Premature Ovarian Failure

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Key Words

Premature ovarian failure • Amenorrhoea • Follicle-stimulating hormone • Hormone replacement therapy • Infertility treatment

Abstract

The diagnosis of premature ovarian failure is based on the finding of amenorrhoea before age 40 associated with follicle-stimulating hormone levels in the menopausal range. Screening for associated autoimmune disorders and karyotyping, particularly in early onset disease, constitute part of the diagnostic work up. There is no role for ovarian biopsy or ultrasound in making the diagnosis. Management essentially involves hormone replacement and infertility treatment, the most successful being assisted conception with donated oocytes. Embryo cryopreservation, ovarian tissue or oocyte cryopreservation and in vitro maturation of oocytes hold promise in cases where ovarian failure is foreseeable as in women undergoing cancer treatments.

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The menopause, as measured by the last menstrual period, occurs at an average age of 50.7 years [1]. This figure has been found to be constant across generations unlike the age of menarche which has fallen particularly over the

first half of the 20th century. The age of menopause in an individual is determined by both genetic [2] and environmental factors [3]. Menopause before the age of 40 is most commonly taken to be the definition of 'premature ovarian failure' (POF) which coincides approximately with the youngest 1% of the frequency distribution of the age of menopause. For every decade before 40 the prevalence of POF is estimated to decrease by a factor of 10. Thus in presence of a normal karyotype 1:1,000 of women at 30 have POF, 1:10,000 at 20 and 1:100,000 of women will present with gonadal failure and primary amenorrhoea. The prevalence of POF, however, varies by ethnicity, with women of oriental origin having a lower risk and African Americans a higher risk compared to Caucasian Americans [5]. In terms of the mode of presentation, POF is the aetiology in 10–28% of the cases with primary amenorrhoea and in 4–18% of those with secondary amenorrhoea [6, 7].

Diagnosis of POF

POF affects 1% of women. The majority of cases are idiopathic. In some, the cause could be: (a) chromosomal and genetic abnormalities involving the X chromosome or autosomes – a large number of genes have been screened as candidates for causing POF, however none has been accepted as a genetic marker for POF; (b) autoimmune ovarian damage – anti-ovarian antibodies are reported

in POF but their specificity and pathogenic role are questionable; (c) iatrogenic following pelvic surgery and cancer therapy, i.e., radiotherapy and chemotherapy, and (d) environmental factors like viral infections and toxins for which no clear mechanism is known.

The clinical presentation of POF is variable. Some women present with symptoms of oestrogen deficiency, others as part of a work up for infertility or menstrual disturbance or as part of a syndromic condition which can be genetic or autoimmune. The diagnosis is based on the finding of elevated serum follicle-stimulating hormone concentrations (>40 IU/l) on at least two occasions separated by a few weeks. The reason for the need for two samples is that the diagnosis is often devastating and certainty is required and also because the natural history of POF can be very variable. While it is the usual expectation that the condition will be permanent, many women follow an unpredictable course of relapse and remission often given the label 'fluctuating ovarian function'. In our clinics we see a pregnancy rate of approximately 1–5% in women with POF. Because of this background fertility, anecdotes of effective treatment of POF must be viewed with caution. On the other hand, it is important to inform women with POF of this phenomenon so that they use contraception when appropriate.

Secondary investigations have the goal of determining the cause of POF or monitoring complications. Ovarian biopsy adds little to the investigative process because the small samples obtained are not predictive of the natural history of the condition. Pelvic ultrasound is similarly not predictive but might have a place in identifying those who may be candidates for oocyte preservation or maturation in the future. Being non-invasive, ultrasonography is often of psychological benefit in coming to terms with and understanding the process with a description of small ovaries with little follicular activity. An autoimmune screen for thyroid and adrenal autoantibodies is an important second line test in order to set the agenda for future surveillance of thyroid, adrenal or vitamin B₁₂ deficiency in particular.

