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Premature ovarian insufficiency: A toolkit for the primary care physician☆

Irene Lambrinoudaki [a,*], Stavroula A. Paschou [a], Mary Ann Lumsden [b], Stephanie Faubion [c], Evangelos Makrakis [d], Sophia Kalantaridou [d], Nick Panay [e]

[a] 2nd Department of Obstetrics and Gynecology, Medical School, National and Kapodistrian University of Athens, Greece
[b] Professor of Gynaecology and Medical Education, University of Glasgow, UK
[c] Mayo Clinic Center for Women's Health, Division of General Internal Medicine, Mayo Clinic, Jacksonville, FL, USA
[d] 3rd Department of Obstetrics and Gynecology, Medical School, National and Kapodistrian University of Athens, Greece
[e] Queen Charlotte's & Chelsea and Chelsea and Westminster Hospitals, Imperial College, London, UK

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ABSTRACT

Premature ovarian insufficiency (POI) refers to the loss of ovarian activity before the age of 40 years, which leads to hypoestrogenism and amenorrhoea. The diagnosis of POI in a young woman has potentially life-changing physical and emotional consequences for both the patient and her family. Therefore, it is very important that the diagnosis is correct and that it is made in a timely manner. Unfortunately, the diagnosis and therefore the effective treatment of POI are often delayed, which underlines the need for education of the broad medical community on the issue. A panel of menopause experts reviewed and critically appraised the literature, and present: 1) the diagnostic approach to POI, 2) the investigation of the etiology of this condition, 3) the therapeutic strategy regarding both hormone replacement therapy (HRT) and fertility and 4) the long-term follow-up and management for ensuring quality of life, as well as urogenital, cardiovascular, bone and mental health. The ultimate goal is to provide a complete toolkit for the primary care physician to have easy access to all the information needed for the optimal management of women with POI, in the context of evidence-based and personalized medicine.

1. Introduction

Premature ovarian insufficiency (POI) or hypergonadotropic hypogonadism refers to loss of ovarian activity, which leads to hypoestrogenism and amenorrhoea, before the age of 40 years. In women with spontaneous POI there may be intermittent resumption of ovarian activity in approximately 25 % of women. The diagnosis of POI in a young woman has potentially life-changing physical and emotional consequences for the sufferer and her family. It is therefore important that the diagnosis is correct and that it is made in a timely manner. There is often a delay in the diagnosis and therefore the effective treatment of POI, but it is also vitally important that such a profound diagnosis is not made erroneously as this can also have a devastating impact on the woman's emotional wellbeing [1]. There are a number of steps which facilitate a correct, timely diagnosis and these will be outlined in the next section.

2. Making the diagnosis of POI (Table 1)

2.1. Menstrual history

It is particularly important that careful consideration is given to assessing the age of menarche and the regularity of menses. Early menarche has been associated with subsequent POI. Primary or secondary amenorrhoea are the pathognomonic symptoms which characterize the diagnosis of POI. The initial presentation may be with oligomenorrhoea (menstrual irregularity), but it is important that POI is not over-diagnosed in those with regular cycles and no history of menstrual disturbance [1]. Although amenorrhoea is not officially diagnosed unless menstruation has been absent for 6 months, there is general agreement that it is justified to commence investigations if menstruation has been absent for 3–4 months. Changes in the length, heaviness or intervals of menstruation should also be investigated, whether or not there are co-existing symptoms. It must not be forgotten that there are

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* Corresponding author at: Aretaieio Hospital, 76 Vas. Sofias Av., GR11528, Athens, Greece.
E-mail address: ilambrinoudaki@med.uoa.gr (I. Lambrinoudaki).

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other common causes of amenorrhoea, e.g. PCOS, hyperprolactinaemia or hypothalamic dysfunction due to stress / weight loss and that these need to be excluded in subsequent investigations.

2.2. Symptoms of POI

Estrogen deficiency symptoms may or may not be present and can vary immensely in frequency, type and severity. The symptoms may be intermittent due to erratic release of ovarian hormones. The classic symptoms of menopause are the vasomotor symptoms, typically hot flushes and night sweats, vulvovaginal atrophy, vaginal dryness and dyspareunia, but other frequent attributed symptoms include insomnia, mood disturbances, cognitive problems, e.g. memory issues, tiredness, loss of libido and weight gain [2]. The presentation may also be with sub-fertility due to the reduction in ovarian reserve associated with POI. Nulliparity and low parity are therefore associated with POI. Symptoms may be more severe in POI than natural menopause, particularly in the case of iatrogenic POI due to the rapid loss of ovarian hormones and fertility; this can have profound psychosocial and psychosexual effects [1,2].

2.3. Family history

It is important to take a careful family history. The incidence of spontaneous POI in first degree relatives is quoted at 10–15 % [2]. A family history of POI or early menopause (<45 years) is often associated with genetic disorders, e.g. Fragile X, which should be enquired about. A recent position statement [3] concluded that the following were predictors of POI (those in italics are strong predictors): *genetic abnormalities; family history of premature or early menopause*; being a child of multiple pregnancy; early menarche; nulliparity/low parity; cigarette smoking (dose–response effect); underweight.

2.4. Biomarkers

2.4.1. Follicle stimulating hormone (FSH)

There is considerable variation in international society guidelines as to what the precise optimum cut off should be for FSH levels to confirm the diagnosis of POI. However, all guidelines agree that the diagnosis should be confirmed by a minimum of two elevated FSH tests, 4–6 weeks apart [4–7]. Women should not be informed they have POI based on the results of one test due to the fluctuation in FSH levels, particularly if there is occasional menstruation.

