Do patients with heterozygote mutations in GALT gene have increased risk for impaired reproductive functions?

To the Editor:

We read with great interest the case report by Gubbels et al. (1) indicating a pregnancy despite undetectable antimullerian hormone levels in a patient with classical galactosemia. A similar 22-year-old patient with compound heterozygote mutation for GALT gene (Duarte type) K285 N/N314D (2) presented to our clinic with a history of two blighted ova, a spontaneous pregnancy resulted in delivery and subsequent death of a galactosemic infant. The couple suffered from infertility for 3 years at admission to our infertility center. On initial evaluation day 3, FSH was 6.2 IU/mL, E_2 was 20 pg/mL, and antral follicle count (AFC) was 8. Her husband, who had asthenozoospermia, had a heterozygous Q188R mutation of GALT gene. The couple previously underwent insemination cycles three times and one intracytoplasmic sperm injection (ICSI) cycle before admission to our unit. In that first ICSI cycle, a suboptimal ovarian response, with four M2 and five immature oocytes, occurred after controlled ovarian stimulation (COS) with 225 IU rFSH. notably, none of the oocytes fertilized. In the subsequent cycle, preimplantation genetic diagnosis was scheduled owing to the previous galactosemic infant delivery, recurrent pregnancy loss, and total fertilization failure (TFF). In the second ICSI cycle, at our clinic, five immature and three M2 oocytes were retrieved after COS with 225 IU rFSH, and TFF occurred again. With an aim to decrease the toxic effects of the high galactose on the gonads, a galactose-free diet was recommended to the couple for 4 months. In the third ICSI cycle, five M2 along with three immature oocytes were retrieved after COH with 150 IU rFSH and 75 IU hMG. After combined use of piezo electrical stimulation and ICSI, one grade B and two grade C embryos could be generated. Despite poor quality, all embryos underwent blastomere biopsy, but none of these embryos were found normal for GALT gene.

It is still unclear whether infertility, ovarian failure, or diminished ovarian reserve and subsequent poor obstetric outcome are associated with nonclassical galactosemia. Patients with low erythrocyte GALT activity had a 14-fold increased risk of menopause compared with those with normal GALT activity. Cramer et al. (3) also described significantly higher serum FSH levels in patients heterozygous for the Q188R mutation or the Duarte variant. Conversely, no increased risk for premature ovarian failure, infertility, or spontaneous pregnancy loss was noted in women with a galactosemic child (4). Moreover, Mlinar et al. purported that the 50% decrease in GALT activity in Q188R or K285 N heterozygotes or the 25% decrease in GALT activity in Duarte heterozygotes does not compromise ovarian function (5). In our case, a notable spectrum began with poor obstetric outcome, continued with infertility and inadequate ovarian response to stimulation, and manifested as TFF or poor-quality embryos despite a galactose-free diet, all of which might have been related to impaired ovarian function. Even though the genetic composition of the male partner may have contributed to the spectrum of poor reproductive outcome in our case, and despite no clear connection demonstrated, it cannot simply be ruled out that there is not any association between premature ovarian failure or diminished ovarian reserve and mutations in GALT gene.

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