lower pituitary secretion of LH and FSH. Glucocorticoids may also play a protective role in maintaining the HPG axis during acute stress through suppression of PGs.

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4. Action of Stress-induced Glucocorticoids in levels of testosterone and interstitial cells of Leydig (Leydig cells)

The major origin of testosterone in men is interstitial cells of Leydig (Leydig cell). The total number of interstitial cells per testis and the steroidogenic competence of these cells determine testosterone levels in circulation. Elevation of serum glucocorticoid concentrations induced by stress plays an inhibitory role in testosterone-biosynthetic enzyme activity, which leads to reduction of testosterone secretion rates (Figure 3) (27). Recently, some studies on men with Cushing's syndrome showed a correlation between the gonad of males and sexual dysfunction related to incremental levels of circulating cortisol (28).

In patients, Cushing's syndrome was developed in turn to long exposure to cortisol, either prolonged exogenous administration of glucocorticoids or during excess production of ACTH. Patients, who had Cushing's syndrome, were with concentrations of low plasma testosterone and little changes in levels of pituitary luteinizing hormone (LH). Besides, the diagnostic administration of dexamethasone more suppressed testosterone levels (29).

The decrease in testosterone as well as the same reciprocal relationship of glucocorticoid increase are almost shown by stress in the different forms, including surgery, anesthesia, battle anticipation or physical training (30).

Patients who had Cushing's syndrome and the GR localization to Leydig cells make hints

to mechanisms, which glucocorticoids as well as stress are used for inhibiting fertility of males. These ideas are in line with the results that other researchers have revealed correlating to influence on production of local testosterone in addition to expression of glucocorticoidregulated LH receptor.

Studies carried out on men, who were trained to combat in military in condition of continual attack threat, physical exertion as well as sleep deprivation, correlated with incremental levels of serumcortisol, reveal the maximum suppression of testosterone. However, LH levels were the same as baseline (31). Based on this data, stress-induced changes, which are in serum glucocorticoid content, might not have any noticeable impact on levels of LH circulating and its binding properties to its receptor, showing that effects of glucocorticoid repressive, which are on Leydig cell steroidogenic capacity, cannot easily be discussed as declined stimulation of the Leydig cell via LH (32). It has been known that glucocorticoids can prevent testicular LH receptor content in both hypophysectomized and intact rats in addition to testicular steroidogenesis (29, 33). Although the exact molecular mechanism that glucocorticoids decline production of testosterone is not completely known, many studies have demonstrated that glucocorticoids prevent the genes transcription, which encode testosterone biosynthetic enzymes, including cytochrome P450-dependent cholesterol side chain cleavage enzyme (P450 SCC), cytochrome P450-dependent 17α-hydroxylase/ C17-C20lyase (CYP17), and finally the cholesterol, which transport steroidogenic acute regulatory protein (StAR) as well (34–36). The steroidogenic genes promoters which are repressed via glucocorticoids do not involve any elements of classical glucocorticoid response, suggesting a mechanism that is not direct. CAMP-inducedStAR transcription in Leydig cells were antagonized by glucocorticoids during dexamethasone-induced binding of active GR to the nuclear receptor NR4A1, making a complex, which is transcriptionally inactive (37). Besides, it is vital to mention that the dangerous impacts of stress and high levels of circulating glucocorticoids on levels of testosterone can be attributed to fast non-genomic mechanisms. CAMP formation can be inhibited by glucocorticoid treatment in mouse Leydig during 15 minutes, and there is a fast decrease in production of testosterone until 30 minutes (38). As it is expected that the genomic mechanism of glucocorticoids requires a longer period in order to register at the levels of protein,

these fast glucocorticoids actions might happen by the "putative" membrane corticosteroid receptor, demonstrated for the receptor of estrogen, or during a receptor release, which interacts protein subsequent ligand binding (39). Moreover, incremental glucocorticoids levels are related with declined testosterone biosynthesis via Leydig cells. The degree resulting in glucocorticoids prevents function of Leydig cell which is defined via some factors, including the intracellular concentration of glucocorticoids, the GR amount in the cell in addition to the oxidative activity of 11β-hydroxysteroid dehydrogenase (11β-HSD), which is an enzyme catalyzing both reductive and oxidative reactions of glucocorticoids.

Both two 11β-HSD isoforms cause Leydig cells to regulate their intracellular concentration of glucocorticoid levels, 11β-HSD1 and -2 (40, 41). The type of cell and intracellular milieu establish the catalytic direction of 11s-HSD1(42). However, it has been obviously revealed that 11β-HSD1 has a predominant behavior in Leydig cells as a dehydrogenase, 11β-HSD1 has a predominant behavior in liver cells as a reductase (43).11β-HSD2, which does not have any noticeable reductase activity, has been known as an only oxidative enzyme.

