

BRIEF REPORT

Ovarian Hyperstimulation Syndrome Due to a Mutation in the Follicle-Stimulating Hormone Receptor

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THE OVARIAN HYPERSTIMULATION SYNDROME MOST OFTEN OCCURS AS an iatrogenic complication of ovarian-stimulation treatments for in vitro fertilization (the incidence of severe forms ranges from 0.5 to 5 percent).¹ The clinical manifestations vary from abdominal distention and discomfort to potentially life-threatening, massive ovarian enlargement and capillary leak with fluid sequestration in a third space.² Although the presence of human chorionic gonadotropin is invariably associated with the condition, the pathophysiological mechanism remains undefined.³

The overproduction of endogenous chorionic gonadotropin during pregnancy has been associated with spontaneous ovarian hyperstimulation syndrome (also termed hyperreactio luteinalis of the first trimester), as well as with hyperemesis gravidarum and transient gestational thyrotoxicosis.⁴⁻⁷ Transient gestational thyrotoxicosis appears to be due to the promiscuous activation of the thyrotropin receptor by chorionic gonadotropin,⁵ but the pathogenesis of hyperemesis gravidarum is incompletely delineated.

In 1998, we described a family with recurrent, severe gestational thyrotoxicosis caused by a mutant thyrotropin receptor that had abnormal sensitivity to normal chorionic gonadotropin levels.⁸ That observation, together with descriptions in the literature of severe cases of spontaneous (sometimes recurrent) ovarian hyperstimulation syndrome with normal levels of chorionic gonadotropin,⁶ led us to postulate that a mutation in the follicle-stimulating hormone receptor might be associated with ovarian hyperstimulation syndrome. The case we present here defines a mutation in the follicle-stimulating hormone receptor that is associated with recurrent, spontaneous ovarian hyperstimulation syndrome.

CASE REPORT

The clinical aspects of this case have been described previously.⁹ Briefly, a woman who is now 40 years of age (height, 1.52 m; weight, 69 kg) presented with spontaneous ovarian hyperstimulation syndrome during each of her four pregnancies (Table 1). A family history revealed that her mother had had uneventful pregnancies (DNA was not available for analysis); the patient's sister is nulligravid, and her father is deceased. During the patient's first pregnancy at 24 years of age, transabdominal ultrasonography at 13 weeks of gestation revealed that both ovaries were multicystic and enlarged. Acne had also developed, as well as increased hair growth on the abdominal wall. The plasma levels of ovarian and adrenal androgens were normal. The diagnosis of theca lutein cysts was made, and the patient was treated conservatively; she delivered a normal, healthy, term female infant weighing 2635 g. The patient's ovaries had returned to their normal size by eight weeks after delivery.

During the patient's second pregnancy at 26 years of age, ultrasonography at 14 weeks again revealed enlarged, multicystic ovaries bilaterally. The condition was man-

Table 1. Clinical Data Related to the Four Pregnancies Associated with Spontaneous Ovarian Hyperstimulation Syndrome.*

Week of Gestation at First Ultrasonographic Examination	Ovaries	Symptoms	Human Chorionic Gonadotropin Level	Diagnosis	Management	Fetal Outcome	Follow-up Ultrasonography
1st pregnancy 13	Enlarged, multicystic	NA	NA	Theca lutein cysts	Untreated	Term delivery, healthy girl, 2635 g	Complete regression at 8 wk post partum
2nd pregnancy 14	Enlarged, multicystic	Fluid visible in pelvis and right hypochondrium on ultrasonography	NA	Spontaneous ovarian hyperstimulation syndrome, grade IV	Untreated	Fetal death in utero at 41.5 wk, 2800 g	Complete regression at 12 wk post partum
3rd pregnancy 9	Enlarged, multicystic	Hydrothorax, abdominal distention with ascites; fluid visible in abdomen and pelvis on ultrasonography	56,200 (9 wk); 21,380 (10 wk 3 days); 7430 (10 wk 5 days)	Spontaneous ovarian hyperstimulation syndrome, grade IV	Paracentesis	Nonviable fetus at 10 wk 3 days; curettage at 10 wk 6 days	Complete regression 8 wk after miscarriage
Before pregnancy	Multiple subcapsular follicles, 5–8 mm in diameter						
4th pregnancy 8	Enlarged, multicystic; thin hyper-echogenic follicular walls and intrafollicular hemorrhage	Hydrothorax, abdominal distention with ascites; fluid visible in abdomen and pelvis on ultrasonography	101,190 (8 wk)	Spontaneous ovarian hyperstimulation syndrome, grade IV	Paracentesis	Term delivery, healthy boy, 2860 g	Complete regression at 8 wk post partum

