ABSTRACT

Introduction: Menstruation is the physical herald to physiologic capacity of conception. Attainment of menarche in a girl brings in a lot of confidence and feminism in a girl. Though the incidence of primary amenorrhea is less than 1%, it accounts for significant amount of psychological trauma. In the present day scenario, there are a lot of investigative and treatment modalities which can at least restore her menstrual functions, if not reproductive, and prevent complications.

Aims: The objective of this study is to note the various causes of primary amenorrhea and the complete clinical picture and the management done in a tertiary care center like Vanivilas Hospital and Bowring Hospital, Bengaluru.

Materials and methods: This is a prospective study done in 40 patients of primary amenorrhea presenting to Vanivilas Hospital and Bowring and Lady Curzon Hospital, Bengaluru during a 2 years period. They were investigated and managed. The patients were followed up for their response to treatment.

Results: Out of the 40 patients studied, Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome (32.5%) and hypergonadotropic hypogonadism (32.5%) were most common. Cryptomenorrhea (17.5%), automatic identification system (AIS) (7.5%) and miscellaneous (4%) were found.

Conclusion: Evidence of primary amenorrhea is less than 1%. A detailed investigation may lead to treatment in many cases.

Keywords: MRKH syndrome, Primary amenorrhea, Psychological trauma, Vaginoplasty.

How to cite this article: Anitha GS, Tejeswini KK, Shivamurthy G. A Clinical Study of Primary Amenorrhea. J South Asian Feder Obst Gynae 2015;7(3):158-166.

INTRODUCTION

Primary amenorrhea is failure to establish spontaneous periodic menstruation by the age of 16 years regardless of whether secondary sexual characteristics have developed. Menarche is the appearance of menstruation for the first time. Menstruation is the physical herald to physiologic capacity of conception. Menarche marks the end of a cascade of events beginning around puberty starting with thelarche, pubarche, growth spurt and ultimately culminating in menarche. Menstruation in a girl is often celebrated as advent of womanhood and some communities even celebrate this by ceremoniously blessing the girl. It empowers the continuum of life and procreation.

Though the incidence of primary amenorrhea is less than 1%, it accounts for significant amount of psychological trauma. If there is delay in its onset, there is anxiety generated among parents who may seek the advice of a doctor. In the present day scenario, there are a lot of investigative and treatment modalities which at least restore her menstrual functions, if not reproductive, and prevent complications.

There are not many studies done regarding primary amenorrhea. The earliest established study was done by James H Evans in 1971 who reported a review of 50 cases of primary amenorrhea. He performed buccal smear, total urinary gonadotropins and estrogen assay in all patients. He found the most common cause to be chromosomal abnormality (24%). This study stresses on the importance of establishing diagnosis prior to initiating therapy. In 1991, Kuntal Rao et al KMC Manipal Hospital, reported a study of 40 patients of primary amenorrhea between 1987 and 1988. The study reported the commonest cause to be uterovaginal dysgenesis (50%). This study emphasizes that laparoscopy gives better information of the functional anatomy of gonads and pelvic contents with precision as compared to clinical and biochemical studies. It provides a cheap, easy way to find the diagnosis immediately and predict prognosis. In 1998, Kumar et al highlighted the role of transabdominal sonography. In 2010, Vijayalakshmi et al reported cytogenetic analysis of patients with primary amenorrhea. The karyotype revealed 71.2% with normal chromosome composition, 27.8% with numerical aberration and 26% showed structural abnormalities. The X chromosome abnormality was observed in 49% of the subject population which is consistent. After excluding the nongenetic causes, primary amenorrhea should receive prompt referral for genetic study.
MATERIALS AND METHODS (Figs 1 to 5)

A total of 40 patients of primary amenorrhea presenting to Vanivilas Hospital, Bengaluru, during the period of 2 years between November 2008 and October 2010, were studied. The inclusion criteria were female of age > 14 years with primary amenorrhea with the absence of secondary sexual characteristics and female with age > 16 years with primary amenorrhea with normal growth and presence of secondary sexual characteristics. The exclusion criteria were female < 14 years and secondary amenorrhea. It is a prospective study. All the patients were subjected to a detailed history taking and a thorough physical examination. All the patients were subjected to ultrasound examination and the reports were reviewed not in isolation but with respect to the clinical findings. Further investigations like karyotyping and hormonal assays were done to reach a final conclusion as directed by the clinical and ultrasonography (USG) findings. An attempt is made to formulate a diagnostic protocol so that it becomes easier to diagnose and also not misdiagnose cases.

