REVIEW ARTICLE

Advances in Neuroendocrine Research on Polycystic Ovary Syndrome: New Hope for Treatment Decoding the Link between Hormones and the Brain

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Received on: 25 December 2022; *Accepted on:* 03 February 2023; *Published on:* 19 April 2023

Abstract

Introduction: The etiopathogenesis of polycystic ovary syndrome (PCOS) is multifactorial. In healthy women, neurokinin B (NKB) controls the release of gonadotropins, the growth of follicles, and the time of ovulation.

Materials and methods: The regulation of estrogen-negative feedback, which has been demonstrated to be changed in PCOS, is influenced by NKB and kisspeptin signaling.

Results and Conclusion: Disruption in NKB secretion can influence the emergence of PCOS. In PCOS women, suppressing the stimulatory effects of kisspeptin by certain receptor antagonists and lowering GnRH production may be therapeutic targets. Kisspeptin antagonists have not yet been employed in this indication, however, NKB antagonists have been extensively studied in this setting.

Keywords: PCOS etiology neuroendocrine, Polycystic ovarian syndrome.

Journal of South Asian Federation of Obstetrics and Gynaecology (2023): 10.5005/jp-journals-10006-2195

Introduction

Based on the diagnostic criteria, PCOS incidence varies. About 7% of reproductive-age women meet the NIH criteria for hyperandrogenic chronic anovulation. Between white and black women, there are no appreciable variations in the prevalence of hirsutism or high circulating testosterone levels.[1–5]

By using the comprehensive Rotterdam criteria, the prevalence of PCOS in women with normogonadotropic anovulation rises to 91% from 55% when using the NIH criteria.[6]

All diagnostic approaches recommend ruling out secondary causes first, including adult-onset congenital adrenal hyperplasia, hyperprolactinemia, and androgen-secreting tumors.

Polycystic ovaries alone are a nonspecific sign that is frequently observed in women who do not have endocrine or metabolic abnormalities.

Etiology

The exact etiology of PCOS is yet unknown, but is considered a multifactorial condition. The genetic contribution to PCOS remains uncertain, and there is currently no recommended genetic screening test. No specific environmental substance has been identified as causing PCOS. Insulin resistance may be central to the etiology of the syndrome Obesity is a comorbidity that may amplify the effects of PCOS. However, obesity is not a diagnostic criterion for PCOS, and approximately 20% of women with PCOS are not obese. Obesity is more prevalent in the United States than in other countries and, therefore, the PCOS phenotype may be different.

Compensatory hyperinsulinemia may result in decreased levels of sex hormone-binding globulin (SHBG) and, thus, more bioavailable circulating androgen, and serves as a trophic stimulus to androgen production in the adrenal gland and ovary. Insulin also may have direct hypothalamic effects, such as abnormal appetite stimulation and gonadotropin secretion. Hyperandrogenism, although central to the syndrome, may have multiple etiologies, some not related to insulin resistance.

Polycystic ovary syndrome is not a single endocrine disorder but rather a constellation of symptoms[7] brought on by a variety of genetic and environmental factors, including intrauterine development disturbances, excessive exposure to androgen in utero, low birth weight, early pubarche, increased risk of obesity, metabolic syndrome, and type-II diabetes.[8] Advanced glycation end products (AGEs), which are frequently included in foods that have undergone thermal processing, as well as diets high in protein and low in carbs, promote insulin resistance.[9,10] Increased levels of circulating insulin play a crucial role in the development of PCOS.[11] Excess insulin acts synergistically with LH. The etiology of PCOS is also aided by neuroendocrine abnormalities, which include increased gonadotropin-releasing hormone (GnRH)

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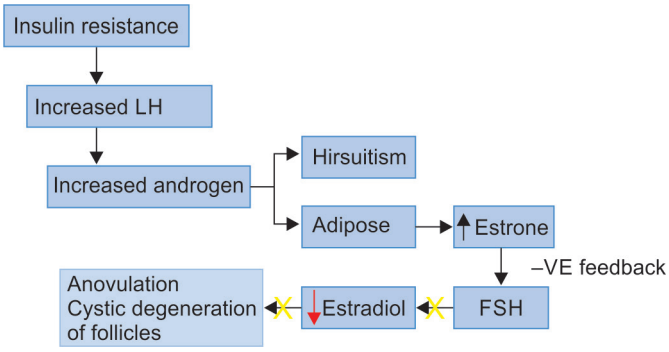
How to cite this article: Garg R, Srivastava J, Agrawal P, *et al*. Advances in Neuroendocrine Research on Polycystic Ovary Syndrome: New Hope for Treatment Decoding the Link between Hormones and the Brain. J South Asian Feder Obst Gynae 2023;15(1):114–119.

