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Evaluation of Etiopathology and Management of Primary and Secondary Amenorrhea in Adolescent and Young Women in North Indian Population

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ABSTRACT

Background: Amenorrhea, the absence of menstruation, is categorized into primary (before menarche) and secondary (after menarche) forms, with significant implications for female reproductive health.

Methods: This observational study conducted at the Department of Obstetrics and Gynaecology, King George's Medical University, assessed the etiological factors and management of amenorrhea in adolescent and young women aged 11-24 years from January 2020 to January 2021.

Results: Out of 73 participants, 42.46% were diagnosed with primary amenorrhea, while 57.54% had secondary amenorrhea. Mullerian anomalies were identified as the leading cause of primary amenorrhea, accounting for 83.8% of cases. Other causes included imperforate hymen (9.67%), constitutional delay (9.27%), androgen insensitivity syndrome (3.23%), and Turner variant (3.23%). In contrast, polycystic ovary syndrome (PCOS) emerged as the most common cause of secondary amenorrhea, observed in 80.95% of cases, followed by hyperprolactinemia (7.14%), hypothyroidism (7.14%), premature ovarian failure (2.38%), and Asherman syndrome (2.38%). Management strategies were tailored to the underlying etiology, with surgical interventions such as vaginoplasty (48.39%), septum excision (3.23%), and cruciate incision (9.68%) being the primary treatments for structural causes of primary amenorrhea. For secondary amenorrhea, out of 42 cases 34 PCOS and 1 premature ovarian failure patient i.e. 83.34% were particularly treated by lifestyle modification and cyclical E+P therapy, 1(2.38%) by Hysteroscopic adhesiolysis for Ashman's Syndrome, 3(7.14) by cabergoline treatment for hyperprolactinemia and 3 (7.14%) hypothyroidism by thyroxin treatment.

Conclusion: The study underscores the importance of early diagnosis and individualized treatment to enhance reproductive health outcomes in affected women. The findings also emphasize the need for further research to evaluate long-term outcomes and refine management protocols for both primary and secondary amenorrhea, ultimately aiming to improve patient care and fertility prospects.

Key-words: Amenorrhea, adolescent, Management, Etiopathology, Women

INTRODUCTION

Amenorrhea is the absence or abnormal cessation of menses. Primary andsecondary amenorrhea describe the occurrence of amenorrhea before and after menarche, respectively [1]. Primary amenorrhea is defined as the absence of menses by 13 years of age when there is no visible development of secondary sexual characteristics or the absence of menses by 15 years of age in the presence of normal secondary sexual characteristics [2].

Secondary amenorrhea is defined as the absence of menses in a female who has previously menstruated and menses are absent for 3 months in females with regular cycles and 6 months in females with a history of

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irregular cycles [2].

According to the World Health Organization, amenorrhea is the sixth leading cause of female infertility, affecting 2-5% of women of childbearing age [3].

Primary and secondary amenorrhea can be caused by a variety of reasons, including structural, endocrine, genetic and environmental ones. Congenital defects such as Mullerian agenesis, androgen insensitivity syndrome and chromosomal disorders like Turner syndrome are frequently the cause of primary amenorrhea. The role of endocrine diseases such as such as hypogonadotropic hypogonadism is significant [4].

Usually, stress, dramatic weight loss, or intense exercise cause disruptions in the hypothalamic-pituitary-ovarian (HPO) axis, which results in secondary amenorrhea. Secondary amenorrhea can often be caused by PCOD, which is associated with hyperandrogenism and persistent ovulation. Other significant factors include premature ovarian insufficiency, hyperprolactinemia and thyroid dysfunction [5].

The underlying cause of amenorrhea and the patient's reproductive objectives govern the course of management. The main goal in treating cases of primary amenorrhea is to determine and correct any anatomical defects or hormonal imbalances. In situations of hypogonadism, hormone replacement therapy is frequently used to produce menstruation and secondary sexual characteristics, however, surgical intervention may be required for structural problems [6].

