Psychoneuroendocrinology 100 (2019) 48–57

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Stress, female reproduction and pregnancy

Georgios Valsamakis[a], George Chrousos[b], George Mastorakos[c,*]

[a] Department of Endocrinology and Metabolic Disorders, University Hospital of Larissa, Medical School of Larissa, University of Thessaly, Larissa, Greece
[b] First Department of Paediatrics, Aghia Sophia University Hospital, Medical School of Athens, Ethnikon and Kapodistriakon University of Athens, Athens, Greece
[c] Unit of Endocrinology, Diabetes Mellitus and Metabolism, Aretaieion University Hospital, Medical School of Athens, Ethnikon and Kapodistriakon University of Athens, Athens, Greece

ARTICLE INFO

Keywords:
Stress
Intrauterine growth restriction
Fetal cortisol
Hypothalamic amenorrhea
Exercise

ABSTRACT

Stress is one of the commonest and underappreciated causes of reproductive frailty in women. The stress system leads to adaptive responses *via* mobilization of hormonal systems. Adaptability and resistance to stress are fundamental to life. The response to stressors depends on the type of stressor, the timing and duration of stress, the genetic predisposition, personality characteristics, and the way of coping with stress. The hypothalamic-pituitary-adrenal (HPA) axis has a direct inhibitory action on the hypothalamic-pituitary-ovarian (HPO) axis at multiple levels. Acute and chronic stress impairs reproduction, eventually acting on varying mechanisms. Undernutrition, over-training, and psychological stress contribute to hypothalamic amenorrhea *via* reduced HPO activity. *In utero* stress exposure is a significant predictor of subsequent adult telomere length. Some of the metabolic consequences of intrauterine growth restriction can be mitigated by ensuring early appropriate catch-up growth, while avoiding excessive weight gain if relative hypercortisolism is not installed. The effect of maternal stress on fetuses regarding fetal HPA axis responsiveness (increased or decreased) remains under investigation. Maternal stress and depression are associated with structural and functional changes of brain parts such as hippocampus. *In utero* stress modifies epigenetically components of the HPA axis which can be transmitted transgenerationally.

1. Introduction

"Stress" is defined as a state of disharmony in the organism or a state of threatened homeostasis. Homeostasis is constantly challenged by internal or external adverse forces-stimuli termed stressors. The stress system coordinates the adaptive responses of the organism to stressors of any kind. In order to restore homeostatic conditions, organisms activate a complex range of responses involving the endocrine, nervous, and immune systems, collectively known as the stress response (Carrasco and van de Kar, 2003). In 1935, Walter Cannon described the flexibility of the body in its ability to respond to stress (Cannon, 1935) and called the stress-induced increases in cardiac output the "fight or flight" response recognizing the importance of adrenal hormones in such response. In 1950, Hans Selye described the stress adaptation system by stating that stressors threatening the organism homeostasis and life in general lead to generalized adaptive responses including mobilization of hormonal systems. He suggested that adaptability and resistance to stress are fundamental to life and that apart from the many specific defense reactions there is an integrated closely interrelated system of adaptive responses to non-specific stressors. The so-called General Adaptation System consists of three stages: the stage of Alarm Reaction, the stage of Resistance and the stage of Exhaustion (Selye, 1950). Adaptation in the face of potentially stressful challenges involves activation of neural, neuroendocrine and neuroendocrine immune mechanisms. This has been called "allostasis", the concept of maintaining stability through change. A number of circumstances can overstimulate or lead to abnormal performance these systems. The amount of stimulation caused by the stressors, is called "allostatic load"

Abbreviation: IUGR, intrauterine growth restriction; HPA axis, hypothalamic pituitary adrenal axis; HPO axis, hypothalamic pituitary ovarian axis; LC/NE, locus ceruleus/norepinephrine; CRH, corticotropin releasing hormone; AVP, arginine vasopressin; PVN, paraventricular nuclei; POMC, proopiomelanocortin; ACTH, adrenocorticotropic hormone; αMSH, alpha-melanocyte stimulating hormone; GnRH, gonadotrophin releasing hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone; PRL, prolactin; IL-1, interleukin -1; PCOS, polycystic ovary syndrome; FHA, functional hypothalamic amenorrhea; HA, hypothalamic amenorrhea; beta HSD2, 11 beta hydroxysteroid dehydrogenase type 2; SGA, small for gestational age; GR, glucocorticoid; MR, mineralocorticoid; GC, glucocorticoid; ADHD, attention deficit hyperactivity disorder; PTSD, post-traumatic stress disorder

* Corresponding author: 3, Neofytou Vamva str, 10674 Athens, Greece.
E-mail address: mastorakg@gmail.com (G. Mastorakos).

https://doi.org/10.1016/j.psyneuen.2018.09.031
Received 6 June 2018; Received in revised form 9 September 2018; Accepted 18 September 2018

(McEwen and Stellar, 1993). Allostatic load provides biophysical and biochemical measures of stress which have improved our understanding in older people. Here is used to describe stress in women of fertile age. Allostatic load can lead to disease over long periods (dyshomeostasis or cacostasis). Types of allostatic load include (Selye, 1950) frequent activation of allostatic systems; (Chrousos and Gold, 1992) failure to shut off allostatic activity after stress; (Ridley, 2004) inadequate response of allostatic systems following stress leading to increased activity of other, normally counter regulated allostatic systems (Mc Ewen, 2006).

Reproduction is the biological process by which new individual organisms – "offsprings" – are produced from their parents. The main endocrine component of the human female reproductive system is the hypothalamic–pituitary–ovarian (HPO) axis (Ridley, 2004). Stress-related activation of the HPA axis leads to the inhibition of the HPO axis at multiple levels leading, thus, to disruption of the latter expressed in different degrees of clinical gravity. The detailed mechanisms by which stress influences reproduction involves a number of endocrine, paracrine and neural components (Einarsson et al., 2008).

