



Investigating menopause in adolescent girls

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Menstrual irregularity can be frequently encountered during adolescence, since the interval of the menstrual cycle during the first years after menarche ranges from 21 up to 45 days [1]. Even though it is often harmless, menstrual irregularity in teenagers can represent a sign of premature menopause. More commonly known as premature ovarian insufficiency (POI), this condition has a reported incidence of 10 cases per 100,000 person-years for girls of 15–29 years of age [2].

The clinical diagnosis of POI at young age is challenging. The phenotypic features vary significantly between affected girls. Ovarian function starts declining relatively quickly, the time span of the woman's reproductive potential shortens and amenorrhoea is manifest within 1 to 2 years of the onset of menstrual irregularity [3].

POI is diagnosed on the basis of clinical and hormonal findings [4,5]. For every girl with suspected POI, a detailed personal and family medical and gynecological history should be obtained. Clinical examination and sonographic assessment of the uterus and the ovaries are required. The diagnosis is formally confirmed when a teen with intact ovaries presents with amenorrhea or oligomenorrhoea, documented for at least 4 consecutive months. Hormonal evaluation, with assessment of follicle stimulating hormone (FSH) and estradiol, should be performed on the third day of the cycle for girls with oligomenorrhoea but can be random for girls with amenorrhoea. The blood test should be repeated on at least two occasions, 4 weeks apart; the results should be within the normal menopausal range as per local laboratory.

The occurrence of POI is likely multifactorial and the precise aetiology may not be identified in the majority of cases. Exclusion of pregnancy, with measurement of levels of beta human chorionic gonadotropin, should be combined with evaluation of prolactin as well as progesterone levels [4–6]. Following confirmation of hypergonadotrophic

hypogonadism in an adolescent girl, a series of further tests should be undertaken [4–6].

- *The first step* includes karyotyping and genetic analysis. Screening for chromosomal abnormalities should test for the presence of Turner syndrome or Y-chromosomal material. Genetic analysis includes evaluation for Fragile X Mental retardation 1 premutation, inhibin B mutation as well as chromosome X abnormalities like mutations of FOXL2, BMP15, FSHR, NR5A1 and Gs alpha genes as well as steroidogenic enzymes.
- *The second step* includes an autoimmune screen with investigation for adrenocortical antibodies, 21hydroxylase antibodies, thyroid peroxidase antibodies, islet cell antibodies, myasthenia gravis, pernicious anaemia, rheumatological disorders, Crohn's disease and primary biliary cirrhosis.
- *The next step* involves exclusion of metabolic disorders like 17hydroxylase deficiency, classic galactosaemia and carbohydrate-deficient glycoprotein deficiency.
- *Finally*, evaluation should be completed with viral screening for varicella, mumps or human immunodeficiency virus, for example.

A diagnosis of premature menopause in a teenage girl has several clinical implications for the adolescent. Hypoestrogenism is linked with future risk for low bone density and higher future cardiovascular risk. Conception is not entirely impossible: a small proportion (5–10%) of young women with POI have been reported to achieve spontaneous ovulation with conception and successful pregnancy [4,5]. The adolescent girl and her family need to be made aware that ovarian activity may not be enhanced medically and an established option to achieve fertility is oocyte donation. Assisted reproduction should be offered early on to the patient, when desiring pregnancy [4–6]. Markers of ovarian reserve include sonographic count of ovarian antral follicles, levels of anti-Mullerian hormone and FSH; however, their specificity and sensitivity remain limited [7].

Management includes lifestyle advice and hormone supplementation [4–6]. Lifestyle advice should emphasise a balanced diet, with the daily recommended amounts of calcium and vitamin D, regular physical activity which includes weight-bearing exercise, maintenance of a healthy weight and avoidance of smoking. Moreover, due to the small possibility of spontaneous ovulation, use of contraceptives is recommended if the girl is sexually active, to avoid unwanted pregnancy [5,6].

Hormone replacement therapy (HRT) represents the cornerstone of treatment, up until the age of natural menopause. The route and dose of HRT should be adjusted according to the characteristics of the individual, such as obesity, history of migraines and family risk of thromboembolism or cancer [5,6]. In pre-pubertal cases, induction is required with commencement of low-dose estrogen-only treatment for an interval of 6 up to 18 months. The dose of estrogen should be increased stepwise

over the first two to three years, aiming to reach the adult dose. Cyclic progestogen should be initiated after 2 years of estrogen-only treatment or in case of breakthrough bleeding. Following achievement of full pubertal development, girls should be offered HRT of adult dose or the combined estrogen/progestogen contraceptive pill, which tends to be more acceptable to young women [5,8].

In conclusion, even though unusual, premature menopause can be the cause of secondary amenorrhoea in teens. A complete clinical, biochemical and sonographic evaluation should be performed on at least two independent occasions, before confirming the diagnosis. Further analysis to identify the potential cause should be attempted, especially in girls with POI, as it is likely to be attributable to underlying systemic diseases. HRT or combined contraceptives represent the best treatment for those girls, and treatment should be continued up until the time of natural menopause.

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