Journal of Scientific Research
Banaras Hindu University, Varanasi

Vol. 62, 2018 : 65-72
ISSN : 0447-9483

# An Overview on Kisspeptin: Its Association with Female Reproductive Disorders

**Anusha Singh**
Department of Zoology, Institute of Science, Banaras Hindu University, Varanasi-221005
Email: anushasinghbhu@gmail.com

## Abstract

Kisspeptin belongs to a family of neuropeptides that has emerged as a key regulator of reproductive activities mediated through regulation of hypothalamic-pituitary-gonadal axis. This neuropeptide has now been scrutinized for its indispensible role in reproductive activities such as onset of puberty, ovulation induction, maintenance of pregnancy and implantation. Various female reproductive disorders such as placental dysfunction, infertility, hyperprolactinaemia and pulmonary embolism have been associated with the altered level of kisspeptin in the circulation. Kisspeptin may also represent a novel potential therapeutic target in the treatment of these disorders. This review aims to concisely describe the known association of kisspeptin with various female reproductive disorders and updates on the current advances pertaining to its role in female reproduction.

Keywords: Kisspeptin; reproductive disorders; infertility

## Introduction

The dynamic control of reproduction involves the neuroendocrine regulation through the involvement of hypothalamic-pituitary-gonadal (HPG) axis. Neuronal control of fertility is assisted and regulated by kisspeptin and its receptors G-protein-coupled receptors 54 (GPR54). The signaling of kisspeptin-GPR54 is fundamental for preovulatory gonadotropin releasing hormone neuron activation and luteinizing hormone surge (Clarkson et al., 2008). Kisspeptin is involved in the direct regulation of gonadotropin releasing hormone (GnRH) secretion which is vital for gonadal maturation (Messager et al., 2005). The physiological role of kisspeptin is diverse and includes its importance for the onset of puberty, stimulation of ovulation, marked upregulation of steroidogenesis, regulation of seasonal reproduction, maintenance of pregnancy and implantation (Pinilla et al., 2012; Clarke et al., 2015). Previous literature suggests that kisspeptin is able to restore the delay in vaginal opening and subsequently is involved in increasing low gonadotrophin and estrogen levels linked with chronic undernutrition in pre-pubertal rats (Castellano et al., 2005).

Pubertal development is closely associated with kisspeptin-GPR54 system. Mutation in kisspeptin receptor gene is known to cause gonadal health problems. Further it was explored that families who suffer from problems like idiopathic hypogonadotropic hypogonadism (IHH) are an outcome of loss of function mutations in the GPR54 gene (de Roux et al., 2003; Seminara et al., 2003). GnRH deficiencies

have been also linked with IHH in many families (Nimri et al., 2011). In addition to this, a developmental reproductive disorder is referred as Idiopathic central precocious puberty that has been linked to GPR54 mutations and Kiss 1 mutations (Teles et al., 2008; Silveira et al., 2010). Other than these reproductive issues there are many female reproductive disorders which have been linked to the disturbed level of kisspeptin. The present review article is an overview on kisspeptin, dealing with its structure, role and its association with female reproductive disorders.

**Structure of kisspeptin and its receptor**

The discovery of kisspeptin was done in 1996 as a metastasis inhibitor in melanoma cell lines (Lee et al., 1996). Kisspeptin is a family of peptides derived from the KISS1 gene with structural similarity. The different forms of kisspeptin are derived from the differential proteolysis of a common precursor. These peptides are classified as an RF amide peptide family which is neuroactive peptides with a common Arg-Phe-NH2 motif (Clements et al., 2001). Among the different forms of kisspeptin, the most abundant one in the human circulation is kisspeptin-54, which can be further cleaved to 14, 13, and 10 amino acid peptides (Kotani et al., 2001).

After the discovery of kisspeptin, its receptor GPR54 was discovered (Gottsch et al., 2009). This belongs to a member of rhodopsin family of G-protein-coupled receptors and showed structural similarity to the galanin receptor (Clements et al., 2001; Kotani et al., 2001). Receptor of kisspeptin is known to be localized in the human placenta and brain (Ohtaki et al. 2001). In brain, it was abundantly found in the cerebellum, cerebral cortex and brain stem (Muir et al. 2001). Expression of Kisspeptin and its receptor have been broadly studied in various tissues such as brain, pituitary gland, placenta, gonads, gastrointestinal tract, liver, and vascular system (Ohtaki et al. 2001; Mead et al. 2007).

**Relationship of kisspeptin with female reproductive disorders**

Altered level of kisspeptin is associated with the onset of various reproductive and metabolic disorders in females. Previous studies mentioned the low levels of plasma kisspeptin in women suffering from diabetes mellitus type 1, gestational diabetes, hypertension, pulmonary embolism, and placental dysfunction compared with healthy pregnant controls (Cetkovic et al., 2012). Hypothalamic amenorrhoea was extensively studied in relation to the low kisspeptin level. This disorder is characterized by low GnRH pulsatile secretion, resulting in a decreased LH compared with FSH secretion along with low ovarian follicular activity. Further an approach was made to administer kisspeptin and examine its impact on this disorder. This was the first disease model which was considered to investigate the therapeutic potential of kisspeptin-54. This administration resulted in achievement of normal level of gonadotrophins (Jayasena et al., 2009). Beside this, increase in gonadotrophins was unable to cause a significant elevation in E2 secretion, signifying that folliculogenesis was not restored (Jayasena et al., 2009).

