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Primary Amenorrhea- A Diagnostic Challenge

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Abstract

Amenorrhoea poses a diagnostic challenge to most gynecologists. Amenorrhoea has various causes and investigation is sometimes complex and time-consuming. Evaluation of amenorrhoea should be logical and systematic. Evaluation and management sometimes need a multidisciplinary approach including neurosurgeon, physician, endocrinologist, and psychiatrist. While dealing with a case of amenorrhea it should be remembered that most of these cases are due to physiological causes like pregnancy, lactation, or menopause.

Keywords: Amenorrhoea, pregnancy, lactation, menopause.

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1. Introduction

Amenorrhoea poses a diagnostic challenge to most of the gynecologists. Amenorrhoea has various causes and investigation is sometimes complex and time consuming. Evaluation of amenorrhoea should be logical and systematic. Evaluation and management sometimes need a multidisciplinary approach including neurosurgeon, physician, endocrinologist and psychiatrist. While dealing with a case of amenorrhea it should be remembered that most of these cases are due to physiological causes like pregnancy, lactation or menopause [1]. Even in remaining 3 -4 % cases majority is attributed to 4 problems that are Polycystic ovarian syndrome, hypothalamic amenorrhoea, hyperprolactinemia and ovarian failure which can be managed easily [2,3].

1.1 Definition of Primary Amenorrhoea

Women who never had menstruation in her life. More precise definition for evaluation is "absence of Menstruation at the age of 15 years in the presence of normal growth and secondary sexual characteristics". Evaluation may be considered at the age of 13 years, if menstruation does not occur in absence of secondary sexual characteristics such as breast development, axillary and pubic hairs. Evaluation and management should be done at any time if patient presents with symptoms of cyclical abdominal pain and/ retention of urine.

2. Epidemiology

Primary amenorrhoea affects 2.4% of female population [4].

Table 1: Epidemiology of causes of Primary Amenorrhoea [4]

	Breast development	:	*30 %*
1.	Mullerian agenesis	:	*10%*
2.	Androgen insensitivity	:	*9%*
3.	Vaginal septum	:	*2%*
4.	Imperforate hymen	:	*1%*
5.	Constitutional delay		*8%*
	No breast development: high FSH	:	*40 %*
1.	46 XX		*15%*
2.	46 XY		*5%*
3.	Abnormal		*20 %*
	No breast development: low FSH	:	*30 %*
1.	Constitutional delay		*10%*
2.	Prolactinomas		*5%*
3.	Kallman syndrome		*2%*
4.	Other CNS		*3%*
5.	Stress, weight loss &anorexia		*3 %*
6.	PCOS		*3 %*
7.	Congenital adrenal hyperplasia		*3%*
8.	Other		*1%*

3. Evaluation and management of causes of Amenorrhea

The following are broad category of causative factors of amenorrhoea

1) Disease of uterus & genital out flow tract
2) Disease of ovary
3) Diseases of Anterior Pituitary
4) Diseases of Hypothalamus or central nervous system.
5) Sometimes cause of amenorrhea involve more than one system for e.g. PCOS.

3.1 Physical Examination in cases of Amenorrhoea [Primary and Secondary both]

1) Growth, height, weight, and arm span, carrying angle
   Stigmata of Turner Syndrome: Short stature low hairline, webbed neck, shield like chest, widely spaced nipples
2) Low body weight [BMI <18.5] – Hypothalamic amenorrhoea
3) Obesity [BMI> 30] – PCOS
4) Secondary sexual characteristics
5) Skin
   [a] Soft, moist texture – Hyperthyroidism
   [b] Dry, thick skin – Hypothyroidism
   [c] Orange discoloration - Hyper Carotinemia due to excessive ingestion of low calorie carotene containing fruits & vegetables in dieting women
   [d] Acanthosis Nigricans – Diabetes, PCOS, Non Classical CAH
   [e] Striae - for ACTH
6) Breast Examination – a reliable indicator of estrogen production or exposure to exogenous estrogens.
   Milky Secretion – Galactorrhea
7) Abdominal Examination: Mass results from hematometra or an ovarian neoplasm.
8) Genital Examination: Clitoral size, pubic hair development, intactness of hymen, vaginal length, presence of cervix, And uterus and ovaries.
   Sexual Infantilism – Gonadal Dysgenesis.
   Lack of pubic and axillary hairs – Androgen Insensitivity Syndrome.
9) Per rectal examination may be necessary for hematocolpos and hematometra
10) Blood Pressure in both the arms - Coarctation of aorta in Turner Syndrome.

