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METABOLIC HORMONAL ALTERATIONS IN FUNCTIONAL HYPOTHALAMIC AMENORRHEA AND ANOVULATION ASSOCIATED WITH POLYCYSTIC OVARY SYNDROME

Shalini Jamwal[1]*, Abhishek Soni[2]

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ABSTRACT
Background: Polycystic ovary syndrome (PCOS) is a multifaceted endocrine disorder affecting many women during their reproductive years. It is characterized by oligo/amenorrhea, anovulatory cycles, polycystic ovaries, and insulin resistance. This review explores the hormonal and metabolic alterations associated with PCOS, comparing them to functional hypothalamic amenorrhea (FHA). Key aspects include the abnormally high LH pulse frequency in PCOS, indicating hyperactive gonadotropin-releasing hormone (GnRH), and the role of hyperandrogenemia in exacerbating the condition by increasing LH pulse secretion from the pituitary gland. Additionally, the review examines the neuroendocrine basis for PCOS. **Methods:** The methodology involved analyzing neuroendocrine pathways and physical manifestations through PubMed, ScienceDirect, and Scopus databases. Findings indicate that PCOS is primarily characterized by androgen excess, ovulatory dysfunction, and disruption of the hypothalamic-pituitary-ovarian (HPO) axis. Hormonal dysregulation includes disturbances in GnRH, insulin, LH/FSH ratio, and androgens. GnRH stimulates LH and FSH release from the pituitary, regulating ovarian function, while Anti-Müllerian hormone (AMH) inhibits follicular development in PCOS. **Conclusion:** The review concludes by highlighting the hormonal alterations, including decreased frequency and amplitude of LH pulses, disruptions in GnRH, LH, and FSH. Genetic predispositions and disturbances in the LH/FSH ratio can lead to impaired follicle growth and polycystic ovaries. This comprehensive exploration underscores the importance of understanding the hormonal and neuroendocrine mechanisms underlying PCOS, contributing to better diagnosis and treatment strategies.

INTRODUCTION

Polycystic ovary syndrome (PCOS) stands out as one of the most prevalent endocrine disorders affecting women of reproductive age. It is characterized by a constellation of symptoms, including hyperandrogenism, chronic anovulation, and the presence of polycystic ovarian morphology [1]. This syndrome presents a multifaceted disruption in the intricate hormonal balance governing reproductive function. At the core of PCOS lies an

[1]*Department of Pharmacology, School of Pharmacy, Abhilashi University, Chail Chowk, Mandi (HP), India*
[2]*Department of Pharmaceutics, Abhilashi College of Pharmacy, Nerchowk, Mandi (HP), India*
For Correspondence:** **abhisoni334@gmail.com

intricate interplay between hormones, particularly androgens, and estrogens, which are pivotal for regulating various physiological processes, including ovarian function. In PCOS, this delicate balance is disrupted, leading to excessive androgen levels, which can manifest as hirsutism, acne, and male-pattern baldness [2]. Moreover, disturbances in estrogen metabolism contribute to irregular menstrual cycles and infertility, hallmark features of PCOS [3]. The pathophysiology of PCOS is intricately tied to dysregulation within the hypothalamic-pituitary-ovarian (HPO) axis. This axis orchestrates the secretion of hormones essential for ovarian function. Dysfunctions within this axis can result in chronic anovulation, where the ovaries fail to release a mature egg during menstrual cycles. Consequently, women with PCOS often experience irregular or absent menstrual periods, contributing to difficulties in conceiving. Polycystic ovaries, characterized by accumulating numerous small follicles within the ovaries, further define PCOS [4]. These follicles, typically numbering 20 or more, disrupt normal ovarian morphology and function. While not present in all cases of PCOS, the presence of polycystic ovaries serves as a diagnostic criterion and underscores the ovarian component of the syndrome. PCOS is a complex endocrine disorder marked by disturbances in androgen and estrogen metabolism, chronic anovulation, and the presence of polycystic ovaries. Understanding the intricate interplay of hormonal dysregulation and ovarian dysfunction is crucial for effectively managing and treating this prevalent condition [5]. Anovulation, a hallmark of PCOS, stems from hormonal imbalances and is a primary driver of infertility in affected individuals. This condition occurs when an egg fails to emerge from the ovary during the menstrual cycle, leading to irregular menstrual cycles, a cardinal symptom of PCOS. Ovulation, a complex process governed by a delicate interplay of hormones, typically occurs around the fourteenth day of a 28-day menstrual cycle [6].

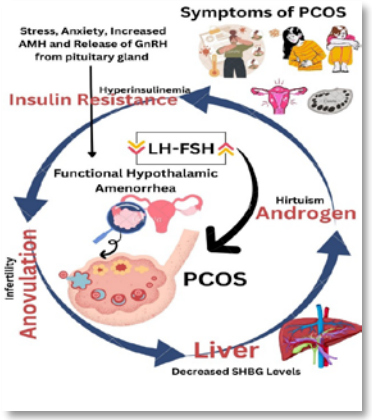

Figure 1: Diagram illustrating the mechanistic pathways associated with PCOS

The hypothalamus orchestrates the initiation of ovulation. It releases gonadotropin-releasing hormone (GnRH), stimulating the pituitary gland to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Figure 1) [7].

Follicles within the ovaries undergo maturation under the influence of FSH between days six and fourteen of the menstrual cycle. By days 10 to 14, a single mature egg emerges from one developing follicle, triggered by an LH surge on day 14, marking ovulation. However, hyperandrogenism disrupts the feedback mechanisms within the hypothalamic-pituitary-ovarian (HPO) axis in PCOS. This disruption leads to excessive secretion of LH, premature luteinization of granulosa cells, and abnormal maturation of oocytes. Dysregulation of hyperandrogenism further contributes to pulsatile GnRH secretion, influenced by aberrant feedback from progesterone and estrogen, resulting in dysregulated gonadotropin secretion, particularly elevated LH levels [8]. Additionally, insulin resistance plays a pivotal role in the pathophysiology of PCOS, further complicating hormonal dysregulation and contributing to metabolic disturbances observed in affected individuals. Monitoring menstrual patterns becomes crucial as they serve as indicators of overall health, with primary and secondary amenorrhea warranting evaluation [9]. Functional hypothalamic amenorrhea (FHA), another cause of secondary amenorrhea, is characterized by severe hypo-estrogenemia and menstrual cessation. FHA often arises from various stressors such as psychological pressure, intense exercise, and disordered eating habits [10]. Recognizing and comprehensively understanding these intricacies are essential for effective management and intervention in PCOS and related menstrual disorders. Early identification and tailored interventions can help mitigate the long-term consequences of these conditions, improving the overall quality of life for affected individuals [11]. This comprehensive review delves into the intricate origins, physiological intricacies, genetic predispositions, and immune system dynamics concerning Polycystic Ovary Syndrome (PCOS).

