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The role of kisspeptin in the pathogenesis of a polycystic ovary syndrome

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Hypothalamic-pituitary gonadal (HPG) axis is responsible for the development and regulation of the female reproductive system. In polycystic ovary syndrome (PCOS), there is a disturbance in the HPG axis. Kisspeptin, a neuropeptide produced by the KISS1 gene, plays a vital role in the regulation of HPG axis by binding with its receptors KISS1R/GPR54, and stimulates gonadotropin secretion from the hypothalamus into pituitary to release luteinizing hormone (LH) and follicle stimulating hormone (FSH). Polymorphisms or mutations in the KISS1 gene can cause disturbance in the kisspeptin signaling pathway and is thought to disrupt HPG axis. Altered signaling of kisspeptin can cause abnormal secretion of GnRH pulse, which leads to increased LH/FSH ratio, thereby affecting androgen levels and ovulation. The increased levels of androgen worsen the symptoms of PCOS. In the present article, we review the molecular physiology and pathology of kisspeptin and how it is responsible for the development of PCOS. The goal of this review article is to provide an overview and metabolic profile of kisspeptin in PCOS patients and the expression of kisspeptin in PCOS animal models. In the present article, we also review the molecular physiology and pathology of kisspeptin and how it is responsible for the development of PCOS.

Key words: KISS1 gene, kisspeptin, PCOS, testosterone, HPG axis

Polycystic ovarian syndrome is the most common endocrine condition among women of this generation. It is also considered as one of the leading causes of infertility. The increased androgen level is referred as hyperandrogenism, a clinical hallmark of PCOS, which can cause prevention of follicular development, multiple cysts formation in the ovaries, anovulation, and disruption in the menstrual cycle. Due to anovulation and disrupted menstrual cycle, it seems impossible for women with PCOS to regulate the normal reproductive functions that are required to be fertile. Kisspeptin, a product of KISS1 gene, is a powerful neuropeptide that stimulates the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary by increasing the gonadotropin-releasing hormone (GnRH) levels. In previous studies, the polymorphism in the KISS1 gene has been found in women with PCOS, which results in the alteration of the structure and function of its product, kisspeptin. Kisspeptin is unable to perform its reproductive function and may lead to an infertility and other symptoms that occur due to disruption of GnRH deregulation. Bearing this problem in mind, this review article examines the possible role of kisspeptin in female infertility. The aim of the present review is to describe the mechanisms responsible for

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the development of infertility and other symptoms of PCOS in women focusing on the emerging role of kisspeptin as a potential biomarker in women with PCOS. The female reproductive capability is critically based on the proper development and active regulation of the hypothalamic-pituitary-ovarian (HPO) axis (Knobil et al. 1980). The pathophysiology of PCOS primarily involves defects in the HPO axis and ovarian functions. Hence, there are two mechanisms, by which kisspeptin may be involved in the pathogenesis PCOS.

The PCOS is an endocrine and reproductive disorder affecting from 7 to 15% of women of reproductive age characterized by clinical or laboratorial hyperandrogenism, oligo-anovulation, and metabolic abnormalities (Collee et al. 2021). PCOS is the first cause of anovulatory infertility nowadays and infertility is found from 70 to 80% of affected women. Infertile patients with PCOS are often characterized with ovulation disorders. These can be due to the diminished ovarian reserves, ovulatory dysfunction (hypothalamic-pituitary-gonadotropin axis or HPG axis) disorders, and ovarian disorders in case of PCOS (Breitkopf et al. 2003). The regulation of fertility by HPO axis involves the pulsatile release of GnRH from the hypothalamus stimulating the release of LH and FSH from the anterior pituitary that in turn acts on the ovaries to control gametogenesis. Kisspeptin is a neuropeptide that regulates the HPG axis by increasing GnRH levels (Kukurt et al. 2020). However, the HPG axis is responsible for normal reproductive function in women. KISS1 gene was discovered as a metastasis suppressing gene by Lee and colleagues in 1996 (Kirby et al. 2010). The product of the KISS1 gene is a 145-amino acid polypeptide, which is cleaved into a 54-amino acid protein known as kisspeptin-54 (Table 1).

The development and regulation of female reproductive competence is critically based on HPO axis function. In normal menstrual cycle during the luteal phase, the GnRH pulsatility reduces the FSH synthesis so that the follicles get stimulated once the corpus luteum breaks down. The GnRH secretion continues to increase, which leads to increased LH pulse frequency (Knobil 1980; Burger et al. 2008). Since it was discovered, a number of studies based on the level of cells, animal models, and even humans reported a key role of kisspeptin in the regulation of the HPG axis. The kisspeptins are structurally-related amidated peptides, which are derived from the differential proteolytic processing of a common precursor of 145 amino acids encoded by the KISS1 gene.

