

Review

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[Dariusz Szukiewicz](#) *

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Review

The Role of Kisspeptin Signaling in the Physiology and Pathophysiology of Early Human Pregnancy

Dariusz Szukiewicz

Department of Biophysics, Physiology & Pathophysiology, Faculty of Health Sciences, Medical University of Warsaw, 02-004 Warsaw, Poland; dariusz.szukiewicz@wum.edu.pl

Abstract: Kisspeptin, the product of the *KISS1* gene and a ligand of the G-protein coupled receptor, *KISS1R* (also known as *GPR54*), is a relatively well-known hypothalamic neurohormone, the secretion of which is intrinsically linked to the kisspeptin, neurokinin B, and dynorphin (*KNDy*) neurons and is involved in the neuromodulation of gonadotropin-releasing hormone (*GnRH*) secretion, playing a key role in the central mechanism controlling the hypothalamic–pituitary–gonadal (*HPG*) axis. In contrast to our knowledge of the importance of kisspeptin neuronal signaling in regulating the onset of puberty and the control of fertility through its effects on the menstrual cycle, the importance of the extraneuronal pool of this hormone after fertilization and during early human pregnancy is far less complete. The very significant increase in the serum extrahypothalamic kisspeptin concentration in the first trimester of pregnancy, which originates from peripheral reproductive tissues, is accompanied by changes in local *KISS1R* expression. These findings suggest an important role of kisspeptin in the regulation of embryo implantation, trophoblast invasion, placentation and early pregnancy. The aim of this review is to present the current state of knowledge regarding the involvement of kisspeptin signaling in the physiology and pathophysiology of early pregnancy in humans. The diagnostic value of kisspeptin levels for early pregnancy outcomes will also be explored to identify potential related therapeutic targets.

Keywords: kisspeptin; *KISS-1* gene; kisspeptin receptor (*KISS1R*); G-protein coupled receptor 54 (*GPR54*); kisspeptin signaling; early pregnancy; kisspeptin (*KISS*)/neurokinin B (*NKB*)/Dynorphin (*Dyn*) neurons; *KNDy* neurons

1. Introduction

Neuroendocrine control of reproduction refers to the coordinated processes in the hypothalamus and pituitary gland that govern the production of hormones [1]. Steroid sex hormones are the main products secreted by the gonads (ovaries or testicles), although they may also be produced (including conversion from other steroids) outside the gonads, namely, in the adrenal glands, liver, brain, adipose tissue, or placenta during pregnancy [2–4]. The neuromodulation of gonadotropin-releasing hormone (*GnRH*) in the hypothalamus, manifested by its pulsatile secretion, is a key phenomenon within the hypothalamic–pituitary–gonadal (*HPG*) axis and determines the pattern of secretion of gonadotropins, follicle-stimulating hormone (*FSH*) and luteinizing hormone (*LH*) from the anterior pituitary [5,6]. Therefore, the *HPG* axis is involved in the onset of puberty, gamete maturation in the gonads, menstrual cyclicity, sex drive, childbirth, milk production and lactation [7,8]. At the beginning of the 21st century, research revealed that the protein that was subsequently named after Hershey's chocolate kisses (Pennsylvania – the place of kisspeptin discovery is the home of the “Hershey's Kisses” sweets), kisspeptin, has the ability to stimulate *GnRH*, which has received increased interest [9,10]. Kisspeptin is a product of the *KISS1* gene and a ligand of the G-protein coupled receptor, *KISS1R* (also known as *GPR54*). Previously, kisspeptin was named metastin because, in 1996, *KISS1* was identified as a human metastasis suppressor gene, the increased expression of which inhibits the metastasis of melanoma and breast cancer [11–13].

Confirmation of the involvement of kisspeptin in the neuroendocrine modulation of reproductive functions as a specific gatekeeper before entering the HPG axis was the starting point for numerous studies in the fields of physiology and pathophysiology [14–18]. Notably, research on the key role of kisspeptin in regulating the onset of puberty and modulating the activity of the HPG axis and, consequently, in the control of fertility is much more advanced than that examining the importance of kisspeptin after conception and the start of pregnancy. This disproportion is not justified in light of the results of recent studies indicating the presence of kisspeptin signaling via KISS1R outside the HPG axis [19,20]. Variable concentrations of extrahypothalamic kisspeptin in peripheral reproductive tissues, accompanied by changes in local KISS1R expression, may suggest an important role of kisspeptin in the regulation of trophoblast invasion, embryo implantation, placentation and early pregnancy [21–25]. Therefore, the aim of this review is to present the current state of knowledge regarding the involvement of kisspeptin signaling in the physiology and pathophysiology of early pregnancy in humans.

2. Kisspeptin

2.1. Structure

Human *KISS1* is located on the long arm of chromosome 1 (1q32) and contains 4 exons [26]. The product encoded by *KISS1*, prepro-kisspeptin, is a 145 amino acid precursor peptide that is cleaved into four shorter peptides called, according to the number of amino acids in the molecule, kisspeptin-54 (also known as metastin), kisspeptin-14, kisspeptin-13 and kisspeptin-10. All these isoforms contain a conserved 10 amino acid core sequence at the C-terminus, containing an Arg-Phe-NH₂ (RF-NH₂) motif that is required for full activation of KISS1R [10,27] (see Figure 1).

