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RESEARCH ARTICLE
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PREVALENCE AND MANAGEMENT STRATEGIES OF PRIMARY AMENORRHEA AT A TERTIARY LEVEL HOSPITAL OF PAKISTAN

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Abstract

Aim: This study aimed to determine the frequency, causes, and management strategies of primary amenorrhea in a tertiary care hospital in Pakistan.

Place and Duration: This study was conducted at PNS Hafeez Islamabad from March 2024 to March 2025

Methods: The study included patients meeting the criteria for primary amenorrhea, excluding those with secondary amenorrhea. Data collection involved detailed medical history, physical examinations assessing height, weight, BMI, nutritional status, and secondary sexual characteristics. Pelvic or rectal examinations evaluated external genitalia and uterine presence. Diagnostic tests, including complete blood count, hormonal assays, karyotyping, and pelvic ultrasonography (transabdominal or transvaginal), were tailored to initial findings. Laparoscopy was performed when indicated, and pregnancy tests ruled out related causes.

Results: Among 878 patients with amenorrhea, 28 were diagnosed with primary amenorrhea (0.29% prevalence). Patients aged 14-22 years, with 14.3% married, underwent karyotyping (92.9%), hormonal assays (53.6%), and laparoscopy (35.7%). Müllerian anomalies were the most common cause (42.9%), followed by premature ovarian failure (28.6%), hypothalamic disorders (14.3%), polycystic ovary syndrome (7.1%), and constitutional delayed puberty (7.1%). Treatments included hormonal therapy for hypoestrogenic states, surgical corrections for anatomical defects, and lifestyle modifications for hypothalamic causes.

Conclusion: Primary amenorrhea, though rare, requires comprehensive evaluation and tailored management. Multicenter studies are needed to explore genetic predispositions and optimize long-term outcomes.

Keywords: Primary amenorrhea, Prevalence, Causes, Müllerian anomalies, premature ovarian failure, management.

Introduction

Amenorrhea is defined as the absence of a menstrual cycle, and it is categorized into two groups: primary and secondary [1]. Primary amenorrhea is defined as the absence of menses by 14 years of age and the absence of secondary sexual character development and growth, or the absence of menses by 16 years of age with normal pubertal development [2]. This condition is distinct from secondary amenorrhea, defined as the absence of the previously menstruating cycles for 6 months or longer [3]. Common causes are gonadal dysgenesis, such as in Turner syndrome, Mullerian agenesis, hypothalamic-pituitary dysgenesis, and outflow tract anomalies, including imperforate hymen [4]. Primary amenorrhea is most commonly caused by anatomic defects, polycystic ovary syndrome (PCOS), and hyperprolactinemia or elevated follicle-stimulating hormone (FSH) levels [4]. Primary amenorrhea has a global prevalence of 2-5% of adolescent women [3]. In developing countries, nutritional deficiencies, infections such as genital tuberculosis, and poor access to medical care may increase prevalence or delay diagnosis [5].

Primary amenorrhea is a common issue in gynecological outpatient settings in Pakistan. In a study from Peshawar, the incidence was reported to be 0.3% in 18,504 patients over five years, with the majority of cases occurring in patients aged 14-20 years [6]. Family history has been documented in about 9% of cases, suggesting a genetic predisposition [6]. Similarly, a study in Karachi reported a prevalence of 0.2% among outpatients who were mainly unmarried urban adolescents with a mean age of 18 years [7]. According to the World Health Organization (WHO), amenorrhea can be divided into three groups based on hormonal patterns: WHO group I comprises women without endogenous estrogen, with normal or low FSH, and with normal prolactin without hypothalamic-pituitary lesions [8]. WHO Group II includes women with normal hormone levels but the ability to secrete estrogen, such as PCOS [8]. Women in WHO group III exhibit rising serum FSH levels, which are suggestive of gonadal insufficiency or failure [8]. If regular menstruation has not been established within 2 years after otherwise normal adolescence begins, congenital absence of the uterus or vagina should be considered, if not already clinically evident [6]. This study will determine the prevalence of cases, etiology, and guide management in primary amenorrhea in a tertiary care hospital setting in Pakistan. It is recommended that primary amenorrhea be investigated if sexual infantilism persists until age 16, or if menstruation has not begun by age 18 despite typical secondary sexual characteristics [2, 3].

Primary amenorrhea, being a rare presentation, is managed at a tertiary-level hospital. Mullerian agenesis is often treated with vaginoplasty, and gonadal dysgenesis is treated with cyclical hormonal therapy [7]. In cases of constitutional delays, reassurance and nutritional support are usually sufficient, resulting in spontaneous menarche [6]. Early detection can help to avoid the long-term complications such as osteoporosis, cardiovascular risks, and mental distress, including anxiety and lower self-esteem in the affected women [9]. This study presents recent data regarding the prevalence and management of primary amenorrhea in a Pakistani tertiary care facility.

