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Premature Ovarian Insufficiency

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Abstract: *Premature ovarian insufficiency (POI) is defined as amenorrhea of more than six months before the age of 40 with an elevated follicle stimulating hormone (FSH) level and low estradiol on at least two separate samples taken a few weeks apart. Its prevalence is 1/10,000 in women under 20 years of age, 1/1,000 in women under 30 years of age and 2 - 4% in women under 40 years of age. It is clinically manifested by impuberism and/or primary or secondary amenorrhea. Apart from iatrogenic causes (radiation or chemotherapy, surgery), the most frequent causes are genetic or chromosomal, such as Turner syndrome and fragile X syndrome. Despite investigations aimed at etiology, premature ovarian failure remains unexplained in about 70% of cases, especially in cases of secondary amenorrhea. Management of patients is aimed at avoiding cardiovascular and bone complications secondary to hypoestrogenism. It involves hormone replacement therapy with a combination of 17 β estradiol and progesterone or an estroprogestogenic pill. Spontaneous fertility is 3 to 10%.*

Keywords: premature ovarian insufficiency, ovary, X chromosome, amenorrhea

Introduction

POI occurs in the majority of cases due to a too rapid decrease in the follicular stock. It is the consequence of an ovarian anomaly. The diagnosis is made in a woman under 40 years of age who is clinically amenorrheic or has spaniomenorrhea. Biologically, her FSH level must be higher than 25 IU/L, on at least two separate samples taken a few weeks apart with a low estradiol level [1].

An elevated FSH level should always be interpreted in the presence of an estradiol assay, to be sure that the sample was not taken at the time of the preovulatory peak.

The prevalence of POI is not exceptional, occurring in 2-4% of women before age 40. It is rarer before the age of 30 and even rarer before the age of 20, with prevalences of 1/1000 and 1/10,000 respectively.

The European Society of Human Reproduction and Embryology (ESHRE) has established recommendations for the definition and management of these patients [2]. Measurement of AMH is not part of the positive diagnosis of POI. However, in the majority of cases, the AMH level has fallen or has become undetectable. Pelvic ultrasound can be falsely reassuring, as in 30-60% of patients with POI, follicles may be visible on ultrasound. There may be fluctuation in POI, especially in the first year after diagnosis. The ESHRE consensus emphasizes that the term early menopause should no longer be used in a woman with POI, as it is often psychologically deleterious. In addition, menopause is a definitive phenomenon due to total depletion of the follicle pool, whereas ovarian function in POI can fluctuate.

Pathophysiology

POI can be explained by three mechanisms: an abnormality in the formation of the follicle pool, a blockage in follicular maturation or an abnormally rapid depletion of the follicular stock. It is necessary to remember that the ovary contains a stock of oocytes present from intrauterine life. These oocytes are subject to apoptosis [3].

The maximum number of oocytes is obtained at 20 weeks of intrauterine life and is approximately 6 million. At birth, the number of oocytes is 1 to 2 million and 400,000 at puberty. Follicular depletion accelerates around the age of 37 and menopause occurs when the number of follicles is less than 1,000 (Figure 1).

