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Letter to the Editor

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# What do we know about kisspeptin?

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**Dear Editor,**

Kisspeptins are a group of peptide fragments that are expressed by the neurons of the hypothalamus mainly in the arcuate, dorsal-medial and antero ventricular, periventricular nuclei of the hypothalamus besides the amygdala.[1] Initially, Kisspeptin via its G protein-coupled receptor 54 (GPR54) was introduced to have an important role in cancer biology with its metastasis suppression effect. In light of recent research, Kisspeptin is found to have a major role in the neuroendocrine reproductive axis through the Kisspeptin 1 (KISS1) gene. The KISS1 gene that encodes Kisspeptin was first discovered in 1996 by researchers from the United States of America. Kisspeptinreceptors are also expressed by the same neurons. Kisspeptin has a pivotal role in reproduction through the hypothalamic-hypophysial axis while exerting an extra hypothalamic function on sexual and emotional behavior.

The peptide Kisspeptin is encoded by the KISS1 gene located on the long (q) arm of chromosome 1 at q32.[2] Kisspeptin and its GPR54 receptors (KISS 1R) in the hypothalamus, act as an important modulator of the pubertal and adult reproductive functions[3] mainly the central control of Gonadotrophin releasing hormone (GnRH) secretion, pubertal onset, sex differentiation in the brain, ovulation, implantation, placentation, and food consumption.[4]

The Kisspeptin precursor (pre-pro Kisspeptin), a protein of 145 amino acids, is converted into a protein of 54 amino acids (with a half-life of 28 minutes) and small peptide fragments of 14, 13, and 10 amino acids (isoforms). Two of these isoforms, Kisspeptin-10 and Kisspeptin-54, were administered peripherally exogenously to investigate clinical applications and were found to play a role in ovulation through GnRH secretion.[5] The KISS1 gene and its receptor (KISS1R) are also found in the placenta, Graff follicles, theca cells, and ovarian epithelium besides the hypothalamus. Moreover, their expression on luminal and glandular epithelial cells of the endometrium was shown.[6]

In an animal study, intracerebroventricular and peripheral administration active isoform of Kisspeptin; Kisspeptin-10 activated the hypothalamic-pituitary-gonadal axis potently most probably through the hypothalamic Luteinizing hormone-releasing hormone (LHRH) system and its effect was dose-dependent.[7] KiSS-1 and GPR54 are also present in human and marmoset ovaries and granulosa-lutein cells and also have a local role in the ovulation mechanism that is regulated by gonadotropins and COX-2: The addition of a Kisspeptin antagonist also inhibits oocyte maturation in porcine cumulus-oocyte complexes (COCs).[8,9] In particular, a significant association between low levels of Kisspeptin in serum and follicular fluid is related to unexplained infertility.[10,11] In a recent study serum Kisspeptin levels were reported to increase during ovarian hyperstimulation in in vitro fertilization (IVF) cycles however serum and follicular fluid Kisspeptin levels in pregnant and non-pregnant patients showed no significance.[12]

Kisspeptin came into the light to be used for oocyte maturation in IVF. Subcutaneous Kisspeptin-54 is proposed to be an alternative to HCG for oocyte triggering in GnRH antagonist cycles.[13] In addition, an improvement in oocyte maturation was noted after the administration of synthetic Kisspeptin due to the controlled increase in Luteinizing Hormone (LH) levels, especially in ovarian hyperstimulation syndrome (OHSS) patients.[14,15] In an animal study ovulation and fertilization were achieved in Kiss1-null mice after administration of gonadotropins that are known to have hypogonadotropic hypogonadism, however, the embryos failed to implant in the absence of Kisspeptin.[16] Jamil et al.[17] proposed to use Kisspeptinlevel on human chorionic gonadotropin (hCG) administration day as a predictor of intracytoplasmic sperm injection success.

Kisspeptin plasma levels increase 900-fold in the first trimester and 7,000-fold in the third trimester compared to non-pregnant women.[18] When Kisspeptin is measured after the 6th week of pregnancy, it has good diagnostic value with an AUC of 0.902 (0.866, 0.937) and even has a higher accuracy potential than hCG in distinguishing between abortion and viable intrauterine pregnancy.[18] However, it should be noted that the ideal measurement time for Kisspeptin released from the placenta is between 6 to 14 weeks.[19]

Mutation of the Kisspeptin receptors in the hypothalamus leads to the absence of pubertal development.[20] The most known cause of delayed puberty is structural delay and idiopathic hypogonadotropic hypogonadism. Measurement of serum gonadotropins (LH and follicle-stimulating hormone (FSH)), poststimulation gonadotropins, and inhibin B with GnRH or GnRH analogs can be used to predict the onset of puberty with a low sensitivity, specificity, or both.[21] GnRH responses to stimulation with Kisspeptin may be utilized as a promising test for predicting pubertal progression in children with pubertal tarda.[22]

The relationship between Kisspeptin signaling and food intake is remarkable.[23] The effect of Kisspeptin proopiomelanocort in neurons has been shown to regulate food intake by exerting an anorexigenic function through inhibition of orexigenic neuropeptide Y neurons.[24] In animal studies, all Kiss1 knockout mice exerted lower apatite than other mice, and gonadal estrogen levels were also reduced.[25] KISS1Rs, which regulate sexual and emotional behaviors and facilitate their interaction with the neuroendocrine reproductive axis, were also found to be involved in the regulation of appetite and food reward in the limbic brain system.[26] The effect of Kisspeptin on food-related olfactory processes has been reported.[27] Increased leptin levels in adipose tissue due to obesity impair Kisspeptin secretion and result in decreased GnRH pulsation and LH secretion.[28]

In summary, Kisspeptin can be used clinically either as a marker or as a pharmacological agent in treatment. Serum or plasma Kisspeptin level measurement needs accuracy with the use of the correct type of collection tubes, and time of collection, storage conditions, and processing times of samples as these factors may alter the results of Kisspeptin measurements. It can be used as a novel and promising method to induce oocyte maturation and increase pregnancy rates in IVF especially in patients at high risk of OHSS. In the future, it may be used as a therapeutic agent in the treatment of recurrent miscarriage and obesity. Kisspeptin has a promising future to be used as a biochemical marker for the diagnosis of puberty tarda and healthy pregnancy.

## ETHICAL DECLARATIONS

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