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Evaluation of stress hormones in women with primary infertility

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Abstract

Hormonal and neuroendocrinal factors play a major role in the etiology of infertility by disturbing reproductive homeostasis. This case-control study evaluated stress and thyroid hormones in women with primary infertility. A total of one hundred twenty women within the age range of 20 to 38 years were studied where seventy-six belonged to the category of primary infertility, and forty-four were normal controls. Early follicular phase morning fasting blood sample was used for estimation of serum cortisol, adrenocorticotropic hormone (ACTH), dehydroepiandrosterone (DHEA), and thyroid-stimulating hormone (TSH) through ELISA. The results indicated significantly higher mean values among the infertile group for cortisol (r=0.32, p=0.005), ACTH (r=0.28, p=0.01), and TSH (r=0.25, p=0.02) compared to the control group whereas DHEA did not show any significant association (r=-0.15, p=0.12). This implies that hyperactivation of the hypothalamic–pituitary–adrenal and thyroid axes may be involved in the pathogenesis of impaired fertility, thereby justifying expanded endocrine assessment in the workup of infertility. The results further support ongoing efforts directed at discovering hormonal biomarkers that can inform treatment strategies.

Keywords: Cortisol, TSH, DHEA, ACTH, Primary Infertility.

Introduction

Infertility is a principal major global health issue that significantly affects the quality of life and psychosocial well-being of couples. The definition by WHO puts it: Medical care for infertility begins after one year of regular, unprotected sexual relations without conception. An estimated 15% of couples globally suffer from this condition; most cases are due to factors attributable to women (WHO, 2021). This underscores considerable concern regarding primary infertility—a situation where the woman has never borne a child—because it brings into play intricate disturbances in reproductive physiology that may be hormonal, anatomical, or even psychological in their origins (Mascarenhas et al., 2012). Biologic considerations aside, increasing attention has recently been focused on the contribution of psychological stress and stress-related endocrine changes to the causation of infertility.

The hypothalamic-pituitary-gonadal (HPG) axis is at the center of female reproductive health. It controls ovulation and follicular development as well as general fertility but does not exist or operate in a vacuum. The HPG has close functional and structural relations with the hypothalamic-pituitary-adrenal (HPA) axis and other endocrine systems that mediate responses to stress (Al-fahham, 2019). Neuroendocrine signaling, glucocorticoid secretion, and sympathetic activation are pathways through which psychological and physical stressors disrupt reproductive function. Endocrine disarray induced by stress is viewed increasingly as an adjustable component of infertility. The exact mechanisms together with pathway biomarkers that interlink stress with reproductive dysfunction are under study (Al-fahham et al., 2016).

HPA, or the hypothalamic-pituitary-adrenal, axes are the principal route by which stress initiates hormonal cascades. The paraventricular nucleus of the hypothalamus releases corticotropin-releasing hormone (CRH) that results in the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH stimulates glucocorticoids' synthesis in and release from the adrenal cortex; in humans, these glucocorticoids are mainly cortisol (Tsigos & Chrousos, 2002). Cortisol is one of those hormones vital to homeostasis under conditions of stress and involves metabolism, immune response, and cardiovascular function. However physiological pathways induced by chronic HPA activation disrupt reproduction through interference with GnRH pulsatility leading to interference with follicular development as well as ovarian steroidogenesis (Whirledge & Cidlowski, 2017). This has led to a situation whereby raised cortisol levels have been associated with menstrual irregularities together with anovulation and reduced fertility outcomes making it imperative a biomarker of stress-related female infertility (Anderson et al., 2010).

Another essential marker of HPA activity is ACTH, since it is an upstream modulator of cortisol. The pituitary component is best assessed by measuring plasma ACTH, while the downstream chronic effects or responses to stress can be assessed by measuring serum cortisol levels. Inappropriate secretion of ACTH has been observed both under conditions of high psychosocial stress and in various endocrine diseases that are associated with reproduction pathology (Charmandari et al., 2005). Therefore, simultaneous measurement of serum concentrations of both hormones will offer a more precise estimation regarding which part of the HPA axis is diseased and will also help differentiate between primary adrenal and central types of abnormalities. Since changes in ACTH secretion directly modify output of adrenal steroids—particularly androgens like dehydroepiandrosterone (DHEA)—its possible involvement in infertility should be further evaluated.

