Anovulatory Cycles — Diagnosis and Treatment

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 failure of 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**

Anovulatory cycles are very common and happen 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. **Chronic anovulation** incidence is approximately 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 can be associated with anovulatory cycles and they are more common in certain populations depending on the etiology of the 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 happen, the hypothalamus, pituitary and ovaries need to function in precise harmony. Any disease that can disrupt the cyclic patterns of **gonadotropin releasing hormone**, **follicle stimulating hormone** (FSH) or **luteinizing hormone** (LH) will result in anovulation.

Accordingly, **hypothalamic primary lesions** such as strokes and tumors, pituitary tumors, *polycystic ovary syndrome* with impaired FSH/LH ratios, and hyperprolactinemia can all cause anovulation by direct deficiency of one of the key players’ hormones or by an indirect feedback mechanism.

**Pathophysiology of Anovulatory Cycles**

Alterations in the pulsatile nature of gonadotropin releasing hormone (GnRH) can happen 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 by either arrest of the ovarian follicles in the antral stage or by the high levels of LH. High LH levels along with the **hyperinsulinemia** eventually leads 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 leads to anovulation as well.

**Clinical Presentation of Anovulatory Cycles**

**Complete history** and **physical examination** can point towards the most likely etiology of anovulation in most of the patients.
Patients with previous history of postpartum hemorrhage are at risk of developing Sheehan syndrome. Patients with family history can point towards a possible hereditary condition. Additionally, previous history of chromosomal analysis for instance for Turner syndrome can explain amenorrhea and anovulation.

Use of injectable progesterone, or intrauterine devices can be linked to anovulation and should be excluded. History of depression, anxiety, or anorexia nervosa should 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 disbranches 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 of these women. Quantitative beta-HCG is indicated to exclude pregnancy, the most common cause of amenorrhea in women in reproductive age.

FSH, LH, and ovarian estradiol and progesterone need to be checked. When FSH and LH are both low with a high GnRH, 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 hypothalamic in origin anovulation disorder. Patients with normal FSH, LH, and GnRH but low estradiol might have primary ovarian failure.
Prolactin and thyroid stimulating hormone should be also checked to exclude both hyperprolactinemia and hypothyroidism, both 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 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 looking for the etiology of the anovulation. Ultrasonography can help evaluate the ovaries and endometrium looking for any anatomical problems, i.e. adnexal agenesis, polycystic ovaries.

Abdominal computed tomography scan is indicated to exclude adrenal gland tumors and/or hyperplasia. Magnetic resonance imaging is helpful in excluding possible pituitary microadenoma, and a bone density scan can be helpful in patients with primary ovarian failure.

Treatment of Anovulatory Cycles
Treatment for anovulation should be classified into etiology-specific and emergency management.

Patients with anovulation might develop acute bleeding due to dysfunction uterine bleeding. Oral estrogen or in more severe cases IV estrogen is indicated, which is known to work 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 removal of that lesion can restore GnRH normal 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 to restore ovulation.

In polycystic ovary syndrome, treatment involves 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 analogues 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 needing 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 the thyroid dysfunction. Similarly, patients with hyperprolactinemia can benefit from medical treatment or by surgical removal of the responsible microadenoma.

References


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