Chapter

The Role of Kisspeptin in the Ovarian Cycle, Pregnancy, and Fertility

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Abstract

Kisspeptins are a group of neuropeptides with regulatory functions related to puberty, fertility, and reproduction. They are primarily produced by hypothalamic nuclei and are thought to regulate the activity of neurons that produce gonadotropin-releasing hormone. They are also expressed by placental syncytiotrophoblasts in developing pregnancies and are likely involved in the processes of trophoblast invasion and placentation. Similarly to beta-hCG, kisspeptins are found in maternal plasma during the first trimester of pregnancy and increase proportionately with gestational age. Because of their role in implantation, there is currently interest in the use of kisspeptins as minimally invasive biomarkers. It is suspected that maternal kisspeptin levels have diagnostic potential in identifying viable early pregnancies.

Keywords: kisspeptin, reproduction, fertility, placentation, biomarker

1. Introduction

Kisspeptins are a family of neuropeptides with diverse functions in humans. They are cleaved from a precursor peptide encoded by the *KISS-1* gene, which was originally identified in melanoma cells as a metastasis suppressor gene [1]. Expression of KISS-1 has subsequently been identified in many other cell lines, including those of the placenta, ovaries, and testes [2]. It is now known that kisspeptin plays a critical role in reproduction and fertility [3]. Kisspeptin is believed to regulate the secretion of gonadotropin-releasing hormone (GnRH) by integrating central and peripheral signals [4]. During the menstrual cycle, gonadal sex steroid concentrations impact the secretion of GnRH from neurons located in the hypothalamus. It is hypothesized that kisspeptin mediates this hypothalamic feedback because 1) GnRH neurons lack gonadal sex steroid receptors but some express kisspeptin receptors [5–7] and 2) kisspeptin neurons express sex steroid receptors [8, 9]. This review will focus on the role of kisspeptins throughout the menstrual cycle and their potential use as a biomarker of viable pregnancy.

2. Kisspeptin in the follicular phase and periovulation

Kisspeptin neurons are primarily located in the preoptic area and hypothalamic arcuate nucleus and function as upstream regulators of GnRH neurons [10]. In

both of these anatomic locations, serum estrogen and progesterone concentrations have been shown to regulate kisspeptin-mediated GnRH secretion [11]. During the early follicular phase of the menstrual cycle, estrogen exerts negative feedback on GnRH stimulation of luteinizing hormone (LH) secretion. As the follicular phase progresses, rising estrogen levels result in pulsatile secretion of GnRH, which then stimulates the pulsatile release of follicle-stimulating hormone (FSH) and LH [10]. This pulsatile secretion pattern is likely mediated by kisspeptin through regulation of GnRH neurons. Involvement of kisspeptin in this regulatory pathway is suspected because GnRH neurons lack estrogen and progesterone receptors, and thus cannot directly respond to serum sex steroid concentrations [12, 13]. The absence of a direct biochemical connection between the gonads and hypothalamus suggests the presence of an intermediary signal. This "missing link" is thought to be kisspeptin neurons, which express estrogen receptors and secrete a ligand that can bind to GnRH [12].

During the early follicular phase when follicles are underdeveloped, kisspeptin levels are low [4, 14]. A study by Zhai et al. showed that kisspeptin levels sharply increase when the dominant follicle reaches 1.2 cm in diameter [14]. Kisspeptin levels during the periovulatory period are then high [4, 14, 15], and may have potential in predicting development of the dominant ovarian follicle [14]. A study by Dhillo et al. demonstrated that administration of exogenous kisspeptin to healthy women results in increased gonadotropin secretion; this response is most potent during the preovulatory phase [16].

A study by Meczekalski et al. demonstrated that kisspeptin and LH are co-secreted (i.e. each kisspeptin pulse is accompanied by a pituitary LH pulse in response to a hypothalamic GnRH pulse) [11]. Another study demonstrated that blockade of the kisspeptin receptor (GPR54) resulted in blockade of pulsatile LH secretion [17]. There is also topographical evidence of the connection between GnRH and kisspeptin neurons – in several species, it has been shown that GnRH neuronal axons extend from the arcuate nucleus, where kisspeptin neurons are located, to the median eminence, where GnRH is secreted [12]. Human studies have not reproducibly demonstrated this neuroanatomy for all GnRH neurons, which may suggest that kisspeptin neuronal connections in humans are more complex [11, 18].

