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Original Research Article

Etiological evaluation of amenorrhea: a cross-sectional study from a tertiary care center in India

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ABSTRACT

Background: To determine the prevalence of etiological causes in cases with primary and secondary amenorrhea in a tertiary care center in Western India.
Methods: A retrospective analysis of 170 medical records of non-pregnant women who presented with either primary or secondary amenorrhea to the Department of Obstetrics and Gynecology, IKDRC-ITS, Ahmedabad, Gujarat from Jan 2014 to December 2022 was done. The clinical profile, presentation, development of secondary sexual characteristics, physical examinations, hormone profile, imaging and cytogenetic study including karyotyping was done.
Results: The most common causes of primary amenorrhea identified were end organ failure (71.49%), among these 69.41% had some form of Mullerian anomalies while three were cases of complete androgen insensitivity syndrome. This was followed by hormonal abnormalities (15.97%) and gonadal failure (7.63%). There were two cases of gonadal dysgenesis, three cases of Turner's syndrome, three cases of complete androgen insensitivity, one case of Swyers syndrome, two cases of ring X chromosomes. Hypergonadotropic hypogonadism was the most common cause of secondary amenorrhea. Three patients had premature ovarian failure. Single kidney was the most common association seen in eleven patients.
Conclusions: This is one of the large studies exploring causes of both primary and secondary amenorrhea in Western India. Mullerian anomaly was the commonest cause of primary amenorrhea followed by hormonal abnormalities and gonadal failure. Hypergonadotropic hypogonadism was the most common cause of secondary amenorrhea. Role of racial, genetic, epigenetic and environmental factors could be an area of future research.

Keywords: Mullerian anomaly, Primary amenorrhea, Secondary amenorrhea

INTRODUCTION

Amenorrhea is the cessation of the menstrual cycle in a woman of reproductive age.[1,2] Amenorrhea can be classified as primary when menarche is not attained by age of 15 years or even after three years of thelarche while secondary amenorrhea is cessation of menses for more than three months in a woman with previous regular cycles or more than six months in a woman who has had at least one previous spontaneous cycle.[1,3] It is estimated that the prevalence of amenorrhea excluding pregnancy, lactation and menopause is around 3 to 4 percent and WHO estimates it as sixth largest cause of subfertility.[4-6] Onset of menstruation can depend on various patient specific factors likewise amenorrhea can be multi-factorial. Both primary and secondary amenorrhea warrant evaluation and cause specific treatment.[7-9] The etiology of amenorrhea is varied and the problem can be identified at different tiers of the hypothalamic- pituitary gonadal axis.[10,11] The common causes can be anatomic and sexual development disorders, chromosomal abnormalities, ovarian insufficiency, pituitary and hypothalamic causes and endocrine disorders. Physiological causes, stress,

medications are commonly associated with secondary amenorrhea. Few studies have been done in India to estimate the prevalence of various etiologies hence this study was undertaken to assess the same in our population.[12]

METHODS

Study design

It was a retrospective study carried out at IKDRC-ITS, a tertiary care centre in western India from January 2014 to December 2022, after clearance from the Institutional Ethical Committee. The study complied with the Declaration of Helsinki.

Inclusion criteria

All nonpregnant patients who had presented with amenorrhea either primary or secondary during the study period were included. The standard evaluation protocol of all patients with amenorrhea included a detailed history, examination, hormonal profile, ultrasound of abdomen and pelvis or MRI pelvis for anatomic anomalies and chromosomal analysis.

Chromosome analysis was performed in the cytogenetic laboratory using standard G-bands by trypsin using giemsa (GTG)-banding techniques on cultured lymphocytes. Peripheral blood was put for 72-h culturing where peripheral blood lymphocytes were induced with phyto-hemagglutinin. Metaphase spreads were obtained from blood lymphocytes using standard procedures. Chromosome analysis was carried out using applied spectral imaging (ASI), Israel software. The records of all enrolled patients were reviewed and the details of history, examination and investigations were filled in pre-designed pro-forma.

