Bangladesh J Obstet Gynaecol, 2025; Vol. 40(1): 30-42

Review Article

Primary Amenorrhea in Adolescents: A Narrative Review

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Abstract

Introduction: *Puberty is a transition that a girl undergoes into a reproductive woman, and its social effects are substantial. Any variation from the standard procedure might induce significant disappointment and anxiety. Primary amenorrhea denotes the lack of menarche and must be assessed about secondary sexual characteristics. Differential diagnosis may be classified according to gonadotropin levels. Conditions like Differences In Sex Development and Complex Obstructed Müllerian Duct Anomalies necessitate investigation and management at a specialised center with a multidisciplinary staff. Psychological assistance is essential throughout this procedure.*

Methods: *It is a narrative review. An electronic search was performed on MEDLINE and PubMed to identify relevant articles from 2000 to 2025. This narrative review focuses on primary amenorrhea and the best practical approach for evaluation and management of affected adolescent females.*

Conclusion: *Primary amenorrhea is an uncommon reason for adolescents to pursue medical consultation. Failure to detect and treat primary amenorrhea can have serious emotional, physical, and health effects. Primary amenorrhea acts as a diagnostic indicator rather than a definitive diagnosis, required further investigation and treatment of the underlying causes by physicians. This research seeks to delineate primary amenorrhea, explore its prevalence, and analyze its etiology, differential diagnosis, and potential treatments.*

Keywords: *Amenorrhea; Adolescents; Primary Ovarian Insufficiency; Hypogonadotropic Hypogonadism; Turner Syndrome.*

Introduction

Puberty represents the coordinated onset of mature functions in the hypothalamus, pituitary gland, gonads, adrenal glands, and uterus. The sequence of physical events has been thoroughly characterized by Tanner. Menarche represents one of the final stages of female reproductive function development.[1] Amenorrhoea means the absence of menstrual periods. Primary amenorrhea is defined as the absence of menses by 14 years of age in the absence of growth or development of secondary sexual characteristics, or the absence of menses by 16 years of age, regardless of normal growth and development, including secondary sexual characteristics.[2,3] The prevalence of the disease in women is less than 1%.[2,4] For a normal menstrual cycle to occur, the following are required:

- Normal functioning hypothalamus: GnRH secreted by hypothalamus
- Normal functioning pituitary glands: hormones secreted from anterior pituitary FSH, LH
- Normal functioning ovaries: synthesis of oestrogens and progesterone. The entire spectrum of follicle development, ovulation and formation of corpus luteum occurs here
- Normal endometrial development: Endometrial lining which responds cyclically to stimulation by oestrogen and progesterone

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- An intact outflow tract: Essential for normal menstrual flow. It requires a patent outflow tract and continuity of the vaginal orifice, vaginal canal and endocervix with the uterine cavity. Any disruption in the above-mentioned departments can result in amenorrhoea.[5-7]

Methodology

A literature search was performed on the electronic databases, including Medline and PubMed, from 2000 to 2025, to identify all relevant studies and reviews. A combination of the search terms included "menstrual, primary amenorrhea, gonadal dysgenesis, polycystic ovary, eating disorder, and adolescent". In this narrative review, we pursue an extensive description and interpretation of previously published writing on primary amenorrhea in adolescents. The reference list also included studies identified manually and studies referenced for other purposes.

An aetiological classification can be derived based on the defects in the following 4 compartments.(7,8)

- Compartment I- Disorders of the outflow tract (uterus and vagina) (Eugonadotrophic amenorrhoea ,FSH & LH -normal)
- Compartment II- Disorders of the ovary (Hypergonadotropic amenorrhea ,FSH &LH'!)
- Compartment III- Disorders of the anterior pituitary (Hypogonadotrophic amenorrhoea FSH/LH "!
- Compartment IV- Disorders of the CNS. (Hypo gonadotrophic amenorrhoea , FSH/LH "!)

Compartment I: Disorders Of The Outflow Tract (Uterus And Vagina)