Puberty and kisspeptin

A continuous rise in the pulsatile release of GnRH from the hypothalamus results from the strengthening of excitatory cues and the reduction of inhibitory signals over GnRH neurons, which marks the beginning of puberty. A spike in gonadotropins and sex hormones, gametogenesis, secondary sex traits, and rapid growth are caused by increased GnRH pulsing, which in turn activates downstream factors and results in the accomplishment of fertility (Lents et al. 2008). The start of puberty varies from male to female and is influenced by a combination of genetic, environmental, and gene-environment interactions. Kisspeptins were discovered to be the endogenous ligands for GPR54, a previously orphan G-protein coupled receptor also known as KISS1 receptor (Castano et al. 2009). The number of studies on kisspeptins as tumor metastasis suppressors somewhat plateaued until the discovery of GPR54 mutations causing hypogonatropic hypogonadism (HH) led to the establishment of the KISS1/GPR54 system as a critical component of the reproductive axis. It has been demonstrated that the interaction between kisspeptins and their associated receptors is necessary for puberty.

The PCOS is a multifactorial disorder characterized by increased androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries (Ndefo et al. 2013). Clinically, PCOS comprises elevated levels of LH and GnRH levels, whereas FSH levels are muted or unaltered (Waldstreicher et al. 1988; Urbanek 2007). In PCOS, due to defects in HPG axis, the GnRH pulsatility is altered, while the LH pulsatility continues through the luteal phase, which causes continuous increase in the ovarian theca cells androstenedione and dehydroepiandrosterone (DHEA) synthesis (Haisenleder et al. 2008). The androstenedione and DHEA do not have androgenic activity, but are converted by tissues in the peripheral compartment to biologically active testosterone (Shannon and Wang 2012). The increased androgen level is referred as a hyperandrogenism, a clinical hallmark of PCOS, which causes prevention of follicular development, multiple cysts formation in the ovaries, anovulation, and disruption in the menstrual cycle (Ndefo et al. 2013). In 2003, people with HH were discovered to have inactivating mutations of GPR54. Thus, numerous investigations have validated the kisspeptin's pivotal functions in regulating various facets of reproduction (De Bond et al. 2013; Kotani et al. 2014; Iijima et al. 2015; Oride et al. 2015; Xie et al. 2015) (Table 1).

Table 1
Different studies showing kisspeptin levels/expression in polycystic ovarian syndrome (PCOS).
PCOS was significantly associated with increased kisspeptin, supporting the hypothesis that an over-stimulation of the KISS1 system might cause increased kisspeptin levels which then further leads to hyper-stimulation of the hypothalamic-pituitary-gonadal (HPG) axis. This is consistent with the idea that an overactive KISS1 system promotes increased HPG axis activity, which in turn causes irregular menstrual periods and excessive androgen secretion in PCOS patients.