DHEA is a steroid hormone produced by the adrenal cortex zona reticularis under ACTH regulation. It works as the precursor of sex steroids-estrogens and androgens-thereby linking stress responses with reproductive physiology. Unlike chronic stress where levels of DHEA are low, protective antiglucocorticoid and neurosteroid effects seem to be lost through reduced available DHEA during prolonged exposure to stress, as described by Maninger et al., 2009. In fact, DHEA seems to play some role in follicular development or oocyte quality since reduced production of this hormone has been associated with diminished ovarian reserve and bad reproductive outcome Weghofer et al., 2012 Moreover on the other hand pathologically increased adrenal androgens hinder normal folliculogenesis and ovulatory function seen in female patients suffering from either pathological increased adrenal activity or polycystic ovary syndrome PCOS Therefore measuring DHEA together with cortisol and ACTH might help bring more details into how stress hormones interfere with fertility problems.

The hypothalamic-pituitary-thyroid axis also makes a great contribution to the fertility condition. The thyroid hormones control the basal metabolic rate and energy homeostasis, as well as reproduction. Most commonly, it is hypo- and hyper-functioning of this gland that leads to menstrual irregularities, and unovulation, and results in infertility. In general, the thyroid hormones are mainly controlled by thyroid-stimulating hormone (TSH) which anterior pituitary releases under the action of thyrotropin-releasing hormone (TRH). Subclinical conditions mostly in the form of somewhat increased TSH often occur in women of reproductive age and can result in reduced fertility even when overt hypothyroidism is not present. Further evidence proves that stress would alter thyroid function via direct interaction with glucocorticoids on one hand or through changing pituitary signaling pathways on the other (Miller et al. 2007). Thus, knowledge about any interference of another axis obtained by studying TSH levels together with those found for stress-related

adrenal hormones could help bring out new dimensions regarding hormonal involvement in primary infertility.

Cortisol, ACTH, DHEA, and TSH are therefore hormonal markers that play key roles in the physiology of stress and reproduction. Cortisol is a classic marker of chronic stress exposure and related reproductive inhibition since it is an end product of HPA axis activation. This pathway provides pituitary-adrenal signaling (central versus peripheral dysregulation) insight. DHEA is another adrenal hormone regulated by stress but important as a reproductive precursor; abnormalities are associated with ovarian reserve and oocyte quality. TSH is informative about thyroid axis function, interacting with both the stresses and reproductive axes, and thus menstrual regularity and ovulatory capacity.

There has been a scarcity of such concurrent evaluations in primary infertile females to date, despite an increasing appreciation of the link between stress and infertility. Most studies continue assessing only cortisol in their attempts to measure stress, thereby ignoring a broader endocrine interaction network that might account for variations in reproductive outcome (Greil et al., 2011). Further, including ACTH and DHEA- will offer a wider view regarding the regulation of HPA axis activities. The inclusion of TSH will throw some light upon this often-neglected triumvirate relationship between thyroid–stress–fertility. This study assesses these four hormones together in an endeavor to bring out the contribution of endocrine changes related to stress causing primary infertility and appropriate biomarkers for early detection as well as management avenues. The result can be very useful because the analysis would give a clear idea about how much psychological trauma due to infertility further enhances stress resulting in hormonal imbalances accompanied by reduced fertility creating a vicious cycle (Gameiro et al., 2014).

The aim of this study is to evaluate the role of stress hormone (cortisol, ACTH, DHEA, and TSH) in the pathophysiology of primary infertility in women.

Methods

Patients and data collection

This case-control study included the evaluation of certain stress-related and thyroid hormones in women having primary infertility. 120 women, between 20 to 38 years of age, were taken from the infertility and gynecology outpatient clinics. Out of these, 76 were diagnosed with primary infertility while the remaining 44 were fertile and served as a control group. To define the diagnosis, primary infertility was defined as the inability to conceive after at least 12 months of regular unprotected sexual intercourse without any previous pregnancy. On the other hand, the controls included those women who had at least one previous spontaneous conception.

