

AN OVERVIEW OF AMENORRHEA

Anu Prasad N*, Narmatha M

Arulmigu Kalasalingam College of Pharmacy, Srivilliputhur, Tamil Nadu, India.

ABSTRACT

Amenorrhea is defined as the nonappearance of menstruation in women. Amenorrhea may be divided into primary and secondary amenorrhea. Primary amenorrhea is caused due to anatomical, genetic, nutritional and other endocrine defects. Anatomical causes include distal obstruction, MRKH and AIS. Primary Ovarian Insufficiency is the foremost cause of primary amenorrhea. The frequent causes of secondary amenorrhea are pregnancy. Other causes of secondary amenorrhea include PCOD, functional hypothalamic amenorrhea, POI. Depending upon the causes, the amenorrhea affected women should experience the symptoms like hair loss, acne, excess facial hair, milky nipple discharge, etc along with the absence of menstruation. Amenorrhea is diagnosed using the patient laboratory data, pelvic ultrasonography, hysteroscopy. Management of amenorrhea is based upon its causes. PCOS patients are usually treated with regular exercise and healthy food diet. Amenorrhea is initially treated with hormonal therapy followed by hysterectomy. Regular intake of vitamin D and calcium is also recommended.

KEYWORDS: FSH [Follicle Stimulating Hormone], LH [Luteinizing Hormone], FHA [Functional Hypothalamic Amenorrhea], GnRH [Gonadotropin Releasing Hormone], Estrogen, Progesterone

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CORRESPONDENCE: Anu Prasad N* ✉ nmanojprasad6@gmail.com, Address - Doctor of Pharmacy, Arulmigu Kalasalingam College of Pharmacy, Krishnan koil, Srivilliputhur, Tamil Nadu, India.

INTRODUCTION

Amenorrhea is a menstrual disorder in which there is an exclusion of menstrual periods in female at the reproductive age of 12-49 years.^[1] It leads to the diverse condition which is examined by the history, examination and investigations. Amenorrhea is classified into primary and secondary. Primary amenorrhea mentions to the failure to attain the arrival of menarche beyond the age of 16 years with or without maturing of secondary sexual characteristics. Secondary amenorrhea mentions to the failure of regular menstruation for the period of three consecutive months or earlier irregular menstruation for the period of six months.^[2] The pathologic response is characterized by the damage of Gonadotropin-releasing hormone from the hypothalamus.^[3] Menstrual cycle disorder or irregularity can be evaluated by assessing whether the patient is pregnant. Investigate other aspects such as maturing of secondary sexual characteristics, ovarian disorders associated with vaginal dryness, hot flashes, night sweats, sleep disturbances, etc. Hypothalamic/pituitary disorders like headaches, milky nipple discharge, etc. Laboratory test like serum prolactin level, follicle stimulating hormone level, estradiol level and imaging test should be monitored.^[4]

Increased administration of hormones and birth control pills leads to amenorrhea which is related with the different diseases like estrogen deficient amenorrhea.^[5] Other amenorrhea related with the health matter like hypothalamic pituitary ovarian axis dysfunction among women's and young girls.^[6] In accordance with American Society Of Reproductive Medicine, Functional Hypothalamic Amenorrhea [FSH] is

accountable for 20-35% of secondary amenorrhea and almost 3% of primary amenorrhea.^[3]

MENSTRUATION AND OVULATION

Menstruation is a monthly cycle which gets rid of the lining of the uterine of female uterus. The menstrual cycle may dissect into two phases;

- Follicular or Proliferative phase (ovum in follicle)
- Luteal or secretory phase (corpus luteum).^[7]

The normal mechanism works by balancing the hormones. Throughout the menstrual cycle, Gonadotropin-releasing hormone is released from the hypothalamus which acts on the pituitary; it stimulates the release of two hormones from the anterior pituitary gland namely Follicle Stimulating Hormone (stimulate development of follicle) and Luteinizing Hormone (causes ovulation) which perform on ovaries and the ovaries eventually produce estrogen and progesterone to function on the uterus.^[8] The average duration of the menstrual cycle is 28 days and the cycle length exceeds between 21-30 days.^[7] During ovulation, increased luteinizing hormone and follicle stimulating hormone flow are related to falling in the estrogen levels.^[9]

PHASES OF THE MENSTRUAL CYCLE

The menstrual cycle is of four phases:

1. Menses phase

Menses phase happens from day 1-5 of the menstrual cycle. During this phase, the uterine lining (endometrium) is shed out through the vagina, if the woman is not pregnant.