No.	Title	Kisspeptin levels/ expression in cells	References
1	Increase of kisspeptin-positive cells in the hypothalamus of a rat model of polycystic ovary syndrome	Upregulated	Kondo et al. 2016
2	Kisspeptin mRNA expression is increased in the posterior hypothalamus in the rat model of polycystic ovary syndrome	Upregulated	Matsuzaki et al. 2017
3	Is there a role for kisspeptin in pathogenesis of polycystic ovary syndrome?	Upregulated	Gorkem et al. 2018
4	Using kisspeptin to assess GnRH function in an unusual case of primary amenorrhea	Upregulated	Vimalesvaran et al. 2017
5	Serum kisspeptin levels in unexplained infertility, polycystic ovary syndrome, and male factor infertility	Upregulated	Kaya 2018
6	Altered expression of the kisspeptin/ KISS1R and neurokinin B/NK3R systems in mural granulosa and cumulus cells of patients with polycystic ovarian syndrome	Downregulated	Blasco et al. 2019
7	Increased expression of KISS1 and KISS1 receptor in human granulosa lutein cells-potential pathogenesis of polycystic ovary syndrome	Upregulated	Hu et al. 2019
8	rs4889 polymorphism in KISS1 gene, its effect on polycystic ovary syndrome development and anthropometric and hormonal parameters in Saudi women	Upregulated	Albalawi et al. 2019
9	Evaluation of biochemical, endocrine, and metabolic biomarkers for the early diagnosis of polycystic ovary syndrome among non-obese Saudi women	No change	Daghestani 2018
10	Kisspeptin and body weight homeostasis in relation to phenotypic features of polycystic ovary syndrome; metabolic regulation of reproduction	Upregulated	Rashad et al. 2019
11	Kisspeptin treatment induces gonadotropic responses and rescues ovulation in a subset of preclinical models and women with polycystic ovary syndrome	Upregulated	Romero-Ruiz et al. 2019
12	Association of Kiss1 and GPR54 gene polymorphisms with polycystic ovary syndrome among Sri Lankan women	Upregulated	Branavan et al. 2019
13	The correlation between hormonal disturbance in PCOS women and serum level of kisspeptin	Upregulated	Ibrahim et al. 2020
14	Serum kisspeptin levels correlated with anti-mullerian hormone levels in women with and without polycystic ovarian syndrome	No change	Mut et al. 2021
15	In depth analysis of the association of FTO SNP (rs9939609) with the expression of classical phenotype of PCOS: a Sri Lankan study	Upregulated	Branavan et al. 2020
16	Kisspeptin levels in relation to sex hormone profile among PCOS patients	Downregulated	Zarei et al. 2022
17	A comparative study of serum kisspeptin levels among women with polycystic ovary syndrome and normal fertile women	Upregulated	Hassan Ali and Mohamad 2021
18	Kisspeptin variations in patients with polycystic ovary syndrome - A prospective case control study	Upregulated	Akad et al. 2022a
19	Treatments in patients with polycystic ovary syndrome and effects on kisspeptin serum levels	Upregulated	Akad et al. 2022b
20	Serum kisspeptin, leptin, neuropeptide Y, and neurokinin B levels in adolescents with polycystic ovary syndrome	Downregulated	Guzelkas et al. 2022
21	Correlation between kisspeptin and biochemical markers in obese and non-obese women with polycystic ovary syndrome	Upregulated	Gao et al. 2023

Role of kisspeptin in the control of gonadotrophin secretion: Kisspeptin is a key regulator of puberty and HPG axis.

The KISS1 gene was discovered as a metastasis suppressing gene by Lee and colleagues (Lee et al. 1996; Nash and Welch 2006; Gottsch et al. 2009; Roseweir and Millar 2009). The product of the KISS1 gene is a 145-amino acid polypeptide, which is cleaved into a 54-amino acid protein known as kisspeptin-54 (West et al. 1998). There are some elements that are responsible for the dynamic regulation of pulsatile GnRH secretion/release that may be either excitatory or inhibitory in nature. These regulatory factors impact, directly or indirectly, through a common pathway, on the neurons producing GnRH, which stimulates pituitary gonadotropin secretion and thereby gonadal function. Among the excitatory elements of the reproductive axis, kisspeptin is a vital upstream regulator of GnRH neurons (Roa et al. 2008a; Oakley et al. 2009; Navarro and Tena-Sempere 2011; Pinilla et al. 2012).

The studies conducted by Gottsch et al. (2006) and Kauffman et al. (2007) have shown that kisspeptin stimulates the secretion of gonadotropin by acting directly on GnRH neurons and not the pituitary gonadotropes. Seminara et al. (2003) and de Roux et al. (2003) have found that mutations in the GPR54 causes recessive idiopathic HH in humans. Whereas, Seminara et al. (2003) have shown that deletion of GPR54 in mice causes defective sexual development and reproductive failure. In addition, d'Anglemont de Tassigny and Colledge (2007) have determined that the targeted deletion of KISS1 gene in mice causes the same phenotype as mutation of the GPR54 gene. These studies have suggested that kisspeptin and its receptor are essential for the normal reproductive activity.

Kisspeptin signaling

The role of kisspeptin in the control of gonadotropin secretion. The KISS1R is activated on binding with kisspeptin, which in turn activates the Gαq