* The week of gestation was the number of weeks since the last menstrual period. The classification criteria defined by Golan et al.² were used for diagnosis. NA denotes not available.

aged conservatively, and the pregnancy seemed uneventful until the fetus died in utero at 41.5 weeks. Postmortem examination revealed no fetal abnormality. Again, the patient's ovaries had returned to their normal size by 12 weeks after delivery yet appeared polycystic on ultrasonography.

During the patient's third pregnancy at 29 years of age, she presented with dyspnea and painful abdominal distention after nine weeks of amenorrhea. Evaluation revealed hydrothorax, ascites, and enlarged, multicystic ovaries bilaterally, findings consistent with a diagnosis of severe (grade IV) ovarian hyperstimulation syndrome.² Ultrasonography revealed a viable intrauterine pregnancy. The patient's serum β human chorionic gonadotropin level was 56,200 mIU per milliliter (normal values for 9 to 11 weeks of gestation, 48,000 to 144,000 mIU per milliliter). The thyrotropin level was normal (2 μ IU per milliliter). The hematocrit was 39 percent, and the prothrombin time, the activated partial-thromboplastin time, the bleeding time, and platelet count were normal. During the next two weeks, multiple paracenteses yielded 11 liters of ascitic fluid. However, ultrasonography at 10.5 weeks revealed a nonviable fetus. The dead fetus was removed by curettage, and the patient's symptoms improved rapidly. The ovaries had returned to their normal size by eight weeks later.

Two years later, the patient consulted us regarding secondary infertility. At that time, her menstrual cycles occurred at regular 30-day intervals. General physical examination and pelvic examination were normal. Ultrasonography revealed typical polycystic ovaries (Table 1). At day 3 of her menstrual cycle, the follicle-stimulating hormone level was normal (7 IU per liter), and the luteinizing hormone level was elevated (18 IU per liter). She became pregnant without treatment. However, eight weeks into a viable singleton pregnancy, the patient again presented with grade IV ovarian hyperstimulation syndrome. The serum β human chorionic gonadotropin level was normal (101,190 mIU per milliliter), the estradiol level was moderately elevated (3270 pg per milliliter [12,004 pmol per liter]), the progesterone level was elevated (12,200 ng per deciliter [388 nmol per liter]), and the thyrotropin level was normal (1.2 μ IU per milliliter). The patient was treated conservatively, and both the size of the ovaries and the ascites gradually decreased during the pregnancy. At term, the patient delivered a healthy male infant weighing 2860 g. Eight weeks after delivery the patient's ovaries had returned to their normal

size. The patient provided written informed consent for this study, which was approved by the ethics committee of the Erasme Hospital in Brussels, Belgium.

METHODS

SEQUENCING OF THE GENE FOR THE FOLLICLE-STIMULATING HORMONE RECEPTOR

DNA was extracted from peripheral-blood leukocytes, and the sequences of all exons of the gene for the follicle-stimulating hormone receptor together with intron-exon junctions were determined as described by Gromoll et al.,¹⁰ with minor modifications (sequences of primers appear in Supplementary Appendix 1, available with the full text of this article at <http://www.nejm.org>). The sequence of the segment harboring the mutation was determined in the product of two independent polymerase chain reactions (PCRs).

FUNCTIONAL CHARACTERIZATION OF THE MUTATION

The mutation identified in the gene for the follicle-stimulating hormone receptor was introduced into complementary DNA (cDNA) of human wild-type follicle-stimulating hormone receptor inserted in an expression vector (pSVL, Pharmacia) with the use of site-directed mutagenesis (QuickChange, Stratagene).¹¹ The sequence of the segment containing the mutation was verified in both strands.

