

# Premature menopause



**Amanda Vincent**

MBBS, BMed Sci, PhD, FRACP

Endocrinologist, Southern Health Menopause Unit, Melbourne; Research Fellow, Jean Hailes Research Unit, Monash University

MENOPAUSE occurring before the age of 40 years is defined as premature and includes spontaneous and medically/surgically induced menopause. The terms premature menopause (PM) and premature ovarian failure (POF) are often used interchangeably.

Approximately 1% of women younger than 40 experience spontaneous PM, rising to 8-10% where PM results from surgery or chemo/radiotherapy. Observational studies have identified family history, smoking, poor response to ovarian stimulation, and epilepsy as risk factors for spontaneous PM.

The causes of PM are summarised in Table 1. In the majority of women the cause of spontaneous PM is unknown and is classified as karyotypically normal spontaneous PM. The rate of chemotherapy-induced PM depends on age, cumulative dose, duration of therapy and agent involved.

## CLINICAL PRESENTATION

PM may develop acutely or gradually. Vasomotor symptoms are present in 50% of women and these may be severe following oophorectomy. A common scenario is the onset of amenorrhoea and/or vasomotor symptoms after cessation of the oral contraceptive pill (OCP). Other symptoms can be experienced and may be more severe than in the typical menopausal woman.

## DIAGNOSIS

PM should be considered with secondary amenorrhoea or menstrual disturbance regardless of menopausal symptoms. While the clinical presentation of PM may be similar to the perimenopause, the diagnosis is often delayed because the woman is considered too young.

The median time to diagnosis has been reported as two years and 61% of women consulted three or more clinicians prior to diagnosis. A high index of suspicion should be maintained in women with risk

factors. Clinical assessment including history (table 2) and examination provides information regarding aetiology, assessment of hormone deficiency and related complications.

Laboratory investigations: The diagnostic criteria for PM include greater than four months of amenorrhoea and FSH levels >40 IU/L on two separate occasions at least one month apart with exclusion of secondary causes of amenorrhoea.

Gonadotrophins should be measured (in the absence of exogenous hormones e.g. OCP). There is no test to predict PM. Pelvic ultrasound may be useful.

## MANAGEMENT

### 1. Psychological issues

Women with PM appear to have greater depression and anxiety, low self-esteem and impaired sexual function. Counselling and listening are beneficial and referral to a psychologist/psychiatrist may be necessary.

### 2. Education and information

Patient satisfaction is related to

time and empathy in consultation. Compliance with hormone replacement therapy (HRT) is dependent upon understanding the consequences of oestrogen deficiency.

### 3. Diet and lifestyle

Modification of dietary and lifestyle factors assists both psychological and physical symptoms and reduces cardiovascular disease and osteoporosis risk.

### 4. HRT

HRT for oestrogen deficiency symptoms in the absence of contraindications is generally accepted. Early initiation and continuation until approximately 50 years of age is appropriate.

There is no consensus regarding optimal HRT in PM, although higher doses of oestrogen (equivalent to 1.25 mg conjugated equine oestrogen) may be needed. The Women's Health Initiative study led to reluctance to use/prescribe HRT. However, key professional societies recommend this data should not be extrapolated to young women.

Monthly withdrawal bleeding can be psychologically important. Where a woman with PM desires contraception, the low-dose OCP may be considered.

### 5. Androgen therapy

Female androgen insufficiency syndrome (FAIS) is described with clinical and biochemical features (low testosterone levels). Positive effects of testosterone therapy have been demonstrated short term. However, androgen replacement remains controversial and there are currently no TGA-approved testosterone preparations specifically for women available in Australia.

### 6. Non-hormonal therapies

A recent meta-analysis of non-hormonal therapies including antidepressants, antihypertensives, gabapentin, red clover and soy isoflavone extracts provided supportive evidence for efficacy of paroxetine, venlafaxine, gabapentin and clonidine (and mixed results for soy isoflavones) in reducing hot flushes. However, benefits were small and long-term efficacy and safety is unknown.

