PREMATURE OVARIAN INSUFFICIENCY DETERMINED BY X CHROMOSOME ANOMALIES

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SUMMARY

Background: Premature ovarian insufficiency (POI) is a condition defined by loss of ovarian activity before the age of 40 years, accompanied by menopausal symptoms. It is marked by amenorrhea or oligomenorrhea, absence of ovulation, elevated gonadotropins, and low estradiol levels. POI can be classified into spontaneous non-iatrogenic and iatrogenic forms. The prevalence of non-iatrogenic POI in the population ranges from 1% to 3.5%. The X chromosome's Numerical and structural abnormalities are key etiological factors.

Objective: To determine the clinical peculiarities and types of POI caused by X chromosome anomalies.

Material and Methods: The study included 26 patients aged 16 to 24 with non-iatrogenic spontaneous POI. Of these, 12 patients were diagnosed with numerical or structural abnormalities of the X chromosome based on clinical, laboratory, and instrumental studies. In some cases, x-chromosome abnormalities were detected using G-banding in peripheral blood lymphocyte cultures; fluorescence in situ hybridization (FISH) and molecular cytogenetic methods were employed.

Results: Among the 26 patients with non-iatrogenic spontaneous POI, four were diagnosed with Turner syndrome. These patients exhibited severe growth retardation, somatic anomalies typical of Turner syndrome, and sexual development according to Tanner's scheme (Ma0PaAx0Me0), including markedly elevated gonadotropins and decreased estradiol levels, By US – streak gonads and uterus, without follicles. Two patients were identified with a 45, X karyotype, while another had a 46, X, i(Xq) karyotype. Additionally, a mosaic karyotype with a 45, X cell line was detected in 5 patients (4 with 45, X/46, XX and 1 with 45, X/47, XXX). Structural abnormalities of the X chromosome, specifically deletions, were found in 2 patients. Patients with mosaicism and structural abnormalities of the X chromosome exhibited mild growth retardation and premature

ovarian failure, which was characterized by primary amenorrhea, hypergonadotropinemia, and a significantly reduced number of antral follicles. Only one patient with a 45, X /47, XXX mosaic karyotype experienced secondary amenorrhea and spontaneous puberty. One patient with tetrasomy X (karyotype 48, XXXX) and POI presented with tall stature, mental retardation, secondary amenorrhea, hypergonadotropinemia, and a few follicles in the ovaries. To initiate puberty, all patients were treated with monotherapy using natural estrogen analogs, followed by replacement therapy with estrogen-gestagens until the age of natural menopause.

Keywords: premature ovarian insufficiency, Turner syndrome, X chromosome abnormalities, numerical anomalies, structural anomalies, mosaicism, growth retardation

Conclusion:

- For all patients with non-iatrogenic premature ovarian insufficiency, despite the absence of subjective signs of estrogen deficiency and the characteristic signs of Turner's syndrome, karyotyping is recommended.
- Oocyte donation is the optimal method to achieve fertility in patients with premature ovarian insufficiency and numerical and structural anomalies of the X chromosome.
- In patients with X chromosome anomalies at an early stage of diagnosis of chromosomal anomalies and in cases of an acceptable number of ovarian follicles, cryopreservation of reproductive materials may be considered with the using genetic testing of the embryo.

INTRODUCTION

Premature ovarian insufficiency (POI) is a condition defined by loss of ovarian activity before the age of 40 years. POI is characterized by amenorrhea or oligomenorrhea, with elevated gonadotropins and low estradiol levels.[1] Distinguish spontaneous non-iatrogenic and iatrogenic forms of premature ovarian insufficiency. It's important to note that earlier studies indicated that the prevalence of non-iatrogenic POI is approximately 1%, while newer studies suggest it could be as high as 3.5%.[2,3,4]

Menstrual history of irregular periods <40 years of age is noteworthy for early diagnosis of POI. Menopausal symptoms may not always be present. Recommended investigations include hormonal tests (FSH, LH, AMH, anti-TPO antibodies, adrenal cortex hormones like cortisol, 17α-OHP, DHEA), 21-hydroxylase antibodies, karyotyping, Fragile X mental retardation (FMRI) gene premutation analysis, ultrasonography for antral follicle count, and bone densitometry (DXA)**.** To confirm the diagnosis of POI, it's necessary to measure FSH and AMH levels twice, with an interval of 4-6 weeks.[5,6]

The etiology of POI can be categorized as follows:

Spontaneous Non-Iatrogenic: Causes include genetic factors related to the X chromosome (such as XO Turner syndrome, X trisomies, X deletions, X translocations), Fragile X FMRI gene premutation (1-5%, rising to 13% with a positive family history), other gene mutations, autoimmune conditions (3-30%), and infections (parotitis, tuberculosis, malaria, cytomegaly).

Induced Iatrogenic: This form of POI is caused by medical interventions such as bilateral ovariectomy, cystectomy, chemotherapy (including anthracyclines), radiation therapy, and embolization of pelvic vessels.

Environmental toxins.

OBJECTIVE

To determine the clinical peculiarities and types of POI caused by X chromosome anomalies.

MATERIALS AND METHODS

A total of 26 patients aged 16-24 years with the spontaneous non-iatrogenic form of premature ovarian insufficiency (POI) were examined. Clinical, laboratory, and instrumental investigations were performed, including:

- **Hormonal investigations:** Prolactin, Estradiol, FSH, LH, TSH, FT4, Anti-Tg, Anti-TPO, AMH.
- **Genital organs ultrasound (US) examination.**
- **Cytogenetic investigation:** Determination of the karyotype in peripheral blood lymphocyte cultures using G-banding.

Fluorescence In Situ Hybridization (FISH) and molecular cytogenetic methods were also used in some cases.

