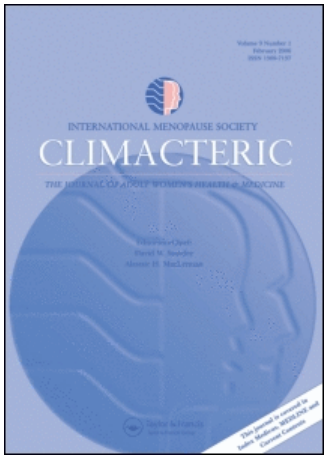

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Premature ovarian failure: a review

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Key words: PREMATURE OVARIAN FAILURE, PREMATURE MENOPAUSE, HORMONE REPLACEMENT

ABSTRACT

Objectives To present an updated review on the etiology, consequences and management of premature ovarian failure.

Design A search of the English language literature using the Cochrane Library database and Medline 1966–2006, with a hand search of the references.

Conclusion Premature ovarian failure is defined as the occurrence of amenorrhea, hypergonadotropinemia and estrogen deficiency in women under the age of 40 years, with the prevalence being 0.9–1.2%. In the majority of cases, the etiology is unknown, but known causes include chemotherapy, radiotherapy, surgery, genetic disorders, particularly involving the X chromosome, associations with autoimmune diseases, infections, smoking and other toxins. The three critical issues of management in these women are the effect of the diagnosis on the psychological health of the patient, the consequent infertility and the long- and short-term effects of estrogen deficiency arising from ovarian decline. Promising methods of screening for premature ovarian failure are being developed.

INTRODUCTION

Premature ovarian failure (POF) is defined as the occurrence of amenorrhea, hypergonadotropinemia, and estrogen deficiency in women under the age of 40 years[1,2]. Another term used to describe POF is premature menopause; however, in women with POF, ovarian failure may not mean complete cessation of function and up to 50% of those so diagnosed will have intermittent and unpredictable ovarian function which may persist for some years[3]. This review focuses on the etiology, consequences and management of this relatively common and poorly understood condition.

METHODS

We conducted a search of the English language literature using The Cochrane Library database and Medline (US National Library of Medicine) from 1966 to 2006, using the key words premature ovarian failure and premature menopause. A hand search of the references of these articles was also performed.

EPIDEMIOLOGY

The prevalence of POF is 0.9–1.2% in women 40 years or younger[2,4,5]. There are ethnic differences ranging from 1.4% in women of African-American and Hispanic descent to 1.0% in Caucasian, 0.5% in Chinese and 0.1% in Japanese women[4]. In women with primary amenorrhea, the prevalence of POF is 10–28%; in those with secondary amenorrhea, the prevalence is 4–18%[6].

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REVIEW

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ETIOLOGY

POF arises from a genetically pre-determined reduced number of ovarian follicles at birth, accelerated follicular atresia, or follicular dysfunction[3]. Although, in 90% of cases, the etiology is unknown, the number of known causes and genetic factors continues to increase.

Chemotherapy and radiotherapy for treatment of malignant disease are the most common known causes of POF. Whilst improved chemotherapy and radiotherapy regimens for cancers in young people have led to increased long-term survival, one consequence has been a diminution in ovarian reserve and thus an increased incidence of premature ovarian failure. The risk of treatment leading to POF increases with age after puberty, with various high-dose chemotherapy regimens and with combined chemo- and radiation therapy[7].

Chemotherapy depletes oocyte numbers and affects the structure and function of oocytes and granulosa cells, in a dose- and drug-dependent manner[8]. Combination chemotherapy and alkylating agents are most likely to cause POF. Induced POF can be temporary; however, the chance of spontaneous recovery of ovarian function decreases with increasing patient age. Some evidence exists that co-treatment with gonadotropin releasing hormone (GnRH) agonists may reduce the gonadotoxic effects of chemotherapy[9,10].

