Amenorrhea in Adults — Causes and Management

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In this article, we are going to discuss the most common causes of primary and secondary amenorrhea in adult females. We will also provide a clinical evaluation approach for these women, and establish some treatment principles related to amenorrhea.

Overview

Amenorrhea is defined as the absence of menses in a woman in the reproductive age and can be classified into primary or secondary amenorrhea.

1. **Primary amenorrhea** is the absence of menstrual blood flow in a woman who is older than 16 years of age with secondary sexual characteristics, or who is older than 14 years and without secondary sexual characteristics, who had never had menses before.
2. Women who had irregular menstrual cycles who present with six consecutive months of no menses can be diagnosed with secondary amenorrhea. On the other hand, women with regular menstrual cycles who do not have their periods for three consecutive months are diagnosed with secondary amenorrhea.

Menstrual cycle terminology

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Description</th>
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<tbody>
<tr>
<td>Oligomenorrhea</td>
<td>Menstrual interval greater than 35 days &lt; 9 menses/year</td>
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<tr>
<td>Polymenorrhea</td>
<td>Menstrual intervals that occur &lt; 21 days</td>
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<tr>
<td>Menorrhagia</td>
<td>Regular but excessive menstrual flow (&gt; 80 ml &gt; 7 days)</td>
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<tr>
<td>Metrorrhagia</td>
<td>Irregular bleeding between menses</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>No menses (either primary or secondary)</td>
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Causes of Amenorrhea in Adults
Causes for Primary Amenorrhea:

Amenorrhea can be addressed by remembering each compartment must be functional and working for menses to occur.

Primary hypogonadism, chromosomal abnormalities and anatomic defects of the outflow tract are common causes of amenorrhea, but are usually identified during adolescence. On the other hand, intrauterine synechiae, cervical stenosis and hypothalamic, pituitary or other endocrine disorders are more commonly associated with secondary amenorrhea and are more commonly seen in adults with amenorrhea.

Anatomic defects of the outflow tract

Mullerian duct agenesis, complete androgen resistance, imperforate hymen, transverse vaginal septum, cervical stenosis and vaginal agenesis are the possible causes of primary amenorrhea in an adolescent. Because these disorders are usually identified during adolescence, they are rarely encountered as a cause of amenorrhea in an adult. The only exception to this rule is delayed recognition of the cause of primary amenorrhea in an adolescent until she becomes an adult.

Secondary amenorrhea due to intrauterine synechiae and cervical stenosis is way more common in adults compared to adolescents. **Intrauterine synechiae are characterized by intrauterine adhesions** and can be associated with a recent curettage procedure of the uterine linings. Cervical stenosis can be caused by surgical instrumentation of the cervix.

The treatment of the anatomical causes of primary amenorrhea can be summarized as the **surgical repair of an imperforate hymen, surgical repair of a transverse vaginal septum, or cosmetic surgery for complete androgen resistance**. There is no treatment for Mullerian duct agenesis.

Ashermann syndrome or intrauterine synechiae cause secondary amenorrhea. This disorder is uncommon in adolescents and is usually a consequence to postpartum endometritis.
The most common causes of primary hypogonadism include gonadal dysgenesis “Turner syndrome”, pure gonadal dysgenesis, and Swyer syndrome”, gonadal agenesis, 17-hydroxylase deficiency, 17,20-Lyase deficiency, aromatase deficiency, idiopathic premature ovarian failure, secondary ovarian failure due to chemotherapy or irradiation, FSH receptor gene mutations, LH resistance, galactosemia or glycoprotein syndrome type 1. These disorders usually present with primary amenorrhea during adolescence and rarely go unrecognized before adulthood. These patients are usually infertile and they require psychotherapy, estrogen replacement therapy, and infertility treatment if possible.

Premature ovarian failure is more common in adults compared to adolescents and should be diagnosed early and managed promptly. Calcium and vitamin D supplementation is needed to lower the risk of osteoporosis in patients diagnosed with premature ovarian failure. Pregnancy in women diagnosed with premature ovarian failure can happen spontaneously. If the woman is indeed infertile, the only option for pregnancy would be in vitro fertilization using donor oocytes.

Hypothalamic causes of amenorrhea

These causes of amenorrhea are the most commonly encountered in adults. Stress, malnutrition, and exercise can all cause amenorrhea in adults. Anorexia nervosa is a condition that is characterized by severe malnutrition due to a food disorder and can be associated with amenorrhea.

