

Anovulatory Cycles — Diagnosis and Treatment

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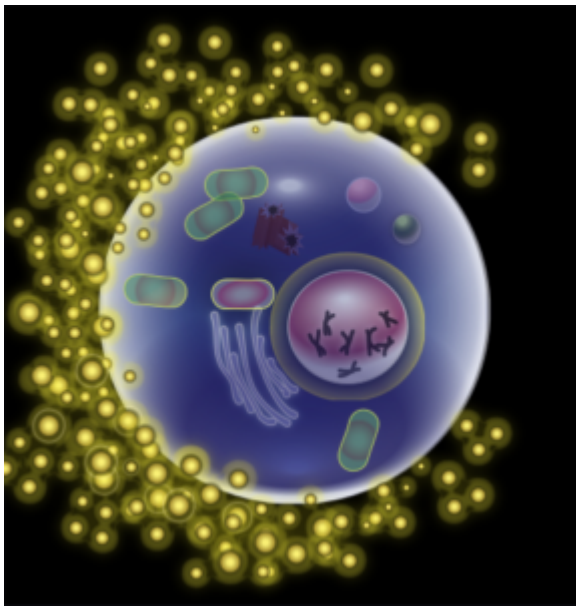
Anovulatory cycles are a symptom and not a disease. Polycystic ovary syndrome, pituitary microadenoma, impaired GnRH release, and hypothyroidism are common etiologies for anovulation and should be excluded. Patients can present with amenorrhea which needs etiology-specific treatment or with acute dysfunctional uterine bleeding which might need emergency treatment. Emergency treatment can be either medical with estrogen or surgical with dilation and curettage. Oral contraceptive pills can be used in an attempt to make the menstrual cycle more regular before trying more specific treatments.



Definition of Anovulatory Cycles

When there is **the failure of the release of a mature ovum** during the normal hormonal monthly cycle, an anovulatory cycle occurs. It is important to note that anovulation is a symptom or a consequence and not a disease itself. Several diseases that involve the **hypothalamic-pituitary-ovarian axis** can cause anovulation.

Epidemiology of Anovulatory Cycles



[Image](#): Diagram of a human egg cell. By KDS444, License: [CC BY-SA 3.0](#)

Anovulatory cycles are very common and occur in all women at some point but this is a **normal physiologic phenomenon** and should be differentiated from the pathological condition in which chronic anovulation happens. The incidence of **chronic anovulation** is approx. 15%.

[Polycystic ovary syndrome](#), hypothalamic amenorrhea, premature menopause, and hyperprolactinemia are more common among epileptics for some unknown reasons and these populations are more likely to have anovulatory cycles.

Several morbidities are associated with anovulatory cycles, and they are more common in certain populations depending on the etiology of anovulation. For instance, patients with polycystic ovary syndrome are more likely to have [diabetes](#) or dyslipidemia.

Anovulation at menarche and during the perimenopausal period is common and normal.

Etiology of Anovulatory Cycles

For ovulation to occur, the hypothalamus, pituitary, and ovaries need to function in precise harmony. Any disease that can disrupt the cyclic patterns of **gonadotropin-releasing hormone (GnRH)**, **follicle-stimulating hormone (FSH)**, or **luteinizing hormone (LH)** will result in anovulation.

Accordingly, **primary lesions in the hypothalamus** such as [strokes](#) and tumors, pituitary tumors, [polycystic ovary syndrome](#) with impaired FSH/LH ratios, and hyperprolactinemia can all cause anovulation by a direct deficiency of one of the key hormones or by an indirect feedback mechanism.