2. Description of the stress system

The stress adaptive response occurs when the organism's homeostasis is threatened or perceived to be so. The latter is challenged by internal or external stressors which may vary from life events (*e.g.* divorce, serious illness or death of a relative or friend) to daily hassles (*e.g.* domestic affairs, financial or relational problems, and queuing) (Table 1). Many stressors listed in Table 1 are behaviors that affect systems biology. The degree of the adaptive response to stressors depends on the type of stressor, the critical timing and duration of stress, the genetic predisposition to stress, personality characteristics, previous experience, support from the social environment, and the way of coping with stress. The stress system is activated in a coordinated fashion, influencing central and peripheral physiologic functions important for adaptation and survival (Chrousos and Gold, 1992). During stress, several physiologic changes take place that help preserve the individual and the species, such as mobilization of adaptive behaviors and peripheral functions, as well as inhibition of biologically costly behaviors and vegetative functions (Chrousos et al., 1998). Neuroendocrine hormones are major mediators of both basal homeostasis and responses to stressors, and are involved in the pathogenesis of diseases resulting from dyshomeostasis or cacostasis. In detail, the stress response presumes that hormonal, behavioral, and physiological mediators co-react in four ranges (Selye, 1950): (a) Predictive Homeostasis is the range encompassing circadian and seasonal variations reflected by the concentrations/levels of mediators reached in response to predictable environmental changes (Chrousos and Gold, 1992); (b) Reactive Homeostasis is the range of concentrations/levels of mediators reached in response to unpredictable or threatening environmental changes. Together, Predictive and Reactive Homeostasis represent the normal reactive range of mediators for each individual. (c) The range of concentrations/levels of mediators above the Reactive Homeostasis range is called Homeostatic Overload (Ridley, 2004), while (d) the range of concentrations/levels of mediators below the Predictive Homeostasis range is called Homeostatic Failure (Einarsson et al., 2008). The ranges of Homeostatic Overload and Homeostatic Failure represent the abnormal reactive range which and corresponds to pathological effects. Thus, they are not compatible with long-term (Homeostatic Overload) or short-term (Homeostatic Failure) health (Romero et al., 2009).

Table 1
XXX.

Stressors
Everyday life's nuisance
Life changes
Natural and other disasters
Starvation, overnutrition
Excessive exercise
Chronic diseases
Socioeconomic status
Loss of job; Loss of life's control
Responsibility for other persons
Substance abuse
Inflammation (septic, aseptic)
Anxiety; depression (typical, atypical); personality disorder
[Attention: Chronicity *vs* Acuity]

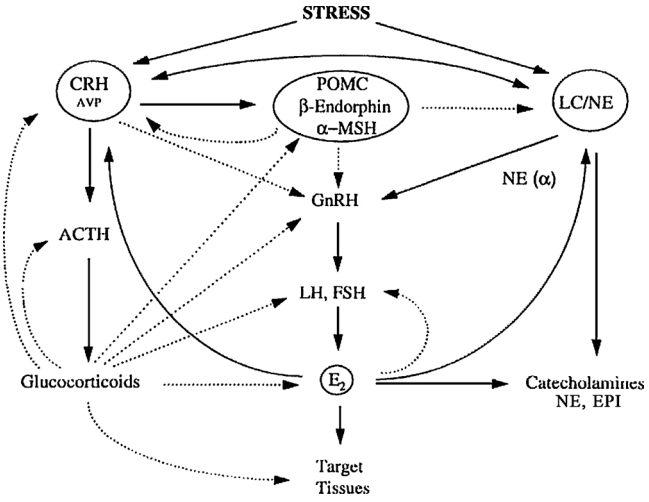

Fig. 1. Interplay among the hypothalamic-pituitary-adrenal (HPA) axis, the locus ceruleus/norepinephrine (LC/NE) sympathetic nervous system (SNS) and the hypothalamic-pituitary-ovarian (HPO) axis. The dotted lines represent inhibition, while the solid lines represent stimulation. Adapted from Annals Internal Medicine volume 129, No3.

The endocrine stress adaptive response is mediated by the stress system, partly located in the central nervous system and partly in peripheral organs. The main endocrine components involved in the stress system response are the hypothalamic-pituitary-adrenal (HPA) axis and the locus ceruleus-norepinephrine (LC/NE) autonomic nervous system (Chrousos and Gold, 1992) (Fig. 1). The physiological stress response begins when the brain detects a homeostatic challenge and activates the sympathetic nervous system (SNS), which releases the catecholamines epinephrine (EPI) and norepinephrine (NE). This is followed by the slower activation of the hypothalamic-pituitary-adrenal (HPA)-axis. Of note, glucocorticoids stimulate phenylethanolamine-*N*-methyltransferase (PNMT), an enzyme that mediates N-methylation of NE to EPI (Plotsky et al., 1989).

The central components of the stress system include: 1) the parvicellular corticotropin releasing hormone (CRH) and arginine-vasopressin (AVP) neurons of the hypothalamic paraventricular nuclei (PVN) and the CRH neurons of the paragigantocellular and parabranchial nuclei of the medulla and 2) the LC/NE and other catecholaminergic cell groups of the medulla and pons (central sympathetic system). Not to be underestimated the role of the amygdala which plays a crucial role in the development and expression of conditioned fear (Davis, 1992a). The amygdala is comprised of at least 13 different subnuclei. The central, the basal and lateral nuclei are mostly defined. The central nuclei regulate many aspects of the fear response, including regulation of the release of cortisol through the PVN nucleus, increase in startle response *via* the midbrain, and modulation of the autonomic nervous system through the lateral hypothalamus (Davis, 1992b). The central effectors of this system include the hypothalamic hormones AVP and CRH, the proopiomelanocortin (POMC)-derived peptides, and the LC/NE and autonomic norepinephrine centers in the brainstem (Chrousos, 2009). CRH and AVP stimulate synergistically the pituitary adrenocorticotropic hormone (ACTH) secretion which in its turn leads to the glucocorticoid secretion by the adrenal cortex. The pituitary

corticotrophs produce a variety of POMC-derived peptides including ACTH, β-endorphin and α-melanocyte-stimulating hormone (αMSH), all of which are released in response to stress (Engler et al., 1989).

The peripheral limbs of the HPA axis and the efferent sympathetic/adrenomedullary system constitute the primary peripheral components of this complex homeostatic system (Chrousos and Gold, 1992). By a feedback loop, the glucocorticoids exert negative feedback actions on the hypothalamo–pituitary unit to regulate the secretion of CRH, AVP and ACTH (Plotsky et al., 1989). The sympatho-adrenal system consists of the sympathetic nervous system and the adrenal medulla. Activation of the sympatho-adrenal system evokes the release of noradrenaline from postganglionic nerve terminals, while preganglionic innervation of the adrenal medulla results in increased secretion of catecholamines, principally adrenaline, into the bloodstream (Goldstein, 1987).

Targets of the stress effectors include the executive and/or cognitive, reward and fear systems, the wake-sleep centers of the brain, the growth, reproductive and thyroid hormone axes, and the gastrointestinal, cardiorespiratory, metabolic, and immune systems. By contrast, excessive or inadequate basal activity and responsiveness of this system might impair development, growth, reproduction and body composition, and lead to behavioral and somatic pathological conditions (Chrousos, 2009).

