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CAUSES OF PRIMARY AMENORRHEA AMONG PATIENT PRESENTING AT A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: The objective of this study was to collect data of patients coming to us with primary amenorrhea. Finding the different causes of this problem and managing them accordingly with the help multidisciplinary team. **Methods:** In this descriptive case series, patients with primary amenorrhea coming to the Gynaecology A Unit, Lahore Medical and Dental college, Lahore, from December 2018 till November 2019 were included. Data was collected on predesigned proforma. Investigations were advised according to the protocol made by our unit. Data was analysed using SPSS version 16. **Results:** Total number of primary amenorrhea cases were 82. Forty-nine (59.8%) were unmarried and 33 (40.4%) were married. The mean age of the sample was 16±5.3 years. In 20 (24%) cases, there was gonadal dysgenesis. Mayer Rokistansky Kuster Hauser syndrome was found in 18 (21.9%) of cases. Constitutional and Turner syndrome in 11 (13.4%), respectively. Imperforate hymen in 7 (8.5%), vaginal septum in 5 (6.1%), swyer syndrome 2 (2.4%). Endometrial receptor deficiency in 4 (4.8%) cases. There were two cases of hypogonadotrophic hypogonadism. One case of hypothyroidism and one case of congenital adrenal hyperplasia (CAH). **Conclusion:** Gonadal dysgenesis was the most common cause as compared to Mullerian duct abnormalities. Patients with endometrial receptor deficiency were more challenging. Primary amenorrhea is a distressing problem for patients as well for parents. These people are misdiagnosed and mismanaged at various occasions.

KEYWORDS: Primary amenorrhea; Gonadal dysgenesis; Swyer syndrome; Mayer Rokistansky; Kuster Hauser syndrome; Congenital adrenal hyperplasia.

INTRODUCTION

Adolescence is a stage of transition from childhood to womanhood. Primary amenorrhea is the most distressing problem arising at puberty which affects the physical, social and psychological behaviour of a girl. Primary amenorrhea is defined as the failure of initiation of menses by the age of 14 years in the absence of secondary sexual characteristics or at the age of 16 years with proper development of secondary sexual characteristics.[1–4] Various studies have given different incidence ranging from 0.065%[5] to 0.75%.[6] It is a symptom not a disease. It results in interruption at any point in the chain of structures controlling the menstruation. It needs normal hypothalamic, pituitary, ovarian axis, anatomical presence and patency of genital tract, responsive endometrium, 46XX karyotyping and active support from other endocrine glands like adrenal and thyroid. Many times, cause is not identified correctly and the young girl is mismanaged or fear of exposure of the defect may be the reason not to seek medical advice. Observing these problems in young girls for over the years, we started a project in our unit. The aim was to help these patients in terms of making correct diagnosis, management according to the cause with the help of multidisciplinary team and provide help for counselling and their adjustment is society.

MATERIAL AND METHODS

This prospective study was done in department of obstetrics and Gynaecology unit A from December 2018 till November 2019. It is ongoing study, a team of gynaecologists, endocrinologist, plastic surgeon, psychiatrist and psychotherapist was formed. The aim was to collect the data of patients with primary amenorrhea and make a protocol for reaching the correct diagnosis. The patients with pregnancy and secondary amenorrhea were excluded from the study.

Study protocol was approved from ethical committee and informed consent of patients/guardian was taken. A proforma was designed which included relevant history and examination special emphasis was on age, marital status, height, weight, development of secondary sexual characteristics and external genitalia. Tanner score was used for breast, pubic and axillary hair development. To reach a final diagnosis a protocol flow chart was design for investigations and patients were individualized for selection of specific investigations.

Initial investigation was ultrasonography of abdomen and pelvic organs. Hormonal Assay FSH, LH, Prolactin, TSH, Oestradiol, Testosterone, 17 hydroxyprogesterone were done

where ambiguity was found on examination and ultrasound. Karyotyping was done when needed like patients with ambiguous genitalia, abnormal gonads found on ultrasound or imbalance of hormones.