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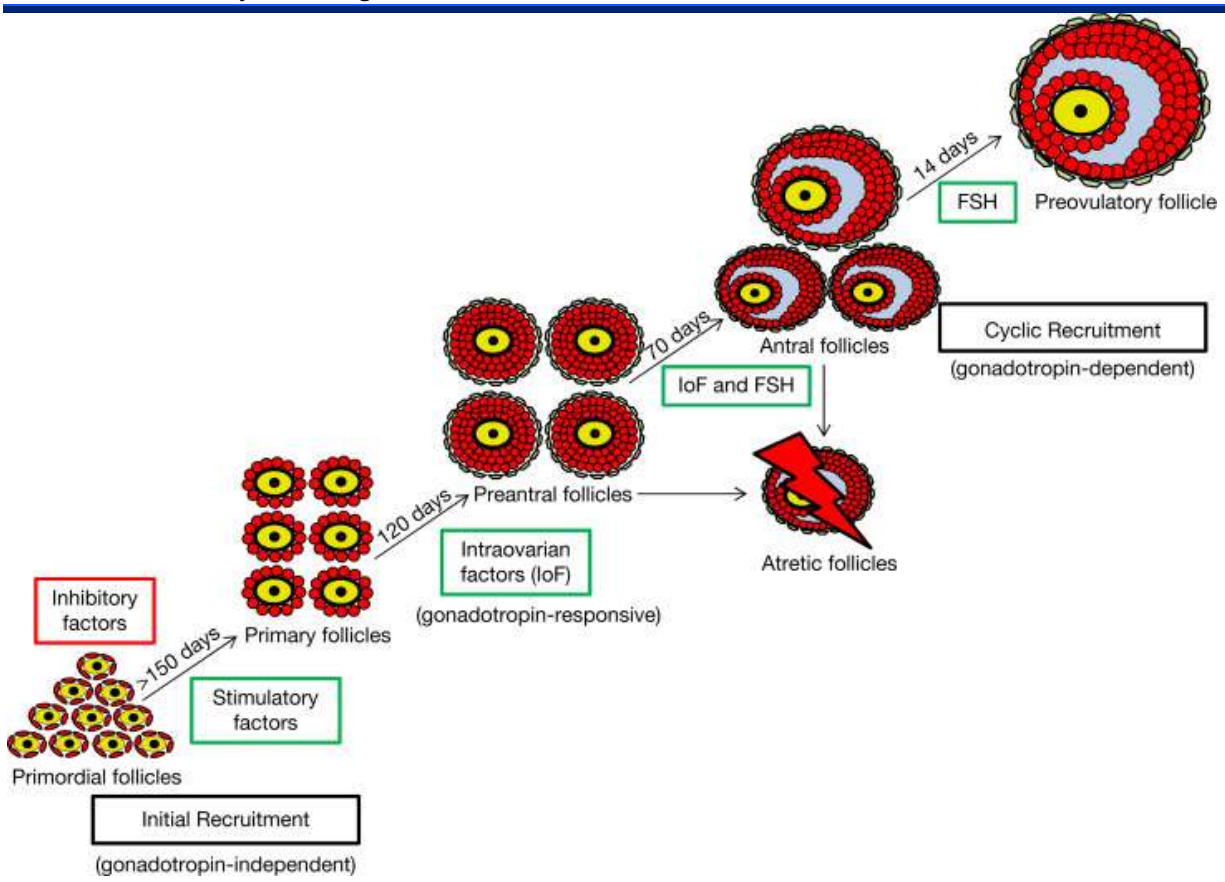

Figure 1: Progression and regulation of ovarian folliculogenesis. The finite supply of primordial follicles remains quiescent under the action of intraovarian inhibitory factors. A decrease in these factors and/or an increase in intraovarian stimulatory factors leads to primordial follicle activation to the primary stage of development. This process is gonadotropin-independent and is known as initial recruitment. Primary follicles develop into preantral and early antral follicles via the action of intraovarian factors and gonadotropins. These follicles are the most susceptible to atresia, or follicle death. Select antral follicles are rescued from atresia by responding to the cyclic changes in FSH secretion, and they become preovulatory follicles that are capable of oocyte release and corpora lutea formation. This final stage of development is gonadotropin-dependent and is known as cyclic recruitment.
Figure modified from (Hsueh, A. J. W., Kawamura, K., Cheng, Y., Fauser, B. C. J. M. (2015). Intraovarian control of early folliculogenesis. *Endocrine Reviews* ***36***(1), 1–24; (McGee, E. A. and Hsueh, A. J. W. (2000). Initial and cyclic recruitment of ovarian follicles. *Endocrine Reviews* ***21***(2), 200–214.).

Diagnosis

POI manifests as either impuberism with lack of breast development, primary amenorrhea, primary-secondary amenorrhea, or secondary amenorrhea. POIs related to a chromosomal abnormality are most often revealed by primary amenorrhea. For the majority of patients, this condition develops after several years of regular menstrual cycles or even after normal fertility. There are few or no symptoms preceding the onset of POI: some patients describe oligoamenorrhea or metrorrhagia. 25% of women have sudden secondary amenorrhea, either postpartum or most often after stopping oral contraception [4].