Anovulation of hypothalamic origin

This is the incapacity to release GnRH in a way consistent with the reproduction physiology. Normal women during the luted phase are detected, with certain situations being a reduction in pulse frequency of one pulse every six hours. There are occurrences where the frequency only increases while you sleep [13]. This promotes the impulsive nature of the puberty state. In

contrast, during the sleep phase, normal women have decreased pulsatility follicular levels. It is crucial to consider the pulse frequency of LH and, by extension, GnRH when analyzing hypothalamic origin anovulation. Even in cases of anovulation, the same woman may exhibit seemingly normal luteal phase or early follicular phase pulsatility at multiple-minute intervals [14]. The incapacity to increase the frequency required for proper follicular maturation is a characteristic of hypothalamic illness, even when pulsatility appears normal. One of the most evident reasons for GnRH insufficiency is organic lesions of the hypothalamus. On the other hand, the functional states are significantly more common and may result from disruptions in the brain regulation of gonadotrophic activity. LPH and ACTH are the two main hormones in the pituitary's anterior lobe within the brain. The latter is the portion of LPH that is carboxy-terminal. Endorphins are mostly found in the active, nonacetylated form of the hypothalamus. The acetylated forms, which have little to no action, predominate elsewhere (pancreas, placenta, and gonads) [15].

Ovulatory Dysfunction (Anovulation): A Precursor to Polycystic Ovaries:

Primordial follicles are drawn into a cluster of developing follicles during ovarian follicular development, and one antral follicle is chosen to ovulate from this group. Reproductive, metabolic, and intraovarian interactions must be coordinated for these processes to occur. Affected intraovarian paracrine signaling, ovarian hyperandrogenism, and hyperinsulinemia due to insulin resistance can all impair follicle growth in PCOS. The ovary's polycystic shape is caused by the buildup of tiny antral follicles at its perimeter, irregular menstruation, and anovulatory subfertility that accompany the resulting follicular halt in PCOS.A [4].

PCOS manifests with a polycystic ovarian morphology characterized by numerous small antral follicles around its periphery, leading to irregular menstruation and subfertility due to ovulation. When granulosa cells in antral follicles naturally start to express aromatase at a size of 7 mm, PCOS patients experience follicular arrest because of abundant intraovarian 5α-reduced androgens that inhibit granulosa cell aromatase activity and hinder follicle growth. The frequent occurrence of concomitant hyperinsulinemia in PCOS aggravates ovarian follicular arrest, which in turn stimulates the activity in theca cells, promoting ovarian hyperandrogenism.[5].Luteinizing hormone (LH) and insulin-like growth factor 1 (IGF1), influenced by hyperinsulinemia, further enhance testosterone production, contributing to ovarian hyperandrogenism. Elevated follicle-stimulating hormone (FSH) levels drive granulosa cell differentiation, potentially leading to premature follicle luteinization. Moreover, excessive insulin secretion can induce premature luteinization, disrupting granulosa cell proliferation and subsequent follicle development. Additionally, granulosa cells' overproduction of anti-Mullerian hormone(AMH) in PCOS appears to antagonize FSH activity, exacerbating disturbances in follicular development. (Figure 2 illustrates these interactions)

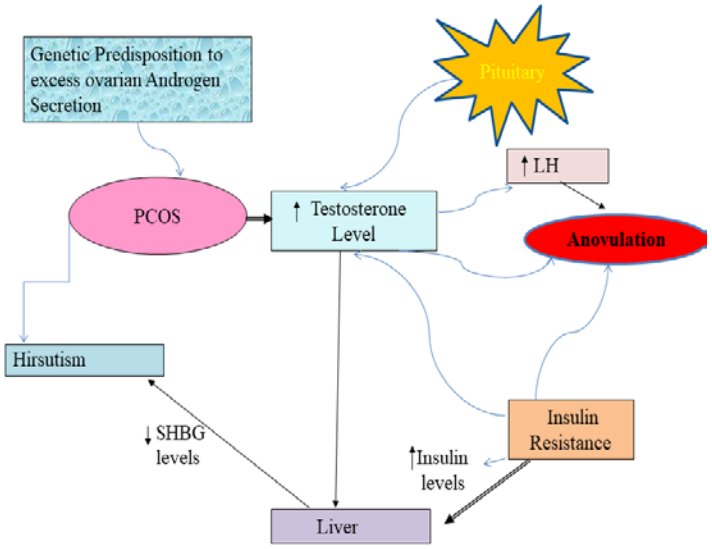

Figure 2: Ovulatory dysfunction and hormonal changes related to the progression of PCOS

Functional hypothalamic amenorrhea:

The abnormalities in pulsatile gonadotropin-releasing hormone (GnRH) release, which impairs two gonadotropins: luteinizing hormone and follicle-stimulating hormone are the major cause for the occurrence of FHA[7]. A complicated hormonal shift with severe hypoestrogenism is the eventual outcome. Low levels of total triiodothyronine, insulin-like growth factor 1 (IGF-1), serum insulin, and mild hypercortisolemia are also present in these patients. From the hypothalamus the pulsatile release of gonadotropin-releasing hormone (GnRH) in variation is referred to as functional hypothalamic amenorrhea (FHA) and falls under the class of hypo-gonadotropichypogonadism [8]. The extensive range of hypothalamic-pituitary abnormalities that can occur in this disorder include a lower mean frequency of LH pulses, the complete deficiency of LH pulsatility, a normal-looking secretion configuration, and a larger mean

frequency of LH pulses. Decrease in gonadotropin secretion, therefore, results in a decrease in the ovary's ability to produce estradiolStress, weight loss, and/or excessive physical exercise are frequently linked with a disturbed hypothalamic-pituitary-ovarian axis, which is one of the most frequent reasons for secondary amenorrhea in FHA cases [9]. FHA is categorized into stress-related, exercise-related, and weight loss-related, depending on the eliciting cause [10]. Infertility and anovulation are two major reproductive function impairments associated with functional hypothalamic amenorrhea.