Depending on the radiation field, radiotherapy may affect the ovaries. There is little risk of POF in women treated with radiation fields outside the pelvis[11]. Age and dosage of radiation are also significant factors for the risk of POF in women; prepubertal ovaries are relatively resistant to radiation[12], whilst direct radiation doses of 9 Grays or higher render ovaries at high risk of failure, although there have been case reports of pregnancy even after this dosage[13].

Several genetic disorders are associated with POF and there have been reports of familial POF, indicative of a genetic inheritable disorder[14,15]. Approximately 20–30% of women with POF have affected relatives, suggesting that the inherited predisposition to POF is common[16]. It is likely that POF is a heterogeneous disorder caused by mutations in multiple genes, with each mutation identified so far causing only a few cases of POF. The majority of genetic disorders are related to the X chromosome[17], but there have also been autosomal recessive and autosomal dominant forms of the disease documented[18].

Several X chromosomal abnormalities have been reported, including partial deletions, translocations, deficiencies and excesses.

Turner syndrome is due to mosaicism or complete monosomy of the X chromosome. It is characterized by ovarian failure, growth restriction and other physical abnormalities. For oogenesis to be complete, it is essential for both X chromosomes to be present and hence in Turner syndrome ovarian function is defective[14]. The loci for ovarian failure have been difficult to identify, but there has been some evidence that one of the critical regions may be on the region of Xp11.2–p22.1[19].

Trisomy X syndrome (47,XXX) is caused by non-disjunction of the X chromosome during maternal meiosis. The association of POF and trisomy X has been reported, but the prevalence of POF in this group of women is unknown[20,21].

Fragile X syndrome is an X-linked genetic disorder with incomplete penetrance. The incidence of POF in women carrying the fragile X syndrome premutations (*FMR1* gene) has been reported to be as high as 20%[22,23]. However, the incidence seems to be partly dependent on whether the *FMR1* gene is paternally or maternally acquired; in one study, 28% of patients with the paternally acquired fragile X premutation had POF compared to only 3.7% of women with maternally acquired fragile X premutation[22].

Deletions in either the short or long arm of the X chromosome have resulted in primary and secondary amenorrhea with elevated gonadotropin levels[24], with identification of two independent loci Xq26–q28 (POF1) and Xq13.3–q22 (POF2)[24].

Balanced X chromosome translocations have been shown to be associated with POF through cytogenetic mapping. However, in this group of rearrangements of the X chromosome, POF seems to be independent of the presence of the X-linked genes and more likely a result of the X chromosome reorganization that occurs during oogenesis and hence may affect the expression of non-linked X genes in the oocyte, leading to ovarian failure[18].

The other X-linked gene for ovarian failure is the *bone morphogenetic protein 15* (*BMP15*) gene. *BMP15* was reported to carry mutations in two sisters who had primary amenorrhea, inherited from their father[25]. No other mutations have been reported and the prevalence in POF is unknown[18].

Galactosemia is a rare autosomal disorder due to a defect in galactose 1-phosphate uridyltransferase (GALT) metabolism. Despite good dietary

control, the prevalence of POF in women with galactosemia is 70–80%[26]. Possible mechanisms include the toxic effect of galactose or its metabolite on follicular structures during fetal life, galactose-induced reductions in the initial number of oogonia, and the glycosylation of gonadotropin subunits leading to biological inactivity[26].

17α-Hydroxylase deficiency is a rare enzymatic defect characterized by primary amenorrhea, sexual infantilism, hypergonadotropism, hypokalemia and hypertension. Development of ovarian failure is due to defective ovarian steroid synthesis and ovarian biopsies have shown disorderly follicular maturation[27]. There has been a case report documenting the retrievability of a fertilizable oocyte despite undetectable levels of estradiol[28].

There are many other genes identified as being associated in the causation of POF. These include mutations of the follicle stimulating hormone (FSH) receptor[29], luteinizing hormone (LH) receptor[30,31], inhibin gene[16] and *FOXL2* gene[16] associated with blepharophimosis–ptosis–epicanthus inversus syndrome (BPES).

