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A review of amenorrhea in women

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ABSTRACT

Amenorrhea is the absence or abnormal cessation of menstrual cycles in a woman of reproductive age. Prolonged cessation of menstrual cycles might result in complications such as infertility, psycho social developmental delays, Osteoporosis, fractures etc. Better understanding of physiology of menstruation is essential to understand the various causes of primary and secondary amenorrhea. Any disruption or functional abnormality in the hypothalamic-pituitary-ovarian axis can result in abnormal menstruation or amenorrhea. Therefore it is crucial to identify this menstrual distress in women at early age to minimize the risks of reproductive dysfunction in premenstrual and post menstrual conditions.

Keywords: LH-(Luteinizing hormone),FSH(Follicle stimulating hormone), GnRH(Gonadotropin releasing hormone),PolyCystic Ovarian Syndrome (PCOS), AN(Anovulation),Thyrotropin releasing hormone(TRH) Müllerian agenesis also known as Mayer–Rokitansky–Küster–Hauser syndrome (MRKH)

INTRODUCTION

Amenorrhea is defined as a female of child bearing age fails to menstruate or the absence of growth and development of secondary sexual characters. The female menstrual cycle usually comprises of 28-30 days per cycle which contains two phases, the secretory phase and the proliferative phase. At the termination of the cycle, the inner uterine layer starts shedding off which results in menstruation in females. However in some cases the absence of menstruation is for two months or more in reproductively active female that results in amenorrhea.

Menstrual cycle is a natural process that only ceases naturally during breastfeeding, pregnancy and menopause. But intake of hormones and birth control results in amenorrhea in some women which is considered abnormal and is associated with various diseases such as estrogen deficient amenorrhea. Estrogen deficient amenorrhea is a condition in which risks of having fractures is

increased along with reduced level of bone minerals. Estrogen replete amenorrhea leads to long term endometrial carcinoma and short-term uterine bleeding. Amenorrhea is associated with hypothalamic pituitary-ovarian axis dysfunction among women. It is caused by physical exercises, anorexia, and stress. In addition, Ovarian failures occurs due to hypergonadotropic amenorrhea.

The hypothalamus stimulates pituitary gland and release of 2 hormones that regulate female reproductive cycling LuiteinizingHormone (LH) and Follicle Stimulating Hormon (FSH). These hormones influence production of Estrogen and Progesterone. These are responsible for the cyclic changes in the lining of the uterus including menstruation.

The presence of menstrual flow depends on the existence and development of the endometrium lining of the uterine cavity. The tissue is stimulated, regulated by the proper quantity and sequence of the steroidhormones, estrogen and progesterone.

Female athletes and women in sports with low body weight, ballet dancing or gymnastics develop amenorrhea.

Amenorrhea is classified into 2 types:

1. Primary Amenorrhea
2. Secondary Amenorrhea.

1. **Primary Amenorrhea**: A woman has no first menstrual period by age 16. It describes the absence of menses (before menarche).This is often due to late puberty and common in teenage girls who are thin or athletic. These young woman are underweight. In some girls it is due to Turner`s syndrome.

2. **Secondary Amenorrhea**: It happens when a woman has menstruated previously but fails for 3months.It describes the cessation of menses (after menarche).

It is caused by pregnancy,menopause,premature ovarian failure(POF),hysterectomy,poly cystic ovary disease,physical stress,weight loss,obesity,hyper thyriodism,cystic fibrosis,cancer,tumors or cysts in ovaries,tumors in pituitary gland.

Incidence

The prevalence of amenorrhea is 1.5–3% of the female population during reproductive years. Whereas primary amenorrhea is quite rare, secondary amenorrhea is not infrequent in women of reproductive age.

