Serum Kisspeptin and Sex Hormones in Women with Hypoactive Sexual Desire: Pathophysiological Insights and Clinical Implications

Abdalla Hasan Kandil[1], Dalia Atef Roshdy Hemead[2], El sayed Mohammed Galal Khater[3]

(1) Professor of Dermatology, Venereology and Andrology Department, Faculty of Medicine - Zagazig University,
(2) MBBCH, Faculty of Medicine, Zagazig University,
(3) Assistant Professor of Dermatology, Venereology and Andrology Department, Faculty of Medicine - Zagazig University,

Corresponding authors: Dalia Atef Roshdy Hemead

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Abstract

Background: Hypoactive Sexual Desire Disorder (HSDD) is the most prevalent form of female sexual dysfunction, characterized by a persistent reduction or absence of sexual desire that leads to personal distress and relational difficulties. The underlying pathophysiology of HSDD is multifactorial, involving neurobiological, hormonal, and psychosocial contributors. Recent evidence highlights the role of endocrine regulators, particularly kisspeptin and sex steroid hormones, in the modulation of female sexual desire. Kisspeptin, encoded by the KISS1 gene, is a potent neuropeptide that governs the hypothalamic–pituitary–gonadal (HPG) axis by stimulating gonadotropin-releasing hormone (GnRH) secretion. Beyond its reproductive functions, kisspeptin has emerged as a key neuroendocrine modulator of limbic brain regions involved in sexual behavior and emotional bonding. Dysregulation of kisspeptin signaling may impair sexual motivation, representing a novel mechanistic pathway for HSDD. In parallel, sex steroid hormones, including estrogen, progesterone, and testosterone, play pivotal roles in female sexual function. Estrogen maintains genital blood flow and enhances sexual receptivity, while testosterone contributes to libido and central arousal mechanisms. Conversely, progesterone has complex effects, often exerting inhibitory influences on sexual desire. Abnormal serum levels of these hormones have been repeatedly observed in women with HSDD, supporting their importance as diagnostic and therapeutic targets. However, the relationship between kisspeptin and sex hormones remains poorly understood, with emerging evidence suggesting a dynamic bidirectional interaction that influences both central desire pathways and peripheral reproductive function This review synthesizes current knowledge on serum kisspeptin and female sex hormones in women with HSDD compared with sexually healthy controls. We highlight experimental, clinical, and translational studies addressing their physiological roles, pathophysiological alterations, and potential clinical applications. Furthermore, we discuss the diagnostic value of these biomarkers, limitations of current assays, and their therapeutic implications, including the potential for kisspeptin analogs or targeted hormonal interventions. By elucidating the interplay between kisspeptin and sex steroid hormones, this review aims to bridge critical knowledge gaps and provide a framework for future research into endocrine-driven mechanisms of HSDD. Ultimately, improved understanding of these biomarkers may facilitate personalized management strategies and enhance therapeutic outcomes for women affected by this distressing condition

Keywords: *Kisspeptin, Sex Hormones , Hypoactive Sexual Desire*

Introduction

Female sexual health represents an integral aspect of overall wellbeing, yet disorders of sexual desire remain poorly recognized and undertreated. Hypoactive Sexual Desire Disorder (HSDD) is the most prevalent female sexual dysfunction, affecting up to 10–15% of premenopausal women and a higher proportion of postmenopausal women worldwide [1]. The condition is defined by a persistent or recurrent lack of sexual desire, often accompanied by distress or interpersonal difficulty. Despite its high prevalence, the pathophysiology of HSDD remains incompletely understood, reflecting the interplay between psychosocial, neurobiological, and hormonal factors [2].

Recent advances in neuroendocrinology have shed light on the complex regulation of female sexual desire. Central neurotransmitters such as dopamine, oxytocin, and serotonin are intimately linked with motivational and emotional aspects of sexual behavior. Importantly, hormonal regulators — including estrogen, progesterone, testosterone, and the more recently identified kisspeptin — provide key modulatory signals that integrate central and peripheral mechanisms of sexual function [3]. Kisspeptin, encoded by the *KISS1* gene, is a potent activator of the hypothalamic–pituitary–gonadal (HPG) axis and has been implicated in both reproductive control and sexual behavior [4].