Plasmids encoding human wild-type follicle-stimulating hormone receptor, luteinizing hormone-chorionic gonadotropin receptor, thyrotropin receptor, or mutant follicle-stimulating hormone receptor were transfected into COS-7 cells, which are derived from fibroblasts from the kidneys of African green monkeys, as described elsewhere.¹¹ Expression on the cell surface was assessed by flow cytometry (FACScan, Becton Dickinson) with mouse monoclonal antibodies (5B2 for follicle-stimulating hormone receptor, 16B5 for luteinizing hormone-chorionic gonadotropin receptor, and BA8 for thyrotropin receptor).¹² Forty-eight hours after transfection, the intracellular accumulation of cyclic AMP (cAMP) was measured at base line and after incubation for 60 minutes with various concentrations of recombinant human follicle-stimulating hormone (Puregon, Organon), recombinant human chorionic gonadotropin (Sigma Chemical), or recombinant human thyrotropin (Thyrogen, Genzyme).¹¹

RESULTS

SEQUENCE DETERMINATION

Direct sequencing of PCR products amplified from genomic DNA of the patient revealed a heterozygous substitution of adenine for guanine at the first base of codon 567 in exon 10 of the gene for the follicle-stimulating hormone receptor, resulting in the replacement of aspartic acid with asparagine (D567N [numbering begins at the first amino acid of the signal peptide of the protein]; GenBank accession number, M65085) (Fig. 1A). Aspartate 567 is conserved in all three glycoprotein-hormone receptors; it is located at the cytoplasmic extremity of the sixth helix of the transmembrane domain (Fig. 2A). The mutation destroys a Tsp45I restriction site (Fig. 1B), resulting in an easy means of screening for the general population. None of 100 unrelated normal subjects carried the mutation, ruling out the possibility of a common polymorphism.

FUNCTIONAL CHARACTERIZATION OF THE MUTANT RECEPTOR

Despite a lower level of expression at the cell surface than that of the wild-type receptor (mean [\pm SE] expression values, 69 ± 3 percent of the wild-type-receptor expression value), the mutant receptor was found to have basal cAMP accumulation in transiently transfected COS-7 cells that was three times as high as that of the wild-type receptor (Fig. 2A). The sensitivity of the mutant receptor to recombinant human follicle-stimulating hormone was identical to that of the wild-type receptor, but the maximal response was slightly greater (Fig. 2B). In contrast, although recombinant human chorionic gonadotropin in concentrations of up to 300 IU per milliliter was only slightly effective in cells expressing the wild-type follicle-stimulating hormone receptor, it caused a clear concentration-dependent increase in cAMP accumulation in cells expressing the mutant receptor (Fig. 2C). Despite this gain of function in terms of the stimulation of cAMP production by chorionic gonadotropin, the mutant follicle-stimulating hormone receptor remains about 1/1000 as sensitive to this hormone as the wild-type luteinizing hormone-chorionic gonadotropin receptor (Fig. 2C). The decrease in the specificity of the mutant receptor was not restricted to chorionic gonadotropin. Indeed, recombinant human thyrotropin, in concentrations of up to 30 mIU per milliliter, also caused a clear concentration-dependent

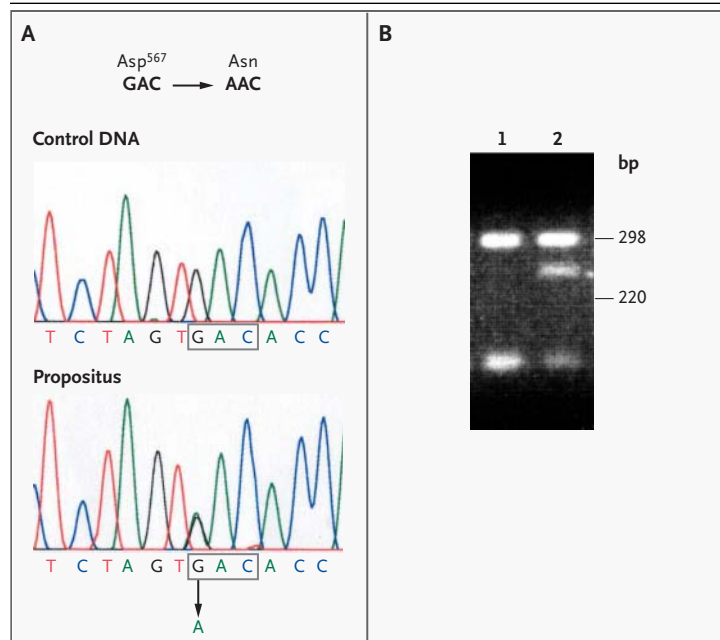


Figure 1. Detection of the D567N Mutation.