The clinical signs are essentially related to estrogen deficiency. They are present in the form of hot flashes, insomnia, asthenia, dyspareunia, mood disorders and libido disorders. Their intensity varies greatly from one patient to another. All these signs are related to hypoestrogenism. They may be masked by taking an estrogen-progestin pill and are sometimes only revealed when contraception is stopped. This mode of revelation is quite frequent in women of childbearing age. Clinically, in the case of proven POI, due to hypo-estrogenism, the progestin test (10 days of progestin) is negative, i.e. no bleeding occurs when the progestin is stopped because the endometrium has not been able to proliferate in the absence of estrogen. It should be noted that primary amenorrhea is not accompanied by symptoms of hypoestrogenism. On the contrary, bilateral castration is accompanied by intense

signs of hypoestrogenism [5]. In some cases of POI, there is a fluctuation in ovarian function with spontaneous resumption of cycles for a variable duration before the definitive cessation of ovarian function. Pelvic ultrasound may reveal gonadal dysgenesis as in Turner syndrome (figure 2) where the ovaries are reduced to simple fibrous bands. In practice, pelvic ultrasound does not confirm the diagnosis of POI. In fact, in many cases, it is falsely reassuring following the detection of follicles. It can even identify corpus luteum scars. Ultrasound, however, allows the uterus to be visualized and the thickness of the endometrium to be assessed, which is a good reflection of estrogen impregnation.

The main differential diagnosis of POI is diminished ovarian reserve. A woman with diminished ovarian reserve consults for infertility: she is still regulated, with most often normal cycles or, in some cases, short cycles that are a sign of ovarian aging; unlike POI, where there is amenorrhea or very infrequent cycles. In diminished ovarian reserve, the FSH level is usually at the upper limit of normal or slightly elevated. In all cases it is below 25 IU/L. On pelvic ultrasound, the antral follicle count is low. The plasma AMH level, which is the best quantitative reflection of the ovarian reserve, is low.

The diagnosis of diminished ovarian reserve is established in certain cases when there is a "poor" response to ovarian stimulation by gonadotropins, within the framework of medical assistance for procreation. It is not known to date whether a woman with a diminished ovarian reserve is likely to present a POI in the years following the diagnosis of diminished reserve.

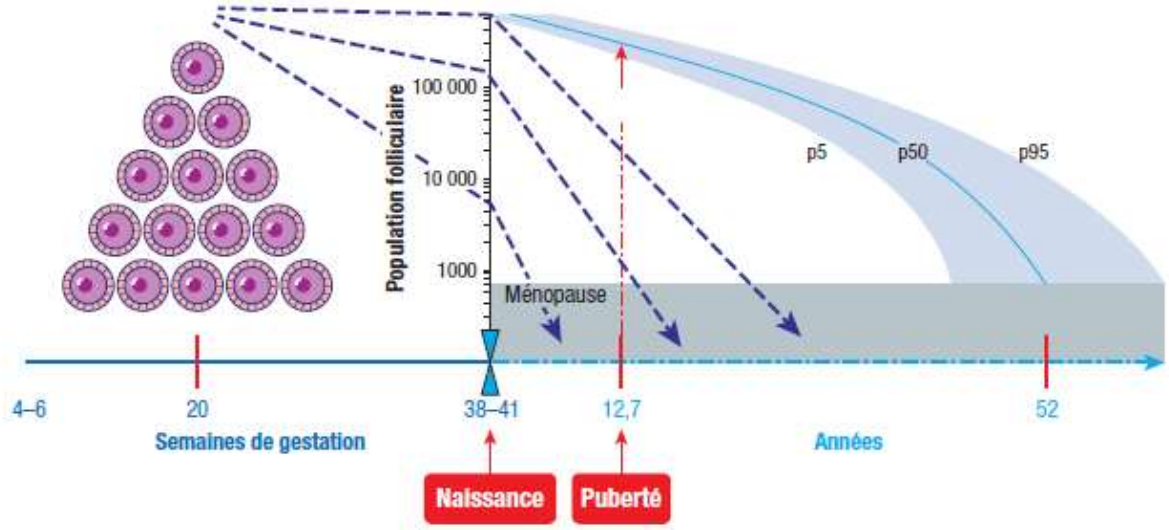

Figure 2: Evolution of ovarian follicle number over a woman's lifetime, starting from intrauterine life. The dotted curves represent examples of accelerated follicular atresia in patients with Turner syndrome. Source : *d'après De Vos M, Devroey P, Fauser BC. Primary ovarian insufficiency. Lancet 2010 ; 376 : 911–21.*

Etiologies of POI

To date, the etiology of POI has only been identified in 30-40% of patients. The main etiologies can be grouped into different categories: toxic, autoimmune or genetic. Surgical etiologies have become exceptional and are most often secondary to bilateral surgery for ovarian endometriomas, for example.