3. Description of the reproductive system

The reproductive system or genital system of the human female is a system of sex organs which co-operate for the purpose of sexual reproduction *via* production of oocytes. In the human, the female reproductive system is immature at birth and develops to maturity at puberty to be able to produce oocytes, and to carry a fetus to full term. The internal female sex organs are the uterus, fallopian tubes, and ovaries. The latter produce the oocytes. The uterus accommodates the embryo which develops into the fetus. Towards the end of puberty, girls begin to release oocytes into one of the fallopian tubes as part of a 28-days period (female reproductive cycle or menstrual cycle). The reproductive cycle is materialized in an ovarian and a uterine cycle. During the uterine cycle, the endometrial lining of the uterus builds up under the influence of increasing levels of estrogens. Follicles develop, and within a few days one is selected to contain a mature oocyte. The latter is released by the ovary at the time of ovulation. After ovulation the uterine lining enters a secretory phase, or the ovarian cycle, in preparation for implantation, under the influence of progesterone which is produced by the corpus luteum. The system is designed to transport the oocyte to the site of conception *via* the fallopian tubes. Reproduction is characterized by two processes. The first, meiosis, involves the halving of the 46 of chromosomes in the female and male gamete. The second process, fertilization, leads the fusion of the mature female (oocyte) and male (spermatozoid) gamete and the restoration of the original number of chromosomes: 23 chromosomes from the paternal side and 23 from the maternal side. During meiosis, the chromosomes of each pair usually cross over to achieve genetic recombination. Fertilization usually occurs in the fallopian tubes and marks the beginning of embryogenesis. The next step for the fertilized oocyte is to implant into the walls of the uterus, beginning the initial stages of pregnancy. The zygote which resulted from the fused gametes will then divide over enough generations of cells to form a blastocyst. This begins the period of gestation and the embryo will continue to develop until full-term.

In addition, the female reproductive system (ovaries) produces female sex hormones that maintain the reproductive cycle which is regulated by the HPO axis. The principal regulator of this axis is gonadotropin-releasing hormone (GnRH), produced by neurons of the preoptic and arcuate nucleus of the hypothalamus into the hypophyseal portal system (Ferin, 1996). GnRH stimulates pituitary follicle stimulating (FSH) and luteinizing hormone (LH) secretion, which in their turn regulate estradiol and progesterone secretion by the ovary. Activins, inhibins, and ovarian steroid hormones (estradiol and progesterone) feedback to regulate the secretion of the gonadotrophins (Namwanje and Brown, 2016).

4. How stress disrupts reproduction

Stressors impact all levels of the hypothalamic–pituitary–gonadal (HPG) axis and interfere with the time course of release of reproductive hormone release within the follicular phase. In rats, alteration of sexual behavior, significant increase in plasma ACTH, prolactin (PRL), corticosterone and progesterone and decrease of FSH are observed in acute stress (Elizabeth et al., 2017). Stressors lead to reduction of the frequency and amplitude of GnRH and LH pulses and delay of the LH midluteal surge, suggesting that they exert their action at the hypothalamus or higher centers in the brain (Bauer et al., 1994). Acute stress leads to suppression of the HPO axis through inhibition of GnRH secretion, thereby suppressing LH release from the pituitary (Elizabeth et al., 2017). In sheep, acute stress suppresses GnRH and gonadotropin release (Dobson et al., 2012). These effects are mediated through suppression of GnRH and GnRH receptor (GnRHR) synthesis, disruption in pituitary release of LH, and enhanced function of the gonadotropin-inhibitory hormone (GnIH; mammalian ortholog gene *Rfrp3*) neurons (Ciechanowska et al., 2016). Restraint stress in mice and rats leads to increased expression of hypothalamic *Rfrp3* associated with elevated circulating levels of corticosterone and decreased functions of the HPG axis (Kirby et al., 2009).

As part of the stress adaptive response, the HPA axis regulates the functions of the HPG axis. Any of the components of the HPA axis has the potential to inhibit reproduction (Fig. 1). In more detail, CRH and POMC peptides, such as β-endorphin, inhibit hypothalamic GnRH secretion (Crofford et al., 1997). Stress adaptive response produces an immediate constant increase in AVP and CRH secretion in ewes, but ACTH reaches a maximum in the first hour while cortisol is highest during the second hour (Chen et al., 1992). Changes in AVP, CRH and ACTH each follow a similar time course, but eventually the secretion of AVP and CRH decreases. Furthermore, studies have revealed the direct effect of CRH in the absence of circulating steroids of adrenal and/or gonadal origin into the reproductive function. Acute administration of ovine CRH into the lateral ventricle of gonadectomized, adrenalectomized female rats, exhibited a rapid and prolonged dose-related inhibition of LH (but not FSH) secretion. Additionally, CRH injected daily to female rats during the first 12 days after mating caused a 40% disruption of pregnancy (Rivier and Vale, 1984).

There is also evidence to support effects at pituitary level because exogenous ACTH reduces the amount of GnRH-induced LH. The decrease of GnRH/LH secretion ultimately deprives the ovarian follicle of adequate gonadotropin support leading to reduced estradiol production by slower growing follicles. Therefore, stressors interfere with the ovary too (Dobson and Smith, 2000).

Furthermore, glucocorticoids suppress the HPO axis at the hypothalamic, pituitary, ovarian and uterine levels (Rabin et al., 1990). High levels of glucocorticoids have inhibitory effects on the GnRH neurons, the pituitary gonadotrophs, and the gonads (Whirledge and Cidlowski, 2017). Studies have demonstrated that secretion of LH and FSH by female rat pituitary cells exhibits differential responsiveness to treatment with glucocorticoids *in vitro*. Basal secretion of LH was inhibited, whereas basal secretion of FSH was enhanced. (Suter and Schwartz, 1985). Other studies have highlighted a negative impact of a basal cycle high FSH/LH ratio (and possibly low LH levels) on follicular development and oocyte quality (Barroso et al., 2001) Chronic corticosterone exposure in mice *in vivo* exhibits decreased LH levels, associated with disrupted neuronal activation in the hypothalamus and disrupted gene expression in the pituitary gonadotroph cells (Luo et al., 2016).

5. The role of time duration in stress and reproduction

"Acute stress" is defined as a stressor applied over a few hours. If such a stressor nuisance is repeated daily for several days it can be called "subacute stress," while if it persists for weeks to months, it can be called "chronic stress." Regarding the duration of stress upon the reproductive functions in the females of many species, two major patterns emerge: (a) acute stress impairs reproduction, if it occurs at a critical time during the precise time-course of endocrine events that induce estrus and ovulation and, (b) chronic stress impairs reproduction in general (Turner and Tillburg, 2006). Literature proposes modified versions of these patterns for certain species. When stress is prolonged, it is likely that secretion of gonadotropins will be suppressed but the effects of acute stress or repeated acute stress on gonadotropin secretion are not clear. Different stressors activate different pathways for varying duration while the stress adaptive response is influenced by the predominance of certain sex steroids in the circulation. (Biran et al., 2015). The most sensitive of the reproductive processes are ovulation, sexual behavior and embryo implantation. They represent the beginning of a "test period for women" directly controlled by the neuroendocrine system.