Methodology

This study involved all patients who qualified under the inclusion criteria of primary amenorrhea but excluded secondary amenorrhea. Patient and family data were kept confidential to guarantee privacy. The evaluation process begins with a thorough medical history and physical examination. Physical examination included height, weight, body mass index (BMI), and nutritional status. Secondary sexual characteristics were also examined, including the development of the breast and the areola and the presence of pubic and axillary hair. Symptoms such as acne, hirsutism and

galactorrhea were closely observed. To gain more insight, the pelvic or rectal examination was performed to examine the external genitalia and screen for an imperforate hymen or a blind-ending vagina. It ensured the integrity or absence of the uterus and cervix.

According to the initial findings of the history and tests, a specific set of laboratory tests was proposed in each instance. This usually involved a complete blood count and other additional tests consistent with the provisional diagnosis. In some cases, diagnostic laparoscopy offered further detail. Pregnancy tests were conducted when necessary to eliminate associated causes. All participants underwent pelvic ultrasonography, either transabdominal or transvaginal, to visualize internal structures and facilitate proper diagnosis.

Results

Our study included a total of 878 patients diagnosed with amenorrhea, out of which 28 patients were diagnosed with primary amenorrhea. The age of the patients ranged from 14 to 22 years. The most prevalent diagnosis was premature ovarian failure, accounting for 8 cases, which typically presents with hypoplastic ovaries and elevated FSH levels, requiring hormonal support. Rokitansky Syndrome (MRKH) followed with 5 cases, characterized by absent or rudimentary uterine structures. Other notable conditions include vaginal septa and hypothalamic disorders, both treated surgically or with hormone support. Imperforate hymen was diagnosed in 2 patients, requiring surgical approach. Among the 28 patients diagnosed with primary amenorrhea, only two cases remained undiagnosed. These patients were later identified as having constitutional delayed puberty and experienced spontaneous menstruation after one and a half years.

Table 1: Paraclinical Findings of Patients with Primary Amenorrhea (n=28)

Diagnosis	No. of Cases	Sonographic Finding	Karyotype	FSH-LH	Treatment
Premature Ovarian Failure	7	Hypoplastic / Streak	46XX	Raised	Hormonal support
Rokitansky Syndrome (MRKH)	4	Absent or rudimentary	Normal 46XX	Not done	Surgical correction
Vaginal Septa	4	Hematometra	46XX	Normal	Surgical
Hypothalamic	3	Hypoplastic	46XX	Low	Hormone support
Absent Cervix	2	Hematometra	Not done	Not done	Surgical
Uterus with Horn, Non-communicating Vagina	2	Double uterus	46XX	Not done	Reassurance
Polycystic Ovarian Disease (PCOD)	2	Normal / Polycystic	Not done	Not done	Medical
Imperforate Hymen	2	Absent hymen	Not done	Not done	Surgical
Undiagnosed	2	Normal uterus and ovaries	46XX	Not done	Hormone support

The prevalence of primary amenorrhea is found to be 0.29% with one patient affected. The patients' age ranged from 14 to 22 years, and 14.3% were married. Most patients had a karyotype test (92.9%) and hormonal assays (53.6%). The most common condition was mullerian anomalies (42.9%), followed by premature ovarian failure (28.6%). Hypothalamic disorders were present in 14.3% of the cases, and polycystic ovary syndrome was observed in 7.1%. Undiagnosed cases, classified as constitutional delayed puberty, also made up 7.1%.

Table 2: Prevalence of Primary Amenorrhea and its Causes among Patients (n=28)

Parameter	No.	Percentage (%)
Prevalence of Primary Amenorrhea	1	0.29%
Age of Patients	14-22 years	–
Married	4	14.3%
Karyotype	26	92.9%
Hormonal Assay	15	53.6%
Laparoscopy	10	35.7%
Mullerian Anomaly	12	42.9%
Premature Ovarian Failure	8	28.6%
Hypothalamic Disorder	4	14.3%
Polycystic Ovary Syndrome	2	7.1%
Undiagnosed (Constitutional Delayed Puberty)	2	7.1%

Regarding age distribution, the largest group of patients, 42.9%, fell within the 16-18 years range, while 28.6% were aged 19-20 years. A smaller proportion, 17.9%, belonged to the 21-22 years age group, and 10.7% of the patients were aged 12-15 years.

Table 2: Distribution of Cases by Age (n = 28)

Age in Years	No. of Patients	Percentage (%)
12-15	3	10.7%
16-18	12	42.9%
19-20	8	28.6%
21-22	5	17.9%

Based on the underlying causes of primary amenorrhea, various treatment strategies were recommended, including adopting a healthy lifestyle, maintaining a balanced diet, ensuring adequate calcium and vitamin D intake, using antidepressant therapy when needed, and implementing stress management techniques.

