Ovarian hyperstimulation syndrome (OHSS) due to mutations in the follicle-stimulating hormone receptor

Syndromes d’hyperstimulation ovarienne dus à des mutations du récepteur de la FSH

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Résumé

Le syndrome d’hyperstimulation ovarienne est généralement une complication des procédures de procréation médicale assistée, plus rarement une complication de grossesses spontanées. La cause de l’hypersensibilité ovarienne aux gonadotrophines utilisées dans les stimulations contrôlées est encore largement méconnue. En revanche, quelques cas d’hyperstimulation ovarienne spontanée ont été élucidés avec l’identification de mutations du récepteur de la follicle-stimulating hormone (FSH) qui élargissent sa spécificité et le rendent hypersensible à la stimulation par l’human chorionic gonadotropin (hCG). De façon surprenante, les mutations étaient localisées dans le domaine transmembranaire du récepteur et pas dans le domaine extracellulaire de liaison de l’hormone. Il n’a pas été retrouvé de telle mutation dans les cas d’hyperstimulation iatrogène. Cependant, il existe une association entre les variants alléliques du récepteur de la FSH et la réponse à la FSH lors des stimulations, ainsi qu’avec la sévérité du syndrome d’hyperstimulation ovarienne lorsqu’il est présent.

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Mots clés : Syndrome d’hyperstimulation ovarienne ; Mutations du récepteur de la FSH

Abstract

Ovarian hyperstimulation syndrome (OHSS) is usually a complication of assisted reproductive techniques, more rarely an affection complicating a spontaneous gestation. The cause of hyper responsiveness of ovaries to the gonadotropins used in the controlled stimulation is still largely unknown. In contrast, a few cases of spontaneous hyperstimulation syndrome have been elucidated by the identification of mutations of the follicle-stimulating hormone (FSH) receptor, broadening its specificity and making it hypersensitive to human chorionic gonadotropin (hCG). Surprisingly, the mutations were located in the transmembrane domain of the receptor rather than in the extracellular hormone-binding site. No such mutation has been found in iatrogenic cases. However, allelic variants of the FSH receptors have been associated with the response to FSH in stimulation procedures, as well as with the severity of OHSS when present.

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Ovarian hyperstimulation syndrome (OHSS) most frequently occurs as a complication of assisted reproductive techniques (ART) with a frequency for moderate to severe forms ranging from 0.2 to 5% of cycles [1,2]. It is characterized by an increase in the size of ovaries, which harbour multiple, sometimes hem-
or hemorrhagic cysts. Also, an increase in body fluids, due to enhanced capillary permeability [3], with peritoneal and pleural effusion is observed, eventually associated with multi-organ failure, electrolytes and coagulation disturbances and the risk of a fatal issue in the most severe forms. Women affected by OHSS are viewed as hyperresponsive to stimulation with follicle-stimulating hormone (FSH) or human chorionic gonadotropin (hCG) or both, and FSH receptor has been largely studied in these women, looking for polymorphisms or mutations that could explain this hypersensitivity [4–8]. Usually, the OHSS can be predicted, by a high concentration of circulating estradiol [9], although this is debated [10], and a high follicular count, before the injection of hCG and the retrieval of oocytes. The temporary withhold of FSH injections until estradiol declines, the so-called coasting usually allows for avoidance of OHSS. This suggests that the ovaries are essentially hyperresponsive to FSH. However, in some cases the hyperstimulation starts a little later which could indicate an abnormal sensitivity to hCG. The controversy regarding the predictive value of estradiol concentration may be due to these two forms of OHSS differing by their timing [2,11].

The same mutation was identified in two of her sisters who she went through, we identified a germline false sense mutation in a patient affected by OHSS during each of the pregnancies: the intensity of response growing from the S/S, through S/N to N/N genotype. Similarly, the spontaneous length of the follicular

1. The follicle-stimulating hormone receptor in spontaneous ovarian hyperstimulation syndrome

After the description of a mutation of the thyrotropin receptor’s extracellular domain broadening its specificity, thus allowing it to be stimulated by hCG and leading to familial recurrent gestational thyrotoxicosis [16], we made the hypothesis that a similar mechanism, though involving the FSH receptor may be responsible for some cases of OHSS, either iatrogenic or spontaneous.

