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CASE SERIES OF PRIMARY AMENORRHOEA

Obstetrics & Gynaecology

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ABSTRACT

INTRODUCTION: Amenorrhoea is absence of absence of menstruation. Amenorrhea can be a transient, intermittent, or permanent condition resulting from dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina. It is often classified as either primary (absence of menarche by age 15 years or thereafter) or secondary (absence of menses for more than three months in girls or women who previously had regular menstrual cycles or six months in girls or women who had irregular menses). Primary amenorrhea, seen in approximately 2.5% of the population, is clinically defined as the absence of menses by age 13 years in the absence of normal growth or secondary sexual development; or the absence of menses by age 15 years in the setting of normal growth and secondary sexual development. However, at age 13 years, if the girl has not menstruated and there is a complete absence of secondary sexual characteristics such as breast development, evaluation for primary amenorrhea should also begin.

- **CASE 1:** 20year old phenotypically appearing female admitted with primary amenorrhoea for further management.
- k/c/o DM since 2 years, on OHA
- Underwent bilateral gonadectomy , final HPE report features are of focal spermatogenesis
- Karyotyping showed 46XY

In patients who develop virilization and have a XY karyotype, the gonads should be removed immediately to preserve the female phenotype and female gender identity. The patients with CAIS should be followed up after gonadectomy as they have the signs and symptoms of postmenopausal woman. Therefore, oral conjugated estrogen or transdermal estrogen should be administered for relieving these symptoms.

- **CASE 2:** A 25year old female was referred to father muller hospital in view of primary amenorrhoea and outside scan showed absent uterus with streak gonads.

Karyotyping showed MOS 45, X0(17)/46, X, r(x)
MRI brain -pituitary showed small size for age.
Patient was started on HRT to maintain secondary sexual characteristics and prevention of osteoporosis.

- **CASE 3:** 17year old phenotypically appearing female was referred in view of primary amenorrhoea and for further management.

Retro-positive status

- She underwent bilateral gonadectomy , final HPE report features are suggestive of testicular regression favours testicular feminisation syndrome.

Karyotyping showed 46XY

- **CASE 4:** 20year old came with primary amenorrhoea with delayed development of secondary sexual characteristics.

Karyotyping showed 46XY.
She underwent laparoscopic bilateral salphingogonadectomy. HPR reported as gonadoblastoma with dysgerminoma.

- **CASE 5:** 16year old phenotypically appearing female admitted with primary amenorrhoea for further management.
  k/c/o seizure disorder
  Underwent bilateral gonadectomy with clitorectomy, final HPE report features are of spermatogenesis
  Karyotyping showed 46XY

CONCLUSION: Early recognition and appropriate investigations will help in improving the quality of life.

- Counselling of both patient and their parents should be done and infertility and reproductive options must be discussed.
- Karyotyping is definitely to be done for evaluation for appropriate counselling.

KEYWORDS

INTRODUCTION

Amenorrhoea is absence of menstruation. Amenorrhea can be a transient, intermittent, or permanent condition resulting from dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina. It is often classified as either **primary** (absence of menarche by age 15 years or thereafter) or **secondary** (absence of menses for more than three months in girls or women who previously had regular menstrual cycles or six months in girls or women who had irregular menses). Primary amenorrhea**,** seen in approximately 2.5% of the population, is clinically defined as the absence of menses by age 13 years in the absence of normal growth or secondary sexual development; or the absence of menses by age 15 years in the setting of normal growth and secondary sexual development. However, at age 13 years, if the girl has not menstruated and there is a complete absence of secondary sexual characteristics such as breast development, evaluation for primary amenorrhea should begin [1].

In general, the first menses should occur within 2–3 years after the initiation of pubertal development. In most young girls (approximately 80%), the first sign of puberty is an acceleration of growth, followed by breast budding (thelarche), and the appearance of pubic hair (adrenarche). In the remainder (approximately 20%) adrenarche precedes thelarche by a brief interval, but the two events typically are closely linked [6].

Primary amenorrhea is usually the result of a genetic or anatomical abnormality.

The most common etiologies were [3]:

- Gonadal dysgenesis, including Turner syndrome – **43 percent**
- Müllerian agenesis (absence of vagina, sometimes with absence of uterus) – **15 percent**
- Physiological delay of puberty (constitutional delay of puberty, chronic systemic disease, acute illness) – **14 percent** (constitutional delay of puberty is common in boys but uncommon in girls)
- Polycystic ovary syndrome (PCOS) – **7 percent**
- Isolated gonadotropin-releasing hormone (GnRH) deficiency – **5 percent** (extremely rare, the incidence in females based upon a national hospital database was only 1 out of 125,000)
- Transverse vaginal septum – **3 percent**
- Weight loss/anorexia nervosa – **2 percent**
- Hypopituitarism – **2 percent**

The less common etiologies (≤1 percent each) include imperforate hymen, complete androgen insensitivity syndrome, hyperprolactinemia /prolactinoma, other pituitary tumors, congenital adrenal hyperplasia, hypothyroidism, central nervous system defects, craniopharyngioma, and Cushing's disease.