Regardless of the precise etiology, FHA can result in a complex syndrome of hypoestrogenism, other endocrinological aberrations, and metabolic abnormalities that affect the entire body's homeostasis [11]. Physiological symptoms of anovulatory disorders occur during adolescence, the postpartum phase, and shortly before menopause. They are among the first signs of a variety of illnesses in pathology, including organic or functional hypothalamic disorders, pituitary damage, improper peripheral hormone feedback, and, most clearly, primary ovarian insufficiency [12]. Their pathology is what interests them. One definition of functional hypothalamic problems is the incapacity to release GnRH normally [13]. Although 20% of anovulation is hyperprolactinemia, which has an antigonadotrophic impact at the hypothalamus level, the exact mechanism by which prolactin inhibits GnRH is still up for debate [14]. The etiology of polycystic ovarian disease is still poorly known despite being one of the most prevalent endocrine abnormalities in women [15].

Hormonal disturbances associated with FHA and neuroendocrine causes of Amenorrhea and Infertility

As earlier mentioned, FHA is transported by depression of the hypothalamic-pituitary-ovarian axis. Disruption in the gonadotrophin and GnRH secretion is the major cause of the disease associated with this characteristic; irregular pituitary hormone secretion is also seen in FHA. Activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress is a widely recognized pathogenetic factor in functional hypothalamic amenorrhea (FHA) [16].

Increased secretion of corticotropin-releasing hormone (CRH) from the hypothalamus leads to higher adrenocorticotropic hormone (ACTH) production from the pituitary gland. This, in turn, stimulates the adrenal glands to produce cortisol. Elevated cortisol levels can negatively affect the hypothalamic-pituitary-gonadal (HPG) axis by reducing the drive of the gonadotropin-releasing hormone (GnRH). There have been reports of elevated cortisol concentrations in the cerebrospinal fluid and serum in FHA [17]. In FHA patients, disturbances in the hypothalamic-pituitary-thyroid axis are also noted. These consist of low to normal levels of thyrotropin, low levels of triiodothyronine, and a high reverse triiodothyronine level [18].

Hypothalamic amenorrhea is also linked to elevated blood growth hormone levels at night and lowered 24-hour prolactin levels. Low levels of insulin-like growth factor 1 (IGF-1) and serum insulin, as well as elevated insulin sensitivity, are characteristics of FHA patients. In addition, it has been documented that FHA patients had reduced testosterone levels when compared to healthy controls [19]. Release of the gonadotropin- hormone (GnRH) is controlled by the hypothalamic-pituitary-ovarian axis, which declines the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) released by the anterior pituitary [20]. This weakened feedback system prevents the ovarian granulosa cells from receiving a signal to produce estradiol. As a result, in a healthy woman, amenorrhea results from endometrial thickening not occurring during the follicular period. When amenorrhea occurs for three months or longer and estradiol (E2), FSH, and LH levels are less than 50 pg/mL, FHA is diagnosed. Other possible causes of the condition, such as pathologies or anatomic disorders like thyroid dysfunction, hyperprolactinemia, and premature ovarian insufficiency (POI), are excluded. Infertility, secondary amenorrhea, the absence of menstruation for three cycles in a row, and the inability to conceive after a year of consistent sexual activity are common problems that primary care doctors, obstetricians/gynecologists, and endocrinologists assess. Disturbances cause secondary amenorrhea in more than half of instances.

About 50% of secondary amenorrhea occurs due to the hypothalamic-pituitary-adrenal (HPA) system disturbance. Thus, understanding the neuroendocrine reasons of amenorrhea and infertility is critical to determining the best course of action for treating patients who currently have these symptoms. This review relates the hormonal mechanisms generating disturbances in the hypothalamic-pituitary-ovarian (HPO) axis and the genetic, pathogenic, and iatrogenic causes of neuroendocrine-associated amenorrhea and infertility [21].

Neuroendocrine Causes of Amenorrhea and Infertility

Neuroendocrine causes of amenorrhea and infertility encompass a range of disorders that disrupt the intricate interplay between the nervous system and the endocrine (hormonal) system, ultimately impacting reproductive function. One notable example is hypothalamic dysfunction, which can result from stress, excessive exercise, or nutritional deficiencies. In such cases, the hypothalamus, a crucial regulator of hormone production, may fail to signal the pituitary gland properly, leading to disrupted menstrual cycles and infertility. Additionally, conditions like pituitary tumors or abnormalities can directly interfere with the secretion of hormones involved in reproduction, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), contributing to amenorrhea and infertility. Moreover, disorders affecting the thyroid or adrenal glands, integral to the endocrine system, can disrupt hormonal balance and menstrual function, further complicating fertility. Understanding these neuroendocrine causes is essential for accurate diagnosis and effective management, often involving a multidisciplinary approach that addresses hormonal imbalances and underlying neurological factors.

