Premature ovarian failure in a 17-year-old woman

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Summary

Introduction: Premature ovarian failure (POF) in a healthy adolescent is a rare event. It is diagnosed by the presence of amenorrhea, hypoestrogenism, and elevated follicle-stimulating hormone (FSH) levels before the age of 40. *Case:* The patient presented with amenorrhoea at 17 years after identifying a change from her regular to irregular and metrorrhagic cycles. No positive medical history was noted regarding smoking, chemotherapy, radiation or autoimmune diseases and the physical examination was normal. Her family history revealed that both her maternal aunt and grandmother were affected by POF, but the karyotype test was normal and the FMR1 screening premutation test was negative. The patient underwent an ovarian biopsy which revealed the absence of functional follicles. She began a replacement therapy with estroprogestogens and she was informed about the most successful means to start a family, including adoption and oocyte donation. *Conclusion:* POF is a heterogeneous, multifactorial, and poorly understood condition that involves medical concerns, psychological sphere, and sexuality of the affected patients. Management should be directed at symptoms resolution, bone protection, and psychosocial support for women facing this unexpected and devastating diagnosis.

Key words: Premature ovarian failure; FMR1 test; Hormone replacement therapy; Infertility.

Introduction

Premature ovarian failure (POF) is a clinical condition characterized by the presence of primary or secondary amenorrhea for at least four months, hypoestrogenism, and elevated serum gonadotropin concentrations due to cessation of ovarian function before the age of 40.

The diagnosis is confirmed by serum follicle-stimulating (FSH) levels in a classical menopausal range (> 40 IU/l) in two measurements at least one month apart [1].

The condition differs from menopause because of varying and unpredictable ovarian function in approximately 50% of cases, and about five to 10% of women conceive and deliver a child after they have received the diagnosis [2].

POF incidence in patients with 46, XX karyotype was estimated in around 1:1,000 women under 30 years old, 1:250 around 35 years old, and 1:100 at 40 years old [3].

Multiple causes of POF can be defined and result in follicle depletion and/or defects in the follicular development. POF may occur due to chromosomal, genetic, autoimmune, metabolic (galactosaemia), infectious (mumps), and iatrogenic (anticancer treatments) causes, but a large proportion of cases remains idiopathic.

Although most cases of primary ovarian insufficiency occur sporadically, there is a positive family history, with an affected first-degree relative, in approximately 10 to 15% of cases [4]. The standard diagnostic procedure in the case of young women with primary or secondary amenorrhea should include a cytogenetic examination and tests for the FMR1 premutation, especially in the case of women under the age of 25.

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Case Report

A 22-year-old caucasian woman had experienced secondary amenorrhea from the age of 17.

She had menarche at the age of 13 and reported regular menses for the following two years. Later she presented metrorrhagic cycles until cessation of ovarian function at the age of 17, when she began experiencing hot flashes and loss of libido. She had received an estro-progestogens association therapy (ethinyl estradiol 0.020 mg and drospirenone three mg for six months, followed by medroxyprogesterone acetate and ethinyl estradiol for six months) which resulted in cyclical bleeding, but she remained anovulatory.

Her careful family history indicated that her maternal aunt and grandmother went through menopause before the age of 40. She was nulliparous. No positive medical history was noted regarding smoking, chemotherapy, radiation or autoimmune diseases.

Her physical examination revealed a healthy appearing woman with body mass index (BMI) of 20 kg/m^2, normal genitalia, and Tanner stage V development. Pelvic ultrasonography showed the body of the uterus to be normal in profile and dimensions, with a homogeneous thin endometrium. Both ovaries were reduced in volume (right ovary 2.1 cm^3, left ovary2.4 cm^3) with the absence of growing antral follicles.

Hormonal pattern cycle was: FSH 60: UI/l, luteinizing hormone: 42 UI/l, estradiol: 42 pg/ml, progesterone: 1.7 ng/ml, anti-Müllerian hormone: 0.4 ng/ml. Serum levels of thyroid stimulating hormone, fT3, fT4, prolactin, androstenedione, free testosterone, and total testosterone were within normal range.

No anti-thyroid, anti-antiadrenal, and anti-ovarian antibodies were found in the blood. Rheumatoid factor (RF) was negative. After a thrombophilic screening the patient showed hyperhomocysteinemia and an homozygous mutation in methylenetetrahydrofolate reductase (MTHFR).

The patient performed a karyotype test on peripheral blood resulting in a normal chromosomal pattern. The fragile X mental retardation 1 (FMR1) screening premutation test was negative.

She underwent a laparoscopy with an ovarian biopsy. The uterus appeared normal for morphology and volume with normal fallopian tubes and streak ovaries. The ovarian specimens were

routinely processed in paraffin and were stained by hematoxylin and eosin (H&E) staining (Figure 1).

At the histological examination, in the right ovary it was observed an atrophic cortex without follicular formations and corpus albicans. In the left ovary it was possible to distinguish an atrophic cortex with residual corpus albicans. On the histological section, non-functional primordial follicles with a single layer of granulose cells were identified. At the immunohistochemical analysis they were c-kit and PLAP negative.

The patient was discharged to home on the second post-operative day and she began a replacement therapy with estro-progestogens associated with folic acid and iron supplement.

A psychologist's consultation was performed to offer an emotional support and to discuss the implications of oocyte donation and adoption.