Pregnancy and implantation gets affected by the disturbed level of kisspeptin. Kisspeptin receptor expression is upregulated in the placental tissue in gestational trophoblastic disease compared to normal placental tissue (Janneau et al., 2002). Probable link between kisspeptin levels and placental dysfunction such as pre-eclampsia and intrauterine growth restriction are explored in order to have their better understanding (Logie et al., 2012; Smets et al., 2008). Issues of miscarriage have also been linked with kisspeptin (Park et al., 2012). The finding of Park et al., (2012) have demonstrated the low level of placental kisspeptin expression in women reporting recurrent miscarriage compared with placental tissues in electively terminated pregnancy (Park et al., 2012). In rats, at the end of gestation the kisspeptin- immunoreactivity was found to be low (Desroziers et al., 2012). Declined level of kisspeptin along with low circulating levels of gonadotropins was monitored in cord blood between the 30$^{th}$ week of prenatal life and birth (Guimiot et al., 2012). Thus kisspeptin, in near future may appear to be an potential novel marker for screening asymptomatic pregnant women which are at increased risk of miscarriage (Clarke et al., 2015). Recently, Anuradha and Krishna, (2017) reported the role of kisspeptin in delayed implantation in bat.

Kisspeptin is known to be linked with abortus imminens as evident by the low maternal plasma kisspeptin-10 levels in individuals with early pregnancy bleeding (Kavvasoglu et al., 2012). Earlier studies have suggested the significant low level of kisspeptin during the first trimester of pregnancy in those women who went through issues like miscarriage compared to normal pregnant individuals (Jayasena et al., 2014). Thus these facts suggest that kisspeptin can be scrutinized as a potential novel marker for carrying out extended study in respect to explore risk of miscarriage in pregnant women.

Infertility disorder such as Polycystic Ovary Syndrome (PCOS) has also been linked with the altered level of kisspeptin. Few studies have mentioned the involvement of kisspeptin in PCOS condition suggesting that circulating kisspeptin level has negative correlation with free androgen levels (Panidis et al., 2006). Thus the most common feature of PCOS such as increased circulating androgen level and insulin resistance is deeply correlated with the low circulating level of kisspeptin. In contrast to this an opposite report suggests positive correlation between kisspeptin level and increased testosterone and LH levels during PCOS (Yilmaz et al., 2014; Jeon et al., 2013). Our recent study in normal and PCOS human subjects have also revealed the varied expression of kisspeptin in the ovary (Singh et al., 2017).

Kisspeptin contributes to events beyond the reproductive age of females. Postmenopausal women which are characterized by low-circulating sex steroids and initially high gonadotrophins due to reduced negative feedback are known to have changed expression of the KISS1 gene and its receptor (Rometo et al., 2007). Studies revealed marked hypertrophy of neurons in the infundibular nucleus of postmenopausal women (Rometo et al., 2007). Further, in ovarectomised monkeys, this study was replicated and an increase in KISS1 neurons was noted and evidence of kisspeptin

neuron hypertrophy was seen in the infundibular nucleus. Subsequently, other studies showed similar confirmation that during menopause, the deletion of sex steroids affects the KISS1 gene expression (Rometo et al., 2007; Oakley et al., 2009).

Other than the above mentioned issues, kisspeptin has association with hyperprolactinaemia which is characterized with low pulsatile LH secretion and decreased GnRH release (Grattan et al., 2007; Sonigo et al., 2012), leading to infertility and amenorrhoea. Hyperprolactinaemia have been linked with reduced KISS1 expression (Sonigo et al., 2012, Araujo-Lopes et al., 2014). Recent research suggests that altered level of this neuropeptide may be an essential contributor behind hyperprolactinaemia-associated hypogonadism (Araujo-Lopes et al., 2014). Thus an effort was made to use kisspeptin for the treatment of hyperprolactinaemia. Kisspeptin-10 was injected intra peritonealy daily, to induce normal estrous cycles in mice with hyperprolactinaemic and acyclicity (Sonigo et al., 2012). This approach appeared to be effective as this resulted in restoration of ovulation as well as the disturbed biochemical effects of prolactin on gonadotrophins were also reversed. Thus this suggested the involvement of kisspeptin neurons in hyperprolactinaemic anovulation and that its administration in such disorders may have therapeutic approach. Still, these trials and findings remain to be experimentally replicated in human studies in order to establish it as a novel drug in treatment of hyperprolactinemia.

## Conclusion

Interplay between the circuits of neuroendocrine regulation of reproduction and upcoming modulators of reproductive activity need great attention, as they can be new targets for developing potential therapeutic drugs in treating various disorders. The fundamental role of kisspeptin/GPR54 in the regulation of HPG axis thus is essential to explore the intricate signaling and crosstalk of factors involved in eliciting various reproductive issues. Existing relationship of reproductive disorders in female with kisspeptin level suggest that a thorough and detailed understanding of this neuropeptide can be extremely essential in targeted approach in management of such disorders. Kisspeptin are to be explored still more as beyond the therapeutic action these peptides have the potential to contribute to reproductive health far more than expected in near future.

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