Spontaneous pregnancy in a patient who was homozygous for the Q106R mutation in the gonadotropin-releasing hormone receptor gene

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Objective: To report the occurrence of a spontaneous pregnancy in a patient who was homozygous for the Q106R mutation in the GnRH receptor (GnRHR) gene.

Design: Case report.

Setting: Reproductive endocrinology unit of an academic medical center.

Patient(s): A 27-year-old woman who initially presented with partial idiopathic hypogonadotropic hypogonadism and who achieved a spontaneous pregnancy 3 months after oral contraceptive pill (OCP) withdrawal.

Intervention(s): Blood sampling for hormonal and genetic investigations, transvaginal ultrasound.

Main Outcome Measure(s): LH, FSH, E2, and hCG serum levels. Ultrasound examination of the uterine cavity.

Result(s): Three months after OCP withdrawal, the patient was amenorrheic. However, the hCG serum level was 149 IU/L. Transvaginal ultrasound 2 weeks later revealed the presence of one intrauterine sac containing two embryos with cardiac activity. At 9 weeks of gestation, no cardiac activity was found. A curettage was then performed, and the pathological examination indicated the presence of chorionic villi.

Conclusion(s): OCP withdrawal might have induced a transient situation with optimal endogenous pulsatile GnRH secretion, thus overriding the GnRH resistance induced by the partially inactivating Q106R GnRHR gene mutation and allowing ovulation to occur. (Fertil Steril 2002;77:1288–91. ©2002 by American Society for Reproductive Medicine.)

Key Words: GnRH receptor gene, mutation, idiopathic hypogonadotropic hypogonadism, pregnancy

Inactivating mutations in the GnRH receptor (GnRHR) gene represent a recently described cause of isolated gonadotropin deficiency in the human. The GnRHR gene is therefore another gene, after KAL-1 and DAX-1, that is responsible for the phenotype of idiopathic hypogonadotropic hypogonadism (IHH) in the human (1). So far, 13 natural point mutations of the GnRHR have been described (reviewed in 1). They are distributed along the coding sequence as it was reported for other G protein-coupled receptors and localized mainly within the transmembrane domains. Two “hotspots,” at residues 106 in the first extracellular loop and 262 in the third intracellular loop, were observed regardless of the geographic origin of the patients (North or South America or Europe) (2). Studies investigating the biological activity of the mutated receptor indicate that mutations in the first extracellular loop might affect ligand binding, whereas the third intracellular domain is probably crucially involved in G protein receptor coupling (3).

In all previously reported families, the phenotype of IHH associated with inactivating mutations was present only when a given patient had inherited two mutations that were either identical (homozygous) or different (compound heterozygote). Although the number of mutations found so far is still small, there is a wide spectrum of phenotypes. This variability is obviously due, in part, to the allelic combination of the mutations. As shown in vitro (3),
the degree of reduced efficiency of inositol triphosphate (IP3) production varies from one mutation to the other and parallels the degree of hypogonadism in patients. In vivo, LH response to pulsatile GnRHR administration varies from no response to a partial and dose-dependent response (reviewed in 1). Indeed, pulsatile administration of high doses of GnRHR induced ovulation in two patients who were compound heterozygotes for GnRHR mutations (4, 5), while it failed in another patient (6). So far, no case of spontaneous pregnancy has been observed in any reported pedigree.

**CASE REPORT**

The patient was first referred to our clinic in 1993 for evaluation of primary amenorrhea when she was 20 years old. She self-reported “slow” pubertal development but nonetheless continued to progress spontaneously to almost complete maturation. There was no family history of delayed puberty or infertility. Examination revealed Tanner stage 3 breast development and pubic hair. Her height was 165 cm and her weight 60 kg. She had no anosmia, hyposmia, or congenital malformations. At abdominal pelvic ultrasound (U/S), the uterus was hypotrophic and the ovaries could not be seen because of their small size. The hypothalamic-pituitary region was normal on magnetic resonance imaging.

Her basal prolactin level was normal (5 ng/mL) and her serum E2 level was low (25 pg/mL). Serum LH and FSH basal levels were normal (2.3 and 7.5 IU/L, respectively), but their responses 20 minutes after an exogenous GnRH 100 µg IV bolus were initially exaggerated (32.5 and 20.6 IU/L, respectively).

The patient was then placed on continuous E2 supplementation, given percutaneously and increased gradually from 0.375 to 1.5 mg/day, for 1 year. She then received an oral diol and 75 g (250 ng/kg) every 90 minutes. Ovulation occurred at GA 15 months. Ovulation induction by pulsatile GnRH administration (15 µg IV bolus every 90 minutes) was successful again, and the patient conceived after the third induction cycle. After an uneventful pregnancy, she delivered a healthy girl at GA 39 weeks weighing 4.5 kg.

The patient’s mother and sister had normal pubertal development and regular menstrual cycles. The sister gave birth to two children after two spontaneous and uneventful pregnancies. The patient’s father and brothers were normally virilized. There was no indication of parental consanguinity.