POF has a close association with many autoimmune diseases. It is estimated that 20% of patients with POF have an associated autoimmune disease[32], most commonly diabetes mellitus, thyroid and adrenal disease[33]. Ovarian failure may occur as part of the autoimmune polyglandular syndrome types I and II. Type I is characterized by hypoparathyroidism, adrenal insufficiency, chronic mucocutaneous candidiasis, POF and hypothyroidism. Type II is characterized by adrenal insufficiency, autoimmune thyroid disease, type I diabetes mellitus and POF.

There has been an association of POF with myasthenia gravis, Sjogren's syndrome, Crohn's disease, vitiligo, pernicious anemia, rheumatoid arthritis, and systemic lupus erythematosis[3].

Antibodies to the ovarian enzymes or tissue components could also cause clinical autoimmune POF. Decades of research have investigated ovarian autoantibodies and their association with POF. Unfortunately, the results are conflicting due to different methods of detection, and thus neither the specificity nor clinical significance of ovarian autoantibodies has been established[34]. Autoantibodies to the zona pellucida also have been described as a cause of follicular dysfunction[35].

Smoking has consistently been shown to be associated with earlier menopause[36,37]. The suggested pathophysiology is that tobacco smoke contains polycyclic hydrocarbons which are toxic to germ cells, leading to follicular exhaustion[38].

Amongst viral infections, mumps oophoritis may cause POF and an incidence of 3–7% has been reported in patients who contracted mumps during an epidemic[39]. There have also been case reports of cytomegalovirus (CMV)-related oophoritis in immunocompromised patients[40].

Pelvic surgery has the potential to compromise blood supply to the ovaries and may cause inflammation. Recurrent surgery for benign ovarian conditions leads to follicular depletion and premature ovarian failure; for example, the rate of post-surgical premature ovarian failure after laparoscopic excision of bilateral endometriomas is 2.4%[41]. Bilateral oophorectomy will obviously precipitate a surgical menopause and hysterectomy may also compromise the ovarian blood supply, leading to an early menopause[42].

DIAGNOSIS

Most women with spontaneous POF present with menstrual disturbances. Often, there is a delay in diagnosis. In one survey, the mean time from presentation to diagnosis was 2 years, with 25% of women not being diagnosed until 5 years after presentation[43]. Some women present with vasomotor symptoms, vaginal dryness and dyspareunia as a result of estrogen deficiency, whilst others present after failed attempts at ovulation induction for infertility.

The diagnosis should always be considered in young women presenting with secondary amenorrhea. A detailed history should include questioning regarding prior ovarian surgery, chemotherapy, radiotherapy, and autoimmune diseases. A family history of autoimmune diseases, POF, fragile X, other X chromosome defects and developmental delay is also significant.

After excluding pregnancy, the core diagnostic criteria are more than 4 months of amenorrhea and two serum FSH values of >40 mIU/ml more than 1 month apart in a woman less than 40 years old[6].

On clinical examination, most women with POF will have no abnormalities, but subtle signs may be present.

Phenotypic features of Turner syndrome, the most common abnormal karyotype found in women with POF, include short stature, webbed neck, high arched palate, shield chest with widely spaced nipples, wide carrying angle and short fourth and fifth metacarpals.

Signs of associated autoimmune disease may be present. Sparse axillary and pubic hair, orthostatic hypotension, increased pigmentation in the skin

creases and vitiligo are features of adrenal insufficiency. Other signs of autoimmune disease include butterfly malar rash, joint tenderness and vitiligo in systemic lupus erythematosis; dry eyes and mouth in Sjogren's syndrome, whilst myxedema, proximal myopathy, a 'hung up' reflex, and alopecia may be present in hypothyroidism.

Pelvic examination may reveal signs of atrophic vaginitis, and rarely ovaries may be palpable due to lymphocytic oophoritis or a steroidogenic enzyme defect[44].

INVESTIGATIONS

Laboratory baseline investigations should include β-human chorionic gonadotropin (β-hCG), LH, FSH, prolactin and estradiol. There is no place for a progesterone withdrawal test, which is inaccurate and may delay diagnosis[39,45].