Source of support: Nil

Conflict of interest: None

pulse frequency, luteinizing hormone (LH) pulsatility, and relative follicle-stimulating hormone (FSH) deficit.[12,13] The combined effect of all these factors is that the pulsatile LH secretion and LH peak are replaced by chronically elevated LH. This elevated LH produces large quantities of androgen from theca cells. The surplus androgen produced by the ovaries is responsible for hirsutism, acne, and alopecia-common complaints at presentation in women with PCOS.[14] The excess androgen also travels to adipose tissue, where it gets converted to estrone which is not usually found in reproductive years.

Polycystic ovary syndrome is a hyperestrogenic condition, but estrone rather than estradiol is the form of estrogen present. The elevated amounts of estrone provide negative feedback on FSH, preventing FSH from assimilation of estradiol from granulosa cells. As a result of which cohort of follicles do not mature, this leads to chronic anovulation. The follicles that do not mature or rupture every cycle eventually undergo cystic degeneration. Polycystic ovarian morphology (PCOM) is defined as enlarged ovaries (>10 cc) with at least 20 small peripherally allocated follicles and without evidence of corpora lutea or dominant follicles.[15]



GnRH Secretion in PCOS Patients

Luteinizing hormone secretion is encouraged by rapid GnRH pulsation frequency, which raises serum LH and FSH levels typically in the lower follicular range. In between 55% and 75% of women with PCOS, an elevated LH to FSH ratio is frequently observed.[16] This hormonal imbalance causes anovulatory cycles because there is inadequate FSH, which is needed to encourage ovarian follicle growth and maturation. A buildup of tiny (2–9 mm) pre-antral follicles results from insufficient FSH levels disrupting the selection of a dominant follicle.[7] Additionally, PCOS causes an increase in anti-Müllerian hormone (AMH), which is normally released by antral follicles and reduces the sensitivity of developing follicles to FSH.[8] In a healthy ovarian cycle, only the dominant follicle is susceptible to the peak spike of luteinizing hormone. In a group of women with PCOS-related anovulation, it was demonstrated that small antral follicles respond prematurely to high levels of LH, which led to those follicles achieving early terminal differentiation.[19] Elevated levels of LH will also stimulate androgen synthesis in ovarian theca cells leading to hyperandrogenemia. Additionally, hyperandrogenemia may cause a higher frequency of GnRH pulsations.

GnRH Pulse Generator – KNDy Neuron

Kisspeptin, neurokinin B, and dynorphin (KNDy) neurons are neurons in the hypothalamus of the brain that are central to the hormonal control of reproduction.

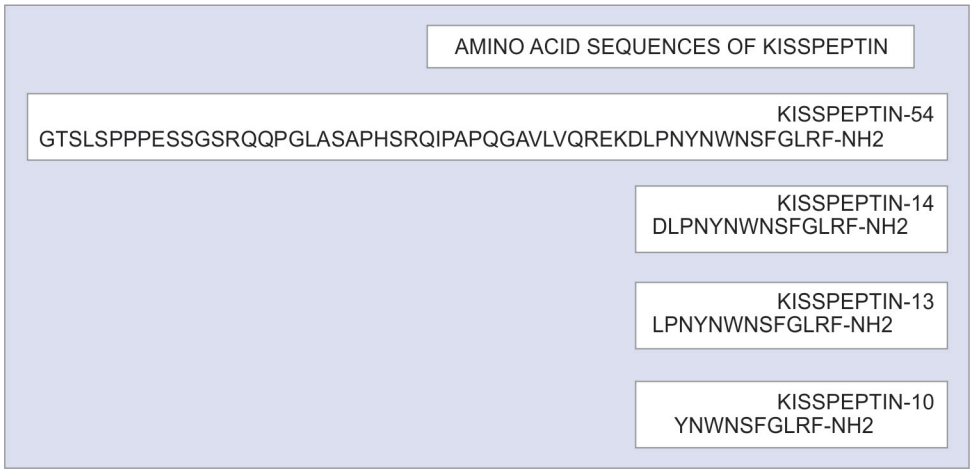
KNDy neurons in the hypothalamus coexpress kisspeptin, neurokinin B (NKB), and dynorphin. They are involved in the negative feedback of gonadotropin-releasing hormone (GnRH) release in the hypothalamic–pituitary–gonadal (HPG) axis. Sex steroids released from the gonads act on KNDy neurons as inhibitors of kisspeptin release (Flowchart 1). This inhibition provides negative feedback control on the HPG axis. GnRH and LH levels fall as a result of estrogen's suppression of kisspeptin and NKB release. Contrarily, estrogen-positive feedback in the late follicular phase causes the preovulatory LH spike.[20]