Physiological Causes

Functional hypothalamic amenorrhea: *Hormonal* mediators contribute to functional hypothalamic dysfunction by disrupting the normal regulation of GnRH secretion-

a. ***HPA axis.***

In moments of intense emotional, dietary, or physical strain, the HPA axis is activated, suppressing the HPO axis through various mechanisms. Specifically, the hypothalamus plays a crucial role, as CRH inhibits the secretion of GnRH within it. CRH has been found to decrease FSH/LH secretion in regularly cycling women notably, yet this inhibition is countered by GnRH, indicating that CRH acts by impeding GnRH secretion [22]. Additionally, cortisol, a key player in the HPA axis, inhibits reproductive activity at the levels of the hypothalamus, pituitary, and uterus [23]. Conversely, observations from individuals taking prednisolone medication or suffering from Cushing's disease suggest that glucocorticoids hinder the pituitary gonadotrophs' responsiveness to hypothalamic signals, as evidenced by a reduced LH response to GnRH. Furthermore, glucocorticoids interfere with estradiol's effects on the uterus [24, 25].

b. Leptin

In women with Functional Hypothalamic Amenorrhea (FHA), there is a notable deficiency in leptin, a hormone produced by adipocytes, which could potentially act as a mediator for amenorrhea [12]. The exact pathway through which reduced leptin levels contribute to anovulation remains unclear. However, it is suggested that these lower levels of leptin influence the mechanism involving kisspeptin, potentially leading to the suppression of Gonadotropin-Releasing Hormone (GnRH).

c. Insulin

Fertility may be impacted by certain circumstances like changes in body weight, including weight increase and decrease. Functional hypoinsulinemia (FHI) is a condition characterized by low insulin levels, often triggered by significant weight loss due to prolonged undernutrition. Conversely, weight gain can contribute to obesity and insulin resistance [8]. However, it is important to note that Functional Hypoinsulinemia (FHI) is also marked by low insulin levels. Studies have shown that insulin plays a crucial role in modulating the HPO axis, and disruptions in insulin levels or function may contribute to infertility. Research indicates that females with neuron-specific deletion of the insulin receptor experience reduced circulating LH levels, leading to a significant decrease in the number of antral follicles, underscoring the critical role of insulin signaling in fertility [27].

d. Fibroblast growth factor-21 (FGF-21)

A hormone from the liver, FGF-21, is produced in greater amounts when a person is starving [28]. Recently, it was demonstrated that FGF-21 interferes with ovulation by acting on the hypothalamus. Low LH levels associated with starvation-induced amenorrhea have been linked to FGF-21 as a possible mediator. GnRH, but not exogenous gonadotropins, causes an ovulatory LH rise. The way that FGF-21 obstructs ovulation may be through kisspeptin, a potent inducer of GnRH secretion. Whether FGF-21 mediates FHA in humans is unknown [29].

Hyperprolactinemia

Pituitary-associated amenorrhea is most commonly caused by hyperprolactinemia, which can have either physiologic or pathophysiologic origins. Although the precise mechanism of hypogonadotropichypogonadism by hyperprolactinemia is unknown, reduced LH-pulse frequency and decreased LH response to estrogen, which may specify that GnRH suppression plays a significant role inhyperprolactinemia. This finding is suggested that when paired with a human chorionic gonadotropin trigger, pulsatile GnRH treatment promotes follicular maturation and ovulation in hyperprolactinemic, amenorrheic women. Additionally, it has been observed that

prolactin-induced GnRH suppression may be significantly facilitated by CRH. It has been revealed that prolactin-receptor mRNA is channelized to kisspeptin neurons in the hypothalamus [30, 31], gonadotropin levels rise, and ovulation is restored. Prolactin suppresses granulosa cell activity. Hence, it may also act in other, directly disrupting ovarian function. Some women with hyperprolactinemia experience ovulatory menstrual cycles, although most of them are amenorrheic, anyway. Treating hyperprolactinemia may be essential even for women who menstruate frequently, as these women may still have noticed low infertility due to a small luteal-phase abnormality. Importantly, while there are various physiological reasons for hyperprolactinemia and amenorrhea, including pregnancy, it is essential to eliminate them as potential causes before initiating any treatment and to prevent PCOS [32].

a. Pregnancy

Pregnancy is the most prevalent reason for hyperprolactinemia, characterized by elevated levels of prolactin in the blood climbing to as high as 600 ng/mL and peaking at delivery. In women who do not breastfeed, prolactin levels undergo many changes initially, decrease in the first 72 hours following delivery, and then recover to normal [33]. Lactation raises prolactin levels in nursing mothers, although this normally goes away 12 weeks after delivery because postpartum estradiol levels fall, which reduces lactotroph hyperplasia. Hyperprolactinemia and the mother's nutritional state about the frequency and intensity of nursing are two factors that contribute to lactational amenorrhea. The length of amenorrhea is correlated with prolactin levels, their response to nursing, and prolactin bioactivity [34, 35]. Further, the LH response to estrogen is decreased. Both lactational amenorrhea and prolactin-induced amenorrhea are associated with alterations in LH (luteinizing hormone) pulse frequency and amplitude; these hormonal changes suppress ovulation and elevate the prolactin level. Furthermore, pulsatile GnRH administration to lactational amenorrhea promotes the luteal-phase function, ovulation, and follicle development, showing that GnRH suppression may play a key factor [36]. Suppose lactation amenorrhea and prolactin-induced amenorrhea associated with alterations in LH (luteinizing hormone) pulse frequency remain untreated. In that case, they are the major causes for the anovulation and FOH, which further causes the PCOS condition.

b. Lactation

Suckling during lactation triggers an increase in prolactin levels in nursing mothers, a phenomenon typically diminishing around 12 weeks post-delivery due to declining postpartum estradiol levels, which in turn reduces lactotroph hyperplasia. Lactational amenorrhea, influenced by both hyperprolactinemia and the mother's nutritional status relative to nursing frequency and intensity, is a result of these factors. The duration of amenorrhea is linked to prolactin levels, their responsiveness to nursing, and the bioactivity of prolactin [36, 37]. Moreover, both lactational amenorrhea and prolactin-induced amenorrhea involve changes in LH (luteinizing hormone) pulse frequency and amplitude. These hormonal alterations suppress ovulation and elevate prolactin levels. Additionally, administering pulsatile GnRH during lactational amenorrhea promotes luteal-phase function, ovulation, and follicle development, suggesting that GnRH suppression may play a pivotal role [38].

Pathophysiological causes of amenorrhea and Infertility-Hyperprolactinemia

As previously discussed, hyperprolactinemia can stem from both physiological and pathological origins. In premenopausal women, pathological hyperprolactinemia often leads to symptoms like amenorrhea and infertility, making it crucial to assess prolactin levels promptly. Thyroid hormones play a vital role in regulating hyperprolactinemia, which can arise from conditions such as chest wall injury, intrinsic hypothyroidism, disruptions in the pituitary stalk, or the presence of lactotroph adenomas [Fig-3].