A careful family history can identify other affected female members in as many as 30% of cases whose relatives can then be offered genetic counselling [8]. Genetic screening is becoming increasingly used for this familial POF group but can also be applied to sporadic presentations where the cost and effectiveness is lower. Note, for instance, the practice of screening for FRAXA pre-mutations which occur in 15% of cases with a positive family history and on 3% of sporadic presentations [9]. At present, the only widely available tests in routine practice are

karyotype and FRAXA pre-mutation screening which should be considered in those with a family history or unusually young onset.

Aetiology of POF

POF may occur due to chromosomal, genetic, autoimmune, metabolic (galactosaemia), infectious (mumps), and iatrogenic (anticancer treatments) causes but a large proportion of cases remain idiopathic [10, 11] despite diagnostic advances.

Genetic Causes of POF

Turner's Syndrome and X Chromosome Defects

Defects of the X chromosome associated with POF include complete deletion of one X (Turner syndrome), trisomy X [12] or partial defects in form of deletions or X-autosome translocations. However, the genetic locus responsible for the POF remains unknown. In the case of Turner syndrome variants, mosaic 45,X/46,XX karyotype can often lack the typical phenotypic feature of the syndrome and present with POF.

X chromosome deletions appear to segregate to two specific regions: POF1 at Xq26-qter [13] and POF2 Xq13.3–Xq21.1 [14]. Several genes responsible for ovary development and/or oogenesis present along the critical region may be interrupted by the balanced translocations leading to POF [15, 16]. However many breakpoints on the X chromosome are not associated with POF [17].

Down's Syndrome

The age-adjusted likelihood of menopause has been reported to be twice as high in women with Down's syndrome as in women with other intellectual disabilities [18]. Treated thyroid conditions do not influence menstrual status and do not modify the relationship between Down's syndrome and menstrual status.

Single Gene Defects Causing POF

A growing number of genes have now been identified which harbour mutations associated with POF (table 1) and these have been reviewed elsewhere [19]. The strength of evidence linking each anomaly with POF is variable. In some, e.g. fragile site mental retardation 1 gene, the association with POF has been widely reported; in others only a single case represents the link (Noggin). The genetic link may be indirect such as galactose-1-phosphate

uridylyltransferase where there is biochemical damage of the ovary and autoimmune regulator which triggers autoimmune damage.

Autoimmune Causes of POF

Autoimmune mechanisms may be involved in the pathogenesis in up to 30% of the cases of POF [20]. Various autoantibodies have been investigated as serological markers of ovarian autoimmunity. These include antibodies against steroidogenic enzymes (like 3β-hydroxysteroid dehydrogenase), gonadotrophins and their receptors, the corpus luteum, zona pellucida and oocyte [21]. However none of these antibody assays has been validated to confirm a clinical diagnosis of autoimmune premature ovarian failure. It is also possible that a serological marker of autoimmunity may not be present despite the disease being autoimmune in nature due to a waning of autoimmune response with progressive destruction and decline in the quantity of autoantigen. Moreover many autoantigens of organ-specific autoimmune diseases like POF may be still unidentified. Therefore in the clinical work up of POF, screening for an autoimmune aetiology is only possible in practice by looking for coexisting autoimmune diseases.

POF is reported to be associated with various endocrine (thyroid, adrenal, hypoparathyroid, diabetes mellitus, and hypophysitis) and non-endocrine (chronic candidiasis, idiopathic thrombocytopenic purpura, vitiligo, alopecia, autoimmune haemolytic anaemia, pernicious anaemia, systemic lupus erythematosus, rheumatoid arthritis, Crohn’s disease, Sjögren’s syndrome, myasthenia gravis, primary biliary cirrhosis and chronic active hepatitis) autoimmune disorders [22, 23]. Belvisi et al. [24] reported that 40% of 45 women with POF were positive for at least one organ-specific autoantibody, the most common being anti-thyroid antibodies (20%). Recently we have investigated the presence of thyroid peroxidase autoantibodies in a large cohort of POF and found it in 24% of these cases [25]. In many cases non-ovarian autoimmune involvement may exist only at sub-clinical level [26]. POF may be part of the autoimmune polyglandular syndromes (APS) when accompanied by other autoimmune endocrinopathies. POF is more common with APS types I and III than with APS type II [27].