Based on the secondary sexual characteristics, patients are grouped into three categories:
1. Normal/appropriate for age
2. Sexual infantilism
3. Discordant or with feature of virilism.

In each of these groups, ultrasound abdomen was done to note the presence of uterus, ovaries and tubes. It was further subdivided based on the size of the uterus, i.e. normal (longitudinal diameter of > 6 cm), hypoplastic (< 6–3 cm) and infantile or rudimentary (< 3 cm).

After the diagnosis of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, echocardiography, cervico-thoracic and lumbosacral spine X-ray and assessment of hearing for any sensorineural deafness must be done.

In our study, intravenous pyelogram (IVP) was done in two patients in whom renal agenesis was found but in present day scenario, it is not necessary since USG can pick up most of structural abnormalities. Karyotyping can provide additional confirmation in cases of MRKH to differentiate it from automatic identification system (AIS) but it is not an absolute necessity as clinical examination would differentiate the two. With a diagnosis of gonadal dysgenesis, the following investigations are done to rule associated anomalies:
1. Karyotyping
2. Complete hemogram
3. Thyroid function tests
4. Lipid profile
5. Renal and liver function tests
6. Echocardiography
7. Fasting blood sugar (FBS), postprandial blood sugar (PPBS)
8. Hormonal analysis
9. Cervicothoracic and lumbosacral spine X-ray.

Computed tomography (CT) scan of brain was done in one of our patients of polycystic ovary syndrome (PCOS) with cervical atresia with elevated prolactin levels.

After the diagnosis, counseling the patient is the most important integral component of management of primary amenorrhea. All the patients were counseled regarding
their condition and their menstrual, coital and reproductive function. They were given psychological counseling to accept their condition and cope with it.

All the cases of MRKH syndrome and one case of AIS were counseled about the need of vaginoplasty. Out of them, seven patients of MRKH syndrome underwent vaginoplasty and the procedures done in our hospital by various techniques were noted. All the cases of cryptomenorrhoea and AIS who underwent surgery were noted with respect to the technique and postoperative complication if any. All the patients with hypergonadotrophic hypogonadism were counseled about their condition and the need for estrogen therapy with the associated risks and benefits. They were started on conjugated estrogen of 0.625 mg once a day (OD)/bi daily (BD) depending upon their hormonal profile for the first
2 months. In the second month, medroxyprogesterone acetate (MPA) 10 mg BD was given for 5 days to produce withdrawal bleeding. Later on patients were maintained with cyclical estrogen and progesterone therapy with calcium replacement.

At each follow-up:
- In MRKH syndrome cases having undergone vaginoplasty, postoperative urinary symptoms or constipation if any noted. Postoperative vaginal length noted. Continuous and regular finger dilatation was advised.
- In cases of gonadal dysgenesis on hormonal therapy liver function test (LFT), appearance of secondary sexual characteristics and menstruation noted.
- In cryptomenorrhea, patency of vagina and regular menstruation noted.
- Normal postoperative follow-up of patients with AIS having undergone gonadectomy.

LIMITATIONS

Resource constraints restricted the researchers from doing karyotyping of the patients.

ETHICAL CONCERNS

The study mandated procedures to ensure informed consent and maximize confidentiality. Participation of all respondents in the survey was strictly voluntary and there was no monetary or other compensation offered for participation. Measures were taken to assure the respect, dignity and freedom of each individual participating in the data collection. Participation was based on informed consent.