Lactotroph adenomas

Prolactin-secreting adenomas, also known as lactotroph adenomas, represent the most prevalent subtype of secretory pituitary adenoma. There is often an association between tumor size and prolactin levels; these tumors are typically benign. Adenomas can exhibit prolactin levels as high as 104 ng/mL; however, cystic or poorly differentiated lesions may present with lower prolactin levels. Consequently, prolactin levels may be lower than expected for tumors of considerable size [37].

Stalk disruption

The hypothalamic axis nucleus produces dopamine neurons, which locally inhibit pituitary prolactin production. Any disruption to the stalk connecting the hypothalamus to the pituitary gland can impede dopamine delivery to the gland, potentially leading to amenorrhea and hyperprolactinemia. Stalk disruption commonly occurs due to large sellar masses or acute injuries.

Chronic renal failure

Hyperprolactinemia can result from both increased prolactin production and decreased renal clearance in chronic renal failure. Reduced responsiveness of lactotrophs to dopamine suppression may contribute to the latter [38]. Although liver disease was previously thought to be a common cause of hyperprolactinemia, recent studies suggest that this is actually very rare [39].

Adrenal: congenital adrenal hyperplasia (CAH)

Reduced activity of adrenal enzymes involved in cortisol production can lead to infertility. CAH encompasses a group of genetic disorders characterized by abnormalities in cortisol production, leading to increased ACTH production due to reduced negative feedback and proliferation of the adrenal glands. While rare forms of CAH, such as 11β-hydroxylase deficiency [45], 17α-hydroxylase deficiency, and 3β-hydroxysteroid dehydrogenase deficiency [46], may primarily contribute to infertility, classic symptoms of hyperandrogenism, such as baldness, acne, frontal baldness, and irregular menstruation, are typically observed. Oligomenorrhea can occur in women with 21-hydroxylase (21-OH) deficiency due to elevated progesterone and/or androgen levels. Reduced LH pulse amplitude and frequency are associated with elevated progesterone and androstenedione levels in classic 21-OH deficiency, resulting in irregular menstrual cycles. Androgens increase the frequency of GnRH pulses [47], leading to elevated LH levels in women. Therefore, while the exact mechanism by which androgens promote oligomenorrhea remains unclear, hyperandrogenemia may contribute to CAH. Another possible cause of irregular menstruation is elevated progesterone levels, a substrate of 21-OH. A decrease in a woman's LH pulse frequency occurs when she receives progesterone and progesterone receptors have been identified in pituitary gonadotroph cells. These findings suggest that both the hypothalamus and pituitary may mediate the gonadotropin-suppressive effects of progesterone [48].

Idiopathic hypogonadotropic hypogonadism (IHH): Hypothalamus

IHH encompasses a range of disorders typically characterized by GnRH deficiency or GnRH receptor mutations, often presenting with characteristic anatomical findings on hypothalamic/pituitary imaging and delayed or absent pubertal development. While IHH is predominantly a male condition, it can also cause infertility in women, with primary amenorrhea being a prominent symptom. Various associated phenotypic abnormalities, including anosmia, sometimes referred to as Kallman's syndrome, are observed. It has been noted that both GnRH and olfactory neurons develop during the same embryonic stage, so genetic disorders affecting neuronal migration can result in concurrent hypogonadism and anosmia. Recent years have seen the identification of genetic mutations associated with Kallman's syndrome. Additionally, mutations in genes responsible for producing the leptin receptor and prohormone convertase 1 have been linked to severe obesity and hypogonadotropic hypogonadism [40, 41]. Furthermore, genetic mutations affecting GnRH function and secretion have been observed in IHH patients with insomnia. Mutations in genes encoding kisspeptin and its receptor, KISS1 and KISS1R, have been implicated in causing hypogonadism, as kisspeptin plays a crucial role in regulating GnRH secretion. Severe obesity and hypogonadotropic hypogonadism have been associated with mutations in genes producing the leptin receptor and prohormone convertase 1. Another consequence of mutations in the GnRH receptor is hypogonadotropic hypogonadism [42] [43]. While individuals with IHH represent a relatively small subset of infertility cases, they may have underlying genetic predispositions that increase susceptibility to developing functional hypothalamic amenorrhea (FHA). The interplay between genetic and environmental factors leading to FHA may thus be facilitated by inherited abnormalities in GnRH biology, potentially lowering the threshold at which external stressors suppress the HPO axis [44].

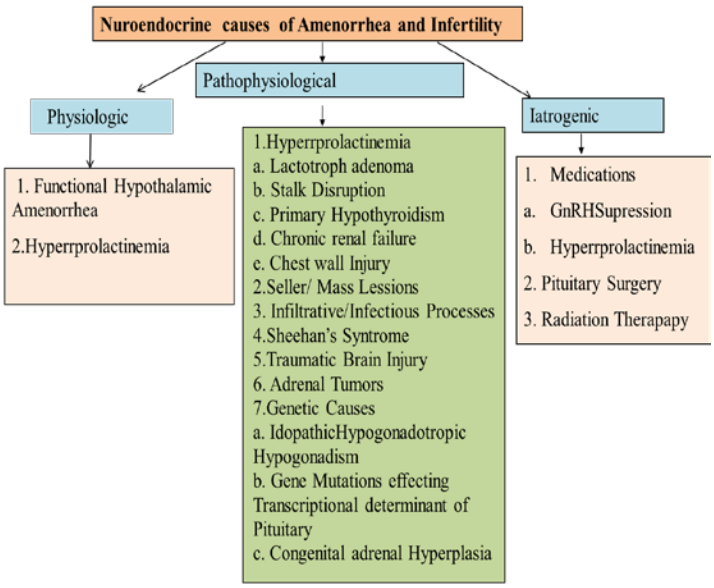

Figure 3: Neuroendocrine causes of amenorrhea & infertility

Importance of understanding metabolic and hormonal alterations

Functional Hypothalamic Amenorrhea (FHA) and Polycystic Ovary Syndrome (PCOS) are distinct reproductive disorders impacting women, each characterized by unique causes and symptoms. FHA typically arises from stress, excessive exercise, or low body weight, disrupting the hypothalamus's hormonal regulation and leading to amenorrhea, alongside potential mood changes and decreased bone density. In contrast, PCOS involves hormonal imbalances, particularly elevated androgen levels, stemming from a combination of genetic and environmental factors. Its manifestations include irregular or absent periods, hirsutism, acne, weight gain, and infertility. Understanding these conditions' metabolic and hormonal alterations is vital for tailored treatment approaches. This understanding aids in addressing fertility issues, mitigating long-term health risks such as cardiovascular disease and diabetes, and enhancing overall quality of life by managing symptoms effectively. Therefore, a comprehensive grasp of the hormonal disruptions in FHA and PCOS is indispensable for optimizing management strategies and improving health outcomes for affected individuals.

