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Original Article

Etiology and management of primary amenorrhoea: A study of 102 cases at tertiary centre

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ABSTRACT

Objective: To determine the prevalence of etiologic causes of primary amenorrhea in Indian population.
Materials and methods: A retrospective study was performed using 102 complete medical records of women with primary amenorrhea who attended the Gynaecologic Endocrinology Clinic, Department of Obstetrics and Gynaecology, AIIMS, New Delhi from September 2012 to September 2015. Cases were analysed according to clinical profile, development of secondary sexual characteristics, physical examination, pelvic and rectal examination, X-ray of chest and lumbo-sacral spine, hormone profile, pelvic USG, MRI, and cytogenetic study including karyotype.
Results: The three most common causes of primary amenorrhea were Mullerian anomalies (47%), gonadal dysgenesis (20.5%), and hypogonadotropic hypogonadism (14.7%) in the present study. There were 3 cases of Turner syndrome (45,XO), 5 cases of Swyer's syndrome (46,XY) and 2 cases of Androgen insensitivity syndrome (46,XY). One case had pituitary macroadenoma and eight cases (7.8%) were of genital tuberculosis.
Conclusions: The present study has currently been the largest case series of primary amenorrhea from North India. Mullerian anomaly is the most prevalent etiological factor leading to amenorrhoea followed by gonadal dysgenesis in our study. Racial, genetic and environmental factors could play role in the cause of primary amenorrhea.

Introduction

Amenorrhoea is absence of menses in women of reproductive age. Primary amenorrhea is defined either as absence of menarche by 14 years of age in the absence of secondary sexual characteristics or absence of menses by 16 years in the presence of normal growth and secondary sexual characteristics [1].

Secondary amenorrhea is characterized as the cessation of previously regular menses for three months or previously irregular menses for six months [1]. According to World Health Organization estimates, amenorrhea stands as sixth largest major cause of female infertility and affects 2–5% of all women in the child bearing age [2].

About 2–5% of adolescent girls present with primary amenorrhea [3]. The incidence is increasing because of increased reporting, better utilisation of healthcare, declining trend in child marriage and increased awareness due to social media. Amenorrhoea is a symptom that reflects some underlying disease anywhere in the hypothalamic-pituitary-ovarian-uterine axis. There are different causes of primary amenorrhoea. It includes anomalies of mullerian development, gonadal dysgenesis, constitutional delayed puberty, tuberculosis, CNS tumors, idiopathic etc [4]. A case of primary amenorrhoea should be evaluated thoroughly as it has impact on both physical and psychological well being of the patient. Early diagnosis and timely intervention is necessary to prevent long term health and social consequences. As soon as the etiology is established in a particular case, the patient can be counselled regarding the prognosis and future fertility options.

There are studies from various regions of the world on etiology of primary amenorrhoea. The two main causes are mullerian anomalies and gonadal dysgenesis with different frequencies in different parts, some have shown anatomic abnormalities as the most common cause while others have reported gonadal failure as the commonest one [5–8]. We conducted this retrospective study

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to evaluate the etiology of primary amenorrhoea in women presenting at tertiary care centre in India.

Materials & methods

The present study was a retrospective study conducted in the Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi. All cases of primary amenorrhoea who attended the Gynaecologic Endocrinology Clinic from September 2012 to September 2015 were included in the study. The data was collected based on the medical records of the patients. As it was a retrospective collection of data, ethical clearance was exempted as per hospital policy. There were total 125 cases of primary amenorrhoea registered over a period of three years (September 2012 to September 2015). The medical records of these patients were reviewed but complete information on history, physical examination, and necessary investigations for final diagnosis was available in 102 cases.

The workup of primary amenorrhoea included the following:

History: Patients were asked about their eating and exercise patterns, changes in weight, medication use, presence of galactorrhoea and symptoms of androgen excess, abnormal thyroid function, or vasomotor instability. History was elaborated regarding withdrawal bleeding to progesterone or estrogen + progesterone, any systemic illness, history of tuberculosis. Family history of primary or secondary amenorrhoea, mental retardation, any other significant illness was also elicited.

Examination: Physical examination included examination of height, weight, built, BMI (body mass index), presence of secondary sexual characters, thyroid palpation, Tanner staging of breast and pubic hairs, local examination of external genitalia. Rectal and/or pelvic examination was done to assess anatomic or mullerian anomalies. Dysmorphic features such as a webbed neck or low hairline and other features of Turner syndrome were recorded.

Laboratory investigations: The initial workup included serum luteinizing hormone, follicle-stimulating hormone, prolactin, and thyroid-stimulating hormone levels, serum free and total testosterone and dehydroepiandrosterone sulphate, estradiol and 17-OHP. A complete blood count and comprehensive metabolic panel, Mantoux test and X-ray of chest was done if history or examination was suggestive of chronic disease. Diagnostic hysteroscopy and endometrial aspirate was taken for histopathology and for TB-PCR (Tubercular Bacillus-polymerase chain reaction) in suspected cases. Pregnancy test was done wherever necessary.

