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Spanish consensus on premature menopause

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ABSTRACT

Introduction: While we recognise that the term *premature menopause* is more accepted by most non-specialist health care providers and by the general population, 'primary ovarian insufficiency' (POI) is currently considered the most apposite term to explain the loss of ovarian function, because it better explains the variability of the clinical picture, does not specify definitive failure, and highlights the specific ovarian source. Its pathogenesis involves a congenital reduction in the number of primordial follicles, poor follicle recruitment, or accelerated follicular apoptosis. However, its cause is unknown in most cases.
Aim: This guide analyses the factors associated with the diagnosis and treatment of POI and provides recommendations on the most appropriate diagnostic and therapeutic measures for women under 40 years of age who experience POI.
Methodology: A panel of experts from various Spanish scientific societies related to POI (Spanish Menopause Society, Spanish Fertility Society, and Spanish Contraception Society) met to reach a consensus on these issues.
Results: Hormonal therapy (HT) is considered the treatment of choice to alleviate the symptoms of hypoestrogenism and to prevent long-term consequences. We suggest that HT should be continued until at least age 51, the average age at natural menopause. The best treatment to achieve pregnancy is oocyte/embryo donation. If a patient is to undergo treatment that will reduce her fertility, she should be informed of this issue and the available techniques to preserve ovarian function, mainly vitrification of oocytes.

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1. Introduction

Different diagnostic terminology has been used in relation to the loss of ovarian function, including *premature* or *early menopause*, *premature* or *early ovarian failure*, and the most recent term, *primary ovarian insufficiency* (POI). The last is currently considered the most apposite because it better allows for the variability of the clinical picture, including its rare reversibility and the fact that it does not necessarily involve definitive failure, and because it specifically highlights the ovarian source of the problem [1].

Although we have no data on its incidence in Spain, records indicate that the condition may have a higher incidence than previously thought and may be present in a young patient who complains of cycle disorders. Its incidence is 1/250 among women aged 35 years and 1/100 among women aged 40 years [2,3]. Moreover, there is evidence that the incidence may be increasing above 1% due to iatrogenic causes [4].

The objective of this guide is to analyse the factors associated with the diagnosis and treatment of POI and to recommend the most appropriate diagnostic and therapeutic measures for women under 40 years of age.

2. Methods

A panel of experts from various Spanish scientific societies related to POI (Spanish Menopause Society, Spanish Fertility Society, Spanish Contraception Society and Spanish Medical-Oncologic Society) met to reach a consensus on these issues. Each society chose its participants. Participants were responsible for reviewing and drafting each part of this guide. All authors were involved in the writing of the statement and approved the final version. The consensus panel considered it appropriate to develop its own recommendations based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system for the elaboration of clinical practice guidelines and to classify the quality of the evidence and the strength of the recommendations (http://cebgrade.mcmaster.ca/).

3. Pathogenesis

Onset of the condition is spontaneous and its cause is unknown in most cases. It may occur after chemotherapy (CT), surgical treatment or radiotherapy (RT). Its pathogenesis involves a congenital reduction in the number of primordial follicles, poor follicle recruitment, or accelerated follicular apoptosis. The most common causes of non-iatrogenic POI are shown in Table 1.

3.1. Iatrogenic POI

Cancer treatment in young women is often associated with POI [8], tending towards greater intensity with higher treatment exposure or a greater surgically excised area. After RT, the risk of POI rises in direct relation to the age of the patient, the dose received, and whether it is directed to the pelvis [9]. POI secondary to CT depends on the type of drug, its dose, and the age of the patient. Alkylating agents, often used in the treatment of lymphomas and certain autoimmune diseases, are the most damaging to oocytes and granulosa cells [10–12].

4. Clinical symptoms

In the short, medium, and long term, POI has a negative effect on the overall health of women. Symptoms are typical of the transition to menopause or natural menopause, and include amenorrhea, vasomotor symptoms, and vaginal dryness. Symptoms are more severe in younger patients and when the presentation is acute (*e.g.* after surgical menopause). Because there is still some hormonal production left in more than half of POI cases, the absence of these symptoms should not rule out its diagnosis [13].

In addition, POI is considered an independent risk factor for cardiovascular disease (CVD), osteoporosis (OP) [14,15], and mood disorders, as well as cognitive impairment [16].

Autoimmune POI (see Table 1), as well as the associated hypoestrogenism itself, decreases certain endocrine functions (*e.g.* growth hormone) and induces a predisposition to other endocrinopathies (mainly thyroid and adrenal) [17].