Pathophysiology of Anovulatory Cycles

Alterations in the pulsatile nature of GnRH can occur because of hyperprolactinemia, [anorexia nervosa](#), or a hypothalamic lesion. This **alteration/deficiency of GnRH** will

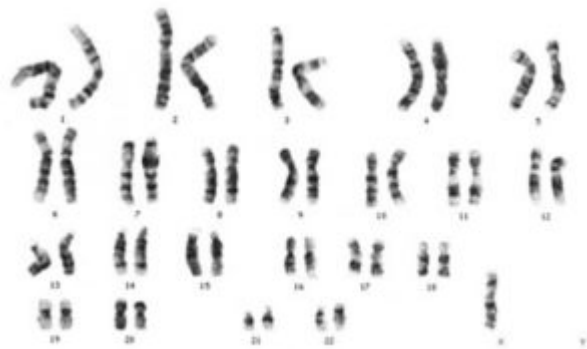
result in poor coordination of FSH and LH and will cause anovulation.

Patients with polycystic ovary syndrome develop anovulation either by the arrest of the ovarian follicles in the antral stage or by high levels of LH. High LH levels along with the **hyperinsulinemia** eventually lead to anovulation and [infertility](#).

Sheehan syndrome is caused by **pituitary apoplexy** due to acute bleeding after childbirth. This leads to **panhypopituitarism** along with FSH and LH deficiency which also leads to anovulation.

Clinical Presentation of Anovulatory Cycles

Complete history and **physical examination** can suggest the most likely etiology of anovulation in most patients.



[Image](#): Karyogram of Turner Syndrome. By No machine-readable author provided. The cat~commons wiki assumed, License: [CC BY-SA 3.0](#)

Patients with a previous history of **postpartum hemorrhage** are at risk of developing Sheehan syndrome. A positive family history suggests a possible **hereditary condition**. For instance in Turner's syndrome, aberrant **chromosomal analysis** can explain [amenorrhea](#) and anovulation.

The use of **injectable progesterone** or **intrauterine devices** can be linked to anovulation and should be excluded. History of depression, anxiety, or anorexia nervosa should also be excluded.

Patients can complain of obesity, hirsutism, and other signs of **hyperandrogenism** in polycystic ovary syndrome. They can have **bilateral milky breast secretions** in hyperprolactinemia. Visual disturbances and headaches can be associated with **pituitary tumors**.

The main presenting feature of anovulation is **amenorrhea, dysmenorrhea, or oligomenorrhea**.

Diagnostic Work-up for Anovulatory Cycles

Laboratory investigations are essential in the work-up for anovulatory cycles.

Quantitative beta-HCG is indicated to exclude **pregnancy**, which is the most common cause of amenorrhea in women in reproductive age.

FSH, LH, and **ovarian estradiol and progesterone** levels need to be checked. When FSH and LH are both low with a high GnRH, **the pituitary disease** is suspected. Patients

with high LH and a normal FSH might have **polycystic ovary syndrome**. Patients with low LH and FSH along with a low GnRH have **an anovulation disorder of hypothalamic origin**. Patients with normal FSH, LH, and GnRH but low estradiol might have **primary ovarian failure**.

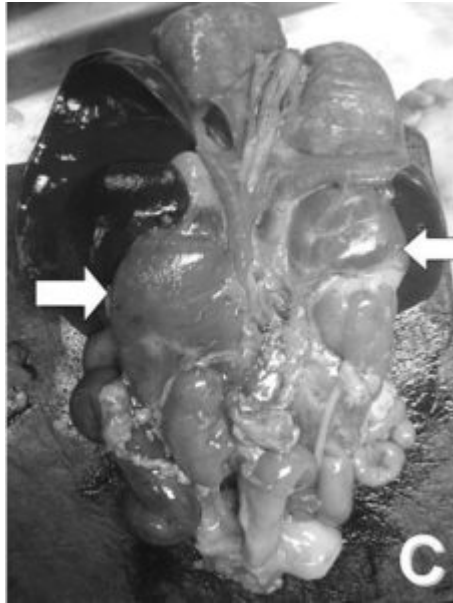


Image: Postmortem examination of a baby showing adrenal hyperplasia. By Patou Tantbiroj, Mana Taweewisit, Suchila Sritippayawan, Boonchai Uerpairojkit, License: [CC BY 2.0](#)

Prolactin and **thyroid-stimulating hormone** should also be evaluated to exclude both hyperprolactinemia and **hypothyroidism**, which are common conditions associated with anovulation. An **elevated dehydroepiandrosterone sulfate level** indicates hyperandrogenism due to adrenal pathology, while an **elevated 17-hydroxyprogesterone** indicates hyperandrogenism due to **congenital adrenal hyperplasia**.