Discussion

Patients often find primary amenorrhea distressing because of associated issues, like infertility, osteoporosis, genital atrophy, and social or psychosexual difficulties [9]. Being more common among younger women, such cases should be handled carefully and involve a multidisciplinary team of specialists [10]. Evaluation of primary amenorrhea begins with a detailed medical history and physical examination, proceeding with specific tests to identify the underlying cause [4]. An examination of the presence or the absence of the secondary sexual characteristics, which is an indicator that the patient has been exposed to estrogen, is one of the most important steps [11]. Clinicians employ the Tanner scale to identify the stages of pubertal development [9]. Normal breast development is characterized by either adequate ovarian estrogen production or the conversion of peripheral androgens; however, complete maturation is less likely with peripheral sources alone, hence this assessment is crucial [2]. Moreover, the evaluation of thyroid functioning and prolactin levels is used to rule out hypothyroidism or hyperprolactinemia, as both hypo- and hyperthyroidism can impact the menstrual periods [12].

Among 878 patients, our study identified a primary amenorrhea frequency of 0.29%. This finding aligns closely with research from regions such as interior Sindh and Quetta, where prevalence rates vary from 0.2% to 0.7%, influenced by population characteristics and the availability of tertiary care facilities in those areas [3, 13]. Our patient cohort, aged 14-22 years with only 14.3% married, reflects typical adolescent presentations, comparable to Korean data where 82% of cases fell in the 14-20 age range [14]. Etiologically, mullerian anomalies dominated at 42.9%, followed by premature ovarian failure at 28.6%, hypothalamic disorders at 14.3%, PCOS at 7.1%, and

undiagnosed cases (likely constitutional delay) at 7.1%. This distribution mirrors patterns in two Indian studies, where anatomical defects like Mullerian agenesis account for 38-55% of cases, often linked to genetic and environmental factors prevalent in the region [15, 16]. In contrast, Western and European cohorts emphasize functional hypogonadotropic hypogonadism (56% in Finnish girls) or primary ovarian insufficiency with normal karyotype as leading causes, potentially due to higher detection of endocrine and lifestyle-related issues [17, 18]. For example, Gaspari et al. highlighted primary ovarian insufficiency as the top etiology [9], while Kim et al. showed declining chromosomal abnormalities like Turner syndrome, now affecting about 20-50/100,000 in Caucasian groups [14]. Our POF rate (28.6%) aligns with global shifts toward premature ovarian insufficiency, estimated at 3.7% worldwide, but our inclusion of PCOS as a cause is atypical, as it usually presents as secondary amenorrhea; this may indicate diagnostic overlaps or early manifestations in our population [19].

Diagnostic approaches in our study included karyotyping in 92.9% of cases, hormonal assays in 53.6%, and laparoscopy in 35.7%, facilitating precise etiological classification. This high karyotype utilization aligns with the study by Banerjee et al., which emphasized chromosomal evaluation for accurate management, revealing abnormalities in up to 12-28% of primary amenorrhea patients [20]. However, compared to multidisciplinary protocols in developed countries, where neuroimaging and genetic sequencing are routine, our methods reflect resource constraints, potentially explaining the 7.1% undiagnosed rate like other low-resource contexts [21].

For patients with primary amenorrhea, transabdominal pelvic ultrasonography often serves as the initial imaging modality of choice, offering a non-invasive way to assess reproductive structures and direct subsequent evaluations [22]. This approach helps identify the presence or absence of the uterus, ovaries, and any structural abnormalities, such as hematometra or hypoplastic organs, without exposure to radiation [22]. In scenarios where vaginal access is limited, such as in adolescents or virgins, transperineal or translabial ultrasound has been suggested as an alternative to better visualize pelvic anatomy and pinpoint etiologies [23].

Treatment options for primary amenorrhea vary by etiology but often include hormone replacement therapy (HRT) for hypoestrogenic states, such as in gonadal dysgenesis, to induce secondary sexual characteristics and prevent osteoporosis. Klein et al. recommend estrogen-progestin regimens until natural menopause age [4]. Surgical interventions, like vaginoplasty for MRKH or hymenectomy for obstructions, address anatomical issues [7]. In hypothalamic amenorrhea, lifestyle modifications like weight gain and stress reduction form the cornerstone. Multidisciplinary care, including psychological support, is crucial for long-term outcomes [10].

Limitations: A key limitation of our study is its single-center design, which may have been influenced by referral patterns, potentially affecting the study population. Additionally, limited follow-up restricted our ability to assess long-term outcomes. There is a clear need for multicenter studies to further investigate the etiology and management of primary amenorrhea, with a particular focus on exploring familial predisposition in cases involving a hypoplastic uterus.

Conclusion

This study found a 0.29% prevalence of primary amenorrhea among patients, with Müllerian anomalies and premature ovarian failure as leading causes. Diagnostic tools like ultrasonography, karyotyping, and laparoscopy guided tailored treatments, including hormonal therapy, surgical correction, and lifestyle changes. Future research should involve multicenter studies to deepen understanding of its causes and improve management strategies, particularly exploring genetic factors to enhance patient outcomes.

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