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REVIEW ARTICLE

Potential use of kisspeptin in ovarian stimulation treatments

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KEYWORDS
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Abstract
Introduction: Kisspeptin hormone has been recently suggested as a new candidate drug to indirectly stimulate secretion of gonadotropins providing a more physiological approach to the ovarian function, due to concerns about the use of gonadotropins such as the risk of ovarian hyperstimulation syndrome (OHSS). This review describes and compares the results of those clinical trials carried out hitherto with exogenous administration of kisspeptin on humans, with special interest on those focused on healthy women. In addition, the potential use of this hormone on programming and inducing ovulation as an alternative for choriogonadotropin (CG) and GnRH agonists in controlled ovarian stimulation (COS) is also addressed.
Material and methods: MEDLINE/Pubmed (US National Library of Medicine) database was searched for articles published between 2000 and 2014. All searches included the terms 'kisspeptin', 'ovarian stimulation' and 'infertility'. Special interest was given to clinical trials.
Results: Administration of kisspeptin seems effective in activating the LH surge in women. All trials reported high increases of LH above baseline levels in the preovulatory phase of the cycle. Recent results indicate that a single subcutaneous injection of kisspeptin-54 is enough to induce egg maturation. This strategy might offer the advantage of avoiding OHSS and without the necessity of following a freeze-all strategy as pregnancy rates are maintained after its use. Furthermore, clinical trials show that administration of this hormone is not harmful for women and does not affect their reproductive physiology.
Discussion: If kisspeptin is able to offer an acceptable ratio of metaphase II oocytes per follicle aspirated with no risk of OHSS and without affecting pregnancy rates in fresh cycles it would be definitely a good option for triggering. Before implementing its routine use, well-designed studies should be carried out in the human model in order to compare IVF results between the different types of triggering proposed to date.

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PALABRAS CLAVE
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Hormona candidata

Uso potencial de la Kisspeptina en tratamientos de estimulación ovárica

Resumen
Introducción: La hormona kisspeptina se ha revelado recientemente como una nueva candidata para la estimulación indirecta de la secreción de gonadotropinas, brindando un efecto más parecido al comportamiento fisiológico del ovario, con el objetivo de evitar riesgos asociados al uso de gonadotropinas, tales como el síndrome de hiperestimulación ovárica (SHO). Esta revisión describe y compara los resultados de los ensayos clínicos efectuados hasta la fecha, con administración exógena de kisspeptina en seres humanos, centrados principalmente en mujeres sanas. Además, se analiza el uso potencial de esta hormona en la práctica clínica, específicamente para la programación y la inducción de la ovulación como alternativa a la gonadotropina coriónica y los agonistas de GnRH en tratamientos de estimulación ovárica.
Materiales y métodos: Se realizaron búsquedas en la base de datos MEDLINE/Pubmed (US National Library of Medicine) de artículos publicados entre 2000 y 2014. Todas las búsquedas incluyeron los términos 'kisspeptina', 'estimulación ovárica' e 'infertilidad'. Se prestó especial interés a las publicaciones sobre ensayos clínicos.
Resultados: En mujeres infértiles la kisspeptina parece resultar eficaz, al activar el pico de LH durante la estimulación ovárica. Los resultados recientes indican que basta con una inyección subcutánea de Kisspeptina-54 para inducir la maduración ovocitaria. Esta hormona podría ofrecer la ventaja de evitar el riesgo de SHO sin tener que llevar a cabo una estrategia de ''congelar todo'', si se mantienen las tasas de embarazo tras su uso. Además, los ensayos clínicos muestran que la administración de esta hormona no presenta efectos adversos en las pacientes y no afecta a su fisiología reproductiva.
Discusión: Si la kisspeptina ofreciera un ratio aceptable de ovocitos metafase II por folículo aspirado sin riesgo de SHO, y sin afectar a las tasas de embarazo en ciclos en fresco, constituiría una muy buena opción para programar e inducir la ovulación. Sin embargo, antes de implementar su uso en la práctica clínica habitual, se deben ejecutar más ensayos clínicos aleatorizados para determinar las dosis apropiadas y poder comparar los resultados clínicos con otros inductores de la ovulación propuestos hasta la fecha.

Introduction

The use of gonadotropins for ovarian stimulation in assisted reproductive treatments (ART) to increase chances of pregnancy insofar as more than a single oocyte is obtained is extensive. Since these drugs were introduced into clinical practice, there is concern about the potential risks derived from their use, such as onset of ovarian hyperstimulation syndrome (OHSS), that is usually mild or moderate, but can be severe or even lethal in some cases (Whelan and Vlahos, 2000). After becoming aware of this problem and attempts having been made to avoid it, in the last decade some strategies have been described to prevent OHSS; e.g., ovulation induction with gonadotropin-releasing hormone (GnRH) agonist in the GnRH antagonist treatment context (Humaidan et al., 2011) to prevent early onset of OHSS; or oocyte and embryo vitrification to prevent late onset of OHSS (Martinez et al., 2013).

Agonist triggering induces LH to peak by simulating the physiological mechanism of final oocyte maturation and ovulation. Its advantage lies in the fact that it avoids the administration of choriogonadotropin (CG) which, in some cases, is the origin of vascular endothelial growth factor (VEGF) release. This, in turn, causes increased capillary permeability and, therefore, the most serious manifestations of OHSS (Soares, 2012).

In the last 10 years, the kisspeptin system, composed of the ligand kisspeptin encoded by the *Kiss1* gene and its receptor GPR54 or KissR, has generated interest (Pasquier et al., 2014) and kisspeptin has been proposed as a new drug candidate to substitute all these hormones. In humans, kisspeptin is capable of inducing the luteinizing hormone (LH) surge, thus it could be used to trigger ovulation in controlled ovarian stimulation (COS) treatments with the additional advantage of avoiding OHSS and providing a similar behaviour to the ovarian physiology (Thomsen and Humaidan, 2015).

Kisspeptin (Kp or Kiss) is a peptide hormone secreted in the hypothalamus, but it is also produced in other tissues such as the placenta, and in very large amounts (Horikoshi et al., 2003). To date, isoforms Kp-10 and Kp-54 have been widely studied and isolated, and their numbers refer to the amount of the peptide's amino acids. All the isoforms of kisspeptin come from a 145-amino acid precursor encoded by the KiSS1 gene, and a C-terminal RF-amide decapeptide is responsible for both its affinity to the receptor and its biological activity (Kotani et al., 2001).

Scientific and academic interest shown in the therapeutic potential of this hormone increased after the discovery that some patients with Hypogonadotropic Hypogonadism (HH) presented mutations in the gene of protein receptor GPR54, which is found in GnRH secretory fibres and whose ligand is