Consideration should be given to karyotyping. All women who experience POF before the age of 30 years, and have a positive family history of POF, developmental delay, ataxia or dementia should have karyotyping and *FMR1* testing. The presence of an inactive Y chromosome in phenotypic women is associated with a substantial risk of cancer of the gonads and these women should have their gonadal tissue removed.

Screening for associated autoimmune diseases has been recommended, in particular screening for hypothyroidism and diabetes mellitus[46]. Adrenal autoantibodies are used to identify women with POF who have associated steroidogenic cell autoimmunity and who are at risk of developing adrenal insufficiency[47,48] and adrenal crisis[3].

Pelvic ultrasound, ovarian biopsy and antiovarian antibodies have no proven clinical benefit in the work-up of these patients. Pregnancies have been documented in women found to have no follicles, suggestive of sampling errors[49]. Antiovarian antibodies do not correlate with the severity or presence of oophoritis and do not predict whether POF will occur[6].

MANAGEMENT

A diagnosis of POF brings with it three critical issues: the effect of the diagnosis on the psychological health of the patient, the consequent infertility, and the long- and short-term effects of estrogen deficiency arising from ovarian decline.

Psychological health

A diagnosis of POF can affect the mental, spiritual and social health of a woman. Patients may experience a sense of helplessness, anger, sadness and guilt following the diagnosis, which may also give rise to a negative impact on body image and perception of femininity[3,50]. Women who wish to have children find the diagnosis of POF particularly traumatic, and the symptoms triggered by this diagnosis are similar to the grief reaction. The loss of reproductive capacity may trigger feelings of loss, grief and shame and may lead to a loss of self-esteem and relationship difficulties.

Alzubaidi[43] found that many young women perceived a lack of quality of care regarding the diagnosis of this condition[43]. Spending more time with patients, expressing appropriate concern and establishing exactly how much the patient knows and wants to know are important parts of the counseling process[50]. An offer of referral to other sources of information and support groups such as the International Premature Ovarian Failure Association (http://pofsupport.org/), the Daisy Network (http://www.daisynetwork.org.uk/) and The Jean Hailes Foundation (http://www.jeanhailes.org.au) are invaluable for these women[50].

In some cases, evaluation by a psychologist or psychiatrist is necessary to evaluate levels of depression, anxiety and coping mechanisms, and group or medical therapy may be required.

Infertility

The combined data of observational, uncontrolled and controlled studies suggest that women with POF have a 5–10% chance of natural conception at some time after diagnosis[51]. The rate of pregnancy loss is similar to that of the normal population, with approximately 80% of pregnancies resulting in the birth of a healthy child.

Only donor egg *in vitro* fertilization and embryo transfer using donor oocytes have demonstrated high success rates in women with spontaneous POF, and this should be considered the fertility treatment of choice[3,26,32]. Many women will seek egg donation from a family member and it is essential that the family is fully counseled regarding the risk of a possible donation of an ovum with genetic abnormalities, including the predisposition for POF, that are unable to be tested for to date.

Such randomized trials that have been done on other therapies for infertility, including gonadotropin therapy, estrogen, oral contraceptives,

steroids, and clomiphene therapy, have failed to show a significant improvement in ovulation or pregnancy[52,53].

Cryopreservation of ovarian tissue prior to gonodotoxic treatments such as chemotherapy and radiation therapy is currently being investigated as an alternative to embryo freezing in the hope of restoring future fertility[54]. The advantage is that a large number of gametes are able to be stored without delaying oncology treatment. There have been several reports of pregnancy and birth following autotransplantation of cryopreserved ovarian tissue in women who have suffered chemotherapy-induced POF[55–57]. Thus ovarian transplantation may soon be a fertility option for women with chemotherapy-induced POF. However, there is a risk of transplantation of metastatic cancer cells during orthotopic transplantation, particularly for blood-borne malignancies[58].