PATIENT EDUCATION

Finally, as in all medical conditions, it is critical that patients be adequately counseled about their diagnosis, the long-term implications of this diagnosis, and the treatment options. Even if not raised by the patient, the potential for future childbearing should be discussed. Many women are under the mistaken impression that it is dangerous not to have a menstrual period, and should be reassured that this is, in and of itself, not a concern. On the other hand, all women with an intact endometrium should understand the risks of unopposed estrogen action, whether the estrogen is exogenous, such as through hormone therapy, or endogenous, such as in PCOS. Hypoestrogenic women should be counseled about the importance of estrogen replacement to protect against bone loss.

RESULTS

A total of 40 patients of primary amenorrhea were studied during the period of November 2008 to October 2010.

AGE AT PRESENTATION OF PRIMARY AMENORRHEA

Ranged from 14 to 44 years with mean age at presentation being 20.925 years. Maximum patients presented in the age group of 16 to 20 years.

Twenty-nine patients were from the lower socioeconomic class and 6 from lower middle class and another 5 from upper middle class. This can be explained by the fact that the study was conducted in a government hospital basically catering to the lower socioeconomic class.

Six patients were married at the time of presentation and the rest were unmarried.

AGE WISE DIAGNOSIS OF PRIMARY AMENORRHEA (Graph 1)

All the patients presenting early had a diagnosis of cryptomenorrhea. In the second group of 16 to 20 years, cryptomenorrhea was found in only one, AIS was seen...
### Table 1: Clinical findings and associated causes

<table>
<thead>
<tr>
<th>Findings</th>
<th>Associations</th>
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<tbody>
<tr>
<td><strong>Patient history</strong></td>
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<tr>
<td>Exercise, weight loss, current or previous chronic illness, illicit drug use</td>
<td>Hypothalamic amenorrhea</td>
</tr>
<tr>
<td>Menarche and menstrual history</td>
<td>Primary vs secondary amenorrhea</td>
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<tr>
<td>Prescription drug use</td>
<td>Multiple, depending on medication</td>
</tr>
<tr>
<td>Previous central nervous system chemotherapy or radiation</td>
<td>Hypothalamic amenorrhea</td>
</tr>
<tr>
<td>Previous pelvic radiation</td>
<td>Premature ovarian failure</td>
</tr>
<tr>
<td>Psychosocial stressors; nutritional and exercise history</td>
<td>Anorexia or bulimia nervosa</td>
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<tr>
<td>Sexual activity</td>
<td>Pregnancy</td>
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<tr>
<td><strong>Family history</strong></td>
<td></td>
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<tr>
<td>Genetic defects</td>
<td>Multiple causes of primary amenorrhea</td>
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<tr>
<td>Pubic hair pattern</td>
<td>Androgen insensitivity syndrome</td>
</tr>
<tr>
<td>Infertility</td>
<td>Multiple causes</td>
</tr>
<tr>
<td>Menarche and menstrual history (mother and sisters)</td>
<td>Constitutional delay of growth and puberty</td>
</tr>
<tr>
<td>Pubertal history (e.g. growth delay)</td>
<td>Constitutional delay of growth and puberty</td>
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<tr>
<td><strong>Physical examination</strong></td>
<td></td>
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<tr>
<td>Anthropomorphic measurements; growth chart</td>
<td>Constitutional delay of growth and puberty</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td>Dysmorphic features (e.g. webbed neck, short stature, widely spaced nipples)</td>
<td>Turner’s syndrome</td>
</tr>
<tr>
<td>Rudimentary or absent uterus; pubic hair</td>
<td>Müllerian agenesis</td>
</tr>
<tr>
<td>Striae, buffalo hump, significant central obesity, easy bruising, hypertension or proximal muscle weakness</td>
<td>Cushing’s disease</td>
</tr>
<tr>
<td>Tanner staging</td>
<td>Primary versus secondary amenorrhea</td>
</tr>
<tr>
<td>Thyroid examination</td>
<td>Thyroid disease</td>
</tr>
<tr>
<td>Transverse vaginal septum; imperforate hymen</td>
<td>Outflow tract obstruction</td>
</tr>
<tr>
<td>Undescended testes; external genital appearance; pubic hair</td>
<td>Androgen insensitivity syndrome</td>
</tr>
<tr>
<td>Virilization; clitoral hypertrophy</td>
<td>Androgen-secreting tumor</td>
</tr>
<tr>
<td><strong>Review of systems</strong></td>
<td></td>
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<tr>
<td>Anosmia</td>
<td>Kallmann syndrome</td>
</tr>
<tr>
<td>Cyclic abdominal pain; breast changes</td>
<td>Outflow tract obstruction or Müllerian agenesis</td>
</tr>
<tr>
<td>Galactorrhea, headache and visual disturbances</td>
<td>Pituitary tumor</td>
</tr>
<tr>
<td>Hirsutism or acne</td>
<td>Polycystic ovary syndrome</td>
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<tr>
<td>Signs and symptoms of hypothyroidism or hyperthyroidism</td>
<td>Thyroid disease</td>
</tr>
<tr>
<td>Vasomotor symptoms</td>
<td>Premature ovarian failure</td>
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</tbody>
</table>