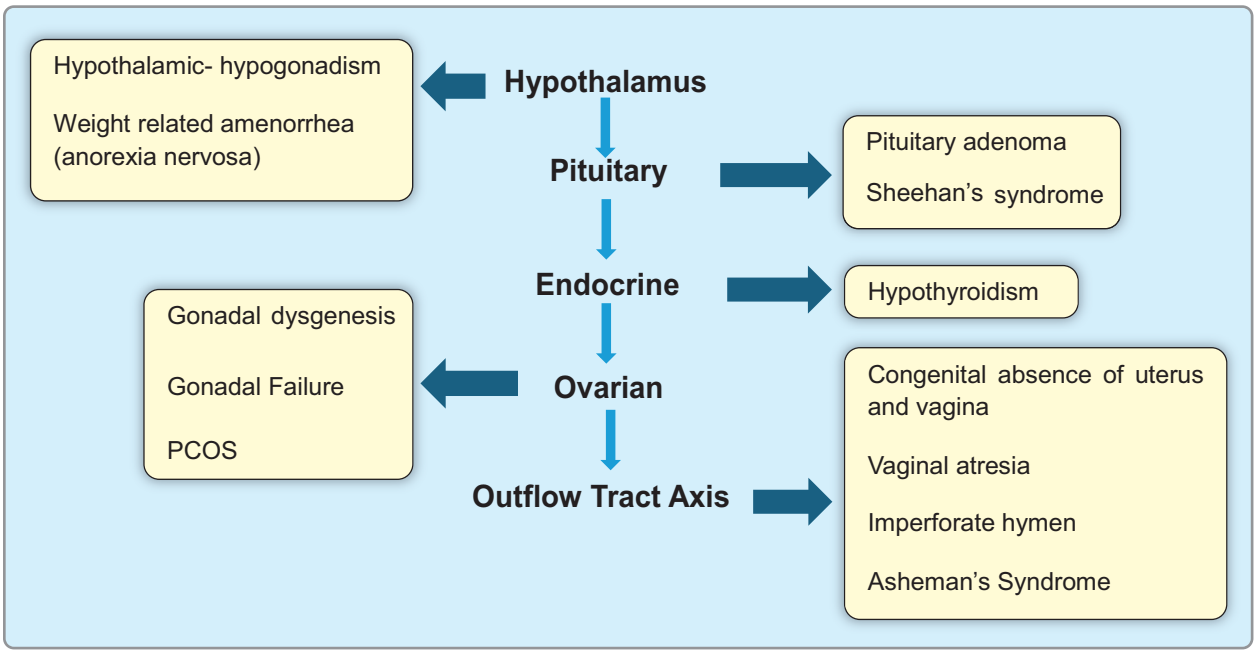
Clinically- Present Breast + Absent uterus.

It includes

- Mullerian agenesis
- Imperforate hymen
- Transverse vaginal septum
- Cervical agenesis
- Androgen insensitivity syndrome
- 5 alpha reductase deficiency
- Asherman's syndrome.

Mullerian agenesis Mayer Rokitansky Kuster Hauser (MRKH) syndrome

Affects 1 in every 4500 female births.(9) Its occurrence is usually sporadic. 46, XX, normal female phenotype and height. Ovarian tissue functions normally; therefore, typical secondary sexual characteristics. Müllerian ducts fail to fuse. Uterine development is rudimentary or absent, with uterine remnants.(10) Vaginal agenesis with short and blind ending vagina.



Flow Chart 1: *Etiology of Primary(56) amenorrhea*

External genitalia appear normal but vagina is short and blind. There may be associated renal anomalies (20%) and skeletal anomalies (12%).[11,12] Diagnosis is confirmed by ultrasound and karyotyping. Treatment is usually delayed until the patient is ready to start sexual activity. Most of them need vaginoplasty just before the commencement of sexual activity. (10)For Sexual function non surgical procedure is – gradual dilatation of vagina (Vecchetti procedure) and surgical procedures to create neovagina are – McIndoe vaginoplasty, tissue expansion vaginoplasty, Williams vaginoplasty. Since ovulation is normal in these girls, oocytes can be retrieved and surrogacy is an option for future fertility.[13,14]

Imperforate hymen Imperforate hymen

Imperforate hymen is a congenital obstructive abnormality of the female genital tract. The incidence is documented as 1 in 2000 female births.(15) Girls are typically presented to emergency services with complaints of recurrent episodes of cyclical lower abdominal pain, dysuria, and occasionally, acute urinary retention. Post-menarche, blood accumulates behind the imperforate hymen, leading to haematocolpos, haematometra, and haematosalpinx, which cause cyclic symptoms. A palpable lump may be present in the lower abdomen upon examination. On genital inspection, visible haematocolpos with a bulging purple/blue, stretching thin hymen at introitus is noticed, a hallmark of the condition. USS may show haematometra and hematocolpos. The definitive therapy is hymenotomy or hymenectomy, typically performed by a cruciate incision.