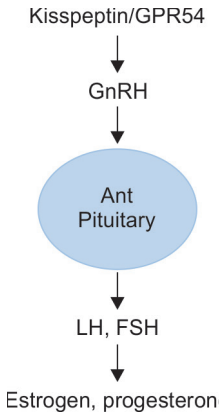
Kisspeptin and PCOS

Kisspeptin is a peptide product of Kiss-1 gene that is expressed in the KNDy neurons in the hypothalamus. Kisspeptin acts via its G-protein receptor, GPR54. Kisspeptin-54 is the endogenous form of hormone in humans.

Milena Gurgel et al. in 2008 reported that a kisspeptin receptor, GPR54, the activating mutation was found in a patient with central precocious puberty. A few years later Kemal Topaloglu et al. in a case report showed that an inactivating mutation of the KISS1 gene causes idiopathic hypogonadotropic hypogonadism in humans. Kisspeptin, a relatively novel neuropeptide, is thought to be a key and potent positive activator of GnRH's pulsatile secretion,[21] leading

Flowchart 1: Association of KISSEPTIN with PCOS





to overactivity of the hypothalamic–pituitary–gonadal axis. This in turn causes menstrual irregularities, hyperandrogenemia, and hyperandrogenism.

Waljit S Dhillo et al. through their study in 2004 showed that kisspeptin stimulates reproductive hormone release in humans. In their study, they gave an intravenous infusion of kisspeptin hormone in their subjects over 90 minutes and observed a dose-dependent rise in GnRH and LH release.

The first study to compare serum kisspeptin levels in PCOS patients and healthy controls was conducted by Tang et al.[22] They discovered a negative correlation between serum kisspeptin levels and indices of insulin resistance, free androgen index, and body mass index. Studies conducted after the initial ones supported the observation of higher kisspeptin levels in PCOS. Twelve articles were discovered in a literature analysis done in July 2018 by Tang et al.[22] that looked at serum kisspeptin levels in PCOS. Out of 12 studies in patients with PCOS, eight showed significantly higher serum levels of kisspeptin. Pérez-López et al.[23] broadening hypothesis states that kisspeptin can be viewed as a separate PCOS biomarker. This claim was based on a comprehensive meta-analysis that included 1282 people, including 699 patients and 583 controls, and found that blood kisspeptin levels were greater in PCOS patients than in non-PCOS patients. The finding that patients with PCOS have higher serum kisspeptin levels was supported by a subsequent meta-analysis by Pérez-López et al.,[23] which was published in 2021. Since then, using kisspeptin as a PCOS diagnostic marker has grown in popularity.

Using mice models, Katulski K et al.[24] investigated the neuroendocrine basis of PCOS. However, the main finding of their study was that elevations in kisspeptin and neurokinin B expression at the level of the arcuate nucleus was probably the main factor contributing to this shift in pulsatility. They noticed that LH pulsatility was increased in PCOS. Kisspeptin and gonadotropin (FSH, LH) pulsatility in PCOS patients were investigated by Katulski et al.[24] They discovered that only in eumenorrheic patients did spontaneous episodic kisspeptin secretion coincide with LH pulses. Patients with oligomenorrheic PCOS were not reported to exhibit kisspeptin pulses coupled to LH pulsatility. Additionally, it was discovered that PCOS patients with oligomenorrhea had a higher kisspeptin pulse frequency. This study supported the idea that kisspeptin coupling to LH pulses is affected by the abnormalities in neuroendocrine function (as found in PCOS).

