Pregnancy and Delivery After Stimulation with rFSH of a Galactosemia Patient Suffering Hypergonadotropic Hypogonadism: Case Report

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Purpose: To determine if hypergonadotropic hypogonadism related to galactosemia could be linked to anomaly of the circulating FSH. A 26-year-old woman, suffering GALT (Galactose-1-phosphate uridylyltransferase) had a premature ovarian failure with amenorrhea since the age of 19. The circulating level for FSH was 83 and 34 mU/mL for LH.

Methods: After treatment with a hormonal substitution cycle including estradiol and progesterone, the patient underwent stimulations with recombinant FSH. The first cycle, one 16-mm diameter follicle and the second cycle one follicle of 17.5 mm of diameter were obtained at the time of ovulation induction.

Results: The patient conceived and delivered a female baby weighting 3.38 kg after the second stimulation protocol.

Conclusions: The impact of galactosemia on the ovary seems rather related to the absence of recognition of circulating FSH by its receptor and not to a toxic alteration of the ovary by itself as it is currently reported. The rFSH treatment following hormonal substitution cycles allows to overcome infertility problems.

KEY WORDS: Galactosemia; hypergonadotropic hypogonadism; ovarian stimulation; rFSH.

INTRODUCTION

Galactosemia is an autosomal recessive disease related to the deficiency of one of three different enzymes in the metabolism of galactose: galactokinase (GALK), galactose-1-phosphate uridylyltransferase (GALT), the most common, or UDP-galactose-4-epimerase (GALE). It has been generally admitted that galactose and its metabolites could be toxic to the ovary (1–2). This generally leads to more or less severe hypergonadotropic hypogonadism. Women with galactosemia have a high incidence of ovarian failures and childbearing is rather rare (3,4), even if spontaneous in some cases (5). Exogenous estrogen and

progesterone are used to assist pubertal changes and to prevent sequelae of early postmenopausal state (6,7). In human gonadotropins, carbohydrate structure is related to bioactivity (8,9). More precisely, the follitropin beta chain shows *N*-acetyllactosamine repeats. On this basis, we postulated that an aberrant biologically inactive form of FSH, preventing a normal ligand–receptor binding and a proper recognition of the circulating FSH was produced.

CASE REPORT

VB a 26-year-old Caucasian patient had regular menses up to 19 years of age. She was carrying the GALT-type galactosemia and was submitted to hormonal substitutive treatment including estradiol and progesterone. She came for ART counselling after having stopped her hormonal substitution treatment

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for 6 months. Her biological parameters were: a circulating FSH at 83 and LH was 34 IU/L, Estradiol 14 pg/mL. Her TSH was within normal range: 1.6 mU/L. We advised the couple to undergo ovarian stimulations with rFSH. Husband sperm is of good quality (114 millions/mL, 5 mL, 85% living cells, 2/3 high quality motility, 33% abnormal forms according to WHO criteria). We chose rFSH as it allows a "pure" stimulation without addition of LH.

The patient was stimulated twice. She was submitted first to an artificial cycle treatment (hormone replacement therapy) including Estradiol (2 tablets of Estradiol 17 beta: Provames 2 mg) followed by dydrogesterone (Duphaston 20-mg intravaginally) during 10 days. She was then stimulated with 75 IU of rFSH (Gonalef SERONO) daily during 7 days, starting on Day 3, followed by 2×75 IU the next 2 days before triggering of ovulation by hCG. At the time of hCG injection the level of estradiol was 125 pg/mL and LH 8.2 IU/L; sonography showed a follicle at 16-mm diameter. No pregnancy resulted. In the second cycle, she received 75 IU of rFSH daily during 11 days. Estradiol reached 227 pG/mL for a follicle at 17.5 mm of diameter at the time of hCG triggering. The level of FSH was not measured during the rFSH stimulation protocol, as the endogenous inactive form and the exogenous form i.e. rFSH were mixed. No extra estradiol was given during stimulation.

She conceived and delivered a healthy female baby with a birthweight of 3.380 kg. As usual in this case she was not allowed to breast-feed her baby. Three months after delivery, her FSH returned to 38 IU/L with an estradiol at 23 pg/mL.

DISCUSSION

To our knowledge, this is the first time that such a management has been used to assist pregnancy in galactosemia patients with amenorrhea. The impact of galactosemia on the ovary seems simply related to the absence of recognition of the circulating FSH by

the receptor. The generally admitted direct toxic effect on the ovary, (1–7) does not fit with our observation. Galactosemia negatively modulates the biological activity of FSH (10), more than probably through a modification of the sugar moiety. Circulating FSH is recognized by the radioimmunoassay but not by the receptor. We are currently investigating the structural modifications of her FSH. In conclusion, the use of rFSH treatment offers new hopes for galactosemia patients, submitted to premature ovarian failure, to achieve pregnancy and give birth.

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