Table 1
Most common causes of non-iatrogenic POI.

Genetic	• Turner syndrome (XO 45) is the most common genetic cause. Sufferers have normal early follicular levels but accelerated follicular depletion • FMR1 (*Fragile X Mental retardation 1*) premutation • Other chromosome X abnormalities: *mutations of FOXL2*, *NR5A1*, *BMP15*, *FSHR*, and *Gs alpha* genes, and of steroidogenic enzymes
Metabolic	• Galactose-1-phosphate uridyltransferase deficiency • *Carbohydrate-deficient glycoprotein* deficiency • 17 alpha-hydroxylase/17, 20 desmolase deficiency Mutations of the aromatase gene
Autoimmune	• Polyglandular autoimmune syndrome • Hypothyroidism • Type I diabetes mellitus • Myasthenia gravis • Systemic lupus erythematosus • Addison's disease • Thrombocytopenic purpura • Vitiligo • Alopecia • Pernicious anaemia or autoimmune anaemia • Rheumatoid arthritis • Crohn's disease • Sjögren's syndrome • Primary biliary cirrhosis
Infectious	• Viral infections (human immunodeficiency virus, varicella), tuberculosis, malaria, shigellosis
Other causes	• Women of Chinese race or Hispanic origin [5] • Environmental toxins (e.g. tobacco, dioxins) [6,7]

5. Diagnosis

Unfortunately, we do not have specific markers for the diagnosis of POI, and most guidelines use the following triad: a woman under 40 with secondary oligomenorrhea or amenorrhea of more than 3 months' duration, and follicle-stimulating hormone (FSH) levels above 40 IU/l [1].

At the initial clinical evaluation, transvaginal ultrasound is recommended. Although the cause will typically not be known, tests for chromosomal, genetic and immunological, disorders and infection will be requested individually (see the POI Diagnostic Algorithm in Fig. 1).

A study of ovarian reserve is essential in women with a desire for pregnancy, preferably by ultrasound count of antral follicles and measurement of anti-müllerian hormone (AMH). Although the determination of AMH levels has no utility at present beyond reproductive prognosis, mathematical models are being designed that incorporate this test in predicting age at menopause and could be of interest for the diagnosis of POI, in particular the differential diagnosis from other forms of amenorrhea [18] (Fig. 2).

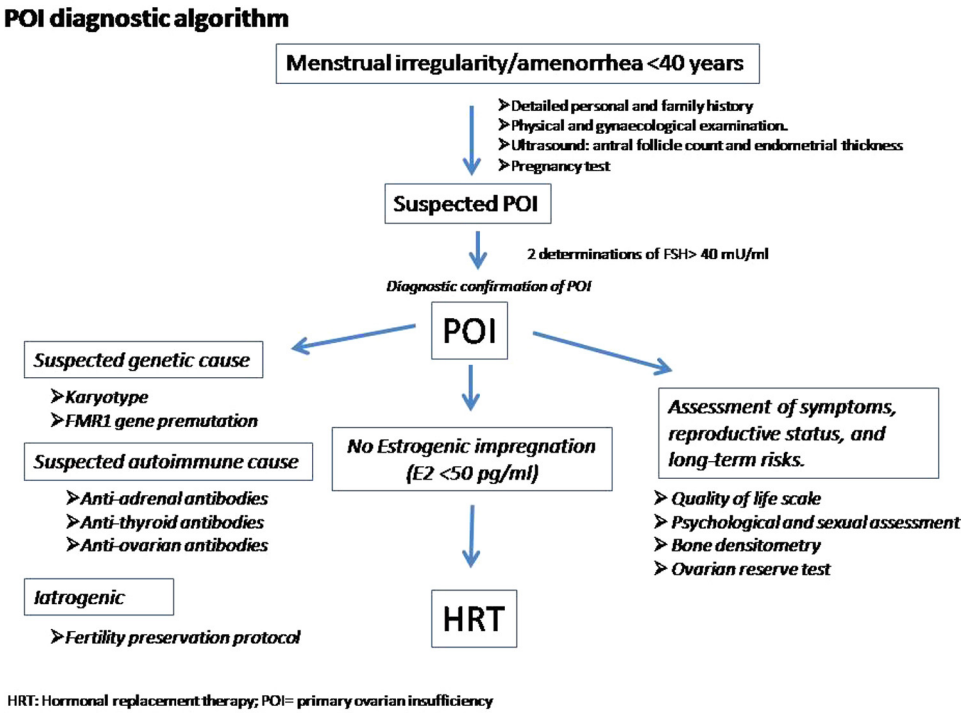

Fig. 1. POI diagnostic algorithm.