3.2 Medical History in Primary Amenorrhoea

History of primary amenorrhea is simple and specific. The following points should be specifically asked:

1) History of Stage of Puberty, age of growth spurt, development of axillary hairs and pubic hairs, apocrine sweat gland development and breast development.
2) Family History of delayed puberty
3) Woman's height in comparison to other female blood relatives [Turner Syndrome or Growth Hormone Deficiency]
4) Symptoms of Hyperandrogenism
5) Stress, weight change, diet, exercise, illness
6) Drug History
7) Galactorrhoea, headache, visual field defects
8) Fatigue, polyuria and polydipsia
9) Cyclic pelvic pain with urinary symptoms then diagnosis of cryptomenorrhea can be made.

3.3 Primary Amenorrhoea due to outflow tract disorders

[a] Mullerian duct developmental failure include

1. Mullerian / Vaginal Agenesis
2. Androgen insensitivity Syndrome

To differentiate between these two entities pubic hairs should be examined.

Failure of vertical fusion include

- Imperforate Hymen
- Transverse Vaginal Septum
- Cervical Atresia

3.4 Imperforate Hymen

Incidence: Incidence of imperforate hymen is 1 in 1000 women [5].

Pathophysiology: The hymen is anatomically formed by invagination of posterior wall of the urogenital sinus and it usually ruptures in prenatal period [6].

Symptoms and Signs:

- Imperforate hymen present at the expected time of menarche
- Cyclical perineal, pelvic and abdominal pressure or pain that results from the gradual accumulation of obstructed menstrual flow (cryptomenorrhoea)
- Acute retention of urine
- Normal secondary sexual characters
- Physical examination reveals absence of vaginal orifice and a thin, often bulging blue perineal membrane and a palpable fluctuant mass suggestive of hematocolpos.

Management: Surgical correction should be done as soon as possible. Definitive surgery is to make a simple cruciate incision in the hymen and to excise its central part up to hymeneal ring to allow drainage and subsequent menstruation [7].

3.5 Transverse vaginal Septum and Cervical Atresia

Incidence: Incidence of Transverse vaginal septum is 1 in 80,000 women [5].

Symptoms and Signs:

- Symptoms are similar to imperforate hymen
- Physical examination reveals a normal vaginal orifice with a short vagina in absence of cervix

- Hematocolpos and pelvic mass resulting from hematometra and hematosalpinx is usually palpable proximal to it.
- A differentiating feature from imperforate hymen is that Valsalva maneuver will cause distension in bulge of imperforate hymen but not in transverse vaginal septum.
- Pelvic ultrasound reveals the extent of hematocolpos and presence of hematometra and hematosalpinx [8].

Investigations: Magnetic resonance imaging is recommended to clearly define the length of atretic segment of vagina which helps in planning the treatment. Chronic retrograde menstruation may result in pelvic endometriosis and adhesions.

Management: Surgical management is excision of the septum or dissection of the atretic segment and primary anastomosis of proximal and distal vaginal canals. Sometimes graft may be required to bridge the gap [9].

Cervical Atresia: Cervical atresia is a rare but challenging case as far as management is concerned. Heroic efforts to restore anatomy and fertility may result in post -operative complications such peritonitis, sepsis, persistence of obstruction and infertility. Many clinicians opine in favor of hysterectomy to prevent severe pelvic endometriosis and adhesions.