In the future, ovarian biopsy may be of use for treatment of infertility, given the first case report of success of *in vitro* oocyte maturation in humans with reduced ovarian reserve resulting in a live healthy infant[59]. *In vitro* maturation of oocytes was initially for women with high risk of ovarian hyperstimulation syndrome, but may be useful for a population with reduced follicular reserve.

Estrogen deficiency

Women with POF often have symptoms of estrogen deficiency including vasomotor symptoms, atrophic vaginitis and dyspareunia. They are also at significant risk of osteoporosis and cardiovascular disease. Hormone therapy should be initiated in these women, not merely for symptom control but also to maintain long-term health, thus fulfilling the criteria of true hormone replacement therapy (HRT). Some women may need HRT before amenorrhea is established because of troublesome symptoms.

No randomized trials have been conducted to determine the ideal dose, regimen or delivery system for women with POF receiving HRT. Estrogens and progestins may be administered orally or transdermally, sequentially to induce a regular withdrawal bleed or in a continuous combined manner to achieve amenorrhea. Regulatory authorities and professional bodies worldwide all advise initiating treatment with a low dose and increasing as required until symptom control is achieved[60,61]. Some young women will require twice the standard dose of estrogen to achieve symptom relief[3]. Women with an intact uterus should receive a progestin either cyclically or continuously although, because of the possibility of spontaneous endogenous ovarian activity, breakthrough bleeding is more common amongst women receiving continuous progestins[32]. Progesterone should be given at least monthly, as less frequent administration may be associated with an increased incidence of endometrial hyperplasia[62].

HRT does not provide contraception and, in women who desire reliable protection from pregnancy, the use of the oral contraceptive pill is appropriate.

Osteoporosis is a major contributor to morbidity and mortality in today's society. An osteoporotic hip fracture is associated with an increase in mortality of 12% in the first year[63]. Bone mass after the age of 30 years is dependent on the maximal bone mass achieved and the annual bone loss rate, which is strongly dependent on age and ovarian function[64,65]. Some studies suggest that reduced bone density and osteoporotic fractures under the age of 65 years are significantly related to premature menopause[65–68], whilst other studies suggest that early menopause is statistically significantly associated with increased fractures during a lifetime[69]. HRT in the doses discussed above will maintain age-appropriate bone density, and randomized trials in older women have also demonstrated that such doses of HRT will significantly reduce fracture incidence[70]. Women with POF should also be given appropriate general health advice regarding calcium intake, daily weight-bearing exercise, vitamin D intake and cessation of smoking. Response to therapy should be followed on a regular basis using bone mineral density measurements.

There is a suggestion that women with POF may be at increased risk of cardiovascular disease and associated mortality[71–75]. Hu and colleagues[75] showed the relative risk for heart disease with each year of decrease in menopausal age was 1.03 (95% confidence interval (CI) 1.01–1.05) and that women who experienced menopause before age 40 were 53% more likely to suffer coronary heart disease compared with women whose menopause occurred after age 55 years. There is little known about the effect of POF and cardiovascular disease, but there is evidence showing that lack of estrogen in women with POF accelerates the process of endothelial dysfunction, a precursor of atherosclerosis[76]. An observational study demonstrated that endothelial dysfunction in women with POF was reversible after 6 months of cyclical HRT[77].

Observational studies showed that HRT commenced by symptomatic postmenopausal women in their fifties reduced the risk of cardiovascular events[78], but large randomized controlled trials of largely asymptomatic postmenopausal women, on average 10 years older than those in observational studies, did not. The Heart and Estrogen/progestin Replacement Study (HERS) showed that HRT did not reduce the rate of cardiovascular events in postmenopausal women with established cardiovascular disease[79], and the Women's Health Initiative studies, investigating primary prevention of cardiovascular disease in healthy postmenopausal women, showed a small increase in the number of cardiovascular events in postmenopausal women receiving combined HRT but not estrogen-only therapy[80].