Neurokinin B and PCOS

The tachykinin family of peptides, which includes neurokinin B (NKB), shares a common C-terminal amino acid pattern (Phe–X–Gly–Leu–Met–NH2). The NKB binds to the neurokinin-3 receptor that is expressed by the TAC3R gene in humans. The entire human nervous system contains NKB and NK3R. Neurokinin B is one of several neuronal and endocrine variables that control GnRH secretion. Clinically, NKB causes an increase in adrenocortical androgen secretion and a decrease in the ovulation ratio, which is a typical presentation in polycystic individuals.[25] In healthy women, NKB controls the release of gonadotropins, the growth of follicles, and the time of ovulation. The regulation of estrogen-negative feedback, which has been demonstrated to be changed in PCOS, is influenced by NKB and kisspeptin signaling. Additionally, PCOS is linked to increased LH pulse amplitude and frequency, which is probably brought on by an increase in GnRH pulsatile production.[26]

Ovulation fails and ovarian testosterone production rises as a result of increased pituitary LH output. According to recent research, the NKB–kisspeptin–GnRH pathway is essential for controlling LH secretion. Patients with genetically compromised NKB signaling were shown to have lower LH production and a lower LH pulse frequency. Therefore, the pharmacological NKB blockade may target the fundamental pathophysiology of LH hyper secretion and hyperandrogenism seen in PCOS.

In a study by Blasco et al., it was discovered that PCOS women's mural granulosa cells (MGCs) and cumulus oophorus cells (CCs) had lower levels of NKB and NK3R mRNA. Furthermore, it was discovered that in the MGCs of healthy women, NKB positively linked with KISS1, whereas no such association was detected in women with PCOS. The TAC3/TACR3 system is upregulated during the shift from MGC to CC in healthy women, whereas this transition does not take place in PCOS.[27] These results strongly imply that a disruption in NKB secretion can influence the emergence of PCOS. Future research is nonetheless required to ascertain the specific mechanism of the NKB pathway and its role in PCOS.

Kisspeptin and NKB Analogs in PCOS

Oocyte maturation and ovulation have been encouraged by kisspeptin-based regimens, which have been suggested as a safer option. Kisspeptins can therefore give the ovary a more physiological gonadotrophin stimulation because they are strong and efficient endogenous GnRH release stimulators. As a result, protocols based on kisspeptin have been suggested as a less risky way to encourage oocyte maturation and ovulation. The clinical value of the kisspeptin pathway may be greatly increased by a therapeutic receptor agonist that targets the kisspeptin receptor (KISS1R).[28] Kisspeptin-54 (KP-54) has been demonstrated to be an efficient oocyte maturation stimulant in women undergoing *in vitro* fertilization therapy.[29] When receiving reproductive treatment, women with PCOS are especially susceptible to ovarian hyperstimulation syndrome (OHSS). According to a study conducted by Abbara et al., kisspeptin-54 use significantly reduced the related risk of OHSS in high-risk women. In PCOS women, suppressing the stimulatory effects of kisspeptin by certain receptor antagonists and lowering GnRH production may be therapeutic targets. When compared to FSH, it has been demonstrated that GnRH pulse frequency stimulates LH secretion significantly more strongly, and a drop in GnRH pulse frequency has the ability to normalize the LH hypersecretion frequently observed in PCOS. The promotion of folliculogenesis and ovulation in PCOS may result from normalizing LH secretion and, in turn, normalizing androgen concentration.[30] Kisspeptin antagonists have not yet been employed in this indication, however, NKB antagonists have been extensively studied in

this setting. In a research by George et al., patients with PCOS underwent pharmacological intervention with AZD4901 (a particular NK3 receptor antagonist) for a period of 28 days. On day 7, it was discovered that patients taking 80 mg/day of the neurokinin-B antagonist had reduced their levels of LH by 52.0%, total testosterone by 28.7%, and LH pulses by 3.55 per 8 hours. A prospective treatment for the central neuroendocrine pathogenesis of PCOS, the NK3 receptor antagonist selectively decreased LH pulse frequency and subsequently blood LH and T concentrations.

Other Neurohormones and Adipokines in PCOS (Phoenixin-14, Galanin, and Glp-1)

An increasing amount of research indicates that phoenixin-14, galanin, and GLP-1 are effective at slowing the progression of PCOS.

Phoenixin (PNX) is a recently discovered peptide that is primarily synthesized in the hypothalamus by proteolytic cleavage of a tiny integral membrane protein. It has been found in a variety of organs, including the pituitary, heart, gastrointestinal tract, pancreatic islets, and adipose tissue.[31] Phoenixin may increase the secretion of pituitary gonadotropins, such as FSH and LH, by altering the expression of the gonadotropin-releasing hormone receptor and further by potentiating and upregulating GnRH receptors, according to *in vitro* investigations of anterior pituitary cells.[32] Additionally, it has been demonstrated that PNX stimulates insulin production, suggesting that it may interact with pancreatic beta cells to regulate blood sugar levels.[33] A recent investigation into PNX's impact on reproductive function revealed that it is a strong intraovarian component. It has been demonstrated to promote follicular cell development by enhancing the proliferative rate of human granulosa cells and increasing estradiol release.[34] Increased serum PNX levels were seen in a rodent investigation using PCOS-affected rats, supporting findings from studies of PCOS patients. Serum PNX-14 levels were substantially greater in PCOS participants than in control groups. This rise was inversely linked with estradiol and positively with testosterone and LH levels (E2).