Mayer-Rokitansky-Kuster-Hauser syndrome

The failure of development and fusion of Mullerian ducts is a quite common cause of primary amenorrhoea.

Pathophysiology: Cause is genetically related but cases are sporadic. It is gene related excess in AMH activity. Patient present in late adolescent with primary amenorrhoea [10].

Symptoms and Signs:

1. Normal and symmetrical secondary sexual characters and pubic hairs.
2. No visible vagina
3. No symptoms of cryptomenorrhoea

In majority of cases ovaries are normal but, in few cases, may be undescended, hypoplastic or associated with inguinal hernia. Urological anomalies are found in 15-40% patients.

Type B Mullerian agenesis is mostly associated with unilateral renal agenesis, ectopic or horseshoe kidney and duplication of ureters .10-15% of cases are associated with skeletal malformation involving the vertebrae, the ribs or the pelvis [11].

Management: A karyotype study is a must to rule out male pseudohermaphroditism. Imaging includes ultrasound and MRI. Surgery or laparoscopy is not needed for evaluation but indicated if women have symptoms of hematometra, endometriosis and inguinal hernia. Primary Treatment in such women is creation of functional vagina [12]. It may be done by progressive vaginal dilatation, McIndoe procedure or Vecchietti operation [13,14].

3.6 Androgen Insensitivity Syndrome

Incidence: It is a rare disorder with incidence of only 1 in 60000 but it forms 5% of all the cases of primary amenorrhoea [15]

Pathophysiology: It is characterized by normal male karyotype (46, XY) with female phenotype and testes which produce both testosterone and AMH. Uterus and cervix fail to develop due to AMH. Inactivating mutation responsible for intracellular androgen receptor causes end organ Insensitivity to androgen and prevents normal masculinization of the internal and external genitalia during embryonic development [16].

Symptoms and Signs:

Features of Complete Androgen Insensitivity are:

- Female Phenotype
- Female External genitalia
- Absent cervix and uterus
- A short blind vaginal pouch
- Above average height
- Eunuchoid body habitus
- Large breasts with small nipples and pale areola
- Lack of public & axillary hair
- Undescended Testes
- Inguinal hernia may be present

In some cases, there may be presence of some public hairs due to incomplete penetrance of gene.

Management:

Investigations: Distinguishing features are [16]

- Karyotype of 46 XY.
- High serum testosterone concentration
- High LH concentration

Treatment focuses on creating a functional vagina with gonadectomy to prevent malignancy in Cryptorchid testes. Gonadectomy and hormone therapy [estrogen treatment] should be postponed until pubertal development is complete that is around 16-18 years. In cases of incomplete AIS, surgery should be done as soon as possible to prevent further unwanted virilization. Risk of malignancy is around 22% but malignancy rarely occur before the age of 20 years [17]

3.7 Ovarian Causes of Amenorrhoea

It is the most common cause of primary and secondary amenorrhea.

Common ovarian dysfunctions are

a. PCOS
b. Obesity
c. Thyroid disorders
d. Hyperprolactinemia
e. Fragile X [F MRI] Permutations
f. Galactosemia

g. Autoimmune Disease
h. Radiation
i. Chemotherapy

4. Investigations for evaluation of ovarian function

Serum Estradiol Concentration [18,19]

Advantage: - It is easy to obtain, relatively inexpensive and objective. Interpretation is as follows:

Normal estrogen levels: - Mild ovarian dysregulation and Chronic anovulation.

Eg.

1. Obesity
2. PCOS

Low Estrogen Levels

1. Ovarian Failure
2. Pituitary Disease
3. Severe Hypothalamic Dysfunction

5. Gonadal Dysgenesis

5.1 Turner Syndrome

Prevalence: Prevalence of Turner Syndrome is 1 in 2000 to 1 in 2500 live female births [20].