The gap in current research lies in understanding how alterations in serum kisspeptin and sex hormones contribute specifically to HSDD in women. While reduced androgen levels have long been associated with decreased libido, the role of kisspeptin as a novel biomarker and potential therapeutic target remains underexplored. This review aims to synthesize available evidence regarding the relationship between serum kisspeptin, sex hormones, and sexual desire, with emphasis on pathophysiological insights and clinical implications [5].

Section I: Physiology of Female Sexual Desire

Sexual desire in women is a multidimensional construct encompassing biological drives, emotional intimacy, and sociocultural influences. At the neurobiological level, sexual motivation is mediated by limbic brain regions, including the amygdala, hypothalamus, and prefrontal cortex. Neurotransmitters such as dopamine facilitate arousal and reward processing, whereas serotonin can exert inhibitory effects on desire. These central pathways interact closely with circulating hormones, which modulate both peripheral genital responses and central neural circuits [6].

Estrogen plays a crucial role in maintaining female sexual physiology. It promotes vaginal lubrication, enhances genital blood flow, and sensitizes neuronal pathways associated with arousal. Beyond its peripheral effects, estrogen augments dopamine activity in the mesolimbic system, thereby influencing sexual motivation. Declines in estrogen, particularly during menopause, are strongly associated with reduced libido and impaired sexual satisfaction [7].

Testosterone, though present at lower levels in women compared to men, is a critical determinant of female sexual desire. It acts centrally to stimulate sexual motivation and peripherally to enhance genital sensitivity. Studies have demonstrated that even modest reductions in circulating testosterone may result in significant decreases in libido and spontaneous sexual thoughts. Progesterone, on the other hand, appears to exert a more complex and sometimes inhibitory influence, particularly when levels are elevated during the luteal phase of the menstrual cycle [8].

Kisspeptin Physiology and Neuroendocrine Role

Kisspeptin, a neuropeptide encoded by the *KISS1* gene, was initially identified as a metastasis suppressor but later recognized as a pivotal regulator of reproductive endocrinology. It exerts its effects via the G-protein-coupled receptor GPR54 (also known as KISS1R), which is abundantly expressed in the hypothalamus. The primary action of kisspeptin is the stimulation of gonadotropin-releasing hormone (GnRH) neurons, thereby activating the hypothalamic–pituitary–gonadal (HPG) axis. This cascade promotes the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn regulate ovarian steroidogenesis. Thus, kisspeptin acts as a master regulator of puberty onset, fertility, and reproductive cyclicity [9].

Beyond its classical role in reproduction, kisspeptin is increasingly recognized as a modulator of sexual behavior and emotional processing. Experimental studies in rodents and primates have shown that kisspeptin administration stimulates sexual partner preference and mating behaviors, independent of gonadotropin release. In humans, kisspeptin infusion has been demonstrated to activate brain regions involved in sexual arousal and romantic bonding, including the amygdala and anterior cingulate cortex, suggesting a direct neuromodulatory role in sexual desire. These findings support the concept that kisspeptin bridges reproductive endocrinology with higher-order sexual and emotional processes [10].

Kisspeptin signaling is also influenced by feedback from circulating sex steroids. Estrogen upregulates kisspeptin expression in specific hypothalamic nuclei, while progesterone and testosterone exert variable modulatory effects. This bidirectional interaction suggests that kisspeptin is not only a regulator of gonadal hormones but also a mediator of their central effects on sexual motivation. Dysregulation of kisspeptin signaling, whether due to genetic, neuroendocrine, or hormonal disturbances, may therefore contribute to impaired sexual desire, offering a potential mechanistic link to conditions such as HSDD [11].