Toxic etiologies mainly include a history of chemotherapy and/or radiotherapy, especially by alkylating agents [6]. There is great variability in the impact of different chemotherapy molecules on ovarian reserve. The mechanisms involved include both an increase in ovarian apoptosis but also the phenomenon of burn-out, i.e. a large number of follicles leaving the primary follicle pool more rapidly than expected.

An autoimmune etiology can be retained, essentially in view of the patient's and/or her family's background. Indeed, the presence of one or more autoimmune pathologies, such as thyroid disease, type 1 diabetes, vitiligo, lupus, rheumatoid arthritis, Biermer's disease, or celiac disease are in favor of an autoimmune etiology of POI. However, there is no biological evidence to support the autoimmune origin of POI. Indeed, anti-ovarian antibodies are neither sensitive nor specific. Antithyroid antibodies can be found positive, but as they are positive in 10% of the general population, their presence is not sufficient to affirm an autoimmune origin of POI.

The antibodies that have the best predictive value for autoimmune POI are the anti-adrenal, or anti-21-hydroxylase antibodies.

If they are positive, an autoimmune etiology of POI is almost certain and there is a risk of adrenal insufficiency in the years following the diagnosis of POI.

The major genetic etiologies of POI include X chromosome abnormalities, particularly Turner syndrome and fragile X premutation involving the Xfra gene. After informed consent has been obtained and signed by the patient, the initial genetic workup should be ordered by a physician with expertise in genetics who can interpret and report the results of the tests. It includes a karyotype and a molecular research of Xfra premutation.

The karyotype may be in favor of a Turner syndrome. Most often, the patient is small in stature. Clinically, there may be a pterygium colli and low hair and ear implantation. The karyotype is, in 50% of the cases, in the form of a 45X monosomy. In the other cases, it is a mosaic 45X, 46XX or an isochromosome X. The formula may also include a Y chromosome or fragments of the Y chromosome. The diagnosis of Turner syndrome is made on average at the age of 8 years. However, it can be established in adulthood in the face of recurrent miscarriages or infertility. The karyotype can also reveal a deletion of the long arm of the X or a translocation between an X and an autosome.

If the deletion only affects the terminal part of the long arm of the X chromosome, downstream of the q23 region, it is not Turner syndrome.

If the karyotype is normal, there may be an Xfra premutation. The Xfra gene is involved in fragile X syndrome. Affected males have mental retardation, which is related to the presence of an abnormal protein, mainly in the brain. This abnormal protein is the result of a number of CGG triplets located upstream of the Xfra gene, located on the long arm of the X chromosome. In Fragile X syndrome, the number of CGG triplets is greater than 200, while the normal number is less than 50. Some women have an allele with a number of triplets between 55 and 199. They are called premature.

The result returned by the molecular biology laboratory includes two numbers, corresponding to each of the alleles. Most often, one of the alleles is of normal size, the second is between 55 and 199 triplets. In case of premutation, women have a 10 times higher probability of developing POI than women in the general population.

The risk is highest for a number of triplets between 80 and 100. The result should be made by a person competent in genetics, as it involves family genetic counseling. The prevalence of this etiology is 13% when there are other cases of POI in the family. Apart from karyotype abnormalities and Xfra premutations, about 60 different genes have been identified to date as candidate genes for POI. The majority of them are involved in folliculogenesis or meiosis.Mutations occur in the majority of cases in non-syndromic forms of POI (NOBOX, GDF9, BMP15, etc.) [7].In some cases, there is a deafness associated with POI: this is the Perrault syndrome. Five different genes have been identified. There may be eyelid disorders, as in blepharophimosis syndrome, or upper function disorders [8]. High-throughput sequencing analyses, testing a panel of genes, should help to clarify the etiologies of POI in the near future.