in two, hypergonadotrophic hypogonadism accounted for the highest number of cases (seven) and MRKH was seen in six cases. After 25 years of age, we only saw cases of hypergonadotrophic hypogonadism in two and MRKH syndrome in another three.

**Graph 3: Etiology of primary amenorrhea**

**Flow Chart 1: Basic diagnostic protocol (USG-ABD: Ultrasonography abdomen)**

- Examine secondary sexual characteristics
  - Normal
  - Abnormal
  - USG-ABD and pelvis
  - Sexual infantilism
  - Discordant secondary sexual characteristics
    - USG-ABD and pelvis
    - USG-ABD and pelvis
Table 2: Comparison of our study with other studies

<table>
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<tbody>
<tr>
<td>Müllerian dysgenesis</td>
<td>32.5%</td>
<td>26.4%</td>
<td>39.45%</td>
<td>54.2%</td>
<td>50%</td>
</tr>
<tr>
<td>Hypergonadotropic hypogonadism</td>
<td>32.5%</td>
<td>15.1%</td>
<td>32.69%</td>
<td>16.6%</td>
<td>25%</td>
</tr>
<tr>
<td>Hypogonadotropic hypogonadism</td>
<td>7.5%</td>
<td>22.6%</td>
<td>12.87%</td>
<td>22.9%</td>
<td>10%</td>
</tr>
<tr>
<td>Cryptomenorrhea</td>
<td>15%</td>
<td>9.4%</td>
<td>0.99%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>AIS</td>
<td>7.5%</td>
<td>1.9%</td>
<td>3.96%</td>
<td>0%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>10%</td>
<td>24.52%</td>
<td>10.04%</td>
<td>6.3%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

Flow Chart 2: Diagnostic protocol for normal secondary sexual characteristics (PhD: Primary gonadal dysgenesis; LH: Luteinizing hormone; FSH: Follicle-stimulating hormone)
Height of the patients ranged from 121 to 178 cm with mean being 149.3. Body mass index (BMI) ranged from 14.2 to 28.92 with mean being 20.104.

**SYMPTOMS AT PRESENTATION (TABLE 1, GRAPH 2, FIGS 1 AND 2)**

The complaint of not having attained menarche is seen in only 50% of the subjects. The other 50% of them present with a variety of symptoms.

Symptoms suggestive of cryptomenorrhea like cyclical abdominal pain, urinary retention, dysuria were seen in all the seven cases.

Dyspareunia was seen in three cases of MRKH syndrome. Two patients had come only for vaginoplasty, both were cases of MRKH syndrome past 40 years preparing to get married. Two patients presented with primary infertility, one was AIS and the other MRKH syndrome. Two patients presented with short stature, one was a case of pure gonadal dysgenesis and the other was a case of Turner’s syndrome. Two patients came to the hospital wanting disability certificate as they had other associated abnormalities.