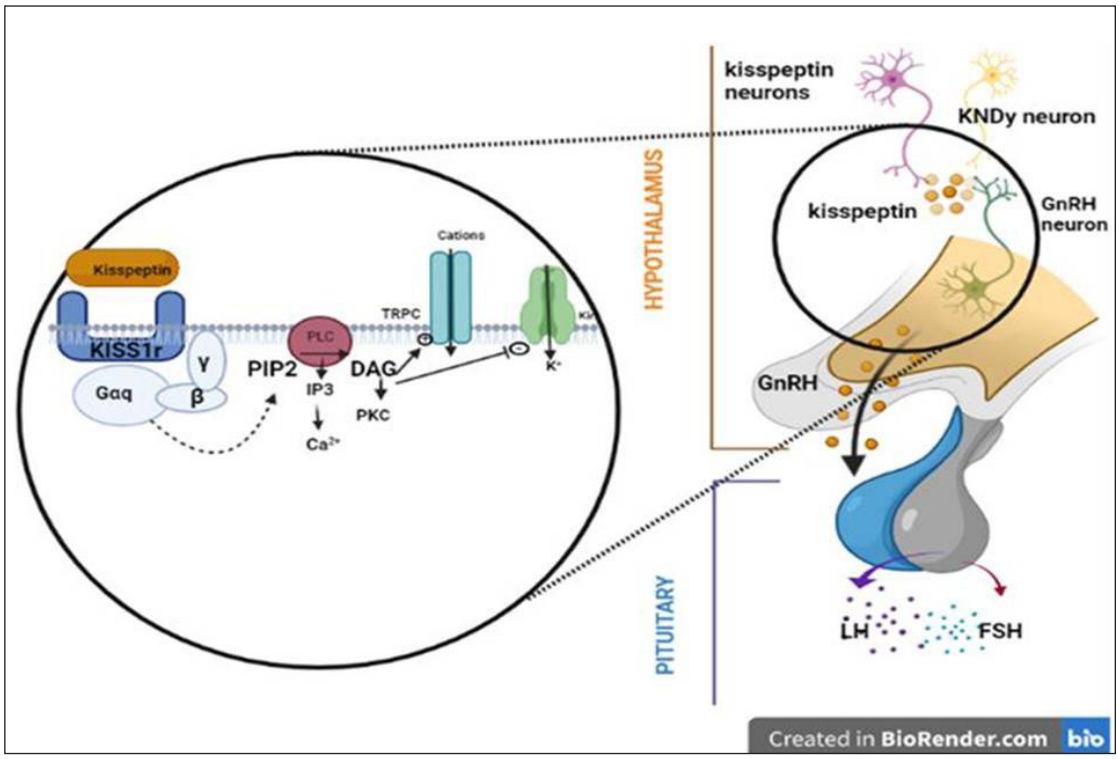

Figure 1. Kisspeptin signaling: the role of kisspeptin in the gonadotropin secretion. Abbreviations: KNDy – kisspeptin neurokinin B and dynorphin neuron; KISS1R – kisspeptin receptor; PLC – phospholipase C; PIP2 – phosphatidylinositol 4,5 bisphosphate; DAG – diacylglycerol; IP3 – inositol triphosphate; TRPC – transient receptor potential canonical like channel; GnRH – gonadotropin releasing hormone; LH – luteinizing hormone; FSH – follicle stimulating hormone; PKC – protein kinase C.

protein (Millar and Babwah 2015). The Gαq protein activates phospholipase C (PLC), which leads to the generation of intracellular second messengers, inositol triphosphate (IP3) and diacylglycerol (DAG). The IP3 mediates intracellular calcium ions (Ca^{2+}) release and DAG activates protein kinase C (PKC). The Ca^{2+} and DAG cause depolarization of GnRH neurons by inhibiting potassium channels and activating transient receptor potential canonical (TRPC)-like channels leading to GnRH secretion (Kotani et al. 2001; Muir et al. 2001; Stafford et al. 2002; Zhang et al. 2008; Constantin et al. 2009). The GnRH (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH2) is synthesized and secreted from the hypothalamic neurons. The neuronal activity of GnRH is modulated by different peripheral and central signals including the stimulatory signals such as norepinephrine, kisspeptin and neuropeptide Y and inhibitory signals such as beta-endorphin, progesterone and interleukin. The GnRH acts on GPCRs of gonadotropes and acts primarily via Gαq/11 to activate PLC, thus elevating cytoplasmic Ca^{2+} and PKC isoenzymes, both of which are important for the synthesis and secretion of gonadotropins (LH and FSH) (Stojilkovic and Catt 1995; Sealfon et al. 1997; Millar et al. 2004; Cheng and Leung 2005; Ciccone and Kaiser 2009; Wang et al. 2010) (Figure 1).