6. Follow-up

Most women with POI, especially younger women or women who have not fulfilled their desire for pregnancy, handle the diagnosis poorly. They require emotional support and detailed information regarding their condition and its consequences in the medium and long term [1,14]. A single visit is generally not sufficient for the patient to understand the significance of the condition and to know the most appropriate treatment options for her particular situation.

6.1. Fertility preservation

Various strategies have been proposed to preserve ovarian function in patients at risk of developing POI. These include surgical transposition of the ovaries, cryopreservation of ovarian

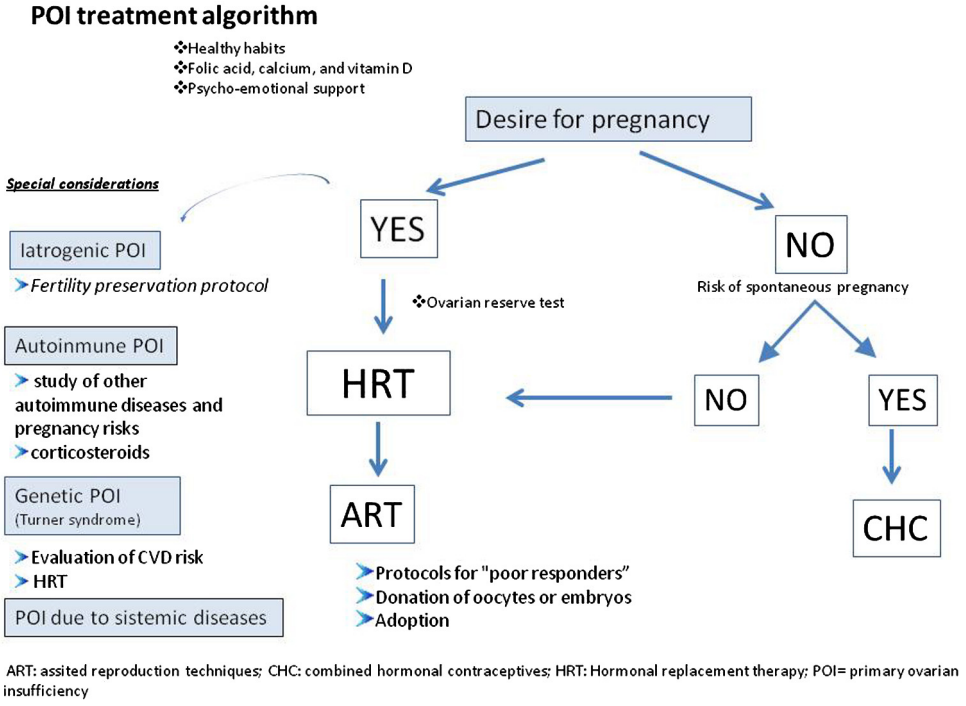

Fig. 2. POI treatment algorithm.

tissue, oocytes or embryos, and *in vitro* oocyte maturation [19].

The cryopreservation of oocytes has improved substantially with vitrification techniques and poses none of the ethical problems of embryo freezing; pregnancy rates of 65.2% are achieved [20]. Controlled ovarian hyperstimulation, which can be performed using aromatase inhibitors in the case of patients with hormone-dependent tumours, is followed by *in vitro* fertilisation of oocytes [21].

There is greater experience with embryo vitrification, and this achieves pregnancy rates comparable to fresh embryo transfer; however, it has the disadvantage of not being suitable for use in minors and there are also ethical issues regarding its use [22].

Surgical transposition of the ovaries may be useful in cases of pelvic radiation, but there are widely varying results, depending on the series [23].

Ovarian cortex cryopreservation and *in vitro* maturation of oocytes constitute other therapeutic alternatives when ovarian stimulation cannot be performed. The former technique would be recommended in girls [24]. During *in vitro* oocyte maturation, small antral follicles are punctured without the need for stimulation. However, there is insufficient evidence to establish any specific recommendation for either of these techniques. Similarly, gonadotropin releasing hormone (GnRH) agonists have been suggested as a treatment to preserve fertility in patients receiving CT [25], but their recommendation is always secondary to the other options above.

Finally, prophylactic salpingo-oophorectomy has been considered an option for patients with BRCA1-2 mutations. We recommend delaying this procedure until all reproductive desires have been achieved because the risk of cancer in these patients increases beyond 35 years, 10 years before the average age at onset of familial ovarian cancer [26].