CT scan, MRI or intravenous urogram was done in selected cases where there was problem in the pituitary gland or doubt about urogenital tract malformation. Diagnostic laparoscopy was performed where there was doubt about presence or absence of gonads or genital tract. Once the diagnosis was made than patients were treated accordingly by multidisciplinary Patients were advised for regular follow up. Data was analysed by using the software, SPSS version 16.

RESULTS

In our study there were 82 patients. Age range from 12–30 years with mean 16±5.3. Thirty-three (40%) patients were married. Main presenting symptom was primary amenorrhea, but patients also had associated symptoms like cyclical pain, retention of urine.

Forty-nine (59.8%) were unmarried and 33 (40.4%) were married. The mean age of the sample was 16±5.3 years. In 20 (24%) cases, there was gonadal dysgenesis. Mayer Rokistansky Kuster Hauser syndrome was found in 18 (21.9%) of cases. Constitutional and Turner syndrome in 11 (13.4%), respectively. Imperforate hymen in 7 (8.5%), vaginal septum in 5 (6.1%) and swyer syndrome in 2 (2.4%). Endometrial receptor deficiency was in 4 (4.8%) cases. There were two cases of hypogonadotrophic hypogonadism, one case of hypothyroidism and one case of congenital adrenal hyperplasia (CAH). (Table-2). The details of clinical features and chromosomal pattern of two major causes of primary amenorrhea in present study are given in table-3 & 4.

Table-1: Associated symptoms of Primary Amenorrhea.

Complains	Frequency	Percentage
Primary amenorrhea	44	53.7
Pain hypogastrium	36	43.9
Urinary retention	02	2.4
Total	82	100

Table-2: Frequency of different causes of Primary Amenorrhea.

Cases	Frequency	Percentage
Gonadal dysgenesis	20	24.3
Rokitansky syndrome	18	21.9
Constitutional delay	11	13.4
Turner syndrome	11	13.4
Imperforate hymen	7	8.5
Vaginal septum	5	6.1
Receptor deficiency	4	4.8
Swyer syndrome	2	2.4
Hypothyroidism	1	1.2
Hypogonadism	2	2.4
CAH	1	1.2
Total	82	100

Table-3: Gonadal dysgenesis.

Total cases	Presentation	Karyotyping
10	Absent uterus and ovaries	46 XX
1	Only uterus band	46 XX
4	Rudimentary uterus	46 XX
5	Small uterus, small gonads (testis or ovaries)	46 XY

Table-4: Rokitansky syndrome.

Total cases	Presentation	Karyotyping
10	Uterus absent with only band normal ovaries. Karyotyping	46 XX
8	Uterus absent with rudimentary horns with normal ovaries. Karyotyping	46 XX

DISCUSSION

Primary amenorrhea remains a challenging problem for the gynaecologists as well as the patients and their families. It can affect the marital, sexual, reproductive and social status of the patient. Sometimes sex of raring becomes a problem. It needs a multidisciplinary team including gynaecologist, endocrinologist, plastic surgeon, psychiatrist and genetic counsellor for the management of patient. A proper protocol for investigation is important to avoid unnecessary investigations. Management plan should be according to cause, marital status, sex of raring. Counselling remains the main component of management.

As for as the cause of primary amenorrhea is concerned gonadal dysgenesis was at the top of the list comprising 20 (24%), which is in contrast to the other studies[7–10], where anatomical defects were more common. Rizwan et al found increased incidence of imperforated hymen (21.05%) in her 14 case series.[6] Gonadal dysgenesis is a developmental problem where there

