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AMENORRHEA: A REVIEW

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ABSTRACT

Amenorrhea is the absence of menstrual cycle in a woman during her reproductive years. Physiological states of amenorrhea can be most commonly seen during pregnancy and lactation period. There may be various causes of Amenorrhea including chromosomal or genetic problem with the ovaries. Hormonal issues stemming due to the problem with the hypothalamus or the pituitary gland. May also be caused due to structural problems of the reproductive organs, such as missing parts of the reproductive system. Amenorrhea is classified into primary and secondary amenorrhea. Amenorrhea seriously effects the changes of becoming pregnant. Examples include menopause, pregnancy, use of birth control, medication side effects, delayed puberty and stress. This article focuses on the menstrual cycle, types, causes, symptoms, diagnosis and treatment of Amenorrhea.

KEYWORDS: Amenorrhea, menstrual cycle, irregular periods, primary amenorrhea, secondary amenorrhea.

INTRODUCTION

Amenorrhea refers to the absence of menstrual periods; it may be either primary which means a woman never developed menstrual periods or secondary that is the absence of menstrual periods in a woman who has previous records of menstrual cycles. The most common causes of primary amenorrhea may include genetic or inborn conditions.[1] The disorders of the ovaries, pituitary gland, hypothalamus, or uterus may result in amenorrhea. Intensive exercising, extreme weight loss, physical illness, and stress can also lead to amenorrhea. Amenorrhea can be associated with clinically challenging pathology and may require lifelong treatment.[2]

As this is not a disease in itself, thus can be prevented. Infertility and bone loss may be the possible complication caused. Various treatments are available for the same.

Definition

Amenorrhea is when a female is not getting her periods even though she have been through puberty, is not pregnant, and have not gone through menopause.

It is nothing related to having irregular periods, but if a female has amenorrhea, she never gets her period. Although it is not a disease, one should inform the doctor about it because it might be a symptom of a medical condition that can be treated.[3]

Normal Menstrual Cycle

1. Menstrual Phase

The menstrual phase is the first phase of the menstrual cycle. This is the part of the cycle when a female has her period. The period consists of a combination of uterus tissue, mucus, and blood. The menstrual phase can last for 3–8 days.[4]

2. Follicular Phase

The follicular phase begins from the first day of menses until ovulation. During the last few days of the preceding menstrual cycle until the release of the mature follicle at ovulation, Folliculogenesis begins.[5-7]

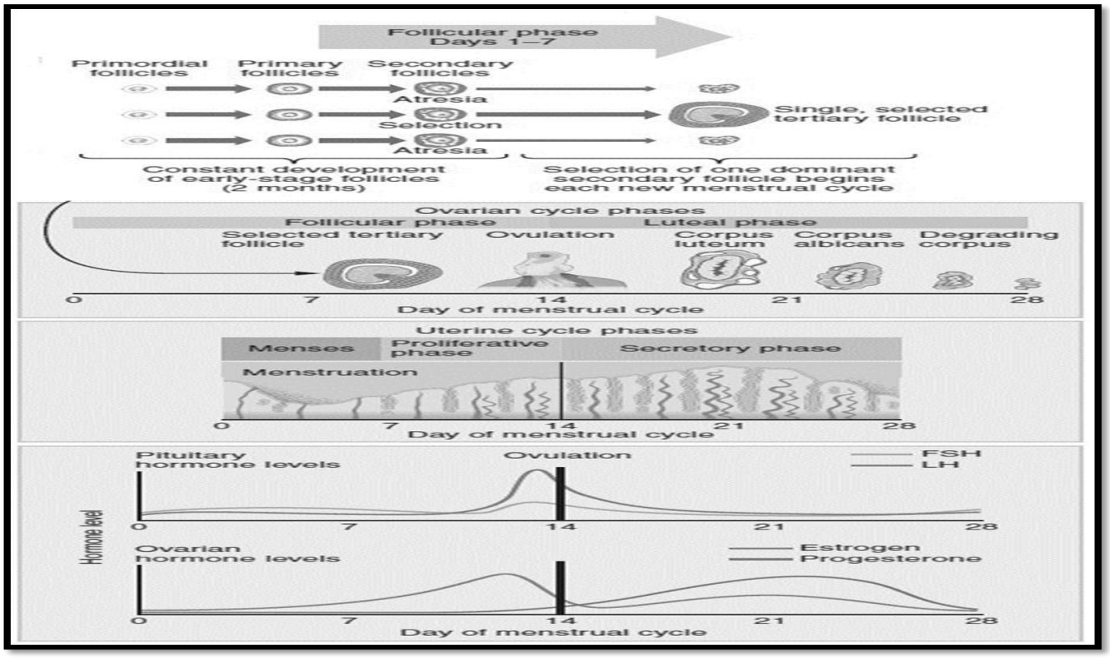

Figure 1: Representation of normal female menstrual cycle.[8]