Female Sex Hormones and Sexual Function

Estrogen is a cornerstone hormone in regulating female sexual function. It enhances genital blood flow, maintains vaginal epithelium integrity, and supports lubrication, all of which facilitate comfortable and pleasurable sexual activity. On a central level, estrogen interacts with dopaminergic and oxytocinergic pathways in the brain, augmenting sexual motivation and emotional intimacy. Clinical studies consistently demonstrate that women with estrogen deficiency, particularly postmenopausal women, report higher rates of sexual dysfunction, including hypoactive desire, vaginal dryness, and dyspareunia. Hormone replacement therapy has been shown to partially restore sexual responsiveness, underscoring estrogen's dual role in peripheral and central mechanisms of sexual function [12].

Testosterone, although circulating at much lower levels in women compared with men, is equally vital in modulating female libido. It promotes sexual fantasy, spontaneous desire, and responsiveness to erotic stimuli by influencing neural reward circuits. Several interventional studies have shown that testosterone supplementation in women with HSDD improves desire, frequency of sexual activity, and satisfaction, highlighting its importance in maintaining sexual motivation. However, the therapeutic window is narrow, as supraphysiological testosterone may cause adverse effects such as hirsutism, acne, and mood changes. This delicate balance underscores the importance of testosterone as both a biomarker and a therapeutic target in female sexual dysfunction [13].

Progesterone has a more nuanced and often inhibitory role in female sexual function. Its effects appear phase-dependent within the menstrual cycle, with higher luteal-phase levels often correlating with diminished sexual desire. Experimental evidence suggests that progesterone may exert central sedative effects, counteracting the stimulatory influence of estrogen and testosterone on sexual motivation. Nonetheless, its modulatory role is complex, as progesterone also contributes to reproductive readiness and emotional bonding, which may indirectly influence sexual behavior. Elevated or imbalanced progesterone levels may therefore contribute to HSDD by tipping the neuroendocrine equilibrium toward inhibition of desire [14].

Pathophysiology of Hypoactive Sexual Desire Disorder (HSDD)

HSDD is a multifactorial condition arising from the interaction of biological, psychological, and relational factors. From a biological standpoint, disruptions in central neurotransmitter systems are pivotal. Dopamine and norepinephrine promote sexual excitation and motivation, whereas serotonin and prolactin are inhibitory. An imbalance between these excitatory and inhibitory pathways contributes to diminished desire. Neuroimaging studies in women with HSDD have demonstrated reduced activation of brain regions involved in reward and emotional processing, such as the nucleus accumbens and prefrontal cortex, supporting the concept of altered central arousal regulation [15].

Hormonal disturbances represent another critical component of HSDD pathophysiology. Deficiencies in estrogen and testosterone are frequently implicated, particularly in postmenopausal women or those undergoing oophorectomy. Estrogen deficiency impairs genital arousal mechanisms, while androgen

insufficiency diminishes spontaneous desire and sexual fantasy. Progesterone, when elevated disproportionately, may further suppress central arousal pathways. Emerging evidence also suggests that impaired kisspeptin signaling may contribute to inadequate stimulation of the hypothalamic–pituitary–gonadal (HPG) axis and reduced activation of limbic regions associated with sexual motivation [16].

In addition to neuroendocrine factors, psychosocial and relational elements significantly influence HSDD. Chronic stress, depression, and interpersonal conflict can blunt sexual desire through hypothalamic–pituitary–adrenal (HPA) axis activation and cortisol excess, which further inhibit gonadotropin release. Medications such as selective serotonin reuptake inhibitors (SSRIs) are also known to suppress libido via serotonergic dominance. Thus, HSDD represents a convergence of biological vulnerabilities and psychosocial stressors, making it both a diagnostic and therapeutic challenge. Understanding the role of kisspeptin and sex hormones within this complex network provides an opportunity to identify more precise biomarkers and potential treatment targets [17].

Kisspeptin in HSDD — Experimental and Clinical Evidence

Animal studies have provided important insights into the role of kisspeptin in sexual behavior. In rodents, central administration of kisspeptin stimulates reproductive behaviors, including lordosis and partner preference, even in the absence of gonadotropin stimulation. These findings suggest that kisspeptin can act directly on neural circuits regulating sexual motivation, independent of its effects on fertility. Moreover, kisspeptin neurons project to limbic brain regions such as the amygdala and hippocampus, which are involved in sexual arousal and emotional processing. This evidence positions kisspeptin as a crucial neuroendocrine link between reproductive physiology and sexual desire [18].

