



## Invited Editorial

## Diagnostic challenges in suspected premature ovarian insufficiency



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Failing ovarian function of a young woman is a rather complicated and challenging diagnosis, which will have lifelong implications if not managed promptly [1]. The prevalence of premature ovarian insufficiency (POI) has not been formally investigated [1]. However, spontaneous POI appears to occur in 1% of women below the age of 40 years and 0.1% of those aged under 30 years [2]. The broad clinical manifestations of POI complicate the diagnosis. The presentation can be primary amenorrhoea, following delayed puberty with absent breast development, or secondary amenorrhoea, where the young woman presents with an initially irregular menstrual cycle, followed by amenorrhoea and normal pubertal development [3]. Most commonly, the progressive loss of ovarian function at under 40 years of age can present in the form of oligomenorrhoea and amenorrhoea of varying intervals in association with symptoms of estrogen withdrawal [3].

The diagnosis of POI is challenged by the lack of uniformly agreed guidelines. In women aged less than 40 years who present with a history of oligo- or amenorrhoea for at least four months, measurement of follicle-stimulating hormone (FSH) levels is recommended worldwide [3]. The most widely utilized criterion for a diagnosis of POI is an FSH greater than 40 IU/L, measured on at least two occasions, which should be four weeks apart [4–5]. The National Institute for Health and Care Excellence (NICE) has recommended an FSH threshold of 30 IU/L. On the other hand, the European Society for Human Reproduction and Embryology (ESHRE) has recommended a slightly lower cut-off, at 25 IU/L [4–5]. ESHRE has opted for the lower cut-off also to incorporate cases of autoimmune-mediated ovarian failure in the POI spectrum, which tend to present with lower levels of FSH [4–5]. Simultaneously, the most common causes of oligo-amenorrhoea (pregnancy, hyperprolactinaemia, hypothalamic dysfunction due to weight loss, and polycystic ovarian syndrome) should be excluded prior to considering the role of further investigations for possible POI [4–5].

The detailed exploration of the aetiology of this diagnosis should not delay counselling on POI, especially in high-risk patients with multiple risk factors such as known genetic abnormalities, nulliparity or multiple pregnancies, early menarche, family history of early or premature

menopause, low body mass index and cigarette smoking [5]. The aetiology remains unknown in 70–90% of women diagnosed with POI, and many causes of POI are considered idiopathic [5]. Overall, the documented causative factors can be classified as X chromosome-linked, genetic (autosomal), autoimmunity, metabolic, infectious, environmental, but also environmental [3,5]. POI is one of the main characteristics of at least a handful of genetic syndromes, like the well-documented Turner syndrome, BPES type 1 (blepharophimosis, ptosis, epicanthus inversus syndrome), Perrault syndrome with ovarian dysgenesis, galactosemia, as well as adult-onset leukodystrophy and autoimmune polyendocrine syndromes [6]. The overall incidence of spontaneous POI remains unchanged [7]. However, the incidence of iatrogenic POI appears to be rising during the last decades due to improved treatment of childhood cancer, with the incidence of acute ovarian failure affecting up to 6.3% of the affected population [8].

Given the challenges of this heterogeneous condition, the possible involvement of the genomic background has been investigated extensively, and up to 80 genetic variants have been claimed as responsible for ovarian failure in young women [9]. As per the current guidelines, routine clinical care for patients with suspected POI includes genetic analysis for the possible identification of the Fragile X Mental Retardation 1 gene and chromosomal analysis for X-linked pathologies [6–9]. Even though multiple extensive genetic investigations will not prove cost-effective, genetic counselling should be offered with priority to patients with early POI (aged less than 30 years) as well as to patients with learning difficulties [5]. The role of genetic counselling should also be considered in pre-symptomatic relatives with a strong family history suggesting premature or early menopause [9].

A possible prediction of the state of ovarian failure appears appealing in an attempt to improve outcomes. The results of the anti-Müllerian hormone (AMH) test can support the diagnosis, but no diagnostic cut-off has been established yet. In addition, AMH levels might be suppressed even five years prior to the final menstrual period, and the test itself might not be available universally [5]. A dedicated transvaginal ultrasound scan can also contribute to the diagnosis through an

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assessment of ovarian volume and an estimate of the antral follicle count (AFC), which, however, is not always consistent with the estimated AMH levels [5]. Recent evidence [10] has shown that markers of ovarian reserve fluctuate between women with normal ovarian function, precursor state of POI, early POI, and premature ovarian failure, which was defined using FSH values as a cut-off. In particular, AMH was proven to have the highest predictive value for complete ovarian failure and precursor states of POI. The combination of AMH and AFC appears promising for earlier prediction of POI [10].

The health consequences related to this life-changing diagnosis are not only cardiometabolic but also psychosexual and psychosocial [3,5]. The treatment options largely depend on the extent of the underlying pathology and the potential for fertility. In any case, early initiation of hormone replacement therapy will improve genitourinary physiology and limit the extent of adverse cardiometabolic changes [3–5]. Fertility preservation strategies, like ovarian cryopreservation, can be of great benefit. A timely diagnosis enables utilization of the available options [3,5].

In conclusion, menstrual irregularity should be carefully evaluated, taking into consideration personal and family history, as well as POI-specific risk factors. Time is ultimately the biggest enemy in the process of this diagnostic evaluation, and it is necessary to minimize the risk of missed opportunities. Detailed clinical and genetic counselling on the diagnosis and the anticipated consequences can equip the female patient to start exploring treatment options and consider possibilities.

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#### References

- [1] R. Rahman, N. Panay, Diagnosis and management of premature ovarian insufficiency, *Best Pract. Res. Clin. Endocrinol. Metab.* 35 (2021), 101600.
- [2] C. Coulam, S. Adamson, J. Annegers, Incidence of premature ovarian failure, *Obstet. Gynecol.* 67 (4) (1986) 604–606.
- [3] L. Webber, M. Davies, R. Anderson, et al., ESHRE guideline: management of women with premature ovarian insufficiency, *Hum. Reprod.* 31 (2016) 926–937.
- [4] I. Lambrinoudaki, S.A. Paschou, M.A. Lumsden, et al., Premature ovarian insufficiency: a toolkit for the primary care physician, *Maturitas* 147 (2021) 53e63.
- [5] N. Panay, R.A. Anderson, R.E. Nappi, et al., Premature ovarian insufficiency: an international menopause society white paper, *Climacteric* 23 (2020) 426e46.
- [6] B. Cloke, J. Rymer, Premature ovarian insufficiency – the need for a genomic map, *Climacteric* 24 (2021) 444–452.
- [7] M.M. Franca, B.B. Mendonca, Genetics of primary ovarian insufficiency in the next-generation sequencing era, *J. Endocr. Soc.* 4 (2019) bvz037.
- [8] W. Chemaitilly, A.C. Mertens, P. Mitby, et al., Acute ovarian failure in the childhood cancer survivor study, *JCEM* 91 (2006) 1723–1728.
- [9] E.J. Tucker, T.Y. Tan, Z. Start, A.H. Sinclair, Genomic testing in premature ovarian insufficiency: proceed with caution, *Biol. Reprod.* (2022) 1–4.
- [10] X. Jiao, T. Meng, Y. Zhai, L. Zhao, W. Luo, P. Liu, Y. Qin, Ovarian reserve markers in premature ovarian insufficiency: within different clinical stages and different etiologies, *Front. Endocrinol. (Lausanne)* 2 (601752) (2021) 1–9.

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