The most widely utilized diagnostic limit for FSH is > 40 IU/l [4,5], although the UK National Institute for Health and Care Excellence guideline suggests > 30 IU/l [6] and the European Society of Human Reproduction and Embryology (ESHRE) guideline suggests a lower cut-off of >25 IU/l [7]. The lower FSH cut off is recommended by ESHRE because some women with POI express FSH levels lower than the typical cut-off values, particularly women with autoantibodies. Women with POI due to steroidogenic cell autoimmunity have been found to have significantly lower FSH levels (n = 26, range 26–64 mIU/mL, median 37 mIU/mL) compared with idiopathic POI (n = 66, range 61–166 mIU/mL, median 99 mIU/mL) (P = 0.001) [8]. Since patients with autoimmune POI should be included in the diagnosis, the ESHRE guideline development group recommended a lower cut off level of FSH > 25 IU/l which is above the physiological range for FSH. In women with amenorrhoea due to hypothalamic dysfunction or hypopituitarism FSH as well as estradiol levels are low and in PCOS, FSH levels are normal. If occasional menstruation is still present, FSH levels should be performed on day 2−3 of the menstrual cycle when estrogen levels are low so that FSH levels are not suppressed by negative feedback.

Table 1
Diagnosis of Premature ovarian insufficiency (POI).

- A careful personal and family history is essential in making the diagnosis of POI
- A family history of POI is common in women diagnosed with POI
- Secondary causes of POI should be enquired about, e.g. genetic disorders, autoimmune disorders, infectious, e.g. mumps/TB and iatrogenic, e.g. surgery, chemo/radiotherapy
- Amenorrhoea may be intermittent or permanent and may occur before menarche (primary) or after menstruation has commenced (secondary)
- Two FSH tests > 25 IU/L at least 4 weeks apart should be performed to confirm the diagnosis
- The diagnosis of POI should not be made after only one FSH test
- AFC and AMH can provide supportive information to confirm the diagnosis

FSH: Follicle Stimulating Hormone; AFC: Antral follicle count; AMH: Anti-müllerian hormone; TB: Tuberculosis.

2.4.2. Anti-Mullerian Hormone (AMH)

Anti-Mullerian hormone is produced by developing antral follicles in the ovaries. There are several different assays and therefore interpretation of results can be difficult, but currently the ultra-sensitive assays are thought to be the most reliable measure of impaired ovarian reserve. However, the test is not widely available in primary care and can be difficult to access in secondary care. As such, it is not recommended as a routine part of the diagnostic work up. However, it can be used where there is diagnostic uncertainty in which case the woman may need to be referred to a specialty centre to have this done [6]. Women undergoing chemo- or radiotherapy for malignancy can also be monitored with AMH tests if a certain degree of recovery of ovarian function is expected [9].

2.5. Pelvic ultrasonography

Pelvic ultrasonography is regarded as a routine part of the diagnostic work-up in women suspected of POI. Useful information can be obtained regarding ovarian volume and the antral follicle count. The ovaries are typically small in POI with few or no antral follicles visible. These findings are usually correlated with the FSH and AMH levels, but occasionally follicles can be seen despite very high FSH and very low AMH levels. Although gonadotropin stimulation can be attempted in these circumstances it is rarely successful [10].

3. Investigating the etiology (Table 2 and Fig. 1)

POI occurs due to a reduction in the primordial follicle pool. This can be due to accelerated follicular atresia or destruction, or due to problems in the support, recruitment or maturation of primordial and/or growing follicles [1]. 'Resistant ovary syndrome' is a rare disorder in which levels of FSH and luteinizing hormone (LH) are elevated despite normal AMH and antral follicle counts. It is thought to occur due to ovarian unresponsiveness to FSH, probably due to genetic or immunological inactivation of the FSH and/or LH receptors [11].

Individual or a combination of etiological factors including genetic, autoimmune, iatrogenic or environmental may precipitate POI. However, in a large proportion of women diagnosed with spontaneous POI, the etiology remains unknown; the term idiopathic is still used in this instance although it is likely that many of these cases have an undetected genetic etiology. It is also possible that spontaneous POI may occur as part of an aging syndrome in some women. There is increasing evidence that epigenetic aging can begin as early as a few weeks post-conception in fetal tissues [12].

The investigation of the etiology of POI will now be discussed from a primary care perspective, considering the recommended pragmatic approaches to assess each etiological category (please refer to Fig. 1a and b).

3.1. Genetic etiology

3.1.1. Chromosomes

If the diagnosis of spontaneous POI appears likely, chromosomal analysis should be offered to all women on the basis that chromosomal

Table 2
Key investigations of the Etiology of POI (Tests in **bold** should regarded as mandatory).

Genetic screening:

- **Karyotype and fragile X**
- Referral for further genetic counselling/investigation if personal or family phenotype consistent with known syndrome

Immunological screening:

- **Adrenal: Adrenal cortex and 21-hydroxylase antibodies**

Adrenal function tests if antibody positive

- **Thyroid: Thyroid peroxidase antibodies**

Thyroid function tests (whether antibody positive or negative)

- Ovary: Antibody screening not indicated due to high false positive rate
- Other autoimmune disorders: Only if indicated by personal or family history

Imaging:

- **Ultrasound +/- MRI: To assess ovarian presence/size/AFC/pathology**

May confirm deficiency or absence of ovarian cortical tissue for congenital or surgical reasons, e.g. dysgenesis/androgen insensitivity syndrome/endometriosis surgery

Infectious screening:

- Infectious disease screening only if indicated by clinical history

Toxic screening:

- Guided by occupational health and clinical history

Metabolic screening:

- Guided by clinical and family history

Investigations for iatrogenic causes:

- Guided by medical and surgical history - may be obvious, but also see imaging above

abnormalities are highly prevalent in POI (Fig. 1a). When primary amenorrhoea occurs, 21 % will have a karyotypic abnormality compared to 11 % with secondary amenorrhoea [13]. Karyotyping is the gold standard to assess chromosomal abnormalities, although newer techniques exist. Turner syndrome (XO) is the commonest chromosomal abnormality in POI; it occurs in 1 in 2500 births and involves the complete or partial loss of one X chromosome. Turner syndrome mosaicism can also occur leading to less severe POI with the possibility of pregnancy. The loss of X-linked genes results in X inactivation of important X-related gene products that escape inactivation by the second X [14]. If Y chromosomal material has been detected, these women should be counselled about the possibility of developing a gonadal tumour and gonadectomy should be offered.