**LABORATORY PROCEDURES**

**Plasma Immunoassays**

Serum gonadotropin levels were evaluated by two immunoassays provided by Cis Bio International (France). These immunometric assays used monoclonal LH and FSH antibodies. Results are expressed in mUI/mL in terms of first International Reference Preparation (IRP) 68/40 (LH) and second IRP 78/549 (FSH) reference preparations. Intra- and interassay coefficients of variation were less than 5% for the two immunoassays. E2 concentrations were measured in duplicate in unextracted serum by RIA using kits provided by Biomérieux, France. Limit of detection is 12 pg/mL. The intra- and interassay coefficients of variation are 9.8% and 8.7%, respectively.

**Genetic Analysis**

Exons of the GnRH receptor were amplified by PCR and then sequenced as described elsewhere (7). Direct sequencing revealed a single homozygous mutation. A substitution of guanine for adenine at nucleotide 317 converted glutamine to arginine at codon 106 (Q106R) in the first extracellular loop of the GnRHR (Fig. 1). Moreover, we also found the Mae III polymorphism at codon 151 as described elsewhere (8) at the homozygous state.

The proband’s mother and father were confirmed to be heterozygous for this mutation, as well as her two brothers
DISCUSSION

To our knowledge, this is the first report of a homozygous Q106R GnRHR mutation (Gln106Arg substitution in the first extracellular loop) in a female patient. Of the 13 sporadic or familial GnRHR mutations described so far (reviewed in 1), the Q106R seems to be the most frequent one. In our experience (9), it was found in four out of seven unrelated families, including one or several cases of IHH due to GnRHR gene mutation. This mutation is therefore located in a mutational hotspot. However, its prevalence within the general population or in other situations than IHH is presently unknown.

The Q106R mutation appears more often in the heterozygous state because the other allele bears a different mutation. Our patient is the second case of homozygosity for Q106R reported so far. Although we cannot exclude rare genetic events such as uniparental disomy, loss of heterozygosity, or gene conversion, the fact that both parents were shown to be heterozygous for the mutation strongly suggests that our patient was truly homozygous.

Our patient represents the female counterpart of a recently described man (10) who carries the same homozygous Q106R mutation. His phenotype corresponds to the fertile eunuch syndrome, characterized by normal testicular size and preserved spermatogenesis. This phenotype is in contrast to the other male cases with GnRHR mutations, whose phenotypic spectrum varies from complete to partial hypogonadism, with small testicular volume and/or cryptorchidism and absent or low GnRH responsiveness (reviewed in 1). Likewise, our patient had spontaneously reached an almost complete pubertal maturation.

According to the clinical and biological data available in the literature about men and women with GnRHR mutations, these two observations suggest that the homozygous Q106R mutation yields the mildest phenotypes described so far. This is in agreement with the in vitro data from de Roux et al. (3), which show that, in spite of the marked decrease in GnRH binding, the Q106R mutated receptor displays a partial biological response (as expressed by IP3 production) after stimulation with a large dose of GnRH agonist.

Moreover, our female patient was able to start a spontaneous twin pregnancy, but miscarried, and then was amenorrheic again. Interestingly, the male patient reported by Pitteloud et al. (10) not only recovered fertility after only 4 months of hCG treatment but also experienced a spontaneous reversal of his IHH after hCG disruption. Although they did not exclude a priming effect of endogenous T on the gonadotrope, the investigators explained this phenomenon by Leydig cell maturation under hCG stimulation. They also suggested that pituitary desensitization of the mutant receptor, due to the hypogonadal fast GnRH pulse frequency, was reversed under hCG-induced endogenous T (10).

In our patient, a spontaneous reversal of her IHH after OCP withdrawal was also observed, leading to ovulation and then pregnancy. In contrast to the previously described findings in the male (10), a direct maturing effect on gonadal function can be eliminated since no exogenous gonadotropins were administered. Thus, our observation supports the hypothesis of an OCP-induced pituitary maturation and/or pituitary desensitization reversal. It was previously shown that estrogens at the hypothalamic level decrease GnRH pulse frequency and/or amplitude (11). Likewise, in ovariectomized monkeys, GnRH cerebral fluid concentration was reduced after E2 treatment (12). Therefore, after OCP withdrawal, and before GnRH pulse frequency returned to the hypogonadal fast pattern, our patient might have been in a transient situation with optimal endogenous pulsatile GnRH secretion, which thus overrode the GnRH resistance induced by the partially inactivating Q106R GnRHR gene mutation.

In conclusion, our case report indicates that, as far as we know, homozygosity for the Q106R mutation represents the mildest form of genetic resistance to GnRH. Whether the recovery of spontaneous and efficient gonadotropin activity is a specific feature of this genotype cannot be ascertained until more cases are described. Nevertheless, these data indicate that the search for GnRHR mutations should not be
restricted to patients displaying clinical and biological signs of complete IHH and being totally insensitive to exogenous GnRH.

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References