

ANOVULATORY CYCLES

BACKGROUND INFORMATION

WHAT IS ANOVULATION?

Anovulation is the term used to describe the failure of a woman's ovary to produce, mature or release ova (eggs).¹

ANOVULATORY CYCLES ARE COMMON

Most women will experience anovulatory cycles at some point during their reproductive lives. They occur most commonly in women close to menarche and menopause due to changing hormone levels, but anovulatory cycles also happen amongst healthy, regularly menstruating women, with preceding and succeeding cycles being ovulatory. This is unlikely to affect the woman's fertility.

However, some women suffer from chronic anovulation, and this may be an indication of an underlying endocrine condition, and can make natural conception difficult.²

The symptoms, diagnosis and management of anovulation vary depending on the cause.



ANOVLUTION IN HEALTHY, REGULARLY MENSTRUATING WOMEN

It has long been recognised that anovulatory cycles can occur amongst healthy, regularly menstruating women. The proportion of women with occasional anovulation is not well established, but a number of studies suggest a prevalence of up to 12%, depending on the population studied:

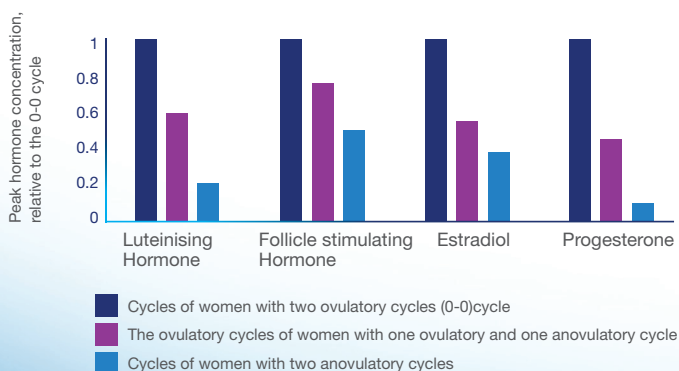
PREVALENCE	NUMBER OF STUDY PARTICIPANTS	DETERMINATION OF ANOVULATION	REFERENCE
12.4%	250	Serum progesterone and LH	Hambridge et al, 2013 ²
11.2%	152	Urinary P3G	Haiman et al, 2002 ³
9.0%	221	Serum progesterone	Haiman et al, 2002 ³
8.0%	125	Urinary P3G and LH	Johnson, 2014 ⁴
6.5%	46	Urinary P3G	Park et al, 2007 ⁵
2.3%	221	Urinary E3G and P3G	Wilcox et al, 1995 ⁶

P3G = Pregnanediol-3-glucuronide
LH = Luteinising hormone
E3G = Estrone 3-glucuronide

Healthy, regularly menstruating women are unlikely to be aware of a sporadic anovulatory cycle unless they are tracking ovulation for example by using ovulation tests, as there are no other symptoms. Changes are however observable in the blood hormone profile. In a prospective cohort study with 250 women, the blood concentrations of LH, FSH, progesterone and estradiol were compared between ovulatory and anovulatory cycles².

This study found that all four hormone concentrations were lower during anovulatory cycles (Figure 1). Additionally, hormone concentrations were reduced in the ovulatory cycle of women who also had an anovulatory cycle.

Figure 1: Estimated relative differences in the blood concentration of hormones in women with ovulatory and anovulatory cycles



Adapted from Hambridge HL *et al* (2013)²

These results may suggest a possible underlying cause of anovulation, such as subclinical endocrine dysfunction. However, there is no evidence of an adverse impact on fertility, and healthy, regularly menstruating women who detect an occasional anovulatory cycle should not be concerned.

POLYCYSTIC OVARY SYNDROME (PCOS)

The most common cause of anovulation is Polycystic Ovary Syndrome (PCOS), a complex endocrine disorder of uncertain aetiology. It is estimated that about 1 in 5 women in the UK have polycystic ovaries⁷. Polycystic ovaries contain a large number of harmless cysts. PCOS is a leading cause of female infertility.

PCOS is characterised by a hormone imbalance. The ovaries or adrenal glands produce more androgens such as testosterone than normal, and women with PCOS have elevated levels of LH throughout their cycle.

It is estimated that more than half of women with polycystic ovaries have no symptoms at all⁷. Some women only discover they have PCOS when they have difficulty conceiving. If present, symptoms can vary from mild to severe, and may include irregular periods or no periods at all (amenorrhea), excess body hair, oily skin, acne, weight gain and depression.

Diagnosis of PCOS involves taking a detailed medical history, and ruling out other potential causes of the symptoms. Pelvic examination and/or ultrasound may be used to detect ovarian cysts, and blood tests are used to establish hormone levels.

PCOS cannot be cured, but for many women symptoms can be effectively managed. For overweight women, the initial recommended course of action is usually to lose excess weight, exercise regularly and have a healthy balanced diet; this can greatly improve many symptoms.