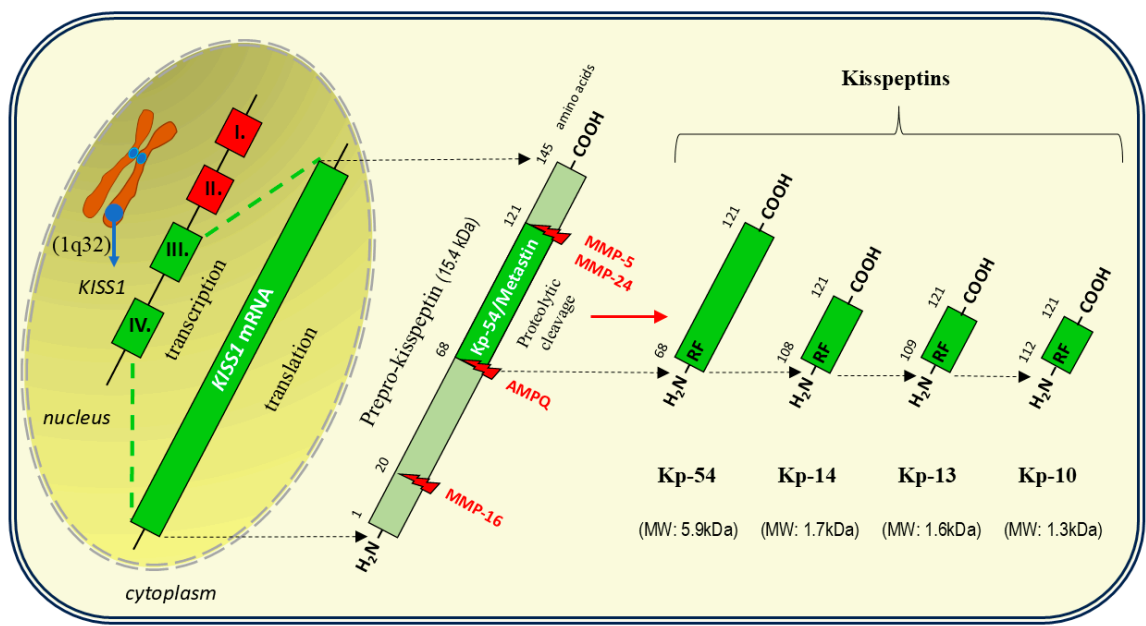


Figure 1. Formation and structure of kisspeptin molecules (inspired by Tena-Sempere [28], modified from López-Ojeda and Hurley [26]). In humans, *KISS1* gene located on the long arm of chromosome 1 (1q32), produces a 145-amino acid precursor protein, prepro-kisspeptin, via two coding exons (III. and IV.) of its four exons. Different kisspeptins are generated by proteolytic cleavage of prepro-kisspeptin, with the 19-amino acid signal peptide cut off from the N-terminus by matrix metalloproteinase 16 (MMP-16), and excision of the central 54-amino acid region (the cleavage sites at 68 and 121), corresponding to kisspeptin-54 (Kp-54, previously known as metastin) by aminopeptidase Q (AMPQ) and matrix metalloproteinases 5 and 24 (MMP-5 and MMP-24). Kp-54 can be cleaved into shorter forms of lower molecular weight (MW), giving rise to Kp-14, Kp-13, and Kp-10. All kisspeptins share a common C-terminus with Kp-54 and contain the RF-amide motif that is able to bind and

activate kisspeptin receptor. COOH – carboxy terminal; kDa – protein product size in kilodaltons; NH₂ – amino terminal. .

The major circulating and tissue form of kisspeptin is a 54-residue fragment (Kp-54), although shorter fragments (kisspeptins 14,13 and 10) appear to be as potent in binding to KISS1R as Kp-54 is [15,29]. Polymorphisms of both KISS1 and KISS1R are associated with central precocious puberty (CPP) and idiopathic hypogonadotropic hypogonadism (IHH) [30]. With respect to KISS1, at least 14 mutations have been detected that contribute to the disruption of the amino acid sequence in the molecules of these gene products (kisspeptins) [30,31].

Owing to the existence of 4 isoforms of kisspeptin, precise assessment of its concentration using commercially available techniques is difficult [32]. There are significant differences in the detection range, sensitivity, and, above all, specificity between the individual assay methods, which may cause uncertainty as to which form of kisspeptin is detected (i.e., Kp-54, Kp-14, Kp-13, or Kp-10) [33,34]. Moreover, the ambiguous or contradictory results of the kisspeptin assay may be influenced by the varying rate of kisspeptin metabolism in the circulatory system, where the half-life of Kp-54 is approximately 30 min, whereas the half-life of Kp-10 does not exceed 4 min [35].

2.2. Sources of Kisspeptin in the Body

2.2.1. Neuronal Kisspeptin in the Central Nervous System (CNS)

The localization of kisspeptin-expressing cells in the CNS has been most fully elucidated in mice. In the mouse hypothalamus, this neuropeptide showed the strongest expression, similar to its mRNA expression, in nuclei involved in the regulation of GnRH and gonadotropin (FSH and LH) secretion, such as the anteroventral periventricular nucleus (AVPV), a small cluster of neurons along the wall of the third ventricle (AV3V, the anteroventral third ventricle) just caudal to the organum vasculosum of the lamina terminalis (OVLT), the periventricular nucleus (PeVN) and the arcuate nucleus (ARC) [29,36,37]. Furthermore, kisspeptin mRNA expression, albeit much weaker than in the above locations, was also confirmed in the anterodorsal preoptic nucleus, the medial amygdala, and the bed nucleus of the stria terminalis [29,38,39]. Sexual dimorphism was found in the amount, but not the distribution, of kisspeptin in the CNS of mice, with females showing significantly greater kisspeptin expression, at least during the peripubertal period [29,40]. These differences in kisspeptin expression between the sexes may, however, vary depending on the period of life, the attainment of sexual maturity, the estrus cycle, or the species. For example, studies in rats have shown that sexual dimorphism in the expression of kisspeptin at the hypothalamic level during estrus is associated with an increase in males and a decrease in females. There was no change in the expression of GnRH or the kisspeptin receptor, regardless of sex, in this study [41].

Owing to ethical constraints, studies of the distribution of kisspeptin (+) neurons in the human brain have also yielded detailed topographic information. Studies conducted in nonhuman primates have established that in males, kisspeptin is present in the anterior part of the ARC and in the internal zone of the median eminence (ME) but is absent in the preoptic area (POA) and the AVPV [42,43]. Moreover, in females, kisspeptin (+) cells were detected in the POA in addition to the ARC, and kisspeptin expression was greater in the late follicular phase of the menstrual cycle than in the luteal phase [44]. Autopsy studies in humans have shown that kisspeptin neurons are found primarily in the infundibular nucleus and POA, which are analogous to the ARC and the rostral periventricular area of the third ventricle (RP3V) of the preoptic area in rodents, respectively [45]. In contrast to that in rodents, the sexual dimorphism of kisspeptin in humans includes not only its expression (increased in females) but also its distribution (increased expression of kisspeptin in the infundibular nucleus in females) [29,46].

2.2.2. Kisspeptin, Neurokinin B, and Dynorphin (KNDy) Neurons

Hypothalamic kisspeptin secretion is intrinsically linked to the KNDy neurons present there, the heterogeneous population of which includes a large subset of cells that, in addition to kisspeptin, coexpress tachykinin peptide neurokinin B (NKB) and the opioid peptide dynorphin (Dyn) [47,48]. The hypothalamic GnRH localization of KNDy neurons in the human brain is considered to reflect the conservation of functional anatomy across most mammalian species, and peptide colocalization was previously confirmed in sheep, rodents, cows and nonhuman primates [47,49].