Transverse vaginal septum Transverse vaginal septum (TVS)

Transverse vaginal septum (TVS) is an uncommon disorder arising from defects in the vertical fusion of the vaginal elements of the Mullerian ducts and the urogenital sinus. There is persistence of the vaginal plate after it meets the Müllerian tract.[11] The reported incidence is 1 in 50,000 to 70,000 females.[16] The septum typically exhibits variability in thickness and can be situated at various levels within the vagina, however it is most frequently observed in the upper and mid-vaginal regions. Clinically, these females exhibit cyclic lower abdominal pain, and occasionally, there may be a palpable lump in the lower abdomen. Accumulation of menstrual blood that distends structures above the septum leads to haematocolpos and haematometra. Vaginal examination reveals a shortened, blind vaginal pouch. TVS is sometimes associated with imperforate anus, bicornuate uterus, coarctation of the aorta, atrial septal defect, and lumbar spine malformations in 37-60% of affected females. The preferred treatment for this is the excision of the vaginal septum with the risk of annular constriction. [17]

Cervical agenesis

According to American fertility society classification, cervical agenesis, classified as type I B Mullerian anomaly, results from abnormal fusion of the Mullerian ducts with the urogenital sinus, or atrophy of a segment of normally formed Mullerian system. The prevalence of cervical agenesis is 0.01% in the general population. It constitutes around 3% of all uterine abnormalities. Cervical agenesis is rarely associated with a functioning uterus and presence of vagina. 4.8% of women with cervical agenesis have functioning uterus and present with hematometra. Attempts at correcting using Foley's catheter through cervical canal usually fail. Following multiple tries, a hysterectomy may ultimately be necessary.[18]

Androgen insensitivity syndrome

Androgen Insensitivity Syndrome (AIS) is an inherited X-linked condition characterized by a 46 XY karyotype. Individuals with AIS have testes that produce normal concentrations of androgens for their age. The primary issue in AIS is the absence of cytosolic androgen receptors, which are essential for the effects of testosterone.(19) The testes produce testosterone and Mullerian inhibiting factor (MIF), which prevents the development of Mullerian structures, resulting in the absence of a uterus. A hallmark of AIS is the feminization of external genitalia at birth. Individuals typically show adequate breast development; however, there is little to no axillary or pubic hair growth during puberty. The testes may be in the abdominal cavity, labia, or inguinal canal. To prevent testicular malignancy, the removal of the testes is typically recommended after puberty, once feminization is complete.[20,21] Alternatively, prepubertal gonadectomy may be performed alongside estrogen replacement therapy. Many individuals with AIS will also have a short vagina, and vaginoplasty may be considered if necessary. It is best if the diagnosis of AIS is explained to the affected individual and family in an empathic environment with both professional and family support.[22,23]

5α reductase deficiency

This condition is an autosomal recessive, sex-limited disorder with a karyotype of 46 XY. Patients present with ambiguous genitalia, including a clitoris-like phallus, bifid scrotum, pseudovaginal perineoscrotal hypospadias, and a rudimentary prostate. The absence of a uterus and fallopian tubes is due to normal Müllerian inhibiting substance secretion. While the testes are usually intact and located in the inguinal canal or scrotum, Wolffian duct differentiation occurs normally, resulting in seminal vesicles, vasa deferentia, epididymides, and ejaculatory ducts that terminate in a blind vaginal pouch. Some patients may experience pubertal gynecomastia, though their serum testosterone and estrogen levels resemble those of typical males. Effective education for parents and patients is crucial to address developmental anomalies and the long-term impacts of gender assignment. A gonadectomy is recommended to prevent or minimize virilization, while estrogen replacement therapy is essential for inducing and maintaining feminization during puberty, ensuring the best outcomes for physical and psychological well-being.(20,24)

Compartment II (Disorders Of Ovary)

Clinically-Absent breast + Present uterus

It includes

- Gonadal dysgenesis
- Pure gonadal dysgenesis
- Mixed gonadal dysgenesis
- Resistant ovary syndrome
- Premature ovarian failure
- Enzyme deficiencies: 17 á hydroxylase, aromatase

Gonadal dysgenesis

Gonadal dysgenesis refers to a range of disorders characterized by impaired development of indifferent embryonic gonads into fully differentiated gonads.[19,25] This group includes pure gonadal dysgenesis (such as 46, XX or 46, XY, known as Swyer syndrome), mixed gonadal dysgenesis (which may present as a mosaic of 45,X0/46,XY, among others), and Turner syndrome.[20,26,27]

Turner syndrome

Turner syndrome is the most common cause of delayed puberty and primary amenorrhea, occurring in approximately 1 in 2,500 to 1 in 3,000 live-born girls. The karyotype of these girls is typically 45X. Turner mosaics may present with karyotypes of 46XX/45X or 46XY/45X. Girls with mosaic Turner syndrome may have normal menstrual periods initially but may later develop premature ovarian failure.[28,29]

Classic features of Turner syndrome include short stature, a webbed neck, cubitus valgus, a low hairline, a shield-shaped chest, and widely spaced nipples. Associated cardiovascular abnormalities may include coarctation of the aorta and bicuspid aortic valves. Other potential complications include renal abnormalities and autoimmune hypothyroidism. Karyotyping of the blood is the definitive method for diagnosis in most cases.

