ORIGINAL ARTICLE

AETIOLOGY AND MANAGEMENT OF PRIMARY AMENORRHOEA

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Background: Amenorrhoea is absence of menstruation. It could be primary, if menstruation has not occurred by the age of 16 years in the presence of normal growth and secondary sexual characters or by the age of 14 years in the absence of secondary sexual characters. It is secondary if periods have not occurred for six months. This study was done with the objective to determine the frequency of etiologic causes of primary amenorrhoea. **Study Design:** Cross-sectional descriptive study. **Methods:** The study was conducted in the department of Obstetrics and Gynaecology Sheikh Khalifha Bin Zyed Al Nahyan /Combined Military Hospital Muzaffarabad Azad Jammu Kashmir (SKBZ/CMH MZD AJK) from December 2014 to November 2017. Women with primary amenorrhoea reported and managed in the hospital are included in the study. Cases were analysed according to clinical profile, development of secondary sexual characteristics, physical examination, pelvic and rectal examination, hormonal profile, pelvic ultrasound, magnetic resonance imaging and cytogenetic study including karyotyping. **Results:** Three most common causes of primary amenorrhoea were Mullerian anomalies (36.7%) followed by gonadal dysgenesis (33.3%), hypothalamic causes (23.3%) and Pituitary causes (6.7%). There were 03 cases of polycystic ovarian syndrome and 02 cases of hyperprolactinemia. **Conclusion:** The most common etiological factor leading to primary amenorrhoea is Mullerian anomalies followed by gonadal dysgenesis. Genetic and environmental factors could also play role in the causes of primary amenorrhoea.

Keywords: Primary amenorrhoea; Mullerian agenesis; Gonadal dysgenesis; Hyperprolactinemia

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INTRODUCTION

Amenorrhoea is absence of menstruation. Based on the previous occurrence of menses it is divided into primary or secondary. It is primary, if menstruation has not occurred by the age of 16 years in the presence of normal growth and secondary sexual characters or by the age of 14 years in the absence of secondary sexual characters.[1] It is secondary if periods have not occurred for six months.[2]

Amenorrhoea if not physiological has a prevalence of 1.8 to 3%; is an important cause of female infertility and affects 2–5% of all women in the reproductive age.[3,4] Normal regular menstruation requires a coordinated interaction between the hypothalamus, pituitary, ovaries and outflow tract. A disturbance at any level lead to amenorrhoea. Different compartments may be involved in occurrence of amenorrhoea.

Disorders of outflow tract includes congenital developmental defects of genital tract in which uterus may be absent with or without absent vagina like Mullerian agenesis (Mayer Rokitansky Kuster Hauser (MRKH) syndrome), lower vaginal aplasia (imperforate hymen) and transverse vaginal septum. Developmental defects may be of endocrine origin, includes testicular feminization or androgen insensitivity syndrome, pseudohermaphrodites (genetic and gonadal male) including inhibition of uterovaginal development, lower vaginal atresia, and acquired conditions of endometrial fibrosis (Asherman's syndrome and pelvic tuberculosis).

Mayer Rokitansky Kuster Hauser syndrome is due to early developmental failure of Mullerian system. It affects 1 in every 4000 female births. It is usually sporadic in occurrence. Affected girls have normal XX karyotyping, normal ovaries and secondary sexual characteristics. These patients have absent uterus and vagina may be absent or hypoplastic. There may be associated anomalies of Wolffian duct system, renal (20%) and skeletal system (12%). Other developmental abnormalities that present with primary amenorrhoea include imperforate hymen and transverse vaginal septum. These individuals may present with cryptomenorrhea, in which bleeding and pain occur every month but bleeding is not revealed. Its incidence is 1 in 4000 to 1 in 10,000 female birth.[5–7]

The second disorder to consider is Testicular Feminization or Androgen insensitivity syndrome. It is an X-linked recessive disorder. Patients have 46XY karyotype, a female phenotype and testes may be present in inguinal canal, labial fold or intra abdominally. The concentration of androgen is according to age. There is nil or scanty

axillary and pubic hair at puberty. Development of uterus and upper vagina is absent as production of anti-Mullerian hormone is normal. Removal of the gonads is done after puberty to prevent 5% risk of testicular malignancy, when feminization is complete. The diagnosis requires careful counselling of individual and family by trained professionals, psychological support and associated therapy.[8]