It seems that, in relatively healthy blood vessels, estrogen prevents or slows development and progression of atherosclerosis, but, in the presence of established atherosclerosis, estrogen fails to reduce this progression and may actually trigger cardiovascular events by a proinflammatory or prothrombotic effect[76]. In animal models, estrogen inhibits plaque formation in oophorectomized monkeys when administered at the time of a surgical menopause, but not when delayed by 2 years from oophorectomy[81,82]. This suggests an age-dependent, or perhaps artery-dependent, response of the cardiovascular system to therapy with HRT. Such a proposition is supported by recent published data from several sources including the Nurses' Health Study and the Women's Health Initiative[83–85]. Hence, in young women, estrogen may help to reduce the risk of plaque formation, but may not be useful for older postmenopausal women who have developed coronary artery disease irrespective of symptom status. It is unknown whether the addition of androgen therapy will confer any change in cardiovascular health for women with POF; in postmenopausal women already receiving HRT, transdermal testosterone has been shown to improve endothelial function[86].

The findings of the Women's Health Initiative studies[70,80,82,87] of absolute increased risk of breast cancer, cerebrovascular and cardiovascular disease with HRT use in older postmenopausal women do not apply to young women with POF. Young women with POF have pathologically low levels of estradiol compared to their age-matched peers. Thus, estrogen administration replaces the estrogen which should have been produced by the ovaries and, in a manner similar to the treatment of hypothyroidism with thyroxine therapy, is true hormone replacement therapy.

The risk/benefit ratio for women with POF is different to that for women using HRT after reaching their menopause at the usual age of 51 years. Their baseline risk of breast cancer and cardiovascular disease is much lower, and the risk of osteoporosis during their lifetime is much higher than for the older women.

Whilst no randomized trials exist, or are likely ever to be conducted, logic suggests, and expert bodies have agreed[60,61], that HRT for women with POF up to the normal age of the menopause will not only alleviate symptoms but also reduce the risk of chronic disease. Whilst oral HRT will increase the risk of thromboembolic disease[88], the absolute risk is small and the overall message for women with POF commencing HRT should be positive and reassuring.

Androgen replacement

Women with POF have lower levels of free testosterone than age-matched normally ovulating controls[3,89–91] and some authors have suggested that testosterone replacement be considered in these women, particularly those with Turner syndrome or those complaining of reduced libido and persistent fatigue despite adequate estrogen replacement[32,92]. Inadequate testosterone has been suggested as a cause for reduced bone mineral density despite estrogen replacement in over two-thirds of women with POF[93–96], and studies are currently examining the effect of testosterone replacement on bone mineral density[97]. Evidence is available that androgens play a role in maintenance of bone turnover and bone mineral density in postmenopausal women, with those women on estrogen replacement and testosterone replacement showing greater increases in bone mineral density compared to women treated with estrogen alone[98].

At present, evidence is insufficient for testosterone therapy to be recommended as a standard treatment for young women with POF, but it should be considered in those with symptoms of androgen deficiency, bearing in mind that there are only limited data available on the long-term effects of androgen replacement therapy[92].

Cognitive function

Several observational studies have suggested a decreased risk of dementia with HRT. Estrogen may be neuroprotective because of its promotion

of cholinergic activity, its effects on the hippocampus and by increasing dendritic spine density[99].

There has been one small study investigating cognitive function in women with POF treated with HRT, comparing those with a normal karyotype with women with Turner syndrome and with normal female controls[100], matched for age and verbal intelligence quota. After comprehensive neuropsychological assessment including evaluation of general cognition, verbal and non-verbal memory, executive abilities and motor function, there was no significant difference between controls and women with POF. However, the women with Turner syndrome had impaired performance on evaluation of non-verbal memory, spatial and constructional abilities, executive function and motor speed. It was concluded that replacement of estrogen in women with POF is sufficient to prevent cognitive defects that may have occurred due to estrogen depletion. However, the cognitive differences in women with Turner syndrome may be related to genetic differences and to changes in neural development. There has been no long-term evaluation of women with POF and their cognitive function. This study provides some reassurance for women with POF taking HRT, especially in light of the publication of the Women's Health Initiative Memory Study (WHIMS)[101,102].