The goal of treating secondary amenorrhea is to get the ovulatory cycle back on track and take care of any comorbidity like PCOD or thyroid issues. Treatment must, getting nutritional counseling and reducing stress, particularly when the condition is related to lifestyle factors. The patient's desired fertility may determine whether to prescribe pharmacological therapies such as ovulation-inducing drugs or oral contraceptives [7].

Early diagnosis and timely intervention are necessary to prevent long-term health and social consequences. Once the etiology is established, patients can be counselled about prognosis and future fertility options [8]. After the brief study, we plan an observational study to evaluate etiological factors and management of primary and secondary amenorrhea in adolescent and young women.

MATERIALS AND METHODS

This observational study was conducted in the Department of Obstetrics and Gynaecology of Queen Mary Hospital, King George's Medical University, Lucknow in collaboration with the Department of CFAR (Centre for Advanced Research, KGMU after the ethical clearance from the institutional ethics committee, KGMU, Lucknow Adolescent females and young women from 11 to 24 years of age were selected to enter in this study from January 2020 to January 2021 with informed consent. Out of the 117 patients approached, 12 patients refused to participate in the study,18 patients were excluded from the study due to loss to follow-up, and 14 patients were excluded from the study as they became COVID-19 positive and could not return for follow-up due to their ill health. Eventually, 73 patients were enrolled in this study. All the cases were included according to inclusion & exclusion criteria:

Inclusion Criteria

1. Patient with age group 11-24 years with complaints of amenorrhoea.
2. Period of amenorrhea >3 months
3. Patients who will give informed consent for participation in the study.

Exclusion Criteria

1. History of hysterectomy
2. Pregnant
3. Patients not giving consent.

Work-up for Amenorrhea- Information on the female adolescents and young women was recorded under history, clinical examination, laboratory investigations, imaging and special investigations on aproforma.

History included the duration of amenorrhea, cyclical abdominal pain, eating habits, presence of stress, exercise patterns, weight gain or loss, presence of galactorrhea, acne, excessive hair growth, heat or cold intolerance, presence of excessive hairfall, and constipation. Presence of withdrawal bleeding after progesterone challenge test or estrogen and progesterone challenge test. History of any past medical or surgical history or chronic medication intake, history of tuberculosis. A family history of similar complaints, mental retardation and any other significant illness was also obtained.

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General physical examination including height, weight, body mass index (BMI), palpation of thyroid, and sexual maturity staging (Tanner staging of breast and pubic hair). Stigmata of Turner Syndrome such as webbed neck, low hairline or cubitus valgus were looked for.

The local examination included inspection and palpation of the external genitalia, per vaginal and per rectal examination with the patient or guardian's consent. Serum levels of thyroid-stimulating hormone, prolactin, luteinizing hormone and follicle-stimulating hormone were tested. The urine pregnancy test was also done. Pelvic ultrasonography was done to evaluate mullerian anomalies and ovaries. Karyotyping was done in all the cases of primary amenorrhea and cases suggestive of gonadal failure. In our study, we used the WHO classification for diagnosing thyromegaly.

Ethical Clearance- Ethical clearance was obtained from the Institutional Ethics Committee (ref code: 101st ECM 11B thesis/P74) of King George's Medical University, Lucknow, India.

RESULTS

Fig. 1 shows that 73 adolescent and young women were included in the study and whether they had 31 (42.46%) had primary amenorrhea, while 42 (57.54%) had secondary amenorrhea.