Women with primary infertility were taken in the patient group. Women with secondary infertility-that is, women who have attained pregnancy earlier-were kept as the exclusion criteria. Patients having any chronic systemic disease like diabetes mellitus, hypertension, or cardiovascular diseases, and chronic renal or liver disease have been excluded from the study. Endocrine disorders in women, such as Cushing's and Addison's disease; overt thyroid disease; known adrenal disorder, were also kept in the exclusion criteria of this study. More exclusion criteria have included those who used hormonal therapy, corticosteroids, or psychotropic medications in the last three months and who are currently pregnant or lactating. The control group will consist only of healthy regularly menstruating women having no chronic illness and a history of infertility. The institutional ethics committee gave its review and approval. All steps followed strick the rules of the Declaration of Helsinki. Written informed consent was gotten from all members before enrollment.

Morning samples were taken at 8:00 and 10:00 AM followed by an overnight fast of 8-10 hours as a way of minimizing diurnal and menstrual cycle variability on hormone values. Blood was drawn during the early follicular phase between days 2 and 5 of the menstrual cycle to provide baseline hormonal values not influenced by luteal fluctuations, thus all subjects were asked to abstain from any vigorous physical exercise, intake of caffeine, alcoholic drinking, or smoking at least for 12 hours before the blood draw. About 5 mL of venous blood will be withdrawn from each subject and transferred into plain vacutainer tubes. The samples will be left to clot at room temperature then they will be centrifuged at 3000 revolutions per minute (rpm) for ten minutes so that serum can be separated. The obtained serum aliquots will be kept at -20°C until analysis time.

The hormones covered in this study were cortisol, adrenocorticotropic hormone (ACTH), dehydroepiandrosterone (DHEA), and thyroid-stimulating hormone (TSH). All concentrations have been determined from serum by the use of commercially

available enzyme-linked immunosorbent assay (ELISA) kits under standard users' protocols as provided by the manufacturers. To result validation, measurements were run in duplicate, and variation for both intra- and inter-assay never exceeded 10%.

Statistical Analysis

Data has been analyzed with the use of SPSS software, version XX. Quantitative variables have been expressed as mean ± standard deviation. An independent sample t-test has been used in the comparison of mean hormone levels between the groups of infertile women and controls. Pearson's correlation analysis has been used in assessing the relationship between hormone concentration and demographic parameters. A p- value less than 0.05 has been taken to indicate statistical significance.

The Results

There was no statistically significant difference in the comparison of age and body mass index (BMI) between the primary infertility group and the control group ($p > 0.05$ for both variables). Most women in both groups were within the age range of 26-35 years; this is the usual reproductive age group presenting for evaluation of infertility. Similarly, BMI distribution patterns did not show any marked difference between the two groups, though a slightly higher proportion of women with infertility were overweight or obese compared to controls. The lack of significant demographic variation between the two groups reiterates that age and BMI factors are well-matched, thus reducing any confounding effect that might be presumed on hormonal analysis.

Table 1. Comparison of age and BMI between infertile and healthy women

Items		Patients (N= 76)		Control (N= 44)		(P value)
		Freq.	%	Freq.	%	
Age	16-25	10	13.2	6	13.6	0.412 (NS)
	26-35	44	57.9	26	59.1	
	36-45	20	26.3	11	25	
	> 45	2	2.6	1	2.3	
BMI	Underweight	5	6.6	4	9.1	0.07 (NS)
	Normal	28	36.8	22	50	
	Overweight	25	32.9	12	27.3	
	Obese	18	23.7	6	13.6	

*** Non- Significant at P value >0.05**

The greatest percentage of women-44.74% had infertility of between 5 and 10 years, while 28.95% had less than five years, and 26.31% had more than ten years. This would also indicate that most patients present for clinical assessment and treatment after many years of unprotected but unsuccessful conception, which may reflect delayed health-seeking behavior, sociocultural factors, or even the possibility of access to fertility care services. The data above support an argument concerning how long a disease can continue untreated among a large number of patients; thus, an early detection program with timely intervention and comprehensive management strategies is required to improve reproductive outcomes.

