

# Premature Menopause

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Women are given a fixed complement of eggs during foetal life and from around 20 weeks of gestational age start to lose them. Menopause or 'last period' normally occurs around the age of 50, with the normal range between 40 and 60 years. Menopause is considered premature if it occurs before the age of 40. The incidence of premature menopause is around 1 per cent.

## Diagnosis of premature menopause

Usually the diagnosis of premature menopause is fairly straightforward. Menstrual periods become irregular and often eventually stop altogether. The following symptoms are associated with premature menopause.

- Hot flushes
- Depression, mood swings
- A crawling sensation under the skin
- Tiredness, Insomnia
- Vaginal dryness
- Poor memory, poor concentration
- Muscle and joint aches

The diagnosis is confirmed by measuring blood levels of follicle stimulating hormones (FSH). Serum FSH levels > 20 u/l are indicative of at least a perimenopausal state (i.e. indicating that the final period is not far off). Laboratory errors can occur and therefore the diagnosis of premature menopause should be confirmed by measuring FSH levels on two and preferably three occasions separated by a couple of weeks on each occasion.

Blood measurement of Anti-Mullerian Hormone (AMH) may give an estimation of egg reserve. Typically, AMH levels become low some years before FSH levels rise and so may be a useful 'early-warning system' for women known to be at risk for early menopause. Both FSH and AMH blood tests are available through most Australian pathologists.

## Causes of premature menopause

The following summarizes the causes of premature menopause.

- Chromosomal (e.g. Turner's syndrome)
- Auto-immune
- Metabolic (e.g. galactosaemia, haemochromatosis)
- Familial
- Infection (e.g. mumps)
- Iatrogenic (e.g. hysterectomy, chemotherapy, radiotherapy)
- Resistant ovary syndrome
- Idiopathic

# Premature menopause

The clinical setting of premature menopause typically presents one of two scenarios. Firstly, there may be a history of significant illness in the past (e.g. treatment for cancer or severe childhood illness). In these cases the diagnosis is usually straight-forward and the cause clear. On the other hand many women present without any significant medical history and so the cause is unclear. Particularly in women under the age of 30 with premature menopause it is wise to check for tissue specific antibodies, including antibodies against the thyroid and the ovaries. In the past some authorities have advocated biopsying the ovaries to demonstrate the presence or absence of follicles. However, ovarian biopsy does not change the treatment options.

## Resistant ovary syndrome

The usual causes of apparent premature menopause result in the loss of all eggs from the ovaries. There is one condition however where the ovaries do contain eggs but for reasons that are not understood the eggs are not normally accessible. This is called 'The Resistant Ovary Syndrome'. The only sure way to diagnose this condition is to perform ovarian biopsy but as we have no effective treatment for this condition ovarian biopsy is invasive and unnecessary.

## Fertility prognosis

Chromosomal causes of premature menopause usually result in permanent infertility although there has been the occasional case report of a successful outcome. About ten per cent of women who have had an apparent premature menopause after chemotherapy resume menstruation and theoretically can conceive. Where no obvious cause is found (idiopathic premature menopause or resistant ovary syndrome) the medical literature would suggest that around one in five of these women will in fact conceive naturally most while on hormone replacement therapy. For those who do not conceive within a reasonable length of time egg donation is a viable option.

Recently, Japanese workers successfully used skin stem cells to produce eggs (and sperm) in mice (see Nature 2013; 500:392-4). Furthermore these stem-cell-derived eggs successfully fertilised and produced offspring. It will probably take a few more years to duplicate this research in humans.

## Treatment

For those women not wishing to conceive, a combined oral contraceptive pill is an effective way of replacing oestrogen and progesterone as well as offering contraception. For those who wish to conceive, hormone replacement is the best option. It should be noted that standard fertility drugs such as clomiphene or FSH therapy do not work in this situation. Cyclical hormone replacement (e.g. Trisequens, Femoston, Estalis sequi) replace the female hormones oestrogen and progesterone but do not inhibit ovulation thus conception is possible whilst on hormone replacement therapy (HRT).

Hormone replacement therapy should be continued at least until the age of 50. Untreated women with premature menopause are at substantially increased risk of both osteoporosis and heart disease and so it is critically important that hormone replacement is taken.

## Conclusion

In conclusion, premature ovarian failure is common. Such affected patients should have blood taken to check for the presence of auto-antibodies and if the patient is under the age of 30 they should have a chromosome check. All of these women should be offered HRT to restore their quality of life and to prevent the long-term sequelae of sex hormone deficiency.

Professor John Eden

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