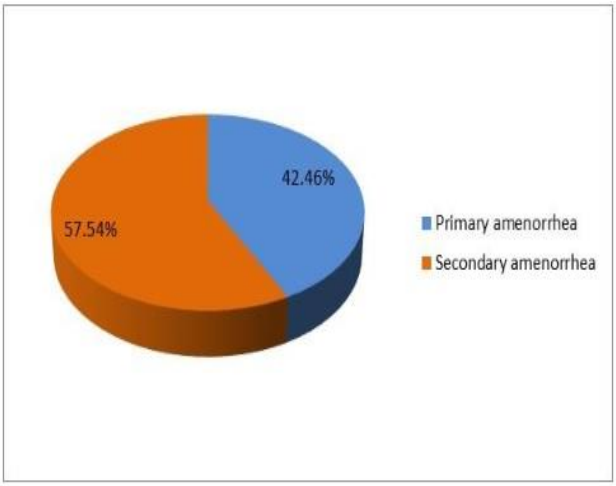

Fig. 1: Pie chart shows the primary and secondary amenorrhea (N=73)

Table 1 shows the ages of adolescent and young women with primary and secondary amenorrhea. Values are expressed as mean, median, ±SD, minimum and maximum. Range of age (years), was 13.0 to 14.0 among primary amenorrhea and 14.0 to 24 in secondary amenorrhea. The mean age was significantly higher in secondary amenorrhea (21.95±1.46 years) as compared to primary amenorrhea (19.26±3.46 years).

Table 1: Age of adolescent and young women in primary and secondaryamenorrhea

	Mean	Median	Std. Deviation	Minimum	Maximum
Primary amenorrhea	19.26	19.00	3.46	13.00	24.00
Secondary amenorrhea	21.95	22.00	1.46	18.00	24.00
t=-4.53, p<0.01*					

*=*Significant (p<0.05)*

Table 2 shows that Mullerian agenesis was the most common etiological factor in 64.52% of cases of primary amenorrhea in our study, imperforate hymen and constitutional delay in 9.67% of each case respectively, 3.23% of cases each of androgen insensitivity syndrome and Turner variant. Polycystic ovary syndrome was the most common cause (80.95%) in secondary amenorrhea, with 7.14% cases of each hyper-

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prolactinemia and hypothyroidism respectively. Premature ovarian failure and Asherman syndrome were the causative factors in 3.23% of cases respectively.

Table 2: Distribution of primary and secondary amenorrhea cases based on Etiology

Provisional diagnosis	Primary amenorrhea (n=31)		Secondary amenorrhea (n=42)		p-value
	n	%	N	%	
Mullerian agenesis	20	64.52	0	0.00	<0.001*
Mullerian anomaly with TVS	2	6.45	0	0.00	0.345
Imperforate hymen	3	9.67	0	0.00	0.144
AIS	1	3.23	0	0.00	0.878
Turner Variant	1	3.23	0	0.00	0.878
Constitutional delay	3	9.67	0	0.00	0.144
TVS	1	3.23	0	0.00	0.878
PCOS	0	0.00	34	80.95	<0.001*
Hyperprolactinemia	0	0.00	3	7.14	0.356
Hypothyroidism	0	0.00	3	7.14	0.356
Ashermann	0	0.00	1	2.38	0.387
Premature ovarianfailure	0	0.00	1	2.38	0.387

Table 3, shows that in the cases of Mullerian agenesis, 15(48.39%) patients were counselled for vaginoplasty. Excision of the septum was done in 2(6.45%) cases of TVS and cruciate incision was given in 3(9.67%) cases of Imperforate hymen. In cases of PCOS-cyclical estrogen and progesterone were given in 3.23% of cases, and vaginoplasty was done in 19.35% of cases.

Table 3: Distribution of cases according to type of management in primaryamenorrhea (N=31)

Type of management	Primary amenorrhea(n=31)	
	N	%
Counseled for vaginoplasty	15	48.39
Counselling regarding physiological causes of delayed menses	3	9.68
Excision of septum f/b vaginoplasty	2	6.45
Cruciate incision (Imperforate hymen)	3	9.68
Excision of septum (Transvaginal Septum)	1	3.23
Vaginoplasty	6	19.35
Cyclical E+P	1	3.23

Table 4 shows that out of 42 cases, 34 PCOS and 1 premature ovarian failure patient i.e. 83.34% were treated by lifestyle modification and cyclical E+P therapy, 1(2.38%) by Hysteroscopic adhesiolysis for Ashman's Syndrome, 3(7.14) by cabergoline treatment for hyperprolactinemia and 3 (7.14%) hypothyroidism by thyroxin treatment.