2. Follicular phase

This phase occurs from 6-14 days of the menstrual cycle. Throughout 10-14 day, follicles will develop a full grown egg.

3. Ovulation phase

Ovulation happens for 14-28 day of menstrual cycle. Throughout this phase, Luteinizing Hormone will bring out the egg from the ovary.

4. Luteal phase

The luteal phase always occurs from day 15-28. During this phase, the egg reaches the fallopian tube. The released estrogen and progesterone will get rid of the uterine lining in the menstrual cycle.^[10]

PRIMARY AMENORRHEA

Primary amenorrhea is mentioned as failure to attain the arrival of menarche beyond the age of 16 yrs.^[2] The incidence of primary amenorrhea is 0.1-0.3%. Women with loss of uterus and vagina, may have their fertilized egg on the surrogate uterus.^[11]

Causes of primary amenorrhea

Primary amenorrhea causes includes the following;

- Anatomical defects
- Genetic defects
- Nutritional defects
- Other endocrine defects.

Genetic defects

Primary ovarian insufficiency [POI] is the first and familiar common causes of primary amenorrhea. Primary Ovarian Insufficiency or Premature Ovarian Failure refers to the end of menstruation occurs before the salted age of menopause. Chromosomal abnormalities has been confess as a cause of primary ovarian insufficiency.^[14] Turner syndrome and classical monosomy (45XO) is almost 50-60% of karyotypes. Other chromosomal dearrangement and 46XX-Pure Gonadal dysgenesis are fewer common. 46XY Gonadal dysgenesis – Swyer syndrome is occurs. Multiple genes on X chromosome, Mitochondria and autosomes are the sign of primary ovarian insufficiency. Single gene disorders on FMR1 gene occurs in Primary Ovarian Insufficiency.^[12]

Anatomical defects

Anatomical defects accounts for 20% of the causes. Distal obstruction like imperforate hymen and transverse vaginal septum are frequently present.^[12] Absence of Mullerian structure encompass Mayer-Rokitansky-Kuster-Hauser syndrome (MRKH) and Androgen Insensitivity Syndrome (AIS). MRKH Syndrome is the damage in development of uterus. It is the second and frequent causes of primary amenorrhea.^[13]

Nutritional defects

Primary amenorrhea is caused due to energy deficiency, weight loss, excessive stress and exercise which suppress the hypothalamic pituitary ovarian axis.^[12]

Endocrine defects

Polycystic ovary syndrome (PCOS), Hyperprolactinaemia (high level of prolactin in blood) are the familiar endocrine disorders.^[15] It is caused due to the environmental and genetic conditions with obesity, ovarian dysfunction, etc. Hyperandrogenism (high levels of androgen secretion) occurs in 60-80% of women.^[16]

Assessment of primary amenorrhea

The assessment of primary amenorrhea is done by the thorough history and physical examination. History includes anosmia (loss of sense of smell), headaches, galactorrhea, visual disturbances may be the indication of pituitary disorder and investigate about the pubertal development. Sometimes delayed menarche may be due to hereditary conditions. Physical examination includes height, weight and Body mass index (BMI), Turner's syndrome like webbed neck, widely spaced nipples and Mullerian agenesis like absence of uterus, pubic hair and thyroid disorders should be examined.^[17]

Diagnosis of primary amenorrhea

Primary amenorrhea should be diagnosed based on the presence or absence of secondary sexual characteristics.

Presence of secondary sexual characteristics

If the female has developed the secondary sexual characteristics like breast development with less or no pubic hair which is diagnosis as Androgen Insensitivity Syndrome.^[18]

If the person has the usual secondary sexual characteristics, they should be tested with Magnetic Resonance Imaging or Ultrasonography to detect the presence of uterus.