5.1. Acute stress and reproduction

ACTH administration during formation of preovulatory follicles impairs steroidogenesis and angiogenesis in association with ovulation failure in lactating cows (Ghizzoni et al., 1997). In the past, we have shown the presence of immunoreactive CRH in rat and human ovaries. CRH immunoreactivity was localized by immunohistochemistry in the cytoplasm of thecal cells surrounding the ovarian follicles, in luteinized cells of the stroma, and in large granulosa-derived luteinized cells of developing corpora lutea. Furthermore, we examined the role of CRH in the ovary and studied its effect (graded doses of CRH) on estradiol and progesterone release by human granulosa cells obtained from women undergoing *in vitro* fertilization. All CRH concentrations employed except for the lowest one (10^{-11} mol/liter) caused a significant decrease of media estradiol and progesterone levels. This phenomenon was abolished by employing an interleukin (IL) 1 receptor antagonist. Thus, it appears that ovarian CRH exerts a CRH- and IL 1- receptor-mediated inhibitory effect on ovarian steroidogenesis and might be actively involved in the still enigmatic processes of follicular atresia and luteolysis (Tarin et al., 2010).

Inversely, female pigs appear to be resistant to acute or repeated acute stress or cortisol increase, even if these acute events occur during the precisely timed endocrine responses that induce estrus and ovulation (Turner and Tillburg, 2006). Estrogen-primed postmenopausal or ovariectomized women display an adrenal-progesterone-induced ovulatory-like LH surge in response to exogenous ACTH administration. Thus, acute stress may induce ovulation in women with appropriate serum levels of estradiol and one or more follicles large enough to respond to a non-midcycle LH surge (Gottschall and Gottschall, 2003). Of note, the percentage of pregnancies resulting from single episodes of forced penile-vaginal intercourse (rape) is significantly higher (8.0% in a sample of 405 women from a national random-digit dialing sample of households in USA) than the percentage of pregnancies resulting from single episodes of consensual, unprotected intercourse (3.1% in a sample of 221 women with no fertility problems planning to become pregnant in USA) (Gottschall and Gottschall, 2003). Whether sex steroids influence the response to GnRH during the imposition of stress it remains to be determined. Observations in female rhesus monkeys indicate that the ovaries, and particularly estradiol secretion, influence the effects of stress on LH secretion (Dierschke et al., 1970). Additional research is necessary to delineate whether the effects of stress on LH pulse amplitude involve central and/or pituitary mechanisms. Findings indicate that stress will impact on reproduction by mechanisms that differ between males and females and perhaps between females in different stages of the reproductive cycle (Tilbrook et al., 2002) It should be mentioned that sex differences in response to stress are due principally to the influence of sex steroids and their secretion at particular times in non rodent animals, even though some sex differences in the brain are not dependent on the actions of sex steroids (Madeira and Lieberman, 1995).

5.2. Chronic stress and reproduction

Glucocorticoids exert a wide range of effects on metabolism. These are primarily catabolic in an effort to utilize every available energy resource against the challenge enforced by stressors. Chronic stress prolongs this adaptive shift towards a generalized catabolic state and, thus, sustained HPA hyperactivity can progressively lead to decreased lean (muscle and bone) body mass, increased visceral adiposity and insulin resistance. Body weight and fat mass is an independent regulator of the HPO axis activity. A more atherogenic plasma lipid pattern was shown either in non-subordinate ovariectomized control female monkeys and in subordinate socially-stressed female monkeys which demonstrate chronic ovarian dysfunction. Thus, it seems that social stress abolishes "female protection" against coronary artery atherosclerosis. In the opposite, socially-non-stressed dominant non-ovariectomized females were protected against development of atherosclerosis. Interestingly, subordinate socially-stressed females had enlarged adrenal glands, suggestive of mechanisms that may influence atherogenesis independently (Mayerhofer et al., 1997). At this point, it is important to discuss the biochemical influence of glucocorticoids upon transformation of NE to EPI *via* stimulation of PNMT. In the past, Padbuty et al have shown higher adrenal gland tissue epinephrine concentrations in female than in male rabbit fetuses (Padbury et al., 1981). It seems that the greater stress-associated cortisol concentrations in pregnant women could lead to increased EPI concentrations which in their turn could result to poor pregnancy outcome and even cardiovascular disease (CVD). This suggested mechanism plus increased androgens in women with polycystic ovary syndrome (PCOS) could explain their higher risk status for the development of metabolic syndrome and CVD (Greiner et al., 2005).

The abnormalities detected in PCOS have been attributed among others to defects of adrenal androgen production. In the past, we have shown that this adrenal hyperandrogenism persists in early postmenopausal PCOS women (Markopoulos et al., 2011). Population studies have confirmed the positive association between anxiety and the incidence of PCOS (Scaruffi et al., 2014). Women with PCOS have relevant personality and psychiatric disorders, when compared with normal subjects (Scaruffi et al., 2014). Interestingly, a prevalence study demonstrated that the prevalence rate of PCOS in underweight, normalweight, overweight, and obese women were 8.2, 9.8, 9.9, and 9.0%, respectively, similar to that observed in the general population suggesting that the risk of PCOS is only minimally increased with obesity (Yildiz et al., 2008). Eventually, disruption of homeostatic models by chronic life stressfull events needs to be studied regarding the PCOS endocrine dysregulation. Of note, among 230 patients with Cushing disease the most common presenting comorbidities included hypertension (67.3%), PCOS (43.5%), and hyperlipidemia (41.5%) suggesting the interconnection between hypercortisolemia and PCOS (Geer et al., 2017).

Furthermore, stress has become a commonly cited factor when discussing unexplained reproductive failures. Experimental, clinical and population-based research suggests the interplay between stress, the immune system and female reproduction (Nepomnaschy et al., 2007). Indeed, psychosexual counseling in conjunction with pharmacotherapy, when needed, enhance fertility results and quality of life (Mulder et al., 2002; Genazzani, 2005).

5.2.1. Functional hypothalamic amenorrhea

Functional hypothalamic amenorrhea (FHA) is a form of chronic

anovulation that is not due to identifiable organic causes but often associated with stressful events, weight loss, excessive exercise or a combination of them. It affects a consistent percentage of women, independently of age and quite often it is diagnosed in adolescents or in girls below 20 years of age. It is characterized by amenorrhea or irregular menses. Undernutrition, excess of training and psychological stress are able to induce FHA which leads to hypoestrogenism due to reduced ovarian activity (Berga et al., 1989). It results from insufficient drive and/or inhibition of the HPO axis. The proximate cause of anovulation is a functional stress-induced reduction of GnRH drive (low pulse frequency) which manifests as reduced LH pulse frequency (Gordon et al., 2017). Reduced GnRH drive results in LH and FSH levels insufficient to maintain full folliculogenesis and ovulatory ovarian function (Gordon et al., 2017). Earlier studies have shown the association between increased HPA axis activity caused by stress-induced alterations of central neural function and reduced GnRH (Berga and Loucks, 2005). Indeed, stress is one of the most common and underappreciated causes of infertility and reproductive compromise in women. Stress-induced hypothalamic hypogonadism increases the acute and chronic health burden for individuals and their offspring (Berga, 1996). Stress reduction results in restoration of ovulation, fertility and amelioration of other neuroendocrine concomitants (Berga et al., 1997). Women with FHA have higher cortisol levels in respect to eumenorrheic women and women with other forms of ovulatory dysfunction (Berga et al., 1997).