Coexpression of the above protein compounds is closely related to the main function of KNDy neurons, namely, the negative feedback of GnRh within the HPG axis [50]. Increased levels of sex steroids released into the blood following GnRH stimulation cause the inhibition of kisspeptin in KNDy neurons, which is the essence of negative feedback control on the HPG axis [51]. The precise modulation of hormonal signals provided by NKB, Dyn and kisspeptin is responsible for generating the pulsatile release of GnRH, with kisspeptin secretion being dependent on NKB and Dyn [51–53]. The initiation of pulsatile GnRH release is mediated by the stimulating effect of NKB via NKB receptors (TACR3, tachykinin receptor 3) expressed on interconnected KNDy neurons, which leads to the release of kisspeptin in an autocrine manner. Activation of KISS1R on GnRH neurons subsequently induces pulsatile release of gonadoliberein (GnRH), whereas stimulation of KNDy neurons with KISS1R further enhances the stimulatory effect of NKB. Finally, the triggered GnRH pulse is terminated by the action of Dyn, which, via kappa opioid receptors (KORs) in KNDy neurons, inhibits both NKB and kisspeptin secretion. Furthermore, Dyn directly inhibits the activity of GnRH neurons by acting on their KORs [18,52,53]. There is still controversy about the coexpression of Dyn with kisspeptin/NKB in neurons of the infundibulum nucleus (the human homolog of the ARC) in humans, which contrasts with the results of previous immunohistochemical and in situ hybridization studies of sheep, goats, and rodents, which indicated that kisspeptin, NKB and Dyn are extensively colocalized in the hypothalamic ARC [54–56].

In addition to their role as GnRH pulse generators, KNDy neurons, mainly through the HPG axis, are also involved in the regulation of puberty onset [57], prolactin production [58,59], reproduction [60], the response of the reproductive system to stress [17,61], and the control of metabolic homeostasis, including thermoregulation [56,62–64]. Metabolic factors influencing the activity of kisspeptin (+) neurons at the subcellular, neuroendocrine and endocrine levels may therefore regulate the onset of puberty and reproductive processes associated with the HPG axis. Kisspeptin signaling pathways within KNDy neurons, particularly those involving glutamate as a cotransmitter, may also play a role in food intake, as their predominant role in energy expenditure has been demonstrated [56].

The general anatomical and functional scheme of KNDy neurons and kisspeptin neurons in relation to GnRH secretion is shown in Figure 2.

2.2.3. Extraneuronal Sources of Kisspeptin

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a type of metastasis suppressor that is capable of modulating the behavior of some cancer cells by suppressing their proliferation, likely via the induction of autophagy and apoptosis, remains unclear and controversial, although many hypothetical mechanisms have been discussed [75–79]. It can be assumed that, in principle, any cellular stress (e.g., hypoxia) is able to increase the expression of *KISS1* in different cell types, which is why, under physiological conditions associated with local angiogenesis accompanying implantation and placenta formation (placentation), an increased concentration of kisspeptin in the circulatory system of extraneuronal origin becomes understandable [80–82].

Notably, kisspeptin is produced in adipose tissue, where *KISS1* mRNA has been detected in humans and rats [69,83]. Fasting induces an increase in *KISS1* mRNA expression in rats, whereas a high-fat diet (HFD) causes it to decrease [84]. In women, however, higher *KISS1* expression was demonstrated in subcutaneous adipose tissue than in visceral fat (the adipose tissue surrounding peritoneal organs), with a positive correlation with the body mass index (BMI) being found only for visceral fat [83]. The fact that, in women, including pregnant women, the kisspeptin concentration is related to BMI may indicate that this neurohormone is a link between metabolic processes and reproduction. In this context, kisspeptin may be a potential therapeutic target in the treatment of infertility due to metabolic disorders, especially obesity and insulin resistance [85–87].

3. Kisspeptin Receptor (KISS1R/GPR54)

All kisspeptins are endogenous ligands for the class A rhodopsin family of seven transmembrane (7TM) G protein-coupled receptors encoded by the *KISS1R* gene, which, previously, was named *GPR54* and known as *AXOR12* or *hOT7T175* [88–91]. In humans, *KISS1R* is located on chromosome 19 (locus 19p13.3) and contains five coding exons [90,92].

Although *KISS1R* does not interact with galanin, significant homology with the galanin receptors GalR1, GalR2 and GalR3 within its putative transmembrane domains has been demonstrated, reaching 45% for GalR1 [93,94].

Broad expression of *KISS1R* in various tissues has been demonstrated in humans as well as common laboratory rodents, whereby the amino acid sequences of the human *KISS1R* protein (398 amino acids) share 82% identity with those of mice (396 amino acids) and display as much as 85% sequence identity (98% identity in transmembrane domains) with those of the rat *KISS1R* protein (396 amino acids) [49,89,95,96]. Human and rodent *KISS1R* homologous sequences (orthologs) are less conserved only in the carboxyl (COOH)-terminal, the amine (NH₂)-terminal and within the third extracellular loop of the receptor [96,97].

Numerous studies on the etiology of CPP and IHH have been accompanied by the discovery of *KISS1R* point mutations resulting in the replacement of single amino acids in the *KISS1R* molecule chain [30,31,98–100]. Since all receptors belonging to the GPCR family show fundamental structural similarity, information obtained from the analysis of *KISS1R* mutations can be used more universally, extending it to improve the understanding of the function of different domains within the GPCR family [30,101,102].

The general structure of *KISS1R* is shown in Figure 3, which also indicates the mutation sites (amino acid exchanges) in the peptide chain leading to inactivation, possible inactivation or activation of the receptor.