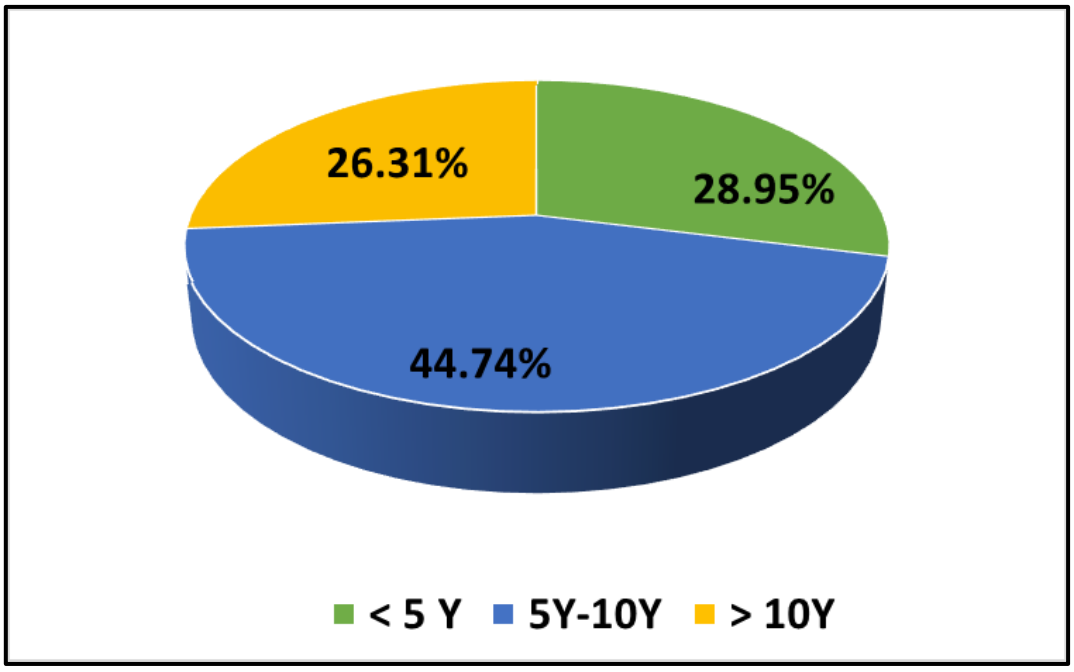

Figure 1. Percentage of patients according to the duration of infertility

There was a significant difference in the level of all measured hormones between women with primary infertility and healthy controls. Cortisol, ACTH, DHEA, and TSH mean levels were higher in patients than in controls indicating that the population under study is suffering from some degree of thyroid maladjustment as well as activation of the hypothalamic-pituitary-adrenal axis. Such changes can result in decreased reproductive function through effects on ovulatory cycles, oocyte quality, and endometrial receptivity. Indeed, prior studies have shown hormonal imbalances induced by stress to be associated with infertility (Table 2).

Table 2. Comparison of levels of hormones between infertile and healthy women

Hormones	Patients (N= 76)		Control (N= 44)		(P value)
	Mean	SD	Mean	SD	
Cortisol (µg/dL)	18.5	4.0	15.0	3.5	0.001 *
ACTH (pg/mL)	55	12	42	10	0.002 *
DHEA (µg/dL)	5.8	1.5	4.5	1.2	0.01 *
TSH (mIU/L)	3.2	0.9	2.5	0.7	0.005 *

*** High Significant at P value <0.01**

Stress-related and thyroid hormones among infertile women by duration of infertility were progressively higher as the period of infertility increased. Cortisol and ACTH levels were high in those women whose infertility has persisted for more than 10 years, thus proving chronic activation of the hypothalamic-pituitary-adrenal axis. Similarly, DHEA and TSH levels manifested modest but progressive elevation in groups which may indicate possible involvement of adrenal and thyroid glands in prolonged infertility. This information brings out very clearly that infertility duration has a direct bearing on endocrine regulation, which can be very useful when applied to targeted therapeutic interventions (table 3).