Signaling pathways triggered upon GPR54 activation by kisspeptin. Kisspeptin can activate a wide range of signals via GPR54, including both traditional G-protein (Gaq/11)-coupled cascades such as PLC-PKC and intracellular Ca2+ mobilization, as well as MAP kinases, ERK1/2, and p38-related pathways that are also linked to GPCRs. However, it appears that kisspeptin selectively activates a specific set of interconnected signals via GPR54 in a cell type-dependent manner to precisely regulate functions as disparate as hormone release stimulation and cell migration inhibition. Furthermore, rather than being linear, straightforward cascades, the pathways activated and required by the kisspeptin/GPR54 system to exert its distinct functions appear to be multiple and intricate, and the mechanisms that enable a given cell to interpret the kisspeptin signal with such fine precision to convey the correct instructions remain unknown. In this context, it will be critical to explore other molecular events that aside from intracellular signaling messengers, can have a substantial impact on kisspeptin/GPR54 function. As a result, as demonstrated by a recent study in immortalized GT1-7 cells, the molecular interaction of GPR54 with other membrane receptors, specifically GnRH, may play a role in modulating kisspeptin effects. Similarly, there is recent evidence that kisspeptin can prevent metastasis to many organs in the absence of GPR54, implying the possibility of additional kisspeptin receptors and signaling pathways yet to be found (Nash et al. 2007; Prentice et al. 2007; Ciaramella et al. 2018). In any case, deciphering GPR54 signaling mechanisms and pathways in reproductive and nonreproductive tissues remains a difficult task that necessitates additional research using different models, particularly on natural kisspeptin targets expressing endogenous GPR54 (Castano et al. 2009; Zhu et al. 2020; Li et al. 2022) (Figure 2).

In previous studies, kisspeptin has been identified as a high affinity RF amide (Arg-Phe-NH2) peptide ligand for an orphan G protein coupled receptor (GPR54). GPR54 is now termed as "KISS1R" for its role as a kisspeptin receptor (Kotani et al. 2001; Muir et al. 2001; Ohtaki et al. 2001). Seminara et al. (2003) and de Roux et al. (2003) reported that mutation in the KISS1R gene is associated with idiopathic hypothalamic hypogonadism and impaired pubertal maturation, which led to physiologists' attention in kispeptin-KISS1R signaling. Therefore, kisspeptin binds with KISS1R and signals GnRH neurons to release GnRH into the portal circulation, which in turn stimulates LH and FSH secretion from the gonadotrophs of anterior pituitary. The evidence suggests that the stimulation of gonadotropin secretion by kisspeptin is by direct activation of GnRH neurons, which is due to the major presence of KISS1R in GnRH neurons and kisspeptin-IR fibers found in close association with GnRH neurons.

Role of kisspeptin in the pathogenesis of PCOS

KISS1 gene polymorphism. The genetic factors of PCOS disease in terms of HPG axis related factors have received considerable attention by researchers. Several previous studies have explored mutations in the HPG axis linked genes such as KISS1, GPR54, GnRHR, LHR and FSHR for the development of PCOS in the adult female population (Prapas et al. 2009; Valkenburg et al. 2009; Chaudhary et al. 2021; Zhao et al. 2022). Among these genes, KISS1 has emerged as one of the potential candidate gene contributing to a regulatory role in the female reproductive system with an essential function in gonadotropin secretion of the HPG axis (Zeydabadi Nejad et al. 2017). KISS1 gene has been considered as the critical regulator in controlling the reproductive system. Previous studies found various single nucleotide polymorphisms (SNPs) in the KISS1 gene leading to disturbance in the functioning of reproductive system by HPG axis

