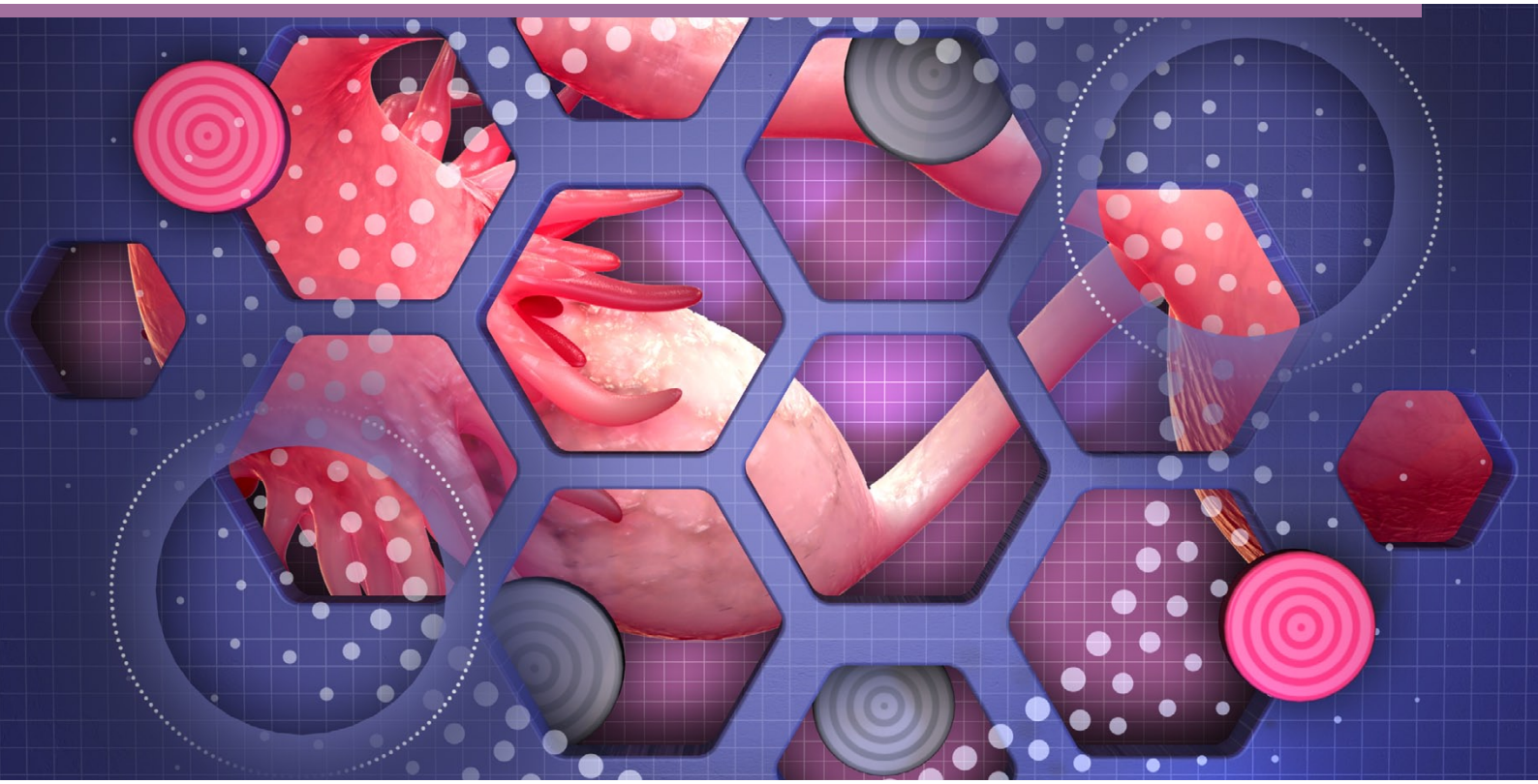

Diagnosing and managing **primary ovarian insufficiency**

Primary ovarian insufficiency is the loss of ovarian function before age 40 years, resulting in menstrual irregularities and menopausal symptoms. Hormone treatment until the age of natural menopause is recommended to alleviate symptoms and reduce the long-term risks of oestrogen deficiency, such as fracture and cardiovascular disease.