5.2.2. Exercise and adipose tissue

Adipose tissue produces factors, including adipokines, cytokines and chemokines which systemically exert endocrine effects on multiple tissues. Adipokines affect the HPO axis both centrally, at the hypothalamic-pituitary level, and peripherally acting on the gonads themselves (Fig. 2). Among the adipokines, leptin, adiponectin, resistin, and chemerin have pleiotropic actions on the HPO axis affecting pubertal

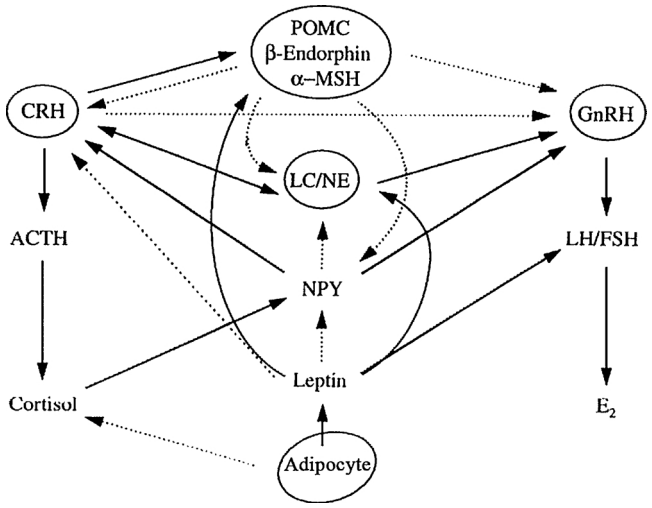

Fig. 2. Interactions of leptin with the stress system and the female reproductive axis. In general, leptin inhibits the HPA axis and stimulates the reproductive system. Leptin provides positive input to the female reproductive axis indirectly *via* chronic inhibition of the HPA axis and the arcuate nucleus POMC, and activation of the LC/NE-SNS. Neuropeptide Y (NPY), on the other hand, acutely exerts a positive effect on GnRH and LH secretion in ovary-intact or estrogen-treated animals (solid line). However, when infused chronically, NPY consistently induces a profound inhibition of the HPO axis (dotted line) suggesting that the increased expression of hypothalamic NPY observed in fasting or unfavorable metabolic conditions may account for the tonic inhibition of pulsatile GnRH release. In this case, the increase of leptin can lead to HPO axis activation *via* inhibition (dotted line) of the inhibitor (NPY). Solid line = stimulation; dotted line = inhibition. Adapted From Annals Internal Medicine volume 129, No3.

development, fertility and reproduction *per se*. The most common causes for low body weight-related amenorrhea include eating disorders, strenuous exercise (such as ballet, gymnastics, swimming, marathon running, *etc*), and stress (Hoek and van Hoeken, 2003). These energy deprivation states include subjects such as those with anorexia nervosa, chronic disease and elite athletes characterized by undernutrition, low adiposity mass and are associated with activation of the HPA axis (increased CRH, ACTH and cortisol levels) and low leptin levels. It is of interest, to extrapolate the anorexigenic role of CRH, a major stimulus of the HPA axis, to the low weight of these girls and women. This low weight is associated to low adiposity and is reflected by low leptin levels. The absence of leptin along with stress, are involved pathophysiologically in the major clinical feature of this syndrome, the amenorrhea that reflects the attenuation of HPO activity (Stoving et al., 1999) Studies in animals and humans have shown that low concentrations of leptin are associated with starvation-induced changes in reproductive hormones (Ackerman et al., 2013). In fact, reproductive disorders seen in ballet dancers represent an adaptive response in low body weight individuals. Energy drain may modify the hypothalamic-pituitary set point of puberty and, in combination with low body weight, may delay puberty initiation. Thus, in ballet dancers, runners and gymnasts low body fat, intense physical activity, inadequate nutrition and stress in combination result to delayed puberty (Warren, 1980, 1983). Energy deficit is considered one of the major factors leading to stress-related FHA.

Exercise represents a physical stress that challenges homeostasis. Sympathetic nervous system and HPA axis are activated during exercise as reflected by the elevation of plasma IL-6, ACTH, cortisol and catecholamines. The HPO axis is inhibited at all levels by various components of the HPA axis including glucocorticoids and catecholamines (Fig. 1). At a higher level CRH suppresses GnRH neurons of the arcuate and preoptic nuclei either directly or *via* arcuate POMC neuron β-endorphin release. During aseptic or septic inflammatory stress, inflammatory cytokines suppress reproductive function at several levels. These effects are exerted directly and indirectly by activating hypothalamic neural circuits that secrete CRH and POMC-derived peptides, as well as by peripheral elevations of glucocorticoids (Mastorakos et al., 2005). Alternatively, chronic exercise in highly trained athletes is associated with a decreased HPA response to exercise while they exhibit a chronic mild hypercortisolism at baseline that may represent a physiological adaptation. There is increasing incidence of exercise-related short- and long- term consequences, regarding the female athlete often described as the so-called "exercise-related female reproductive dysfunction". These consequences include hypogonadotrophic hypogonadism and amenorrhea, infertility, eating disorders, osteoporosis, coronary heart disease and “euthyroid sick” syndrome. Strenuous exercise can also affect the age of menarche if it is initiated before menarche (Mastorakos and Pavlatou, 2005).

6. Stress and pregnancy

Pregnant women are also confronted with stress factors including physical alterations, hormonal changes (often associated with rapid changes in mood), and pregnancy-specific anxiety, for example, fear of child integrity and fear of pain during delivery. Young age, poor education, low socioeconomic status, sexual abuse, unwanted pregnancy, having no partner, poor preparation for pregnancy or delivery, depressive symptoms and a psychiatric history are known to negatively influence psychic well-being of the pregnant woman, while other factors (adequate social support, older age, and having a paid job) contribute positively to this (Challis et al., 2001).

6.1. Maternal and fetal HPA axis in pregnancy and placental CRH

Pregnancy is a transient period of relative hypercortisolism. During pregnancy, placenta-derived CRH progressively increases in the

maternal circulation, especially during the third trimester, resulting to relatively increased circulating concentrations of cortisol which in its turn suppress maternal hypothalamic CRH secretion (Magiakou et al., 1996a). During late gestation, the activity of fetal HPA axis is enhanced, while premature activation of this axis may result from an adverse intra-uterine environment, such as hypoxemia and/or inflammation (Magiakou et al., 1996b). Placenta is considered a stress-sensitive organ and placental CRH by activating fetal HPA axis may trigger labor. Increased, normal or decreased placental CRH concentrations have been associated with pre-term, term, or post-term labor, respectively (Rakers et al., 2018). In the past, Newsham J et al found that pre-term fetuses had significantly greater umbilical arterial plasma EPI concentrations compared to term fetuses suggesting that stress in pre-term birth is different in preterm fetuses in general (Newnham et al., 1984). Higher concentrations of CRH and cortisol encountered in pre-term labor, support the role of the glucocorticoid-regulated PNMT enzyme in coverting NE to EPI as a mechanism explaining the higher EPI concentrations reported by Newsham et al in pre-term fetuses (Newnham et al., 1984).

