Premature menopause

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Menopause

= the last natural menstrual period
  – depletion of oocyte (egg) reserve

• Median 51-52 years

• Normal 45-55 years

• Early menopause
  – <45 years (5% of women)

• Premature menopause
  – <40 years
Premature menopause

- Prevalence ~1%

Higher incidence:

- Smoking
- Nulliparity
- Hysterectomy
- HIV infection
- Illicit drug use
- Adverse life events

Davis S et al. Nature Reviews Disease Primers 2015;1-19
Premature menopause

Increased risks of:

• Cardiovascular disease
  – 40% increase in risk

• Osteoporosis and fracture
  – 2-3 fold increase in risk

• Cognitive decline / dementia
  – 2 fold increase in risk

• Type 2 DM

• Parkinson’s disease

• Glaucoma

Shuster L et al. Menopause Int. 2008;14:111-6
Parker W et al. Obstet Gynecol 2013;121:709-16
Deaths from major causes Australian females

Figure 1.1b Proportion of deaths from major causes, all ages, women and girls, 2012

- IHD 13%
- Stroke 9%
- Other CVD 10%
- Colorectal cancer 2%
- Lung cancer 4%
- Breast cancer 4%
- Other cancers 15%
- Respiratory disease 9%
- Injuries and poisoning 5%
- All other causes 29%

32%
# Premature menopause

## Causes:

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic/cytogenetic</td>
<td>Fragile X</td>
</tr>
<tr>
<td></td>
<td>Turner syndrome</td>
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<tr>
<td>Enzymatic defects</td>
<td></td>
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<tr>
<td>Immune disturbances</td>
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<tr>
<td>Defects in gonadotropin structure or actions</td>
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<td>Idiopathic</td>
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<tr>
<td>Physical insults</td>
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<td></td>
<td>Ionizing radiation - pelvic</td>
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<tr>
<td></td>
<td>Chemotherapy</td>
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<td></td>
<td>- older age / greater cumulative dose / cyclophosphamide</td>
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<tr>
<td></td>
<td>Viral infection</td>
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<td></td>
<td>Cigarette smoking</td>
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<td>Bilateral oophorectomy / gynaecological surgery</td>
</tr>
</tbody>
</table>
Primary ovarian insufficiency - POI

• Previously called Premature Ovarian Failure (POF)
• 90% - no cause
• Genetic and autoimmune links
  - Fragile X carriers
  - Turner syndrome
• At higher risk of developing autoimmune conditions:
  – Hypothyroidism (1 in 4 women)
  – Adrenal insufficiency or type 1 DM (3%)
  – Pernicious anaemia
  – Myasthenia gravis
  – Connective tissue disorders
  – Hypoparathyroidism
Primary ovarian insufficiency - POI

• Intermittent ovarian function may occur in ~50%
  – Erratic menstrual cycles
  – Spontaneous conception in 5-10% of women

• Higher incidence of anxiety and depression, low self-esteem, isolation

Schmidt P et al JCEM 2011;96:E278-87
Schmidt P et al JAMA 2006;295:1374-6
Premature menopause – key issues

- Diagnosis
- Education
- Symptom management
- Fertility management
- Psychological support
- Prevention
  - Cardiovascular disease
  - Osteoporosis
  - Cognitive decline
Premature menopause - diagnosis

• FSH >40 IU/L on 2 occasions at least 1 month apart following 4-6 months of amenorrhoea (not on hormone therapy / OCP)

• Exclude secondary causes of amenorrhoea
  – Hypothalamic amenorrhoea
    • High levels of exercise / low body weight or BMI / low calorie or fat-restricted diet / Type A personality / low FSH and LH levels / low oestradiol levels
  – Hypothyroidism
  – Pregnancy
  – Polycystic ovary syndrome
Investigations

- Oestradiol / FSH / LH
- Prolactin
- TSH
- Testosterone / SHBG / calculated free testosterone
- DHEAS
- Cortisol
- Thyroid antibodies
- FBG
- Vitamin B12
- +/- β-hcG

- Gynaecological ultrasound
Premature menopause - diagnosis

• AMH – issues with assay sensitivity; not necessary for diagnosis

• Diagnosis can take time and may be associated with considerable patient anxiety

• Referral to specialist / tertiary referral centre with expertise – Endocrinologist / Gynaecologist / Menopause Clinic
  – Fragile X / chromosomal analysis
  – DXA
  – Adrenal antibodies
Menopause symptoms

80% of women

20% of women:
- NO symptoms
- SEVERE symptoms
- symptoms for > 5 years

Vasomotor symptoms
- Hot flushes
- Night sweats

Sleep disturbance

Urogenital symptoms including:
- Vaginal dryness

Other symptoms
- Formication (itchy skin)
- Joint pains
- Difficulty concentrating
- Irritability
- Fatigue
- Anxiety
- Palpitations
- Low mood
- Low libido

80% of women

20% of women:
• NO symptoms
• SEVERE symptoms
• symptoms for > 5 years
Treatment – Premature menopause