Thus, 11s-HSD has been known as a testicular steroidogenesis gatekeeper in stress times.

In Leydig cells, the 11β-HSD oxidative capacity in stressful conditions might be surpassed until high levels of glucocorticoids, which lead to suppressing testosterone biosynthesis. Moreover, for a dynamic coupling between enzymes in charge of testosterone biosynthesis as well as 11s-HSD, there is evidence, which would account more for the fast impacts of glucocorticoids on the testosterone production suppression as well.

5. Action of Stress-induced Glucocorticoids in apoptosis of testicular germ cells and Leydig cells

Moreover, GCs can stimulate Leydig cell apoptosis and the fast effects of glucocorticoids on production of testosterone, which cause reduction of the Leydig cells number per testis(FIG 3).

Besides, GCs improve spermatogonia apoptosis in the seminiferous tubules (44, 45).

Through exposing these cells to corticosterone (CORT, the endogenously secreted GC in animals) in high concentrations, the apoptosis frequency is increased in them. According to findings of studies on immobilization stress, there is a direct relationship between stress-induced CORT elevation and apoptosis of Leydig cells. Oxidative inactivation of GC via 11β-hydroxysteroid dehydrogenase (11βHSD) modulates access to GC receptors in interstitial cells of Leydig. Type 1 11βHSD (oxidoreductase) and type 2 (unidirectional oxidase) are expressed by these cells. Redox potential is generated through synthesizing the enzyme cofactor NADPH, which is a product of glucocorticoid metabolism by 11βHSD-1. It can augment testosterone biosynthesis since steroidogenic enzymes like type 3 17β-hydroxysteroid dehydrogenase uses NADPH as the cofactor. In this case, steroidogenesis would be inhibited just in stress-induced circumstances since high levels of CORT as input is beyond the capacity of oxidative inaction by 11βHSD. Autonomic catecholaminergic activity alterations could have a contribution to the suppression of the function of interstitial under stressful conditions. The quick initiation of inhibition can also be explained by these changes (27).

In Leydig cells, glucocorticoid-induced apoptosis contains a decrease in generation of ROS, the mitochondrial membrane potential in addition to the Fas system activation and procaspase-3 cleavage (46). In individuals, serious psychological stress is correlated with reduced concentration of sperm that are able to be ascribed to either glucocorticoid induced-apoptosis of Leydig cells or testicular spermatogonia apoptosis (47).

Based on GR expression in spermatocytes of separated steps of spermatogenesis, glucocorticoids can directly affect the cycle of spermatogenic in a stage-specific way.

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hough transient increase, which is in serum corticosterone in addition to serum testosterone reduction made due to immobilization stress can improve apoptosis of testicular germ cell in rats, the precise apoptosis mechanism in these kinds of cells has not been known yet (48). One study investigated dexamethasone incremental expression of BAX, and a proapoptotic gene in cells of testicular germ (49). Stages from VII toVIII are the most impressionable to dexamethasone-induced apoptosis, which are consistent with a stage of GR-expressing spermatogenic. At these stages, since viability is androgen dependent, the raise in expression of BAX, which is in testicular germ cells, likely correlated to the inhibitory glucocorticoids impact on androgen biosynthesis, which is in Leydig cells. Furthermore, higher doses of dexamethasone cause androgen-independent stages of apoptosis of the spermatogenic cycle, in addition to a controlled fragment of Sertoli cells. Bax expression does not have any increase in the apoptotic Sertoli cells, offering that other factors are involved in apoptosis of glucocorticoid-induced in these kinds of testicular cells.

6. Stress-induced Glucocorticoids Action in macrophage migration inhibitory factor (MIF), and Bax expression

Because of the well-characterized immune changing glucocorticoids actions, GR identification in the macrophages nuclei, and resident cells of testis, has not been any surprise.

Glucocorticoids can change macrophage function, which is dependent on concentration and is able to control responses of the immune host to pathogens. Function of macrophage is improved at levels of low corticosterone. However, high concentrations are immunosuppressive (50). Immunosuppressive actions suppress the macrophage migration inhibitory factor (MIF) expression, which is a vital pro-inflammatory cytokine expressed at inflammation sites in human lung epithelial cells (A549) in addition to human T lymphoblasts (CEM C7A) (51). Production of MIF decreased compared to repressed via macrophages at glucocorticoids with low concentrations (52). In addition, MIF is expressed in the testis via the Leydig cell, responding to treatment of glucocorticoid based on stimulation of MIF expression. As production of Sertoli cell inhibition is modulated with MIF secretion by the Leydig cell, the response of MIF to glucocorticoids might have a vital effect on another mechanism of feedback along the HPG axis by the Leydig cells (53).

