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ORIGINAL ARTICLE

Müllerian Anomalies: A Cause for Primary Amenorrhea

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ABSTRACT

Introduction: Primary amenorrhea is a challenging entity as it affects the reproductive outcome. Primary amenorrhea is an absence of secondary sexual characters until 14 years of age or absence of menstruation with secondary sexual characters until 16 years of age.

Aim: The aim of this article is to study the frequency, etiologic causes, presentation, diagnosis, and optimal mode of management of primary amenorrhea.

Materials and methods: All girls who had not attained menarche until 16 years of age in the absence of secondary sexual characters and until 14 years, if no secondary sexual characters, and were willing for follow-up were subjected to investigations and were treated as per the etiology.

Results: Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome was the most common cause of primary amenorrhea (42.85%) followed by imperforate hymen (28.57%) and transverse vaginal septum (21.42%), one each of low, mid, and high varieties. There was one case of androgen insensitivity syndrome.

Conclusion: Establishing correct diagnosis is essential for planning treatment and management strategies in primary amenorrhea as treatment goals are preservation of fertility and progression of normal development.

Keywords: Müllerian anomalies, Primary amenorrhea, Vaginal septum.

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INTRODUCTION

Amenorrhea is the absence of menstrual period in a woman at reproductive age. In Greek, A stands for negative, men for month, and rhoea for flow.[1]

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Primary amenorrhea is the absence of secondary sexual characters until 14 years of age or absence of menstruation with secondary sexual characters until 16 years of age.[2]

The incidence of primary amenorrhea is 0.3%.[3] It is due to congenital absence of uterus or failure of ovary to receive or maintain egg cells. The anomalies commonly associated with primary amenorrhea relate to its embryogenesis and define therapy and prognosis. There are a wide variety of defects whose ethology is not known, and they vary from patient to patient, so management needs to be individualized.

The anomalies are asymptomatic, so are frequently missed in routine gynecological examination. They affect the reproductive prognosis of a woman, and as the presentation is complex; 62% of them require more than imaging modality.

There is paucity of data for diagnosis and management. Only two randomized controlled trials are available on PubMed and Cochrane databases; the rest of them are cases or case series. This puts the treating clinician in a quandary.

Early diagnosis and specific management are essential for planning treatment for a healthy sexual relationship and achievement of successful reproductive outcomes in primary amenorrhea.

AIMS AND OBJECTIVES

- To study the frequency of primary amenorrhea in a population.
- To study etiologic causes of primary amenorrhea.
- To study presentation, diagnosis, and optimal mode of management of primary amenorrhea.

MATERIALS AND METHODS

This prospective hospital-based study was carried out at a rural tertiary care hospital after obtaining ethical committee approval.

Over a period of 3 years from January 1, 2012 to December 31, 2015, there were 32,400 women attending gynecology outpatient department (OPD). Of them, there were 14 girls with primary amenorrhea.

Inclusion Criteria

- All girls who had not attained menarche until 16 years of age in the absence of secondary sexual characters and until 14 years if no secondary sexual characters.
- Willing for follow-up.

The exclusion criteria were pregnancy and age <14 years.

All the girls were subjected to careful history taking for psychological and emotional stress, family history of genetic anomalies, clinical assessment for physical problems, such as nutritional status, abnormal growth, per abdominal examination, local examination of the hymen, and per rectal examination; these were done in all patients to determine the presence or absence of uterus. Ultrasonography (USG) was done to determine presence of uterus and its anomalies, endometrial thickness and associated mass if any. The computed tomography/magnetic resonance imaging were done in some cases, if USG seemed inadequate. Laparoscopy and Barr body were done when required.

Investigations like prolactin, thyroid-stimulating hormone, complete blood count, erythrocyte sedimentation rate, and Mantoux test were also done. They were then subjected for operative procedures depending upon the etiology. They were all counseled for being financially independent. Intraoperative and postoperative complications were noted. Girls with Mayer–Rokitansky–Küster–Hauser syndrome were counseled and underwent vaginoplasty 6 months prior to marriage.

Cruciate incision was given and hematometra was drained for imperforate hymen and low transverse vaginal septum.

High vaginal septum was managed by abdominovaginal route; a pull-through surgery was done. Thick low transverse vaginal septum was resected, and vagina was sutured by Z plasty per vaginally.

Androgen insensitivity syndrome (AIS) – counseled for gonadectomy after secondary sexual characters are developed and hormone replacement therapy (HRT) was advised.