3. Ovulatory Phase

Ovulation occurs approximately 10-12 hours after the LH peak.[9] The LH surge is initiated by a dramatic rise of estradiol produced by the preovulatory follicle.[10] The beginning of the LH surge occurs roughly 34 to 36 hours prior to ovulation and is a relatively precise predictor for timing ovulation.[11]

4. Luteal phase

This phase is usually 14 days long in most women. After ovulation, the remaining granulosa cells that are not released with the oocyte continue to enlarge, become vacuolated in appearance, and begin to accumulate a yellow pigment called lutein.[12] Eight or nine days after ovulation, approximately around the time of expected implantation, peak vascularization is achieved.[13]

Table 2: Production Rate of Sex Steroids in Women at Different Stages of the Menstrual Cycle.[14]

	DAILY PRODUCTION RATE		
SEX STEROIDS	**Early follicular**	**Preovulatory**	**Mid-luteal**
Progesterone (mg)	1	4	25
17α-Hydroxyprogesterone (mg)	0.5	4	4
Dehydroepiandrosterone (mg)	7	7	7
Androstenedione (mg)	2.6	4.7	3.4
Testosterone (µg)	144	171	126
Estrone (µg)	50	350	250
Estradiol (µg)	36	380	250

In a normal female body, a small amount of testosterone is produced. An increase in the level of androgen will inhibit the production and release of LH and FSH, which results in a decline in the levels of LH, estrogens, progesterone and FSH in the serum. This results in the inhibition of the formation of follicles, ovulation and irregularity in the menstrual cycle. The irregularities of menstrual cycle are characterised by amenorrhea.[15]

Types of amenorrhea

There are two types of amenorrhea.

1. Primary amenorrhea- This is when young women have not had their first period by the age of 15.[16]

2. Secondary amenorrhea- This is when you have had normal menstrual cycles, but they stop for 3 or more months.[17]

Causes of Amenorrhea

The different types of amenorrhea have different causes.

- Common causes of primary amenorrhea include.[18]

1. Chromosomal or genetic problem with the ovaries (the female sex organs that hold the eggs).
2. Hormonal issues stemming from problems with the hypothalamus or the pituitary gland.
3. Structural problem with the reproductive organs, such as missing parts of the reproductive system.

- Common causes of secondary amenorrhea include.[19]

1. Pregnancy (which is the most common cause of secondary amenorrhea).
2. Breastfeeding.
3. Menopause.
4. Some birth control methods, such as Depo Provera, intrauterine devices (IUDs) and certain birth control pills.
5. Chemotherapy and radiation therapy for cancer.
6. Previous uterine surgery with subsequent scarring (for example, if you had a dilation and curettage, often called D&C).

- Other causes of secondary amenorrhea can include.[20]

1. Stress.
2. Poor nutrition.
3. Weight changes — extreme weight loss or obesity.
4. Exercising associated with low weight.
5. Ongoing illness or chronic illness.

- You may also have conditions that can cause secondary amenorrhea.[21]

1. Primary ovarian insufficiency, when you experience menopause before age 40.
2. Hypothalamus disorders, such as functional hypothalamic amenorrhea (FHA) — which is also called hypothalamic amenorrhea (HA). FHA is a condition where amenorrhea is associated with stress or weight loss but isn't clearly caused by an organic issue with a woman's body.
3. Pituitary disorders, such as a benign pituitary tumour or excessive production of prolactin.
4. Other hormonal problems, such as polycystic ovary syndrome, adrenal disorders or hypothyroidism.
5. Ovarian tumours.

6. Surgery to remove uterus or ovaries.

Table 3: The differential diagnosis of primary amenorrhea.[22-24]

Hyperprolactinemia	Hypergonadotropic hypogonadism	Hypogonadotropic hypogonadism	Norm gonadotropic	Other
Prolactin ≤ 100 ng per mL (100 mcg per L)-	Gonadal dysgenesis	Kalman syndrome	Cushing's disease	Pregnancy
Altered metabolism- Liver failure Renal failure	Turner's syndrome	Sheehan's syndrome	Asherman's syndrome	Thyroid disease
Ovarian dermoid cyst	Postmenopausal ovarian failure	Anorexia or bulimia nervosa	Cervical stenosis	
Renal cell carcinoma	Premature ovarian failure	Constitutional delay of growth and puberty	Transverse vaginal septum	
Hypothyroidism	Genetic 17-hydroxylase deficiency syndrome	Central nervous system tumor	Polycystic ovary syndrome	
Prolactin > 100 ng per mL-	Idiopathic Mumps	Excessive weight loss or malnutrition	Androgen-secreting tumor (ovarian or adrenal)	
Empty Sella syndrome	Pelvic radiation	Severe depression or psychosocial stressors	Mullerian agenesis	
Pituitary adenoma	Autoimmune Chemotherapy	Hypothalamic or pituitary destruction	Androgen insensitivity syndrome	

Symptoms of Amenorrhea[25-27]

The main symptom of amenorrhea is the absence of your monthly period. It often signifies a larger health problem or condition.