It is believed that elevated LH and androgen production is linked to increased phoenixin-14 expression in PCOS patients.[35]

The neuropeptide galanin is widely distributed throughout the central and peripheral nervous system as well as the reproductive tract.[36] It is synthesized in the hypothalamus and anterior pituitary, where estrogens greatly promote its production. As an intraovarian regulatory peptide, galanin regulates steroidogenesis in ovarian tissue and preovulatory surges of LH and prolactin.[37] Galanin can drastically lower levels of LH, insulin, glucose, insulin resistance (IR), and testosterone while increasing the secretion of FSH. Galanin also has a moderating influence on steroid hormones. It could regulate PCOS gene expression as well as metabolic, inflammatory, and hormonal disorders. This may imply that galanin contains a target pathway that may one day be utilized to treat PCOS.

A class of drugs used to decrease blood sugar called glucagon-like peptide-1 receptor agonists (GLP-1 RA) mimics the effects of the hormone incretin. They have been approved for the management of disorders like PCOS as well as the treatment of type II diabetes mellitus more recently. However, enteroendocrine cells that are located in the gut release hormones called incretins that promote pancreatic insulin secretion. Treatment with GLP-1 RA raises plasma GLP-1 levels that are accessible to supraphysiologic levels, which increases glucose-dependent insulin secretion, lowers glucagon production, slows stomach emptying, and boosts satiety.[38]

The few trials that have been conducted on GLP-1 RA in PCOS have all been brief in length and have all demonstrated improvement in glucose and metabolic parameters with varying findings in regard to fertility and hyperandrogenism.[39]

Neurotransmitters in PCOS

The underlying neurotransmitter structure and functionality must be considered while determining the etiology of PCOS. As was already mentioned, the pathogenesis of this illness is thought to be primarily characterized by inadequate pulsatile production of the gonadotropin-releasing hormone (GnRH) and dysregulated hypothalamic–pituitary–ovarian axis, which supports significantly related neurotransmitter activity. GnRH secretion may be inhibited by neurotransmitters such as GABA, glutamate, serotonin, dopamine, and acetylcholine as well as the opioid system. The primary inhibitory neurotransmitter in the central nervous system is gamma-aminobutyric acid (GABA) (CNS). Since GABA has an excitatory effect on GnRH secretion, it is commonly acknowledged that it plays a role in the pathophysiology of PCOS. According to Silva et al.'s research, GABA neurons coming from the arcuate nucleus promote GnRH release and cause a significant reaction in the secretion of luteinizing hormone (LH).[40] Similar studies discovered that PCOS patients had higher amounts of GABA in cerebral fluid than eumenorrheic, ovulatory women.[41] Additionally, it is thought that GABAergic innervation of GnRH neurons causes the observed decreased sensitivity to progesterone-negative feedback of GnRH and LH pulsatile production.[42] The function of glutamate, the primary excitatory neurotransmitter in the CNS, in the pathophysiology of PCOS, is largely unknown.

In a study of 27 PCOS-diagnosed women, Kawwass et al. discovered comparable levels of glutamate in cerebral fluid to a control group.[43] However, higher glutamate levels and high N-methyl-D-aspartate (NDMA) receptor expression have been seen in PCOS-induced rats in animal model studies.[44] The endorphin, enkephalin, and dynorphin-3 families of peptides make up the opioid system, and they function in central and peripheral nervous systems, respectively. Analgesia, the stress response, affective processes, and neuroendocrine reproduction are all regulated by endorphins. Enkephalins influence the etiology of obesity, the maturation of follicles during the reproductive cycle, and the secretion of insulin. The powerful peptide hormones known as dynorphins interact with several opioid receptors, both centrally and peripherally, and have a wide range of downstream actions.