Placental CRH, secreted in a pulsatile fashion drives maternal HPA axis in a non-circadian fashion. Maternal HPA axis is probably driven in a circadian fashion by another major ACTH secretagogue, the AVP of parvocellular PVN origin (Sandman et al., 2006). Increased uterine contractility at term and preterm results from activation and then stimulation of the myometrium. Activation can be provoked by mechanical stretch of the uterus and by an endocrine pathway activated from increased activity of the fetal HPA axis. Elevated maternal cortisol early in pregnancy predicts third trimester levels of placental CRH suggesting that early detection of stress signals by the placenta induce placental CRH release increasing thus, the risk for preterm delivery (Jones et al., 1989). Furthermore, the positive association of serum IL-1β and CRH levels in women with pre-term labor suggest the involvement of IL-1β in this pathophysiologic mechanism. A positive interaction might exist between IL-1β and placental CRH leading to enhanced production of the second, facilitating, thus, the onset of labor (Vitoratos et al., 2007).

6.2. How stress in pregnancy affects the fetal-maternal unit

Recently, we have suggested that stressful events during pregnancy accompanied by the stimulated maternal peripheral sympathetic nervous system could lead to enhanced placental CRH secretion *via* reduction of uterine blood flow, explaining the positive correlation of maternal stress state with placental CRH concentrations in normal human pregnancies (Goldstein, 2003). Fetuses of highly anxious women have been found to be more active than those of low anxious women suggesting that maternal stress reaches the fetus (Goldstein, 2003). Maternal stress during pregnancy might be associated with stress-induced secretion of catecholamines by the brain arousal and sympathetic systems (LC/NE) (Hobel et al., 1999). In the second trimester, assessment of maternal stress and CRH concentrations have been suggested as potential markers for women at risk of preterm birth (Hobel et al., 1999). An increased risk of spontaneous abortion has been found for a recent life stressful event (death of a relative or being victim of criminality) and for stress in the work place (Neugebauer et al., 1996).

Long-term maternal stress is associated with decreased insulin sensitivity and increased maternal stress hormones (CRH, cortisol) during pregnancy suggesting a direct effect of the long-term stress into decreased maternal insulin sensitivity during the human pregnancy (Fig. 3) (Valsamakis et al., 2017). Depression, anxiety and forms of work stress when experienced during the first trimester seem to be associated with an increased risk for preeclampsia in a later phase of pregnancy (Neugebauer et al., 1996; Kurki et al., 2000). Patients who eventually develop preeclampsia often have increased serum concentrations of placental CRH from 18 to 20 weeks of gestation onwards (Neugebauer et al., 1996). Finally, high levels of anxiety and depression result in reduced birth weight and smaller head size (a measure of brain development). This effect of prenatal stress is of the same magnitude as the effect of smoking (Lou et al., 1994). Evidence in animal models suggests that the HPA response to maternal depression is responsible, *via* induction of cortisol secretion, for these critical effects in both the mother and offspring (Weinstock, 2005). Prenatal stress transmits its affect *via* developing fetus even to the adult offspring. This results in impaired neurodevelopment, delayed cognitive and motor development with impaired behavior towards stressful conditions (Fatima et al., 2017).

Placental CRH, cortisol and other hormones, such as met-enkephalin, when crossing the placenta could result to slow growth rate, reduced birth weight and precipitate preterm labor in prenatally stressed infants (Paarlberg et al., 1999). Maternal stress is known to disturb the fetal glucocorticoid environment. The chance of delivering a low birth weight baby is higher if exposure to stress, daily hassles in particular, occurs during the first three months of pregnancy (Paarlberg et al., 1999). Excessive concentrations of glucocorticoids due to maternal administration of synthetic corticosteroids or to sustained endogenous fetal cortisol production, might result to intrauterine growth restriction (IUGR) (Del-Favero et al., 2004).

6.3. In utero stress and stigmata in adult life. Paradigms of intrauterine adaptive changes

In humans, the exposure of the mother to prenatal psychosocial stress could be associated with decreased insulin sensitivity in the offspring assessed during young adulthood (Entringer et al., 2008). Animal studies confirmed that increase in stress hormones and pro-inflammatory cytokines in the fetal compartment during sensitive or critical developmental windows can impact the structure and function of the brain and peripheral targets related to body composition, energy balance homeostasis, and metabolic function (*i.e.* adipose tissue, pancreas, and liver) (Entringer, 2013). A recent study showed that either reported maternal stress or elevated basal maternal salivary cortisol concentrations or both, were strongly and persistently associated with the infants' microbiota composition (Ziljmans et al., 2015). In addition, in rats increased norepinephrine plasma levels during pregnancy, under sympathetic stress conditions, correlated with decreased placental norepinephrine transporter functionality that provoked changes in the development of progeny and their fertility in adulthood (Piquer et al., 2017). In a recent study, prenatal stress exposure is a significant predictor of subsequent adult telomere length in the offspring (Entringera et al., 2011).

6.3.1. The IUGR paradigm

The term is assigned to newborns with a birth weight and/or birth length below the third percentile for their gestational age with pathologic restriction of fetal growth. IUGR is usually due to maternal, fetal, or placental factors. In rats, maternal stress was associated with IUGR and glucose intolerance (Paternain et al., 2013). Maternal stress disturbs the fetal glucocorticoid environment. In fetuses at term, maternal stress was associated with reduced body, adrenal and pancreas weight as well as plasma corticosterone and glucose levels (Ziljmans et al., 2015). Indeed, excess amounts of CRH and cortisol reaching the human fetal brain *in utero* during chronic maternal stress could alter personality and predispose to emotional or cognitive problems, attention deficit, hyperactivity, anxiety, language delay and depressive illness *via* changes in neurotransmitter activity (Fatima et al. 2017; Ward, 1991).