3.1.2. Fragile X

The commonest genetic abnormality in POI involves a premutation in the fragile X mental retardation I gene (FMR-I) (Fig. 1a). It is carried in 1 in 250 women and affects the copies of the CGG trinucleotide repeat in this gene in the 5' area of X chromosome. The normal finding is 5–45 repeats; when 55–200 repeats are present, referred to as a "pre-mutation", there is a 20 % chance of developing POI. Genetic screening of the woman and her family is recommended; affected female family members might wish to consider pregnancy planning to prevent mental disability, which can be particularly severe in male offspring [15].

3.1.3. Autosomal gene mutations

A number of autosomal genes have been suggested as causative of POI; some mutations have been identified, while others are candidate genes. However, routine screening for autosomal gene mutations in POI patients cannot be recommended except in specialty research settings [7]. If the phenotypic characteristics of the woman correlate with a specific gene mutation, she should be referred for genetic counselling and possible testing.

Whole genome sequencing techniques offer hope for the future identification of novel causative genomic factors not yet detected by targeted gene sequencing [16], thereby helping to unravel the actual etiology in a significant proportion of women who are diagnosed with idiopathic POI. Possible rare genetic disorders linked with POI are beyond the scope for discussion in this paper but summarised in Fig. 1b for reference.

3.2. Autoimmune etiology

The incidence of autoimmune disorders in POI is higher than the general population. It is therefore recommended that autoantibody testing should be performed. Up to 20 % of women with spontaneous POI have evidence of adrenal autoimmunity with histological evidence of autoimmune oophoritis, and 10–20 % of patients with Addison's disease have POI [17]. Adrenal cortex or 21-hydroxylase antibodies occur in approximately 4% of women with POI; these should be screened for in all POI patients and if positive, these women should be referred to an endocrinologist to have formal adrenal function testing. It should be stressed that POI may occur prior to development of severe adrenal insufficiency and therefore prompt referral is recommended if adrenal antibodies are present [18].

Thyroid peroxidase autoantibodies and thyroid function should also be tested for due to the frequent co-existence of autoimmune thyroid disorders such as Hashimoto's thyroiditis. Other linked autoimmune disorders include type 1 diabetes, rheumatoid arthritis and inflammatory bowel disease. There is insufficient evidence to recommend routine screening for type 1 diabetes in POI. Ovarian antibody testing is not recommended due to a high rate of false-positive results [17].

3.3. Infectious etiology

Although POI has been linked to conditions such as mumps or tuberculosis, in practice these infectious etiologies are diagnosed very rarely. More recently a link to human immunodeficiency virus has been recognized, either due to antiviral medications or the virus itself [19]. There is insufficient evidence to routinely screen for these diseases in women diagnosed with POI unless this is indicated by the history or clinical findings, as in exposure to HIV.

3.4. Toxic etiology

There has also been an association of POI with polycyclic aromatic hydrocarbons as found in cigarette smoke. Although this is not routinely tested for in clinical practice, it reinforces the advice that smoking should be avoided, especially in women seeking to optimize their fertility. Appropriate occupational health measures should also be instituted to avoid exposure to environmental pollutants such as phthalates and bisphenol-A found in plastic production [20].

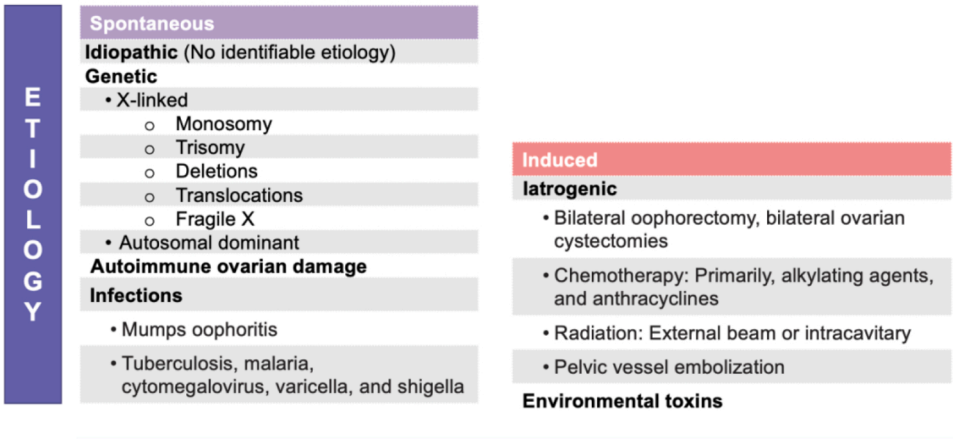
3.5. Metabolic etiology

Although galactosemia is a rare metabolic disorder, occurring in 1 in 30,000–60,000 newborns, there is a well-recognized link with POI. It caused by a deficiency of galactose-1-phosphate uridylotransferase (GALT) and is associated with accumulation of galactose in organs with high GALT expression (liver, kidney, ovary and heart). It can cause toxic levels of galactose in the oocyte leading to pre pubertal POI [21]. It is usually screened for in newborns who are failing to thrive and cannot tolerate milk and in those with a family history of the condition. GALT enzyme or genetic (autosomal recessive) testing can be carried out; however, even with complete exclusion of milk containing products, galactosemia can still lead to POI in young women due to some endogenous production of galactose. Other rare metabolic disorders linked with POI are beyond the scope of discussion in this paper.