Table 3. Comparison of levels of hormones among groups of infertile women classified according to duration of infertility

Hormones	5 Years (N= 22)		5-10 Years (N= 34)		> 10 Years (N= 20)		(P value)
	Mean	SD	Mean	SD	Mean	SD	
Cortisol (µg/dL)	17.5	3.5	18.8	4.0	19.5	4.2	0.04 *
ACTH (pg/mL)	52	11	56	12	59	13	0.03 *
DHEA (µg/dL)	5.5	1.3	5.9	1.5	6.2	1.6	0.05 *
TSH (mIU/L)	3.0	0.8	3.2	0.9	3.4	1.0	0.04 *

*** Significant at P value <0.05**

The correlation analysis of BMI with selected hormonal biomarkers disclosed differential associations. As presented in both the table and scatter diagrams, BMI has a moderately positive relationship with cortisol (r = 0.32, p = 0.005) and ACTH (r = 0.28, p = 0.01). This indicates that high BMI may be associated with increased activity of the hypothalamic-pituitary-adrenal (HPA) axis. Equally importantly, a significant positive relationship was also found between BMI and TSH (r = 0.25, p = 0.02). This could indicate an adaptive or compensatory mechanism of thyroid dynamics in regulation concerning high body mass. On the contrary, the relationship that existed between BMI and DHEA was negative but not significant statistically (r=-0.15, p=0.12), indicating that this adrenal androgen is not very strongly influenced by BMI within the studied group (table 4, figure 2).

Table 4. Pearson correlation coefficient between BMI and list of hormones used in the study

Hormones	Pearson correlation coefficient (r)	P value*
Cortisol	0.32	0.005 **
ACTH	0.28	0.01 **
DHEA	-0.15	0.12
TSH	0.25	0.02 *