In a subgroup of IUGR fetuses reduced placental 11β-hydroxysteroid-dehydrogenase-type 2 (11βHSD2) activity and mRNA is observed, accompanied by a decrease in the ratio of cortisone to cortisol in the umbilical artery. These observations suggest that not only placental but also fetal 11βHSD2 activity may be compromised in idiopathic IUGR leading to newborns with lower cord blood glucose concentrations (Dy et al., 2008). Furthermore, other studies conclude that lower cortisol levels in children born IUGR may reflect impaired function of

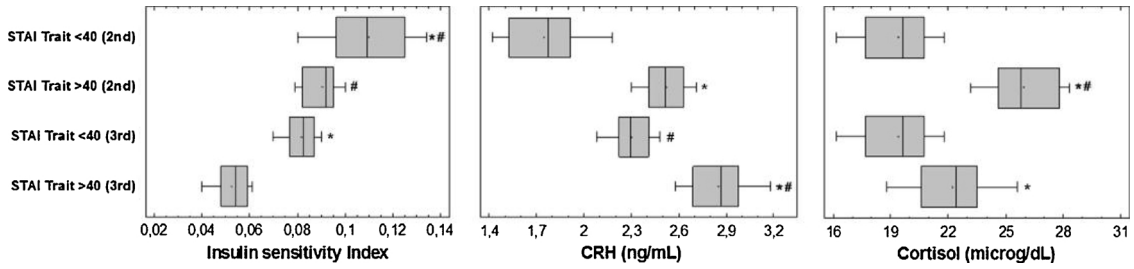

Fig. 3. Comparison of maternal ISI, CRH and cortisol values depending on STAI trait scores > 40 and < 40 in the 2nd and 3rd trimesters of normal pregnancy. Symbol "∗" indicates a statistically significant difference between groups of pregnant women compared within the same trimester; Sym ol "# "indicates statistically significant difference between groups of pregnant women with STAI scores either > 40 or < 40 in different trimesters. Statistical significance was set at $p < 0.01$. Boxes represent interquartile range; perpendicular lines inside boxes represent median value; cross represents mean marker; whiskers represent the lowest and highest observations, respectively (Adapted from reference No 71).

the HPA axis associated with this condition (Fattal-Valevski et al., 2005; Strinic et al., 2007). In pregnancies with IUGR or maternal prenatal anxiety, fetuses are not protected from increased maternal cortisol exposure leading to newborns with relatively lower cortisol concentrations (O Donnel et al., 2012).

There is no clear evidence regarding the effect of fetal sex upon fetal growth under maternal stress. The mechanisms of intrauterine programming, the critical time necessary to cause injury and participation of other factors remain unclear. Of note, certain authors have suggested that female fetuses are more likely to develop IUGR (Radulescu et al., 2013). In a retrospective study of 66,387 pregnancies female fetuses were more likely to experience fetal growth restriction. The authors concluded that fetal gender is independently associated with adverse pregnancy outcome although the added risk is relatively small (Melamed et al., 2010). Furthermore, it has been suggested that the timing of post-natal "catch-up growth" affects metabolism and appetite regulation in male rats born IUGR. Cianfarani et al. (Cianfarani et al., 2006) reported that children born small for gestational age (SGA) who do not show catch-up growth have significantly higher fasting levels of plasma cortisol than children born SGA and achieve catch-up growth. Although the vast majority of SGA children show catch-up growth by the second year of age, one in 10 does not. There is evidence to suggest that some of the metabolic consequences of intrauterine growth retardation in children born SGA can be mitigated by ensuring early appropriate catch-up growth, while avoiding excessive weight gain (Saenger et al., 2007). Another study concluded that catch-up growth in IUGR children might be affected by intrauterine reprogramming of the HPA axis, which may result in a permanent modification of the neuroendocrine response to stress: children with increased cortisol secretion may be at higher risk of growth failure (Cianfarani et al., 2007). In addition, in a study assessing chronic fetal stress authors found that umbilical cord plasma CRH level is extremely elevated in growth-retarded fetuses compared to that in normal fetuses with a trend of higher umbilical cord cortisol levels too (Goland et al., 1993). In many of the above studies the mode of stress applied to fetus is not clear and the methodology vague. In conclusion, the effect of pregnancy-related stress on IUGR fetuses regarding fetal growth and fetal HPA axis activity (increased or decreased) remains still unclear regarding the pathophysiological mechanisms involved (Fig. 4).

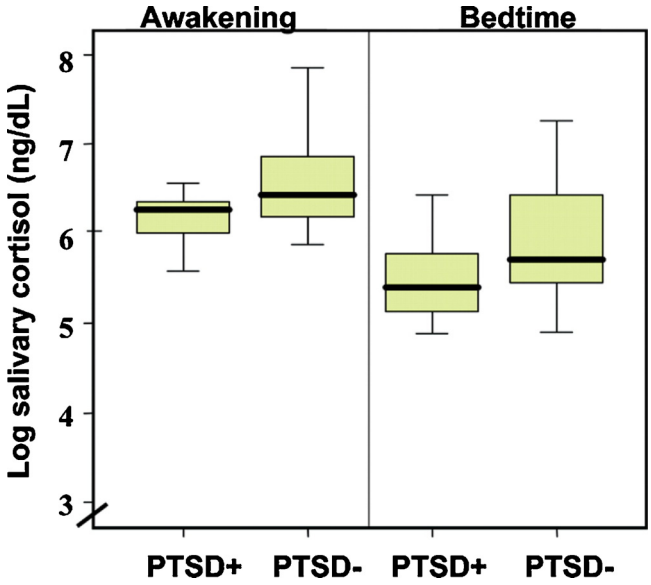

Fig. 4. Infant cortisol levels at awakening and bedtime, divided on the basis of presence or absence of maternal PTSD. The darkened vertical lines in each box represent the median values for the data, with the boxes representing data points within the upper and lower hinges (75th and 25th percentiles). No data points were more than 1.5 times the interquartile range from the median (*i.e.*, outliers). The logtransformed mean awakening cortisol levels in infants with and without maternal PTSD, respectively, were 6.39 ± 0.51 and 7.14 ± 1.14 pmol/liter, and bedtime levels were 4.90 ± 0.79 and 7.14 ± 1.14 pmol/liter (Adapted from reference No 97).

6.3.2. *The paradigm of parental stress*

In rats, gestational stress and excess maternal and fetal plasma corticosterone cause down-regulation of fetal glucocorticoid and mineralocorticoid receptors and impairment of the HPA axis feedback in infancy and adulthood. Early life stress, partially mediated by long-term glucocorticoid and/or neurotrophin signaling pathways, affects stress-susceptible regions of the brain. Maternal stress and depression lead to increase in fetal glucocorticoids influencing structural and functional development of hippocampus, hypothalamus and pituitary. Reprogrammed HPA axis leads to long life behavioral and functional changes affecting offspring neurogenesis and adult behavior (Paarlberg et al., 1999). Previous studies show a blunted ACTH fast feedback during normal aging. Hippocampal atrophy appears to be related to increased basal measures of HPA axis activity. It remains possible that age-associated changes in fast feedback may be related to changes to other brain sites, such as hypothalamus or pituitary (Wolf et al., 2002).