Causes

The causes of amenorrhea are likely to be alterations in the hypothalamus, ovaries, or uterus.It includes anatomicab normalities of the genital system, genetic defects, endocrinopathies, ovarian failure, pituitary dysfunction, and hypothalamic dysfunction. The relative frequency of each etiology is population dependent. Although some investigators have found polycystic ovarian syndrome (PCOS) to be the most frequent cause of anovulation, others have found that weight loss-related amenorrhea is the leading cause of cessation of menstruations. In most of the studies approximately two-thirds of all amenorrheic patients are hypoestrogenic due to either hypothalamic–pituitary dysfunction or end-organ resistance to gonadotropins.

Causes of primary Amenorrhea

There are many causes of primary amenorrhea some of which are as follows:

a. **End organ disorders**: It includes abnormalities of chromosomes such as turner syndrome which causes gonadal dysgenesis or the absence of breast bud by the age of 13 to 14 years indicates estradiol deficiency resulting in ovarian failure.
b. **Outflow tract obstruction:** It includes, imperforated hymen, testicular feminization, transverse vaginal septum and atresia.
c. **Central regulatory disorders**: Disorders such as pituitary disorders, hypothalamic disorders, pituitary tumours, androgen insensitivity, congenital gonadotropin-releasing hormone (GnRH) deficiency and Kallmann syndrome are some examples of central regulatory disorders that causes primary amenorrhea.
d. **Secondary amenorrhea**: Occurrence of secondary amenorrhea in women's is about 3% to 5%. Absence of menstruation cycle for 2 to 3 consecutive fertility cycles in women or if the cessation is for 6 or more months results in secondary amenorrhea.

Causes of secondary Amenorrhea

There are many causes of secondary amenorrhea such as pregnancy, low or normal FSH, anorexia, nonspecific hypothalamic, chronic anovulation, hypothyroidism, cushing syndrome, abnormalities, asherman syndrome, ovarian dysfunction etc.

Etiology of Amenorrhea

The following factors are responsible for causing amenorrhea:

a. **Natural factors**: The natural factors that causes amenorrhea includes breastfeeding, age, menopause and pregnancies.

b. **Role of medicine**: Intake of high medicinal drugs are responsible for disturbing menses and causing amenorrhea such drugs includes anti-allergies, injectable contraceptives, anti-BP drug, anti-psychotics, birth control pills, anti-depressants etc.
c. **Nutritional deficiency**: Nutritional deficiency causes hypothalamic disorders leading to severe menstrual issues.
d. **Behavioral and lifestyle factors:** Malnourished diet, weight issues, alcohol consumption, elevated intake of coffee, tea and smoking periodically effects the natural menstrual cycle n females.
e. **Exercise:**Generally, exercise-induced amenorrhea results from the suppression of GnRH leading to hypoestrogenism and delayed menstrual cycle.
f. **Dietary factors:** High intake of fruits and vegetables delays the onset of menopause and prolongs the reproductive lifespan because of the presence of antioxidants in fruits and vegetables that counteracts the adverse effects of reactive oxygen species on the number and quality of ovarian follicles.
g. **Hormonal imbalance**: Due to hormonal imbalance amenorrhea in women may result in serious consequences such as thyroid malfunction, polycystic ovary syndrome, tumor of pituitary gland sarcoids, premature menopause, premature ovarian failure, postpartum necrosis etc.
h. **Female reproductive system**: Abnormalities like reproductive organ, birth defects, genital tract defects, ovary infections etc. are also responsible for causing amenorrhea.
i. **Genetic defects**: Genetic defects are also one of the factors that causes amenorrhea in women such as chromosomal abnormalities like Turner syndrome, sawyer syndrome, Fragile X syndrome and Kallmannsyndrome.
j. **Less common causes**: The unusual causes of amenorrhea includes autoimmune disorders, head injuries, over growth of tissue from placenta and polyps, cancer, cushing syndrome, chronic disorders, AIDS, adrenal gland malfunction, fibroids and chemotherapy.

Epidemiology of Amenorrhea

Amenorrhea is not life-threatening, but the lack of menstrual cycle has been associated with high risk of hip and wrist fractures. In the, amenorrhea affects about 1 % of women. Recent studies indicated that childhood obesity may contribute to the early onset of amenorrhea.