*** Significant at P value <0.05; ** High Significant at P value <0.01**

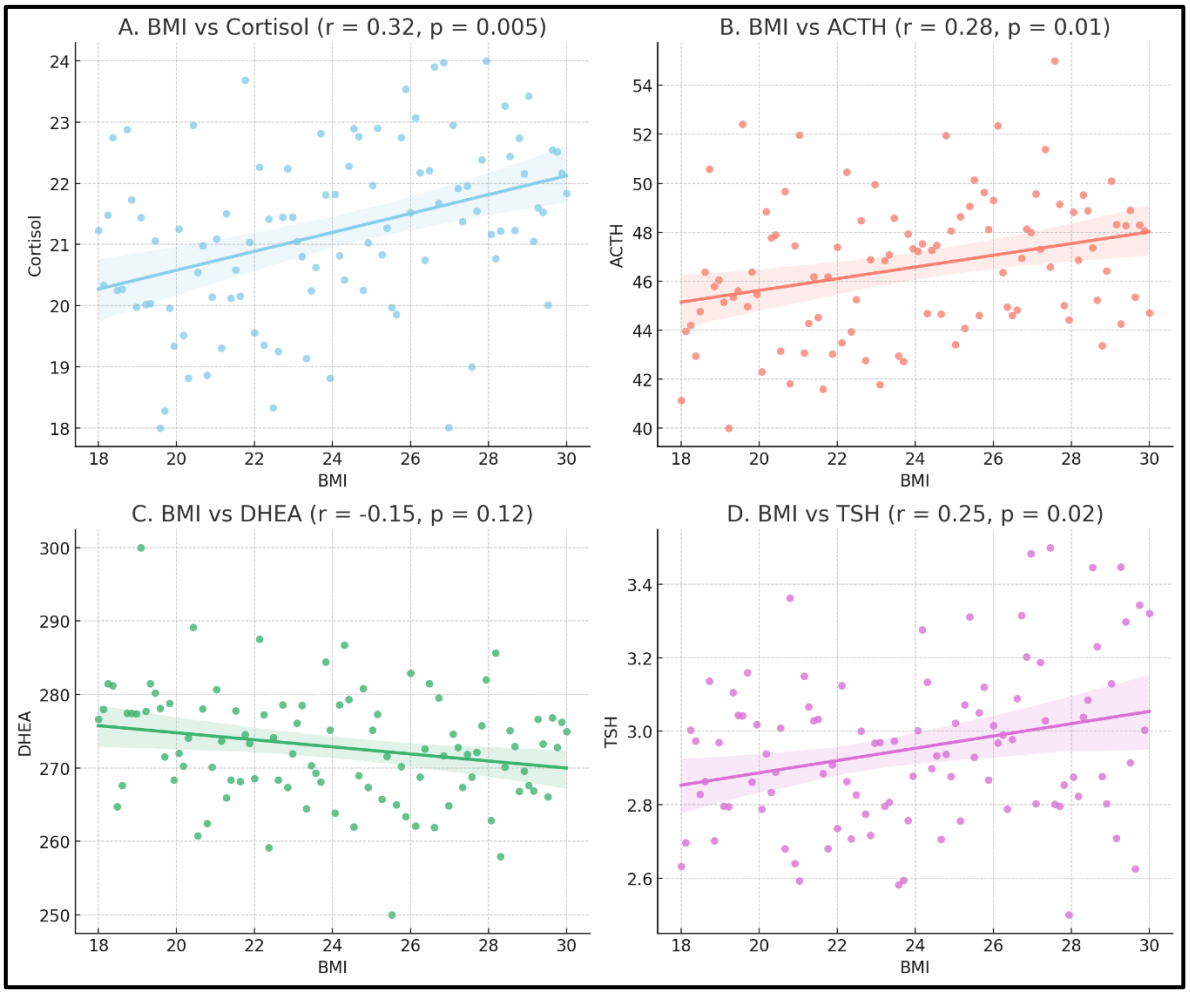

Figure 1. Scatter plots for correlation between Body Mass Index (BMI) and Hormonal Biomarkers (Cortisol, ACTH, DHEA, and TSH) with Corresponding Pearson's r and p-values

Discussion

The relationship between infertility and stress hormonal balance depicts complex feedback systems that eventually merge to help sustain homeostasis during metabolic stress. Increased BMI is an active participant in driving endocrine shifts through very many axes-from central nervous system adjustments to peripheral metabolic requests. Among the major systems most typically brought into play here is the hypothalamic–pituitary–adrenal, or HPA axis. High adiposity has been associated with dysfunctional regulation of this axis in various populations across the globe such that changes go well beyond static endocrinological levels to include alterations in rates of cortisol clearance, receptor sensitivity, and even central drive. Fat tissue is particularly abdominal fat tissue is very rich in glucocorticoid receptors; therefore, obesity-related impaired feedback inhibition determines sensitivity reduced by exposure to long-term cortisol (Adam & Epel, 2007). Also, the 11β-hydroxysteroid dehydrogenase type 1 enzyme 11β-HSD1 upregulates more abundantly in fat depots. Cortisol bioactivity at the local level is amplified and systemic regulation is influenced (Walker & Tomlinson, 2015; Duma, Jewell, & Cidlowski, 2015). Besides this, obesity increases allostatic load. This means there is more chronic psychosocial and metabolic stress that keeps HPA activity heightened wherein a dynamic response to small stimuli is elicited in a state of pathology (McEwen & Stellar, 1993; GonzálezClemente et al., 2014).

Whereas cortisol and ACTH seem to follow this path, adrenal androgens like dehydroepiandrosterone (DHEA) most often present a different pattern. The split between glucocorticoids and adrenal androgens shows how complicated the process of steroidogenesis is. Competition for precursor pools in the adrenal cortex under conditions of high ACTH drive allows for favoring the production of one hormone, usually cortisol, while DHEA synthesis is lessened (Arnaldi & Boscaro, 2006). Binding proteins such as sex hormone–binding globulin

(SHBG) further change free fractions of hormones lowering effective DHEA activity though total concentrations remain binding proteins such as SHBG are often reduced in obesity (Langer et al., 2019). Age does because naturally over the lifespan, DHEA falls; therefore, this path may overlay with that added fatness (Labrie, 2010). The cortisol-to-DHEA ratio has thus been advanced as a better sensitive indicator of metabolic stress than any one hormone alone. High ratios have consequently been associated with fast aging, and immune maladjustment added cardiometabolic risk.