If uterus is absent or abnormal, in such condition, karyotype analysis should be done to check the person is genetically female. If the uterus is normal, amenorrhea is caused due to the anatomical defects. i.e., outflow tract obstruction.^[19]

Absence of secondary sexual characteristics

If the female has not developed the secondary sexual characteristics, laboratory data analysis should be performed. Based on the result of the laboratory data, Low level of FSH and LH is consider as Hypogonadotropic hypogonadism which delays the puberty. Elevated level of FSH and LH is consider as Hypergonadotropic hypogonadism. Then, karyotype analysis should be performed.^[19]

IMAGING STUDIES**1) Ultrasound sonography test**

This test is used to determine the presence or absence of uterus.

2) Hystersalpingography

It is an X-ray test to detect the internal shape of the uterus.

3) Computed tomography or Magnectic resonance imaging

This test is used to identify the causes of primary amenorrhea.^[28]

MANAGEMENT OF PRIMARY AMENORRHEA

Primary amenorrhea management is based upon the etiology and the patient history.

Anatomical defects

Distal obstruction can be treated using hysterectomy (Surgical removal of uterus).^[20] Mayer-Rokitansky-Kuster-Hauser Syndrome and Mullerian hypoplasia were treated with vaginoplasty and laparoscopic Davydov vaginoplasty. Androgen Insensitivity Syndrome was treated with Laparoscopic Bilateral Gonadectomy.^[21]

Genetic defects

Hormone Replacement Therapy (HRT) should be done in Primary Ovarian Insufficiency. The Post-Menopausal regimen of HRT is 100 mcg of transdermal estradiol daily or 0.625 mg of oral conjugated equine estrogen daily + 200 mg of micronized oral progesterone daily for 12 days each month.

HRT may decrease the vasomotor symptoms. Estrogen decreases the thromboembolism risk. Along with HRT, Regular intake of 1200mg of Calcium daily and 1000 Units of Vitamin D to prevent the loss of bone mineral density.^{[20][21]}

Endocrine defects

In PCOS patient, regular exercise and healthy food habits are recommended. Patient with elevated BMI, weight loss in PCOS this helps to reimpose the menses. The first line therapy for menstrual disorders is combined hormonal contraceptives. In patient with impaired glucose tolerance and for those who shows contraindication to contraceptives, Metformin is recommended. Metformin helps to prevent the diabetes mellitus and regulate regular menstrual cycle.^[20]

SECONDARY AMENORRHEA

Secondary amenorrhea is mentioned as the failure of the regular instances of menstruation for the period of 3 months and earlier irregular menses for the period of 6 months.^[2] The prevalence rate of secondary amenorrhea is 4.4% .^[22]

Causes of secondary amenorrhea

Secondary amenorrhea causes is categorized into the following;

- Physiological causes
- Pathophysiological causes
- Iatrogenic causes

Physiological causes

Functional Hypothalamic Amenorrhea (FHA) and Hyperprolactinemia are the general causes. FHA is the frequent causes of secondary amenorrhea and which is noticed in patients with chronic disease, under nutrition, excessive exercise, emotional stress. Lactation and pregnancy are the frequent causes of Hyperprolactinemia. This condition increases the level of prolactin above 600 ng/ml.

Pathophysiologic causes

- ✓ Pituitary causes includes Sheehan's syndrome, Hyperprolactinemia
- ✓ Adrenal tumors

- ✓ Ovarian causes includes Primary ovarian insufficiency, Polycystic ovarian syndrome
- ✓ Nutritional causes includes excess weight
- ✓ Genetic causes include Idiopathic hypogonadotropic hypogonadism.

Iatrogenic causes

- Medications like Opioids, glucocorticoids, antihypertensives, hypophysitis and GI Motility agents
- Radiation therapy
- Pituitary surgery.^[23]

Assessment of secondary amenorrhea

The assessment of secondary amenorrhea is done by the thorough history of the patient and physical examination. Investigate the patient history like galactorrhea, hirsutism, acne, sexual activity associated pregnancy, menstrual history, thyroid disease, weight loss, poor nutrition. Physical examination includes high BMI associated with polycystic ovary syndrome. Turner syndrome, Cushing syndrome, outflow tract obstruction should also be examined.^[1]

Diagnosis of secondary amenorrhea

Laboratory data includes serum LH, FSH, TSH, Prolactin level, Pregnancy test, Pelvic ultrasonography are performed. If the patient having abnormal TSH level, Thyroid function test should be carried out and then treat the thyroid disease.