Karyotype: In Turner syndrome karyotype is 45 X. In another situation of gonadal dysgenesis there may be deletions, ring and isochromosome of other structural chromosomal and X chromosome which may present in all the cells or only in some of the cells of the body (Mosaicism) [21].

Features of Turner syndrome [22]:

Phenotype of Turner syndrome is female with

- Short stature
- Absent sexual development
- Webbed neck
- Low set ears
- Posterior hairline
- Widely spaced nipples (shield chest)
- Short fourth metacarpals
- Cubitus valgus
- Primary amenorrhoea
- Absent sexual development

In another subset of individuals having mosaic 46, XX with 45 X, gonads may have some functional ovarian tissue with some degree of sexual development resulting in menstruation and even possibility of pregnancy. Some level of pubertal development is present in 15% patients and only 5% have menarche with complete pubertal development [23]. Stature is usually short and natural pregnancy if at all take place is associated with aneuploidy and miscarriage.

Other health problems associated with Turner Syndrome are [24]:

- Cardiovascular anomalies
- Bicuspid aortic valve
- Coartation of the aorta
- Mitral valve prolapse
- Aortic aneurysm
- Renal anomalies
- Autoimmune disorders
- Hearing loss

Diagnosis of Turner syndrome: Investigations reveal hypergonadotropic hypogonadism . Karyotyping is diagnostic which is usually 45 X. It may reveal a cell line containing a Y chromosome otherwise not suspected or identified [45, X with 46, XY] in 5% of cases. It is important to identity a Y chromosome because these women are at 20-30% risk of gonadoblastoma.

Treatment: Goals of treatment are [25]:

- Achieving appropriate height [more than 150 cm]
- Achieving secondary sexual development
- Diagnosis and management of other health issues

Appropriate height of more than 150 cm may be achieved with administration of growth hormone before estrogen therapy in cases which are diagnosed early. Estrogen therapy should be commenced between 12-15 years. It should begin at low dose such as 0.25-0.5 mg of micronized estradiol or its equivalent daily. Doses should be increased gradually at intervals of 3-6 months according to response. Target is to achieve pubertal development within 2-3 years of commencement of therapy [26]. Vaginal bleeding if achieved then progesterone should be added cyclically to protect endometrium from the effects of unopposed estrogen.

Pregnancy: If individual is willing for pregnancy then she should be offered options of donor oocytes and simultaneously be counseled about the complications such as aortic dissection or aortic rupture which increases risk of death to 100-fold in pregnancy [27].

5.2 Swyer Syndrome:

It is less common form of gonadal dysgenesis in which karyotype is 46, XY. Phenotype is feminine because of presence of streak gonads which produce neither AMH nor androgens. It occurs due to mutation of the sex determining region which is located at the short arm of the Y chromosome [Y pll 3]. Patient with Swyer syndrome presents with amenorrhoea with delayed sexual maturation. Gonadectomy is indicated soon after diagnosis due to risk of malignant transformation in occult Testicular element [20-30%]. These patients are at high risk of Gonadoblastoma, Dysgerminoma, Endodermal sinus tumor, Embryonal cell carcinoma and Choriocarcinoma. Individuals have normal growth and brain development. Pregnancy may be achieved with in vitro fertilization using donor oocytes.

Pituitary Causes of Amenorrhoea

[1] Pituitary adenomas
[2] Metastasis [lung & breast]
[3] Cystic pituitary abscess
[4] Lymphocytic hypophysitis
[5] Sarcoidosis
[6] Tuberculosis
[7] Carotid arteriovenous fistula
[8] Sheehans syndrome
[9] Infiltrative hemosiderosis due to frequent transfusion
[10] Hereditary hemochromatosis
[11] Traumatic brain injury
[12] Mutations in the GnRh receptors.

5.3 Lactotroph Adenoma

Function lactotroph adenoma consists of 40 % of all clinically recognized pituitary adenomas. Tumours less than 10mm in size are called microadenoma and those 10mm or larger are called macroadenoma.