Clinical research in humans has extended these observations. Functional magnetic resonance imaging (fMRI) studies demonstrate that kisspeptin infusion enhances activity in brain regions associated with sexual and emotional processing, including the amygdala, anterior cingulate cortex, and striatum. Women receiving kisspeptin show increased responsiveness to erotic stimuli and improved mood scores, suggesting a dual role in enhancing both desire and emotional wellbeing. Importantly, these effects appear independent of acute changes in gonadotropin or sex steroid hormone levels, supporting a direct neuromodulatory role of kisspeptin in female sexual behavior [19].

Despite promising findings, data on serum kisspeptin levels in women with HSDD remain limited and somewhat inconsistent. Some studies report significantly lower circulating kisspeptin in women with reduced libido, while others fail to demonstrate clear differences compared with healthy controls. Variability in assay sensitivity, study populations, and comorbidities may partly explain these discrepancies. Nevertheless, the available evidence supports the hypothesis that impaired kisspeptin signaling — whether centrally or peripherally — may contribute to the pathophysiology of HSDD. This highlights the need for standardized measurement techniques and larger clinical studies to validate kisspeptin as a biomarker of female sexual dysfunction [20].

Sex Hormones in HSDD

Estrogen deficiency is strongly associated with diminished sexual desire in women, particularly during the menopausal transition. Reduced estrogen leads to vaginal dryness, dyspareunia, and impaired genital blood flow, which in turn reduce sexual activity and motivation. Neuroimaging studies suggest that estrogen modulates dopaminergic activity in reward-related brain regions, and its absence is linked with blunted neural responses to erotic cues. Clinical interventions with estrogen therapy have shown improvements in arousal and comfort, though restoration of sexual desire often requires additional factors such as androgen supplementation or psychological support [21].

Androgen insufficiency is increasingly recognized as a central factor in HSDD. Testosterone influences both spontaneous sexual thoughts and responsiveness to sexual stimuli through its actions on central neural pathways. Women with low circulating testosterone, whether due to natural decline with age, surgical menopause, or adrenal insufficiency, often report decreased libido and reduced frequency of sexual activity. Randomized controlled trials of testosterone supplementation in postmenopausal women with HSDD demonstrate significant improvements in sexual desire, arousal, and satisfaction, underscoring the hormone's therapeutic relevance. However, challenges remain in establishing safe

dosing regimens and long-term monitoring due to concerns over metabolic and cardiovascular side effects [22].

Progesterone's role in female sexual desire is complex and sometimes contradictory. Elevated luteal-phase progesterone is often correlated with reduced libido, suggesting an inhibitory influence on sexual motivation. Mechanistically, progesterone may exert sedative and anxiolytic effects via modulation of GABAergic signaling, which could dampen arousal pathways. However, progesterone also contributes to reproductive readiness and may support bonding behaviors, indicating context-dependent effects. In the setting of HSDD, excessive progesterone or altered progesterone-to-estrogen ratios may exacerbate sexual dysfunction, but more clinical studies are needed to clarify its exact role [23].

Interplay between Kisspeptin and Gonadal Hormones

The relationship between kisspeptin and gonadal hormones is bidirectional and tightly regulated within the hypothalamic–pituitary–gonadal (HPG) axis. Kisspeptin stimulates GnRH release, which drives the secretion of LH and FSH, ultimately promoting ovarian steroidogenesis. In turn, sex steroid hormones provide both positive and negative feedback on kisspeptin expression. Estrogen enhances kisspeptin activity in the anteroventral periventricular nucleus, facilitating ovulation, while exerting inhibitory effects in the arcuate nucleus. This dual regulation ensures cyclical hormonal fluctuations and reproductive cyclicity in women [24].

Emerging evidence suggests that the interplay between kisspeptin and sex steroids extends beyond reproduction to influence sexual motivation. Estrogen has been shown to increase kisspeptin-mediated neuronal excitability, potentially amplifying its effects on limbic brain regions associated with arousal and desire. Conversely, progesterone may dampen kisspeptin activity, consistent with its inhibitory role in sexual motivation. Testosterone, though less studied in this context, may also regulate kisspeptin pathways indirectly through aromatization to estrogen or direct modulation of kisspeptin neurons. Such interactions may explain why sexual desire varies across the menstrual cycle, with peaks during mid-cycle estrogen surges and reductions during progesterone-dominant phases [25].