1. Hormonal association with PCOS

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder affecting reproductive-aged women, characterized by a myriad of symptoms, including irregular menstrual cycles, hyperandrogenism, and polycystic ovaries. Understanding the hormonal associations with PCOS is crucial in both diagnosing and managing this condition effectively. One of the hallmark features of PCOS is its association with hormonal imbalances, notably involving follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin. Studies have consistently shown that PCOS patients tend to have higher levels of LH and LH/FSH ratio compared to individuals without the condition. This dysregulation in the gonadotropin levels contributes to disrupted ovarian function and follicular development, leading to anovulation and irregular menstrual cycles characteristic of PCOS. Elevated androgen levels, particularly testosterone and its derivatives, are another prominent feature of PCOS. Androgens are typically produced by the ovaries, adrenal glands, and peripheral tissues, and their excess production can lead to symptoms such as hirsutism, acne, and male-pattern baldness. The etiology of hyperandrogenism in PCOS is multifactorial, involving increased ovarian androgen secretion, enhanced adrenal androgen production, and alterations in androgen metabolism and clearance. Importantly, elevated LH levels have been implicated in stimulating ovarian theca cells to produce excess androgens, contributing to the hyperandrogenic phenotype observed in PCOS.Furthermore, PCOS is often associated with obesity and metabolic disturbances, with many patients exhibiting higher body mass index (BMI) and insulin resistance. Insulin resistance plays a pivotal role in the pathogenesis of PCOS by increasing androgen production, disrupting ovarian follicular development, and impairing glucose metabolism. The interplay between insulin resistance and hyperandrogenism creates a vicious cycle, exacerbating the symptoms of PCOS and increasing the risk of developing comorbidities such as type 2 diabetes and cardiovascular disease. In summary, PCOS is intricately linked to hormonal dysregulation, with elevated LH, FSH, prolactin, and androgen levels contributing to its pathophysiology. Understanding these hormonal associations is essential for accurate diagnosis and tailored management strategies aimed at addressing the underlying hormonal imbalances, optimizing reproductive health, and mitigating long-term metabolic risks associated with PCOS.

2. Genetic predisposition & PCOS:-

Numerous genes, such as CAPN10, Cytochrome P450 family, Insulin gene, AR, FTO, and FSHR, have been extensively studied for their strong genetic associations with Polycystic Ovary Syndrome (PCOS). These genetic factors play pivotal roles in various aspects of PCOS pathophysiology, including insulin resistance, androgen excess, and follicular development. Understanding the genetic underpinnings of PCOS not only sheds light on its etiology but also holds promise for personalized diagnostics and targeted therapeutic interventions aimed at mitigating the symptoms and complications associated with this complex endocrine disorder.

Androgen Receptor Gene (AR)

Situated on chromosome Xq12 and spanning 11 exons, this gene encodes a protein exceeding 90 kb in length, comprising three distinct functional domains. Additionally, the androgen receptor (AR) has been associated with PCOS. X chromosome inactivation disrupts the androgen signaling pathway, influencing AR activity. Since AR is an X-linked gene, a single copy of the X chromosome markedly affects the entire pathway. The Genome-Wide Association Studies for PCOS have facilitated the discovery of novel mutations (see Figure 4).

Additional genetic variations linked to PCOS etiology. The receptor for follicular stimulating hormone (FSHR) contains 14 exons. This gene, chromosome 2p16.3, is essential for the growth of gonads and encodes a protein recognized as G-coupled receptors. The endocrine, reproductive system is impacted by disturbed hormone levels. In addition to other hormone imbalances, a high level of FSH is also linked to the severity of PCOS. The Follicular Stimulating Hormone receptor encodes FSH. Any anomaly in the FSHR disrupts follicular and ovarian functions [51].

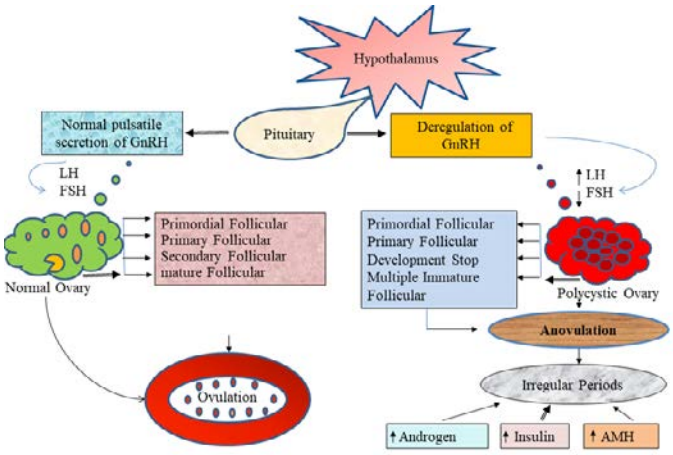

Figure 4: Hormonal association and pathogenesis of PCOS

Fat Mass Obesity (FTO) FTO

Alpha-ketoglutarate-dependent dioxygenase is another name for this gene, which has 14 exons and a cytogenic position of 16q12.2. Studies have demonstrated a correlation between FTO and patients with PCOS who had type 2 diabetes, obesity, and high BMI.[58]. It has 12 exons, and this gene is linked to type 2 diabetes; its protein is a heterodimer. It is situated in the type 1 diabetes mellitus non-insulin dependent region. Cysteine proteases are encoded by the CAPN10 chromosomal region. It has been discovered that calpain 10 affects the activity and secretion of insulin. Because type 2 diabetes and insulin resistance are linked to PCOS, any anomaly or variation in CAPN10 causes PCOS therefore it is also a candidate gene that is known to be responsible for PCOS [52]