Beta-endorphins, peptide hormones that serve as opioid receptor agonists, are present throughout the central nervous system (CNS) as well as in the pancreatic islets, where they stimulate the release of insulin and glucagon and raise blood glucose levels.[45] In their study, Kiaka et al. found that patients with PCOS had higher serum levels of-endorphins than the controls, and these results were likewise connected with higher insulin levels and lower SHBG. Naltrexone and naloxone, two opioid antagonists, were found to considerably diminish the insulin response to the oral glucose tolerance test (OGTT) in a group of hyperinsulinemic PCOS patients, according to studies on their usage as opioid antagonists for the treatment of PCOS.[46] Acne, hirsutism, and amenorrhea were shown to be improved by naltrexone, and it was also reported to lower serum testosterone and insulin levels while regaining sensitivity to clomiphene citrate in patients who were resistant to it.[47]

When thinking about the emergence of PCOS, acetylcholine (ACh), the primary transmitter of the parasympathetic nervous

system, should not be disregarded. The vagus nerve is primarily responsible for providing the ovaries with parasympathetic nerve transmission. In rats with estradiol valerate injection-induced PCOS who had unilateral or bilateral vagus nerve sections, a study by Linares et al. found that 75% of patients experienced a return to spontaneous ovulation in both ovaries. There is little research on how monoamine neurotransmitters like serotonin, norepinephrine, and dopamine contribute to the onset of PCOS.[48]

Neuropeptide Y

Neuropeptide Y is an important peptide in the mechanism by which leptin and insulin inform the hypothalamus about the nutritional state of an individual. Neuropeptide Y stimulates appetite and the pulsatile release of GnRH and gonadotropins. In the absence of estrogen, neuropeptide Y inhibits gonadotropin secretion. Because undernutrition is associated with an increase in neuropeptide Y and increased amounts have been measured in cerebrospinal fluid (CSF) of women with anorexia and bulimia nervosa, neuropeptide Y is viewed as at least one link between nutrition and reproductive function.

The level of the neuroendocrine activity involved in reproduction is sensitive to an individual's energy state, or more simply, to the availability of sufficient body fuel to support reproduction.