Panel A shows nucleotide-sequence traces of follicle-stimulating hormone receptor around codon 567, in a control subject and in the patient with recurrent spontaneous ovarian hyperstimulation syndrome. The control subject is homozygous for the wild-type allele (GAC, Asp), whereas the patient is heterozygous for a G→A substitution in the first position of codon 567 (GAC→AAC, Asp→Asn). Panel B illustrates the results of a restriction-fragment-length polymorphism assay for the detection of D567N. PCR was used for specific amplification of a 530-bp segment of exon 10 of the follicle-stimulating hormone receptor centered on the mutation (primers for exon 10C are listed in Supplementary Appendix 1, available with the full text of this article at <http://www.nejm.org>). Tsp45I cleaves twice the 530-bp PCR product obtained from the DNA of control subjects, generating one fragment of 290 bp and two fragments of 120 bp each (lane 1). The D567N mutation destroys the second Tsp45I restriction site, thus generating a mutation-specific band at 240 bp. Since the patient is heterozygous, the restriction pattern obtained with her DNA was a superposition of the two patterns (lane 2).

increase in cAMP production in cells containing the mutant follicle-stimulating hormone receptor but only a minimal increase in cells containing the wild-type receptor (Fig. 2D).

The binding affinity of the D567N mutant receptor for follicle-stimulating hormone was similar to that of the wild-type receptor (data not shown). No substantial displacement of labeled follicle-stimulating hormone by chorionic gonadotropin or thyrotropin could be observed in binding experiments, whether involving the mutant receptor or the wild-type receptor (data not shown).

