The Role Of Kisspeptin Kiss 1r In Endometrial Implantation In Patient With Assisted Reproductive Technology

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THE ROLE OF KISSPEPTIN / KISS 1R IN ENDOMETRIAL IMPLANTATION IN PATIENT WITH ASSISTED REPRODUCTIVE TECHNOLOGY

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ABSTRACT

We conducted a review of literatures regarding the role of kisspeptin in endometrial implantation in patients with assisted reproductive technology. Study results showed kisspeptin has an important role. Of several types of kisspetin, kisspeptin-10 as physiological activator of KISS1R in the human placenta, plays the most important role in humans. Kisspentin also regulates in development process of stromal cell decidualization so as to increase adhesion and implantation of the blastocyst in the endometrium and deficiency of plasma cispeptin on the day of the HCG tiggered will reduce the embryo implantation possibility. In Kisspeptin IVF position also can reduce the level of vascular permeability and VEGF thereby reducing the risk of the occurrence of OHSS due to the process of gonadotrophin stimulation.

Keywords: kisspeptin, endometrial implantation, assisted reproductive technology

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INTRODUCTION

Kisspeptin consists of 145 amino acids polypeptide and encodes the KISS1 gene and was initially identified as a metastatic suppressor gene in humans from melanoma malignancy in Hershey, Pennsylvania USA.[1] In humans, the KISS1 gene encoding Kisspeptin is located on the long arm of chromosome 1 in q32 and then splits into 4 active peptide biology with their amino acid counts, namely kisspeptin-10,13,14 and 54 (52 in mice). But kisspeptin has the largest proteolytic production, which consists of 52 amino acids, kisspeptin 54 and the shortest peptide is kisspeptin 10, which indicates that the terminal part C of this peptide contributes to the high affinity bond with activation of the kisspeptin / KISS1R receptor.[2]

During women's menstrual cycles, estrogen levels will suppress the gonadotrophin secretion, but in the middle

of the cycle the effects of estrogen hormone on the hypothalamic-pituitary-ovarian axis will changes the positive feedback effect and causes a spike in plasma LH and then ovulation occurs. Evidence of an increase in hypothalamic-kisspetin signal plays a role in preovulatory LH generation, which is needed in women with normal menstrual cycles. Expression of the kisspeptin/KISS1R gene in ovarian cells is affected by the level of menstrual cycle, while its expression in the endometrium varies depending on the species. In human endometrium, the immunostaining of the kisspeptin peptide and KISS 1R is very strong and limited to epithelial cells and undetected in stromal cells.[3] Another study states that the expression of kisspeptin and KISS 1R are present in epithelial cells with weak or even inactive expression in endometrial stromal cells during the proliferation and initial secretion phases. However, the expression of kisspeptin is very prominent in endometrial cell stroma in the final secretion phase, this indicates that kisspeptin has a function in the desidualization of endometrium in adequate placenta preparation.[4] However, it is different in animals that endometrial cells shows no significant expression alteration of kisspeptin peptide and KISS 1R on changes in the ovarian cycle.[5] In animal experiments using cat as the subject, showed that the endometrium did not show significant changes of kisspeptin and KISS1R peptides expression on ovarian cells, besides the absence of kisspeptin or KISS1R expression alteration in both the epithelial gland and stromal cells during the menopause phase in humans, indicating that the kisspeptin/KISS1R system may not have a fundamental role in endometrium at this stage.

In mice's endometrial tissue, kisspeptin can trigger phosphorylation of p38 and ERK1 / 2 in the uterus on 4th day of pregnancy, this shows that kisspeptin/KISS1R can affect endometrial function in mice. In addition, the expression of KISS1 and KISS1R mRNA will gradually increase according to the stromal cell decidualization development in the endometrium of mice that have been removed by ovaries. The development of stromal cell decidualization will be significantly blocked when the expression of KISS1 is weakened by a small and disturbing RNA. A study shows that kisspeptin treatment can increase the mice blastocyst adhesion with collagen, this can occur because of the possibility through MMP down-regulation activity pathways (especially MMP-2 and MMP-9) through the ERK1/2 signaling pathway and protein kinase. [6]

Kisspeptin can inhibit the activity of matrix = metalloproteinase-9 (MMP-9) and MMP-2 by blocking the nucleus translocation system from xB (NF-xB) nucleus factor, and can also inhibit VEGF by stimulating the secretion of hormone secretion and the occurrence of apoptosis and inhibiting metastasis, migration, angiogenesis and proliferation.[7,8,9,10] Of the 4 kisspeptin, only kisspeptin-10 produces an increase in intracellular ca in trophoblast cells in the early phase of placentation and can inhibit trophoblast migration but not in cell proliferation, this indicates that kisspeptin-10 is a physiological activator of KISS1R in the human placenta. The same study also illustrates that kisspeptin-10 can stimulate decreased collegenase activity and reduce MMP-2 activity which results in a reduction in trophoblast migration.[11]