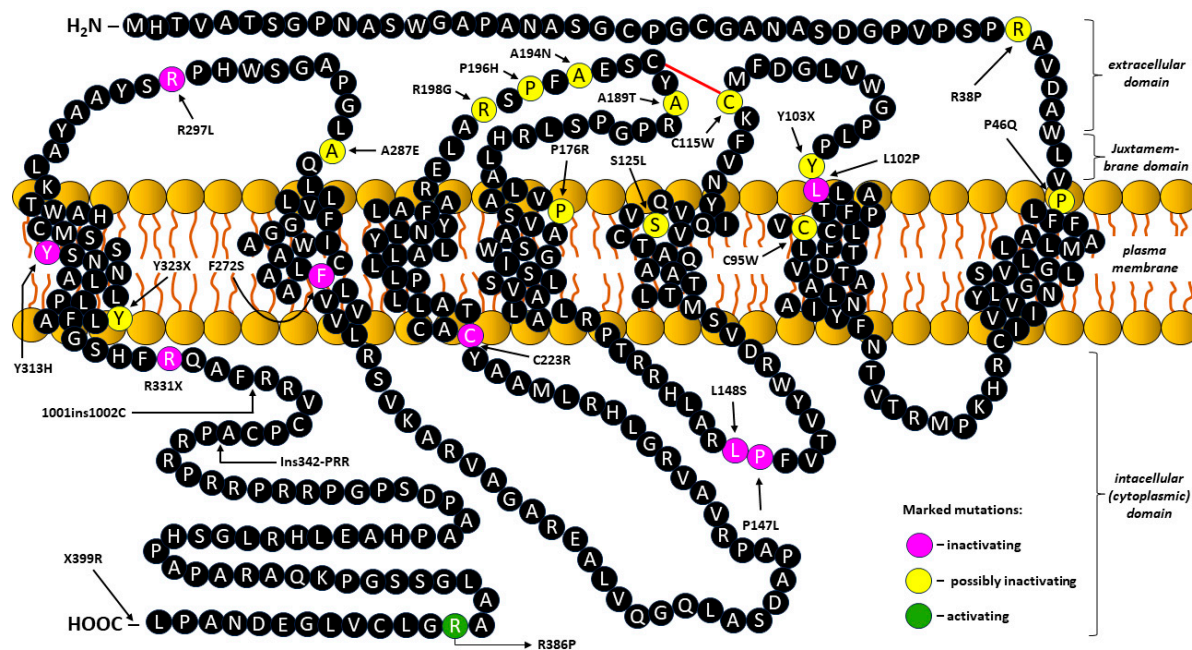


Figure 3. Human kisspeptin receptor (KISS1R/GPR54): general structural diagram showing mutations in the peptide chain that result in amino acid exchange leading to inactivation, possible inactivation or activation of the receptor (marked in pink, yellow and green, respectively). Modified and updated from Pinilla et al. [27], Roa et al. [103], Abbara et al. [104], Gianetti and Seminara [105] and Franssen and Tena-Sempere [106].

3.1. Kisspeptin/KISS1R Signaling

Owing to a conserved 10 amino acid core sequence, all kisspeptin isoforms of different chain lengths (Kp-54, Kp-14, Kp-13 and Kp-10; see Figure 1.) resulting from proteolytic cleavage of prepro-kisspeptin show affinity for KISS1R [26,28]. When these ligands bind to KISS1R, a typical 7TM GPCR, they act as guanine nucleotide exchange factors (GEFs), leading to a conformational change in the three-dimensional (3-D) structure of KISS1R [90,107].

The heterotrimeric G protein is activated at the level of the Gαq/11 subunit through the exchange of a guanosine diphosphate (GDP) for a guanosine triphosphate (GTP). Activated KISS1R dissociates into Gαq/11-GTP and Gβγ to further initiate Gαq/11-dependent intracellular signaling [50]. Next, Gαq/11 activates phospholipase C (PLC)-β, an essential enzyme in the metabolism of phosphoinositide in the cytoplasm. The hydrolytic activity of PLC-β is responsible for the breakdown of the inner membrane component phosphatidylinositol-4,5-bisphosphate (PIP2) into inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) [108–110]. Because IP3 and DAG are key signaling molecules that influence various cellular functions and are precursors of other signaling molecules, PLC can be considered a hub for numerous interconnected signaling pathways. IP3 acts as a second messenger in the release of calcium ions (Ca²⁺) stored in the endoplasmic reticulum (ER) [111,112], whereas DAG acts as a second messenger in the activation of protein kinase C (PKC) [113,114]. The mobilization and intracytoplasmic release of Ca²⁺ result from the interaction of IP3 with IP3-sensitive Ca²⁺ channels, which can promote a variety of different functions, depending on the cell type and its functional state. For example, an increase in the Ca²⁺ concentration may provide kisspeptin with the ability to release GnRH and modulate its ability to inhibit cell proliferation, including antimetastatic effects [115,116]. DAG acts as an allosteric activator of PKC, which subsequently causes a phosphorylation signaling cascade and ultimately leads to the activation of kinases belonging to the serine/threonine mitogen-activated protein kinase (MAPK) family, including extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (p38MAPK) [117,118]. Therefore, as a consequence of the action of DAG, the activation of the PKC/Ras (kinases)/Raf

(kinases)/MEK/ERK1/2 pathway and the PKC/Ras/Raf/MEK/p38MAPK pathway can be distinguished [119].

Additionally, KISS1R signals independently of $G_{\alpha q/11}$ via the adaptor proteins β -arrestins 1 and 2, leading to the inhibition or recruitment of the ERK1/2 pathway, respectively [120–122]. Although β -arrestins function to "arrest" G protein signaling to promote GPCR desensitization and internalization, as modulators of downstream KISS1R signaling, they have been shown to function both as passive scaffolds and as active allosteric regulators of enzymatic activity [123].

KISS1R activation may, depending on the cell type and functional state, stimulate or inhibit PI3K (phosphatidylinositol 3-kinase)/Akt (serine/threonine kinase Akt, also known as protein kinase B (PKB)) phosphorylation, although the mechanisms of this phenomenon, including intermediary compounds, have not been elucidated [124,125]. Through signaling via the PI3K/Akt/NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) or the ERK1/2/NF- κ B pathways, upon KISS1R stimulation, decreased expression of the matrix metalloproteinase-9 (MMP-9) gene also occurs [126,127]. MMP-9 directly degrades extracellular matrix (ECM) proteins and regulates tissue remodeling via cytokine/chemokine mediators in both physiological (e.g., embryonic development, reproduction, angiogenesis, and wound healing) and pathological (e.g., asthma and arthritis) processes [128–133]. Therefore, during the process of blastocyst implantation, kisspeptin may attenuate the excessive migration and invasion of trophoblasts through the inhibition of MMP-9 and, to a lesser degree, matrix metalloproteinase-2 (MMP-2) [134–136]. These findings confirm that the specific action of kisspeptin is dependent on the cell type, differentiation state and functional state.

The signaling pathways involved in the interaction of kisspeptin with KISS1R are shown in Figure 4.