Symptoms and Signs:

- Hyperprolactinemia result in amenorrhoea and galactorrhea .
- Osteopenia due to hypogonadism.
- Neurological symptoms such as visual impairment [28].
- The classic complaint is bitemporal hemianopsia [tunnel vision].
- Headache
- Cerebrospinal fluid rhinorrhoea
- Pituitary apoplexy [sudden hemorrhage into the adenoma].
- Hormone deficiency due to mass effects on pituitary stalk.
- Gonadotropin deficiency causes amenorrhoea and vaginal atrophy.

Management of Lactotroph Adenoma -

Medical Treatment of Hyperprolactinema:

Dopamine agonists are the first choice of treatment for women with functional lactotroph adenoma & it decreases the size of 90% of such tumours. Bromocriptine and Cabergoline both are effective. Cabergoline is selective dopamine receptor type 2 agonist and is more potent than Bromocriptine and has lesser side effects long term use of cabergoline has risk of hypertrophic valvular heart disease. Bromocriptine is a safer option [29].

Surgical Management

- Trans-sphenoid surgery should be offered to women who do not tolerate or prove resistant to dopamine agonist treatment.
- Very large macroadenomas (>3cm) and patient willing for pregnancy [30].

Pituitary Incidentaloma

Incidence of pituitary incidentaloma is approximately 10%. Pituitary incidentalomas >10mm in size should be evaluated and treated in the same way. For smaller pituitary incidentalomas < 10mm only serum prolactin level should be done and MRI should be repeated after 1-2 years.

Empty Sella Syndrome:

It is a misnomer because the Sella is enlarged and appear empty on imaging as it contains cerebrospinal fluid within the subarachnoid space but it extends downwards in the pituitary fossa. It most commonly occurs due to previous removal or destruction of pituitary adenoma by surgery, radiation or infarction [31]. It may be caused from congenital defect in Sellar diaphragm [32].Residual pituitary tissue is flattened against the Sellar floor which eventually become demineralised due to increased pressure within pituitary fossa.

Such patients should undergo annual surveillance with serum prolactin assay and MRI for next few years.

5.4 Sheehan's Syndrome:

Sheehan's syndrome is a result of acute infarction and ischemic necrosis of the pituitary gland resulting from post-partum hemorrhage and hypovolemic shock .It is one of the common causes in underdeveloped and developing countries.

Symptoms and signs:

Clinical symptom depends upon severity of pituitary damage [33]. Patients present with

- Failure of lactation;
- Severe Hypopituitarism
- Lethargy
- Anorexia
- Weight loss
- Secondary Amenorrhoea
- Decrease in sexual hairs
- Less severe symptoms are like 'fatigue 'which is reported weeks or months after delivery.
- Common hormone deficiencies are of growth hormone, prolactin and gonadotropins.
- Most patients also have ACTH and TSH deficiencies [34].
- 30% of patient have hyponatremia
- Partially or completely empty Sella.

Management: It is similar to other causes of hypogonadotropic hypogonadism except that ACTH stimulation test should be deferred until 6 weeks after delivery as it requires time to develop after delivery [35].

Savage Syndrome: Also known resistant ovary syndrome. It results from intrinsic defects in follicular development. These are defects in intraovarian regulation, steroidogenesis, enzyme defect and abnormalities in gonadotropins and their

receptors. These patients are resistant to even high doses of exogenous gonadotropins.

5.5 Infiltrative Pituitary Lesions

Such lesions may also cause hypogonadotropic hypogonadism. Two lesions worth mentioning are hemochromatosis & lymphocytic hypophysitis.

Hemochromatosis: There is parenchymal iron overload and subsequent tissue damage. Damage to pituitary results in hypogonadotropic hypogonadism[36]. TSH & ACTH deficiencies are less commonly seen. Similar situation may be seen due to frequent transfusion in cases of severe anemia. Evaluation by "fasting transferrin saturation" that is a ratio of serum Iron to serum Iron binding capacity. Value greater than 45% is indicator for "HFE "gene on 'chromosome 6' genotyping. Early treatment with phlebotomy and chelation therapy can prevent serious side effects later [37].