**ETIOLOGY OF PRIMARY AMENORRHEA (GRAPH 3)**

Our study found MRKH syndrome and human growth hormone (HGH) to be the major causes accounting for 65% of the cases. Next most important cause is cryptomenorrhea accounting for 18% of cases. Automatic identification system was seen in three cases accounting for 8%. The miscellaneous category of 10% included two cases of constitutional delay, one case of polycystic ovarian syndrome and one case of hypogonadotropic hypogonadism.

**DISCUSSION (TABLE 2)**

Age at menarche has been following a steady decline in the past few decades with girls attaining menarche at a mean age of 12.5 years in India. Awareness regarding the problems associated with not having attained menarche is also increasing. We did not see any patients in the age group of 30 to 40 years because most of the inquisitive patients are diagnosed by then or have lost hopes of receiving treatment. Body mass index did not correlate well with the condition of primary amenorrhea in our
study. We found only one patient with chronic malnutrition with low BMI causing primary amenorrhea. Short stature was limited to the group of hypergonadotropic hypogonadism indicating hypoestrogenism. Symptoms at presentation surprisingly varied from not having attained menarche to primary infertility. On careful questioning, they revealed that they either hide the fact that they are not menstruating or assumed the dirty white discharge to be the scanty monthly bleed.

According to most of the literature, gonadal dysgenesis is the most common cause of primary amenorrhea. But, now the number of cases of MRKH is on the rise probably because more girls are ready to get themselves surgically treated and also the popularity of the surgical facilities available. Most important aspect is to do the procedure of vaginoplasty when the patient is mentally prepared to do it and to keep the patient motivated to continue doing postoperative vaginal dilatation. Any case of müllerian agenesis with rudimentary or hypoplastic uterus in the presence of an endometrial lining has to be removed. In cases of hypogonadotropic hypogonadism, counseling the patient regarding estrogen therapy, its risks and benefits must be explained. It is important to start estrogen therapy to bring about development of secondary sexual characteristics, prevent bone demineralization and also to keep the uterus in a functional state for the theoretic possibility of a surrogate pregnancy with donor ovum.

In the Table 2, we have compared our study with other studies. We have considered two Indian studies and two done abroad. Pourafkari et al is an Iranian study of 53 cases in 2008 which highlights the use of ultrasound in the diagnosis of primary amenorrhea. Rattanachaiyanont et al are a retrospective study of 101 cases done in Thailand. After 1998, to the best of our knowledge, we did not find any published report of a study of primary amenorrhea in the Indian population.

**DIAGNOSTIC PROTOCOL (FLOW CHARTS 1–4 AND FIGS 1–5)**

Primary amenorrhea can become an enigma to the patient and the treating physician if not approached in a systemic method. It is of prime importance to follow a systematic approach or it is very easy to get mislead by our own findings. We are proposing a diagnostic protocol to be followed in order to minimize the errors made in the diagnosis of primary amenorrhea. This protocol was devised after having studied more than 40 patients during the study period and learning from our own mistakes. Due consideration has been given to the most common causes of primary amenorrhea and also to advise investigations only when necessary.

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**Flow Chart 4: Diagnostic protocol for discordant secondary sexual characteristics (CAH: Congenital adrenal hyperplasia)**

- **Discordant secondary sexual characteristics-ultrasound**
  - Normal breasts, absent/sparse axillary and pubic hair
  - Ultrasound
    - Absent uterus
      - Karyotyping
        - 46XX
          - Laparoscopy
            - Streak ovary, malformed testes
            - Mixed gonadal dysgenesis
          - 46XY
            - Laparoscopy
            - Gonads found
            - Androgen insensitivity syndrome
  - Normal breasts, axillary and pubic hair, signs of virilization
  - Ultrasound
    - Normal uterus and ovaries
      - Hormonal analysis
        - LH:FSH ratio
        - PCOS
        - 17-OH progesterone
        - Adult onset CAH
    - Pelvic/adenal mass
      - Androgen insensitivity syndrome
REFERENCES