KEY PRACTICE POINTS:

- Primary ovarian insufficiency can be diagnosed in women aged < 40 years with four to six months of amenorrhoea (after excluding other causes) and two FSH tests > 40 IU/L, at least four weeks apart
- Treatment options include menopausal hormone therapy or combined oral contraceptives. Treatment selection should be individualised to improve adherence, considering any relevant history, co-morbidities, need for contraception and patient preference.
- Hormone treatment should be continued at least until the age of natural menopause (approximately age 50 years)
- Patients should be reviewed annually, including an assessment of symptom control, cardiovascular risk and adherence to treatment; bone mineral density should be checked every two years

Primary ovarian insufficiency: an overview

Primary (or premature) ovarian insufficiency* is a clinical syndrome defined by the loss of ovarian function before the age of 40 years.[1] It is characterised by menstrual irregularities (infrequent menstrual cycles or amenorrhoea) with elevated FSH and LH levels and low oestradiol levels.[1] Approximately one in 100 women aged < 40 years and one in 1000 women aged < 30 years have primary ovarian insufficiency.[2] It results in menopausal symptoms and reduced fertility, and increases the risks of fracture, cardiovascular disease and premature mortality.[3]

* Also referred to as premature menopause, premature ovarian failure or primary ovarian failure. These terms can be misleading as women with primary/premature ovarian insufficiency do not always stop menstruating or have a complete loss of ovarian function.

Primary ovarian insufficiency may be spontaneous (e.g. idiopathic, genetic, associated with autoimmune diseases or environmental factors) or due to medical treatments (e.g. chemotherapy, radiation therapy, single or bilateral oophorectomy, hysterectomy, uterine artery embolisation, bilateral ovarian surgery for cysts or endometriosis).[3]

N.B. This is distinct from secondary ovarian insufficiency where ovarian function is normal, but hypothalamic or pituitary function is impaired.

Diagnosing spontaneous primary ovarian insufficiency

Women with primary ovarian insufficiency typically present to primary care with menstrual irregularities, infertility or menopausal symptoms (e.g. hot flushes, mood changes, sleep disturbance, urogenital atrophy, altered libido).[3] A diagnosis of primary ovarian insufficiency can be made on the basis of four to six months of amenorrhoea in women aged < 40 years after excluding other causes of secondary amenorrhoea, and two FSH tests > 40 IU/L, conducted four to six weeks apart.[3] Oestradiol levels should be measured to support the FSH results. Measurement of Anti-Müllerian hormone levels for the diagnosis of primary ovarian insufficiency has not been validated and is not recommended.[3]

Consider referring or discussing women with primary ovarian insufficiency with a gynaecologist or endocrinologist.

Diagnosis can be distressing

Primary ovarian insufficiency can have a significant effect on a woman's life plans (e.g. if she wishes to have biological children) and sense of identity; depression and anxiety are common.[4] Hormone treatment may help to improve mood symptoms and women should be referred for psychological interventions as appropriate.[4]

The likelihood of natural conception is low

The likelihood of natural conception in women with primary ovarian insufficiency is 1– 5% over a lifetime.[4] Most women with primary ovarian insufficiency who achieve pregnancy do so by *in vitro* fertilisation using a donor oocyte or embryo.[4] Ovarian stimulation may be tried, but has a low rate of success.[4]

Although the chances of spontaneous pregnancy are low, women who do not want to become pregnant should use contraception.[4] Treatment options that will provide both oestrogen replacement and contraception include oral or transdermal oestrogen with a levonorgestrel intrauterine system, or a combined oral contraceptive (COC). Alternatively, women may choose to use barrier contraception.