Ethical considerations

All the adult participants and parents of adolescent individuals signed a written consent form**.**

RESULTS

Out of 26 investigated patients with non-iatrogenic POI, 24 patients had primary amenorrhea, and two patients – had secondary amenorrhea. None of the patients had subjective menopausal symptoms. Patients with primary amenorrhea had a delay in sexual development and developed secondary genital signs on the background of hormone replacement therapy before presenting to us. All patients had an elevated level of FSH – more than 25 IU/ml, with 2-fold testing and a decreased estradiol level. Ultrasonography showed a markedly hypoplastic uterus, and antral follicle counts reduced to 1-2 (0.5-1.5mm), or the follicles were not visualized. By karyotyping, 14 patients were diagnosed with a normal female karyotype and 12 patients with numerical or structural anomalies of the X chromosome.

Diagnosis of Turner syndrome with karyotypes 45, X and 46, X, i(Xq) is not difficult against the background of characteristic clinical manifestations (severe retardation of growth and sexual development, typical somatic anomalies, increased gonadotropins and decreased estradiol levels, by US streak gonads and uterus.[7, 8]

Admission of such patients in reproductive clinics before the manifestation of hypogonadism is relatively rare because they are admitted to the growth centers due to growth retardation.

Out of 12 patients with premature ovarian insufficiency due to X chromosome anomalies, only four patients had typical Turner syndrome with 45, X (2) and 46, X,i(Xq) (2) karyotypes, primary amenorrhea was presented in all four patients with Turner syndrome.

In cases of 45, X cell line containing mosaicism (45, X/46, XX,45, X/47, XXX) and X chromosome structural anomalies, the leading clinical manifestations were premature ovarian insufficiency on the background of mild growth retardation and single somatic anomalies. According to literature data, the degree of symptoms expression in cases of mosaicims is variable and in some cases spontaneous menarche and even pregnancy can be expressed.[9] Among the patients examined by us, spontaneous menarche and secondary amenorrhea were diagnosed in one patient with 45, X/47, XXX mosaicism, and growth retardation, which is also described in the literature.[9]

According to our data, two patients with POI and structural anomalies of the X chromosome had mild growth retardation. One of them (16 yr.) had delayed sexual development. Another 24-year-old patient was treated with estrogen-gestagens before referring to us. The growth of mammary glands and induced menstruations were expressed on the background of hormone replacement therapy.

In both cases, a two-time study determined a sharp increase in the FSH level and a decrease in the estradiol level. Ultrasonographic examination revealed a hypoplastic uterus and a markedly reduced number of antral follicles in the ovaries (1-2 follicles).

The situation is different in cases of polysomy X. The clinical manifestations of patients with triple X are characterized by a widely expressed polymorphism; therefore, the diagnosis is made in only 10% of cases, or in other cases, the diagnosis is delayed.[10]

Based on individual case reports, women with triple-X have been shown to have decreased AMH values, reduced ovarian reserve, and have an increased risk of early menopause and POI.[11] The risk of POI is estimated to be five times higher in women with 47, XXX than in women with 46, XX karyotype.[12]

An 18-year-old patient examined by us was diagnosed with tetraploidy X, which is a rare condition. Only 60 cases of tetraploidy X have been described in the worldwide literature. This disorder is characterized by a comprehensive clinical polymorphism, and considering that the literature more often represents individuals in early puberty, the types and frequency of sexual development disorders in these patients are not specified. [13,14,15,16]

In contrast to Turner's syndrome, our patient with 48, XXXX karyotype showed rapid and intense height growth (179 cm). The patient had secondary amenorrhea, sexual development according to Tanner Ma4P4Ax3, clinodactyly, microgenia and polysomy X-specific mental retardation (IQ- 59), and premature ovarian insufficiency. The FSH level by two-time testing was > 25 IU/ml, and the ultrasonography showed a markedly hypoplastic uterus and ovaries with single follicles.

After the diagnosis, the issue of treatment with sex hormones was considered for all patients with POI. In the cases of Turner's syndrome, in combination with the use of growth hormone, after reaching the appropriate growth for the initiation of puberty, small doses of monotherapy with natural estrogens were prescribed for 1-2 years, and then hormone replacement therapy with natural estrogen-gestagens until the age of natural menopause. In other cases, depending on the need, monotherapy with natural estrogens was used at the initial stage, and estrogen-gestagens combination for long-term treatment, as recommended in the literature, for prevention of long-term negative consequences of estrogen-deficient conditions (Osteoporosis, CVD, Alzheimer's disease, etc.).

It is known that in cases of non-iatrogenic POI, spontaneous pregnancy is possible in up to 15 % of cases.[17,18,19]

Egg donation is considered an optimal method of achieving fertility in cases of X chromosome anomalies.[19]

However, on the background of secondary amenorrhea and mild decrease in the number of antral follicles in some cases of 45, X cell line mosaicism, and structural anomalies of the X chromosome in cases of early diagnosis, the possibilities of cryopreservation of reproductive materi-

als can be considered with using genetic testing of embryos. Spontaneous puberty and pregnancy, interestingly, are more common in patients with 45, X/47, and XXX karyotypes than in patients with 45, X/46, and XX karyotypes.[20]

Conclusion

- For all patients with non-iatrogenic premature ovarian insufficiency, despite the absence of subjective signs of estrogen deficiency and the characteristic signs of Turner's syndrome, karyotyping is recommended.
- Oocyte donation is the optimal method to achieve fertility in patients with premature ovarian insufficiency and numerical and structural anomalies of the X chromosome.
- In patients with X chromosome anomalies at an early stage of diagnosis of chromosomal anomalies and in cases of an acceptable number of ovarian follicles, cryopreservation of reproductive materials may be considered with the using genetic testing of the embryo.

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