Statistical analysis

Data was entered in excel sheet and analysis was done using SPSS 20.

RESULTS

A total of 170 patients were evaluated for amenorrhea mostly primary amenorrhea (PA) (84.7%) (Table 1). The distribution according to age range has been illustrated in Table 2 and Table 3. Most patients with PA were less than 20 years and the most common cause was end organ failure seen in 103 patients (71.49%) among these 69.41% had some form of Mullerian anomalies while three were cases of complete androgen insensitivity syndrome as shown in Table 4. This was followed by hormonal abnormalities (15.97%) and gonadal failure (7.63%) and other causes as described in Table 5.

The common cause of presentation for patients with PA were not attaining menarche, referral for vaginoplasty/uterine transplant, pain abdomen and infertility as shown in Table 6. The most common etiology for secondary amenorrhea was hypergonadotrophic hypogonadism (50%) of cases while cause was unknown in 23% of patients as shown in Table 7 and all patients presented with infertility as shown in Table 8.

Table 1: Distribution according to type of amenorrhea.

Indication	Total no. of patient	%
Primary amenorrhea	144	84.70
Secondary amenorrhea	26	15.29
Total	170	

Table 2: Age wise distribution (Primary Amenorrhea).

S. no.	Age group (in years)	No. of cases	%
1	10-13	10	6.94
2	14-20	66	45.83
3	21-25	40	27.77
4	26-30	18	12.5
5	31-38	10	6.94

Table 3: Age wise distribution (Secondary Amenorrhea).

S. no.	Age group (in years)	No. of cases	%
1	14-20	4	15.38
2	21-25	8	30.76
3	26-30	7	26.92
4	31-38	7	26.92

Table 4: Amenorrhea details.

Primary amenorrhea	Secondary amenorrhea
Height- Min- 60 cm	Height- Min- 146 cm
Max- 175 cm	Max- 170 cm
Average- 152 cm	Average- 151 cm
Weight- Min- 21 kg	Weight- Min- 36 kg
Max- 95 kg	Max- 98 kg
Average- 47 kg	Average- 54.69 kg

Table 5: Etiology of primary amenorrhea.

S. no.	Findings	No. of patients	%
A	**End organ failure**	103	71.49
1	Mullerian agenesis	77	53.47
2	Cervical agenesis	02	1.38
3	Transverse vaginal septum (TVS)	10	6.94
4	Unicornuate uterus	04	2.77
5	Bicornuate uterus	05	3.47
6	Complete androgen insensitivity syndrome (CAIS)	03	2.08
7	Uterine Didelphys	02	1.38
B	**Gonadal failure**	11	7.63
8	46, XX Gonadal dysgenesis	02	1.38
9	45, XO (Turner syndrome)	03	2.08
10	45, X/46, X (r) (Ring X chromosome)	02	1.38
11	46, X,del (X) (p11.3)	01	0.69
12	Mos 45, X (40)/46, XY (60)	01	0.69
13	46, XX,t (12;21)(q22:q22.3) (Translocation)	01	0.69
14	46, XY (Swyer syndrome)	01	0.69
	Hormonal cause	23	15.97
15	Hypergonadotropic hypogonadism	13	9.02
16	Hypogonadotropic hypogonadism	09	6.25
17	Polycystic ovarian disease (PCOD)	01	0.69
	Others	7	4.86
18	Non-classic congenital adrenal hyperplasia (NCAH)	01	0.69
19	Normal	05	3.47
20	CKD	01	0.69
	Total	144	

Table 6: Symptoms at presentation (Primary Amenorrhea).

S. no.	Symptoms	No. of cases	%
1	Not attained menarche	74	51.38
2	Infertility	13	9.02
3	Referred for uterine transplant	05	3.47
4	Referred for vaginoplasty	29	20.13
5	Pain abdomen	18	12.5
6	Short stature	04	2.77
7	Conceiving pregnancy	01	0.69
	Total	144	

Table 7: Etiology of secondary amenorrhea.