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Table 4: Distribution of cases according to type of management in secondaryamenorrhea (N=42)

Type of management	Secondary amenorrhea(n=42)	
	N	%
Lifestyle modification and cyclical E+P therapy	35	83.34
Hysteroscopy adhesiolysis	1	2.38
Cabergoline treatment	3	7.14
Thyroxine therapy	3	7.14

DISCUSSION

The study found that the mean age of participants with secondary amenorrhea was significantly higher than those with primary amenorrhea. This difference may be attributed to the delayed recognition and diagnosis of secondary amenorrhea, which often occurs in women who have already established menstrual cycles.

The etiological factors identified in this study for primary amenorrhea were predominantly Mullerian agenesis, constituting 64.52% of cases. Mullerian agenesis also called MRKH (Mayer Rokitansky Kuster Hauser) syndrome, is characterized by the uterus and upper two-thirds of the vagina being underdeveloped or absent. These results are consistent with other research that indicates MRKH syndrome is one of the most prevalent causes of primary amenorrhea, affecting 1 in 4500 women globally [14,16]. This finding is consistent with much literature, which identifies Mullerian agenesis as a major cause of primary amenorrhea [9-13]. According to Mishra RK et al, MRKH was most responsible for nearly half of the instances 46.7% [9]. Other Indian research has been referenced in the literature to support this conclusion. The mullerian anomaly was found to constitute 47% (48 out of 102) of primary amenorrhea cases in the North Indian population, according to research by Kripalani *et al.* [10]. Incidence was reported to be 44% in Gujarat research [11] 52% by Kumar and Mittal [12] and 38.60% by Jain *et al.* [14] The most frequent cause, according to Thai research was Mullerian abnormality (39.7%) [15]. However, in some studies gonadal dysgenesis was the most prevalent cause of primary amenorrhea, Know *et al.* show 28% in Korea [15], and 48.5% in the American population by Reindollar *et al.* [16]. Other less common causes of primary amenorrhea included imperforate hymen, constitutional delay, androgen insensitivity syndrome, and the Turner variant in our study. These conditions highlight the need for comprehensive diagnostic evaluations in patients presenting with primary amenorrhea [4].

In contrast, PCOS was the most common cause of secondary amenorrhea, accounting for 80.95% of cases in our study. This is consistent with other studies that report PCOS as a leading cause of secondary amenorrhea due to its impact on hormonal balance and ovulatory function [5,15,17]. A study done by Kwon *et al.* found 48.4% PCOS in Korea [15]. Raitha *et al.* [17] noted 89% and Goswami *et al.* [18] 75% in India. Due to nutritional, lifestyle and genetic variables, PCOS is very common in South Asia [19]. Other etiological factors for secondary amenorrhea included hyperprolactinemia, hypo-thyroidism, premature ovarian failure, and Asherman syndrome in our study, which are also well-documented in the literature as contributing factors [7,17-20]. According to the American Society of Reproductive Medicine Practice Committee 2008, PCOS followed by ovarian failure, hypothalamic amenorrhea and hyper-prolactinemia were the four most prevalent causes of amenorrhea [20].