Related symptoms can include.

1. Headache.
2. Vision changes.
3. Nausea.
4. Extra facial hair.
5. Hair loss.
6. Changes in breast size.
7. Milky fluid, or discharge, from breasts.

Diagnosis of Amenorrhea

- Your healthcare provider may want to do some tests, including.[18,25,26]

1. Pregnancy test.
2. Blood tests to check hormone levels and detect thyroid or adrenal gland disorders.
3. Genetic testing, if you have primary ovarian insufficiency and are younger than 40.
4. MRI, if your provider suspects a problem with the pituitary gland or hypothalamus.

Differential Diagnosis of Primary Amenorrhea

Causes of primary amenorrhea should be evaluated in the context of the presence or absence of secondary sexual characteristics. Table 3[22-24] includes the differential diagnosis of primary amenorrhea.

- Presence of secondary sexual characteristics.

1. If a patient with amenorrhea has breast development and minimal or no pubic hair, the usual diagnosis is androgen insensitivity syndrome (i.e., patient is phenotypically female but genetically male with undescended testes). A karyotype analysis is needed to determine proper treatment.[29]
2. If a patient has normal secondary sexual characteristics, including pubic hair, the physician should perform MRI or ultrasonography to determine if a uterus is present. Müllerian agenesis (the congenital absence of a vagina and abnormal uterine development [usually rudimentary]) causes approximately 15 percent of primary amenorrhea.[30] The etiology is thought to involve embryonic activation of the antimullerian hormone, causing malformation of the female genital tract.[31,32] Patients may have cyclic abdominal pain if there is endometrial tissue in the rudimentary uterus, mittelschmerz, or breast tenderness. Karyotype analysis should be performed to determine if the patient is genetically female.[33]
3. If the patient has a normal uterus, outflow tract obstruction should be considered. An imperforate hymen or a transverse vaginal septum can cause congenital outflow tract obstruction, which typically is associated with cyclic abdominal pain from blood accumulation in the uterus and vagina.[29] If the outflow tract is patent, the physician should continue an evaluation similar to that for secondary amenorrhea.[22,23]

- Absence of secondary sexual characteristics.

1. Diagnosis of patients with amenorrhea and no secondary sexual characteristics is based on laboratory test results and karyotype analysis. The most common cause of

hypogonadotropic hypogonadism (low FSH and LH levels) in primary amenorrhea is constitutional delay of growth and puberty.[30,32]

2. A detailed family history also may help detect this etiology, because it often is familial. Hypogonadotropic hypogonadism associated with constitutional delay of growth and puberty is indistinguishable from that associated with hypothalamic or pituitary failure.[34]
3. Watchful waiting is appropriate for constitutional delay of growth and puberty. Kalman syndrome, which is associated with anosmia, also can cause hypogonadotropic hypogonadism.[35]
4. Hypergonadotropic hypogonadism (elevated FSH and LH levels) in patients with primary amenorrhea is caused by gonadal dysgenesis or premature ovarian failure.
5. Turner's syndrome (45, XO karyotype) is the most common form of female gonadal dysgenesis. Characteristic physical findings include webbing of the neck, widely spaced nipples, and short stature.
6. Mosaicism occurs in approximately 25 percent of patients with Turner's syndrome. These patients often have a more normal phenotype with spontaneous onset of puberty and menarche.[36]
7. Other rare causes of pure gonadal dysgenesis can occur with a 46, XY or XX karyotype.[31]

Differential Diagnosis of Secondary Amenorrhea

After pregnancy, thyroid disease, and hyperprolactinemia are eliminated as potential diagnoses, the remaining causes of secondary amenorrhea are classified as norm gonadotropic amenorrhea, hypogonadotropic hypogonadism, and hypergonadotropic hypogonadism; each is associated with specific etiologies (Table 3).