Infertility due to PCOS can be treated with fertility drugs such as Clomiphene. Clomiphene acts by stimulating the pituitary gland to release FSH. Gonadotrophins may also be used to directly stimulate the ovary. Other treatments may also be available.

With treatment, most women with PCOS are able to become pregnant⁷.

OTHER CAUSES

Anovulation and amenorrhea can occur in a wide range of other conditions.

Diagnostic procedures vary depending on the presenting symptoms and patient history.

Management depends on the underlying disorder.

OVARIAN DYSFUNCTION

Anovulation may result from premature ovarian failure, where the ovaries stop producing normal levels of estrogen before the age of 45, and ovarian function is lost⁸. Premature ovarian failure is also known as 'primary ovarian insufficiency' and 'premature menopause'.

It affects about one in 100 women before the age of 40 and five in 100 women before the age of 45⁸.

Premature ovarian failure can be caused by chemotherapy or radiotherapy, autoimmune diseases such as diabetes or thyroid disease, and in rare cases, some infections, such as tuberculosis, mumps, malaria and varicella. However, most of the time, no cause is found (idiopathic premature ovarian failure).

Signs and symptoms of premature ovarian failure are typical of estrogen deficiency. They include amenorrhea, hot flashes, night sweats, vaginal dryness, irritability, difficulty concentrating and decreased sexual desire. Longer term consequences of depleted estrogen include reduced bone density and an increased cardiovascular risk.

A small number of women still have intermittent ovarian function, and they may be able to conceive; approximately 5–10% of women with idiopathic premature ovarian failure will become pregnant over their lifetime⁸.

Premature ovarian failure cannot be cured, but estrogen replacement can help combat the longer term health consequences and manage the symptoms.

HYPOTHALAMIC DYSFUNCTION

Gonadotrophin-releasing hormone (GnRH) is secreted by the hypothalamus, which controls pituitary production of LH and FSH, and therefore also controls ovulation. Excessive exercise, low body weight, being overweight/obese, and stress and anxiety can disrupt the normal feedback mechanisms, and consequently disturb ovulation and the menstrual cycle. This may delay or prevent ovulation for that cycle, or may stop for an extended period if not addressed. Menstruation may become erratic or cease (secondary amenorrhea)^{9, 10}.

Normal cycles and ovulation may return by achieving a healthy weight and a moderate exercise programme, and managing stress/anxiety as appropriate.

Long term use of contraceptives that intentionally disrupt the hypothalamic-pituitary-ovarian axis (such as long-acting injectable steroid contraceptives) can also cause anovulation and amenorrhea. Normal cycles and ovulation usually return within 3-6 months of drug cessation.

RARER CAUSES

Chronic anovulation can be a feature of some rare conditions such as tumours of the ovary including granulosa-theca cell tumours, Brenner tumours and cystic teratomas. These tumours produce excess estrogen, or androgens that undergo aromatisation into estrogen; estrogen in turn provides negative feedback to the pituitary gland, inhibiting gonadotrophin secretion^{11,12}.

Anovulation may be a symptom of rare endocrine conditions such as Cushing's syndrome, congenital adrenal hyperplasia (resulting from an enzyme deficiency), or hyperprolactinaemia. Such conditions usually lead to anovulation because of a disruption to the hypothalamic-pituitary-gonadal axis; the impaired secretion of gonadotrophin releasing hormone in turn inhibits follicle stimulating hormone (FSH) and the release of luteinising hormone (LH)^{11,12}.



ANOVLATION AND CLEARBLUE PRODUCTS

Sporadic anovulation during a woman's reproductive years is very common. Many have no symptoms so are unlikely to be aware, unless they are actively trying to conceive.

If a healthy, regularly menstruating woman is using ovulation tests, or the Clearblue Advanced Fertility Monitor, and detects an occasional anovulatory cycle, she should be reassured that this is normal, and it should have no impact on her fertility. However, if she has three consecutive cycles with no LH surge, further investigation is warranted.

Ovulation tests and fertility monitors are not designed for women with chronic anovulation due to an underlying endocrine disorder such as PCOS, so they may get misleading results if they use these products. As more than half of women with PCOS have no symptoms, she may not be aware until she has difficulty conceiving. If she is using ovulation tests or a fertility monitor, she may see unexpected results, and seek advice from her healthcare provider.

Clearblue ovulation tests identify impending ovulation by detecting a surge of LH above baseline. Women with PCOS have a high baseline level of LH, and there may not be a sufficient change in LH for the test to detect a surge, so ovulation will not be indicated. Or the baseline may be so high that it appears the surge is already underway, and the test will indicate ovulation on the first day of testing.

The Clearblue Digital Ovulation Test with Dual Hormone Indicator and Clearblue Advanced Fertility Monitor measure estrogen as well as LH, to identify more fertile days than is possible with LH alone. Women with PCOS may also have a high baseline level of estrogen. Women with PCOS may therefore see more 'high fertility' days than expected, or an incorrect result due to high background levels of LH.



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