Causes of primary amenorrhea can be classified according to WHO as:

- **Hypogonagotropic hypogonadism (Group I):**

Decreased estrogen, normal or low FSH, and no lesion in hypothalamic pituitary region.

1. Physiologic delay.

2. Kallman syndrome (Hypothalamic Failure).
3. CNS tumors.
4. Hypothalamic /pituitary dysfunction

- **Hypergonadotrophic hypogonadism (Group II):**

Decreased estrogen but increased FSH.

1. Gonadal dysgenesis
2. Turner Syndrome
3. Transverse vaginal septum
4. Imperforated hymen.

- **MATERIALS AND METHODS:**

Five individuals with primary amenorrhea who were referred to FMMCH, Mangalore, were included in the study.

CASE STUDIES

	Case 1	Case 2	Case 3	Case 4	Case 5
Age(years)	20	25	17	20	16
Chief complaint	Primary amenorrhoea	Primary amenorrhea	Primary amenorrhea	Primary amenorrhoea and delayed development of secondary sexual characters.	Swelling in the Groin
Associated medical history	DM and hypothyroidism	-	Retrovirus positive	History of tubercular lymphadenitis 3 years back	History of seizures in childhood

On examination

	Case 1	Case 2	Case 3	Case 4	Case 5
Height(cm)	190	138	168	152	165
Weight(kg)	95	50	66	44	71
Breast tanner stage	3	1	2	2	1
Pubic hair tanner stage	2	2	2	2	2
Axillary hair	Sparse	Sparse	Sparse	sparse	sparse
Associated findings	Acanthosis nigricans, arachnodactaly	Hyperpigmentation present on forehead & cheeks	Nil	Nil	High arched palate
External Genitalia	Well developed	Clitoris appears normal, Hymen visible	Well developed	Normal development of labia majora and minora. Hymen was intact	Well developed with clitoromegaly
Palpation	Gonads in labia majora	Nil	Gonads in left groin	no swelling felt	Swelling in left labia majora

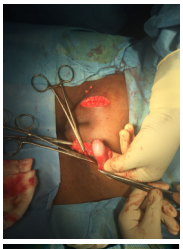
Investigations:

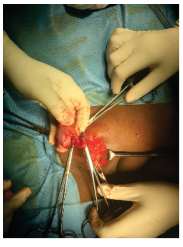
	Case 1	Case 2	Case 3	Case 4	Case 5
S. FSH (m IU/ml)	15.81	63.94	25.12	60.55	19.48
S. LH (m IU/ml)	45.70	13.91	32	30	16.69
S.Prolactin (mg/ml)	-	5.85	-	-	39.52
S.Testosterone (ng/ml)	0.202	0.085mg/ml	0.025	0.045	-
S.Estradiol(pg/ml)	12	<10	-	15	-
S. TSH (µg/dL)	14.37	1.06	2.04		1.51
USG	Absent uterus with gonads in labia majora	Absent uterus with streak gonads	Absent uterus and gonads in left groin	infantile uterus with streak gonads	Absent uterus with gonads in left labia majora
Karyotyping	46XY	Mosaic 45, X [17] / 46, X, r(x)(3)	46XY	46XY	46XY
Diagnosis	Complete androgen insensitivity syndrome	Turner mosaic syndrome	Complete androgen insensitivity syndrome	Swyer syndrome	Complete androgen insensitivity syndrome

Management

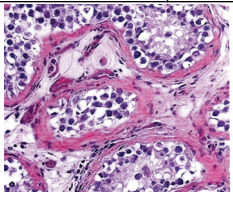
	Case 1	Case 2	Case 3	Case 4	Case 5
Treatment	Bilateral gonadectomy	HRT	Bilateral gonadectomy	Laparoscopic bilateral salphingogonadectomy	Bilateral gonadectomy Clitorectomy
HPR	Features of focal spermatogenesis	-	Complete androgen insensitivity syndrome	Gonadoblastoma with dysgerminoma and extensive calcification.	Complete androgen insensitivity syndrome