- Depends on the cause
- Unless contraindicated, some form of oestrogen and progestogen replacement until around the age of natural menopause
  - 45-50yrs
- Either combined oral contraceptive pill (COCP) or MHT (HRT)
  - COCP may be more acceptable; in line with peers and offer contraception if pregnancy not desired (in POI)
  - Oestrogen and progestogen if intact uterus
  - Oestrogen only after hysterectomy
- If MHT higher doses recommended
  - Symptom relief
  - Bone protection
- Vaginal oestrogen / moisturisers / lubricants
- ?Testosterone?
Benefits of hormone treatment

• Symptom relief

• Reduced risk of cognitive decline
  Rocca W et al Neurology 2007;69:1074-83

• Reduction in fracture risk
  van der Klift M et al J Bone Miner Res 2004;19:1172-80

• Reduction in CVD risk
  – presumed from studies of natural menopause
Hormone Replacement Therapy Versus the Combined Oral Contraceptive Pill in Premature Ovarian Failure: A Randomized Controlled Trial of the Effects on Bone Mineral Density.

30 spontaneous POF, 18-44 yrs
- Oestradiol 2mg + NETA 1mg (oral) vs. Microgynon 30 OCP vs. no Rx
- 2yrs

<table>
<thead>
<tr>
<th>Groups</th>
<th>Lumbar spine BMD</th>
<th>Femoral neck BMD</th>
<th>Bone turnover markers: CTx / PINP</th>
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<tr>
<td>HRT</td>
<td>↑</td>
<td>⇨</td>
<td>↓</td>
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<tr>
<td>OCP</td>
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<tr>
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<td>↓</td>
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*All P<0.05 for differences

Cartwright B et al JCEM 2016;101(9);3497-505
Risks and benefits of MHT between 50-59 yrs or <10 yr after menopause

- **Risks**
  - Fractures
  - Diabetes
  - Breast cancer
  - Colorectal cancer
  - Overall mortality
  - Coronary heart disease
  - Endometrial cancer
  - Lung cancer
  - Venothrombotic episodes
  - Stroke
  - Cholecystitis

- **Benefits**

  - oestrogen only
  - oestrogen + progestogen

No of women per 1000 per 5 years of use

Santen R J et al. JCEM 2010;95:s1-s66
Risks and benefits of MHT between 50-59 yrs or <10 yr after menopause

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☐ oestrogen + progestogen

Santen R J et al. JCEM 2010;95:s1-s66
Incidence of Cardiovascular Disease by Age, Sex and Menopausal Status

Rate 1000 per year

ELITE study – oral oestradiol in early vs. late postmenopausal women: carotid artery intimal thickness

“window of opportunity”

P <0.01

Management - other

- Psychological support
- Fertility counselling
- Sexual counselling
- CVD and osteoporosis risk reduction:
  - Avoid smoking and alcohol excess / encourage weight bearing exercise / adequate calcium in diet / vitamin D
- General screening
  - Lipids / BP / FBG / Pap smear / breast exam
- Osteoporosis medications
  - If osteoporosis / fracture and hormone therapy contraindicated
- Non-hormonal treatments for flushes / sweats
  - If hormone therapy contraindicated
  - Venlafaxine / SSRIs / Clonidine / Gabapentin

Take home messages

• Premature menopause is not common but is associated with increased risks for cardiovascular disease, osteoporosis and cognitive decline.

• Unless contraindicated women should be offered some form of oestrogen +/- progestogen (MHT/HRT or COCP) until at least the average age of menopause; ~50yrs.

• Women with premature menopause should be assessed by someone with expertise in this area.

• Psychological support and fertility management are important considerations in addition to the usual management of the postmenopausal woman.
Premature & early menopause

Last updated 01 December 2016 — Last reviewed 03 March 2014

Menopause that happens earlier than the expected age of around 50 years is called premature or early menopause. This may be due to primary ovarian insufficiency where the periods spontaneously stop, as a result of chemotherapy treatment for cancer or surgically induced menopause when the ovaries are removed. The impact on physical health, emotions, mood, body image and relationships can be significant, but there are treatment options and ways to manage premature and early menopause, which can help.

Spontaneous Premature Ovarian Insufficiency

Definitions and Epidemiology

Menopause occurring spontaneously in women younger than 40 years of age affects approximately 1% of women. This was previously referred to as premature ovarian failure; however, the preferred term is now premature (or primary) ovarian insufficiency (POI). Premature menopause is menopause occurring before age 40 years and includes surgical removal of ovaries (bilateral oophorectomy). POI may also be included under this heading although cessation of ovarian function in POI is not always irreversible. Menopause occurring between 40-45 years of age is called early menopause, with spontaneous early menopause affecting approximately 5% of women.

Factors associated with an earlier menopause include smoking, nulliparity, hysterectomy, HIV infection, illicit drug use, a family history of early menopause and adverse life events. There is no evidence that early menopause is associated with the use of oral contraceptives, fertility drugs or artificial hormones in the environment. Childhood caloric restriction, emotional stress at a young age, lower socioeconomic position and environmental toxins are factors identified in some but
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