Management of premature ovarian failure

The announcement of the diagnosis of POI is very delicate and must be accompanied by psychological support [9]. Moreover, this pathology raises two main problems: estrogenic hormonal deficiency and infertility management.Contrary to hormonal treatment of the menopause, which prolongs the duration of exposure of women to estrogens, hormonal treatment of patients with ovarian insufficiency is really a replacement treatment because it compensates for hypoestrogenism and its long-term harmful effects. Indeed, the risk of osteoporosis is high in these women: more than two thirds have a pathological bone densitometry at one and a half years after diagnosis [10].

In practice, it is desirable to propose hormone replacement therapy (HRT) with a combination of 17β estradiol and progesterone or an estrogen-progestin pill. It is necessary to remind patients that the risk of spontaneous pregnancy is not zero. The route of administration of estradiol may be oral, transcutaneous, or dermal, and should be discussed with the patient. Progestin administration can be continuous or sequential (10 to 14 days per month). Sequential treatment makes it possible to preserve withdrawal bleeding: it is therefore preferable to the continuous regimen from a psychological point of view in younger patients. It is important to educate patients to motivate them to take the treatment. If possible, HRT should be continued until the physiological age of menopause, which is approximately 50-52 years [2]. Only in the case of a previous hysterectomy can estrogen be administered alone. The purpose of progesterone is to prevent endometrial hyperplasia. If the patient does not wish to have withdrawal bleeding, continuous estrogen treatment can be considered. One of the primary objectives of HRT is to prevent osteopenia and even osteoporosis. HRT also has a trophic effect on the skin, improves vaginal secretions, prevents hot flashes and reduces cardiovascular risk. Indeed, epidemiological studies have shown that an early age of cessation of ovarian function, in the

absence of HRT, increases the risk of cardiovascular mortality at an older age. In addition, a Dutch study showed an increased cardiovascular risk in women with poorly substituted POI, with long periods of estrogen deficiency [11].

Even if the molecules of HRT are identical to the molecules of menopausal hormone therapy (MHT) with, in both cases, a combination of estrogen and progesterone or a progestin, it is important to distinguish between HRT and MHT. Indeed, it has now been shown that the impact of estrogens is not the same in a young woman with no cardiovascular risk (where the impact of estrogens is entirely beneficial on cardiovascular risk) as in an older woman, who potentially has a higher cardiovascular risk. In addition, it is important to emphasize that monitoring of HRT is not the same as for HRT: in young women with POI on HRT, screening mammography is not necessary, except in a particular family context of breast cancer risk; the risk of breast cancer is not a priori increased on HRT. However, it is useful to perform a bone densitometry every 5 years to assess bone mass.When HRT is prescribed, the desire for contraception or, conversely, the desire for fertility must be considered with the patient. Indeed, POI should no longer be called early menopause because, unlike physiological menopause, the cessation of ovarian function is not definitive in all cases. There is a potential reversibility of POI which occurs in 5 to 7% of patients, depending on the studies. In the event of a desire for fertility, referral to an oocyte donation center is advisable, since the success rate of this technique is approximately 50%.Ideally, patients at risk of POI and their families should be counseled before the onset of POI to consider oocyte freezing. Unfortunately, in the majority of cases, by the time the patient presents with POI, her ovaries are already devoid of follicles. In most cases, it is too late to consider oocyte freezing, since an average of at least 10 frozen oocytes is needed to have a chance of achieving a future pregnancy.

In the particular case of Turner syndrome, care in a rare disease center specialized in this syndrome is necessary. Indeed, these patients must benefit throughout their life from a multidisciplinary follow-up, including cardiac evaluations, in particular of the aortic diameter, and regular liver, digestive, renal and bone evaluations. Their cardiovascular risk is higher than that of the general population, with a risk of hypertension and aortic dissection leading to earlier death. A disturbance in the liver balance may lead to a preference for the transdermal route but should not lead to discontinuation of estrogen replacement.

Conclusion

POI is a rare pathology, most often secondary to a too rapid depletion of the ovarian follicle stock. Its diagnosis is difficult to accept by the patients, who often present anxiety-depressive disorders at the time of the announcement. Although the number of identified etiologies has increased in recent years, it remains insufficient. Hormone replacement therapy is essential for quality of life as well as for cardiovascular and bone prevention. The use of estroprogestative contraception may be discussed in certain cases.

Declaration of interest: *The authors declare that they have no conflicts of interest in relation to this article.*

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