Consequences of Amenorrhea

The following are some of the short/long term consequences of amenorrhea that are reported in females such as pelvic pain, decreased bone density, hair loss, excessive facial/body hair, infertility, nipple discharge,headache,vaginal dryness, infertility, increased muscle size, decreased sex drive, acne and vision problems.

Physiology

The physiologic basis for hypothalamic amenorrhea is the disruption of the hypothalamus' pulsatile secretion of GnRH. A number of studies have shown a depression in GnRH pulsatility associated with starvation. This suggests that the GnRH pulse generator may be affected by metabolic fuels and/or is able to sense a drop in weight below a certain setpoint. When energy expenditure is greater than dietary intake, GnRH inhibition occurs, thereby lowering the release of LH and FSH from the anterior pituitary and shutting down or limiting ovarian stimulation and estradiol production.

Prepubertal LH and FSH patterns are characterized by decreased and low-amplitude pulsations. However, studies have shown that follicular maturation and even menstruation can be induced in many patients by the pulsatile administration of exogenous GnRH. Therefore, as is seen in patients who recover their weight, the amenorrhea can be reversible when normal hormone pulsatility is restored.

Gonadotropin levels are reduced in patients with AN and GnRH stimulation testing in patients with AN demonstrates a blunted LH response with a preserved FSH response and very low levels of estradiol. LH pulsatility may revert to prepubertal patterns in adolescents who have previously achieved pubertal status. The amenorrhea is also marked by strikingly reduced leptin levels. Leptin serves as a metabolic signal of energy status and nutritional reserve and thus may have a permissive role for the initiation of the complex hormonal dynamics necessary for normal reproductive function.The rise in leptin upon weight gain is associated with increases in gonadotropin secretion, suggesting that leptin serves a permissive role for the activation of the hypothalamic-pituitary-gonadal axis.

Tests

A variety of blood tests may be necessary, including:

- **Pregnancy test.** This will probably be the first test your doctor suggests, to rule out or confirm a possible pregnancy.
- **Thyroid function test:** Measuring the amount of thyroid-stimulating hormone (TSH) in your

blood can determine if your thyroid is working properly.

- **Ovary function test:** Measuring the amount of follicle-stimulating hormone (FSH) in your blood can determine if your ovaries are working properly.
- **Prolactin test.** Low levels of the hormone prolactin may be a sign of a pituitary gland tumor.
- **Male hormone test.** If you're experiencing increased facial hair and a lowered voice, your doctor may want to check the level of male hormones in your blood.

Laboratory tests (including gonadotrophins, prolactin, and thyroid-stimulating hormone) and imaging (pelvic or sella turcica) may be indicated. If there is evidence of hyperprolactinemia or thyroid dysfunction, appropriate investigation and management should restore menses.

Low gonadotrophin levels (i.e., hypogonadotropic hypogonadism) suggest an abnormality of the pituitary or hypothalamus.

Hormone challenge test

For this test, you take a hormonal medication for seven to 10 days to trigger menstrual bleeding. Results from this test can tell your doctor whether your periods have stopped due to a lack of estrogen.

Imaging tests

- **Ultrasound.** This test uses sound waves to produce images of internal organs. If you have never had a period, your doctor may suggest an ultrasound test to check for any abnormalities in your reproductive organs.
- **Magnetic resonance imaging (MRI).** MRI uses radio waves with a strong magnetic field to produce exceptionally detailed images of soft tissues within the body. Your doctor may order an MRI to check for a pituitary tumor.

Scope tests

Hysteroscopy — a test in which a thin, lighted camera is passed through your vagina and cervix to look at the inside of your uterus.