Observations

During the study period, the total number of patients attending the gynecology OPD was 32,400. We had 14 girls who presented with primary amenorrhea. The incidence of primary amenorrhea in our institute was 0.04%, which is very low (Table 1).

The MRKH syndrome was the most common cause of primary amenorrhea (42.85%) followed by imperforate hymen (28.57%) and transverse vaginal septum (21.42%), one each of low, mid, and high varieties. There was one case of AIS (Table 2).

It was observed that patients with obstructive anomalies presented earlier than those with Müllerian agenesis, as they developed complaints because of obstruction (Table 3).

Table 1: Frequency of Müllerian anomalies

Anomaly	*Number*	*Percentage*	*Frequency*
MRKH syndrome	6	42.85	0.0185
Imperforate hymen	4	28.57	0.012
Transverse vaginal septum	3	21.42	0.009
AIS	1	7.14	0.0030
	14/32,400 0.0432%		

Table 2: Age at registration

Anomaly	*Number*	*Mean age in years*
MRKH syndrome	6	19.83
Imperforate hymen	4	16.5
Transverse vaginal septum	3	16.6
AIS	1	17

Table 3: Clinical presentation

	MRKH syndrome	*Imperforate Hymen*	*Transverse vaginal septum*	*AIS*
Primary amenorrhea	4			1
Pain in abdomen		2	2	
Retention of urine		3	3	
Infertility	2			

Table 4: Mode of diagnosis

Anomaly	*Clinical diagnosis*	*Pelvic USG*	*Laparoscopy*	*Cytogenetics*
MRKH syndrome	+		+	
Imperforate hymen	+			
Transverse vaginal septum	+	+		
AIS	+	+		+

It was seen that only patients with Müllerian anomalies presented with amenorrhea as a primary complaint, while in others, the presenting symptom varied (Table 4).

Clinical examination clinched the diagnosis of the various Müllerian anomalies. Pelvic USG was helpful for diagnosis of high transverse vaginal septum, and inguinal testes for AIS. A band was seen on laparoscopy in MRKH syndrome. The XY pattern in cytogenetics helped in the diagnosis of AIS (Table 5).

Vaginoplasty was done in 6 girls who were to get married. Its 5 of the 6 girls had Mcindoe and 1 had vichetti. High vaginal septum was approached abdominovaginally,and low and imperforate hymen were approached vaginally. Low transverse vaginal septum and imperforate hymen were managed by a cruciate incision on septum and drainage.

Table 5: Management for primary amenorrhea

Diagnosis	*Parikh et al*[5]	*Incidence in general population*	*Incidence in our study*	*Tanmahansut et al*[4] *n = 295*
Primary amenorrhea[3]	0.022 (14/60,958)	0.3	0.043	
Imperforate hymen[7]	0.006 (4/60,958)	0.1	0.012	2.0
Transverse vaginal septum[4]	0.001 (1/60,958)	0.00002 (2/100,000)	0.009	0.3
Müllerian agenesis[8]	0.013 (8/60,958)	0.00025 (1/4,000)	0.0185	39.7
AIS[9]	0.001 (1/60,958)	1.010 (1/99,000)	0.0030	5.1

Two of the six girls who underwent vaginoplasty stopped using mold and had cicatrization of vagina. The girl who underwent Vichetti vaginoplasty developed vesicovaginal fistula (VVF) on the 10th postoperative day. She was advised to come for repair.

DISCUSSION

Primary amenorrhea is usually due to gross error in development of either uterus or ovaries, and is, therefore, not amenable to treatment. Genetic (39%) and anatomic abnormalities (42%) appear to be remarkable causes of primary amenorrhea.[4]

The true incidence of obstructive Müllerian anomalies is unknown, but is believed to be between 0.1 and 3.8%. Incomplete canalization of the urogenital sinus with the Müllerian system can lead to imperforate hymen. A variety of hymenal and septal abnormalities exist, and this abnormality may present at different stages of life. After puberty, imperforate hymen presents in association with cyclic pain and amenorrhea.

In our study, incidence of primary amenorrhea is 0.043, which coincides with the study by Parikh et al,[5] where it was 0.02. It is less as compared with clinical summaries of 2009, where it was 0.3. This may be due to small data and referral pattern at a tertiary care hospital. Age at registration coincides with study by Parikh et al.[5]

In our study, Müllerian agenesis (58.17%) was the most common cause, which was compatible with Tanmahasamut et al[4] (Thailand). This is in contrast to the American study by Reindollar et al.[6] Gonadal dysgenesis was commonest (48.5%) in the American study. This verified that racial and environmental factors played an essential part in the causes of primary amenorrhea.