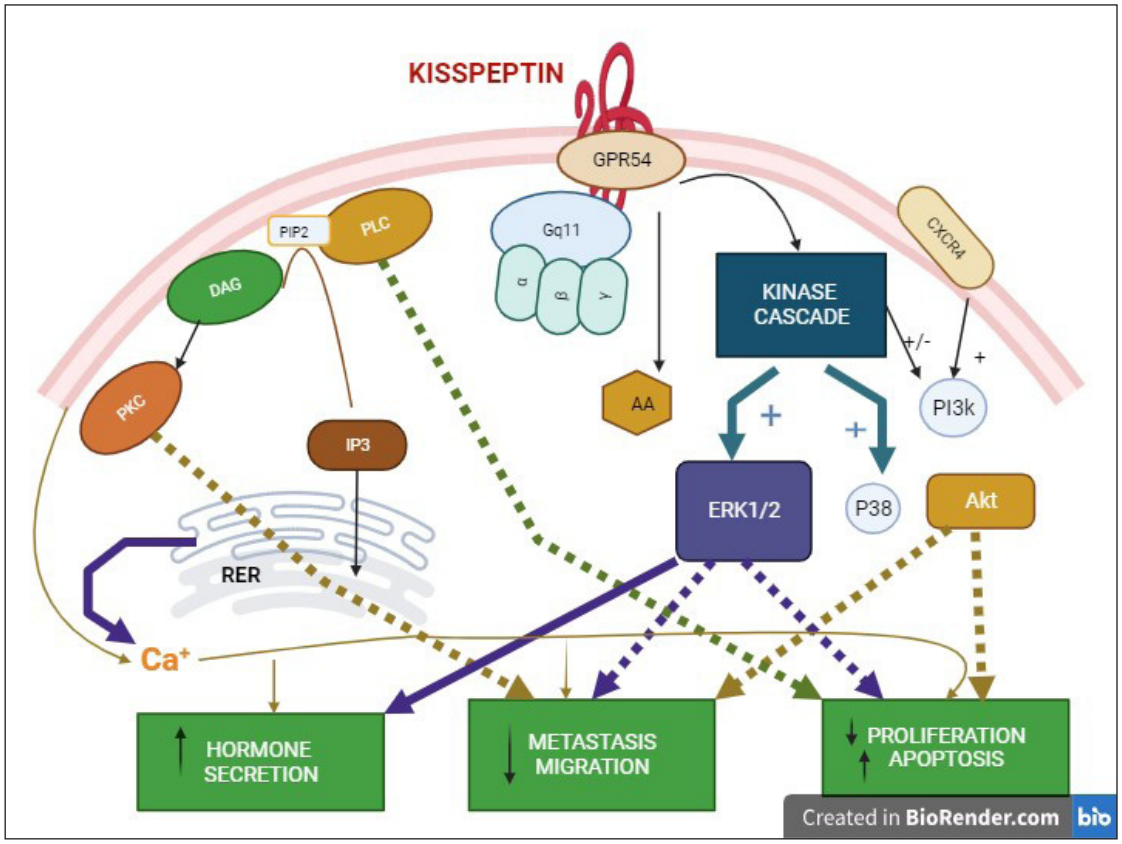

Figure 2. Schematic diagram illustrating the signaling pathways that are involved in kisspeptin action upon GPR54 activation. Solid arrows: the pathways that have been demonstrated and are important in KISS1/GPR54 mediated effects; dotted arrows: pathways whose potential involvement in KISS-1/GPR54 action have been proposed but are still not clearly proven or are considered marginal with respect to other pathways.

that plays an essential role in etiopathogenesis of PCOS (Figure 3).

The SNPs in KISS1 gene are found to disrupt the healthy functioning of the female reproductive system through HPG axis and are postulated to play an essential role in PCOS etiopathogenesis. In a study conducted by Farsimadan et al. (2021), the SNP rs4889 C>G showed a significant association with PCOS through the recessive, co-dominant and allelic model and concluded that rs4889 C>G had a significant association with PCOS. Furthermore, Albalawi et al. (2018) have found that SNP rs4889 (C/G) was found more frequently in PCOS women than in controls and the frequency of GG genotype was significantly higher in PCOS subjects compared to controls. On the other hand, Farsimadan et al. (2021) have found no significant association between rs4889 and PCOS and concluded that it did not affect the synthesis of kisspeptin in PCOS. The KISS1 gene variant (rs4889) reported by Farsimadan et al. (2021) have shown the substitution of a proline by arginine (P81R) residue in the coding region of the KISS1 gene. The mutation may alter the structure, function, and binding of kisspeptin to its receptor, GPR54/KISS1R. As mentioned above, kisspeptin regulates GnRH via binding to its receptor GPR54. However, due to polymorphism, there is abnormal secretion of GnRH, which result in an increase in LH that causes the luteal phase to elongate and therefore, there is an increase in androgen (testosterone and estradiol) production from gonads.

Overexpression of KISS1. Kisspeptin is a hypothalamic peptide encoded by the KISS1 gene that plays a key role in the regulation of HPG axis. The local or systemic administration of kisspeptin leads to increased GnRH and gonadotropin secretion in animals (Ohtaki et al. 2001; Irwig et al. 2004; Castellano et al. 2005; Roa et al. 2006; 2008b; Pielecka-Fortuna et al. 2008). Several studies have reported that kisspeptin exerts a direct effect upstream of GnRH neurons in terms of depolarization. Although, the presence of KISS1R on pituitary has been reported,