Physical Examination

The physician should measure the patient's height, weight, and body mass index, and perform thyroid palpation and Tanner staging. Breast development is an excellent marker for ovarian estrogen production. Acne, virilization, or hirsutism may suggest hyperandrogenemia. Genital examination may reveal virilization, evidence of an outflow tract obstruction, or a missing or malformed organ. Thin vaginal mucosa is suggestive of low estrogen. Dysmorphic features such as a webbed neck or low hairline may suggest Turner syndrome.

Anatomic Abnormalities

Müllerian agenesis, a condition characterized by a congenital malformation of the genital tract, may present with normal breast development without menarche, and may be associated with urinary tract defects and fused vertebrae.Other congenital abnormalities that may cause amenorrhea includes imperforate hymen and transverse vaginal septum. In these conditions, products of menstruation accumulate behind the defect and can lead to cyclic or acute pelvic pain. Physical examination, as well as ultrasonography or MRI, is key to diagnosis, and surgical correction is usually warranted.

Rare causes of amenorrhea include complete androgen insensitivity syndrome, which is characterized by normal breast development, sparse or absent pubic and axillary hair, and a blind vaginal pouch; and 5-alpha reductase deficiency, which is characterized by partially virilized genitalia.In these conditions, serum testosterone levels will be in the same range as those found in males of the same age. The karyotype will be 46,XY, and testicular tissue should be removed to avoid malignant transformation.

A structural cause of secondary amenorrhea is Asherman syndrome: intrauterine synechiae caused by uterine instrumentation during gynecologic or obstetric procedures, which can be evaluated and treated with hysteroscopy.

Evaluation of Amenhorrea

A careful history and physical examination is evidence for psychological dysfunction or emotional stress.Family history of apparent genetic anomalies,signs of physical problems with focus on nutritional status.Abnormal growth, development,presence of normal reproductive tract.

CNS disease,Galactorrhea is an important clinical physical sign.These include anatomic defects in the outflow tract; primary dysfunction of the ovary; disruption of hypothalamicor pituitary function; systemic disease affecting the hypothalamic-pituitary-gonadal axis and pathology of other endocrine glands.

Steps to workup with Amenorrhea patient

After excluding pregnancy,begins with a measurement of Thyriod stimulating hormone(TSH),Prolactin level and progestational challenge.

Initial step in patient presenting with galactorrhea regardless menstrual history also includes TSH and prolactin measurement,lateral X-ray view of Sella Tursica. X-ray omitted in patients

with galactorrhea,regular,ovulatory menstrual cycles.

Only few patients with amenhorrea and galactorrhea will have hypothyriodism. Its duration is important. Long duration then higher incidence of galactorrhea and high prolactin levels. Thyrotropin releasing hormone(TRH) stimulates effect on pituitary cells to secrete prolactin.Patients with hypothyriodism and hyperprolactinemia can be present in either primary amenorrhea or secondary amenorrhea.

Gonadotropin Assay

In an amenorrheic woman the result of the gonadotropin assay is there is no bleeding following the progestational agent will be abnormally high or low than the normal range. Gonadotropin secreting tumors require surgery.

Patient with amennorhea has high or elevated gonadotropins despite presence of ovarian follicles. Absence of gonadotropin receptor on follicles or post receptor signalling defect,laparotomy is the only definitive way to evaluate the ovaries because follicles are deep within ovary. Stimulation by exogenous gonadotropins.

Secondary amennorhea is caused by premature ovarian failure(POF) due to auto immune diseases. POF includes Myasthenia gravis, Idiopathic thrombocytopenic purpura, Rheumatoid arthritis, Vitiligo,auto immune hemolytic anemia and endocrine disorders.

High levels of gonadotropin patients with an enzymatic deficiency in both ovaries and the adrenal gland ,17 hydroxylase deficiency,absence of secondary sexual development,hypertension and high levels of the progesterone in blood.