The most well-known endocrine disorder affecting women in our generation is polycystic ovarian syndrome (PCOS). The signs of hyperandrogenism, irregular menstrual periods, and insulin resistance are the hallmarks of PCOS. Type 2 diabetes, insulin resistance, and infertility are among the issues that are more common in women with PCOS. The PCOS board aims to lower blood sugar and weight, improve fertility, manage excessive body or scalp hair growth, reinstate the usual feminine cycle, and prevent miscommunications.[53]. Aromatase inhibitors can induce ovulation with results that are almost identical to or better than those reported with clomiphene citrate (CC), despite the fact that CC has long been the gold standard for ovulation induction in the event of ovulatory infertility.Aromatase inhibitors have the ability to induce ovulation with outcomes that are either better or almost identical to those observed with CC. An increasing degree of therapeutic advancement is indicated by ovarian incitement conventions that cleverly use gonadotropins, gonadotropin-delivering hormone competitors, the technique of ovarian boring, and supported conceptual innovations with in vitro oocyte development[54].

LH and thecal cell dysfunction in PCOS

The source of ovarian androgen is the stroma (thecal) and theca cells. Although thecal cells' ability to secrete androgen is LH-dependent, intraovarian autocrine and paracrine processes control the androgenic response to LH. This regulation helps to synchronize the secretion of estrogen and androgen production. Others that block ovarian androgen release include active and sex steroids [55]. Although low dosages of LH can stimulate normal thecal cells extremely well, peak androgen output happens at LH levels in the upper limit of the physiological range. LH causes desensitization to itself, which is the reason for limiting androgen output in response to overstimulation [56]. Homologous desensitization happens in a dose- and time-dependent way. LH receptors and cholesterol side-chain cleavage activity are first down-regulated due to it. In PCOS, FSH and granulosa cell dysfunction it seems that PCOS impairs the function of granulosa cells that are dependent on FSH. Granulosa cells, for instance, seem to multiply at a subnormal pace [57].

Furthermore, IGF-I and IGF-II mRNA are expressed by PCOS follicles in a manner that is consistent with follicular maturation arrest. Nonetheless, PCOS patients' granulosa cells have the ability to produce more oestradiol than usual in response to FSH stimulation. [58].These findings raise the possibility that FSH activity may be inadequate in PCOS-affected women. This is presumably because an excess of androgen supplies oestrogen with a substrate, and an excess of oestrogen tends to restrict FSH release below the individual threshold level.

Considering that the follicular microenvironment's FSH level is typically normal [59]. Numerous paracrine, autocrine, and other endocrine variables have been linked to alterations in the granulosa cells' response to FSH. These consist of active insulin, transforming growth factor-c (TGF~), IGFs, IGF-binding proteins (IGFBPs), and epidermal growth factor (EGF) [60].

The gonadotropin-releasing hormone (GnRH) in the pituitary's molecular mechanism of action

The hypothalamus releases Gonadotropin-releasing hormone (GnRH), which travels to the pituitary gland through a portal system. This stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These gonadotropins enter the bloodstream and regulate the development of gametes and steroid genesis in the gonads of both males and females. As a crucial link between the nervous and endocrine systems, GnRH plays a pivotal role in clinical and experimental settings. Its actions extend to modulating fertility in men and women, as well as treating conditions such as steroid-dependent neoplasia, cryptorchidism, and early puberty, among others, through the use of GnRH and its analogs [61].

Factors Regulating Gonadotrope Responsiveness to Releasing Hormone

Different numbers of pituitary GnRH receptors depend on endocrine conditions, age, and sex. In addition to GnRH itself (homologous regulation), other chemical messengers like as steroids, opiates, catecholamines, and indoleamines (heterologous regulation) also control the GnRH receptor and cellular responsiveness [62]. An important topic of research is the mechanism regulating gonadotrope responsiveness.

The basis for many of the clinical uses of stable agonist analogs of GnRH, where the goal is to reduce circulating levels of gonadotropins and steroids, is the reduced responsiveness that is induced after the drug is administered. Research centered on the connection between gonadotrope responsiveness changes induced by GnRH and the density of GnRH receptors, as well as the function of signal transduction pathways in these changes. Desensitization occurs, for instance, when distributed pituitary cells in superfusion systems are continuously exposed to large levels of GnRH [63].The "self-priming effect" refers to the phenomenon wherein pulsatile administration, such as short pulses given every hour, may impede or postpone the start of desensitization in gonadotropes or possibly enhance their sensitivity to GnRH, Figure 5.

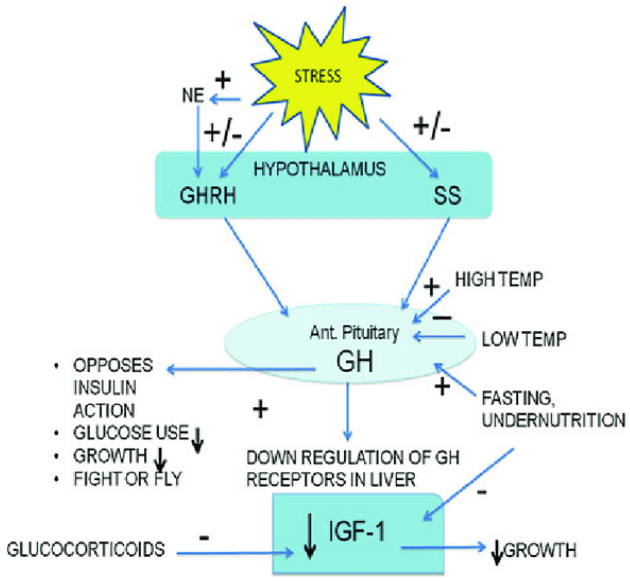

Figure 5: Factors regulating gonadotrope responsiveness to releasing hormone

Gonadotropin abnormalities Triggering PCOS:

A significant proportion of women with PCOS experience elevated serum levels of immunoactive and bioactive LH, attributed to the hyper-secretion of LH, affecting nearly 70% of individuals with this condition. This hyperactivity is further underscored by an increase in both the amplitude and frequency of LH pulses, resulting in a notable elevation in circulating LH levels compared to FSH levels in the bloodstream [64]. The heightened LH pulse frequency observed in PCOS is driven by diminished negative feedback from steroid hormones on LH synthesis, primarily due to excess androgen levels, leading to an augmented release of hypothalamic gonadotropin-releasing hormone (GnRH) [65]. Adolescent girls with PCOS have been effectively treated for this neuroendocrine anomaly using the androgen receptor blocker, flutamide, highlighting the role of excess androgen in dampening hypothalamic feedback inhibition and consequently increasing GnRH pulsatility during puberty. However, not all teenage females with PCOS exhibit decreased hypothalamic feedback inhibition in response to androgen excess, suggesting potential variability influenced by the duration of androgen exposure or genetic predisposition [66]. Moreover, women with PCOS manifest other neuroendocrine abnormalities, including an amplified response to GnRH and a LH release pattern resembling that of individuals with congenital adrenal virilizing illnesses rather than typical women without PCOS. Furthermore, thin women with PCOS are prone to alterations in the circulating LH:FSH ratio, potentially attributed

to the influence of obesity on LH pharmacokinetics and pulse amplitude, leading to decreased blood LH levels and an increase in body fat percentage [67,68].

Women's Health Challenges: A Global Overview of FHA and PCOS

The global impact of functional hypothalamic amenorrhea (FHA) and polycystic ovary syndrome (PCOS) is significant, with both conditions affecting millions of women worldwide. While the prevalence rates may vary across different populations and regions, FHA and PCOS collectively represent substantial burdens on women's health and well-being [22].Functional Hypothalamic Amenorrhea (FHA): FHA is recognized as a common cause of secondary amenorrhea, particularly among women of reproductive age. It is estimated that FHA affects up to 5-10% of women in this demographic group[15]. The condition can arise from various stressors, including excessive exercise, disordered eating habits, weight loss, or emotional stress. FHA not only disrupts menstrual function but can also have broader implications for bone health, fertility, and overall quality of life [4]. While FHA is often reversible with appropriate interventions addressing the underlying stressors, it remains a significant concern in women's health globally [8].

Polycystic Ovary Syndrome (PCOS): PCOS is one of the most prevalent endocrine disorders affecting women of reproductive age, with estimates suggesting that it affects 5-20% of this population worldwide[10]. The syndrome encompasses a wide range of symptoms, including hyperandrogenism, chronic anovulation, insulin resistance, and metabolic disturbances. PCOS is a leading cause of female infertility due to ovulatory dysfunction, and it also increases the risk of other health complications such as type 2 diabetes, cardiovascular disease, and endometrial cancer. The global burden of PCOS is further compounded by challenges in diagnosis and management, as the syndrome can present with varied clinical manifestations and requires a multidisciplinary approach for effective treatment [55].

Current Status

Both FHA and PCOS pose significant challenges in clinical practice, research, and public health efforts worldwide. Efforts to improve awareness, education, and early detection of these conditions are essential for timely intervention and management [67]. Research into the underlying mechanisms, risk factors, and treatment modalities for FHA and PCOS continues to advance, with a focus on personalized approaches tailored to individual patient needs [66]. Moreover, initiatives to address the broader socio-economic and cultural factors influencing women's health, such as access to healthcare services, nutritional support, and mental health resources, are critical for mitigating the global impact of FHA and PCOS [68]. Overall, addressing the complex challenges posed by FHA and PCOS requires a comprehensive and integrated approach involving healthcare providers, policymakers, researchers, and advocacy organizations on a global scale [69].

CONCLUSION

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder characterized by hyperandrogenism, chronic anovulation, and polycystic ovarian morphology, disrupting the crucial hormonal balance needed for reproductive function. Dysregulation within the hypothalamic-pituitary-ovarian (HPO) axis leads to chronic anovulation, irregular menstrual cycles, and the accumulation of small follicles in the ovaries. This disrupted hormonal milieu, marked by excessive androgen secretion and insulin resistance, contributes to ovulatory dysfunction, infertility, and metabolic disturbances observed in PCOS.Understanding the complexities of PCOS is crucial for effective management and intervention. Insights into the underlying mechanisms offer potential therapeutic targets, including interventions aimed at restoring hormonal balance and improving reproductive outcomes. Early identification and targeted management strategies are essential for mitigating the long-term consequences of PCOS and related conditions, ultimately enhancing reproductive health and well-being.

Functional hypothalamic amenorrhea (FHA) and PCOS collectively represent significant burdens on women's health globally. FHA, a common cause of secondary amenorrhea, affects up to 5-10% of reproductive-age women and can impact menstrual function, bone health, fertility, and overall quality of life. PCOS, affecting 5-20% of women in this demographic, poses challenges in diagnosis and management, increasing the risk of infertility and other health complications. Addressing these challenges requires enhanced awareness, education, and early detection efforts, alongside ongoing research and initiatives addressing broader socio-economic and cultural factors.In conclusion, accurate recognition and appropriate treatment of hormone level alterations associated with PCOS are vital to avoid short- and long-term medical effects. A

comprehensive, integrated approach involving healthcare providers, policymakers, researchers, and advocacy organizations is essential for mitigating the global impact of FHA and PCOS and improving the overall health and well-being of affected individuals. This comprehensive review aims to provide an in-depth understanding of polycystic ovary syndrome (PCOS) and its impact, elucidating the detailed physiological mechanisms underlying its manifestations and effective management strategies.

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CONFLICT OF INTEREST
The authors declare no conflict of interest

AUTHOR CONTRIBUTION
Both authors conceived and designed the idea for this paper, collected and analyzed the data, and drafted the paper. Abhishek Soni analyzed the data and revised the final paper. All authors read and approved the final manuscript**.**

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