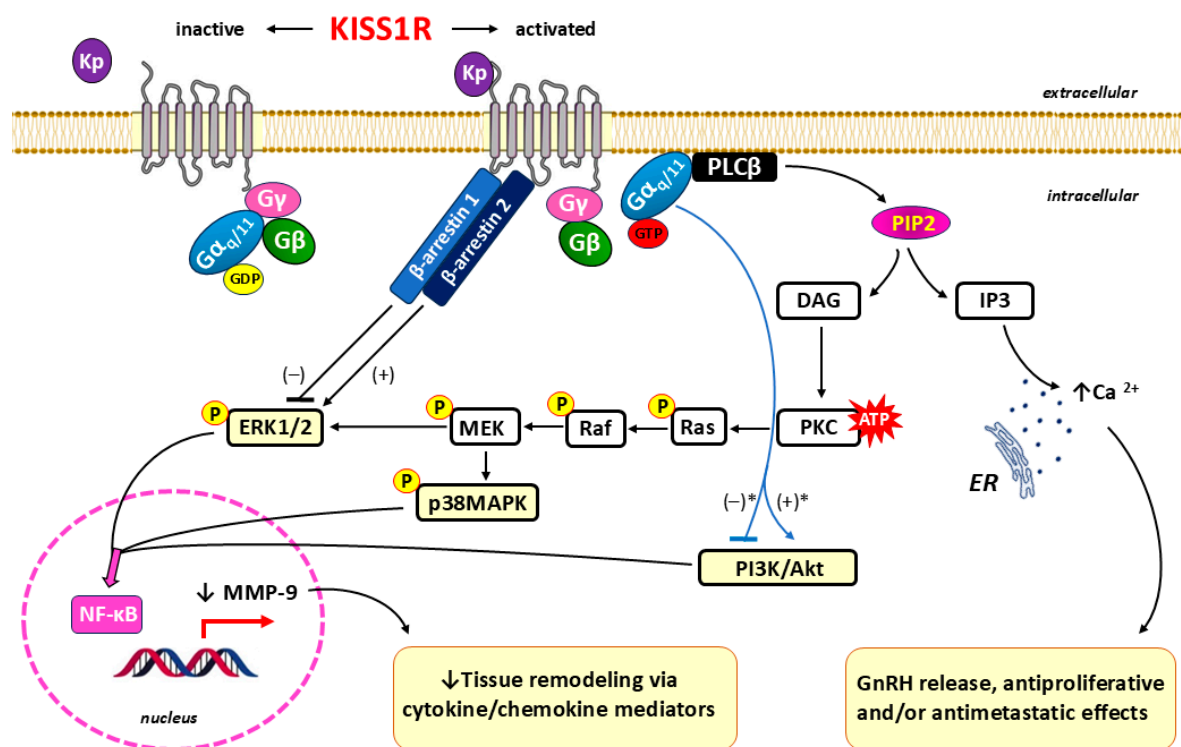


Figure 4. Kisspeptin signaling via its receptor KISS1R [also known as G-protein-coupled receptor-54 (GPR54)]. After binding of the ligand (kisspeptin) to KISS1R, changes in the structure of the receptor protein occur within the extracellular domain. The activation of the intracellular signal cascade is initiated by the exchange of the guanosine diphosphate (GDP) for a guanosine triphosphate (GTP) in the $G_{\alpha q/11}$ subunit of the heterotrimeric G protein, with subsequent dissociation into $G_{\alpha q/11}$ -GTP and $G\beta\gamma$. Next, the hydrolytic action of $G_{\alpha q/11}$ -GTP-activated phospholipase C (PLC)- β leads to the disintegration of the inner membrane component, phosphatidylinositol-4,5-bisphosphate (PIP2), into inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG).

IP3 acts as a second messenger in the release of calcium ions (Ca^{2+}) stored in the endoplasmic reticulum (ER), which plays a key role in KISS1R-dependent gonadotropin-releasing hormone (GnRH) release, as well as in antiproliferative and antimetastatic effects. As an allosteric activator of protein kinase C (PKC), DAG leads to the phosphorylation signaling cascade via activation of the serine/threonine mitogen-activated protein kinases (MAPK), including extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (p38MAPK). Independently of $\text{G}\alpha\text{q}/11$, KISS1R can transduce signals through adaptor proteins, β -arrestins 1 and 2, which leads to inhibition or recruitment of the ERK1/2 pathway, respectively. Signaling through PI3K/Akt/NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) or the ERK1/2/NF- κ B pathways is accompanied by decreased cellular synthesis of matrix metalloproteinase-9 (MMP-9), which is involved in tissue remodeling via cytokine/chemokine mediators. * Depending on the cell type and its functional state, KISS1R activation can both stimulate and inhibit PI3K (phosphatidylinositol 3-kinase)/Akt [serine/threonine kinase Akt, also known as protein kinase B (PKB)] phosphorylation through a mechanism that has not been sufficiently explained. ATP – adenosine triphosphate; P – phosphorylation; Raf – Raf kinases; Ras – Ras kinases.

4. Kisspeptin in Early Pregnancy

Early pregnancy, defined in humans as the first 12 weeks after fertilization, is a crucial period in the development of the fetus. This stage includes the germinal stage, which lasts 10 days and refers to the period from fertilization to the completion of blastocyst implantation in the decidual endometrium, i.e., the formation of the early embryo [137,138]. During the embryonic stage, which lasts from approximately the third week to the end of the eighth week of pregnancy, organogenesis takes place, during which a developing embryo establishes the rudimentary structures of all of its organs and tissues from the ectoderm, mesoderm, and endoderm [139]. At the beginning of the ninth week, the embryo is termed a fetus [140].

In addition to its role in the hypothalamus, nonneuronal kisspeptin action in peripheral tissues also has many regulatory functions, including during pregnancy [20,22,141]. As mentioned earlier, the concentration of circulating kisspeptin increases many times from the first weeks of pregnancy, and its main source is the placenta [19,21,33,67]. Kisspeptin is believed to regulate the manner in which this temporary organ is formed [21,25,142]. For example, the kisspeptin-54 concentration measured using an immunoenzymatic method clearly linearly increased with gestational age, reaching 1230 pmol/L in the first trimester and a maximum of 9590 pmol/L in the third trimester, after which it returned to nonpregnancy values (< 100 pmol/L) shortly after delivery [69].