- **Case 1**





Bilateral gonadectomy

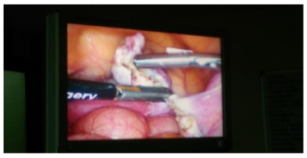


Histopathology showing spermatogenesis

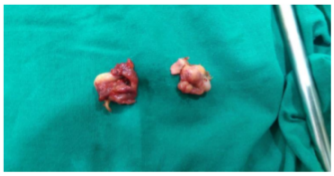
Case 2

Karyotyping report

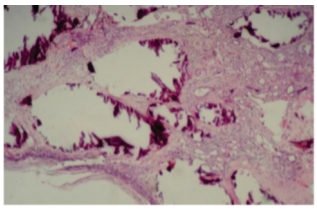
Case 3



Laparoscopic gonadectomy



Bilateral streak gonads with normal tubes



Histopathology showing Sertoli cell

DISCUSSION

The basic requirements for normal menstrual function include four anatomically and functionally distinct structural components-the genital outflow tract including the uterus, the ovary, the pituitary, and the hypothalamus. The evaluation of amenorrhea begins with a careful medical history and physical examination, which always provide valuable diagnostic clues.

The workup of primary amenorrhoea should be very meticulous including history, physical examination, hormone evaluation, pelvic imaging (either ultrasound or MRI).

Height, weight, and body mass index (BMI) should be determined and recorded. Short stature (less than 60 inches) and sexual infantilism are hallmarks of gonadal dysgenesis. Low body weight frequently is associated with hypothalamic amenorrhea resulting from poor nutrition (eating disorders, malabsorption syndromes) or physical, psychological, or emotional stress. Obesity or an increased waist-hip ratio (>0.85) are common features of women with PCOS.

Primary amenorrhea is evaluated by determining the presence or absence of uterus, the presence or absence of breast development (a marker of estrogen action and therefore function of the ovary, except in complete androgen insensitivity syndrome), and the serum follicle-stimulating hormone (FSH) level.

The defects have been compartmentalised and may lie within the uterus, ovaries, pituitary or hypothalamus. Genetic and chromosomal anomalies also contribute to a major portion of primary amenorrhoea especially in cases of gonadal failure.

Breast development is a reliable indicator of estrogen production or exposure to exogenous estrogens. The Tanner stage of breast development should be noted. A secondary arrest of breast development suggests a disruption of the hypothalamic-pituitary-ovarian (HPO) axis. When menarche has not followed breast development at the expected time, a developmental anomaly of the reproductive tract also should be considered. The presence of pubic hair growth reliably reflect androgen production or exposure.

- **Complete androgen insensitivity syndrome:**

Incidence ranging from 1/20,000 to 1/65,000 births. It comprises of 5% of cases of primary amenorrhoea [(2)].

Androgen insensitivity syndrome (AIS) was first reported and published in 1953 by

J. M. Morris, an American gynaecologist [(4)].

AIS is a rare X-linked recessive disorder of male pseudo-hermaphroditism hroditism.

Mutations in androgen receptor gene resulting in deficient action of androgens and therefore incomplete masculinisation. Approximately 40% of patients with complete AIS have no family history of the disorder [(5)]. Rarely recognised in infancy.

AIS have traditionally been classified into three clinical subgroups based on the genital phenotype [(4)]:

1.) Complete Androgen Insensitivity syndrome (CAIS): Individuals with CAIS have normal female external genitalia. They typically present either before puberty with swelling in the inguinal canal that are subsequently identified as testes or at puberty with primary amenorrhea and sparse to absent pubic or axillary hair. Sexual identity and orientation are unaffected.
2.) Partial androgen insensitivity syndrome (PAIS): Individuals with PAIS are predominantly female, predominantly male, or ambiguous genitalia. However affected individuals have signs of external genital masculinization including clitoromegaly or posterior labial fusion.
3.) Mild androgen insensitivity syndrome (MAIS): Individuals with MAIS having typical male genitalia. They usually present with gynecomastia at puberty. Spermatogenesis may or may not be impaired. In some instances, the only observed abnormality appears to be male infertility; therefore, MAIS could explain some idiopathic male infertility.

According to Quigley et al. [(6)], there are five grades of PAIS: in the first one there is normal female genital phenotype, with androgen-dependent pubic and/or axillary hair development at puberty; in the second grade, there is a female phenotype with mild clitoromegaly or small degree of posterior labial fusion; in the third grade, there are undifferentiated phallic structures intermediate between clitoris and penis, and the urogenital sinus presents perineal orifice and labioscrotal folds; the fourth grade is a predominantly male phenotype with perineal hypospadias, small penis, cryptorchidism or bifid scrotum; the fifth and last grade presents isolated hypospadias and/or micropenis [(6).]