Early initiation of growth hormone therapy may help increase height for Turner syndrome patients with short stature. This therapy, started at ages 5 or 6 and continued until about 15 or 16, involves daily injections that can help increase height by approximately 5 cm (about 2 inches). The National Institute for Health and Care Excellence (NICE) has guidelines on somatropin, a growth hormone used for Turner syndrome, which can also increase height by around 5 cm. Treatment is personalized based on discussions between the specialist, the girl, and her parents. Somatropin should be stopped if there is insufficient growth, the girl nears her final height, experiences side effects, or reaches her final height. Oestrogen and progesterone therapy may be recommended, as these hormones are essential for female sexual development.[28,30] Girls with Turner syndrome may not undergo puberty often and adequately require hormone treatment until around age 50 when menopause occurs. Oestrogen therapy typically starts around age 11 and may be initiated earlier in increasing doses to simulate natural puberty. It can be given as a gel, tablet, or patch. Progesterone therapy is generally introduced after oestrogen to establish menstrual cycles.[30,31]

Most women with Turner syndrome are infertile, but some may conceive naturally. Assisted techniques like egg donation and IVF can be options for those wishing to have children.[32] Pregnant women with Turner syndrome will need regular heart check-ups due to increased strain on the heart. Some girls and women with Turner syndrome may face psychological challenges, such as low self-esteem or depression, often linked to social interactions. Counseling or cognitive behavioral therapy (CBT) may be beneficial. While most girls with Turner syndrome have normal

intelligence, some may face learning difficulties. Seeking help from a psychologist and engaging with schools can provide the necessary support for their educational needs.[30,33,34]

Pure gonadal dysgenesis

Individuals affected by Swyer syndrome are typically phenotypic females with streak gonads and no chromosomal abnormalities. Their karyotype may be either 46XX or 46XY. In cases with an XY karyotype, it is recommended that the gonads be surgically removed. Swyer syndrome is linked to a mutation in the SRY gene, which leads to dysgenetic testes that do not produce testosterone or anti-Müllerian hormone. Consequently, the Müllerian duct persists, and the patient may develop a rudimentary uterus and vagina.[35-37]

The management of Swyer syndrome often requires a coordinated effort from a team of specialists, including pediatricians, endocrinologists, urologists, psychiatrists, and other healthcare professionals. Comprehensive planning is essential to ensure the best treatment outcomes for individuals affected by this condition. Swyer syndrome is typically treated with estrogen replacement therapy, which is often combined with progestin after one to two years of continuous estrogen use. This approach helps induce the development of secondary sexual characteristics, initiates a pubertal growth spurt, and promotes optimal bone mineral accumulation. (38)The timing of hormone therapy is crucial; early initiation is recommended to maximize opportunities for breast development, pubic hair growth, and other normal aspects of puberty. However, for females without a uterus, there is no evidence supporting the benefit of adding cyclic progesterone.

Individuals with Swyer syndrome are at an increased risk of developing gonadal malignancies due to gonadal dysgenesis. Therefore, regular screening and gonadectomy in early childhood are recommended to prevent the occurrence of gonadal tumors. Living with Swyer syndrome can be challenging, as it may impact an individual's self-image and identity. Counseling and support groups can be valuable resources, helping individuals navigate emotional and psychological issues related to gender identity and gender role determination.[39]

Mixed gonadal dysgenesis

Patients have streak gonads on one side and malformed testes on the other side. They will have ambiguous genitalia. A mutation in the SRY gene is considered one of the aetiologies. Mild undervirilisation need Orchidopexy, regular self-examination (every 3 months) and ultrasound (annually) from puberty onward, one prepubertal biopsy (ideally between ages 1 and 9 yr or in combination with an orchidopexy procedure) and one post pubertal biopsy (e.g. at 17-25 yr of age) to assess tumor risk by specialised immunohistochemistry, in case of premalignant changes (OCT3/4 positive cells on the basal lamina/ expression of SCF/presence of UGT) or in situ neoplasia: gonadectomy (or irradiation?)[35,40,41]. in case of ambiguous genitalia Low threshold to perform gonadectomy (e.g. insufficient hormone production necessitating hormone replacement therapy; impossibility to bring the gonad in a stable scrotal position; suspicion for malignancy on physical examination or ultrasound; immunohistochemical abnormalities related to pre-CIS lesions, such as OCT3/4 positive cells on the basal lamina or positive stem cell factor staining; or presence of UGT on the biopsy). For female phenotype, consider elective gonadectomy (if the patient is reluctant to undergo gonadectomy, consider leaving the gonads in place and discuss possible effects of hormone production during puberty). Cryopreservation may be considered.[40,41]