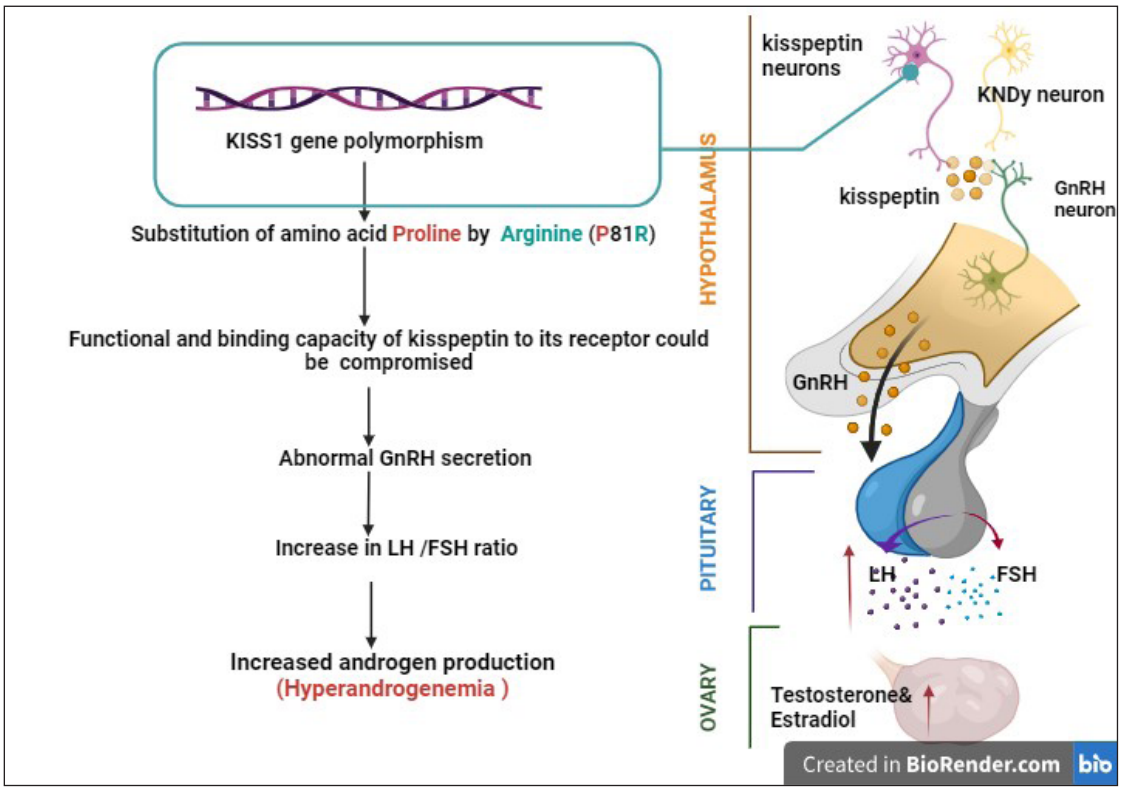

Figure 3. Kisspeptin in the pathogenesis of the polycystic ovary syndrome (PCOS).

it has a limited stimulatory effect on gonadotropin release suggesting that the effect of kisspeptin on GnRH neurons is the major pathway (Plant 2006; Lerchbaum et al. 2014; Rehman et al. 2019).

According to the survey by Tang et al. (2019), the circulating kisspeptin levels are higher in PCOS women population, which supports the hypothesis that an overactive KISS1 system might be a cause for the onset of the syndrome, due to which it shows increased HPG-axis activity, leading to irregular menstrual cycle and excessive androgen release. Lerchbaum et al. (2014) have found an increased free testosterone level in PCOS women and suggested that the women are at increased metabolic risk. A classic example of negative feedback is the ability of testosterone to act at the level of hypothalamus to suppress GnRH and thereby regulate gonadotropin secretion (Kotani et al. 2001). It is hypothesized that abnormal level of steroid hormones may act on GnRH and HPO axis through the kisspeptin-Gpr54 signaling pathway to affect the development of PCOS. Increased testosterone causes suppression of GnRH, which ultimately leads to PCOS, due to which PCOS phenotypes develops symptom like male pattern baldness, hirsuitism, acne vulgaris (Abbott et al. 2019; Ashraf et al. 2019; Zeng et al. 2020; Besenek and Gurlek 2021). Since there is persistent increase in LH pulsatility, the level of FSH decreases, which results in anovulation and arrest of follicle stimulation that causes polycystic ovaries (Lerchbaum et al. 2014) (Figure 4).

Although some studies show a positive correlation of circulating kisspeptin levels with PCOS, while others show no association at all. However, studies suggest that kisspeptin levels are not increased in all PCOS patients (Emekci Ozay et al. 2016) with menstrual irregularities, excessive hair growth and acne. The LH levels and LH/FSH ratios were significantly higher in PCOS patients compared with controls and showed positive correlation with LH (Saadia 2020; Mitrasinovic-Brulic et al. 2021; Atoum et al. 2022). In a meta-analysis by Jeon et al. (2013), the LH levels and the LH/FSH ratio were significantly higher in the PCOS group compared with controls. Women with PCOS had higher total testosterone compared to controls and kisspeptin were significantly higher in women with PCOS compared with controls. Finally, LH, LH/FSH, testosterone and kisspeptin levels were significantly higher in the PCOS group than in control group. However, the