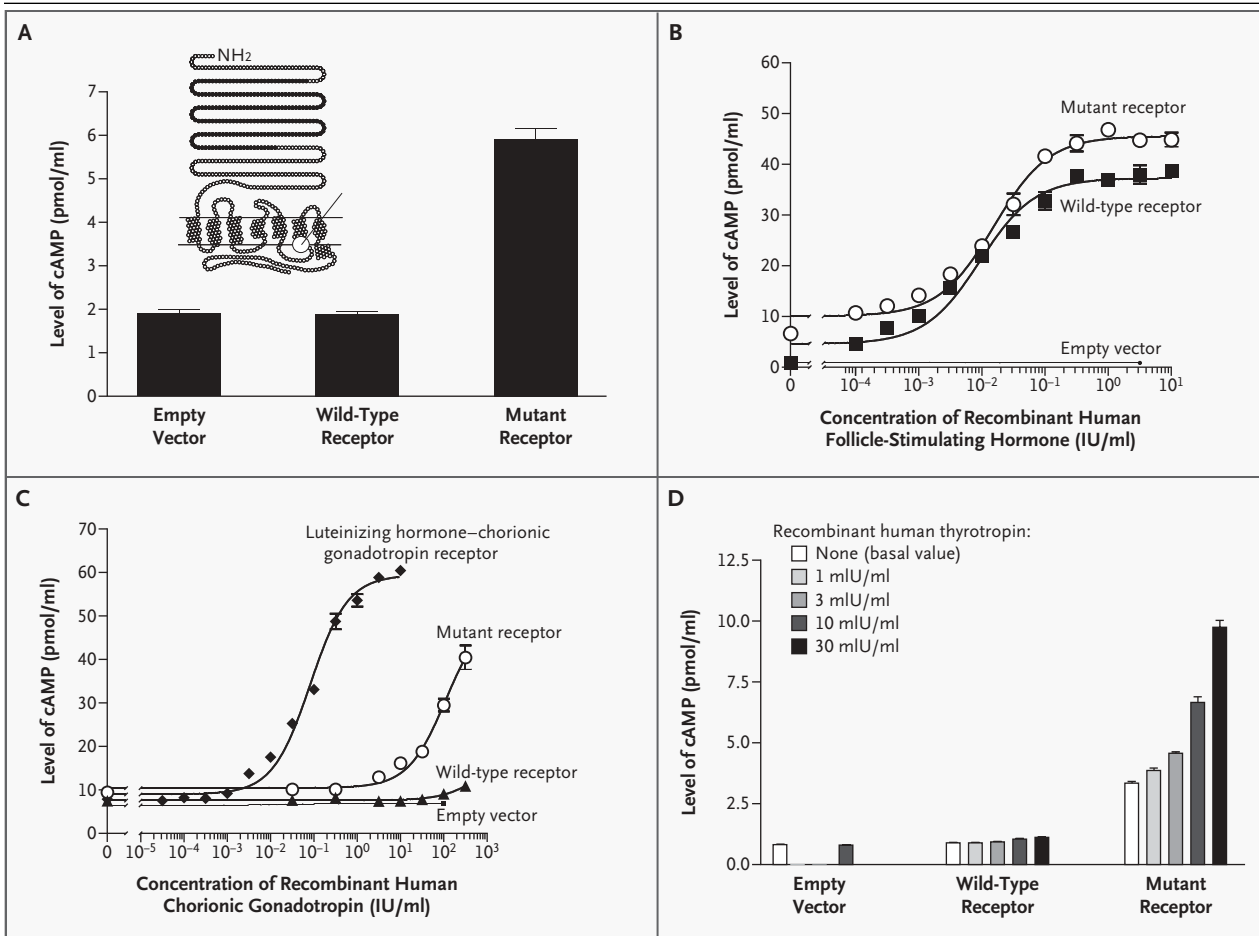


Figure 2. Functional Characterization of the D567N Mutation.

Panel A shows the levels of cAMP observed with cells transfected with the empty vector, wild-type follicle-stimulating hormone receptor, and mutant follicle-stimulating hormone receptor, in the absence of any stimulation by a hormone. Basal production of cAMP was three times as high in cells expressing the mutant D567N receptor as in cells expressing the wild-type receptor. The inset is a schematic representation of follicle-stimulating hormone receptor with the location of the D567N mutation highlighted. The seven transmembrane helices are shown as helical nets. Solid circles in the N-terminal extension represent the portion of the ectodomain that is rich in leucine repeats, which is responsible for high-affinity hormone binding. Panels B, C, and D show the levels of cAMP observed with cells transfected with empty vector, wild-type, and mutant D567N follicle-stimulating hormone receptors (Panel B) or luteinizing hormone–chorionic gonadotropin receptor (Panel C), during stimulation with increasing concentrations of recombinant human follicle-stimulating hormone (Panel B), recombinant human chorionic gonadotropin (Panel C), or recombinant human thyrotropin (Panel D). The mean effective concentration of recombinant human follicle-stimulating hormone causing a 50 percent increase in activation (EC_{50}) of the wild-type receptor was 0.009 ± 0.001 IU per milliliter; the EC_{50} for the D567N mutant receptor was 0.015 ± 0.002 IU per milliliter. COS-7 cells transiently transfected with the various constructs were stimulated by increasing concentrations of recombinant hormones, and intracellular cAMP values were determined by radioimmunoassay. Prism software, version 3.03 (GraphPad Software), was used to fit the curves and to calculate the EC_{50} . Each graph represents the results of at least two separate experiments. I bars represent standard errors.

DISCUSSION

Deriving from a common ancestor, the hormone-specific beta subunits of the four glycoprotein hormones (thyrotropin, follicle-stimulating hormone, luteinizing hormone, and chorionic gonadotropin)

are substantially similar. The three corresponding receptors (thyrotropin receptor, luteinizing hormone–chorionic gonadotropin receptor, and follicle-stimulating hormone receptor) also most likely evolved from a common ancestral gene. These receptors constitute a subfamily of G-protein–coupled

receptors characterized by a serpentine, rhodopsin-like domain with seven transmembrane helices that are responsible for the activation of intracellular regulatory cascades (e.g., the adenylyl cyclase-dependent generation of cAMP, in the present case) and an extracellular domain that is responsible for recognition and binding of specific hormones.¹³⁻¹⁵ In this evolutionary context, it would be expected that the extremely high level of chorionic gonadotropin achieved during pregnancy in primates could override the barrier of specificity and thus stimulate the thyrotropin or follicle-stimulating hormone receptors — in so-called promiscuous stimulation (Fig. 2C).^{5,16}