Resistant ovary syndrome

Resistant Ovary Syndrome (ROS) is a rare endocrine disorder characterized by hypergonadotropic hypogonadism, also known as Savage syndrome. Individuals with ROS have a normal female karyotype and display a female phenotype.(42,43) In this condition, there is an elevated plasma level of follicle-stimulating hormone (FSH), but the ovaries contain primordial follicles that are resistant to the effects of gonadotropins. In vitro fertilization (IVF) using donor oocytes is the only available treatment option for those with ROS.[44]

Enzyme deficiencies

17á-hydroxylase deficiency and aromatase deficiency are conditions that result in the absence of sex steroid production, leading to delayed puberty. Individuals with 17á-hydroxylase deficiency can have a karyotype of either 46XX or 46XY. In those with a 46XY karyotype, the uterus is absent.[45] Children with 17á-hydroxylase deficiency often experience hypernatremia, hypokalemia, and hypertension due to increased production of mineralocorticoids. As a result, they

require corticosteroids in addition to estrogen and progesterone for treatment. In the case of aromatase deficiency, there is an elevated level of androgens, which may cause female children to experience virilization, leading to ambiguous genitalia and primary amenorrhea.[20,46]

Compartment III (Disorders of Anterior Pituitary)

It includes Congenital disorders like Hypopituitarism and Isolated FSH deficiency.

Acquired disorders include pituitary adenomas (macroadenoma), drug induced hyper prolactinemia, hypothyroidism, empty sella syndrome.

Hypopituitarism

Congenital panhypopituitarism presents early in childhood, resulting in amenorrhea due to a deficiency of gonadotropins.[20]

Isolated FSH deficiency

An extremely low serum FSH concentration characterizes isolated FSH deficiency due to a mutation in the FSH β subunit. True isolated FSH deficiency presents as idiopathic hypogonadotropic hypogonadism and is a rare cause of primary amenorrhoea. Individuals with this condition exhibit high levels of LH and low levels of FSH, and treatment involves administering exogenous FSH. the combination therapy of FSH replacement and assisted reproductive technology (ART) could be effective treatments for infertility in patients with *FSH*β mutations.[44]

Hyperprolactinemia

Hyperprolactinaemia is the most common pituitary cause of amenorrhoea, although it is not frequently seen in adolescents with primary amenorrhoea. This condition occurs due to the development of a tumor, specifically a microadenoma (less than 10 mm), which leads to the overproduction of prolactin. Additionally, the mass effect of the tumor disrupts the tonic inhibition normally exerted by hypothalamic dopamine. Up to 30% of patients may experience associated galactorrhea, while only about 5% may have visual field defects. The diagnosis is typically made through serum prolactin measurements and pituitary imaging, such as MRI, which are both sensitive and specific.

For management, a conservative approach involves the use of dopamine agonist medications. Bromocriptine, for example, is usually started at a dose of 1.25 mg per night for the first five nights, with a gradual increase up to 7.5 mg daily, taken in two or three divided doses over approximately three weeks. Due to potential long-term side effects, cabergoline is often preferred. Cabergoline (0.25-1 mg administered twice weekly, up to 1 mg daily) is longer-acting and tends to be better tolerated by many patients. Surgery, specifically transsphenoidal resection of the adenoma, is reserved for patients who experience intolerable side effects from medication, for non-functioning macroadenomas, or for cases where there is suprasellar extension that has not resolved with medical therapy.

Empty Sella syndrome

This benign condition arises due to the congenital absence of the sellar diaphragm. It can also occur following surgery, radiotherapy, or the development of a tumour. Usually manifests as hyperprolactinemia. [47]

COMPARTMENT IV (DISORDERS OF HYPOTHALAMUS)

It includes Congenital Kallmann syndrome, anorexia nervosa, extreme exercise, stress, and obesity, excessive secretion of hormones, and constitutional delay.[47]

Congenital Kallmann syndrome

This rare familial disorder affects about 1 in 50,000 individuals and is characterized by a deficiency in gonadotropin-releasing hormone (GnRH), often leading to anosmia or hyposmia. The karyotype is typically 46XX. Importantly, since the gonads are responsive to gonadotropins, ovulation can be induced with exogenous gonadotropins, providing promising reproductive options.