LIF is a cytokine needed for implantation, which is produced in the diuterine glandular epithelium which initiates embryonic and uterine communication which causes the embryo attach and decidualize the stroma.[12] In murine experimental animals that were removed by KISS 1, LIF was very weakly expressed on the uterine level on the day of implantation and when giving

exogenous LIF to those removed by KISS 1 could save the implantation factor in experimental rats.[13] Based on the data above indicates that kisspeptin is an upstream regulator of LIF[6] and the mechanism by which kisspeptin influences the implantation process by regulating LIF levels, where LIF can cause decidualization and implantation of the uterus by estrogen receptor ablation in mice,[14] so it was concluded that KISS 1 with E2 would stimulate LIF expression. Some studies indicate that the E2-kisspeptin-LIF pathway will regulate the process of implantation, so a clinical study states that a deficiency of plasma cispeptin on the day of HCG triggered will reduce the possibility of implantation in the uterus after ICSI.[15]

RESEARCHES IN KISS 1 R IN ASSISTED REPRODUCTIVE TECHNOLOGY

Table 1. Below are some research comparisons of Kisspeptin/KISS 1 R research in Assisted Reproductive Technology

No	Title (Authors)	Subject	Method	Result
1	Cross Talk Between Serum Kisspeptin - Leptin during Assisted Reproductive Techniques Rehana Rehman Zehra Jamil, Aqsa Khalid, Syeda Sadia Fatima	Females with an age range of 25 -37 years who have duration of unexplained infertility for more than two years	Cross Sectional Study from August 2015 until May 2017	Highest Kisspeptin and Leptin levels were seen in the normal weight group (374.80 ± 185.08ng / L; 12.78 ± 6.8 pg / ml) respectively, yet the highest number of clinical pregnancy was observed in overweight group (42%). A strong correlation of Kisspeptin with Leptin (r = 0.794, p = 0.001) was observed in the overweight females
2	Potential Roles for The Kisspeptin / Kiss Peptin Receptor System in Implantation and Placentation Kai-Lun Hu, Hsun- Ming Chang, Hong-Cui Zhao, Yang Yu, Rong, Li Jie Qiao	The search included human and other studies starting from the init ial identificatio n of kisspeptin in 1996 until July 2018	Literature searches using either PubMed or Google Scholar focuses on the advancement of kisspeptins and KISS1R in embryo implantation, placentation and early pregnancy-related complications.	The regulation of the kisspeptin system may negatively affect the processes of implantation as well as placentation. Clinical studies indicate that the circulating levels of kisspeptins or the expression levels of kisspeptin / KISS1R in the placental tissues may be used as potential diagnostic markers for women with miscarriage and gestational trophoblastic neoplasia.
3	Kisspeptin / kisspeptin Receptor system in the Ovary	A systemati c review of English-language publications	A systematic literature search was performed using PubMed and Web of	Uterine kisspeptin and KISS1R regulate embryo implantation by controlling the availability of endometrial glandular secretions, such as leukemia inhibitory

	Kai Lun Hu, Hong Cui Zhao Hsun Ming Chang Yang Yuand Jie Qihao	was carried out using th e following keywords: Kiss1, kisspeptin, metastin, KISS1R, GPR54, ovary, kisspeptin signaling	Science for all English-language articles up to November 2017.	factors, which are essential for embryo adhesion to the uterine epithelium.
4	Kisspeptin 10, a KiSS-I / metastin-derived decapeptide, is a physiological inasion of primary human trophoblasts. Bilban M, Ghaffari-Tabrizi N, Hintermann E, Bauer S, Molzer S, Zoratti C, Malli R, Sharabi A, Hiden U, Graier W et al.	mRNA signatures of trophoblast cell isolated from first trimester (high invasiveness) and term placentae (no / low invasiveness) were compared using U95A GeneChip microarrays yielding 220 invasion / migration related genes	Placental tissue was obtained after termination of normal pregnancies by vacuum suction; term placentae were collected after uncomplicated pregnancy and vaginal delivery. Tissues were immediately used for experiments or fixed for 48 hours in 20% formal n buffered with 0.1 M phosphate buffer, pH 7.4, embedded in paraffin and cut into 4 µm (immunohistoch emistry) or 7 µm (in situ hybridization) sections. Five different placentae with at least ten section of each were examined	In this 'invasion cluster', KISS-1 and its G-protein-coupled KISS-1R receptor were expressed at higher levels in the first trimester trophoblasts than at term of gestation. These results are identified as Kp-10 as a novel paracrine / endocrine regulator in fine-tuning the trophoblast invasion generated by the trophoblast itself.
5	Kisspeptin-54	6 male	This was a	Kisspeptin-54 infusion