Patients with certain **autoimmune disorders** can develop **primary hypothalamic or pituitary failure** and therefore antinuclear antibodies, rheumatoid factor, and thyroid-specific antibodies should be checked. Women with certain dysmorphic features might benefit from **karyotyping**.

Imaging studies are helpful in the evaluation and determination of the etiology of anovulation. **Ultrasonography** can help evaluate the ovaries and endometrium by assessing for any anatomical problems, i.e., adnexal agenesis, polycystic ovaries, etc.

Abdominal CT is indicated to exclude adrenal gland tumors and/or hyperplasia. **MRI** is helpful for excluding possible pituitary microadenoma, and a **bone density scan** can be helpful in patients with primary ovarian failure.

Treatment of Anovulatory Cycles

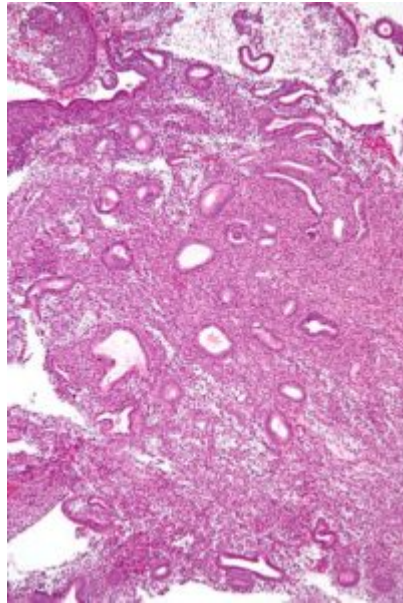


Image: Intermediate magnification micrograph of simple endometrial hyperplasia without nuclear atypia. H&E stain. Endometrial biopsy. Histomorphologic features: Normal gland-to-stroma ratio (~1:3). Proliferating pseudostratified glandular epithelium. Irregular endometrial glands: Dilated glands or gland with variable size. Non-ovoid/non-circular glands. By Nephron, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Treatment of anovulation should be classified into **etiology-specific** and **emergency management**.

Patients with anovulation might develop **acute bleeding** due to dysfunctional uterine bleeding. **Oral estrogen** or, in more severe cases, **IV estrogen** is indicated, which is known to be effective in most patients. Patients who do not respond to this regimen might benefit from **dilatation** and **curettage**. Endometrial hyperplasia is usually evident and a **biopsy study** can be performed at this stage. Patients with anovulation can also present with **amenorrhea**. Pregnancy should be excluded; otherwise more specific treatments are needed.

Patients with **hypoestrogenic states** due to ovarian failure might benefit from **cyclic estrogen and progesterone supplementation**. Patients with a low GnRH could have a brain tumor compressing the hypothalamus, and the removal of that lesion can restore normal GnRH pulsatile release.

Patients with depression, anxiety, or **anorexia nervosa** usually have a low GnRH level as well. **Psychotherapy** along with possible **pharmacotherapy** is usually indicated and is sufficient for restoring ovulation.

In **polycystic ovary syndrome**, treatment involves **the correction of the hyperandrogenic state** and **fertility treatments**. The hyperandrogenic state can be corrected by the administration of metformin due to the close relationship between hyperandrogenism and hyperinsulinemia.

Weight loss can also help with hyperandrogenism. **GnRH analogs** can be used to induce ovulation when fertility is an issue, but it should be noted that metformin can achieve ovulation in a number of women without the need for clomiphene citrate.

In selected patients, **in vitro fertilization** might be needed to achieve a viable

pregnancy. If all of these fail, patients might benefit from **ovarian cyst drilling**.

Women with **hyperthyroidism** or **hypothyroidism** can achieve ovulation by correcting thyroid dysfunction. Similarly, patients with **hyperprolactinemia** can benefit from medical treatment or from surgical removal of the responsible microadenoma.

References

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