- Hypothyroidism

Other clinical signs of thyroid disease are usually noted before amenorrhea presents. Mild hypothyroidism is more often associated with hypermenorrhea or oligomenorrhea than with amenorrhea. Treatment of hypothyroidism should restore menses, but this may take several months.[37]

- Hyperprolactinemia

A patient with markedly elevated prolactin levels, galactorrhea, headaches, or visual disturbances should receive imaging tests to rule out a pituitary tumor. Adenomas are the

most common cause of anterior pituitary dysfunction.[24] A prolactin level more than 100 ng per mL (100 mcg per L) suggests a prolactinoma, and MRI should be performed. If tumor is excluded as the cause, medications (e.g., oral contraceptive pills, antipsychotics, antidepressants, antihypertensive, histamine H2 blockers, opiates) are the next most common cause of hyperprolactinemia. Medications usually raise prolactin levels to less than 100 ng per mL.[24] Table 3 lists common etiologies of hyperprolactinemia.

If asymptomatic microadenomas (smaller than 10 mm) are found on MRI, repeat prolactin measurements and imaging should be performed to monitor for progression. Microadenomas are slow growing and rarely malignant. Treatment of microadenomas should focus on management of infertility, galactorrhea, and breast discomfort. A dopamine agonist can help improve symptoms and fertility.[38] Macroadenomas may be treated with dopamine agonists or removed with trans sphenoidal resection or craniotomy, if necessary.

Treatment of Amenorrhea[39-41]

1. In some women, nutritional deficiencies induced by dieting can cause amenorrhea. Such women should eat a properly balanced diet.
2. In some women, excessive body weight can be the cause of amenorrhea. These women should restrict the amount of fat in their diet, and they should exercise moderately to maintain an ideal body weight.
3. More than 8 hours of vigorous exercise a week may cause amenorrhea. A moderate exercise program may restore normal menstruation.
4. In women with anorexia nervosa or excessive weight loss, normal menstrual cycles can often be restored by undergoing treatment to restore and maintain a healthy body weight.
5. If amenorrhea is caused by emotional stress, finding ways to deal with stress and conflicts may help.
6. Maintaining a healthy lifestyle by avoiding alcohol consumption and cigarette smoking is also helpful.

Amenorrhea Medical Treatment[42-45]

Treatment depends on the cause of amenorrhea. Once the cause is determined, treatment is directed at correcting the underlying disease, which should restore menstruation. In case of anatomical abnormalities of the genital tract, surgery may be indicated.

Some causes of amenorrhea can be managed by medical (drug) therapy. Examples include the following.

1. Dopamine agonists such as bromocriptine or pergolide, are effective in treating hyperprolactinemia. In most women, treatment with dopamine agonists medications restores normal ovarian endocrine function and ovulation.
2. Hormone replacement therapy consisting of an estrogen and a progestin can be used for women in whom estrogen deficiency remains because ovarian function cannot be restored.
3. Metformin is a drug that has been successfully used in women with polycystic ovary syndrome to induce ovulation.
4. In some cases, oral contraceptives may be prescribed to restore the menstrual cycle and to provide estrogen replacement to women with amenorrhea who do not wish to become pregnant. Before administering oral contraceptives, withdrawal bleeding is induced with an injection of progesterone or oral administration of 5-10 mg of medroxyprogesterone (Provera) for 10 days.

Amenorrhea Surgery Options[39]

1. Some pituitary and hypothalamic tumours may require surgery and, in some cases, radiation therapy.
2. Women with intrauterine adhesions require dissolution of the scar tissue.
3. Surgical procedures required for other genital tract abnormalities depend on the specific clinical situation.

How to prevent amenorrhea[46]

Living a healthy lifestyle can help prevent some causes of secondary amenorrhea. Try to:

1. Maintain a healthy weight and eat a healthy diet.
2. Be aware of your menstrual cycle (so you'll know if you miss a period).
3. Get regular gynaecological appointments, including having a pelvic exam and Pap test.
4. Get regular and adequate sleep.

CONCLUSION

The causes leading to the development of amenorrhea related to menstrual cycle disturbance are so diverse that in some complex cases, the situation is best addressed by a multidisciplinary team. For example, the involvement of experts in endocrinology, human

genetics, psychiatry, and reproductive surgery can benefit a patient with complete androgen resistance.

With hereditary causes of amenorrhea, such as Kalman syndrome, the counselling of patients and their families regarding the disorder, a geneticist's expertise can be helpful. In some unusual cases, such as with vaginal agenesis, consult with a reproductive surgeon with extensive experience in the specific disorder. In many cases, exercise-induced amenorrhea is due to an imbalance in energy intake and expenditure. Nutritional counselling to increase energy intake without reducing exercise is a means of reversing the underlying pathology. Women who are underweight or who appear to have nutritional deficiencies should receive nutritional counselling and can be referred to a multidisciplinary team specializing in eating disorders. In certain cases, in which an underlying chronic disease process is present, the insights of an internist may be needed.

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