



Premature ovarian failure (POF)

for further information see www.pofsupport.org

Definition: Most women experience the natural loss of ovarian function, the event we call menopause, between the ages of 45 and 55 years, with little variation in this figure between different countries and different ethnic groups. This age range reflects the individual variation in biological ageing of the ovaries between different women.

Menopause is considered to be *premature* when it occurs spontaneously in a woman before the age of 40 years.

This means the ovaries are no longer able to produce adequate amounts of the sex hormones oestrogen, progesterone and testosterone, or to develop a mature egg for ovulation.

Normal menopause is an irreversible condition, whereas approximately 50% of women with premature ovarian failure experience intermittent ovarian function after their periods initially stop. Therefore some women will produce estrogen intermittently and may ovulate, despite having hormone levels that are consistent with being postmenopausal. Pregnancies have occurred after the diagnosis of premature ovarian failure.

Primary ovarian failure: This is when a woman never ovulates and never experiences natural menstruation.

Secondary ovarian failure: This is when menstruation occurs for months to years, but then stops prematurely as the ovaries have failed.

Causes of Premature Ovarian Failure (POF)

In most cases there is no identifiable cause of POF. In this situation it is described as **spontaneous**. Spontaneous POF is due to unexplained early degeneration of the cells of the ovary.

It is not uncommon for a woman with spontaneous POF to have a family history of premature menopause in either her mother or sister.

Autoimmune: This is when there is an immune attack on the ovaries. Women who have autoimmune ovarian failure are at increased risk of having adrenal failure, thyroid failure (hypothyroidism), hypoparathyroidism, or a rare condition called mucocutaneous candidiasis.

Genetic disorders: Females have two X chromosomes. The genetic defects causing POF usually are associated with an abnormality of the long arm of one of these X chromosomes. In the absence of two normal X chromosomes, or critical material from



one of the X chromosomes, the cells of the ovaries undergo early deterioration which may even occur as complete degeneration before birth. When the latter occurs, the ovaries are replaced by a white thin fibrous streak and is known as a 'streak gonad'.

Chromosomal abnormalities are detected in 40-50% of women who do not experience spontaneous puberty. The most common genetic abnormality causing POF is a condition known as Turner's syndrome in which there is only one X chromosome instead of two. Short stature is the most frequent feature of Turner syndrome but affected girls also frequently have heart or kidney abnormalities. Many women with Turner's syndrome appear to enter puberty normally. However it is more common for affected girls not to enter into puberty and in such instances hormone therapy is required to achieve development of breasts and body hair. HT is also important for affected girls in order not to miss out on achieving full bone strength.

There are several other less common genetic conditions which are responsible for very early ovarian failure. Some young women with these conditions may menstruate for a time and even experience an apparently normal puberty before their ovaries fail in their teenage years or twenties.

All women who experience POF before the age of thirty years must have a blood test for chromosomal assessment. This is because occasionally, in addition to having an abnormality in an X chromosome, some women may have an inactive Y chromosome in their genetic material. The presence of a Y chromosome in this case is associated with a substantial risk of future cancer of the undeveloped ovaries.

All young women with POF due to a genetic abnormality with the presence of a Y chromosome, must have their ovaries or ovary-like tissue, surgically removed to eliminate their considerable risk of developing cancer.

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Cancer therapy as a cause of POF

Women who have had **radiotherapy** of the pelvis and chemotherapy may experience an early menopause as the ovaries are extremely sensitive to the effects of radiation. The radiation dose which causes complete ovarian failure depends on the number of eggs present in the ovaries, which usually is determined by a woman's age. In women over the age of forty years, a radiation dose to the ovary greater than 600 Rads will usually result in ovarian failure. In contrast, younger women who have had up to 3000 Rads to the pelvis have gone on to conceive. Radiation is more toxic to the ovaries than chemotherapy, therefore when the two treatments are combined, ovarian failure is more commonly due to the radiation exposure.



An important factor in the development of POF is the position of the ovaries in relation to the radiotherapy field. Thus, some women may have their ovaries moved surgically so that they are out of the range of the radiation area.

The likelihood of developing ovarian failure after **chemotherapy** depends on the age at treatment, drug type, dose, and duration of treatment. In general younger women are

more resistant to the ovarian effects of chemotherapeutic agents than older women. In some younger women ovarian function returns after a period of loss of periods and menopausal symptoms.

Galactosemia occurs due to a deficiency in the enzyme galactose-1-phosphate uridyl transferase (GALT). It is a rare autosomal recessive disorder with some people being severely affected. Most women with galactosemia develop POF.

Infectious agents: Mumps oophoritis has been implicated as a rare cause of POF. However, patients with mumps oophoritis should be reassured that in most cases following recovery of the mumps normal ovarian function is expected to resume. Ovarian failure has also been reported to occur following *Shigella* infections, malaria, and varicella, but a cause and effect relationship has not been established.

Surgical menopause: Women who have both their ovaries removed are by definition postmenopausal.

Symptoms of premature ovarian failure

The age at which POF occurs is dependent on the underlying cause, if any, as well as the timing and rapidity of loss of ovarian function.