3.6. Iatrogenic etiology

The proportion of young women with iatrogenic POI as a result of chemo- and radiation therapy, surgery or other iatrogenic interventions is increasing as cancer survival rates continue to improve [22]. Preservation or recovery of ovarian reserve following chemotherapy depends

(a)



(b)

Categories	Chromosomes	Genes
Identified mutations	X	FMR1,2, BMP15
	Autosomal genes	ESR1, FSHR, LHR, FSHβ, LHβ, inhibin A, GALT, AIRE, NOGGIN, POLG, CYP19A1, forehead box L2 FOXO3, steroidogenic factor 1
Non-identified mutations	X	AT2, c-kit, sox 3
	Autosomal genes	MIS
Candidate genes	X	DIAPH2, DFFRX, XPNPEP2
	Autosomal genes	ATM

Fig. 1. (a) Etiology of POI (b) Genes implicated in POI.

on the type, dosage, previous ovarian reserve, and age at administration [23]. Women who have received anthracyclines and alkylating agents are at risk and those who undergo allogeneic stem cell transplants are at very high risk of POI (>90 %) [23]. Pelvic surgery and uterine artery embolization procedures which have the potential to impair ovarian blood supply can rarely lead to POI or early menopause. It is therefore important that women receive adequate counselling about fertility as well as short- and long-term health related to estrogen deficiency if iatrogenic interventions are planned that might impact ovarian reserve [22].

4. Treatment plan

4.1. Hormone replacement therapy (Table 3 and 4)

Hypoestrogenism associated with POI can lead to symptoms associated with estrogen deficiency such as vasomotor symptoms, vulvovaginal atrophy (VVA) and also subfertility which can have devastating consequences in a young woman. On the longer term, decreased bone density and increased risk of cardiovascular disease (CVD) are also of significance.

Women with POI, therefore, should be treated as patients with any endocrine deficiency and physiological replacement of ovarian steroid hormones (estrogens and progestogens) is indicated up to the age of normal natural menopause [24,25]. Hormone replacement therapy (HRT) should be individualized according to age, patient characteristics and patient needs and preferences [7,24–27]. Younger women may require higher estrogens dose than those used in older women. For some,

Table 3
Hormone replacement therapy regimens for women with premature ovarian insufficiency.

Estrogens	Progestogens (for women with intact uterus only)
17β-E2 2–4 mg orally or CEE 0.625–1.25 mg orally or 17β-E2 50–100 μg transdermally and topical vaginal estrogens when VVA/GSM is diagnosed	Natural progesterone orally 200 mg cyclically or 100 mg continuously or Dihydrogesterone 10–20 mg orally or Norethisterone 1–5 mg orally or Norethisterone 0.25 mg transdermally

E2: estradiol; CEE: conjugated equine estrogens, VVA: vulvovaginal atrophy, GS: genitourinary syndrome.

Table 4
Monitoring of women with premature ovarian insufficiency on hormone replacement therapy.

Baseline	• Body weight and height • BMI • Renal function • Liver function • Thyroid function • Fasting glucose and HbA1c* • Lipids levels* • Calcium and vitamin D* • Blood pressure • CVD risk estimation • BMD (if normal, repeat in 2–3 years) • Fracture risk estimation • Mammography (as per national guidelines, no additional breast screening is required in women on HRT for POI unless clinically indicated) • Cervical cancer screening (as per national guidelines)
Follow-up	• Body weight and height • BMI • Blood pressure • Thyroid function (depending on baseline evaluation) • CVD risk estimation • Fracture risk estimation • Mammography (as per national guidelines, no additional breast screening is required in women on HRT for POI unless clinically indicated) • Cervical cancer screening (as per national guidelines)

HRT: hormone replacement therapy; POI: premature ovarian insufficiency; BMI: body mass index; HbA1c: glycated hemoglobin; CVD: cardiovascular disease; BMD: bone mineral density.
* Recommendations vary according to national guidelines.

to achieve optimal sexual function, vaginal estrogen maybe required. Since the ovary produces androgens in significant amounts during the reproductive years, androgen replacement should be considered for some women with POI.

Management of young women presenting with primary amenorrhea requires close collaboration with pediatric endocrinologists. In that case, proper induction of puberty with optimal breast and uterine development is very important [24]. An efficient strategy is the initiation of low dose estrogen treatment initially, while progesterone withdrawal bleeds should follow after several months. The common practice of starting a low dose combined oral contraceptive does not offer the best outcome for puberty induction and uterine development, and therefore should be avoided [7,24,28].

For women of reproductive age, HRT with standard or low doses of oral or transdermal estrogens and progestogens should be used initially. The dose should not be titrated only for symptoms management, but should aim to approximate estrogen levels in a premenopausal woman. Specifically, 17β estradiol (E2) 2–4 mg or conjugated equine estrogens (CEE) 0.625–1.25 mg are the oral route options, the former being preferred in the UK and Europe, since it is "body identical". Transdermal 17β-E2 50–100 μg is another option, available in patches or gels [7, 24–27]. Topical vaginal estrogens may be used as an adjunct to systemic therapy, especially when vulvo-vaginal atrophy (VVA) is diagnosed, a condition often termed as genitourinary syndrome of menopause (GSM). VVA presents with various symptoms, such as vaginal dryness, irritation, itching or dyspareunia. Estrogen-containing creams, tablets and vaginal rings appear to be equally effective [29,30] (Table 3).

Estrogen only therapy is the most appropriate treatment of hypoestrogenism for women after hysterectomy. In women with an intact uterus, a progestogen should be added to prevent endometrial hyperplasia. Natural progesterone 200 mg, dihydrogesterone 10–20 mg, oral norethisterone 1–5 mg or transdermal norethisterone 0.25 mg are recommended [7,24–27] (Table 3). Oral progestogens are administered once or twice daily sequentially for 10–14 days per month, leading to regular monthly menstrual bleeding. Transdermal norethisterone is administered twice weekly for 14 days per month, resulting in regular monthly bleeding [24,25]. Some women prefer to take a daily progestogen as part of a "continuous combined" regimen without menstrual bleeding, in which case lower doses can be given. Cyclic regimens are preferable for those who wish to maximize their chances of achieving a spontaneous pregnancy (albeit unlikely) and those planning oocyte donation IVF in the near future.