Pelvic ultrasonography (transabdominal or transvaginal) was done for presence of uterus, adnexae, and any reproductive tract anomaly. In cases where USG was inconclusive, MRI was done to visualise Mullerian structures, gonads and renal anomalies. Laparoscopy and hysteroscopy was also done for diagnosis and management as and when indicated.

Cytogenetic study for karyotype detection was done in cases of primary gonadal failure and those with symptoms of androgen excess.

The causes of primary amenorrhoea are classified into five groups based on the organs involved in the etiology [4]:

Compartment 1: End-organ failure or out-flow tract obstruction
Compartment 2: Gonadal failure
Compartment 3: Pituitary cause
Compartment 4: Hypothalamic cause
Other causes.

The patients were classified into 4 groups based upon the organ involved in the etiology of primary amenorrhoea.

Results

The analysis of 102 patients with primary amenorrhoea was done and the diagnosis was made on the basis of all medical records available. The etiological factor in 102 patients is given in Table 1 along with their clinical features. The common causes of primary amenorrhoea were mullerian anomalies (48 cases, 47%), gonadal dysgenesis (21 cases, 20.5%) and hypogonadotropic hypogonadism (15 cases, 14.7%) in the decreasing order of frequency. Cytogenetic study was available in 45 patients. All patients with gonadal dysgenesis (21 cases) were subjected to cytogenetic study by karyotyping. There were 13 cases of 46,XX gonadal dysgenesis, 3 cases were of Turner syndrome and 5 had Swyer syndrome (46XY). Androgen insensitivity syndrome (AIS, 46XY) was found in two cases. Amongst three cases of Turner syndrome, karyotype revealed 45XO/del(x); 45XO(67%)/46XX(33%) and 45XO/46XY.

There were 48 cases of mullerian anomalies with 27 cases of MRKH (Mayer-Rokitansky-Kuster-Hauser syndrome), 11 cases of cervicovaginal agenesis, 5 with transverse vaginal septum, 4 with mullerian hypoplasia and one had imperforate hymen. Patients with MRKH (Mayer-Rokitansky-Kuster-Hauser syndrome) and Mullerian hypoplasia were treated with Mc Indoe's vaginoplasty (24 cases), and laparoscopic Davydov vaginoplasty (5 cases). Two cases had partially canalised vagina and did not require surgery. Jeffcoate's vaginoplasty was done in 5 cases with transverse vaginal septum. Cervico-vaginal agenesis was treated by cervicovaginoplasty in 8 cases and two patients required ysterectomy. The patients with absent uterus were counselled regarding the future fertility option of surrogacy to have their own biological child or adoption.

Patients with primary gonadal failure were put on combined hormone therapy with estrogen for 21 days (conjugated equine estrogen 0.625 mg daily) and progesterone (medroxyprogesterone acetate 10 mg daily) in last 12 days of the month. They were also given calcium and vitamin D supplementation to prevent bone loss. Laparoscopic bilateral gonadectomy was done in cases of Swyer syndrome, AIS (Androgen insensitivity syndrome) and one case of Turner mosaic with Y line in karyotype. As far as fertility is concerned, these patients require donor-oocyte IVF (in-vitro fertilization).

We had 15 patients with hypogonadotropic hypogonadism. Out of these, three had primary infertility and were given ovulation induction with gonadotropins. Two of them had successful pregnancy. One underwent in-vitro fertilization at our centre only.

In the present study, we found genital tuberculosis contributing to 8 (7.8%) cases of primary amenorrhoea. These patients were treated with anti-tubercular therapy (ATT) for 6 months. They did not respond to hormone therapy for menstruation. Only two patients started having cyclical spotting after taking ATT. This has a very important implication on the fertility outcome as these patients often do not resume their menstrual cycle and may require surrogacy for fertility.

Discussion

Adolescent girls with primary amenorrhoea are brought to the physicians by their mothers with major concern regarding their reproductive life. 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. The workup of primary amenorrhoea should be very meticulous including history, physical examination, hormone evaluation, pelvic imaging (either ultrasound or MRI). The

Table 1
Causes of primary amenorrhoea according to the compartment involved in the etiology.

Serial number	Causes	No. of cases(102)	Age at presentation (mean)
1	**Compartment 1-(End organ failure)**	**62**	
a)	Mayer Rokitansky Kuster Hauser	27	21.41
b)	Mullerian hypoplasia	4	19.75
c)	Transverse vaginal septum	5	18.16
d)	Imperforate hymen	1	15
e)	Cervico-vaginal agenesis	11	17.45
f)	Tubercular endometritis	8	20.25
g)	Androgen Insensitivity Syndrome	2	28
h)	Absent endometrium	4	22.33
2	**Compartment 2**	**21**	
a)	46,XX gonadal dysgenesis	13	18.15
b)	45,XO (Turner)	3	17.67
c)	46, XY (Swyer)	5	17
3	**Compartment 3**	**1**	
a)	Hyperprolactinemia	1	19
4	**Compartment 4**	**18**	
a)	Hypogonadotropic hypogonadism	15	19.53
b)	Polycystic ovarian Syndrome	3	18.67

importance of cytogenetic studies and karyotype cannot be overemphasized in establishing the diagnosis. It should be done in all cases of hypergonadotropic hypogonadism and patients with androgenic features. Karyotyping helps in establishing the diagnosis and also guides the treatment, especially for psychological counselling of the patient. It aids in decision for gonadectomy in the presence of Y line and future pregnancy option.