is premature loss of primordial germs cells in developing gonads resulting in hypoplastic / dysplastic or streak gonads.[11] There are two types of gonadal dysgenesis, complete or partial on the basis of morphology of gonads.[12,13] In complete gonadal dysgenesis, no gonadal development occurs and as a consequence patient is phenotypically female.[14] We had two cases of complete or pure gonadal dysgenesis which is known as swyer syndrome. Patient was phenotypically female, with normal Mullerian structures/bilateral streak gonads and 46XY chromosomes this was typical presentation of swyer syndrome.[15] In this condition there is mutation and deletion in the SRY gene on Y chromosome. Presence of Y chromosomes renders the patient at increased risk of gonadal malignancy and gonadectomy in these patients should be done. Patna Yak R *et al* has reported similar case but in his case, patient had pelvic mass which on histopathologically revealed dysgerminoma.[16] Bagic G has also reported two similar cases.[17] Mixed gonadal dysgenesis is a condition of unusual and asymmetrical gonadal development leading to an unassigned sex differentiation, Arora A has reported a case of such type[18], but we did not have such a case.

In our series 18 (21%) of case were of Mayor Rokistansky Kuster Hauser (MRKH) syndrome with its typical presentation of primary amenorrhea, well developed secondary sexual characteristics, female external genitalia, blind vagina, absent or rudimentary uterus and 46XX chromosomes. This is in contrast to the study by Parichi et al where he reported MRKH syndrome the most common cause constituting about 58% in his series.[19] The incidence of MRKH syndrome is one in 4500.[20,21] Majority of these are sporadic[8] but in some cases genetic familial tendency has been described.[22,23] Mayor Rokistansky Kuster Hauser is either type-I (isolated) or type-II MURS associated with mullerian duct aplasia, renal dyspasia and cervical somite anomalies.[24] In our series we did not find any case with type II MRKH. Pai *et al* has reported a case, where there was blind vagina, rudimentary uterus, absent left kidney, macrocephaly and Dandy Walker malformation.[25] In our series constitutional and Turner syndrome went side by side 11 (34%) in each group. Patients with Turner syndrome had phenotypic features, infertile uterus, streaked ovaries and 45XO chromosomes. Jabbar *et al* has reported relative high incidence of turner syndrome, 4 cases in series of total 18 cases.[7] Vaddadi *et al* has reported a rare case where the patient had typical feature of Turner syndrome with complete absence of uterus, cervix and streaked ovaries.[26] There were 7 (8.5%) cases of imperforate hymen and 5 cases of vaginal septum. Rizwan *et al* has reported 21% cases of imperforate hymen in his series.[7] There were 4 (48%) cases, which were quite challenging for us. In these patients all the investigations were normal and

these did not show any response to combined oral contraceptive pills for 3 months. We labelled these cases as receptor deficiency, in one case patient has large bilateral endometriotic cysts. Similar case has been reported by Tava Suli *et al*.[27] The cause could be endometrial hypoplasia as the endometrial thickness in all cases were less than 4 mm. Baker *et al* also reported similar cases where every investigation was normal and endometrial biopsy revealed absence of endometrial.[28]

There were two cases of hypogonadotrophic hypogonadism and one case of hypothyroidism. Tadmore *et al* has reported a case with similar presentation, but that patient had hyperprolactinemia and enlarged pituitary gland.[29] Shahani *et al* also reported similar case.[30] There was single case of congenital adrenal hyperplasia of late onset. Patient had primary amenorrhea with signs of hyperandrogenism. There was clitoromegaly, small uterus, 17 hydroxyprogesterone levels was high and 46XX karyotypes. Though this is a rare cause but Moayeri *et al* has reported the incidence as 6.6% in his 105 cases.[31] Siddiqui SA has also reported a case of CAH of simple virilizing type presented later in childhood.[32]

CONCLUSION

Gonadal dysgenesis was the most common cause as compared to mullerian duct abnormalities. Patients with endometrial receptor deficiency were more challenging. Primary amenorrhea is a distressing problem for patients as well for parents. These people are misdiagnosed and mismanaged at various occasions. Primary amenorrhea may not be a common problem but most of the time it is under reported. It is still a challenging problem for gynaecologist; dedicated team is required for the diagnosis and management.

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