The Pathogenesis of Autoimmune Damage of the Ovary

The exact pathogenesis of autoimmune POF has not been clearly defined [28]. Anti-ovarian antibodies are re-

Table 1. Genes implicated in premature ovarian failure

	Gene	Gene locus
X chromosome genes	BMP15	Xp11.2
	FMR1	Xq27.3
	FMR2	Xq28
	POF1b	Xq21.1–q23.3
Autosomal genes	FSH receptor	2p21–p16
	LH receptor	2p21
	Inhibin A	2q33–q36
	FOXL2	3q22–q23
	GALT	9p13
	FSH beta variant	11p13
	EIF2B2, 4, and 5	14q24.3, 2p23.3, 3q27
	POLG	15q25
	NOGGIN	17q22
	LH-β	19q13.32
	AIRE	21q22.3

For references and discussion, see Goswami and Conway [19].

ported in POF by several studies but their specificity and pathogenic role are questionable. The incidence of anti-ovarian antibodies in POF in different studies has been reported to vary from 4 to 69% [20, 29]. Such variable results are the result of the different stages of the disease being tested, methodological differences and by the multiplicity of potential immune targets.

An animal model of autoimmune oophoritis that develops in the mouse after neonatal thymectomy has helped in understanding the potential pathogenetic mechanisms of autoimmune POF and ovarian antigens [30]. Both animal and human disease show several similarities such as similar histological distribution of the ovarian lymphocytic infiltration, the production of anti-ovary autoantibodies and a reduced natural killer cell activity. Altered T cell regulation has been implicated in the pathogenesis of autoimmune premature ovarian failure in the mouse model, and oophoritis can be adoptively transferred by cells with a T helper phenotype. Tong and Nelson [30, 31] cloned a novel gene that encodes an ooplasm-specific antigen associated with autoimmune oophoritis in mice. Based on its role in pre-implantation development, they designated this antigen Maternal Antigen That Embryos Require (MATER). This was followed by cloning and characterization of the human MATER gene and its protein [32]. Whether human MATER plays an antigenic role in the autoimmune pathogenesis of clinical POF has not yet been reported in women with POF.

Patients with idiopathic POF show an increased number of activated T cells in their peripheral blood. Similar findings have been described in other autoimmune endocrinopathies, such as recent onset Graves' disease, IDDM and Addison's disease. However, postmenopausal women may also show raised numbers of activated peripheral T cells and oestrogen substitution has been shown to lower the number of activated peripheral T cells in women with POF. Therefore it is difficult to ascertain whether the raised numbers of activated blood T cells is the cause or result of ovarian failure in these women [22].

Miscellaneous Causes of POF

Viral oophoritis is often assumed to underlie many cases of idiopathic POF. Mumps oophoritis has been considered to be a cause of POF [33]. Other reported associations are cigarette smoking and epilepsy [34, 35]. The available data regarding the effects of endocrine disruptors, heavy metals, solvents, pesticides, plastics, industrial chemicals, and cigarette smoke on female reproduction are equivocal [36].

In patients developing malignant diseases, radiotherapy and chemotherapy can lead to POF. The effect of radiotherapy is dependent on dose and age and on the radiation therapy field. Complete ovarian failure occurs with a dose of 20 Gy in women under 40 years of age and with only 6 Gy in older women [37]. The prepubertal ovary is relatively resistant to gonadotoxicity due to radiotherapy and chemotherapy [38]. There is little risk of premature menopause in women treated with radiation fields that exclude the pelvis [39]. Ovariopexy which involves transposition of the ovary away from the radiation field preserves ovarian function in 60–100% of patients [40].