CEE is used less frequently now than in the past because of a greater risk of hypertension and thrombosis compared to 17β-E2, which is more physiological as a "body identical" hormone [31,32]. 17β-E2 is also available in transdermal regimens. The transdermal route of estrogen administration results in attainment of physiologic hormone levels with lower daily doses. Furthermore, this route avoids first pass liver metabolism and is associated with lower risk of thromboembolism [25,33]. Some young women with POI and even some physicians find the combined oral contraceptive pills (COCP) to be more socially acceptable (as opposed to a regimen designed for postmenopausal women) and easier option for estrogen replacement. Although randomized data are currently lacking, it is generally felt that COCP should not be the first line approach for a number of reasons. First, COCP does not represent a physiological replacement scheme in terms of both type and dose of steroid hormones, as is the case with CEE. Furthermore, the pill-free week amounts to three months of estrogen deficiency per year which may coincide with relevant estrogen deficiency symptoms and can result in bone loss and other long-term complications. Of course, COCP can be taken continuously with no pill-free week to avoid these consequences [34,35]. If break-through bleeding occurs with the continuous regimen, four to seven days can be taken off before resuming, and typically this will not occur for several months [36]. Moreover, the thrombotic risk is higher for COCP as compared to HRT. In case of the use of COCP in women with POI, those with lower dose ethinyl estradiol and second-generation progestogens present the lowest thromboembolic risk [37].

HRT presents numerous beneficial effects for women with POI. It has been proven to improve body fat composition, increase insulin sensitivity, decrease various cardiovascular disease (CVD) risk factors and to improve vascular function *per se* [38,39]. Furthermore, HRT improves bone mineral density (BMD) and decreases fracture risk in later life [25]. There have been some concerns regarding the increased risk for breast cancer and thrombosis associated with HRT use. However, the reality is that these concerns mainly derive from studies involving older, postmenopausal women. Women with decreased or absent estrogen production are at reduced risk of breast cancer compared with their peers who have normal menstrual cycles. This concept is supported by observational data on the association between the age of menopause and the risk of breast cancer. Although administration of HRT is likely to increase the risk of breast cancer when compared with those who have untreated POI, it does not appear to result in an overall increase in women under the age of 50 years when compared to women with normal menstruation. Regarding thromboembolic risk, there is lack of data in women with POI, and findings from studies with older women cannot be directly extrapolated since age is a significant risk factor for venous thromboembolism. The transdermal route of estradiol administration should be always considered in women with POI who are at increased risk of thrombosis, such as those with obesity [25,37,40,41].

Androgen replacement therapy in women with POI, although not routinely recommended, when considered, should follow suggestions for use and monitoring as in older postmenopausal women [42]. Androgen therapy is indicated in women with persistent sexual dysfunction despite optimized HRT [42,43]. Treatment should only be with testosterone formulations that can achieve blood concentrations of testosterone that approximate premenopausal physiological concentrations. Physicians should bear in mind that most testosterone preparations available in Europe are not officially licensed for use in women, as they are prepared for men. These formulations can be judiciously used in customized doses for women, and blood testosterone concentrations must be monitored regularly [42,43].

HRT should be continued in women with POI up to the age of normal natural menopause, approximately 51 years. Meticulous baseline and annual clinical follow-up is required in order to assess symptoms, as well as the risks and benefits of HRT in terms of CV risk factors, bone and other possible health issues relevant to the individual woman. A number of laboratory tests should also help to estimate the individual fracture and cardiovascular risk. Mammography and cervical cytology for cervical cancer screening should be performed as indicated for the general population of the same age in the woman's own country (Table 4) [7, 24–27]. The aim is to achieve effective hormone replacement with as few adverse effects as possible, as continuation of treatment may be required for many years.

4.2. Fertility (Fig. 2)

Fertility impairment is a critical adverse feature of POI. As ovarian function diminishes and ceases, the loss of fertility is inevitable. Clinically, appropriate counselling and management must be distinguished between women with established POI and those at risk for or with imminent POI. Referral to or collaboration with a specialist in Reproductive Endocrinology is imperative.

4.2.1. Women with established POI

4.2.1.1. Natural conception. Ovarian activity may appear unexpectedly in a significant proportion (up to 25 %) of women with POI [44], and this is more likely to happen early after the onset of the disorder; consequently, spontaneous conception may occur. Positive predictive factors for resumption of ovarian activity include serum estradiol and inhibin B levels (but not serum AMH levels), the presence of follicles on ultrasound, secondary (vs. primary) amenorrhea, and (surprisingly) a family history of POI [44]. In various studies the chances of spontaneous pregnancies in women with POI range between 1.5 % and 10 % [44–47]. Obviously, advice should be given for not abandoning / delaying efforts to achieve pregnancy, but also for the use of contraceptive methods if a pregnancy is undesirable. HRT is not contraceptive unless estrogen is combined with a levonorgestrel intrauterine system.

The underlying cause of POI (if any) should be taken into account in pregnancy counselling and follow up. In cases of idiopathic POI, miscarriage rates, embryo aneuploidy rates, pregnancy complications and neonatal risks do not seem to be increased compared to general population [7,45,48]. In cases of FMR1 premutation carriers, preconception counselling regarding potential risks of intellectual disability and fragile-X-associated tremor/ataxia syndrome (FXTAS) in the offspring (both primarily in males) should be provided [49,50], along with the option of preimplantation genetic diagnosis. Spontaneous pregnancies in women with Turner syndrome (TS) may occur (usually in those with mosaic karyotype); prognosis may be better compared to pregnancies achieved with oocyte donation in TS (in general pregnancies in TS are considered to be at very high risk, see below) [51], even though a high miscarriage rate (up to 45 %) has been reported [52]. In cancer survivors, spontaneous pregnancies after chemotherapy have not been associated with increased adverse outcomes and/or congenital anomalies in the offspring [53]; some studies reported an increased incidence of low birth weight especially after the administration of anthracyclines [54], whereas exposure to the latter may be cardiotoxic leading to peripartum heart failure [55]. On the contrary, history of abdominal-pelvic radiotherapy has been robustly associated with a variety of adverse outcomes, such as late abortion, prematurity, low birth weight, stillbirth, placental disorders, uterine rupture and postpartum haemorrhage [56–58].

