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CASE REPORT

Patients with 47, XXX karyotype who experienced premature ovarian failure (POF): two case reports

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Abstract
Purpose Pubertal onset and sexual development are usually normal in 47, XXX individuals; however, we report two cases of premature ovarian failure (POF) in infertile women with trisomy X.
Methods Chromosome analysis was conducted with G-banding and fluorescence in situ hybridization using X- and Y-bearing probe. Hormonal administration was primarily Kaufmann's treatment or long-term estradiol treatment, followed by withdrawal bleeding from estrogen and progesterone.
Results Two patients with trisomy X, aged 31 (patient 1) and 27 years (patient 2), were diagnosed with POF due to hypergonadotropic hypogonadism. Their ovaries were small. Patient 1 had a FSH level of 44.6 mIU/ml and patient 2 had a FSH level of 74.6 mIU/ml. In patient 1, with Kaufmann's treatment, the FSH decreased to 13.5 mIU/ml; however, follicle growth did not occur following HMG stimulation. In patient 2, FSH did not decrease despite Kaufmann's treatment; therefore, she was given a GnRH agonist and her FSH level decreased to 7.1 mIU/ml. However, her ovaries never responded to HMG stimulation.
Conclusion We report on two patients with a 47, XXX karyotype who became infertile due to POF. We recommend that when a patient is diagnosed with trisomy X, the possibility of POF must be strongly considered.

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Introduction

The 47, XXX genotype is a sex chromosome anomaly with a variable phenotype caused by the presence of an extra X chromosome. It is the most common female chromosomal abnormality, occurring in approximately 1 in 1,000 female births [1].

It was first described in 1959 in a 35-year-old woman with normal cognitive function who presented with secondary amenorrhea at 19 years of age [2].

Although major medical abnormalities are not present in most cases, some lesser abnormalities may be associated with trisomy X. The most common are genitourinary abnormalities, ranging from a unilateral kidney and renal dysplasia to ovarian malformation [3].

Pubertal onset and sexual development are usually normal in trisomy X; however, there have been cases of ovarian or uterine dysgenesis described in children and young adults with trisomy X [4]. It should be noted that the most common cause of POF is sex chromosome aneuploidy, especially Turner's syndrome (45, X). Other abnormalities are XXX, XXXX, and mosaics [5]. POF is a condition in which the ovarian functions of hormone production and oocyte development become impaired before the typical age for menopause. There are some case reports of women with trisomy X and POF who have the endocrinologic finding of hypergonadotropic hypogonadism [2, 5–11].

In assisted reproductive technology (ART) treatment, we sometimes encounter a patient with 47, XXX karyotype who is infertile due to POF. Therefore, we describe two cases of POF in infertile women with trisomy X.

Case reports

Patient 1

A 31-year-old married gravida 0 para 0 woman had amenorrhea of 10 month's duration. Her menarche occurred at the age of 12; however, she subsequently experienced oligomenorrhea. Her chief complaints were amenorrhea and infertility of 1 year's duration. She was referred to our clinic for infertility evaluation. Her height was 168 cm, her weight was 80.5 kg, and her karyotype was 47, XXX [30/30].

An ultrasound examination revealed that both ovaries and the uterus were slightly small. A gynecological examination revealed a normal vulva and perineum as well as a female escutcheon. Hormonal studies were: LH, 55.4 mIU/ml; FSH, 64.0 mIU/ml; E_2, 20.4 pg/ml; PRL, 3.8 ng/ml; and T, 22.4 ng/ml. Thyroid function, RA test, LE cell, anti-DNA antibody, anti-CL antibody, and antinucleic antibody were within normal limits.

With Kaufmann's treatment, the FSH level decreased to 13.5 mIU/ml; however, follicular growth did not occur despite HMG administration.

Patient 2

A 27-year-old married gravida 0 para 0 woman had a 6 month history of amenorrhea. Her menarche occurred at the age 12. However, she subsequently developed oligomenorrhea and became amenorrheic at 25 years of age. Her chief complaints were amenorrhea and 1 year of infertility. She was referred to our clinic for infertility evaluation. Her height was 168 cm, her weight was 45 kg, and her karyotype was 47, XXX [30/30] by G-banding. However, her sex chromosomes by FISH were distributed as: XXX 490/500 (98.0 %), XX 7/500 (1.4 %), XXXX 2/500 (0.4 %) and X 1/500 (0.2 %).