POF is important sequelae of cytotoxic chemotherapy given for various malignant diseases in young women. Alkylating agents increase the risk of POF by a factor of 9 [41]. Teenagers receiving chemotherapy have a 4 times increased risk of POF. This risk is increased by a factor of 27 among women aged 21–25 years [42].

Almost any pelvic surgery has the potential to damage the ovary by affecting its blood supply or causing inflammation in the area. The exact risk is however very small for routine operations. Other interventional techniques in pelvis like uterine artery embolisation may also lead to POF by compromising the vascular supply to the ovary [43].

Management of POF

Management of POF comprises medical, fertility and psychology, each of which needs to be reviewed at each clinic visit. The major medical issues revolve around the quality of life and bone protection offered by hormone replacement therapy (HRT). Options for reproduction include oocyte donation, but adoption should not be overlooked. Women also require personal and emotional support to deal with the impact of the diagnosis on their health and relationships. Long-term follow-up is essential to monitor HRT and for health surveillance and to consider emerging associated autoimmune pathology.

Hormone Replacement Therapy

Physiological replacement of ovarian steroid hormones until the age of normal menopause at 50 is generally accepted as routine. We must accept, however, that there are little risk/benefit data for this young population. The principle of HRT use in young women differs only slightly from that in older women with the main treatment goal being optimal quality of life. Young women may require a higher oestrogen dose than that used in an older age group. Also, expectations for sexual function can be higher, commonly requiring consideration of vaginal oestrogen and androgen replacement. An HRT regimen should be based on the individual preferences of each patient who should be encouraged to undertake a trial and error approach through the wide variety of products available.

Management of oestrogen replacement for young women presenting with primary amenorrhoea requires liaison with paediatric endocrinologists with experience in the induction of puberty in order to optimise breast and uterine development. For instance, a popular strategy is to maximise the time between the introduction of oestrogen and starting progesterone withdrawal bleeds is thought to benefit breast development. Conversely, the common practice of starting a low-dose combined oral contraceptive in this circumstance may not offer the best outcome of uterine development.

Among oral oestrogen choices, conjugated equine oestrogen and 17 β -oestradiol have consistent and comparable effects on hot flashes and may have similar short-term adverse effects [44]. Some young women with POF find the combined oral contraceptive pills a more acceptable option for oestrogen replacement but careful assessment of the pill-free week is advised. The pill-free week amounts

to 3 months of oestrogen deficiency each year which may coincide with symptoms of oestrogen deficiency or bone loss. Transdermal oestrogen avoids first-pass liver metabolism, has rapid onset and termination of action, involves non-invasive self-administration and attainment of therapeutic hormone levels with low daily doses [45]. This route of oestrogen administration also appears to be free of an excess risk of thrombosis [46]. Subcutaneous oestrogen replacement involves placement of 25–50 mg oestradiol pellets usually in the lower abdomen or buttocks in a minor office procedure. One can also include testosterone implants if indicated. Return of symptoms, combined with serum levels of oestradiol, can be used to determine the timing of re-dosing, which is about every 6 months for most women [47]. Topical vaginal oestrogen may be used as an adjunct to systemic oestrogen. Creams, pessaries, tablets and vaginal rings appear to be equally effective for control of symptoms [48].

Once the choice of oestrogen has been made, separate consideration can be given to the progestin in women with an intact uterus. Progestins vary from the more potent such as norethisterone to the weaker such as dydrogesterone. Trial and error will allow the user to find the most suitable progesterone preparation. The route may be oral, transdermal or uterine. With the oral and transdermal routes there is a choice between continuous or sequential (for 10–14 days each month) delivery. A sequential regimen ensures a monthly menstrual bleed. A continuous regimen avoids menstrual flow but breakthrough bleeding may be more common in young women compared to an older age group in whom there is greater uterine atrophy. Uterine delivery with the levonogestrel intra-uterine device (Mirena) has the advantage of avoiding the adverse effects of oral progestins highlighted in the studies of older women [49, 50].