The growing evidence for the involvement of kisspeptin/KISS1R signaling in embryo implantation, trophoblast invasion and placentation justifies the consideration of this neurohormone as a potential biomarker in early pregnancy; its levels correlate with the risk of miscarriage, preeclampsia/eclampsia, GTN, and fetal growth retardation [21,23,67–69,143–146]. Kisspeptin measurements have been shown to have potentially comparable or greater accuracy than human chorionic gonadotropin (HCG) in differentiating between miscarriage and viable intrauterine pregnancy after 6 weeks of gestation [147,148]. Kisspeptin deficiency in the serum of females with unexplained infertility was associated with a reduced chance of implantation after intracytoplasmic sperm injection (ICSI) [149].

4.1. Embryo Implantation

Implantation, the process by which a blastocyst attaches to the decidualized endometrium of the uterus to achieve pregnancy, can be divided into three distinct, increasingly advanced stages: apposition (unstable adhesion), adhesion and invasion (penetration) [150]. During this highly orchestrated process, there is an interaction between the receptive endometrium and the competent embryo within a precisely defined time frame called the "window of implantation", which includes contact of the blastocyst with the implantation site (apposition), attachment of the trophoblast cells of the blastocyst to the receptive endometrial epithelium (adhesion) and crossing the endometrial epithelial basement membrane toward the endometrial stroma by invasive trophoblast cells (invasion) [151].

The expression of the functional form of the kisspeptin/KISS1R system has been demonstrated at each of the above stages, as well as during decidual transformation of the endometrium [21,152]. In gametes, the expression of kisspeptin and KISS1R has been documented in human oocytes and in human spermatozoa [153–155]. In the latter, both kisspeptin and KISS1R are localized mainly in the sperm head, around the neck and in the flagellum [155]. Single-cell RNA sequencing (RNA-Seq) analyses have confirmed the expression of KISS1R in human embryos (from the zygote stage to the blastocyst stage), with some doubts regarding the production of kisspeptin by dividing germ cells [22,156].

Trophectoderm cells derived from the blastocyst give rise to cytotrophoblast cells, which, after proliferation and differentiation, finally give rise to the syncytiotrophoblast and an outwardly developing multilayer of mononuclear cells of the invasive extravillous cytotrophoblast (EVT) [157]. This invasive behavior is due to the ability of cytotrophoblasts to secrete matrix metalloproteinases (MMPs), and kisspeptin may regulate trophoblast migration and invasion by influencing the activity of MMP-9 and, to a lesser extent, MMP-2 [69,135,158]. Moreover, the contradictory results of the kisspeptin/KISS1R signaling studies may suggest that kisspeptin is a factor that bidirectionally regulates trophoblast invasiveness and migration, either by promoting or inhibiting it during embryo implantation and placentation [159]. Kisspeptin/KISS1R-dependent adhesion of EVTs to type-I collagen, a major component of the human placenta, plays a key role in this regulatory mechanism. Both the rapid and transient nature of this increased adhesion have been shown to be due to the activation of secondary effectors such as PKC and ERK1/2 in EVT cells following KISS1R activation [82].

Blastocyst implantation and the development of early pregnancy are not possible without decidual transformation of the endometrium. During decidualization, mainly under the influence of high progesterone levels, changes occur in endometrial cells that increase glandular epithelial secretion, increase glycogen storage, and enhance stromal vascularity [160]. Kisspeptin is recognized as a physiological modulator of stromal decidualization, which stimulates this process by upregulating leukemia inhibitory factor (LIF), a major cytokine regulator of decidualization in humans and mice [161,162]. Using quantitative PCR, a dynamic increase in kisspeptin and KISS1R mRNA levels was demonstrated in the mouse uterine mucosa during early pregnancy and during artificial decidualization *in vivo*. The expression of the kisspeptin and KISS1R proteins was then observed in a spatiotemporal manner in decidualization stromal cells in intact pregnant females as well as in pseudopregnant mice subjected to artificially induced decidualization [163]. The promotion of endometrial decidualization by the kisspeptin/KISS1R system is associated with the activation of the ERK1/2 signaling pathway, resulting in increased expression and secretion of LIF. In line with the above findings, in patients with recurrent spontaneous abortion (RSA), both serum kisspeptin levels and decidual kisspeptin expression are lower than those in normal pregnant individuals. These kisspeptin deficiencies are accompanied by reduced expression of decidualization markers, including prolactin (PRL) and insulin-like growth factor-binding protein 1 (IGFBP-1), in the decidua [152].

Recently, it has also been suggested that kisspeptin may regulate the decidualization process by modulating the neurogenic locus notch homolog protein 1 (Notch1)/Akt/forkhead box protein O1 (FOXO1) signaling cascade. In this signaling system, downregulation of kisspeptin expression may cause suboptimal decidualization and consequently contribute to the development or progression of RSA [164].

During implantation, KISS1R negatively regulates estrogen receptor alpha (ER α) signaling, in part by inhibiting ER α overexpression and preventing detrimentally high ER α activity [165]. Therefore, while the growth and development of the uterus itself are largely dependent on ovarian estradiol (E2) output via central kisspeptin signaling, peripheral kisspeptin signaling is indispensable for achieving full functional competence of the endometrium at the time of implantation [165,166].

Another important mechanism of action of kisspeptin in pregnancy is related to maternal immunological tolerance, which is necessary to avoid fetal rejection [141,167]. This immunomodulatory action of kisspeptin is revealed as early as the last stage of embryo implantation,

invasion, which starts with the penetration of the syncytiotrophoblast through the uterine epithelium with subsequent infiltration of the mononuclear cytotrophoblast invading the entire endometrium [69]. In vitro studies have shown that incubation of T cells in medium containing kisspeptin at concentrations corresponding to those present during pregnancy results in increased differentiation of human naive T cells into T-regulatory cells [168]. Moreover, the transformation of CD4⁺ T lymphocytes into inducible regulatory T cells (iTregs) following interaction with kisspeptin was accompanied by concomitant inhibition of the differentiation of interleukin 17 (IL-17)-producing T helper (Th17) cells [169].

4.2. Trophoblast Invasion–Vascular Remodeling–Placentation

The process of invasive growth of the trophoblast into the decidualized endometrial stroma and inner third of the myometrium, initiated at the last stage of blastocyst implantation, is crucial for the formation of the placenta and the establishment of definitive maternal–fetal circulation [150,151]. This includes endovascular trophoblast invasion, which occurs in two stages, with infiltration into the decidual segments of the spiral arteries between 8 and 10 weeks of gestation and invasion into myometrial segments of the spiral arteries between 16 and 18 weeks of gestation [151,170,171]. In the early weeks of pregnancy, migrating extravillous cytotrophoblasts plug the spiral vessels, presumably to prevent premature immunization associated with the appearance of maternal blood in the intervillous space [172,173]. This sealing of the lumen of the spiral arteries disappears around the 10th to 12th week of pregnancy, when the final vascular remodeling leads to the establishment of low-resistance circulation in the developing maternal–fetal unit [173,174]. Failure of trophoblast invasion and spiral artery remodeling results in pregnancy-induced hypertension and/or fetal growth restriction (FGR) [175–177].