	stimulates the hypothalamic-pituitary gonadal axis in human males Wajid S Dhillo, Owais B Chaudhri, Michael Patterson, Emily L Thompson, Kevin G Murphy, Michael K Badman, Barbara M McGowan, Vian Amber, Sejal Patel, Moh A Ghatel, Stephen R Bloom	volunteers were recruited. Each volunteer received a 90-min iv infusion of kisspeptin-54 (4 pmol / kg x min) and a control infusion of saline (0.9%) in random orders.	double-blind, placebo-controlled, crossover study	significantly increased plasma LH, FSH, and testosterone concentrations compared with saline infusion (mean 90-min LH: kisspeptin, 10.8 +/- 1.5 vs. saline, 4.2 +/- 0.5 U / liter, P <0.001; mean 90-min FSH: kisspeptin, 3.9 +/- 0.7 vs. saline, 3.2 +/- 0.6 U / liter, P <0.001; mean 180-min testosterone: kisspeptin, 24.9 +/- 1.7 vs. saline, 21.7 +/- 2.2 nmol / liter, P <0.001). The plasma half-life of kisspeptin-54 was calculated to be 27.6 +/- 1.1 min. The mean metabolic clearance rate was 3.2 +/- 0.2 ml / kg x min, and the volume of distribution was 128.9 +/- 12.5 ml / kg.
6	Kisspeptin-54 trigger egg maturation in women undergoingi n vitro fertilization Channa N. Jayasena, Ali Abbara, Waljit S. Dhillo	53 women were administered a single subcutaneous injection of kisspeptin-54	Following superovulation with recombinant follicle-stimulating hormone and administration of gonadotropin-releasing hormone antagonists to prevent premature ovulation, 53 women were administered a single subcutaneous injection of kisspeptin-54 (1.6 nmol / kg, n = 2; 3.2 nmol / kg, n = 2; 3; 6.4 nmol / kg, n = 24; 12.8 nmol /	Egg maturation was observed in response to each tested dose of kisspeptin-54, and the mean number of mature eggs per patient was generally increased in a dose-dependent manner. Fertilization of eggs and transfer of embryos to the uterus occurs in 92% (49/53) of kisspeptin-54-treated patients. Biochemical and clinical pregnancy rates were 40% (21/53) and 23% (12/53), respectively.

			kg, n = 24) to induce a luteinizing hormone surge and egg maturation. Eggs were retrieved transparently 36 hours after kisspeptin injection, assessed for maturation (primary outcome), and fertilized by intracytoplasmic sperm injection with subsequent transfers of one or two embryos.	
7	Kisspeptin-10 inhibits OHSS by suppressing VEGF secretion Junyu Zhai, Jiansheng Liu, Shigang Zha, Han Zhao, Zi Jiang Chen, Yanzhi Du, Weiping Li	A total of 18 immature 22-day-old female Wistar rats	The rats were randomly divided into three groups: the OHSS group, the OHSS + Kp-10 group and the control group. In the OHSS group, rats were subcutaneously injected with 10 IU PMSG for 4 consecutive days to promote follicular development. They were then given 30 IU hCG (sc) In the OHSS + Kp-10 group, the management was the same as the OHSS group except that the	Kp-10 prevents the increased VP of OHSS probably by the activation of KISS1R and the inhibition of VEGF.

			animals were given 30 IU hCG and 40 nmol Kp-10 (intravenous) together on day 5. In the control group, the 24-day-old rats were pretreated with 10 IU PMSG. Two days later, 10 IU of hCG was injected into the control group to mimic a routine ovarian stimulation	
8	Predictive value of serum kisspeptin concentration at 14 and 21 days after frozen-thawed embryo transfer Kai Lun Hu, Yongli Zhang, Zi Yang, Huiyu Xu, Yang Yu, Rong Li	133 patients undergoing frozen – thawed embryo transfer	Patients were divided into non-pregnant and pregnant groups (including biochemical pregnancy, singleton pregnancy, miscarriage and twin groups).	Serum kisspeptin levels on day 21 were significantly higher than day 14 in singleton pregnancy, miscarriage and twin groups (all $P < 0.0001$), but not in the biochemical pregnancy group. Similarly, human chorionic gonadotrophin (HCG) serum levels were higher on day 21 compared to day 14 except for the biochemical pregnancy group. Compared with the twin groups (296.9 pg / ml), the other four groups showed significantly higher serum kissing levels on day 14 (non-pregnant 548.9, biochemical pregnancy 440.4, miscarriage 434.9, singleton pregnancy group 420.9 pg / ml, $P < 0.01$, $P = 0.016$, $P = 0.034$, $P = 0.036$, respectively). The miscarriage (762.2 pg / ml), singleton pregnancy (730.8 pg / ml) and twin groups (826.3 pg / ml) had significantly higher kisspeptin levels than the biochemical pregnancy group (397.3 pg / ml) on day 21 ($P < 0.001$, $P < 0.01$. $P < 0.001$,

				respectively). Serum kisspeptin levels on day 14 were negatively correlated with embryo implantation rate (P = 0.035, R2 = –0.880). The serum kisspeptin levels on day 21 have a poor predictive value of miscarriage compared to serum HCG levels (area under the curve = 0.53 and 0.78, respectively). Serum kisspeptin levels on day 14 are negatively correlated with embryo implantation rate. The kisspeptin serum levels on day 21 have a poor predictive value of miscarriage.