Prenatally stressed human infants have lower scores at the postnatal neurologic examination (Weinstock, 2005). However, other authors conclude in a review that there is little evidence, so far, that prenatal stress-associated altered function of the HPA axis mediates behavioral or cognitive alterations in childhood (Glover et al., 2010). In psychiatric literature, exposure to prenatal maternal stress is often regarded an important factor underlying several forms of psychopathology, including attention deficit hyperactivity disorder, schizophrenia, and depression. Stressful life experiences, in interaction with the genotype, result in epigenetic changes ultimately affecting the risk for mental disorders (Nestler, 2014). Many studies focused on methylation of the glucocorticoid receptor exon 1 F promoter following an initial observation that changes in this region could be modulated by the

environment. It is useful to examine whether methylation at specific sites within this promoter region may be particularly relevant to psychiatric vulnerability to stress-related outcomes although the extent of submethylation necessary for the induction of the gene expression as well as that of overmethylation necessary for the suppression of the gene expression are not known (Daskalakis and Yehuda, 2014). Furthermore, there is growing evidence from epidemiological, clinical, and molecular studies suggesting that conditions during early human development (*i.e.* embryonic, fetal and early postnatal periods of life) interact with the genome and may alter the structural and functional integrity of the developing brain and other peripheral systems. Indeed, telomere biology (*i.e.* chromosomal telomere length and the activity of the enzyme telomerase) during development may be receptive to the influence of intrauterine and other early life conditions (IShalev et al., 2018). Thus, the intrauterine impact of stressful stimuli warrants particular consideration as a candidate mechanism implicated in the programming of the telomere biology system (Entringer et al., 2012). These stimuli may alter or program the telomere biology system (*i.e.* the initial setting of telomere length and telomerase expression capacity) in a manner that accelerates cellular dysfunction, aging and disease susceptibility over the lifespan (Entringer et al., 2013)

Lower cortisol levels were observed in both mothers and babies of mothers who developed post-traumatic stress disorder (PTSD) in response to September 11 compared with mothers who did not develop PTSD and their babies. Lower cortisol levels were most apparent in babies born to mothers with PTSD exposed in their third trimester. The effects of maternal PTSD related to the HPA axis reactivity can be observed very early in the life of the offspring and underscore the relevance of *in utero* contributors to putative biological risk for PTSD (Yehuda et al., 2005). In fact, acute maternal stress perceived during different trimesters in pregnancy, may modify the offspring's HPA axis reactivity, eventually *via* epigenetic alterations. This hypothesis was investigated in cohorts and other populations of Holocaust survivors offsprings by showing that Holocaust exposure had an effect on FKBP5 methylation observed in exposed parents as well in their offsprings (Yehuda et al., 2016). FK506-binding protein 2 in humans is encoded by the *FKBP5*gene. It is a member of the immunophilin protein family, which play a role in immunoregulation and basic cellular processes involving protein folding and trafficking. Genetic studies have identified a role for FKBP5 in PTSD, depression and anxiety (Binder et al., 2008). Methylation of FKBP5 leads to decreased action of FKBP5 protein resulting to increased sensitivity of glucocorticoid receptor that leads to lowering of the inhibition threshold for the HPA axis (Binder et al., 2008). Subsequently, circulating cortisol levels are found decreased. Interestingly, Yehuda et al. have shown that the Holocaust experience induced transgenerational effects on the methylation of the FKBP5 gene at the level of germline cells. Methylation of the FKBP5 gene of the first generation correlated positively with that of the second generation (Lehrner et al., 2014). In addition, maternal PTSD was associated with greater sensitivity to glucocorticoids in the offspring of Holocaust survivors (Bowers and Yehuda, 2016).

These findings have been extended to less extreme forms of stress, where differential physical, behavioral, and cognitive outcomes are observed in affected offspring. Parental stress-mediated effects in the offspring could be explained by genetics or social learning theory (Dy et al., 2008)

7. Conclusions

Stress is a physiological adaptive mechanism developed through evolution as a "physiological" response to stressors. The degree of the adaptive response to stressors depends on genetic factors, personality characteristics, previous experience, support from the social environment, and the way of coping with stress. Any of the components of the stress pathways has the potential to inhibit reproduction. Acute stress impairs steroidogenesis and angiogenesis in association with ovulation failure whereas in some other instances it may induce ovulation. Chronic stress has become a commonly cited factor when discussing unexplained reproductive failures. Chronic stress prolongs a generalized catabolic state and, thus, sustained HPA hyperactivity can progressively lead to decreased lean body (muscle and bone) mass, increased visceral adiposity and insulin resistance thus affecting HPO axis. In PCOS, chronic life stress needs to be studied as another homeostatic disruption model leading to endocrine dysregulation. FHA is a form of chronic anovulation that is not due to identifiable organic causes but often associated with stress, weight loss, excessive exercise or a combination of them. Reduced GnRH drive results in LH and FSH levels insufficient to maintain full folliculogenesis and ovulatory ovarian function. Energy drain may have an important modulatory effect on the hypothalamic pituitary set point at puberty and, in combination with low body weight, may prolong pre-pubertal state and induce amenorrhea.

In pregnancy, maternal stress is known to disturb fetal glucocorticoid environment. Fetuses of high anxious women have been found to be more active than those of low anxious women illustrating that maternal stress signal reaches the fetus. An increased risk of spontaneous abortion has been found for a recent life event (death of a relative or being victim of criminality) and for stress in the work place. In humans, maternal exposure to prenatal psychosocial stress could be associated with decreased insulin sensitivity in the offspring assessed during young adulthood as well as in animals in IUGR cases. The chance of delivering a low birth weight baby is higher if exposure to stress, daily hassles in particular, occurs during the first trimester of pregnancy. Animal studies confirmed that increase in stress hormones and pro-inflammatory cytokines in the fetal compartment during sensitive or critical developmental windows can impact the structure and function of the brain and peripheral targets which are related to body composition, energy balance homeostasis, and metabolic function (*i.e.* adipose tissue, pancreas, and liver). Stressful life experiences, in interaction with the genotype, result in epigenetic changes that result in altered gene expression, ultimately affecting the risk for mental disorders. The effect of pregnancy-related stress on IUGR fetuses regarding fetal growth and fetal HPA axis activity (increased or decreased) remains still unclear regarding the pathophysiological mechanisms involved.

Finally, regarding the mother, pregnancy acts as a medical stress test. Pregnancy can temporarily unmask subclinical diseases, which may return later in the mother's life as *e.g.* type 2 diabetes mellitus (Williams, 2003). Indeed, women who develop pregnancy-induced hypertension, pre-eclampsia and gestational diabetes mellitus are at increased risk for developing cardiovascular disease later in life (Sibai et al., 1986) while early and late pre-eclampsia are associated with low and high birth weight babies, respectively (Xiong et al., 2000). Interestingly, women who delivered pre-term (before 37 weeks of gestation) are at an increased risk of death from stroke (Irgens et al., 2001). There may be a pathophysiological link between early pre-eclampsia, preterm labor, low birth weight and maternal cardiovascular disease (Smith et al., 2001).

Author contributions

Georgios Valsamakis wrote the article and contributed to the general outline and concept of the article, George Chrousos reviewed the article, George Mastorakos suggested the concept, drew the general outline of the article and reviewed the article.

Financial disclosure statement

Authors have nothing to declare. All authors agreed to the content of the article.

Conflict of interest

Authors have nothing to declare.

Declarations of interest

None.

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