- **POF occurring before puberty** results in failure of sexual development and spontaneous menstruation does not occur.
- **Ovarian failure after puberty** results in loss of menstruation after the establishment of apparently normal cycles in a young woman with normal sexual development.

Some girls experience full sexual development followed by one or two menstrual cycles before the ovaries fail. Others, for example most patients with chromosomal defects, are sexually undeveloped and fail to menstruate at all, although there are a few girls who have a small amount of ovarian tissue which functions briefly, and who have some sexual development and a few menstrual cycles.

Girls who have POF before puberty do not experience the classic symptoms of oestrogen deficiency as exposure of the body to adult levels of oestrogen and subsequent oestrogen loss appear to be necessary for the development of such symptoms. Young women who develop POF after puberty frequently experience hot flushes, night sweats, fatigue and



mood changes including emotional lability, irritability and depression. Vaginal dryness and discomfort with intercourse are also common features of oestrogen lack. Women with POF not only suffer from lack of oestrogen and progesterone but also from lack of testosterone. In the past testosterone was considered as a 'male' hormone but we now know it is also important in women, being produced by both the adrenal glands and the ovaries.

Diagnosis of POF

Young women who do not menstruate by the age of seventeen years or who stop menstruating for more than six months should be formally assessed in order to identify the underlying cause.

There are several reasons why periods might not occur or might stop ranging from abnormal gynaecological anatomy through to central brain dysfunction due to stress or hormonal imbalances.

Measurement of hormones is the key to diagnosis, but POF **cannot be diagnosed on a single blood test**. A low oestrogen level PLUS a high FSH level must be detected on at least three separate occasions each at least one month apart for a firm diagnosis to be made.

Chromosomal analysis is essential for all women experiencing ovarian failure before the age of thirty years.

Older women should discuss the option of chromosomal studies, as identification of an abnormality may influence other family members, sisters or daughters, who carry the same defect in terms of planning pregnancies. Women less than 160cm tall are more likely to have a chromosomal defect. When chromosomal abnormalities are found, the diagnosis of POF can be made with certainty.

Fertility

Infertility is probably the most distressing consequence of POF.

Women with **spontaneous POF** commonly have a few healthy nests of eggs left in their ovaries, although they are immature and their numbers are insufficient to produce much in the way of sex hormones. Infrequently, one of these remaining eggs unpredictably responds to the stimulation of high blood FSH levels, oestrogen production switches on and the egg starts to develop. Why this can suddenly occur, sometimes years after the diagnosis of POF has been made, is not understood. In most instances when this happens the development of the egg is flawed and ovulation does not occur. Rarely however, ovulation may happen spontaneously, usually in women with low levels of FSH.

Thus the possibility of a pregnancy in young women suffering spontaneous POF is less remote than previously believed with a 10 to 15 percent life time chance of conception. Successful pregnancy is usually limited to women taking hormone therapy (HT). This is because without hormones, the lining of the uterus is undeveloped and unreceptive to a fertilised egg. Women taking HT are more likely to have a uterus with a suitable lining for implantation of a fertilised egg and an ongoing pregnancy. Blood levels of hormones are poor predictors of ovulation. However, ovulation and conception are more common



in women with one or two FSH measurements below 40 u/l. When FSH is found to be greater than 100 u/l ovarian failure is probably permanent and irreversible.

For women with specific causes of POF the likelihood of fertility is remote and for women with streak ovaries or surgical premature menopause, infertility is absolute. No therapies have been demonstrated to be effective in restoring fertility in women with POF.

Disproven treatments include oestrogens, anti-oestrogens, gonadotrophin therapy and the drugs Danazol, Clomiphene citrate and Bromocriptine. Thus, any attempts to induce ovulation should be restricted to specific controlled clinical trials.

The first report of a successful pregnancy with the delivery of a healthy baby in a woman with POF through oocyte (egg) donation was in 1984. Oocyte donation is an option for women with POF with pregnancy rates being reported by some groups to be as good or better than *in vitro* fertilisation. The rates vary between different infertility treatment centres and with the specific programs used. Oocyte donation is a physically and emotionally demanding process as it involves monitoring egg development, egg retrieval from the donor, fertilisation outside the body (test tube fertilisation) implantation of the embryo into the women desirous of the pregnancy and a receptive uterus for the implanted embryo.

POF and hormone therapy

Most women who experience POF require long term hormone therapy (HT) in order to maintain good overall health. In addition to the loss of fertility, women with POF are at increased risk of developing early atherosclerotic cardiovascular disease in midlife as well as being at increased risk of osteoporotic fractures at an early age. The earlier the loss of normal levels of ovarian hormones, the greater the risk of bone loss. HT in this instance is not a controversial issue and is not comparable to the use of HT after menopause after the age of 50 years. Women who experience early loss of ovarian function are relatively oestrogen, progesterone and testosterone deficient when compared to other normal women of the same age. Taking HT for POF is generally considered no different to someone with an under active-thyroid taking thyroid hormone replacement or a diabetics using insulin. Whether or not women with POF choose to continue using HT beyond the average age of natural menopause, fifty-one years, is a different issue.