3. Kisspeptin in ovulation

At mid-cycle, estrogen secreted by the preovulatory follicle eventually triggers GnRH neurons to transition from pulsatile GnRH secretion to sustained secretion. The mechanism by which estrogen transforms from a negative to positive feedback signal on the hypothalamus still remains unclear. Estrogen binds to the ERα receptor on kisspeptin neurons in the arcuate nucleus, inhibiting kisspeptin secretion and subsequent GnRH secretion [15]. In the anteroventral periventricular nucleus, estrogen binds kisspeptin ERα receptors and exerts positive feedback, which ultimately initiates the LH surge associated with ovulation.

The sustained secretion of high concentrations of GnRH (GnRH surge) occurs for over 24 hours and triggers the pituitary gland to secrete high levels of LH (LH surge) [19]. The LH surge is what ultimately triggers ovulation [7]. The LH surge is also the target of at-home ovulation predictor kits [14]. This cascade of hormone surges is thought to be primarily regulated by kisspeptin; in fact, kisspeptin is the most potent activator of GnRH neurons discovered to date [5]. It is suspected that rising estrogen levels during the follicular phase stimulate kisspeptin neurons, which then activate GnRH neurons to initiate the GnRH surge [7]. In contrast,

administration of a monoclonal antibody that blocks kisspeptin has been shown to prevent ovulation in rat models [20].

It is postulated that kisspeptin could be useful as a biomarker of the periovulatory/ovulatory phase [14]. This would be clinically useful because kisspeptin surges prior to LH and therefore could predict the time of ovulation before it happens (rather than as it happens). The target of most ovulation prediction kits is LH, which surges at the time of ovulation. According to Zhai et al., the probability of ovulation is increased when kisspeptin surges on the 11th day and LH surges on the 14th day [14]. In comparison, a study by Goto et al. showed that administration of a kisspeptin antagonist resulted in shrinkage of ovarian follicles and delayed ovulation [21].

4. Kisspeptin in the luteal phase and implantation

Kisspeptin is not only expressed in the central nervous system – it also performs peripheral functions. Expression of kisspeptin and its receptor KISS-1 has been demonstrated in the human ovary, fallopian tube, uterus, and placenta [22]. It is thought that kisspeptin primarily functions in the hypothalamus, but also interacts between the signaling pathways of the central and peripheral reproductive systems [23]. In fact, several studies have supported the idea that kisspeptin exerts direct effects on ovarian tissue via ovarian kisspeptin receptors [24–26].

A number of studies have demonstrated that kisspeptin is expressed at the maternal-fetal interface of many species, including humans [27]. In the human uterus, kisspeptin is expressed in the endometrial epithelial and stromal cells, but not in the myometrium [28]. In the early placenta, kisspeptin is initially produced by villous cytotrophoblast cells, then villous syncytiotrophoblast cells and the placental bed [29, 30]. As pregnancy progresses, placental production of kisspeptin declines [31, 32].

Kisspeptin expression in the endometrium is absent during the proliferative and early secretory phases but becomes abundant during the late secretory phase [27, 33]. This indicates a potential role of kisspeptin in the preparation of endometrial tissue for implantation. Kisspeptin knockout mice exhibit thin, weak uteri with almost no endometrial glands, suggesting kisspeptin is an important regulator of normal endometrial development [34]. Kisspeptin may also act as a mediator that facilitates implantation of the growing embryo to the uterine wall. It has been shown that exogenous kisspeptin administration strengthens adhesion of kisspeptin-expressing trophoblast cells to collagen present in uterine tissue [34]. Immediately after implantation, kisspeptin levels are known to rise; this suggests involvement of kisspeptin during the decidualization process [35]. A study by Wu et al. demonstrated a dose-dependent relationship between kisspeptin expression and inhibition of cell invasion/migration in human decidualized endometrial cells [29]. In contrast, a kisspeptin antagonist called kisspeptin 234 stimulates the process of decidual invasion and migration [29]. Similarly, when small interfering RNAs that antagonize kisspeptin are introduced, stromal decidualization is impaired [35]. In a study by Calder et al., ablation of the KISS-1 gene and subsequent absence of kisspeptin expression resulted in infertile mice [36]. Even in mice that received rescue gonadotropins and estradiol, which restored ovulation, the mice embryos could not implant in the mice that lacked KISS-1. These embryos were, however, able to implant in wildtype mice [36].