Disorders of ovaries include: Turner syndrome (XO), Turner Mosaic (XX/XO) which presents with primary amenorrhoea and secondary amenorrhoea in mosaic. There is X chromosal deletion, abnormality or mosaicism. Typically, these patients have streak ovaries, are of short stature and have typical phenotype. There may be other features like webbed neck, wide spaced nipple and coarctation of aorta. In Turner girls 10–20% experience spontaneous puberty. In gonadal dysgenesis the development of the indifferent embryonic gonads to differentiated gonads is inhibited. The group includes pure or mixed gonadal dysgenesis (46 XX or 46 XY Swyer syndrome).9 In XY gonadal dysgenesis the testis fails to develop due to loss or mutation of sex determining region of Y chromosome. The gonads are streaks. Malignant transformation is very high. So gonadectomy is the definitive treatment.10 Resistant ovary syndrome is a condition characterized by normal cohort of primordial follicles and absence of auto immune disease. The condition is due to defect in gonadotrophin receptors. 17α hydroxylase deficiency and aromatase deficiency may lead to primary amenorrhoea. Mumps, tuberculosis, radiotherapy, chemotherapy and galactosaemia in early life may lead to premature ovarian failure.

Disorders of pituitary include: Congenital Isolated FSH deficiency due to mutation in B subunit of FSH and congenital absence of pituitary is very rare. Tumours, surgery, radiation, mumps, encephalitis, infarction and pituitary macro adenoma may lead to acquired failure. Amenorrhoea occurs because of lack of gonadotropins. Hyperprolactinemia may occur due to pituitary microadenoma or extra pituitary tumour compressing pituitary stalk. Although it is uncommon presentation in adolescents with primary amenorrhoea, approximately 15 to 20 % of women with secondary amenorrhoea display elevated serum prolactin levels.

Hypothalamic Disorders include: Congenital Kallman syndrome, which is associated with congenital absence of GnRH secretion along with olfactory disorder. Hypothalamic amenorrhoea may also occur in encephalitis, meningitis, radiation, chemotherapy, auto immune disorders, extreme exercise, stress, obesity, polycystic ovarian syndrome and constitutional delay. Constitutional delay is considered as a retrospective diagnosis.[11] Successful management of primary amenorrhoea depends upon correct diagnosis and timely intervention according to the need of individual along with careful counselling of the family and individual.

Various studies have been conducted from different part of the world on the causes of primary amenorrhoea. Mullerian anomalies and gonadal dysgenesis are the commonest aetiologies, though the frequency may vary in different studies.[12–15] This study had been conducted to evaluate the aetiology of primary amenorrhoea in women presenting at SKBZ/CMH MZD.

MATERIAL AND METHODS

This cross-sectional study had been conducted with primary data in the department of Obstetrics and Gynaecology Sheikh Khalifha Bin Zyed Al Nahyan /Combined Military Hospital Muzaffarabad Azad Jammu Kashmir (SKBZ/CMH MZD AJK). Consecutive individuals with primary amenorrhoea who attended gynaecology clinic from December 2014 to November 2017 were included in the study with permission from hospital ethical committee. The data was collected from patients. Detailed history of all patients including diet, change in appetite, weight loss or gain, exercise habit, enquiry about social events producing psychological stress, presence of galactorrhoea, drug history, symptoms of androgen excess such as hirsutism, acne and balding, voice change, history of hormone replacement therapy, withdraw bleeding with progesterone or combine oestrogen and progesterone preparation. Past history of meningitis, encephalitis, tuberculosis, auto immune disease, mumps, trauma, surgery, radiotherapy were recorded. Family history of delayed menarche, amenorrhoea or any surgery on genitalia was obtained. In general, physical examination, height, weight, BMI, thyroid, any feature suggestive of Turner syndrome or any other chromosomal anomaly were also recorded. breast development, presence or absence of axillary and pubic hairs, Examination of external genitalia, including vaginal /rectal examination was performed.