Image: “Genes involved in migration or activation of GnRH releasing neurones into the hypothalamus” by The genetic basis
Idiopathic hypogonadotropic hypogonadism can also cause secondary amenorrhea in an adult. Tuberculosis and syphilis are two infectious etiologies of hypothalamic caused amenorrhea. Brain tumors can also cause hypothalamic-pituitary axis disruption and amenorrhea.

Treatment of anorexia nervosa should focus on the restoration of normal nutrition and the administration of hormonal therapy. Transdermal hormonal therapy is preferred over oral hormone replacement therapy because oral intake might be impaired in women with severe anorexia nervosa. Insulin-like growth factor 1 and leptin should be also administered to these patients.

Pituitary causes of amenorrhea

Hyperprolactinemia is the most common cause of pituitary amenorrhea. Prolactinomas, craniopharyngioma, metastatic tumors to the pituitary gland, empty sella syndrome, arterial aneurysms, postpartum pituitary necrosis “Sheehan syndrome”, panhypopituitarism, sarcoidosis, and hemochromatosis can all cause amenorrhea due to pituitary gland hormonal dysfunction. These disorders of the pituitary gland are more common in adults compared to adolescents. In fact, most causes of secondary amenorrhea are more commonly encountered in adults whereas causes associated with primary amenorrhea are usually identified in adolescent females.

The management of hyperprolactinemia due to a pituitary adenoma can be medical or surgical. Bromocriptine and cabergoline can be used to treat the hyperprolactinemia state in these women. If medical treatment fails, or if mass-effect symptoms of the tumors are evident, minimally-invasive surgical intervention is indicated.

Multifactorial Causes of Amenorrhea

Polycystic ovary syndrome can also cause amenorrhea. Treatment of polycystic ovary
syndrome includes weight loss by diet and exercise and the administration of metformin. Metformin is known to help the patient lose weight, to decrease the symptoms and signs of insulin resistance, to lower the severity of the hyperandrogenic state, and to restore normal menstrual cycles in a significant proportion of patients. In fact, metformin has been shown to improve fertility in women with polycystic ovary syndrome.

**Lifestyle factors contributing to amenorrhea**

1. **Low body weight:** This is one of the factors in your lifestyle that aid in amenorrhea. Low weight obstructs the hormonal balance and gives potential eating disorders such as anorexia nervosa or bulimia.
2. **Stress in women:** Contributes to many imbalances in the body and interrupts with the functions of the hypothalamus since it is the hormonal regulator of your body. It can hinder normal monthly ovulation and menses.
3. **Physical stress:** Females who are athletes, or who do certain physical activities such as extreme gym sessions or ballet, can suffer a loss of periods due to low body fat and vigorous training.

**Clinical Evaluation of Amenorrhea**

The first step in the clinical evaluation of amenorrhea in an adult is **history taking and physical examination**. Past medical history, family history, and social history can also provide some clues towards the most likely cause of amenorrhea in the woman.

Physical examination is helpful in the exclusion of certain signs of systemic diseases known to cause amenorrhea. For instance, women with signs and symptoms suggestive of hyperthyroidism should alert the physician towards the possibility of endocrine-induced amenorrhea. The **gynecological examination is also indicated to exclude some less common causes** of amenorrhea in adults, such as an imperforate hymen.

Serum levels of follicle stimulating hormone and luteinizing hormone should be measured. Elevated serum levels of follicle stimulating hormone and luteinizing hormone are suggestive of primary gonad’s disease. Low levels of these gonadotropins indicate pituitary dysfunction or hypothalamic disorders.
A pregnancy test should be performed when indicated. It is always useful to remember that the most common cause of amenorrhea in an adult is pregnancy. Ultrasonography is helpful in assessing the ovaries and the endometrium in patients with amenorrhea. Ultrasonography might be helpful in excluding certain anatomical defects of the uterus.

The presence of acne, hirsutism, deepening of the voice and clitoromegaly is suggestive of hyperandrogenism, another common cause of secondary amenorrhea. Patients with secondary amenorrhea should get FSH, LH, testosterone, and dehydroepiandrosterone sulfate levels measured. Moderate elevation of testosterone and an LH/FSH ratio that is above 2 suggests polycystic ovary syndrome. Dehydroepiandrosterone sulfate levels between 5 and 700 mg/dl indicate possible adrenal gland disorder and require further diagnostic workup. When the levels of dehydroepiandrosterone sulfate are above 700 mg/dl, the diagnosis of late onset
type congenital adrenal hyperplasia becomes very likely.

Patients with secondary amenorrhea and no signs of hyperandrogenism should get their FSH, LH and thyroid stimulating hormone levels checked. Hyperprolactinemia due to a pituitary adenoma can also cause secondary amenorrhea in an adult.

References


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