Patients with complete AIS most commonly present after the age of puberty in late adolescence or in young adults with primary amenorrhea. They exhibit asymmetrical secondary sexual development (breast development with absent or scant pubic hair), a short vagina with no visible cervix and have no other complaints. They also may be recognized at birth or in childhood when they may present with an inguinal mass or hernia, particularly when the disorder is reasonably suspected because other family members such as a sister or maternal aunt are affected.

Diagnosed after puberty as a result of primary amenorrhoea or infertility phenotypically female while having 46 XY karyotype .

In patients with AIS, the options for creation of a neovagina with progressive vaginal dilation and vaginoplasty.

Gonadectomy is indicated because the incidence of neoplasia in cryptorchid testes is relatively high. 5–10% overall incidence of gonadal tumors.

It is better delayed in those with AIS, for two reasons. First, the smooth pubertal development that results from endogenous hormone production is difficult to achieve with exogenous hormone treatment, and second, gonadal tumors develop less often in patients with AIS and rarely before puberty. Therefore, gonadectomy and hormone therapy are best postponed until after pubertal development is complete, by approximately age 16–18 years [(5)].

- **Variant turners syndrome:**

Most women with Turner syndrome have primary amenorrhea and no pubertal development. However, some develop normally and later present with secondary amenorrhea. Approximately 15% of patients with Turner syndrome begin but do not complete pubertal development and approximately 5% complete puberty and begin menstruation.

Mosaicism in women with Turner syndrome has important clinical implications besides those relating to a cell line containing a Y chromosome. In those with a mosaic 46, XX cell line (e.g., 45, X /46,

XX), the gonad may contain functional ovarian cortical tissue, resulting in some degree of sexual development, or even menses and the possibility of pregnancy.

Successful pregnancies do occur in women with Turner syndrome and are associated with a relatively high risk for aneuploidy and spontaneous abortion [5].

Future fertility for patients with turner syndrome is an important consideration. Women with Turner syndrome who possess Y chromosome have an increased risk of germ cell tumours such as gonadoblastoma and dysgerminoma. Prophylactic gonadectomy is recommended for patients with Turner syndrome and Y chromosome material such as 45, X/46, XY mosaicism [7].

Oocyte donation and IVF offers the possibility of pregnancy to patients with Turner syndrome, but the cardiovascular effects of pregnancy pose unique and potentially serious risks that must be carefully considered. The risk of death during pregnancy is increased as much as 100-fold, primarily due to complications of aortic dissection or rupture. Risk increases with pre-existing abnormalities such as a bicuspid aortic valve or a dilated aortic root. Consequently, Turner syndrome generally should be regarded as a relative contraindication to pregnancy [5].

- **Swyer syndrome [5]:**

Swyer syndrome is an uncommon form of 46 XY gonadal dysgenesis, causing primary amenorrhoea. It is a form of pure gonadal dysgenesis. Despite the presence of a Y chromosome, the phenotype is female because the dysgenetic gonads produce neither AMH nor androgens. Consequently, the vagina, cervix, uterus, and fallopian tubes develop normally and the internal and external genitalia do not masculinize.

In 10–15% of affected individuals, one of the causes is mutation of the SRY gene [Sex-determining region of the Y chromosome; located on the short arm, Yp11.3] [5].

It occurs in 1/100000 people. The condition first becomes apparent in adolescence with delayed puberty and primary amenorrhoea.

Swyer syndrome can be differentiated from complete androgen insensitivity syndrome where the karyotyping is also XY, but there is absence of mullerian strutures, presence of testes in the path of its descent and high serum levels of testosterone.

The prompt diagnosis has a crucial importance like the early institution of hormone replacement therapy and close monitoring, because of the risk of gonadal malignancy. The major risk is the development of gonadoblastoma. The incidence of malignant gondoblastoma in patients with dysgenetic gonads is as high as 25 – 35%. The risk increases with age; it is reported that the risk is 50 – 70% in the third decade while being as high as 80% in the fourth decade. The overall survival is 90 to 100% in cases diagnosed in the early stages but decreases to 54% in those diagnosed in the advanced stages. Hence it is necessary to do early bilateral gonadectomy. Also, hormone replacement is necessary to prevent osteoporosis and for the development and maintenance of secondary sexual characters. Pregnancy achieved with in vitro fertilization using donor oocytes.

CONCLUSION:

Early recognition and appropriate treatment will help in improving the quality of life.

- Counselling of both patient and their parents should be done and infertility and reproductive options must be discussed.
- Karyotyping is definitely to be done for evaluation and for appropriate counselling. the need for early and prompt diagnosis in order to start hormone replacement therapy, to initiate and maintain puberty and the need for early gonadectomy to prevent malignancy. Also, we wish to highlight the psychosocial counseling of XY female on the girl as well as the family and the need to do karyotyping in girls presenting with primary amenorrhoea.

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