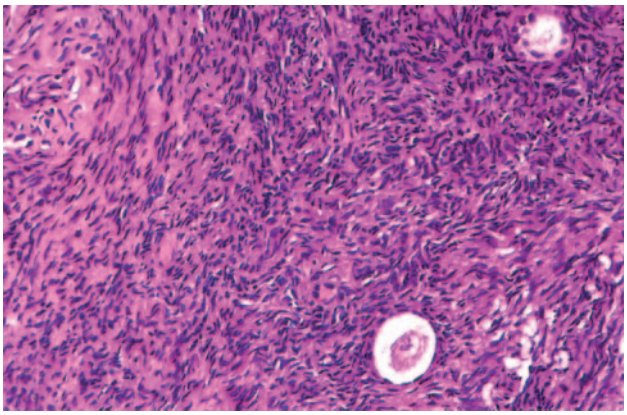

Figure 1. — Histopathology of the left ovary (H&E staining): atrophic cortex with non-functional primordial follicles.

Discussion

About one percent of women in the general population experiences cessation of ovarian function under the age of 40. Many women who presented a spontaneous POF, in a percentage from four to 31 percent, had an inherited character [5, 6].

The patient of this case report showed a strong association between her idiopathic form of POF and its manifestation in her family, as demonstrated by the fact that her maternal aunt and grandmother went through menopause before 40 years. There is a clear correlation between menopausal age of mother and daughter probably due to genetic mutations or deletions. The physiological decline of quality and quantity of oocytes causes a progressive loss of female fertility depending on the age of the patient [7]. The lack of specific markers of ovarian failure reveals the difficulty to anticipate how fast a patient with elevated FSH serum levels will develop an ovarian insufficiency [6]. Studies of pedigrees on affected families show a mode of inheritance suggestive of autosomal dominant sex-limited tranmission or X-linked inheritance with incomplete penetrance [8]. In recent years, the candidate gene approach has aided to identify genes and pathways involved in POF. Therefore, the pathogenic mechanism still remains unknown in most of the cases. However, when a genetic alteration is found in a woman, family counselling can be useful to predict the female relatives who are at higher risk for POF and fertility loss in young age. The FMR1 premutation accounts for 1.0% - 7.5% of sporadic and 13% of familial cases of POF. Thus, according to the American College of Obstetrics and Gynaecology, testing for the fragile X premutation should be recommended in all women with POF [9]. In addition, the American College of Medical Genetics recommends that testing should be considered in 'women who are experiencing reproductive or fertility problems associated with elevated FSH levels, especially if they have (a) a family history of premature ovarian failure (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed mental retardation' [10].

Women with POF should ideally be managed within specialist multidisciplinary teams to address their complex physical and psychological needs. Therapeutic goals of POF are emotional health, hormone replacement therapy (HRT), maintenance of bone health, and concern about associated disorders, such as cardiovascular and metabolic diseases.

Many women with POF would benefit from symptom relief by the use of exogenous steroids, to compensate for the loss of ovarian estrogens, and possibly progesterone and androgens. Menopausal symptoms, such as hot flushes, night sweats, fatigue, sexual disfunction, and vaginal dryness, can be alleviated by estrogen replacement, such as sequential HRT or oral contraceptive pill. Women who are concerned about avoiding pregnancy are often advised to take the combined oral contraceptive pill. For women with an intact uterus, estrogen should be administered in combination with a progestin to avoid endometrial hyperplasia [11]. The dosage and the route of administration of HRT is extremely complex because of the chronicity (many years of treatment) and because during that period of time many changes take place at both the physical and psychological level. An HRT regimen should be based on the individual preferences of each patient who should be encouraged to undertake a trial and error approach through the wide variety of products available. There is no doubt that all women with POF must replace their missing steroid hormones until the age of natural menopause [12].

To date, no data are available to evaluate the impact of HRT on risks encountered by postmenopausal women, including the development of breast cancer, endometrial cancer, and cardiovascular events, as reported from the Women's Health Initiative. Recent data demonstrating decreased coronary atherosclerosis in young postmenopausal women taking estrogen replacement provides additional reassurance [1].

Infertility is a significant issue for most women undergoing POF. Although many women will ovulate at some

point following the diagnosis and spontaneous pregnancies can occur in five to ten percent of those with idiopathic forms, this cannot be predicted with any reliability. There are many case reports and small series reporting use of various medical therapies in an attempt to restore ovarian function and fertility. Evidence suggests that pregnancies might occur if women with POF are managed to suppress their high FSH concentrations, either with ethinyloestradiol or with gonadotrophin-releasing hormone analogues, and then follow ovulation induction protocols using low-dose gonadotrophins [13]. However, randomized therapeutic trials fail to demonstrate any significant improvement in ovulation and pregnancy rates. Assisted reproductive technique with donated oocytes remains the only means for fertility treatment that carries high success rate. Cryopreserved embryos have also been employed for ovum donation in POF with a high pregnancy rate of 30% per transfer [8].

For most women, POF can be an unexpected and distressing diagnosis, with deleterious psychological impact, made worse by the fact that it coincides with infertility. Emotional support should be addressed to maintain their well-being. A positive and optimistic lifestyle should be encouraged to be maintained, including engaging in regular weight-bearing exercise, maintaining an adequate intake of calcium (1,200 mg daily) and vitamin D (at least 800 IU daily), and eating a healthy diet to avoid obesity. Regular screening for bone loss and cardiovascular risk factors is also recommended [13].

Conclusion

In conclusion, POF is a heterogeneous, multifactorial, and poorly understood condition that involves the psychological sphere and the sexuality of the affected patients. An early diagnosis and an immediate replacement treatment can prevent health associated problems, can relieve menopausal symptoms, and could provide considerable psychological support.

A genetic component reinforces the importance of a detailed family history. The difficulty to discover a determining factor should press to investigate other candidate genes through a gene mapping and establish their critical role in ovarian dysfunction. It is likely that this information may assist us to diagnose the condition earlier, and therefore provide a way to save or protect remaining good follicles before the development of POF. It is also possible that if a better understanding of the biology of POF is achieved, this may lead to possible therapeutic avenues for defective follicles to be developed further.

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