The vital target of glucocorticoid action is Leydig cells whose effects are mediated by Glucocorticoids in the Leydig cell during the GR in classical genomic mechanisms for MIF as well as Bax expression, and via fast non-genomic mechanisms. However, the total testis apoptosis has an important impact on normal testicular physiology, fertility can be modulated by glucocorticoids during stress-induced decrease in cell number. Moreover, in emotional or physical stress times, reasons would change from the reproductive process to those which are needed for self-preservation.

7. Stress action in sperm parameters

Two items, including depression score and hospital anxiety are used to investigate stress-associated psychological disturbances (54,55). To investigate the psychological stress level in infertile couples, HADS has been used in some studies (56,57), based on which, it can be deducted that a noticeable male partner proportion of infertile couples are under marked psychological stress in their lives. According to studies, there is a noticeable relation between male infertility and HADS (56,57).The people, suffering from HADS anxiety and having depression score≥8 had lower and higher levels of serum entire testosterone, and serum FSH as well as LH, respectively, in comparison with people with normal HADS. With increasing the psychological stress level of the people, level of testosterone decreases. In a study carried out by Delhez et al. (58), it was also shown that there was a negative relationship between the

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depression severity and levels of free testosterone. Based on the results, psychological stress effect on level of suppressing testosterone is the important impact that does not change during FSH, LH as well as GnRH.

Since serum LH as well as FSH are well-known for negative feedback control of serum testosterone, the increase in serum LH as well as FSH is the second factor for decreasing the levels of serum testosterone (59).

The people suffering from HADS anxiety and having depression score≥8, had lower morphologically normal spermatozoon, sperm motility and finally sperm count than people with normal HADS (60).

In addition, in animal experimentation, it was revealed that there is lower count of sperm in animals, which were induced to stress(61). Based on studies carried out on humans, in males, depression correlated to inclined concentration of sperm (62).

The level of serum entire testosterone had noticeable positive relationship with sperm motility as well as sperm count. Levels of serum of FSH and LH had noticeable negative relations with these parameters, showing that the alterations in seminal parameters in people, who have psychological stress are mediated during levels of low testosterone, since testosterone is for influencing spermatogenesis(59). Impact on levels of serum FSH and LH is secondary compared to lower level of serum testosterone. Serum GnRH was known for a noticeable negative relation with sperm morphology, showing that this hormone may have an impact on sperm morphology.

8. Stress-induced Glucocorticoids action in reproductive function

Several different types of stressors have been linked to reduced male reproductive function, including examination stress (school/university), occupational stress, and stressful life events (63). The prevailing hypothesis is that excess glucocorticoids as a part of the stress response lead to impaired testicular function (64). Infertile men experienced a significantly higher number of stressful life events than fertile men of a similar age and possibly stress is a major reason for severe reductions in testicular function leading to infertility (65).

Conclusions

The HPA and HPG endocrine axes function in a flexible manner to ensure both reproductive viability and survival. The actions of gonadal hormones to mediate adaptive neuroendocrine and behavioural responses may be completely impaired in the face of chronic stress exposure. Stress has inhibitory effects on male reproductive function, which are mediated in part by direct actions of the stress hormone, glucocorticoid, on Leydig cells in the testis. Although levels of basal glucocorticoid are vital for fertility, upregulation owing to activation of acute HPA axis can have deteriorating impacts on fertility. Incremental HPA activity is correlated with changed gonads functions. Because of stress or exogenous glucocorticoid exposure, reproductive dysfunction has been registered in some HPG axis tissues. On the other hand, stress via upregulation of glucocorticoid mainly reduces serum levels of testosterone through suppressed androgen synthesis and reductions in the numbers of Leydig cells as a result of apoptosis. Recent studies indicate that the suppressive actions of glucocorticoid are in part due to rapid non-genomic pathways present in Leydig cell mitochondria. Excessive glucocorticoid exposure has an effect on seminal quality via declining sperm motility, sperm count, and morphologically normal spermatozoon count. Increase in serum FSH as well as LH is secondary to decline level of serum testosterone. Stress management is necessary for the fertility of male partners.

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Conflict of Interest

None of the authors have any conflict of interest to declare.

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