S. no.	Findings	No. of patient	%
	Pituitary cause		
1	Hypergonadotropic hypogonadism	13	50

Continued.

S. no.	Findings	No. of patient	%
2	Hypogonadotropic hypogonadism	04	15.38
3	Premature ovarian failure (POF)	03	11.53
4	Unknown cause	06	23.07
	Total	26	

Table 8: Symptoms at presentation (Secondary Amenorrhea).

S. no.	Symptoms	No. of cases	%
1	Infertility	26	100
	Total	26	

Table 9: Spectrum of renal anomalies associated with cases of amenorrhea.

S. no.	Kidney	No. of patient	Findings
1	Single kidney	11	Mullerian agenesis
2	Ectopic kidney	5	Mullerian agenesis
3	Horseshoe kidney	2	ring X – 1 Mullerian agenesis-1
4	Small kidney	2	Turner- 1 Mullerian agenesis-1
5	Rt kidney in pelvis	1	Mullerian agenesis
6	Solitary kidney	2	Mullerian agenesis-1 Trans vaginal septum-1
7	Malrotated kidney	1	Mullerian agenesis
8	Reniform kidney	1	Mullerian agenesis
9	Normal	22	Mullerian agenesis

Twenty-five patients with primary amenorrhea had some form of associated renal anomalies which have been listed in Table 9. Single kidney was the most common association seen in eleven patients of mullerian anomalies.

DISCUSSION

Amenorrhea has a varied etiology ranging from end organ failure or genital tract obstruction, gonadal failure, disorders of the hypothalamo-pituitary, hormonal causes etc. Both primary and secondary amenorrhea need evaluation and the etiologies may be overlapping. The diagnostic algorithm should include detailed history, physical examination including development of secondary sexual characteristics, hormone analysis, imaging modalities including pelvic ultrasonography and MRI in indicated cases. Cytogenetic analysis including karyotyping is also an important evaluation especially in cases of gonadal failure, premature ovarian failure etc as they constitute an important cause especially in cases of PA.

Studies done worldwide have found that gonadal dysfunction and outflow tract obstruction and hypothalamo- pituitary causes as three most common causes of amenorrhea.[12-14] In our study the common cause of PA was end organ failure or outflow tract obstruction (71.49%) most prominently Mullerian agenesis which constituted 53.4% of cases. Various studies done in India and various parts of South East Asia report similar findings, however studies done in the west report gonadal failure as the leading cause of amenorrhea, especially PA.[12-14] The reason for this observation could be racial and environmental factors. The high incidence of Mullerian agenesis could also be due to the fact that this is a referral center for a large catchment area in North Western India and it also offers services like uterine transplant.

Cytogenetic evaluation is an important cause in the evaluation of amenorrhea, especially PA. In our study 7.6% of patients had cytogenetic abnormalities.[15] The common abnormalities seen were gonadal dysgenesis, Turner's and its mosaic form, structural abnormalities like deletion, translocations and male karyotype. This was similar to other studies done in different parts of India.[6,13,14] The present study shows Turner syndrome to be the most common chromosomal abnormality detected in cytogenetic testing which is similar to other studies.[16,17] Most common presentation was amenorrhea, referral for surgery, dysmenorrhea and infertility which was similar to other studies. Unilateral renal agenesis was the most common association seen in our patients as Mullerian agenesis is often associated with the same.[18,19] Unlike studies done in other parts of India we did not get any patients with genital tuberculosis as a cause of amenorrhea which could be low prevalence in this part.[13,20] The strengths of this study were, it included a good number of patients, both primary and secondary amenorrhea cases were included.

CONCLUSION

This is one of the large studies exploring causes of both primary and secondary amenorrhea in Western India.

Mullerian anomaly was the commonest cause of primary amenorrhea followed by hormonal abnormalities and gonadal failure. Hypergonadotropic hypogonadism was the most common cause of secondary amenorrhea. Role of racial, genetic, epigenetic and environmental factors could be an area of future research.

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