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Mullerian Anomalies: A Cause of Primary Amenorrhoea

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Abstract: ***Background**: The objectives of this study were to determine the etiologic causes of amenorrhea, the prevalence of müllerian anomalies as a cause of primary amenorrhea and the different varieties of müllerian anomalies causing primary amenorrhea. **Methods**: This study included all the women presenting with primary amenorrhea who presented to the department of obstetrics and gynecology, Nalanda Medical College and hospital, Patna from March 2016 to March 2017. **Results**: The causes of primary amenorrhea in our study due to imperforate hymen was 35.7%(n = 5) , transverse vaginal septum 14.28% (n = 2) and müllerian agenesis were 50% (n=7) . **Conclusions**: Mullerian agenesis is the most prevalent cause of primary amenorrhea in our study.*

Keywords: Primary amenorrhea, Mullerian agenesis, Obstructive mullerian anomalies

1. Introduction

Amenorrhea is the absence of a menstrual period in a woman of reproductive age. The term is derived from Greek: a = negative, men = month, rhoia = flow.1 Primary amenorrhea (menstruation cycles never starting) may be caused by developmental problems such as the congenital absence of the uterus, or failure of the ovary to receive or maintain egg cells. Also, delay in pubertal development will lead to primary amenorrhea.

It is defined as an absence of secondary sexual characteristics by age 14 with no menarche or normal secondary sexual characteristics but no menarche by 16 years of age. 2 The incidence of Primary amenorrhea is: 0.3% (Clinical Knowledge Summaries, 2009). 3 By compartment: The reproductive axis can be viewed as having four compartments: 1. Outflow tract (uterus, cervix, and vagina), 2. Ovaries, 3. Pituitary gland and 4. Hypothalamus.

2. Methods

This study was done at Nalanda Medical College and Hospital, Patna from March 2016 to March 2017. Total number of patients attending GOPD during this period was 5406.

The objective was to determine:
- The etiologic causes of amenorrhea
- The prevalence of müllerian anomalies as a cause of primary amenorrhea
- The different varieties of müllerian anomalies causing primary amenorrhea

The inclusion criterion was: H/o primary amenorrhea.

The exclusion criterion was: Pregnancy and age< 14years
Patients with features of Turner's syndrome or absent vagina were to be included even if they presented before 14 years of age

A careful history was taken to determine psychological or emotional stress, family history for genetic anomalies. Clinical assessment was done for signs of physical problems with focus on nutritional status and abnormal growth, per abdomen, local hymen examination and per rectal examination was done in all patients to determine presence or absence of uterus.

Ultrasonography was done to determine presence of uterus and its anomalies, endometrial thickness and associated mass if any. CT/MRI were done in some cases if USG seemed inadequate RBS, S. LH, S.FSH, S. Prolactin and S. TSH were done depending on patient's clinical examination. Due to lack of facility cytogenic evaluation was done in only 2 cases.

Further investigations were aimed to elucidate associated abnormalities like renal and skeletal.
Once the diagnosis was established, the patients were counselled and treated accordingly

3. Results

During this period total number of patients attending the gynaec outpatient department was5406. We had 14 patients who presented with primary amenorrhea. The incidence of primary amenorrhea in our institute was 0.258% .

Table 1: Age at presentation and Marital status

Causes	Number (%) (n=14)	Age at presentation (years) Mean ± SD	Marital Status	
			S	M
Imperforate Hymen	5	15.75±1.7(14 – 18)	5	
Transverse Vaginal septum	2	16	1	1
Mullerian Agenesis	7	19.25±3.2 (16 – 25)	6	1

S = Single, M= Married

It was observed that patients with obstructive anomalies presented earlier than those with müllerian agenesis as they developed complaints because of obstruction.

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The observation table with presenting complaint is shown below (Table 2). It was seen that only patients with müllerian anomalies presented with amenorrhea as a primary complaint while in others the presenting symptom varied.

Table 2: Observation With Presenting Complaint

Diagnosis	Total patients	Abdominal pain	Urinary complaint	Abdominal mass	Primary amenorrhoea
Imperforate Hymen	5	2	1 (retention)	1 (16 – 18 ks mass arising from pelvis)	1
Transverse vaginal septum	2	1			
Mullerian agenesis	7		1 (incontinence)		6

Table 3: Incidence in Relation to General Population

Diagnosis	Incidence in our study	Incidence in general population	Reference
Primary amenorrhoea	0.258	0.3	Clinical Knowledge Summaries 2009
Imperforate Hymen	0.092	0.1	Am J of Obstet & Gynec 2001
Tranverse Vaginal septum	0.03	2 in 100,000 females	Archives Gynecol Obstet 2012
Mullerian agenesis	0.12	1 in 4000 – 5000 females	J Negat Results Biomed 2006

In our study müllerian agenesis (50 %) was the most common cause which was compatible with Tanmahasamut et al (Thailand). 4 This is in contrast to American study by Reindollar et al. 5 gonadal dysgenesis was commonest (48.5%) -American study. This verified that racial and environmental factors played an essential part in the causes of primary amenorrhea.