5.6 Lympocytic Hypophysitis

It most commonly occurs in first 6 months of the post-partum period. It causes enlargement of the pituitary gland that mimics a pituitary tumor. It is a result of chronic inflammatory process resulting in focal or diffuse pituitary destruction. Patients mostly have a coexisting autoimmune disorder. Management is similar to other pituitary tumors that are transsphenoidal surgery, dopamine agonists, anti-inflammatory or immunosuppressive drugs or pituitary radiotherapy [38].

6. Hypothamic Causes of Amenorrhoea

6.1Evaluation of Hypothalamic Function

Functional hypothalamic amenorrhoea is a diagnosis of exclusion. Pathophysiology behind functional hypothalamic amenorrhoea is suppressed pulsatile hypothalamic GnRh Secretion which results in decreased Gonadotropin Secretion, absent follicular Development and anovulation. Hormone Profile reveals low FSH, LH and estradiol. Sometimes hormones may be in normal range.

6.2 Hypothalamic Causes of Amenorrhoea

It is a diagnosis of exclusion based on investigations revealing a low or normal serum FSH concentration with low estrogen, absence of Sellar mass lesion. Its causes may be [39,40].

1. Extreme Physical stress
2. Nutritional deficiency
3. Emotional Stress
4. Kallmann's Syndrome
5. Celiac disease
6. Tumors of hypothalamus (craniopharyngioma)
7. Constitutional delay of puberty

Regardless of cause majority of women show abnormal pattern of hypothalamic GnRH secretion both in frequency and amplitude [41].

6.3 Eating Disorders: Psychological, biological, genetic and social factors contribute to eating disorders. There may history of dieting, preoccupation with weight and leanness and possibly sexual abuse. Some women have similar history in their first degree relatives. Psychological problems like anxiety, obsessive compulsive disorders, personality disorder, and substance abuse family stress are also common. There is possible genetic susceptibility for anoxexia nervosa on chromosome I and for bulimia nervosa on chromosome 10. The metabolic abnormalities are dysfunctional appetite, thirst, temperature, sleep, autonomic balance and endocrine secretion.

Treatment of eating disorders: The treatment of anorexia nervosa & bulimia nervosa is complex and it require nutrition, medical monitoring and cognitive behavioral therapy. Antidepressant drugs may help bulimia but nor anorexia. Osteopenia and Osteoporosis are most serious complications. Patient with psychological stress and weight loss recover spontaneously and menstruation is resumed in over 70% in 6-8 years. [42]

6.4 Congenital GnRh Defifiency

Kallmann's Syndrome: In kallmann's Syndrome congenital GnRh deficiency is associated with anosmia or hypoosmia [absent or grossly decreased sense of smell] [43]. It is caused by a variety of genetic mutations in the "KAL" gene located on the short arm of the X chromosome Xp 22.3. Kallman syndrome also be inherited in an autosomal dominant or recessive fashion. Both male and females with Kallmann's syndrome at puberty usually present with delayed growth and sexual development but presence of sexual hairs. Most distinguishing finding is inability to perceive odors. There may be family history of delayed puberty. Other findings are cleft lip and cleft palate, urogenital tract abnormality and syndactyly.

7. Conclusion

Amenorrhea is a common presenting complaint encountered by Gynaecologist .The four most common causes are polycystic ovary syndrome, hypothalamic amenorrhea, ovarian failure, and hyperprolactinemia. Evaluation of primary amenorrhea may be considered at the age of 13 years in case menses have not occured in absence of secondary sexual characteristics such as breast development, axillary and pubic hairs . If patient presents with symptoms of cyclical abdominal pain and/ retention of urine evaluation and management should be done immediately. Proper diagnosis of cause of primary ammenorhea is essential for planning of treatment and future pregnancies of the patient.

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