Anorexia nervosa

It is a rare cause of primary amenorrhoea. A normal phenotypic and underdeveloped secondary sexual characteristics are present in the affected individuals. Addressing the underlying cause of this issue is essential for treatment. In cases of eating disorders, this process can reveal significant psychological conflicts and distorted body image.[48,49]

Effective treatment requires identifying the underlying cause, which can reveal significant psychological issues, particularly in the context of eating disorders, extreme exercise, or stress.[50]

Extreme exercise, stress

These are functional disorders of the hypothalamic-pituitary axis. There is decrease in GnRH activity in the hypothalamus, resulting in decrease in gonadotropins.[51,52]

Constitutional delay

It is considered as a retrospective diagnosis. The individuals have a delayed maturation of HPO axis.(51) Their bone age is also delayed. The difference of delay is not more than 1 year of chronological age. Follow up is needed to confirm the diagnosis.[53]

DIAGNOSTIC WORKUP

When a girl with primary amenorrhoea comes, the diagnosis can be made with the aid of (14)

- History
- Physical examination
- Imaging studies
- Hormonal evaluation
- Karyotyping

Table-I

History taking in an adolescent PA(24)

History	
Age	H/o Siblings age at menarche
Growth chart (if available)	Maternal age at menarche
Age at onset of thelarche	Neonatal/childhood encephalitis
Cyclic abdominal pain	Inguinal/abdominal surgery
Any disorder of smell perception	Prior radiotherapy/ chemotherapy.
Family history	

Table-II

Examination of an adolescent PA (24)

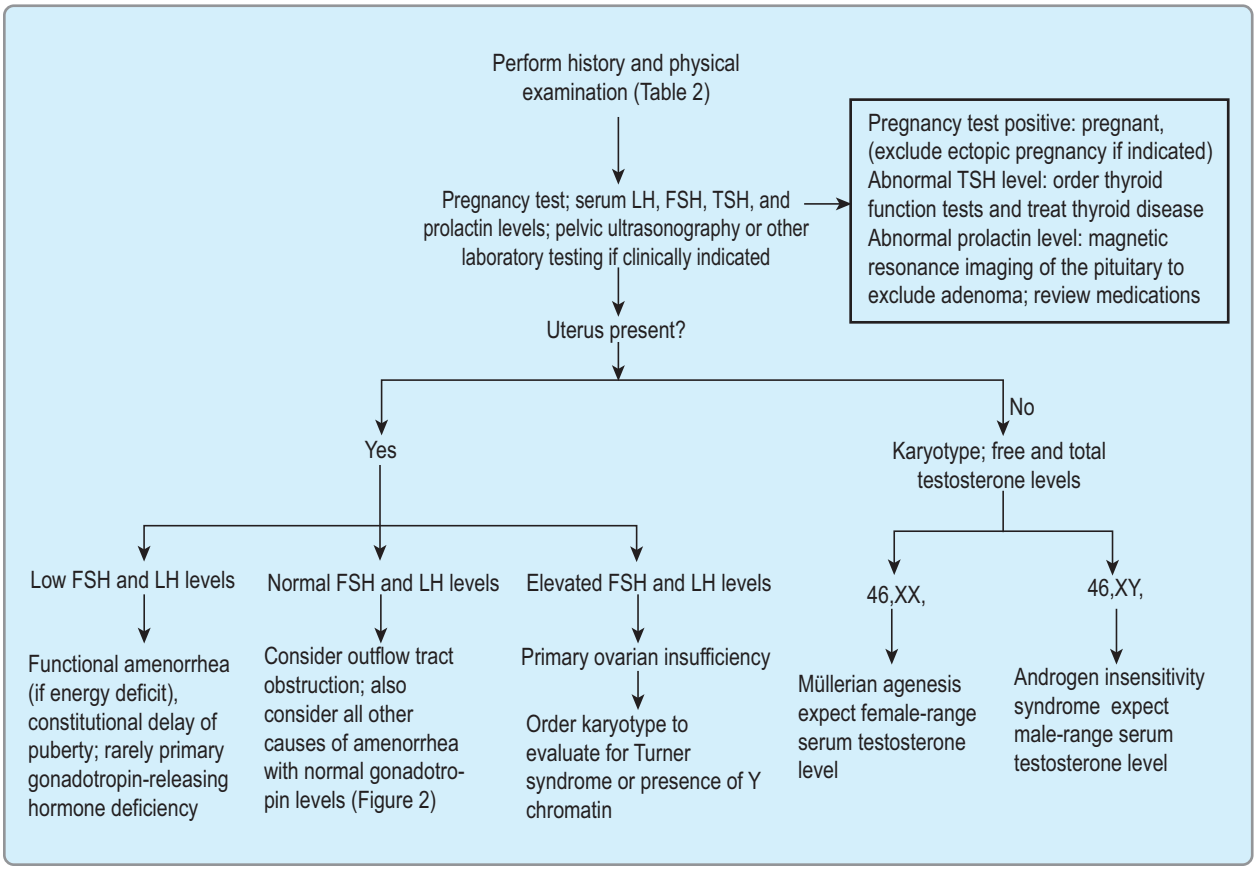
Examination of the adolescent with primary amenorrhoea	
General	Weight, height, body mass index
	Blood pressure
	Clinical thyroid status
	Dysmorphic signs
	Tanner's breast, axillary, and pubic hair stages
	Arm span/upper & lower segment ratio
	Features of Turner's syndrome
Abdomen/pelvis	Mass arising from pelvis
	Groin nodes/herniae
Perineum	Inspection is often all that is required, especially in the non-sexually active. Note presence and distribution of pubic hair, clitoral size, configuration of hymen, relationship of anus, vagina and urethra to hymen, the degree of oestrogenisation and perineal hygiene. The hymen and vestibule may be visualised with gentle lateral spread of the labia majora with two fingers and a deep inspiration/Valsalva manoeuvre by the patient. Depth of vagina/bulging bluish membrane