Previous studies have been reported from all parts of the world indicating the frequency of various etiologies, cytogenetic abnormalities in cases of primary amenorrhoea. Gonadal dysfunction has been considered as the commonest factor for primary amenorrhoea worldwide followed by pituitary/hypothalamic disorder and outflow tract anomalies [5]. Literature shows greater prevalence of gonadal dysfunction leading to primary amenorrhoea in western countries while that of outflow tract anomalies in Asian- African countries. Most of the studies from United States have mentioned gonadal dysgenesis as the most common cause of amenorrhoea while a large study from Thailand of 295 cases has shown Mullerian anomaly as the commonest cause in Thai population [5–8]. In our study, we also found Mullerian anomalies as the most common attributing factor to primary amenorrhoea followed by gonadal dysgenesis and hypogonadotropic hypogonadism. The proposed reason for this difference might be the environmental and racial or genetic influence.

There are reports from India elaborating the cytogenetic evaluation of these patients and mentioning the contribution of chromosomal abnormalities in primary amenorrhoea [2,9–11]. A large study from Andhra Pradesh in India had earlier reported abnormal karyotype of 21.5% women presenting with primary amenorrhoea [12]. Our findings were similar to previous study of 48 cases of primary amenorrhoea reported in 1998 from same centre in India where they have found mullerian anomalies in 54.2% cases followed by hypogonadotropic hypogonadism (22.9%), hypergonadotropic hypogonadism (16.6%) and genital tuberculosis (6.3%) [10]. Eren E et al. reported a study elaborating various causes of primary amenorrhoea in 39 cases [13]. They showed chronic diseases, prolactinomas, insulin resistance and mullerian agenesis leading to normogonadotropic hypogonadism as the commonest cause. People have also studied the patterns of chromosomal abnormalities in cases of primary amenorrhoea and gonadal failure. A previous study from Turkey had shown high incidence of chromosomal abnormalities in one-fourth cases (25%) of primary amenorrhoea or premature ovarian failure [14].

We have reported this study to highlight etiology and management of primary amenorrhoea at a tertiary centre in the north India. The present study had few limitations. Firstly, it was a retrospective study based on collection of data from the available medical records of the patients. Secondly, not all patients with primary amenorrhoea were registered in the speciality clinic. Third, it was a single center study at tertiary hospital so the study population was somewhat affected by the referral pattern.

Female genital tuberculosis is prevalent in India and it is one of the important causes of primary amenorrhoea with guarded prognosis [15]. It affects all the reproductive organs including uterus, fallopian tubes, and ovaries leading to amenorrhoea either primary or secondary infertility. It has worst outcome when endometrial lining is affected and it leads to endometrial damage thereby causing primary amenorrhea [15,16]. In the present study, 8 patients were diagnosed endometrial tuberculosis on the basis of clinical symptoms with history, histopathology of endometrial aspirate and other laboratory tests. The plausible mechanism is due to damage to the endometrium and adhesion formation inside the uterine cavity leading to Asherman syndrome. They were given anti-tubercular therapy (ATT) for 6 months. Patients with Asherman syndrome require hysteroscopic adhesiolysis. The chances of resumption of menses in these patients are very less. As far as pregnancy is concerned, the chances are further remote due to failure of implantation and surrogacy is often required [16].

In patients with hypogonadotropic hypogonadism, the prognosis in terms of fertility outcome is good because they respond very well to exogenous hormone therapy. These patients have low levels of serum pituitary gonadotropins, decreased drive to ovaries for production of estrogens and progesterone, thereby leading to amenorrhoea. When exogenous gonadotropins are given for ovarian stimulation, there is favourable response and most of these patients conceive with ovulation induction.

Being a major concern in pubertal girls, primary amenorrhea affects physical, mental, psychological and social life of the patient. Team approach involving gynaecologist, geneticist, psychologist and paediatrician should be followed for individualising the management and counselling. Treatment and prognosis in terms of future fertility depends on the primary etiology of amenorrhoea.

Author contributions

All the authors contributed to the preparation of manuscript.

Author 1 had major role in the design, planning, conduct of study, data analysis, and manuscript writing.

Author 2 was involved in the conduct, data analysis and manuscript writing.

Author 3 had role in conduct of the study and helped in manuscript writing.

Author 4 was involved in data analysis and manuscript writing.

Author 5 was involved in manuscript writing.

Conflicts of interest

The authors report no conflict of interest.

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