Table 4: Investigations for Confirmation of Diagnosis and Treatment

Investigations	Total No.	Diagnosis	Findings	Management
Ultrasound Imaging	14	Imperforate hymen (5)	Hematocolpos – 3 Hematometra - 2	Drainage
		Mullerian agenesis (7)	Absent Uterus – 4 Blind vagina/ Lower one third of vagina developed- 6 Rudimentary horns – 3 Ovaries normal -10 Streak ovaries - 2	Vaginoplasty – just before marriage
		Transverse vaginal septum(2)	Hematocolpos with low transverse vaginal septum- 2	Drainage and reconstruction of vagina
MRI	6	Rudimentary Horns with renal anomalies (2) Streak ovaries (2) Transverse Vaginal Septum (2)		

For the work up of primary amenorrhoea, ultrasound imaging was dome in all patients. Out of the total 5 patients with imperforate hymen, Hematocolpos was seen in 3 while hematometra was seen in 2 patients. These patients were treated with drainage of hematocolpos and hematometra.

Among patients with Mullerian agenesis, Absent uterus was seen in 4 patients while Rudimentary horns were seen in 3 cases. Blind vagina or development of only the lower one third was seen in 6 out of 7 cases with Mullerianagenis.Ovaries were found to be normal in 12 patients while 2 patients had streak ovaries. Those with blind vagina had to undergo vaginoplasty just before marriage.

Müllerian agenesis affects only females.In almost all reports, karyotype of patients was that of normal 46, XX women. Rare chromosome abnormalities have been found associated with Müllerian aplasia, such as mosaicism, rearrangements/deletions.8 Cytogenic study was done in only 2 cases and reported to be normal.

Transverse vaginal septum was seen in 2 patients who showed hematocolpos with presence of low transverse vaginal septum. These patients were treated with drainage and reconstruction of vagina.

Ultrasound was also done to find out concurrent renal abnormalities. Horse shoe shaped kidney was seen in one patient while absence of kidney on one seen was seen in 2 patients with Mullerian anomalies

4. Discussion

Amenorrhea is a symptom, not a disease, and has a variety of causes. Clinical classification of amenorrhea into primary and secondary gives us a rough guide to etiology and prognosis. 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 cause 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 abnormalities exist and this abnormality may present at different stages of life. After puberty, imperforate hymen presents in association with cyclic pain and amenorrhea. Physical examination often reveals a bulging hymen with a bluish hue. Some adolescents also present

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with painful urination, back pain,and painful defecation, as well as amenorrhea.

Imperforate hymen must be differentiated from a low transverse vaginal septum; this can be accomplished with Valsalva. Imperforate hymen should bulge with Valsalva and transverse vaginal septum should not.

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.7 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. 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 two patients with transverse vaginal septum, which was 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 re-repair with vaginal reconstruction may be required later for adequate menstruation and coital function. Postpubertal patients generally present with cyclic pain, vaginal discharge, abnormal menstruation, and development of pelvic mass. Magnetic resonance imaging is currently the gold standard for delineating the anatomy.

Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome consists of vaginal aplasia with other müllerian (i.e. paramesonephric) duct abnormalities. The frequency of congenital absence of vagina and uterus is not yet entirely clear, although reported incidences vary from 1 in 4,000 to 5,000 female births. Type I or The typical form is characterized by laparoscopic or laparotomy findings of symmetric muscular buds (the Müllerian remnants) and normal Fallopian tubes; this is referred to as the so-called Rokitansky sequence, where only the caudal part of the Müllerian duct (upper vagina and uterus) is affected. The type II or atypical form is marked by other malformations; these include vertebral, cardiac, urologic (upper tract), and otologic anomalies. In our study we had one patient of type II who had vertebral, urologic and facial anomaly. In both types, the extent of vaginal aplasia varies, ranging from virtually absent to virtually inconsequential.

Mayer-Rokitansky-KusterHauser syndrome usually remains undetected until the patient presents with primary amenorrhea despite normal female sexual development. It is the second most common cause of primary amenorrhea. 5 Though in our study müllerian agenesis (58.17 %) was the most common cause in our study. The frequency of type II is much greater. Though in our study Type I variety was found be more common. Familial clustering is reported with increasing frequency as was seen in our study. The overall features clearly differentiate the MRKH syndrome from other defects of genital tract development such as androgen peripheral insensitivity (patients 46, XY) or Turner's syndrome (patients 45, X). As all the cases in the study were involving compartment I, diagnosis was produced by only simple clinical information, that is, medical history, physical examination, and reproductive hormonal profile.

Cytogenic analysis was suggested in those with streak gonads. This is to identify the Y chromosome or its fragment(s). The gonads or gonadal ridges of these patients are at high risk of malignant transformation. As tumour transformation in gonadal ridge could occur at any age, the streak gonads should be removed in as soon as diagnosis is made.Except in case of androgen insensitivity syndrome, in which gonadectomy can be delayed until patient has completed pubertal development.

The limitations of this study are that it was conducted in a tertiary hospital so the study population were somewhat affected by referral patterns and what referring physicians were comfortable taking care of. Also the study population was small in comparison to other studies.

5. Conclusion

Racial, genetic and environmental factors appear do play a part in the causes of primary amenorrhea. Obstructive Müllerananomalies present most frequently in childhood and adolescence. A high index of suspicion is necessary for proper diagnosis. Clinicians who care for adolescents must consider Obstructive Müllerian anomalies in the differential diagnosis when abnormal bleeding, amenorrhea, or cyclic pelvic pain is present. Magnetic resonance imaging is currently the gold standard for delineating the anatomy. Goals of therapy in the care of young women with these anomalies are relief of the obstructive symptoms and restoration of normal menstrual egress and sexual function, with preservation of reproductive potential. Gonadal dysgenesis is not common in androgen insensitivity and mulerian agenesis. Although Mullerian agenesis has psychologically devastating consequences, its physiological defects can be surgically treated in many cases. Following diagnosis, surgical intervention allows patients to have normal sexual function. Reproduction may be possible with assisted technique.

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