6.2. Fertility treatments

According to a recent review [27], there is no optimal means to attempt pregnancy except oocyte or embryo donation, although it seems appropriate to achieve a decrease in basal FSH levels prior to ovulation stimulation. Of the various strategies studied, only estrogens appear to be effective for folliculogenesis, by decreasing FSH levels and increasing the intrafollicular expression of its receptors, which may explain the occurrence of spontaneous pregnancies in women with POI receiving hormonal therapy (HT).

One double-blind randomised controlled trial (RCT) significantly increased ovulation *versus* placebo (32% *versus* 0%) when ethinyl estradiol was used (0.05 mg/8 h two weeks prior to ovarian stimulation), decreasing FSH levels to below 15 mIU/ml [28]. Estrogen treatment is also required in POI patients who have not had adequate genital development (Turner syndrome) [29].

Dehydroepiandrosterone (DHEA), used in patients with poor response to fertility treatments, was used in a small double-blind RCT *versus* placebo (25 mg/8 h for 16 weeks) and was associated with increased follicular count, ovarian volume, and testosterone, DHEA sulfate, and estradiol levels [30].

The use of GnRH agonists prior to stimulation does not improve ovulation, and the use of antagonists or clomiphene citrate may even be harmful. Moreover, based on studies with germ-line stem cells, it has been proposed that dietary restrictions may increase the quality of oocytes [31].

Before any fertility treatment is proposed to a patient with POI, it is advisable to assess the risk inherent in pregnancy itself. Pregnancies in women with a Turner karyotype have an elevated risk of maternal mortality from aortic dissection and morbidity from hypertensive disorders [32].

6.3. Treatment to restore hormonal status

Therapeutic strategies for POI patients without reproductive intentions are aimed primarily at relieving symptoms and preventing long-term risks. Such treatment focuses on hormonal therapy (HT), with a focus on psychological adaptation. The clinician must strive to explain to the patient the nature of the condition, and allow time for the patient to assimilate the information, address concerns that may arise, and provide sources of further information and support [33].

We recommend starting HT as soon as POI is diagnosed and maintaining it until the age of at least 51, the age of natural menopause [34]. The appropriate doses or formulations of HT for young women with POI have not been clearly established. Although there is no evidence of greater efficacy or safety for any of them, we suggest, as a general recommendation, that administration should be easy, to improve compliance. Additionally, it is recommended that patients be examined annually to monitor their condition and detect any associated or newly emerging pathology.

Estrogens and testosterone can be used in women with surgical menopause and hypoactive sexual desire disorder. However, testosterone is available only as a magistral formula; therefore, considering the hormonal deficit of these patients, the use of tibolone is recommended to improve the sexual health of women with surgical menopause [35].

Although HT reduces the risk of fracture and CVD, other lifestyle measures are necessary, such as regular exercise, cessation of substance abuse, and a diet rich in or supplemented with calcium and vitamin D [36].

6.4. Alternatives to HT

In patients for whom HT is contraindicated, such as breast cancer survivors [37], there are several options, depending on the symptoms and risks (see Table 2). Regarding the treatment of osteoporosis, the use of other antiresorptive agents would be indicated, but the long-term risk observed with some of them (mainly alendronate) has suggested other strategies are required, such as therapeutic holidays and sequential therapy. Selective estrogen receptor modulators (SERMs) do not appear to have the long-term effects described with alendronate, and they provide added protection against breast cancer and CVD [38,39]. Their only drawback is thrombotic risk, but that risk is very low in young women, such as those suffering from POI. For this reason, if HT cannot be administered, we recommend the use of a SERM for a number of years, with a switch to a more potent anti-fracture treatment when required [40].

It should be noted, though, that there is no evidence from RCTs for the use of antiresorptive agents such as bisphosphonates and SERMS in this age group.

6.5. Contraception

Spontaneous recovery of ovarian function (20%) and pregnancy (5–10%) are exceptional but possible scenarios, so the provision of combined hormonal contraceptives (CHCs) is recommended for patients not desiring pregnancy. Some clinical practice guidelines explicitly state that there is no reason to deny the use of CHCs according to age unless the user is a smoker or has a disease for which estrogens are contraindicated [41]. However, there is a consensus that specific follow-up protocols are not recommended; the decision regarding the discontinuation of CHCs must be based on individualised advice because there is no test presently available to confirm when ovarian function definitely ceases [42].

Although HT has been shown in some studies to be preferable to CHCs for maintaining bone mineral density (BMD) and lowering

Table 2
Recommendations in POI patients who cannot use HT [37].