References

1. Dunaif A, Givens JR, Haseltine FP, et al. Polycystic Ovary Syndrome. Boston (MA): Blackwell Scientific Publications; 1992.
2. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81(1):19–25. DOI: 10.1016/j.fertnstert.2003.10.004.
3. Azziz R, Carmina E, Dewailly D, et al. Positions statement: Criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: An Androgen Excess Society guideline. Androgen Excess Society. J Clin Endocrinol Metab 2006;91(11): 4237–4245.
4. Dunaif A. Insulin resistance and the polycystic ovary syndrome: Mechanism and implications for pathogenesis. Endocr Rev 1997;18:774–800.
5. Azziz R, Woods KS, Reyna R, et al. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89(6):2745–2749. DOI: 10.1210/jc.2003-032046.
6. Broekmans FJ, Knauff EA, Valkenburg O, et al. PCOS according to the Rotterdam consensus criteria: Change in prevalence among WHO-II anovulation and association with metabolic factors. BJOG 2006;113(10):1210–1217. DOI: 10.1111/j.1471-0528.2006.01008.x.
7. Taylor HS, Pal L, Seli E. Speroff's Clinical Gynecologic Endocrinology and Infertility. 9th ed. Department of Obstetrics, Gynecology and reproductive Sciences, Yale School of Medicine: New Haven, CT, USA; 2019.
8. Franks S, McCarthy MI, Hardy K. Development of polycystic ovary syndrome: Involvement of genetic and environmental factors. Int J Androl 2006;29(1):278–285. DOI: 10.1111/j.1365-2605.2005.00623.x.
9. Diamanti-Kandarakis E, Piperi C, Korkolopoulou P, et al. Accumulation of dietary glycotoxins in the reproductive system of normal female rats. J Mol Med 2007;85(12):1413–1420. DOI: 10.1007/s00109-007-0246-6.
10. Conway G, Dewailly D, Diamanti-Kandarakis E, et al. The polycystic ovary syndrome: A position statement from the European Society of Endocrinology. Eur. J. Endocrinol 2014;171(4):P1–P29. DOI: 10.1530/EJE-14-0253.
11. Gonzalez F, Hatala DA, Speroff L. Adrenal and ovarian steroid hormone responses to gonadotropin-releasing hormone agonist treatment in polycystic ovary syndrome. Am J Obstet Gynecol 1991;165:535–545. DOI: 10.1016/0002-9378(91)90280-5.
12. Wildt L, Hausler A, Marshall G, et al. Frequency and amplitude of gonadotropin-releasing hormone stimulation and gonadotropin secretion in the rhesus monkey. Endocrinology 1981;109(2):376–385. DOI: 10.1210/endo-109-2-376.
13. Speroff L, Vande Wiele RL. Regulation of the human menstrual cycle. Am J Obstet Gynecol. 1971;109:234–47. [PubMed] [Google Scholar].
14. Naftolin F, Tolis G. Neuroendocrine regulation of the menstrual cycle. Clin Obstet Gynecol 1978;21(1):17–29. DOI: 10.1097/00003081-197803000-00003.
15. Azziz R. Polycystic ovary syndrome. Obstet Gynecol 2018;132: 321–336. DOI: 10.1097/AOG.0000000000002698.
16. De Leo V, Musacchio MC, Cappelli V, et al. Genetic, hormonal and metabolic aspects of PCOS: An update. Reprod Biol Endocrinol 2016;14:1–17. DOI: 10.1186/s12958-016-0173-x.
17. Dewailly D, Robin G, Peigne M, et al. Interactions between androgens, FSH, anti-Müllerian hormone and estradiol during folliculogenesis in the human normal and polycystic ovary. Hum Reprod Update 2016;22(6):709–724. DOI: 10.1093/humupd/dmw027.
18. Franks S, Stark J, Hardy K. Follicle dynamics and anovulation in polycystic ovary syndrome. Hum Reprod Update 2008;14(4):367–378. DOI: 10.1093/humupd/dmn015.
19. Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Clin Endocrinol 2018;89(3):251–268. DOI: 10.1111/cen.13795.
20. Matsuda F, Nakatsukasa K, Suetomi Y, et al. The luteinising hormone surge-generating system is functional in male goats as in females: Involvement of kisspeptin neurones in the medial preoptic area. J Neuroendocrinol 2015;27(1):57–65. DOI: 10.1111/jne.12235.
21. Coyle C, Campbell RE. Pathological pulses in PCOS. Mol Cell Endocrinol 2019;498:110561. DOI: 10.1016/j.mce.2019.110561.
22. Tang R, Ding X, Zhu J. Kisspeptin and polycystic ovary syndrome. Front Endocrinol 2019;10:298. DOI: 10.3389/fendo.2019.00298.
23. Pérez-López FR, Ornat L, López-Baena MT, et al. Circulating kisspeptin and anti-müllerian hormone levels, and insulin resistance in women with polycystic ovary syndrome: A systematic review, meta-analysis, and meta-regression. Eur J Obstet Gynecol Reprod Biol 2021;260: 85–98. DOI: 10.1016/j.ejogrb.2021.03.007.
24. Katulski K, Podfigurna A, Czyzyk A, et al. Kisspeptin and LH pulsatile temporal coupling in PCOS patients. Endocrine 2018;61(1):149–157. DOI: 10.1007/s12020-018-1609-1.
25. Wang T, Han S, Tian W, et al. Effects of kisspeptin on pathogenesis and energy metabolism in polycystic ovarian syndrome (PCOS). Gynecol Endocrinol 2019;35(9):807–810. DOI: 10.1080/09513590.2019.1597343.
26. Osuka S, Iwase A, Nakahara T, et al. Kisspeptin in the hypothalamus of 2 rat models of polycystic ovary syndrome. Endocrinology 2017;158(2):367–377. DOI: 10.1210/en.2016-1333.
27. Blasco V, Pinto FM, Fernández-Atucha A, et al. Altered expression of the kisspeptin/KISS1R and neurokinin B/NK3R systems in mural granulosa and cumulus cells of patients with polycystic ovarian syndrome. J Assist Reprod Genet 2019;36(1):113–120. DOI: 10.1007/s10815-018-1338-7.
28. Cortés ME, Carrera B, Rioseco H, et al. The role of kisspeptin in the onset of puberty and in the ovulatory mechanism: A mini-review. J Pediatr Adolesc Gynecol 2015;28:286–291. DOI: 10.1016/j.jpag.2014.09.017.
29. Jayasena CN, Abbara A, Comninos AN, et al. Kisspeptin-54 triggers egg maturation in women undergoing in vitro fertilization. J Clin Investig 2014;124(8):3667–3677. DOI: 10.1172/JCI75730.
30. Abbara A, Jayasena CN, Christopoulos G, et al. Efficacy of kisspeptin-54 to trigger oocyte maturation in women at high risk of ovarian hyperstimulation syndrome (OHSS) during in vitro fertilization (IVF) therapy. J Clin Endocrinol Metab 2015;100(9):3322–3331. DOI: 10.1210/jc.2015-2332.