Kisspeptin was originally identified as a suppressor of cancer metastasis; its function in the regulation of cellular proliferation and growth is also integral to the

process of placentation. The early placenta expresses high levels of kisspeptin, perhaps to tame the invasive and migratory capability of trophoblasts [32]. Kisspeptin decreases the activity of collagenases, matrix metalloproteinases, and vascular endothelial growth factor, which are all signaling proteins involved in trophoblast proliferation [31, 37]. Kisspeptin also supports the adhesion of extravillous trophoblasts to the endometrium, which inhibits migration [38]. This careful balance between invasion and the prevention of invasion is essential to the placentation process as well as the appropriate remodeling of the maternal uterine wall [34]. As the placenta develops throughout pregnancy, it exhibits a pattern of kisspeptin expression that follows a circadian rhythm [39]. The term placenta demonstrates kisspeptin surges at 0400 and 1200 daily. This rhythm correlates with circadian expression of other proteins involved in placental physiology, including TNFα, melatonin, and oxytocin [39].

5. Kisspeptin in pregnancy

Maternal kisspeptin levels rise dramatically during pregnancy, then return to normal within 15 days of delivery [28]. Unlike β-hCG, kisspeptin levels rise steadily and do not plateau [40]. It is thought that the primary source of maternal kisspeptin is placental tissue [27], and that maternal kisspeptin levels reflect the volume of viable placental tissue [41]. Kisspeptin may be useful as a biomarker of pregnancy due to its association with placental invasion and apoptosis [42]. It also has potential utility as a biomarker of miscarriage.

Spontaneous abortion (SAB) is a common experience, seen in 10–20% of clinically recognized pregnancies [43]. A study by Jayasena et al. showed that maternal plasma kisspeptin is significantly lower in women with early pregnancies who later develop SAB compared to women who have a viable intrauterine pregnancy (IUP) [44]. Maternal kisspeptin levels also had higher diagnostic performance than β-hCG in detecting SAB [44]. Wu et al. demonstrated that women with recurrent SAB have decreased decidual kisspeptin expression compared to women with IUP [45]. Kavvasoglu also showed decreased maternal kisspeptin levels in women with SAB compared to healthy IUPs [46]. Sullivan et al. validated a serum kisspeptin-54 assay as well as confirmed that maternal kisspeptin levels are positively correlated with fetal gestational age and pregnancy viability [40].

There is currently no established clinical test for early miscarriage; diagnosis relies on serial β-hCG measurements and correlation with ultrasound. This requires multiple maternal encounters with the healthcare system, a prolonged timeframe, and can involve considerable distress of the patient and partner. Jayasena et al. describes the current diagnostic pathway for establishing fetal viability as having limited clinical utility due to delay and a high degree of uncertainty [44]. Thus, there is interest in establishing a more accurate and streamlined diagnostic marker of viable IUP vs. SAB.

Kisspeptin has been shown to be massively downregulated in the case of ectopic pregnancy [47]. Ectopic pregnancy occurs when a fertilized ovum implants and develops outside the uterine cavity. Similarly to SAB, ectopic pregnancy is currently diagnosed by serial β-hCG measurements in correlation with ultrasound. Definitive diagnosis may require direct visualization via laparoscopy [48]. A study by Romero-Ruiz et al. explored the roll of kisspeptin in individuals with ectopic pregnancy. They found that maternal circulating kisspeptins gradually increased during the first trimester of pregnancy in healthy controls. However, in those with ectopic

pregnancy, kisspeptin levels were suppressed. The study correlated these results to levels of microRNAs (miRNA) (small noncoding RNAs that can modulate gene and protein expression). In particular, miR-324-3p is known to inhibit kisspeptin function. Romero-Ruiz et al. found that in ectopic pregnancies, miR-324-3p was significantly increased in placental tissue (though maternal circulating levels were low). This finding suggests defective export of the miRNA from its embryonic/placental source in ectopic pregnancy, which may further contribute to the local suppression of kisspeptin. The authors suggested that correlation of maternal miR-324-3p with kisspeptin and β-hCG levels could provide a better modality for timely diagnosis of ectopic pregnancy, especially considering the stability of miRNA in maternal serum [46].