4.2.1.2. Fertility interventions - assisted conception. Many interventions for ovulation induction and/or autologous in vitro fertilization have been tried in women with established POI, with no or deniable results. These included: daily administration of oral estradiol for 6 months [59], oral ethinyl estradiol for two weeks before and during gonadotrophin administration [60], treatment with GnRH analogue and gonadotrophins with co-administration of dexamethasone [61], and treatment with azathioprine in cases of autoimmune POI [62]. In all these interventions, ovulation was more likely to have occurred spontaneously rather than due to a treatment effect. As expected, any efforts for fertility preservation by the means of oocyte/embryo cryopreservation in women with established POI is highly unlikely to be successful and therefore not to be recommended.

Currently, the only realistic solution for women with established POI seeking pregnancy is oocyte donation. The origin of the donated oocytes may be from anonymous donors or from a known donor (usually a relative, e.g. sister); note that legislation differs between countries regarding the allowed origin of the oocytes. There are no apparent

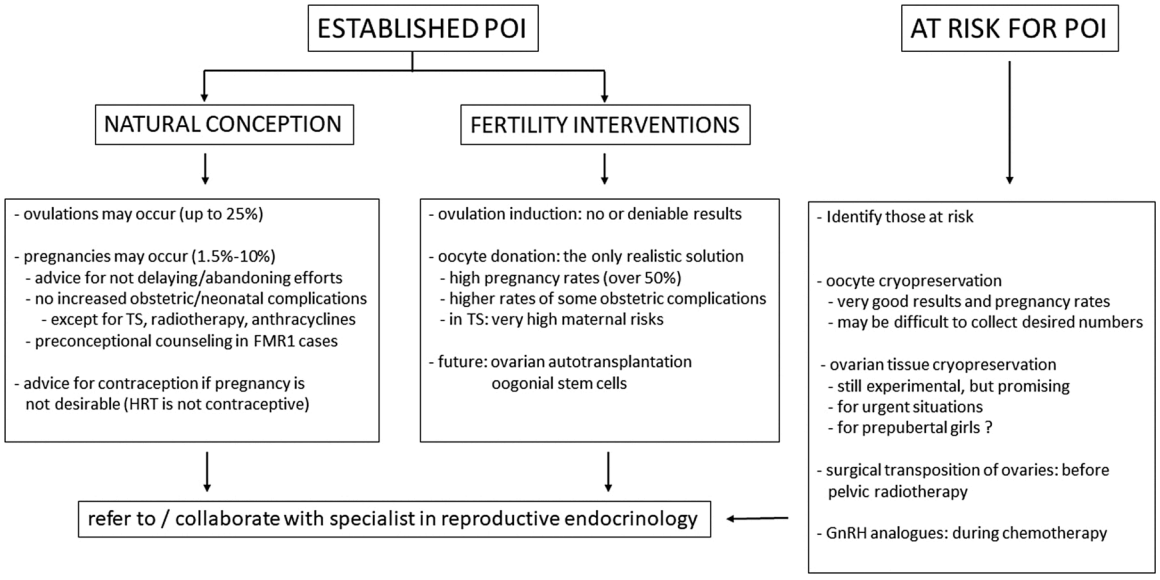


Fig. 2. Fertility for women with premature ovarian insufficiency (POI).

differences in results in completed cycles after the use of anonymous vs. known donors, but in the POI population, a sister donor may not be ideal as a similar genetic defect may jeopardize the availability of viable oocytes leading to high rates of cycle cancellation [63]. Endometrial preparation for oocyte donation cycles in POI women is achieved with the exogenous administration of sex steroids. Oocyte donation is an extremely successful assisted reproduction technique with live birth rates higher than 50 % per embryo transfer [64,65]. However, pregnancies achieved with donated oocytes have been associated with increased risk of some obstetric complications. Threatened abortion, low birth weight and pregnancy-induced hypertension/preeclampsia are the most consistently reported complications [66–68]; notably, the latter was not found to be significantly increased in the most recent study [69]. Nevertheless, all POI women receiving donated oocytes should undergo pre-conception medical assessment especially regarding their cardiovascular and renal function status, and their pregnancies should be followed with expert obstetric care. Pregnancies with donated oocytes in women with TS represent a specific high-risk subcategory due to the underlying increased maternal morbidity and mortality. A maternal mortality rate up to 3.5 % has been reported, mainly due to aortic dissection and cardiovascular incidents [51]; obstetric complications rates up to 10 % have been reported, with pregnancy-induced hypertension, preterm delivery and low birth weight being the most common [51,70]. Obviously, all women with TS should undergo detailed pre-conception screening, especially for cardiovascular risks, and those at high risk must be informed about the potential for life-threating complications. Cardiovascular risk assessments are essential throughout pregnancy. The same applies for cancer survivors having received cardiotoxic treatments (anthracyclines and/or cardiac irradiation).

Finally, possible future horizons for women with established POI, as presented in limited experimental reports, include the in vitro activation of dormant follicles followed by auto-transplantation of the extracted and processed ovarian tissue [71,72] as well as the identification and manipulation of oogonial stem cells that may exist in ovarian cortex [73–75].

4.2.2. Women at risk for or with imminent POI

This diverse population includes women with idiopathic low ovarian reserve, women with a history of extensive ovarian surgery, women with a strong family history of POI, some women with TS showing ovarian activity for an unpredictable period after menarche, survivors of childhood or adolescent cancer, and patients that will receive gonatodoxic chemotherapy or radiotherapy. The goal for this population is to provide realistic consultation about the necessity of not delaying efforts for spontaneous conception (if applicable), and to offer some type of fertility preservation (if possible). AMH levels should be evaluated, as low AMH has been associated with reduced fecundability in women over the age of 30 years [76].