Androgen replacement is useful in some instances when fatigue and loss of libido persist despite optimised oestrogen replacement [51]. Transdermal testosterone administration and dehydroepiandrosterone treatment are two of the options for androgen replacement in these women [52].

Infertility

Women with POF have a 5% chance of spontaneous conception at some time after diagnosis, as in some cases hormone levels and disease activity fluctuate and return to biochemical normality; but the likelihood of recovery of ovulation is not possible to predict. Pregnancy loss in

those who conceive is reported to be 20%, which is similar to that of the normal population [53]. Several medical therapies have been tried to induce ovulation in women with POF; however, in a systematic review all were reported to be equally ineffective [53]. Assisted conception with donated oocytes has been used to achieve pregnancy in women with POF since 1987 [54]. Presently it remains the only means of fertility treatment that carries high success rate in POF. Cryopreserved embryos have also been used to achieve pregnancy in POF with a high pregnancy rate of 30% per transfer [55]. Recently Silber et al. [56] described a successful pregnancy following ovarian transplantation between monozygotic twins discordant for POF.

The use of ovarian tissue cryopreservation for later use has been explored in young women undergoing anticancer treatment [57]. The first live birth after orthotopic transplantation of cryopreserved ovarian tissue has been reported [58]. Pregnancies and live births have been reported after oocyte cryopreservation and subsequent intracytoplasmic sperm injection [59]. This approach requires ovarian stimulation to retrieve mature oocytes. Because of the effect on meiotic spindle and formation of ice crystals the success rates are limited. Use of newer methods of cryopreservation, i.e. vitrification is now being reported [60]. It involves rapid cooling in high concentrations of penetrating cryoprotectants which avoids formation of intracellular ice and resulting damage during cooling and warming. In vitro maturation of oocytes, in which immature oocytes are retrieved from unstimulated ovaries, has also emerged as a safe and effective treatment for women with cancer who are undergoing gonadotoxic therapy [61]. Successful pregnancy is possible following in vitro maturation of oocytes from antral follicles [62].

Psychology

The diagnosis of POF is an extremely devastating life experience. Women with POF report high levels of depression and low levels of self-esteem with negative effects on sexuality [63, 64]. Many women with POF report moderate to severe stress at the time of diagnosis and are unsatisfied with the amount of information given to them by their clinician [65]. Access to a clinical psychologist is recommended. Often several visits will be required for detailed information on aetiology and fertility options to be retained. Regular specialist follow-up is recommended so that women have access to accurate fertility informa-

tion and so that the need for psychology support can be reassessed at intervals. Often crises arise some years after the original diagnosis, for instance when a near relative achieves a pregnancy.

Conclusions

POF is a complex condition that requires specialist services. The diagnostic workup is aimed at determining the aetiology where possible and is followed by a screen for syndromic conditions. Oestrogen replacement and fertility options need to be reassessed at intervals and clinicians have to be vigilant for psychological sequelae.

Issues in the Management of Women with POF

Education and Counselling

1. Remission: The likelihood of recovery of ovulation is not possible to predict.
2. There is no proven effective treatment for infertility.

3. Adoption and oocyte donation are among the available options, but require guidance and counselling.
4. Access to follow-up counselling is important as issues return with life events such as pregnancy in the family.

Investigations

5. Thyroid function tests are useful as thyroid involvement is a common association.
6. Autoantibody screen including thyroid, adrenal antibodies, parietal cell, intrinsic factor and antinuclear antigen.
7. Karyotype for early onset POF and genetic screen for FRAXA pre-mutation.
8. Pelvic ultrasound and ovarian biopsy do not alter the management.

Treatment

9. Oestrogen and progesterone replacement is usually indicated.
10. There are no comparative data to guide oestrogen use in young women as most studies on HRT involve postmenopausal women.
11. Inform on all oestrogen preparations – oral, transdermal and implants.
12. Inform about media HRT scares and relevance to young women.
13. Consider vaginal oestrogen and testosterone supplements.

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