Though the incidence of primary amenorrhea was quite low in our study, the incidence of transverse vaginal septum, Müllerian agenesis, and androgen insensitivity was quite compatible. The MRKH syndrome is associated with vaginal genesis and is thought to be due to mutation and polymorphism in anti-Müllerian hormone gene and its receptors, or alterations in HOX gene or N314D gene.

The mean age for MRKH syndrome was 19.83 years. It matters for creation of neovagina vaginoplasty, as it has to be done 3 to 6 months prior to marriage.

As Müllerian anomalies have varied presentations or are asymptomatic, girls with MRKH syndrome presented with primary amenorrhea or came to get investigated for infertility. This corresponds to the study by Parikh et al.[5] The MRKH syndrome is the most common cause of primary amenorrhea in our study, which coincides with the study by Parikh et al[5] and Tanmahasut et al[4] (Table 6).

More than one diagnostic modality is required in 62% cases of primary amenorrhea. This is true in our study. Clinical examination, USG, and laparoscopy clinched the diagnosis. Cytogenetic study was done in one girl due to financial problem.

There has been an evaluation of treatment for MRKH syndrome over the years for use of skin grafts, intestine, amnion, and now laparoscopic peritoneal pull-through. Dilatation with mold is the key for patency of the created neovagina. The girl who has had Vichetti operation for creation of neovagina had VVF, which may be due to faulty direction of pressure and was lost to follow-up.

Table 6: Comparison of incidence of anomalies

Diagnosis	*Parikh et al 2013*	*Incidence in general population*	*Incidence in Our study*	*Tanmahansut et al 2012 N=295*	*Reference*
Primary Amenorrhea	0.022 (14/60958)	0.3	0.043		Clinical K summary March 2009[3]
Imperforate Hymen	0.006 (4/60,958)	0.1	0.012	2.0	JOG 2001[6]
Transverse vaginal septum	0.001 (1/60,958)	0.00002 (2/100,000)	0.009	0.3	Archiver Gynecol Obstet 2012[7]
Müllerian Agenesis	0.013 (8/60,958)	0.00025 (1/4,000)	0.0185	39.7	Neat results Biomed 2006[8]
Androgen insensitivity Syndrome	0.001 (1/60,958)	1.010 (1/ 99,000)	0.0030	5.1	Reproductive med

For imperforate hymen or low transverse vaginal septum, cruciate incision followed all aseptic precautions.

The exact etiology of transverse vaginal septum is unknown, but its incidence has been reported to be 2 in 100,000 female live births, making it one of the rarest anomalies of the female genital tract.[8] The etiology of the condition is unknown, although most cases are thought to be the result of female sex-limited autosomal recessive transmission. In transverse vaginal septum, a vertical fusion disorder exists between the Müllerian ducts and the urogenital sinus.[9,10] The septa may occur at any level in the vagina with the following frequencies: 46%, upper vagina; 40%, mid vagina; and 14%, lower vagina. Septa may be complete or incomplete. They are generally less than 1 cm in thickness, with thicker septa noted to be more common near the cervix.[4] In our case study, we had one patient with transverse vaginal septum, which was of low variety. An imperforate transverse vaginal septum may present before or after puberty. Repair before puberty is associated with a high rate of vaginal stenosis, and rerepair with vaginal reconstruction may be required later for adequate menstruation and coital function. Localization of septum is important for future obstetric outcome as higher the septum more are chances for hematosalpinx and endometriosis, thus affecting fertility. Approach for high septum is abdominal or abdominovaginal with pull-through operation.

In case of AIS, gonadectomy is delayed until patient has completed pubertal development with HRT.

CONCLUSION

Racial, genetic, and environmental factors appear to play a part in the causes of primary amenorrhea. The MRKH syndrome was the most common type of anomaly for primary amenorrhea, which relates to its embryogenesis and defines therapy and prognosis.

Thorough history, clinical examination, and laboratory testing narrow differential diagnosis as the presentation is varied. Multiple diagnostic modalities are required for diagnosis.

So, individualization of management taking anatomical and clinical characteristics into consideration and patient's wish is required.

Establishing correct diagnosis is essential for planning treatment and management strategies as treatment goals are preservation of fertility and progression of normal development.

Critical test of procedure's value is patient's postoperative ability to have healthy sexual relation and achieve successful reproductive outcomes.

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