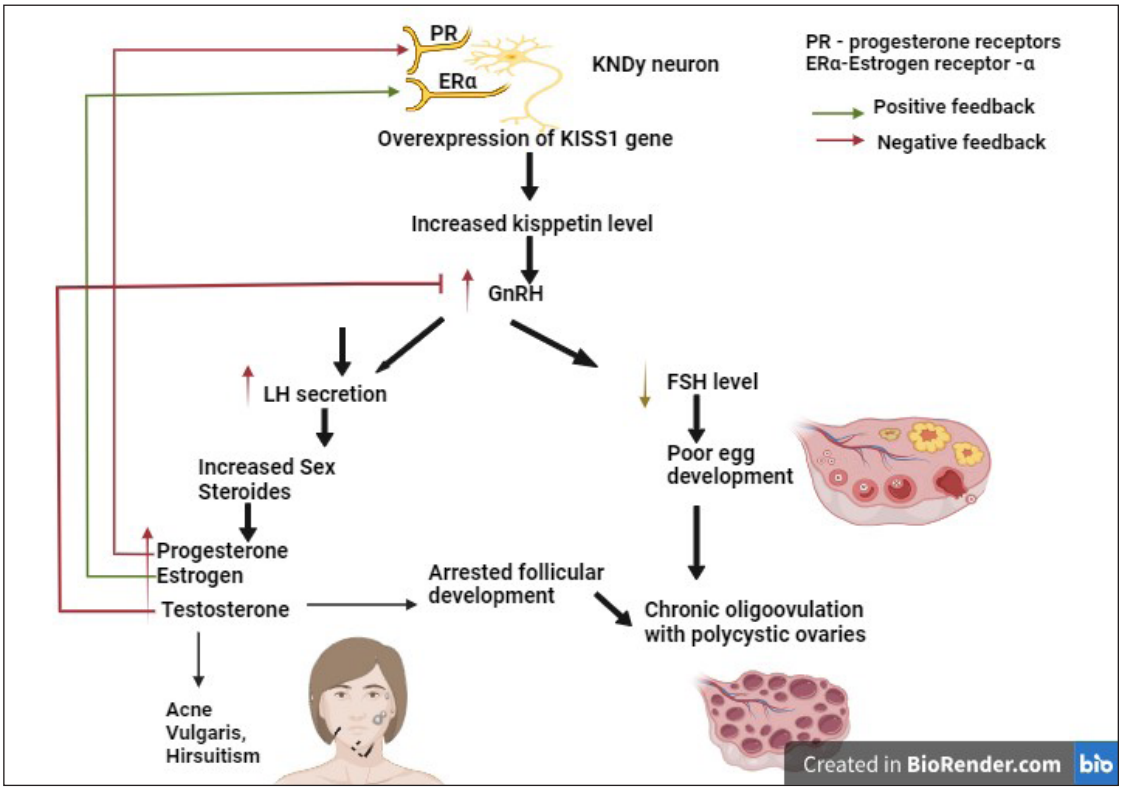

Figure 4. Kisspeptin levels in the development of the polycystic ovary syndrome (PCOS).

increased level of kisspeptin is found to be positively correlated with PCOS than in normal women, which signifies that overexpression of KISS1 system may be a cause for the development of PCOS.

Conclusions

One gene that is associated as risk factors for PCOS includes KISS1 and is considered as a candidate gene to study the pathogenesis of PCOS. Kisspeptin, a product of KISS1 gene, acts as a potent stimulator of GnRH neurons, which release GnRH required for ovulation and normal menstrual cycle. The studies reported a link of kisspeptin in the pathogenesis of PCOS. Therefore, we have presented a literature review to determine the genetic linkage of KISS1 gene in the pathogenesis of PCOS. Hence, it is hypothesized that disruption in KISS1 gene might cause disturbance in kisspeptin signaling resulting in abnormal GnRH secretion leading to PCOS. The studies show circulating that kisspeptin levels are higher in PCOS women population and as it is reported that kisspeptin exerts a direct effect upstream of GnRH neurons in terms of depolarization. These findings support the hypothesis that an overactive KISS1 system might be a cause for the onset of the syndrome, due to which it shows increased HPG-axis activity leading to irregular menstrual cycle and excessive androgen release. This review article examined the association of kisspeptin with female infertility and found that kisspeptin has a key role in the HPG axis and can be potentially used as a molecular marker in early diagnosis of reproductive disorders, including hypogonadism, infertility and PCOS.

Conflict of interest: *The authors declare that there is no conflict of interest.*

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