Thyroid function can also be considered as a reaction to the state of body composition, and it is in this context that BMI-related variations in the TSH come into focus. The major pathway involved includes increased leptin, an adipokine of which levels are elevated in adiposity and which signals energy sufficiency to the hypothalamus. Leptin stimulates TRH secretion by which pituitary TSH release is increased, consequently affecting thyroid hormone production (Moretto et al., 2010). Changed deiodinase activity in obesity may further increase peripheral transformation of T4 to T3 creating a higher set point for TSH without any real decrease in thyroid hormone available (Araujo et al., 2013). While for some clinicians such an increase would indicate subclinical hypothyroidism, others would argue that it presents a compensatory physiological response to maintain energy expenditure with increased body mass (Michalaki et al., 2006). This means that overdiagnosing thyroid dysfunctions within the obese population can be avoided if adaptive and pathological responses are clearly separated.

Endocrine axes do not function independently. There is cross-talk between the HPA and hypothalamic–pituitary–thyroid (HPT) axes. In general, glucocorticoids can inhibit the secretion of TRH and TSH. Receptor sensitivity rather than simple direct chronic moderate glucocorticoid inhibition recalibrates sensitivity, allowing leptin-driven stimulation to TSH to remain or even dominate(McAdams-DeMarco et al., 2020). That type of low-grade chronic inflammations also find a way in through their effects on both these axes via cytokines, particularly interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α), since they also affect baseline settings for hormones(Pearce, 2008; Cizza & Rifai, 1996). Another result of obesity that complicates matters is insulin resistance because this will influence not only deiodinase activity but also 11β-HSD1 expression and hence links thyroid and cortisol metabolism with metabolic control(Livingstone et al., 2000; Meier et al., 2015). This has suggested that the systemic endocrine stress imposed by adiposity reverberates across several hormonal axes.

From a clinical point of view, the relevance of these interplays goes much beyond descriptive endocrinology. Hormonal ratios, and particularly the cortisol-to-DHEA ratio, may become a more accurate biomarker for metabolic health and resilience to stress than the levels of individual hormones. High ratios have been associated with adverse outcomes of vulnerability to cardiovascular disease, cognitive decline, and general frailty (Luo et al., 2014). This makes an immediate assumption about possible clinical applications in risk stratification and monitoring intervention efficacy. Further studies show pharmacological research that is encouraged by results in modulating relevant enzymatic pathways. For instance, selective 11β-HSD1 inhibitors demonstrate benefits in visceral adiposity as well as improving insulin sensitivity hence validating therapeutic hope on cortisol metabolism in obesity (Rafacho et al., 2014).

Endocrine responsiveness to obesity underscores the role of precision medicine in the management of this disease. Polymorphisms, early life exposures, and epigenetic modifications ensure individual variability in endocrine responsiveness, thus suggesting that personalized approaches would optimize treatment. A description of patients with maladaptive HPA or HPT responses will go a long way in refining interventions that may include stress reduction or thyroid hormone support anti-inflammatory strategies or even metabolic therapies. There is a need for longitudinal studies in order to further clarify whether observed alterations in hormonal levels are causally related to the development of obesity or are adaptive responses. Such studies constitute intervention studies whereby lifestyle modification, pharmacotherapy, and bariatric surgery are introduced that will further elucidate whether and how normalization of body weight alters these endocrine axes.

Other limitations in the interpretation of endocrine-obesity relationships have to be noted. Cross-sectional designs do not permit causality, and such confounders as age, sex, circadian rhythms, and medication usage make interpretation difficult. Many hormones show diurnal variation, single sampling cannot adequately appreciate this complexity even when standardized by time of day.

Also, this population most likely does not fully represent broader demographics; therefore, results have limited generalizability. It should consequently inspire future studies to include repeated sampling and stress challenge protocols on wider biomarker panels that would incorporate inflammatory mediators and metabolic indices. The integration of endocrine data with genomic and epigenetic markers may help identify why certain individuals are more vulnerable to obesity-related endocrine dysregulation.

Conclusion

Endocrine regulation reflects the multifactorial relationship between neuroendocrine, metabolic, and inflammatory pathways in the control of infertility. Previous evidence fully supports the claim that hypothalamic-pituitary-adrenal and thyroid axis disturbances play a major role in eliciting improper output regarding reproduction while making a weaker or inconsistent relationship with adrenal androgens. More insight can be gained by analyzing hormonal ratios and longitudinal patterns. Mechanistic pathways and specific interventions to restore hormonal balance and bring about improved fertility outcomes are matters for future study.

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