Table-III

Investigations of an adolescent PA (24)

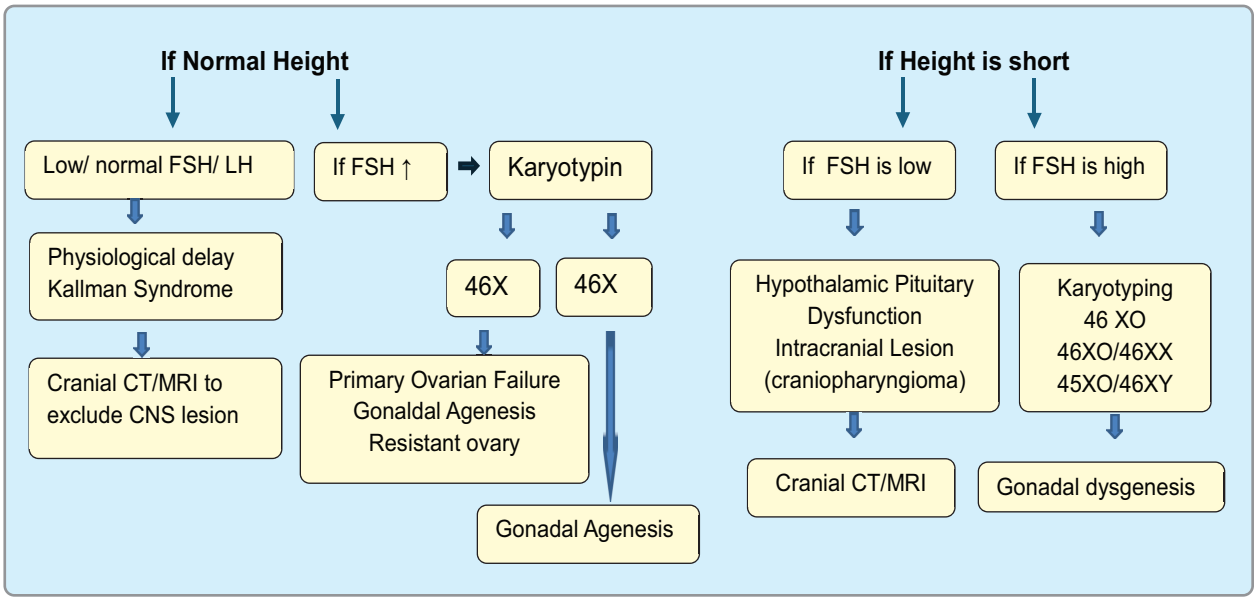
Investigation	**Interpretation**
Urine pregnancy test negative	Rule out pregnancy
Ultrasound scan	Transabdominal route in non-sexually active to identify presence of uterus, cervix and upper vagina (rules out Müllerian agenesis), and ovaries (rules out gonadal agenesis). An endometrial stripe indicates oestrogen responsiveness (making PCOS more likely than hyperprolactinaemia which is an oestrogen-deficient state)
Serum prolactin concentration (normal range <500 mU/L)	Cause and typical prolactin level Stress/recent breast examination: <1000 mU/L Hypothyroidism/PCOS: 700−2500 mU/L Non-functioning macroadenoma: <3000 mU/L Functioning microadenoma: 1500−4000 mU/L Functioning macroadenoma: 5000−8000 mU/L Levels >1500 mU/L warrant further assessment of the pituitary fossa
Serum TSH and T4 Concentration (normal range: TSH 0.2−6.0 mU/L, free T4 12−27 nmol/L)	Raised TSH (and TRH) due to malfunctioning (low free T4) thyroid hormone feedback (usually autoimmune or inflammatory) interferes with tonic dopamine inhibition of prolactin
Serum D_3 FSH (3 to 10 IU/L)	Low levels (<2 IU/L) suggest hypothalamic failure FSH levels >15 IU/L (outside an ovulatory surge) suggest impending ovarian failure and >40 IU/L confirm ovarian failure
Serum D_3 LH (2 and 8 IU/L)	LH elevation in isolation (outside an ovulatory surge) can suggest PCOS
Karyotyping	MRKH-46XX Turner's-45XO AIS-46XY Gonadal dysgenesis-46XX, 46XY .
Imaging studies	USG: Presence/absence of uterus HSG/SIS: Uterine synechiae CT/MRI: Hypothalamic/pituitary cause.
TSH: thyroid stimulating hormone; free T4: free thyroxine; TRH: thyrotropin releasing hormone; FSH: follicle stimulating hormone; LH: luteinising hormone; CAH: congenital adrenal hyperplasia	