Complications of Amenorrhea

- **Infertility and problems with pregnancy.** If you don't ovulate and don't have menstrual periods, you can't become pregnant. When hormone imbalance is the cause of amenorrhea, this can also cause miscarriage or other problems with pregnancy.
- **Psychological stress.** Not having periods when your peers are having theirs can be stressful, especially for young people who are transitioning into adulthood.
- **Osteoporosis and cardiovascular disease.** These two problems can be caused by not having enough estrogen. Osteoporosis is a weakening of the bones. Cardiovascular disease includes heart attack and problems with the blood vessels and heart muscle.
- **Pelvic pain.** If an anatomical problem is causing the amenorrhea, it may also cause pain in the pelvic area.

Symptoms

- The main symptom is a lack of menstruation.
- milky nipple discharge
- hair loss
- a headache
- vision changes.

In those with primary amenorrhea, there may be a lack of breastdevelopment.Hormonal imbalance with excess body or facial hair,acne,lowering of voice,altered sex drive,breast milk secretions,weight gain.

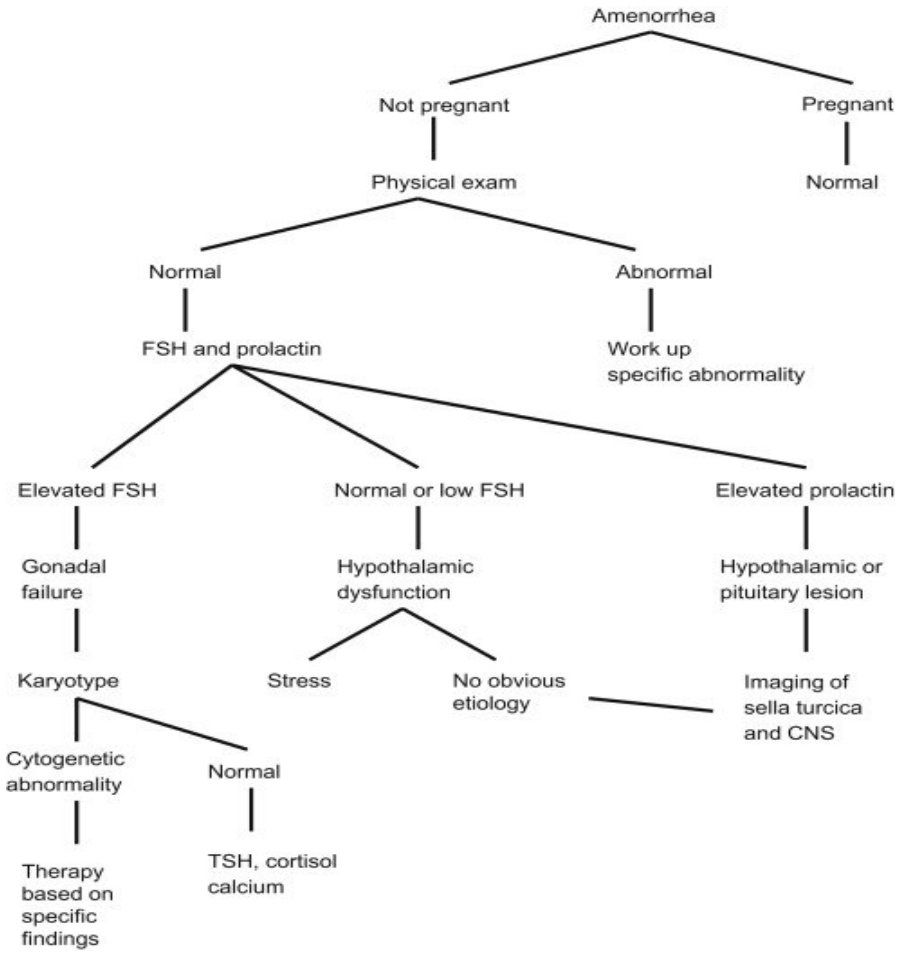

Fig 1: Diagnostic algorithm for amenorrhea.

Prognosis: Amenorrhea is rarely caused by life threatening condition. In most of the cases it is reversible and treatable.