If the patient Laboratory test shows with increased FSH and LH levels, karyotype analysis should be performed, to find out Turner syndrome or variant.

If the Patient laboratory test shows normal or decreased FSH and LH levels, Verify for disordered eating, high intracranial pressure, Hyperandrogenism.^[1]

Progesterone Challenge Test – This test is done to determine the difference between the anovulation and anatomic causes of amenorrhea.^[24]

MANAGEMENT OF SECONDARY AMENORRHEA

Management of secondary amenorrhea is based upon its causes and patient history.

Polycystic ovarian syndrome

The initial treatment of PCOS is weight loss and regular exercise. The normal endometrium is maintained by the administration of oral contraceptive pills or cyclic progestational agents. Metformin can lower the insulin resistance.

Hypogonadotropic hypogonadism

Hypothalamic amenorrhea is the abnormalities in the gonadotropin – releasing hormone secretion. It is caused by overweight loss, exercise. Menstrual cycle will get back after healthy body weight is achieved. Bisphosphonates is used to treat post menopausal disorders. Intake of vitamin D and calcium is also recommended.^[1]

Primary Ovarian Insufficiency

Hormone replacement therapy (HRT) is indicated for POI. Combination of oral micronized progesterone and estrogen is the long term HRT which is used for the management of secondary amenorrhea and dysfunctional premenopausal bleeding.^[25]

SIGNS AND SYMPTOMS OF AMENORRHEA

Based on the causes of amenorrhea, the amenorrhea affected patients experiences the signs or symptoms along with the lack of menstruation are listed in the following;

- ❖ Hair loss
- ❖ Vision changes
- ❖ Headache
- ❖ Milky nipple discharge
- ❖ Excess facial hair
- ❖ Pelvic pain
- ❖ Acne.^[26]

COMPLICATIONS OF AMENORRHEA

Menstruation is important for the hormonal imbalance and pregnancy. Deficiency of estrogen has a major influence on cardiac, skeletal, psychological and reproductive system. Secondary amenorrhea is mostly caused by the Functional Hypothalamic Amenorrhea.

Cardiac complications

Genetic conditions like Turner's syndrome - 45X and primary ovarian insufficiency - 46XX leads to the deficiency of estrogen. This estrogen deficiency causes the cardiovascular diseases like hypertension, hyperlipidemia which results in increased death factor.

Skeletal complications

Estrogen deficiency causes Bone Mineral Density reduction on the skeletal system. Severe osteopenia was developed in patients with extended amenorrhea. Hormones like parathyroid and thyroid hormones are responsible for maintaining the normal bone mineral density. Increased level of cortisol causes the variation in vitamin D absorption.

Psychological complications

Menstrual irregularities is also caused by higher anxiety, increased depression and stress which are associated with elevated cortisol levels.

Reproductive complications

During the abnormal menstruation, gonadotropin-releasing hormone release is inhibited by the hypothalamus. So, the release of pituitary hormones like FSH and LH is also decreased which causes the deficiency of estrogen and anovulation. In the absence of estrogen, ovary can't produce egg for fertilization. Women's with psychological stress and low Body Mass Index (BMI) having a higher chance of miscarriage pregnancy.^[27]

CONCLUSION

Amenorrhea is a disorder which disrupts the menstrual cycle in women. It is caused due to genetic, endocrine and nutritional defects in women. Diagnosis differs by the types of

amenorrhea. Primary amenorrhea is based on the maturing of secondary sexual characters. Secondary amenorrhea is based on the laboratory data results which include the levels of Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), Thyroid stimulating Hormone (TSH) and Prolactin. Management of amenorrhea depends upon its causes. The first line treatment of amenorrhea is hormonal therapy followed by the surgery. Hormone therapy is used to balance the secretion of hormone in the body. If amenorrhea is not treated which results in the complications like infertility, reduced bone mineral density, hypertension, etc.

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