DISCUSSION

Many study results shows that kisspeptin is very important in stimulation process in patients with Assisted Reproduction Technology. Dhillo et al in 2005 conducted a study of human kisspeptin test for the first time by injecting kisspeptin-54 intravenously for 90 minutes continuously, the result showed a steady increase of LH level in the blood in normal people (0.25-12 pmol/kg/min). Subcutaneous kisspeptin-54 injection can stimulate gonadotropin secretion in normal women, and body response to exogenous kisspeptin differs at various stages of the menstrual cycle: in the follicular phase, a small dose of kisspeptin-54 (0.4 nmol/kg) can only slightly increase LH serum level [(0.12 ± 0.17) IU/L]; but the same dose of kisspeptin-54 can increase LH serum level to 20.64 ± 2,91 IU/L in the pre-ovulation period. These results indicates that the use of Kisspeptin in vitro can induce LH peaks in pre-ovulation, but this is still needs further investigation whether Kisspeptin can be used to induce the in vitro fertilization cycle and play a role in the embryo transfer process.[20]

In 2014, Dhillo et al conducted tests to evaluate the feasibility of Kisspeptin as a trigger drug in the IVF-ET cycle. Tests carried out by giving women some single injections subcutaneously of Kisspeptin-54 in different doses: 1.6; 3.2; 6.4, and 12.8 nmol/kg at 36 hours before egg cell collection. After 12 to 14 hours of Kisspeptin-54 injection, an assessment of serum LH levels in each group was found higher than the baseline level. The results showed that the number of mature oocytes was positively correlated with Kisspeptin-54 dose, but had no effect on oocyte maturation rates. They also said that the peak duration of the LH peak caused by Kisspeptin-54 was shorter than the physiological LH peak.[21]

Experiments on mice have proven that giving Kisspeptin-10 from outside directly works on kisspeptin receptors in ovarian tissue and the lungs of mice with symptoms of OHSS (Ovarian Hyperstimulation Syndrome) by reducing the level of vascular permeability and endothelial growth factor (VEGF)), so as to reduce the incidence of OHSS risk. Giving KISS-10 injection from outside

can reduce VP (Vascular permeability) and VEGF by increasing KISS R in OHSS mice without affecting ovulation. Therefore the KISS-10 injection is very promising which can effectively and safely prevent OHSS. KISS-54 injection can also induces egg maturation and reduces the incidence of OHSS in women at high risk.[16]

Since the decline in KISS1R involved in the occurrence of OHSS, we have also conducted further investigation on the mechanism of serum estradiol levels on the day of the hCG trigger as an important indicator in predicting OHSS.[25,26,27] Moreover, the estradiol hormone can inhibit the transcription of KISS1R in pituitary cells. Estradiol inhibits the expression of KISS1R and increases VEGF and NO. Then, high estradiol levels will increase the risk of OHSS by inhibiting KISS 1R which will result in an increase of VEGF and VP which can cause edema, ovarian enlargement and pleural effusion. Estradiol not only suppresses KISS 1 R in endothelial cells but also regulates the expression of KISS1 in the arctic nucleus (ARC) with negative feedback (Smith 20005). This is consistent with the hypothesis that high estradiol levels will inhibit KISS1/KISS1 R and induce OHSS events.

Hu et al, 2019 also analyzed the relationship between Early pregnancy results of 133 patients' frozen embryo transfer and kisspeptin concentration in the blood at 14 days and 21 days after frozen embryo transfer, and found that blood kisspeptin concentration at 14 days after embryo transfer was negatively correlated with embryo implantation rates, whereas blood kisspeptin results on day 21 after embryo transfer has a poor predictive value for miscarriage compared to serum blood HCG levels (area under the curve 0.53 and 0.78 respectively).[24]

CONCLUSION

Kisspeptin/KISS 1 receptor gene expression is involved in many reproductive physiology processes and also very important in ART (assisted reproductive technology) such as in oocyte maturity, it helps the formation of LH peaks before ovulation and also ovulation processes, moreover it plays a role in embryo implantation and predicts pregnancy and prevent the ovarian hyperstimulation syndrome as a complication due to ART program.

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