The baseline endocrine investigations include exclusion of pregnancy, measurement of serum gonadotrophins (FSH and LH levels) oestradiol and prolactin concentration and markers of thyroid function (Thyroxine/ thyroid stimulating hormone) if there were clinical sign of thyroid

disease or sign of hyper prolactinemia. Serum androgen level were measured in subjects with sign of hirsutism or androgenization. Transabdominal ultrasound and where necessary transvaginal scan were performed. Magnetic resonance imaging was done to see obstructive outflow lesions urogenital or Mullerian abnormalities in suspected cases where necessary. Computed Tomography scan was performed if pituitary or other tumour suspected. Complete blood picture, erythrocyte sedimentation rate, autoantibodies, chest X ray if history suggestive of tuberculosis or autoimmune diseases. Karyotyping was done in suspected cases of gonadal failure or androgen excess.

RESULTS

We had 30 individuals with primary amenorrhea who were the part of this study. Average age of the patients was 18.7 years (SD 3.04). The etiological factors of patients are described in Figure-1. The two prevalent aetiologies of primary amenorrhoea were Mullerian anomalies (36.7%) and gonadal dysgenesis (33.3%), followed by hypothalamic causes (23.3%) and Pituitary cause (6.7%). Karyotyping was performed in all patients with gonadal dysgenesis. There were 6 individuals of 46XX gonadal dysgenesis, 2 patients of Turner syndrome and 2 with Androgen insensitivity syndrome (AIS,46 XY). (Table-1, Figure-1)

Vaginoplasty was also done in patient with testicular feminization and two patients with Mayer Rokitansky Kuster Hauesr syndrome. Testis were also removed in 2 cases of testicular feminization from labial fold. Individuals with absent uterus were counselled regarding future fertility prognosis.

We started sex steroid replacement therapy with cyclical oestrogen and progesterone in patients with primary gonadal failure. They were also prescribed calcium and vitamin D supplementations to prevent osteoporosis.

In this study four cases with hypo gonadotrophic hypogonadism who were given combined oestrogen progesterone preparations for menstruation. Imperforate hymen was resected in three patients when they reported for cyclical pain. Raised prolactin level was found in two cases who were given bromocriptine and cabergoline who had menstruation after their prolactin level dropped. One patient had pituitary adenoma who was referred to neurosurgeon. We had three patients with resistant polycystic ovarian syndrome who were given metformin and dianette for periods. Ovarian drilling was done in one patient who had regular periods after drilling.

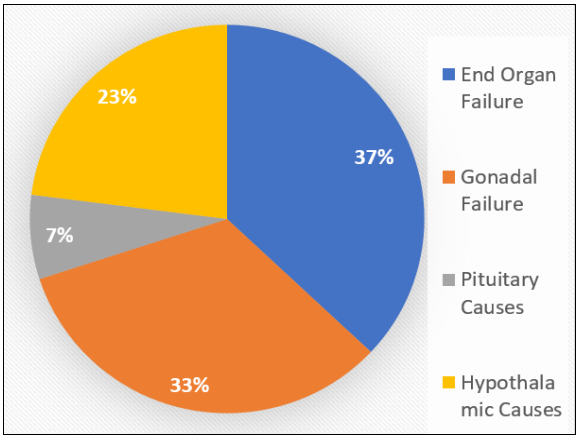

Figure-1: **Description of aetiology of primary amenorrhea (n=30)**

Table-1: Aetiology of primary amenorrhea

Compartment	Causes	Frequency (%)
Compartmant-1 (End organ failure)	Mayer Rokitansky Kuster Hauser	4 (13.3)
	Transverse vaginal septum	2 (6.7)
	Imperforate hymen	3 (10)
	Androgen Insensitivity Syndrome	2 (6.7)
Compartment - 2 (Gonadal Failure)	46 XX gonadal dysgeneses	6 (20)
	45XO (Turner)	2 (6.7)
	Resistant ovary syndrome	1 (3.3)
	46XY (Swyer)	1 (3.3)
Compartment - 3 (Pituitary causes)	Hyperprolactinemia	2 (6.7)
Compartment - 4 (Hypothalamic causes)	Hypo gonadotrophic hypogonadism	4 (13.3)
	Polycystic ovarian syndrome	3 (10)

DISCUSSION

Research in reproduction continues to provide critical insights into our knowledge of the mechanism responsible for amenorrhoea in women. Aetiology of primary amenorrhoea can still be classified into four main groups, anatomical causes, end organ or gonadal failure, hypothalamic and pituitary (endocrine causes) and constitutional delay.