The substitution of asparagine for aspartate 567 at the cytoplasmic end of transmembrane helix VI (Fig. 2A) causes an increase in the basal activity of the mutant receptor, which also becomes abnormally sensitive to both chorionic gonadotropin and thyrotropin. The first characteristic is in accord with the findings that a different substitution of the same residue (D567G), which has been reported in a man,¹⁷ and mutations of the homologous residues in other G-protein-coupled receptors have caused an increase in basal activity.¹⁸⁻²⁰ It is more difficult to explain the decreased specificity, since aspartate 567 is clearly located outside of the hormone-binding domain. According to our current model, the activation of glycoprotein hormone receptors would take place in two steps: first, the ligand would bind to the ectodomain (the extracellular portion of the receptor); second, the ligand-ectodomain complex would interact with the serpentine (transmembrane) portion of the receptor and activate it.²¹ Given the identical ligand-binding characteristics of the wild-type and mutant receptors, the small but definite stimulatory effects of chorionic gonadotropin and thyrotropin on the wild-type follicle-stimulating hormone receptor and the higher maximal response of the mutant receptor to follicle-stimulating hormone lead us to hypothesize that the mutation of aspartate 567 would facilitate the second step by releasing an inhibitory constraint that is normally present in the serpentine domain of all G-protein-coupled receptors.²⁰

On the basis of the observation that the effects of a single amino acid substitution in the follicle-stimulating hormone receptor can closely mimic pharmacologically induced ovarian hyperstimulation syndrome, it is tempting to speculate that there is a parallel between the phenotype of the mutant receptor *in vitro* and the pathophysiology of the iatrogenic

disease: During controlled ovarian stimulation, the administration of exogenous follicle-stimulating hormone induces recruitment and growth of multiple antral follicles, and ovulation is triggered by the administration of human chorionic gonadotropin. The development of the ovarian hyperstimulation syndrome is associated with the sustained luteotropic effect of both exogenously administered chorionic gonadotropin and endogenous placental gonadotropin after implantation.^{3,22}

In our patient, the constitutive activity of the mutant receptor would continuously recruit numerous follicles, which might explain the polycystic appearance of her ovaries as visualized on ultrasonography. During pregnancy, these numerous unlueteinized follicles, which, in contrast to the corpus luteum, still express follicle-stimulating hormone receptor,²³ would be hyperstimulated by placental chorionic gonadotropin, causing them to enlarge. Thereafter, chorionic gonadotropin, acting at its own receptor, would cause luteinization as well as hypersecretion of vasogenic molecules that might induce a systemic capillary leak and a shift of fluid into a third space.^{3,24,25}

Symptoms in spontaneous cases of ovarian hyperstimulation syndrome appear later than those in iatrogenic cases (at 8 to 14 weeks of pregnancy, as compared with 3 to 8 weeks).^{1,2,6,7,22} According to our hypothesis, in spontaneous cases, massive enlargement of multiple follicles would be induced through the hyperstimulation of the follicle-stimulating hormone receptor by endogenous chorionic gonadotropin, whereas in iatrogenic cases, it would be induced by exogenous follicle-stimulating hormone before ovulation.

Both the constitutive activity of the mutant receptor and its increased sensitivity to chorionic gonadotropin would be implicated in the generation of spontaneous ovarian hyperstimulation syndrome. Alternatively, the promiscuous activation of the follicle-stimulating hormone receptor by chorionic gonadotropin might be sufficient to induce the condition, as suggested by the spontaneous occurrence of the syndrome in patients with trophoblastic disease.^{6,7}

Our study indicates that inappropriate stimulation of the follicle-stimulating hormone receptor is a key element in the development of ovarian hyperstimulation syndrome, suggesting that the susceptibility to iatrogenic disease might be associated with polymorphisms at the locus of the gene for this receptor.

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