Normal secondary Sexual Characters (SSC)



Flow Chart 2 : *Investigations and their association with an adolescent PA(56)*

Poor or absent secondary sexual characters (SSC)



Flow Chart 3: *Investigations and their association with an adolescent PA based on SSC & height (56)*

Treatment Of Primary Amenorrhoea

Objective

- To initiate full reproduction potential for those in whom it is possible.
- In whom fertility is not possible appropriate surgical /medical management to allow adequate physical development & normal coital relations

Correction of short stature.

- Anabolic steroids
- Human growth hormone and oxandrolone – growth hormone should be started before use of oestrogen progesterone i.e before epiphyseal closure
- Exogenous gonadotrophins –to induce ovulation if pregnancy is desired.

Correction of sexual infantilism by exogenous steroid to induce secondary sexual characters. Possible regimens.

- Combined oral pill (50 Mg of ethinyl cyclical estradiol + progesterone) may take 2-3 yrs. or
- Estradiol Velerate + progesterone 1-2 mg /days for 21 days + medroxy progesterone acetate 10mg for last 10 days = continuous.

When to start hormone treatment? No consensus. After puberty so that all sorts of potential growth is achieved. Before puberty, the acceleration of development / secondary sexual characteristics occurs well.

Surgical treatment

Surgical treatment is required in Craniopharyngioma, Pituitary tumour, Galactorrhea – Prolactinoma, 46XY karyotype or 46XY mosaics (Surgical removal of testicular tissue both normal or streak-gonad to prevent malignancy), 5-á reductase deficiency or absent antimullerian factor (Gonadectomy -to avoid the unpleasant virilizing effects of usual androgen at puberty in an individual brought up as a female). In Isolated vaginal atresia, Uterovaginal atresia, 5- á reductase deficiency or Androgen end organ defect (Construction of an artificial vagina): Vaginoplasty. Cryptomenorrhea –hymenectomy or abdominal route in a high variety.

Pregnancy

Primary ovarian failure, Turner's syndrome & in Gonadal Agenesis by oocyte donation

Conclusion

Although primary amenorrhea is uncommon, it can present significant diagnostic challenges. Using a systematic approach can aid in identifying potential causes related to embryology, anatomy, or endocrinology. A comprehensive evaluation of estrogen levels, hypothalamic function, and the presence of Müllerian structures is crucial for an accurate diagnosis. In some complex cases, a multidisciplinary team best manages the adolescent, including a pediatrician, endocrinologist, gynecologist, geneticist, surgeon, radiologist, and psychologist. Primary amenorrhea XY adolescents with a female phenotype are considered non-exceptional and should be managed at reference centers. Next-generation sequencing for gene screening should be offered to all adolescents with amenorrhea and idiopathic primary ovarian insufficiency (POI).(54,55) Attention should be focused on pubertal development, anatomical considerations, and future fertility. Timely diagnosis and treatment are essential, as delays can harm long-term health and reproductive potential.

Conflicts Of Interest: No potential conflict of interest relevant to this article was reported.

Funding: No funding sources

Ethical approval: Not required

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