Disruption of this delicate kisspeptin–sex hormone cross-talk may contribute to the pathophysiology of HSDD. In women with estrogen deficiency, reduced stimulation of kisspeptin neurons may impair both GnRH release and limbic system activation, leading to diminished sexual motivation. Similarly, inadequate androgen levels may limit kisspeptin responsiveness, further reducing desire. These findings highlight kisspeptin not only as an upstream regulator of gonadal hormones but also as a mediator of their central effects on sexual behavior. Understanding these dynamics may pave the way for novel therapeutic strategies, such as kisspeptin analogs or combined hormone–kisspeptin modulation, in the management of HSDD [26].

Clinical and Diagnostic Implications

The measurement of serum kisspeptin and sex hormones offers a potential biomarker-based approach to the assessment of HSDD, but current clinical application remains limited. Assays for kisspeptin are not yet standardized, with significant variability in sensitivity and specificity across studies. Reported serum levels in women with HSDD range widely, complicating comparisons between populations. Despite these challenges, kisspeptin measurement may provide valuable insight into the neuroendocrine status of patients, particularly when combined with sex hormone profiling. Together, these biomarkers could help distinguish hormonally driven HSDD from cases primarily rooted in psychological or relational factors [27].

Sex steroid hormone evaluation remains a cornerstone of the clinical assessment of female sexual dysfunction. Estrogen, progesterone, and testosterone levels provide essential diagnostic information, particularly in postmenopausal women or those with suspected ovarian insufficiency. Low androgen levels, in particular, are consistently associated with decreased libido, supporting their role as a diagnostic marker. However, interpreting these values can be challenging, as normal reference ranges for women are narrow and influenced by age, menstrual cycle phase, and assay methodology. Moreover, serum levels may not always reflect tissue-level hormonal action or central neuroendocrine effects, limiting their predictive value [28].

Integrating kisspeptin and hormone assessment into clinical practice may enhance diagnostic precision and allow for more personalized treatment strategies. For example, women with confirmed low androgen and reduced kisspeptin activity might benefit from combined hormonal and kisspeptin-targeted therapies. Similarly, monitoring biomarker responses could provide objective endpoints in clinical trials evaluating new interventions for HSDD. Nevertheless, before routine clinical use is feasible, larger studies are needed to validate cutoff values, establish standardized testing protocols, and clarify the relationships between circulating biomarker levels and sexual desire outcomes [29].

Therapeutic Insights and Future Perspectives

Hormone-based therapies have long been explored in the management of HSDD, with estrogen and testosterone supplementation forming the backbone of treatment strategies. Estrogen therapy improves vaginal atrophy, enhances genital blood flow, and may indirectly improve sexual desire by reducing discomfort during intercourse. Testosterone supplementation has shown stronger effects on restoring libido, particularly in postmenopausal women with low androgen levels. However, the long-term safety of exogenous testosterone remains under investigation, as concerns persist regarding cardiovascular risk, lipid metabolism, and breast health. These limitations highlight the need for adjunctive or alternative therapeutic approaches beyond traditional hormone replacement [30].

Kisspeptin has emerged as a promising therapeutic target due to its dual action on reproductive endocrinology and sexual behavior. Experimental studies in humans demonstrate that kisspeptin administration enhances sexual brain processing and mood, suggesting a potential role as a novel therapeutic agent for HSDD. Unlike conventional hormones, kisspeptin may directly modulate limbic brain networks implicated in desire while simultaneously restoring HPG axis function. Kisspeptin agonists and analogs are under preclinical development, but clinical trials are still limited. If proven effective and safe, kisspeptin-based therapies could provide a more targeted option for women with hormonally mediated HSDD [31].