Vasomotor symptoms
- Gabapentin, SSRIs, and clonidine have proven effective in the treatment of hot flashes in breast cancer survivors (Grade 2B).

Vaginal atrophy
- Regular sexual activity helps to maintain vaginal health.
- Smoking cessation is recommended for its health benefits and because smoking decreases estrogen levels.
- It is convenient to use vaginal moisturisers and lubricants during intercourse (Grade 2B).
- The practice of pelvic floor exercises is advised.
- Address possible underlying psychological factors (anxiety or depression) that may interfere with sexuality.
- For women with breast cancer who present a low risk of recurrence or who are taking tamoxifen, as well as for women for whom moisturising/lubricating creams are not effective, topical low-dose estrogens or ones with no absorption are recommended, after weighing the risks/benefits in consultation with the patient and the oncologist (Grade 2B).
- We do not recommend any treatment with topical estrogens in women treated with aromatase inhibitors (Grade 2C).

Contraception
- Chemotherapy and anti-estrogen therapy are teratogenic. Women with POI and the risk of pregnancy should use safe contraception during treatment.
- According to the eligibility criteria of the WHO, CHC are not indicated in women with breast cancer, and barrier methods or copper IUDs are preferred.
- The use of progestin-only methods may be considered in a woman with a history of breast cancer in circumstances where the benefits outweigh the risk of recurrence.

Osteoporosis
- The best alternatives to HT in these patients are SERMs (bazedoxifene or raloxifene), maintained as long as they are effective, except in the case of thrombotic risk, in preference to bisphosphonates and other antiresorptive agents.
- Healthy habits are always recommended (diet, regular exercise, and cessation of substance abuse) in addition to calcium and vitamin D supplements.

cardiovascular risk, CHCs have been successfully used for the treatment of menstrual cycle disorders in women of all ages. It has even been suggested that in healthy women over 40, their use could reduce certain gynaecological cancers and bone loss.

Women with POI have more mood changes, are more prone to depression, and have a higher risk of CVD, especially when POI occurs early [43]. Some guidelines advise the use of specific CHCs for women of this age, especially CHCs with natural estrogens or natural estrogen with the levonorgestrel intrauterine system, which has a reduced thrombotic risk and a lower incidence of heavy menstrual bleeding [44].

7. Recommendations

- While we recognise that the term 'premature menopause' is widely accepted among non-specialist health care providers and by the general population, we recommend using the term *primary ovarian insufficiency* to refer to the loss of ovarian hormonal function in women under 40 years of age.
- POI treatment begins from the moment of diagnosis. The first step is a detailed and sensitive discussion of the diagnostic methods that can be used and of the reproductive prognosis and the therapeutic measures available. Emotional support from a psychotherapist will often be needed, especially in younger women.
- In POI patients, HT is the treatment of choice to alleviate the symptoms of hypoestrogenism and to prevent long-term consequences (Grade 1B).
- Any formulation of HT or CHC is valid for women with POI, and we suggest that therapy be continued until the age of at least 51, the average age of natural menopause (Grade 2B).
- HT prevents or delays the onset of cardiovascular disease, fracture, and mood and cognitive disorders in women with POI.
- HT is also recommended in women who wish to become pregnant because its isolated use or use prior to ovarian stimulation has been accompanied by higher pregnancy rates (Grade 2C).
- A healthy lifestyle is recommended to improve fertility, associated symptoms, and bone and cardiovascular health. This should include regular exercise and adequate intake of calcium and vitamin D (Grade 1A).
- The treatment of women with autoimmune POI is similar to the treatment of POI due to other causes.
- We recommend not using androgen replacement therapy in women with spontaneous POI with normal adrenal function (Grade 2B).
- Given that some women with POI have spontaneous pregnancies, we recommend the use of combined hormonal contraceptives for patients not desiring pregnancy if there is no contraindication (Grade 2B).
- The treatment of choice to achieve pregnancy is oocyte/embryo donation.
- No treatment with the patient's own oocytes has been effective, although previous estrogenic impregnation has been successful in isolated studies.
- We recommend a prior cardiovascular assessment in women with Turner syndrome as well as candidate oocyte donation, due to their CVD risk during pregnancy.
- If a patient is to undergo treatment that is likely to reduce her fertility (surgery, RT, or CT), she should be informed of this issue and of the available techniques to preserve ovarian function. Of these techniques, the most effective are the vitrification of oocytes and embryos.

Contributors

N. Mendoza, P. Llaneza and R. Sanchez-Borrego: conception and design of the idea, data interpretation and preparation of manuscript.

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