Women with breast cancer may experience hot flushes due to chemotherapy-induced PM, oophorectomy and/or secondary treatment with tamoxifen/aromatase inhibitors. Non-hormonal therapies may be useful in this setting; however, paroxetine may interfere with tamoxifen metabolism. The efficacy and safety of herbal/

**Table 2 : History**

<b>Presenting symptoms</b>
<ul style="list-style-type: none"> <li>menstrual disturbance</li> <li>menopausal symptoms</li> <li>pregnancy/infertility</li> <li>galactorrhoea</li> </ul>
<b>Gynaecological history</b>
<ul style="list-style-type: none"> <li>menarche</li> <li>menstrual history</li> <li>parity</li> <li>previous gynaecological surgery including surgery for endometriosis, hysterectomy and oophorectomy</li> </ul>
History or symptomatology of autoimmune disorders especially adrenal or thyroid dysfunction
<b>Past history</b>
<ul style="list-style-type: none"> <li>inherited conditions such as Turner syndrome</li> <li>previous cancer and treatment including radiotherapy or chemotherapy</li> <li>viral infections including mumps and cytomegalovirus</li> <li>eating disorder</li> <li>cardiovascular disease risk factors</li> <li>osteoporosis</li> </ul>
Exclude causes of secondary amenorrhoea
Medication: OCP, chemotherapy, antipsychotics
Family history of PM, autoimmune disorders, cardiovascular disease, osteoporosis
Lifestyle assessment: smoking, alcohol, diet, exercise

**Table 1: Causes of premature menopause**

CAUSE	
<b>Idiopathic</b> (normal karyotype)	<b>60%*</b>
<b>Genetic abnormality</b>	<b>10%*</b>
<ul style="list-style-type: none"> <li>■ X-linked                             <ul style="list-style-type: none"> <li>Turner syndrome</li> <li>47XXX</li> <li>Fragile X syndrome</li> </ul> </li> <li>■ Autosomal                             <ul style="list-style-type: none"> <li>FSH/LH receptors</li> <li>LH/FSH/inhibin subunits</li> </ul> </li> </ul>	
<b>Iatrogenic</b>	
<ul style="list-style-type: none"> <li>Chemotherapy</li> <li>Pelvic radiotherapy</li> <li>Pelvic surgery including hysterectomy</li> <li>Uterine artery embolisation</li> </ul>	
<b>Autoimmune disorders</b> - clinical or subclinical presentation (autoantibodies only)	<b>20-40%*</b>
<ul style="list-style-type: none"> <li>Associated autoimmune disorders e.g. thyroid, adrenal, pernicious anaemia, SLE, type 1 diabetes</li> <li>Isolated autoimmune ovarian failure</li> <li>Autoimmune polyglandular syndromes</li> </ul>	
<b>Metabolic</b>	<b>rare*</b>
<ul style="list-style-type: none"> <li>Galactosaemia</li> <li>Enzyme deficiencies</li> </ul>	
<b>Infection</b>	<b>unknown*</b>
<ul style="list-style-type: none"> <li>Viral oophoritis (mumps, cytomegalovirus)</li> </ul>	
* % of cases of PM	

complementary preparations is not established.

### 7. Fertility

Spontaneous remission is observed in PM with a lifetime chance of conception of 5-10 per cent. Currently the only proven therapy for obtaining a pregnancy is via use of donor oocyte. The option of freezing embryos/eggs or ovarian tissue should be considered prior to chemo/radiotherapy.

### 8. Long-term sequelae

- Monitoring of the long-term complications associated with specific causes of PM (e.g. Turner syndrome) is necessary. Although the natural history of associated autoimmune dysfunction is unclear, yearly TFTs and fasting glucose is recommended.
- CVD risk is increased and monitoring and treatment of risk factors is recommended
- Osteopaenia is common and risk factors need to be considered. Therapy follows conventional measures with calcium and vitamin D supplements as necessary. HRT is indicated but the role of other agents including bisphosphonates is less clear.
- Recurrent malignancy is a concern where PM is secondary to cancer therapy. ☺

■ The Jean Hailes Foundation for Women's Health is a national, non-profit health organisation. Professional development opportunities plus patient resources are available at [www.jeanhailes.org.au](http://www.jeanhailes.org.au)

Suggested reading: [www.medicalobserver.com.au](http://www.medicalobserver.com.au)