Fertility preservation techniques include embryo, oocyte or ovarian tissue cryopreservation. Recent developments in oocyte cryopreservation allowed for exceptionally favorable clinical outcomes; fertilization, pregnancy, and live birth rates after IVF using cryopreserved / thawed oocytes are similar to those using fresh oocytes, and the technique is no longer considered experimental [77]. Embryo/oocyte cryopreservation involves the administration of ovarian stimulation protocols in an effort to collect the highest possible number of oocytes; a minimum of 8–10 oocytes is considered to be essential for obtaining acceptable future outcomes [78], but this is usually a difficult task for this population. Multiple collection cycles are usually needed. Ovarian tissue cryopreservation (and later auto-transplantation) is still considered as experimental but may be the only option for patients requiring immediate gonadotoxic treatment or for prepubertal girls [79]; the number of reported live births following this technique is still relatively small, but it appears promising [80,81]. Ovarian tissue may be transplanted into a pelvic (orthotopic) or extrapelvic (heterotopic) site. For cancer patients who require pelvic radiation, surgical (laparoscopically) transposition of the ovaries out of the radiation field may prevent iatrogenic POI [82]. For women who require potentially gonadotoxic chemotherapy, a cryopreservation technique should be offered before initiation of treatment, whereas in the most recent meta-analysis the co-administration of a GnRH agonist during chemotherapy proved to be effective in protecting the ovaries in terms of ovulation, resumption of menstruation and POI [83]. Finally, for postmenarchal patients with TS and evidence of some ovarian activity, oocyte cryopreservation should be discussed and offered. For prepubertal girls with TS, the situation is more complicated as the only reasonable technique would be ovarian tissue cryopreservation which is still experimental; a management plan with frequent serial evaluation of AMH has been proposed to determine the urgency of a decision [84].

5. Long-term follow up (Table 5)

5.1. Quality of life

The quality of life of women with POI may be adversely affected by a number of factors, including menopausal symptoms, mood disturbances, fertility concerns, poorer self-esteem, poorer perceived social support and psychosocial functioning, and lower overall satisfaction with life [85–89]. Women with POI who have bothersome hot flashes and night sweats are less likely to receive support from peers who are not going through the menopause transition, and therefore may experience greater psychosocial distress related to these physical symptoms such as social anxiety and frustration [86,88]. Women with POI have demonstrated significantly lower satisfaction with life versus comparator groups (including samples of students and older adults) [85]. Women with partners and those who already had children have reported higher levels of satisfaction than those without [85]. Many women with POI

Table 5
Recommendations for long term follow-up of women with POI.

Quality of Life	• Use empathic communication skills and leave ample time to discuss the diagnosis • Provide information and education on POI • Use shared decision making to develop a personalized management plan
Mental Health	• Screen for mood disorders regularly • Antidepressants and psychotherapy are proven strategies for management of depression • Estrogen therapy may have positive effects on mood
Sexual Health	• Screen for sexual dysfunction regularly • Treat VVA/GSM with systemic and/or local vaginal estrogen therapy • Androgen therapy is not routinely recommended Use a multidisciplinary approach to the management of sexual dysfunction
Cardiovascular Health	• Balanced diet • Exercise (weekly aerobic) • No smoking • Reduced salt intake • Investigate and treat dyslipidemia, diabetes or hypertension • Consider referral to specialist in cases of high CVD risk
Bone Health	• Balanced diet • Exercise (weekly weight-bearing) • Adequate intake of calcium and vitamin D • No smoking • Reduced alcohol consumption • Consider referral to specialist when: - BMD declines despite optimal HRT - Low-trauma fracture occurs

VVA: vulvovaginal atrophy; GSM: genitourinary syndrome of menopause; HRT: hormone replacement therapy; POI: premature ovarian insufficiency; BMI: body mass index; HbA1c: glycated hemoglobin; CVD: cardiovascular disease; LDL: low density lipoprotein; BMD: bone mineral density.

experience a delay in diagnosis and feel that their symptoms are not taken seriously, and therefore, may perceive a lack of appreciation of the ramifications and emotional toll of the diagnosis by their health care providers and subsequently a lack of quality care [87]. It has also been reported that women with POI lack satisfaction with the information provided on long-term consequences of premature menopause and confidence in managing their condition, potentially because of the inability to determine the cause of POI in many cases [90]. Data suggest that satisfaction with medical care correlates with mental health, vitality and social functioning. Factors contributing to satisfaction with medical services include being provided with access to information about their diagnosis, adequate opportunity to ask questions about their diagnosis and sensitivity in how they were informed of their diagnosis [86,91]. In addition to adequate time for education and counseling and empathetic communication, there are important opportunities to personalize care for women with POI utilizing an individualized assessment of needs and a tailored treatment plan utilizing shared decision making.

5.2. Mental health

Women with POI are at increased risk for depressive symptoms and for major depression [85,86,89,90,92]. A study investigating lifetime histories of depression in women with POI found that the onset of depression correlated with onset of menstrual irregularities indicative of altered ovarian function, but often predated the diagnosis of POI [92]. These finding are consistent with studies suggesting that fluctuations in estrogen levels during the menopause transition are associated with depressive symptoms [93] and that recurrence of depressive symptoms may occur following withdrawal of exogenous estrogen in post-menopausal women who experienced depression during the menopause transition [94]. The duration of estrogen exposure during the reproductive years has also been associated with risk for depression. In the Study of Women's Health Across the Nation, longer duration of estrogen exposure from menarche to the menopause transition was associated with a significantly reduced risk of depression during the menopause transition and in the 10 years following menopause onset, as was longer duration of oral contraceptive use [95]. Similar findings were noted in a meta-analysis of 14 studies that linked a shorter reproductive lifespan and younger age at menopause with greater risk for depression after menopause, highlighting the neuroprotective and anti-depressive effects of endogenous estrogen. Thus, it is important that women with POI be regularly screened for the presence of depressive symptoms given the high rates of depression. Data regarding management of mood disorders in women with POI are sparse, and psychotherapy and antidepressants are proven therapies for management of depression. Estrogen therapy, while not approved for treatment of depression, has antidepressant effects in perimenopausal women [96] and, in addition to multiple other potential benefits in women with POI, may improve depressive symptoms.