Future therapeutic strategies may involve personalized medicine approaches that integrate hormonal profiling with neuroendocrine biomarkers. By identifying women with specific deficiencies in kisspeptin or sex steroids, clinicians could tailor interventions to restore both central and peripheral mechanisms of desire. Combination therapies — such as low-dose testosterone with kisspeptin agonists — may offer synergistic benefits. Additionally, neuroimaging biomarkers may complement serum assays in monitoring treatment response. Future research should also explore the role of lifestyle, stress modulation, and psychosexual interventions alongside endocrine therapies, as multimodal approaches are likely to yield the greatest clinical benefit for women with HSDD [32].

Conclusion

Hypoactive Sexual Desire Disorder remains a complex condition with multifactorial origins, where biological, psychological, and relational contributors intersect. Growing evidence underscores the importance of endocrine biomarkers, particularly kisspeptin and sex steroid hormones, in the regulation of female sexual desire. Estrogen and testosterone deficiencies have long been associated with reduced libido, while progesterone exerts context-dependent modulatory effects. Kisspeptin has recently emerged as a critical neuroendocrine regulator, linking the hypothalamic–pituitary–gonadal axis with limbic brain regions that govern sexual motivation. Dysregulation of kisspeptin and its interaction with gonadal hormones may therefore represent a key pathophysiological mechanism underlying HSDD [33].

Clinically, the integration of kisspeptin and hormone measurement offers new opportunities for diagnosis and personalized treatment. Although current evidence is limited by small sample sizes and assay variability, kisspeptin shows promise as both a biomarker and a therapeutic target. Future research should focus on validating standardized serum assays, elucidating mechanistic pathways, and testing kisspeptin analogs or combined hormone–kisspeptin therapies in larger clinical trials. A multidisciplinary approach that integrates neuroendocrinology, psychosexual therapy, and personalized medicine is essential to improve outcomes for women suffering from HSDD. By advancing our understanding of kisspeptin and sex hormone interplay, clinicians may ultimately develop more precise, effective, and patient-centered strategies to restore sexual health and quality of life [34].