Kisspeptin could also have diagnostic utility in identifying women at risk of preeclampsia. A study by Qaio showed that the placentas of term preeclamptic pregnancies express significantly lower kisspeptin levels compared to healthy pregnancies [49]. These findings were reproduced by Farina et al., which demonstrated lower KISS-1 expression in preeclamptic patients compared to healthy pregnant patients [50]. The study also suggested KISS-1 cell-free mRNA has potential to serve as a predictive biomarker of preeclampsia [50]. Matjila et al. investigated the relationship between maternal kisspeptin levels and placental kisspeptin expression in preeclamptic pregnancies – they found that preeclamptic placentas demonstrated high kisspeptin expression but low maternal kisspeptin levels [30]. It is speculated that elevated kisspeptin expression in diseased placentas may inhibit trophoblast invasion and contribute to the development of preeclampsia [30, 34]. Kisspeptin therefore has potential to offer predictive information about the risk of preeclampsia.

6. Kisspeptin in in vitro fertilization

Because of its apparent role in reproduction and fertility, there is interest in the use of kisspeptin as a tool to aid in assisted reproductive technology. Exogenous kisspeptin has been used to trigger oocyte maturation in women undergoing in vitro fertilization (IVF) with very low rates of ovarian hyperstimulation syndrome (OHSS) [41, 51]. Oocyte maturation is the process during which an oocyte transitions from metaphase I to metaphase II; at this time, it is capable of becoming fertilized [51]. Jayasena et al. demonstrated that a single kisspeptin bolus was capable of producing an LH surge that induced oocyte maturation in women undergoing IVF [41]. This was an important study, as it was the first to label kisspeptin as an effective maturation trigger. 92% of the study participants who received kisspeptin had at least one embryo available for transfer [41]. A study by Owens et al. then demonstrated that when kisspeptin is administered as an oocyte trigger during IVF cycles, granulosa cell gene expression is altered in such a way that increases FSH and LH receptor expression [52]. This altered gene expression is postulated to augment downstream signaling, resulting in increased sex steroid synthesis [52]. In fact, kisspeptin is currently considered to be the most potent stimulator of GnRH secretion [53, 54].

OHSS is considered a serious adverse event during IVF treatment and is typically related to the use of hCG as a trigger for oocyte maturation. This syndrome is characterized by extreme vascular permeability, which can result in pleural effusions, ascites, renal impairment, and in severe cases, death [51]. This vascular permeability is a downstream effect of hCG-mediated release of vascular endothelial growth factor (VEGF) from the ovary [55]. Kisspeptin has been shown to

directly inhibit ovarian VEGF production, which significantly decreases the risk of OHSS when used as a trigger for ovulation induction [56]. Moreover, kisspeptin acts to release endogenous GnRH, which triggers an LH surge dependent on the individual's own GnRH reserves, and is unlikely to excessively or pathologically stimulate the ovaries [57].

7. Kisspeptin in puberty

In addition to its role in pregnancy and fertility, kisspeptin is also implicated in sexual development in humans. The target of the kisspeptin molecule is G-protein coupled receptor 54 (GPR54) [58]. A study by de Roux et al. demonstrated that humans with a defect in the *GPR54* gene exhibit isolated hypogonadotrophic hypogonadism, suggesting that kisspeptin is an important regulator of gonadal axis development [59]. This finding was then reproduced by an independent study by Seminara et al., who evaluated a large family with idiopathic hypogonadotrophic hypogonadism and generated *GPR54* knockout mice, which failed to undergo adult sexual development and had low serum gonadotropin levels [47]. In contrast, exogenous kisspeptin administration in prepubertal rodents and primates has been shown to induce precocious puberty [60]. Furthermore, Teles et al. describes a female with an activating mutation of *GPR54* who exhibited idiopathic central precocious puberty [61].

Kisspeptin is thought to be imperative in all phases of sexual development, beginning in the embryonic phase. During the second trimester of pregnancy, GnRH secretion first occurs and is required for normal testicular development [62]. Aberrant gonadal pathways can result in male infants born with microphallus or cryptorchidism [63]. Kisspeptin is suspected to be crucial in the stimulation of GnRH secretion in both infancy and puberty [62].

8. Conclusion

Kisspeptins have a multitude of regulatory neuroendocrine functions that span the sexual life cycle. Though its mechanisms are not entirely characterized, there is strong evidence supporting its involvement in puberty and development, ovulation, implantation, and pregnancy. Because of their role in these reproductive processes, kisspeptins have potential to be useful as biomarkers in a variety of contexts, such as ovulation prediction and diagnosis of viable IUP. Kisspeptins may also be useful in the advancement of assisted reproductive technology. Continued exploration of kisspeptin function will help to develop and standardize practices that harness its diagnostic and therapeutic potential.

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