By sequencing the coding sequence of FSH receptor gene in a patient affected by OHSS during each of the pregnancies she went through, we identified a germline false sense mutation. The same mutation was identified in two of her sisters who had had an OHSS also [17]. A hypersensitivity of the mutant receptor to hCG was demonstrated in vitro. In the same period another mutation leading to the same phenotype was also identified by the Vassart’s group in Brussels. Interestingly enough, inhibin B, a marker of the action of FSH on granulosa cells, normally absent during gestation, was elevated during pregnancy in the first patient. By repeated measurement we could show that it had a kinetic parallel to the one of hCG, demonstrating in vivo the illegitimate stimulation of the FSH receptor by hCG [17].

The surprise came from the location of the mutation in the FSH receptor. In both cases, it was localized in the transmembrane, or serpine domain of the FSH receptor, whereas the binding site for the hormone, and the as yet identified determinants of specificity are located in the large extracellular domain.

A few other mutations have been found in cases of spontaneous OHSS, all but one located in the serpine domain [18–21].

Besides the enhanced sensitivity to stimulation by hCG, the mutant receptors display an increased basal activity, i.e. a production of cAMP, the second messenger, in absence of ligand. Furthermore, this constitutive activity correlates with the sensitivity to hCG. The higher the spontaneous activation the higher the response to hCG is. In addition, the mutant receptors were shown to respond to thyrotropin also [20]. In contrast to the mutation found in the up to now unique case of hereditary gestational thyrotoxicosis, where illegitimate response of the thyrotropin receptor was restricted to stimulation by hCG [16,22], the mutations of the serpine domain of the FSH receptors led to a real loss of specificity. The mutation identified in the extracellular domain in one case of spontaneous OHSS [19] as well as the artificial mutations generated in a systematic search for the determinants of specificity [23], preserved some degree of specificity, allowing hCG only to stimulate the mutant FSH receptor. The identification of these mutations led to a modification of models of activation of this class of receptors. The dichotomy between the extracellular domain, where the hormone binds and the serpine domain, responsible for the signal transduction, is still valid but the serpine domain of the FSH, strictly constrained, prevents the signal transduction of low affinity interaction between the extracellular domain and illegitimate ligands. As proposed by Costagliola et al., [14] a binding specificity and a functional specificity rely on both overlapping and different parts of the receptor.

2. The follicle-stimulating hormone receptor in iatrogenic ovarian hyperstimulation syndrome

Mutations have been extensively looked for without success in cases of iatrogenic OHSS [4].

In addition, the relationship between some polymorphisms of the FSH receptor and OHSS has been investigated. Several studies have linked the presence of variants at position 680 of the FSH receptor to the response to stimulation in ART procedures. The cumulated dose of FSH necessary to induce a (controlled) hyperstimulation of ovaries appears to be correlated to the presence of a serine (S) or an asparagine (N) at position 680. The S allele is associated with higher doses and poorer response in contrast to the N allele, in different ethnic backgrounds [5–8]. Several studies have found a dosage effect of these variants with the intensity of response growing from the S/S, through S/N to N/N genotype. Similarly, the spontaneous length of the follicular
cycle and the spontaneous FSH concentration in early days of the cycle have been associated to these polymorphisms [24]. No significant relation between the occurrence of iatrogenic OHSS and the polymorphisms has been documented. However, the severity of the OHSS when present was higher in patients with the N variant [25,26].

3. The follicle-stimulating hormone receptor in ovarian hyperstimulation syndrome associated with severe hypothyroidism

Spontaneous OHSS has also been described in few cases of severe primary hypothyroidism, which are spontaneously cured by the recovery of euthyroidism. Because, the few mutations identified in spontaneous OHSS made the receptor sensitive to TSH also, the same mechanism was expected to be involved in OHSS secondary to severe hypothyroidism. The analysis of the FSH receptor gene did not reveal any mutation in these exceptional cases [18]. In addition, the polymorphic variants of the FSH receptor did not display any difference in sensitivity to TSH [27]. It is proposed that the very high concentration of TSH by itself is sufficient to stimulate the FSH receptor and to produce the hyperstimulation syndrome.

4. Conclusions and perspectives

Mutations of the FSH receptor have been identified in a limited number of cases of OHSS. The characterization of the mutants has brought to light some of the mechanisms of activation and maintenance of specificity of the receptors for glycoprotein hormones. Such cases, although rare, are extremely precious in that view and should be systematically investigated to further progress in our knowledge of OHSS and reproduction. In particular, the dosage of inhibin B in spontaneous cases of OHSS is of great value to identify the patients in which an abnormal stimulation of the FSH receptor-signalling pathway is involved. The hyperresponsiveness to gonadotropins of some patients during ART requires further studies to be elucidated.

5. French version

A French version of this article is available at doi:10.1016/j.jando.2010.02.019.

Conflict of interest

The authors have not declared any conflict of interest.

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