Both ovaries were somewhat small; however the uterus was normal sized. Hormonal values were: LH, 34.4 mIU/ml; FSH 74.6 mIU/ml and PRL, 7.1 ng/ml. She received Kaufman's treatment; 3 weeks after the first laboratory analysis her hormonal values were: LH, 65.4 mIU/ml; and FSH, 183.5 mIU/ml. Despite Kaufmann's treatment, the FSH level did not decrease; therefore, a GnRH agonist was administered, and as a result, the FSH level decreased to 7.1 mIU/ml. However, her ovaries did not respond to HMG administration.

Discussion

Two patients who were diagnosed with a 47, XXX karyotype experienced POF. X-chromosome trisomy is a result of the nondisjunction of sex chromosomes during the first meiotic division. The defect is closely related to maternal age: the risk of XXX trisomy occurring in the daughter with increased maternal age. According to Deng et al. [12], in cases of X polysomy, the additional X chromosome originates from the mother. The first case of a woman with X trisomy was described by Jacobs [2]. Apart from a secondary amenorrhea, she did not display any other psychological, physical, or sexual disorders. The standard diagnostic procedures for young women with primary or secondary amenorrhea should include a cytogenetic examination.

As emphasized in the introduction, there is no typical phenotype for women with 47, XXX. However, immunological disorders and POF may occur [13].

Goswami et al. [14] examined 52 patients with POF and found that in two of them, in addition to X trisomy, autoimmune thyroid disease occurred. Lanoble et al. [15] described a 47, XXX patient with systemic visceral lupus. Even though our patient did not display an immunologic, thyroid, or adrenal disorder, the extra X chromosome may still play an important role in immune system function; thus, the patient should undergo a meticulous medical evaluation.

An extra X chromosome in a woman may result in tall stature [16]. Also, this was found in our cases; both women were of tall stature of 168 cm, despite being in a recent generation that did not only include tall members. Furthermore, patient 2 was not a pure 47, XXX because mosaicism was found with FISH. This case illustrates the possibility that patients with trisomy XXX may have different clinical presentations. A literature review revealed cases of women with 46, XX/47, XXX mosaicism [5, 17]. Previously we reported that mosaicism including X chromosome patients were sometimes failure of ovulation and poor quality embryo in IVF. Therefore, we want to check large number of cells for X chromosome by FISH with X-bearing probe.

Initially, we treated these patients as usual infertile women, because they had normal physical status with a little taller height and amenorrhea, until we examined chromosome analysis and obtained a diagnosis of 47, XXX. When we found trisomy X (47, XXX), we considered whether the patient related with POF. Mosaicism was detected by FISH. In our case, patient 1 was not examined via AMH. Patient 2 was 0.43 ng/ml and was low-level. We never detected antral follicle in the small ovary at the time. Therefore, we couldn't find particular clinical aspects for mosaicism which, implies 47XXX, until we conducted FISH examination. Structural and functional changes of the reproductive system are considered to not be present in 47, XXX trisomy patients; however, patients with trisomy X exhibit POF before the age of 40. Our cases suggest that

47, XXX is closely related POF. Cases of 47, XXX are estimated to occur approximately in one every 1,000 females [1]. Turner's syndrome is also an X aneuploidy abnormality, and its incidence occurs at a rate of about 0.3/1,000; therefore, 47, XXX has a higher rate than Turner's syndrome [18].

The standard diagnostic procedure for women under age 25 includes a cytogenetic examination; however, this examination is often not performed for older patients.

If an infertile woman who has irregular menstruation is referred for ART treatment, gynecologists should consider that POF may be associated with 47, XXX or trisomy X. Our cases of 31- and 27-year-old patients with POF and the 47, XXX karyotype confirmed to us the aforementioned recommendation. Therefore, we recommend that a cytogenetic examination should be performed in infertility patients with primary or secondary amenorrhea at an early stage of the workup. Also, we stress that if patients with a 47, XXX karyotype achieve a pregnancy, they must be carefully managed throughout their pregnancy and delivery.

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