Consistent with the original findings of the discovery of kisspeptin, which in the Kp-54 form was named metastatin to emphasize its antimetastatic activity, KISS-1 gene products inhibit cellular invasion, migration and angiogenesis [178,179]. High levels of endogenous kisspeptin and marked expression of KISS1R in placental trophoblast cells have been found to be associated with direct regulation of trophoblast proliferation and invasiveness and to indirectly influence the development of the placental vascular network [21,142]. Kisspeptin limits the invasiveness of trophoblasts by inhibiting MMP-9 and MMP-2, both at the transcriptional and protein levels [158]. Reduced extracellular matrix (ECM) degradation limits the ability of the cytotrophoblast to infiltrate the uterine wall, and the effect of kisspeptin, although restricted to MMP-9 and MMP-2, mimics and supports endogenous tissue inhibitors of MMPs (TIMPs), which have been shown to be expressed in both the human decidua and the trophoblast [180,181]. Owing to this effect of kisspeptin/KISS1R signaling, trophoblastic cells, with their strictly controlled propensity for invasive growth, have limited similarity to malignant cells [182,183].

In trophoblast invasiveness studies conducted in the KISS1R knockout (KO) model, the expression of the trophoblast invasion marker MMP-2 mRNA was greater in the placental labyrinth zone of KISS1R KO mice than in that of wild-type mice [23]. Similarly, the migratory potential of cytotrophoblast-like cells was inhibited after kisspeptin treatment in a human trophoblast (BeWo) cell line cultured in vitro, with previously confirmed kisspeptin protein expression [23].

The demonstration of the role of kisspeptin/KISS1R signaling in limiting trophoblast invasiveness has become the starting point for recognizing it as a potential risk factor for the occurrence of poor trophoblast cell invasion, inadequate uterine vascular remodeling, and placental hypoperfusion. These crucial placental disorders are clearly part of the pathophysiology of preeclampsia/eclampsia, a frequently occurring metabolic/hypertensive complication that poses a threat to the health and life of women and fetuses [184,185]. It has been suggested that insufficient trophoblast invasion into spiral arteries, leading to pregnancy-induced hypertension, may be a consequence of the inhibitory effect of kisspeptin on macrophage migration inhibitory factor (MIF) [158]. MIF is a multifunctional proinflammatory cytokine highly secreted by the first-trimester placenta, mainly in villous and extravillous trophoblasts, that plays an important role in the

activation of innate and adaptive immune responses. Moreover, trophoblast MIF is induced by hypoxia to promote trophoblast cell invasion and migration [186,187].

Many other data, often requiring verification, suggest possible functional links between kisspeptin and placental trophoblast invasiveness, angiogenesis and immunology in early pregnancy. For example, the kisspeptin/KISS1R system inhibits the expression of vascular endothelial growth factor (VEGF), and increased placental KISS1R expression is positively correlated with tumor necrosis factor alpha (TNF α) synthesis, whereas interferon gamma (IFN γ), interleukin 6 (IL-6), and interleukin 10 (IL-10) synthesis are negatively correlated with placental KISS1R expression [80,184,188–190].

Optimal control of EVT invasiveness causes them to invade the decidua and move toward the spiral arteries in early pregnancy, where they first form trophoblast plugs and, after destroying the vascular smooth muscle layer, lead to vascular remodeling with the creation of low-resistance blood flow [172,191]. The abovementioned phenomena constitute the essence of the hemochorial placentation process, which begins in humans approximately 8–9 days after fertilization and leads to the formation of the placenta, in which maternal blood comes in direct contact with the fetal chorion. Ultimately, approximately 120–140 spiral arteries undergo remodeling, which, after developing the final form of uteroplacental circulation, are able to provide a flow at the level of 20% of the cardiac output of the pregnant woman during full-term pregnancy [171]. Kisspeptin/KISS1R signaling in trophoblast cells affects intracellular skeletal organization, and cell migration and collagenase activity may play crucial roles in this process [11,134].

Given that kisspeptin has been proposed as a biomarker of healthy placentation, it could be used to recognize both anatomical and locational abnormalities of the developing placenta in early pregnancy [67,69]. Low-lying placentas, placenta previa and abnormally invasive placentas are the most frequently occurring placental abnormalities in terms of location and anatomy, whereas ectopic pregnancy is a complication of pregnancy in which the embryo attaches outside the uterus (e.g., placentation in the fallopian tube) [192–194].

The evaluation of the kisspeptin concentration in the serum revealed a significant decrease in pregnant women with placenta previa compared with the control group (healthy pregnancies with normal intrauterine placenta locations). Moreover, in cases of placenta previa, biochemical, immunohistochemical and genetic analyses consistently revealed reduced expression of the KISS1 gene, accompanied by a very significant (170-fold) increase in KISS1R expression [143]. Further studies, including tissue modeling with assessments of angiogenesis, migration and the degree of cell invasiveness, are necessary to fully understand the importance of kisspeptin/KISS1R signaling disorders in the pathomechanism of placenta previa development.

In ectopic pregnancy, a significant reduction in the serum kisspeptin concentration is also observed compared with that in the first trimester of normal pregnancy. In addition, the reduced kisspeptin levels were correlated with reduced levels of KISS1 expression in human embryonic/placental tissue obtained from ectopic pregnancies, which may be due to increased expression of the microRNA miR-324-3p, a putative repressor of KISS1 in human embryonic/placental tissue at <12 weeks of gestation [195,196]. The above results provide a basis for considering circulating kisspeptin and miR-324-3p as potential biomarkers of ectopic pregnancy at early gestational stages [67,69,196].

Data on the kisspeptin concentration and KISS1 and KISS1R expression in trophoblast/placental tissue in early pregnancy (gestational age ≤ 12 weeks) with a physiological and complicated course are summarized in Table 1.

Table 1. Kisspeptin concentration and expression of kisspeptin and kisspeptin receptor genes (KISS1 and KISS1R, respectively) in early human pregnancy (gestational age ≤ 12 weeks): normal pregnancy versus selected pregnancy complications.