Patient information and support is available from: **www.earlymenopause.org.nz**

Managing primary ovarian insufficiency

Hormone treatment until at least the age of natural menopause is recommended

Hormone treatment, either with MHT or a COC, is recommended for women with primary ovarian insufficiency (unless there are contraindications) to alleviate symptoms, improve their quality of life, and reduce the long-term risks of oestrogen deficiency.[5] Treatment should be continued until at least the age of natural menopause (approximately age 50 years).[4] Treatment may be continued beyond this if the woman has menopause symptoms affecting her quality of life, after considering the balance of benefits and risks.[5]

Higher doses of MHT are recommended for women with primary ovarian insufficiency than women of menopausal age as the treatment goal is to achieve hormone levels in the pre-menopausal range (Table 1).[6] The benefit-risk considerations for initiating MHT in women with primary ovarian insufficiency differ from those in women who enter menopause at the usual age. In the absence of hormone treatment, women with primary ovarian insufficiency may be at greater risk of adverse outcomes such as cardiovascular disease, osteoporosis and fracture, and cognitive decline.[7] Although oestrogen + progestogen MHT is associated with small increase in the risk of breast cancer in women initiating treatment at the natural age of menopause, observational data suggest that MHT does not increase the risk of breast cancer in women aged < 50 years.[1]

For information on the risks of MHT in women at the natural age of menopause, see: **www.bpac.org.nz/2019/mht.aspx**

Treatment options

Various treatment options are available to manage primary ovarian insufficiency:[6, 7]

- High dose menopausal hormone therapy (MHT) (Table 1):
  - An oestrogen + progestogen MHT regimen (if the woman has a uterus)
  - Oestrogen-only MHT (if the woman does not have a uterus)
- A COC; for further information see: **www.bpac.org.nz/2019/contraception/oral-contraceptives.aspx**

Currently, there is no conclusive evidence regarding the optimal hormone treatment regimen. Treatment selection should be individualised to improve adherence, taking into account any relevant history, contraindications to MHT or COC use, co-morbidities, need for contraception and patient preference.

For further information MHT regimens, formulations and subsidised products, see: **www.bpac.org.nz/2019/mht.aspx**

Factors to consider when selecting a treatment: [4, 6, 7]

- MHT may be preferable to a COC for optimisation of bone and cardiovascular health, but this must be weighed against the need for contraception
- A cyclical MHT progestogen + oestrogen regimen may be used by women with a uterus who wish to have a monthly withdrawal bleed. This regimen may be preferred in women trying to achieve pregnancy as it stimulates regular endometrial proliferation.
- A continuous MHT progestogen + oestrogen regimen may be preferred for women who have not had a menstrual period in two or more years
- A COC should be used in an extended or continuous regimen (i.e. running packets together) to avoid menopausal symptoms in the hormone-free interval
- A levonorgestrel intrauterine system (Mirena) used in combination with oestrogen is likely to be associated with less systemic progestogen adverse effects than oral formulations and also provides contraception
- Transdermal oestrogen is recommended for women at increased risk of venous thromboembolism, migraines or liver disease
- Oestrogen-only treatment is recommended for women who have had a hysterectomy

Follow up with patients annually once a treatment regimen is established

Women with primary ovarian insufficiency should be reviewed at least annually, including an assessment of symptom control, adherence to treatment and cardiovascular risk.[1] It is recommended that bone mineral density be assessed every two years, however, the availability and accessibility of DEXA scans for this patient group varies between DHBs and clinicians should refer to their local Health Pathways for further information.[4] Some patients may choose to access DEXA scans privately. Breast cancer screening with mammography is recommended every two years from age 45 years (until age 69 years).[7] Routine monitoring of hormone levels, e.g. oestradiol, is not usually necessary.[1, 5]

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N.B. Expert reviewers are not responsible for the final content of the article.

Table 1. Suggested MHT formulations and doses for women with primary ovarian insufficiency [5, 6, 7]

	Recommended dose
Oestrogen component	
Transdermal estradiol	75–100 micrograms/24 hours patch, twice weekly application
Oral estradiol	2 mg, daily
Ethinylestradiol	10 micrograms, daily
Conjugated equine oestrogens	1.25 mg, daily
Estradiol valerate	2 mg, daily
Progestogen component – required for women who have a uterus	
Long-acting intrauterine system (Mirena)	52 mg device; delivers 20 micrograms/daily
Medroxyprogesterone acetate	Cyclic: 10 mg, daily, for 12 days per month Continuous: 2.5–5 mg, daily
Micronised progesterone	Cyclic: 200 mg, daily, for 12 days per month Continuous: 100 mg, daily

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