Work up of cases of primary amenorrhoea requires a detailed history and general physical examination which includes the examinations of external genitalia and internal reproductive organs, combined with hormonal profile and cytogenetic studies where required. By this approach, we will be able to recognize the commonest aetiologies of amenorrhoea.[16] The causes of primary amenorrhoea can range from anatomical abnormalities to endocrine dysfunction, there may be genetic involvement in many cases. An anatomical anomaly can be suspected if a girl presents with cylical pain and imperforate hymen.[17]

In our study, the commonest aetiology of primary amenorrhoea was Mullerian anomalies or anatomical causes, followed by ovarian or end organ failure. These two causes were approximately similar 36.7% versus 33.3% followed by endocrine causes. Hyperprolactinemia and polycystic ovarian syndrome were also present in significant patients in our study. It is shown from various studies that outflow tract anomalies is common cause of primary amenorrhoea in Asian and African countries while gonadal dysfunction is more prevalent in western countries. A large retrospective study was conducted in India, New Delhi on 102 cases shown Mullerian anomalies was the commonest cause in nearly half of individuals, followed by gonadal dysgenesis and hypogonadonadotrophic gonadism in nearly one fifth of cases. Mullerian anomaly was also a common cause of primary amenorrhoea in a study which was conducted on 295 cases of Thai peoples.[12–15] Gonadal dysgenesis was found to be the most common cause in various studies conducted in western countries and United States.

In a study, Cytogenetic evaluation was performed in 1843 cases of disorder sexual development in India Andhra Pradesh and it was noted that karyotypic abnormalities are also prevalent in 21.5% of individuals of primary amenorrhoea.[3–8,18]

A study was conducted on 48 cases of primary amenorrhoea in India in 1998 which also found that Mullerian anomalies were present in over 50% of cases followed by pituitary hypothalamic dysfunction in one fifth and gonadal failure in one fourth of cases,[19] but in our study cases of Mullerian anomalies and gonadal dysgenesis were nearly comparable. A study on etiological evaluation of 39 adolescents of primary amenorrhoea found that cytogenetic abnormalities were present in nearly 20% of individuals.[20]

Treatment in patients of amenorrhoea depends upon the needs of individual and whether fertility is required or not. If fertility is not required, regular withdrawal bleeding may be induced with cyclical oestrogen and progesterone therapy with the use of oral contraceptive pills or other combinations. In patients with polycystic ovarian syndrome, or chronic anovulation cyclical progesterone therapy or combined oestrogen and progesterone may be used for endometrial protection against unopposed oestrogen effects. The patient with ovarian failure also require oral contraceptives or other combined preparations to avoid unnecessary side effects of oestrogen deficiency and for bone protection. The conception is possible only by using in vitro fertilization using donor oocyte in these patients. The cases of hypothalamic pituitary hypogonadism respond well to exogenous gonadotrophins and hormone therapy. They require ovulation induction with gonadotrophins and pulsatile GnRh therapy.

Patients with Mullerian agenesis require careful counselling by trained personnel and psychological support for both individual and family and associated therapy may lead to live a nearly normal social life.

CONCLUSION

Mullerian anomalies and gonadal dysgenesis are the two commonest etiological causes leading to primary amenorrhea. The successful management of primary amenorrhoea is dependent upon correct diagnosis and assessment of requirement of individual. Every individual will articulate different needs which may include advice for delayed secondary sexual characteristics, treatment of hirsutism, future fertility prospects and protection from osteoporosis and endometrial protection from unopposed oestrogen. Management involves multi-disciplinary approach with the type of intervention based on exact aetiology. An appropriate surgical intervention provides cosmetic solution and resolves psychological and social issues.

AUTHORS' CONTRIBUTION

AI: Conception and design, acquisition of data, analysis and interpretation. MZ: Acquisition of data, analysis and interpretation. SW, UN: Analysis and interpretation

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