Parameter	Normal pregnancy	Abnormal pregnancy [#]			
		Ectopic pregnancy	GTN	Placenta previa	Miscarriage
Kisspeptin concentration in plasma or serum	↑* [33,197,198]	↓ [67,69,195,196,200]	↑ [68]	↓ [143]	↓ [145,146,148,198-203] or INC [32]
KISS1 expression in trophoblast/placental tissue	N/A	↓ [196]	↑ [182]	↓ [143]	↓ [32,203,204]
KISS1R expression in trophoblast/placental tissue	N/A	N/D	↑ [182]	↑ [143]	↓ [32,204] or WNR [203]

* compared to non-pregnant women; [#]compared to normal pregnancy; GTN – gestational trophoblastic neoplasia; INC – inconclusive; N/A – not applicable; N/D – no data; WNR – within normal range.

5. Concluding Remarks

In addition to its direct effects on reproductive function within the HPG axis, the neurohormone kisspeptin plays an important role in processes accompanying key stages of early human pregnancy, such as embryo implantation with trophoblast invasion and vascular remodeling, which are thought to ensure successful placentation. This is confirmed by the fact that the spectacular, approximately 900-fold increase in the serum kisspeptin concentration in the first trimester of pregnancy, compared with that in nonpregnant women, is due to its extraneuronal pool, which is functionally unrelated to KNDy neurons. The source of this extraneuronal kisspeptin is primarily populations of trophoblast cells, the dynamic proliferation of which determines the formation of the placenta, and its tissue supports the production of this hormone.

Previous findings that the kisspeptin (then called metastin)/KISS1R (then called GPR54) signaling pathway plays a role in cancer biology as a suppressor of metastatic spread by inhibiting cell proliferation, probably via the induction of autophagy and apoptosis, have been extended to the control of trophoblast invasiveness in early pregnancy. Defective trophoblast invasion has been shown to be closely associated with pregnancy complications, including ectopic pregnancy, GTN, placenta previa and miscarriage. Optimal control of KISS1 and KISS1R expression during early trophoblast development is therefore essential for initiating processes leading to eutopic placentation with adequate invasion into spiral uterine arteries to develop low-resistance vessels in the hemochorial placenta.

Considering these findings, circulating kisspeptin could be used as a potential biomarker for the detection of, among other factors, the well-being of early pregnancy and the risk of miscarriage, GTN, or its abnormal location (ectopic pregnancy). When kisspeptin is used as a marker of the above pathologies of early pregnancy, one should remember the methodological difficulties in determining kisspeptin levels, which are caused by the existence of 4 isoforms of this hormone (i.e., Kp-54, Kp-14, Kp-13, or Kp-10), which additionally differ significantly in their rate of metabolism in the body. It is necessary to refine laboratory methods for detecting kisspeptin and promote those that are characterized by adequate sensitivity and repeatability under clinical conditions.

The need for future studies arises from the demonstration that the kisspeptin concentration in women, including pregnant women, correlates with BMI and, in particular, with KISS1R mRNA expression in visceral fat. This allows for the linkage of the metabolic actions of kisspeptin with its reproductive regulatory functions at the level of the HPG axis and early pregnancy tissues. Therefore,

in metabolic disorders associated with infertility, such as obesity and insulin resistance, targeting the kisspeptin signaling pathway may yield beneficial therapeutic effects.

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Abbreviations

7TM GPCR – seven-transmembrane G protein-coupled receptor

ARC – arcuate nucleus

AV3V – anteroventral third ventricle

AVPV – anteroventral periventricular nucleus

BMI – body mass index

CNS – central nervous system

CPP – central precocious puberty

DAG – diacylglycerol

Dyn – dynorphin

E2 – estradiol

ECM – extracellular matrix

ER – endoplasmic reticulum

ER α – estrogen receptor alpha

ERK1/2 – extracellular signal-regulated kinase 1/2

EVT – extravillous cytotrophoblast

FGR – fetal growth restriction

FOXO1 – forkhead box protein O1

FSH – follicle stimulating hormone

GalR1, GalR2, GalR3 – galanin receptors type 1, 2 and 3 respectively

GEFs – guanine nucleotide exchange factors

GnRH – gonadotropin-releasing hormone

GTN – gestational trophoblastic neoplasia

HCG – human chorionic gonadotropin

HFD – high fat diet

HPG axis – hypothalamic-pituitary-gonadal axis

iTreg – inducible regulatory T cells

ICSI – intracytoplasmic sperm injection

IFN γ – interferon gamma

IGFBP-1 – insulin-like growth factor-binding protein 1

IHH – idiopathic hypogonadotropic hypogonadism

IL-6, IL-10, IL-17 – interleukins 6, 10 and 17, respectively

IP3 – inositol 1,4,5-trisphosphate

KISS1 – gene encoding kisspeptin

KISS1R – KISS1-derived peptide receptor is a G protein-coupled receptor (also known as GPR54)

KNDy neurons – kisspeptin, neurokinin B, dynorphin neurons

KOR – kappa opioid receptor

Kp-54, Kp-14, Kp-13, Kp-10 – the four kisspeptin isoforms

LH – luteinizing hormone

LIF – leukemia inhibitory factor
 MAPKs – mitogen-activated protein kinases
 MIF – macrophage migration inhibitory factor
 MMP-2, MMP-9 – matrix metalloproteinase 2 and 9, respectively
 MMPs – matrix metalloproteinases
 NF- κ B – nuclear factor kappa-light-chain-enhancer of activated B cells
 NKB – neurokinin B
 Notch1 – neurogenic locus notch homolog protein 1
 OVLT – organum vasculosum of the lamina terminalis
 p38MAPK – p38 mitogen-activated protein kinase
 PeVN – periventricular nucleus
 PIP2 – phosphatidylinositol-4,5-bisphosphate
 PKB – protein kinase B (also known as serine/threonine kinase Akt)
 PKC – protein kinase C
 PLC- β – phospholipase C beta
 POA – preoptic area
 PRL – prolactin
 RNA-Seq – RNA sequencing
 RSA – recurrent spontaneous abortion
 TACR3 – tachykinin receptor 3 (NKB receptor)
 Th17 – T helper 17 cells
 TIMPS – tissue inhibitors of matrix metalloproteinases (MMPs)
 TNF α – tumor necrosis factor alpha
 VEGF – vascular endothelial growth factor

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