Prevention: Primary amenorrhea is prevented by helping teen age girls with a sensible exercise program and by maintaining a normal weight for their height and age. Anatomic abnormalities cannot be prevented.

Secondary amenorrhea is prevented by eating low fat diet,ideal body weight,muscle tone,emotional stress,balance work,recreation,rest, avoid excessive alcohol consumption and cigarette smoking.

Treatment: Primary amenorrhea is caused late puberty then treatment is not necessary because condition resolves on its own. If genetic defect prevents ovaries from functioning properly then supplemental ovarian hormones are given to develop secondary sexual characteristics and to prevent osteoporosis due to low estrogen. If it is structural abnormality such as vagina is irregularly shaped or lacks opening then surgery is necessary.

Secondary amenorrhea due to menopause or hysterectomy then doctor will prescribe medications to prevent osteoporosis and other complications of low estrogen levels. Stress management course,lose weight,improvement of fitness,supplemental hormones,cysts or tumors in ovaries then surgery is necessary.

This will depend on the underlying cause.

Lifestyle factors: If the person has been exercising excessively, a change of exercise plan or diet may help to stabilize the monthly cycle.

Stress: If emotional or mental stress is a problem, counseling may help.

Excessive weight loss: This can happen for different reasons. The person may need a professionally supervised weight gain regime. If an eating disorder is a possibility, treatment may include a weight-gain regime and counseling sessions with a psychiatrist and a nutritionist or dietitian.

Some health conditions can cause weight loss. A doctor may test for these and offer treatment as appropriate.

Underactive thyroid: If menstruation stops because of an underactive thyroid, the doctor may prescribe treatment with thyroxine, a thyroid hormone.
Polycystic ovary syndrome (PCOS): The doctor will suggest appropriate treatment. If PCOS has led to excess weight, they may recommend a weight-loss diet.
Premature ovary failure: Hormone replacement therapy (HRT) may cause menstruation to return.
Menopause: Menopause starts around the age of 50 years, but sometimes it can start as early as 40 years. Family history can affect this.

If menopause starts early, there is a higher risk of osteoporosis. The person may need treatment to prevent this complication.

Home Remedies

Treatment for amenorrhea is consume these 6 foods. They are unripe Papaya,Aloe vera, Cinnamon,Coffeeseeds,Ginger and Pineapple.

When to call a professional?

One should contact doctor if girls reach 14th birthday and their is no development of secondary sexual characteristics. If a woman not had her 1st menstrual period.

If girls miss a period then pregnancy test is done. If sexually inactive,irregular periods,missed 3 consecutive periods.

Diagnosis

Doctor will ask about

1. Date of last menstrual period.
2. Whether sexually active or not
3. Birth control methods.
4. Pregnancy history
5. Eating habits and weight fluctuations
6. Age when mother entered menopause
7. Stress management
8. Exercise and medications
9. Acne,dryskin,increased body hair
10. Constipation
11. Hair loss and unusual breast secretions.
12. Blood and urine test
13. Pelvic ultrasound
14. Progesterone challenge test.

Expected duration

- The length of amenorrhea depends on type and cause.
- Primary amenorrhea in teen age girls puberty is late and no permanent abnormality.
- Secondary amenorrhea duration depends on cause. If emotional/physical stress then block in the release of luteinizing hormones. Rapid weight loss or gain then girls miss their 1 or more periods.
- Amenorrhea is permanent in woman after menopause or hysterectomy.

Pharmacological treatment

Metformin,Clomifenecitrate,Bromocriptine,Cabergoline,Hormone Replacement Therapy(HRT)consisting of Estrogen and Progesterone.Drydrogesterone,Progesterone micronized.

CONCLUSION

It is concluded that amenorrhea is a menstrual associated problem affecting women all over the world. Therefore it is important to identify those factors responsible for causing primary/secondary amenorrhea in adolescent girls and women for the sake of their healthy reproductive functioning.

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