References

1. Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: prevalence and correlates. *Obstet Gynecol*. 2008;112(5):970-978.
2. Basson R. Women's sexual dysfunction: revised and expanded definitions. *CMAJ*. 2005;172(10):1327-1333.
3. Clayton AH, Goldfischer ER, Goldstein I, DeRogatis LR, Lewis-D'Agostino DJ, Pyke R. Validation of the Decreased Sexual Desire Screener (DSDS): a brief diagnostic instrument for generalized acquired female hypoactive sexual desire disorder (HSDD). *J Sex Med*. 2009;6(3):730-738.
4. Pinilla L, Aguilar E, Dieguez C, Millar RP, Tena-Sempere M. Kisspeptins and reproduction: physiological roles and regulatory mechanisms. *Physiol Rev*. 2012;92(3):1235-1316.
5. Khosla S, Dean CB, Tenenbaum A. Sexual desire disorders in women: a clinical overview. *Int J Gynaecol Obstet*. 2019;147(2):144-150.
6. Pfaus JG. Pathways of sexual desire. *J Sex Med*. 2009;6(6):1506-1533.
7. Kingsberg SA, Althof S. Evaluation and treatment of female sexual disorders. *Int Urogynecol J*. 2009;20(1):33-43.
8. Davis SR, Tran J. Testosterone influences libido and well being in women. *Trends Endocrinol Metab*. 2001;12(1):33-37.
9. d'Anglemont de Tassigny X, Colledge WH. The role of kisspeptin signaling in reproduction. *Physiology (Bethesda)*. 2010;25(4):207-217.
10. Comninos AN, Demetriou L, Wall MB, et al. Kisspeptin modulates sexual and emotional brain processing in humans. *J Clin Invest*. 2017;127(2):709-719.
11. Clarkson J, Herbison AE. Hypothalamic control of the male neonatal testosterone surge. *Philos Trans R Soc Lond B Biol Sci*. 2016;371(1688):20150115.
12. Nappi RE, Lachowsky M. Menopause and sexuality: prevalence of symptoms and impact on quality of life. *Maturitas*. 2009;63(2):138-141.
13. Kingsberg SA, Clayton AH, Pfaus JG. The female sexual response: current models, neurobiological underpinnings, and clinical management of desire and arousal disorders. *Fertil Steril*. 2015;104(4):934-941.
14. Graham CA. The role of progesterone in female sexual desire and behavior. *Horm Behav*. 2010;58(1):145-153.
15. Arnow BA, Millheiser L, Garrett A, et al. Women with hypoactive sexual desire disorder compared to normal females: a functional magnetic resonance imaging study. *Neuroscience*. 2009;158(2):484-502.
16. Goldstein I, Kim NN, Clayton AH, DeRogatis LR, Parish SJ, Simon JA. Hypoactive sexual desire disorder: International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. *Mayo Clin Proc*. 2017;92(1):114-128.
17. Brotto LA, Atallah S, Johnson-Agbakwu C, et al. Psychological and interpersonal dimensions of sexual function and dysfunction. *J Sex Med*. 2016;13(4):538-571.
18. Pineda R, Aguilar E, Pinilla L, Tena-Sempere M. Physiological roles of the kisspeptin/GPR54 system in the neuroendocrine control of reproduction. *Prog Brain Res*. 2010;181:55-77.
19. Comninos AN, Wall MB, Demetriou L, et al. The effect of kisspeptin on brain response to sexual and bonding stimuli in men. *J Clin Invest*. 2018;128(2):664-676.
20. Jayasena CN, Abbara A, Comninos AN, et al. Kisspeptin and reproduction: physiological roles and therapeutic potential. *Endocr Rev*. 2014;35(6):747-779.
21. Dennerstein L, Alexander JL, Kotz K. The menopause and sexual functioning: a review of the population-based studies. *Annu Rev Sex Res*. 2003;14:64-82.
22. Davis SR, Davison SL, Donath S, Bell RJ. Circulating androgen levels and self-reported sexual function in women. *JAMA*. 2005;294(1):91-96.
23. Roney JR, Simmons ZL. Hormonal predictors of sexual motivation in natural menstrual cycles. *Horm Behav*. 2013;63(4):636-645.
24. Oakley AE, Clifton DK, Steiner RA. Kisspeptin signaling in the brain. *Endocr Rev*. 2009;30(6):713-743.
25. Mittelman-Smith MA, Williams H, Krajewski-Hall SJ, McMullen NT, Rance NE. Role for kisspeptin/neurokinin B/dynorphin (KNDy) neurons in controlling gonadotropin-releasing hormone pulse generator. *Endocrinology*. 2012;153(10):5054-5065.
26. Tena-Sempere M. Keeping puberty on time: novel signals and mechanisms involved. *Curr Top Dev Biol*. 2013;105:299-329.
27. Millar RP, Babwah AV. Kisspeptin and the regulation of reproduction: an update. *Reproduction*. 2015;150(5):R53-R68.
28. Davis SR, Baber R. Testosterone therapy in women: a review of efficacy and safety. *J Steroid Biochem Mol Biol*. 2019;191:105377.
29. Jayasena CN, Comninos AN, Dhillo WS. Kisspeptin: neuroendocrine regulators of reproduction. *Nat Rev Endocrinol*. 2016;12(11):673-682.
30. Simon JA, Braunstein GD, Nachtigall LE, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab*. 2005;90(9):5226-5233.
31. Abbara A, Clarke SA, Dhillo WS. Novel concepts for inducing ovulation with kisspeptin. *Reproduction*. 2018;156(1):R1-R10.

32. Clayton AH, Kingsberg SA, Goldstein I. Evaluation and management of hypoactive sexual desire disorder. *Sex Med*. 2018;6(2):59-74.

33. Pfaus JG, Everaerd W, Jones SL, Kippin TE, Flanagan-Cato LM. Theoretical integration of the mechanisms of sexual desire. *Horm Behav*. 2016;80:97-110.

34. Parish SJ, Hahn SR, Goldstein SW, Giraldi A, Kingsberg SA, Larkin LC. The International Society for the Study of Women's Sexual Health process of care for the management of hypoactive sexual desire disorder in women. *Mayo Clin Proc*. 2019;94(5):834-851.