The management of primary and secondary amenorrhea varied based on the underlying etiology. Most of the Mullerian agenesis (48.39%) patients were counselled for vaginoplasty and after counselled 19.35% of cases were managed by vaginoplasty. For Mullerian anomalies, counseling for vaginoplasty indicates a preference for surgical intervention in these cases [9,20,21]. According to the other studies vaginoplasty is still the recommended therapeutic option for Mullerian agenesis in the Indian population [9,10]. Septum excision and cruciate incision for imperforate hymen were other surgical options employed. These surgical treatments are standard practices in managing structural anomalies causing primary amenorrhea [22]. In our study, 3(9.68%) patients with imperforate hymen were treated with a cruciate incision on the bulging membrane with drainage of the retained menstrual blood. In the study conducted by

Kriplani *et al.* out of 102 cases of primary amenorrhea, there was 1 case of Imperforate hymen also treated by cruciate incision [10]. In a prospective study conducted by Acar *et al.* among 65 women with Imperforate Hymen. These women were treated with a central incision in the imperforate hymenal membrane followed by 16 French catheter insertions which were kept for 2 weeks, which was followed by estrogen cream application for 2 weeks [23]. Surgery is frequently used to treat imperforate hymen, an uncommon but treatable cause of amenorrhea. Although it is caused by genetic or environmental factors, can still affect the development and health of adolescents. Since constitutional delay usually goes away on its own, patients with this illness often need no medical intervention. Counselling and maintaining mental health, particularly in cultures where delayed puberty may be stigmatized socially or culturally [24].

In cases of secondary amenorrhea caused by PCOS, lifestyle modification combined with cyclical estrogen and progesterone therapy was the predominant treatment approach, utilized in 80.95% of cases Metformin was given to reduce insulin resistance and hirsutism was treated with antiandrogens. This aligns with previous guidelines recommending lifestyle changes as the first-line treatment for PCOS [8]. Additionally, treatments for hyperprolactinemia, hypothyroidism, and Asherman syndrome were tailored to the specific conditions, reflecting an individualized approach to patient care according to the standard method by Lord *et al.* [25]. In our study premature ovarian failure was treated by lifestyle modification and cyclical Estrogen + Progesterone (E+P) therapy, Ashman's Syndrome by Hysteroscopic adhesiolysis, cabergoline treatment for hyperprolectinemia and hypothyroidism by thyroxin treatment. In a retrospective study conducted by Kwon SK et al. to investigate the causes of amenorrhea among 89.1% of Korean women with amenorrhea. There were 14% cases of secondary amenorrhea and premature ovarian failure treated by estrogen plus progesterone therapy [15]. A study conducted by Nari Yamamoto N et al. in Japan where twenty-seven patients with Asherman's Syndrome were also treated by hysteroscopic adhesiolysis [26]. Cabergoline is a dopamine agonist that lowers prolactin levels and returns ovulatory cycles to normal was used to treat hyperprolectinemia by Molina and Kelly [26]. As in our present study, in the study, for the treatment of hypothyroidism-related amenorrhea, Thyroxin was used [27].

In certain complicated situations, a multidisciplinary team of a pediatrician, endocrinologist, surgeon, geneticist, radiologist and psychologist is the most effective in managing the adolescent [27]. In some instances, a delay in the diagnosis and treatment of teenage amenorrhea may result in decreased bone density and other detrimental long-term health effects [28]. Female-phenotyped XY adolescents are not exceptional and need to be treated in reference centers [21].

Every adolescent with amenorrhea and idiopathic primary ovarian insufficiency should be offered next-generation sequencing for gene screening. Adolescent amenorrhea may be at risk due to exposure to endocrine-disrupting chemicals during childhood, adolescence and pregnancy [28,29].

CONCLUSIONS

This study underscores the diverse etiological factors contributing to primary and secondary amenorrhea and the importance of targeted treatment strategies. Early identification and appropriate management can significantly improve the reproductive health and overall well-being of affected individuals. Further research is needed to explore long-term outcomes of different treatment modalities and to develop optimized management protocols for amenorrhea.

CONTRIBUTION OF AUTHORS

Research concept- Dr. Sujata Deo
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Data collection- Dr. Shubham Singh
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Critical review- Dr. Sujata Deo & Dr. Monica Agarwal
Article Editing- Dr. Pratibha Kumari
Final Approval- Dr. Sujata Deo

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