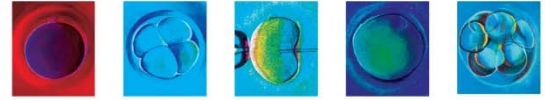


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# FERTILITY FACT SHEET

San Ramon / Orinda / San Jose

## Premature Ovarian Insufficiency

Premature Ovarian Insufficiency (POI) is a term used to describe women whose reproductive function declines or ceases at an early age. It replaces an older term, premature ovarian failure (POF). It is a condition that affects about one in every thousand women. POI typically presents as the absence of menses or with irregular and infrequent menses. Sometimes the term is applied to women who still have menstrual cycles but hormone tests indicate that the ovary has a very low number of functioning eggs and ovarian failure is thought to be imminent.

Our present understanding of a woman's fertility is that it is closely linked to the number of functional eggs in the ovary. In the third month of fetal life, germ cells in the ovary produce eggs that are stored in small fluid-filled sacs, called follicles. At birth, a female infant may have as many as 4 million eggs. But the egg cells die over time and it appears that no new eggs are generated to replace those that are lost. The fact that egg cells die is not so unusual as most cells in the body die after a time. However, most cells are replaced by new cells. It is this lack of replacement that is unique. By the time an adolescent reaches puberty the number of eggs in the ovary has already significantly decreased and may be less than one million. This egg loss continues and in time, once a critical low number has been reached (some say 125,000), ovulation stops and a woman is no longer able to conceive. Peak fertility occurs shortly after puberty and stays high until around age 35 and then begins to decline. Most women will start experiencing difficulty conceiving by age 40 which is about ten years before menopause. In that pre-menopausal phase, the number of eggs is declining and it is associated with a decline in conception.

Women with POI experience a loss in fertility at a younger age. The diagnosis of POI is made by the clinical history of irregular or no menstruation and by laboratory tests. Two hormones, FSH, or follicle stimulating hormone and estradiol are measured to determine if a woman has POI. The FSH hormone is produced by the pituitary and is responsible for stimulating a follicle within the ovary to mature an egg for ovulation. The follicle not only matures the egg, but also produces the hormone, estrogen or estradiol. When the ovary fails to respond to the FSH, the estrogen levels stay very low and the pituitary secretes even more FSH to try to "wake" the ovary. So, as the ovary fails to mature an egg, it also fails to produce estrogen, and the pituitary FSH levels rise and rise. From a fertility standpoint, optimal FSH levels in a fertile woman stay low, and are typically less than 10 MIU/mL. POI is confirmed as a diagnosis when the FSH levels are > 40 MIU/mL, the estrogen levels is < 20 pg/mL and a woman has not had a period for more than 6 months. Since POI does not happen overnight, there can be a gradual transition in FSH levels from normal range to very elevated. Generally, the higher the FSH level, the more likely there is a depletion of eggs in the ovary and in overall fertility.

Anti-Mullerian Hormone or AMH is another hormone test that can be used to confirm the diagnosis of POI. AMH is produced by the follicles in the ovary and secreted into the blood. The more follicles in the ovary, the more AMH is in the blood. Measuring AMH can confirm for the physician and patient if there are any functioning follicles or eggs left.

Normal AMH levels are between 1 – 2 ng/dL. Very low AMH levels are < 0.1 ng/dL. In the future, AMH may be used more pro-actively as a test for women in their teens and twenties to help predict whom might be at risk for POI.

Why do some women develop POI? The causes can be varied. Two genetic conditions have been associated with POI. One is Turner's syndrome and the other is Fragile X pre-mutation, both of which involve the X chromosome. For Turner's Syndrome, women are born with only one X chromosome, instead of the usual two. Typically, it is known at birth if an infant has Turner's Syndrome because there are certain physical features that are characteristic. Some women, however, have a more mild condition, called Mosaic Turner's. In this condition, some of their cells have two XX chromosomes, but some have only one X, hence the term "mosaic." These women will experience POI and sometimes repeated miscarriages. Fragile X pre-mutation is a condition in which an area on the X chromosome has more than the average number of DNA base pairs. This elongation of the X chromosome is associated with POI. It may be valuable to know if this is a cause because women who have Fragile X permutation can pass that X chromosome on to their children. The elongated DNA sequence can become longer in each generation, making the abnormality more significant. In males, it can be associated with mental retardation. In females, it can be associated with more mild learning disorders and POI.

Another cause of POI may be an auto-immune disorder. The immune system normally works to protect an individual from infection from viruses or bacteria. Immune cells produce antibodies that "tag" or identify foreign cells for destruction. Sometimes, however, the immune system makes antibodies to one's own cells (hence the term "auto" referring to one self). Antibodies to the egg cells or follicles have been described. A blood test can be done for antibodies to the ovaries, but the test is not always accurate. Often, autoimmune POI is suspected when other antibodies, such as to the adrenals or thyroid gland, can be detected. If an auto-immune cause is suspected, the individual is at increased risk of developing autoimmune failure in other endocrine glands such as the pancreas, parathyroid gland, thyroid gland, and adrenal. Periodic testing for diabetes, calcium, thyroid and cortisol should be done over the life of that individual.

There are other, even more rare causes of POI, such as abnormal FSH receptors in the ovary. In this situation, there are a normal number of eggs but the follicles cannot respond to the FSH signal because there is an abnormality in how the cell receives that signal. This is a difficult diagnosis to make and is often limited to research centers.

Once the diagnosis of POI is made, what can be done? Unfortunately, there is no treatment that restores or regenerates eggs. Some women with POI do conceive but the overall pregnancy rate is about 5% over the rest of their life time. Ovulation can be erratic and unpredictable. Normal testing with estrogen levels, ultrasounds, urine LH testing are fraught with inaccuracies because the normal process of follicle development is so abnormal that it does not follow any predictable course. Trying to track ovulation ends up being frustrating and ineffective. Women with POI do not respond to fertility medications. Since the basic problem is lack of eggs and inability of the ovary to respond to FSH, there are no medications at present to stimulate ovulation or to enhance fertility. From a fertility standpoint, the only reliable treatment at this time is egg donation, a treatment in which another woman donates her eggs to the woman with POI. Women with POI normally have a healthy uterus and can carry a pregnancy. Pregnancy rates with egg donation are about 70% with each attempt.

What are the long term health concerns for a woman with POI? Loss of ovulation means low estrogen levels. Estrogen is an important hormone that maintains bone mass, so when women have low estrogens at a young age, they begin to lose bone mass at a young age and are, over time, at risk of developing osteoporosis or thinning of the bones. Osteoporosis can put a woman at risk for bone fractures particularly of the hip and forearm.

Estrogen replacement therapy is often prescribed to women with POI under the age of 40 years who have stopped menstruating. Other ways to maintain a healthy bone mass are to take calcium supplements (daily requirement is 1500 – 2000 mg calcium/day) and Vitamin D. Weight-bearing exercise such as running, walking, and weight lifting are beneficial. Periodic testing (every 2 – 3 years) for bone density should be done. If bone thinning occurs, appropriate prescription medication should be considered.

Resources for women with POI include a website: [www.POFsupport.org](http://www.POFsupport.org) and the National Institute of Health (NIH) <http://www.nichd.nih.gov/publications/pubs/pof/index.cfm>.

#### Testing for POI:

- FSH, estradiol, AMH
- Chromosome analysis
- Fragile X screening
- Thyroid antibodies
- Adrenal antibodies
- Ovarian antibodies
- TSH (thyroid stimulating hormone)
- Glucose
- Calcium
- Cortisol