31. Skorupskaite K, George JT, Veldhuis JD, et al. Kisspeptin and neurokinin B interactions in modulating gonadotropin secretion in women with polycystic ovary syndrome. Hum Reprod 2020; 35(6):1421–1431. DOI: 10.1093/humrep/deaa104.
32. Yosten GLC, Lyu R-M, Hsueh AJ, et al. A novel reproductive peptide, phoenixin. J Neuroendocrinol 2013;25(2):206–215. DOI: 10.1111/j.1365-2826.2012.02381.x.
33. Billert M, Kołodziejski PA, Strowski MZ, et al. Phoenixin-14 stimulates proliferation and insulin secretion in insulin producing INS-1E cells. Biochim Biophys Acta Mol Cell Res 2019;1866(12):118533. DOI: 10.1016/j.bbamcr.2019.118533.
34. Nguyen XP, Nakamura T, Osuka S, et al. Effect of the neuropeptide phoenixin and its receptor GPR173 during folliculogenesis. Reproduction 2019;158(1):25–34. DOI: 10.1530/REP-19-0025.
35. Kalamon N, Błaszczyk K, Szlaga A, et al. Levels of the neuropeptide phoenixin-14 and its receptor GRP173 in the hypothalamus, ovary and periovarian adipose tissue in rat model of polycystic ovary syndrome. Biochem Biophys Res Commun 2020;528(4):628–635. DOI: 10.1016/j.bbrc.2020.05.101.
36. Altinkaya SO. Galanin and glypican-4 levels depending on metabolic and cardiovascular risk factors in patients with polycystic ovary syndrome. Arch Endocrinol Metab 2021;65(4):479–487. DOI: 10.20945/2359-3997000000340.
37. Baranowska B, Radzikowska M, Wasilewska-Dziubińska E, et al. Neuropeptide Y, leptin, galanin and insulin in women with polycystic ovary syndrome. Gynecol Endocrinol 1999;13:344–351. DOI: 10.3109/09513599909167578.
38. Rasmussen CB, Lindenberg S. The effect of liraglutide on weight loss in women with polycystic ovary syndrome: An observational study. Front Endocrinol 2014;5:140. DOI: 10.3389/fendo.2014.00140.
39. Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2013;98(12):4565–4592. DOI: 10.1210/jc.2013-2350.
40. Lamos EM, Malek R, Davis SN. GLP-1 receptor agonists in the treatment of polycystic ovary syndrome. Expert Rev Clin Pharmacol 2017;10(4):401–408. DOI: 10.1080/17512433.2017.1292125.
41. Kawwass JF, Sanders KM, Loucks TL, et al. Increased cerebrospinal fluid levels of GABA, testosterone and estradiol in women with polycystic ovary syndrome. Hum Reprod 2017;32(7):1450–1456. DOI: 10.1093/humrep/dex086.
42. Ruddenklau A, Campbell RE. Neuroendocrine impairments of polycystic ovary syndrome. Endocrinology 2019;160(10):2230–2242. DOI: 10.1210/en.2019-00428.
43. Chaudhari N, Dawalbhakta M, Nampoothiri L. GnRH dysregulation in polycystic ovarian syndrome (PCOS) is a manifestation of an altered neurotransmitter profile. Reprod Biol Endocrinol 2018;16(1):37. DOI: 10.1186/s12958-018-0354-x.
44. Reid R, Yen SC. Beta-endorphin stimulates the secretion of insulin and glucagon in humans. J Clin Endocrinol Metab 1981;52:592–594. DOI: 10.1210/jcem-52-3-592.
45. Kiałka M, Milewicz T, Spałkowska M, et al. β-endorphins plasma level is higher in lean polycystic ovary syndrome (PCOS) women. Exp Clin Endocrinol Diabetes 2016;124(1):55–60. DOI: 10.1055/s-0035-1564094.
46. Ahmed MI, Duleba AJ, El Shahat O, et al. Naltrexone treatment in clomiphene resistant women with polycystic ovary syndrome. Hum. Reprod 2008;23(11):2564–2569. DOI: 10.1093/humrep/den273.
47. Linares R, Hernández D, Morán C, et al. Unilateral or bilateral vagotomy induces ovulation in both ovaries of rats with polycystic ovarian syndrome. Reprod. Biol. Endocrinol 2013;11:68. DOI: 10.1186/1477-7827-11-68.
48. Linares R, Acuña XN, Rosas G, et al. Participation of the cholinergic system in the development of polycystic ovary syndrome. Molecules 2021;26(18):5506. DOI: 10.3390/molecules26185506.