WHIMS showed a doubling in risk of dementia for postmenopausal women taking estrogen plus progestins and almost doubling in risk of dementia in women taking estrogen alone. However, women enrolled in WHIMS (a subgroup of the WHI study), were aged 65 and older and results may not be applicable to younger women with POF. A 'critical period hypothesis' has been raised, similar to that for cardiovascular risk and hormone therapy, suggesting hormone therapy confers optimal cognitive benefits when initiated close in time to the menopausal transition[103].

Screening and prevention

Currently, no screening is available for POF. There has been increasing interest in tests of ovarian reserve, initially developed to help predict successful outcome of assisted conception techniques. These may be potentially useful in patients who, although asymptomatic, are at risk of premature ovarian failure. Ovarian reserve tests aim to measure the remaining primordial follicular pool, since it has been suggested that a critical number of follicles determine menopause[104]. These tests may be useful in those women who have asymptomatic accelerated follicular decline. However, not all cases of premature ovarian failure are due to accelerated follicular decline.

Ovarian reserve tests include day 3 basal FSH levels, estradiol, inhibin B, antimullerian hormone (AMH), and antral follicular counts measured by transvaginal ultrasound[105]. Estradiol and inhibin B are produced by early antral follicles in response to FSH stimulation. With the reduction in the follicular pool, serum estradiol and inhibin B decrease with the concomitant increase in FSH[106]. However, these changes occur relatively late[107]. Antimullerian hormone is expressed in granulosa cells of growing ovarian follicles[108]. Expression is highest in pre-antral and small antral follicles and gradually diminishes in the subsequent stages of follicular development[108], thus reflecting the size of the primordial follicular pool. In a longitudinal observational study looking at young premenopausal women with normal menstrual cycles compared to postmenopausal women, de Vet and collegues[109] measured early follicular phase hormones at a 3-year interval. They found that AMH levels declined significantly prior to changes in inhibin B and FSH levels, despite the presence of regular menstrual cycles. A strong correlation between AMH and antral follicular count was also found. Thus, this study suggests that AMH declines whilst women are asymptomatic and early in the events leading to ovarian failure.

The antral follicular count may also be a promising screening tool when used to estimate the remaining primordial follicular pool[105]. Antral follicular counts and serum antimullerian hormone seem to be the most sensitive non-invasive markers of ovarian reserve[110] at present; however, further research is necessary to prospectively evaluate these markers and their clinical applicability.

FOLLOW-UP

Women with POF should be seen annually to monitor their response to hormone therapy, to address individual health issues and to review ongoing management in light of current research. If autoantibodies have been detected at the initial investigation, these, and thyroid and adrenal function, should be monitored annually. There is no evidence to recommend frequency of bone density screening, but we recommend that bone density should be monitored every 2 years initially to demonstrate skeletal protection and thereafter as clinically appropriate. A screening interval of

less than 2 years is not warranted because the precision error of densitometry may be higher than the bone lost during this time[111].

CONCLUSIONS

Premature ovarian failure has a significant impact on the physical and psychological health of young women with the disorder. Effective management should involve early diagnosis, sensitive and sympathetic management and counseling of the individual and the use of hormone therapy to alleviate symptoms of estrogen deficiency and to reduce the burden of long-term disease such as osteoporosis.

There is no effective screening available for the diagnosis of premature ovarian failure, but there are promising new avenues of research investigating markers of ovarian reserve. Regular long-term follow-up and review are essential.

Conflicts of interest Dr Nippita nil. Associate Professor Baber has conducted clinical trials sponsored by several pharmaceutical companies involved in the manufacture of phytoestrogens, hormone replacement therapy and bone-sparing treatments and has given continuing education talks on management of the menopause sponsored by Schering, Organon, Wyeth Ayerst, Servier Laboratories, Novartis and Novogen Laboratories.

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