5.3. Sexual health

The impact of POI on sexual function is complex, with both biological and psychosocial contributing factors [97]. Because of its impact on wellbeing, loss of fertility, self-esteem, body image, sense of femininity, and other aspects of health, POI may adversely affect a woman's relationship with her partner, the quality of intimacy, and even a woman's motivation to start a new relationship [98]. Aside from reproductive function and psychosocial aspects contributing to sexual dysfunction, women with POI may experience reduced androgen production in addition to the loss of estrogen [99,100]. Because androgens are believed to play an important role in sexual functioning in women, and trials of testosterone treatment in women have shown improvements in sexual function [101], loss of androgens may have a negative impact on sexual functioning. However, studies to date have failed to demonstrate a significant correlation between androgen levels and sexual functioning in women generally [43] and in those with POI, specifically [102,103]. In addition to menopausal symptoms, loss of estrogen commonly results in genitourinary changes including loss of lubrication and elasticity, vaginal dryness, and dyspareunia, as well as urinary tract symptoms such as dysuria, urinary frequency, urinary urgency, and more frequent urinary tract infections [29]. Persistent genitourinary symptoms may lead to pelvic floor muscle hypertonicity and both superficial and deep dyspareunia and avoidance of sexual activity [104]. Because of the multifactorial nature of female sexual dysfunction, assessment of sexual function utilizing a biopsychosocial model that includes the biological, psychological, relational, and sociocultural factors that may be contributing to sexual dysfunction is important [105]. Similarly, women with POI may benefit from a multidisciplinary approach to management of sexual dysfunction which may include treatment with local estrogen therapy alone or in combination with systemic estrogen to reverse the genitourinary symptoms, including dyspareunia [30]. Androgen therapy in women with POI, although not routinely recommended, should follow recommendations for use and monitoring in postmenopausal women with low sexual desire, if used [105]. Targeted sexual health education in combination with cognitive behavioral strategies was associated with improvements in sexual functioning in a pilot involving women undergoing risk reducing bilateral salpingo-oophorectomy and deserves further study [106]. Psychosexual counseling to understand and address the multiple and often complex factors contributing to sexual dysfunction in women with POI remains critical.

5.4. Cardiovascular health

The premature estrogen decline in women with POI poses them at increased risk for diabetes mellitus type 2 (T2DM), cardiovascular disease (CVD) and osteoporosis [7,25–27]. Regarding T2DM, a recent meta-analysis indicated that women with POI have a 50 % increased risk of the disease compared with those aged between 45 and 55 years at menopause [107]. The meta-analysis included 191,762 women in total, of whom 21,664 cases developed T2DM (OR 1.50 for women with POI). Similar results emerged when women with POI were compared with those aged >45 years at menopause (OR 1.53) [107]. There is also strong evidence from early studies that women with POI are at higher risk for CVD compared to women with normal menstrual function [108]. This has been confirmed by a recent meta-analysis, which included 190,588 women from 10 studies in total [109]. These women were followed up for 4–37 years and 9440 CVD events were reported, namely 2026 events of ischemic heart disease, 6438 of stroke and 976 of total CVD events. It was concluded that POI is associated with increased risk of ischemic heart disease (HR 1.69), as well as increased risk of total CVD outcomes (HR 1.61). However, there was no association of POI with increased risk of stroke (HR 1.03) [109].

5.5. Bone health

POI has been also associated with reduced BMD and increased risk of fracture later in life. A recent meta-analysis resulted that the women with early menopause showed a 36 % increased fracture risk compared with women who experienced menopause after the age of 45 (OR 1.36). This meta-analysis included 462,393 women in total with 12,130 fractures reported. It seems that there is no distinct effect on the site of fractures [110]. COCP have been used as an acceptable and easy option for estrogen replacement instead of HRT by women or even recommended by physicians. In the case of a pill free week as happens usually, this amounts to three months of estrogen deficiency per year which can result in bone loss. This is not the same if continuous COCP treatment is provided, however standard dose HRT should be considered as the most physiological, efficient and safe type of replacement therapy concerning bone mass preservation [34,35].

The optimal follow up of women with POI must be lifelong. These women should be advised to adopt a healthy lifestyle, which includes

both balanced diet and exercise throughout their lifespan [25,27]. Adequate intake of calcium and vitamin D is important, while combination of weekly aerobic and weight-bearing exercise are the recommended types of physical activity for fitness and maintaining a normal body weight. Avoidance of smoking and moderation of alcohol consumption should be an essential part of each medical counseling [7, 25–27]. These lifestyle interventions are the cornerstone for prevention of CVD risk factors and osteoporosis.

In addition to the above recommendations that should apply to all women with POI, appropriate screening for diabetes, dyslipidemia and hypertension needs to take place. Baseline and follow-up measurements of body weight, body mass index, blood pressure, fasting glucose, glycated hemoglobin (HbA1c) and lipids levels are part of the work-up [25, 27]. Regarding bone health evaluation, bone mineral density (BMD) should be measured at baseline. If normal, this should be repeated in two to three years. In cases of a low-trauma fracture or a continuous decline in BMD despite optimal HRT, referral to a specialist is advisable [27, 111]. The optimal decision for the choice of the appropriate agents, such as anti-diabetic medications, statins and anti-osteoporotic therapies, must derive after taking into consideration the various metabolic, cardiovascular and bone health effects of these agents in the context of personalized medicine [1,112].

Contributors

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