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Original Research Article

Exploring Clinical and Cytogenetic Aspects of Primary Amenorrhea

Aaditi Abhijit Shah[1], Shailly Gupta[2]

[1]Associate Professor, Department of Anatomy, Pacific Institute of Medical Sciences, Udaipur, Rajasthan, India

[2]Assistant Professor, Department of Anatomy, Pacific Institute of Medical Sciences, Udaipur, Rajasthan, India

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Corresponding author: Dr. Shailly Gupta

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Abstract

Background: Primary amenorrhea is a complex clinical condition arising from diverse genetic, anatomical, and endocrine causes. Cytogenetic evaluation plays a pivotal role in establishing diagnosis and guiding long-term management.

Material and Methods: A cross-sectional study of 120 patients with primary amenorrhea was conducted, assessing clinical features, hormonal patterns, pelvic imaging, and cytogenetic findings using standard G-banded karyotyping.

Results: Chromosomal abnormalities were identified in 48 cases, including 45,X, mosaic patterns, structural X-chromosome alterations, and 46,XY gonadal dysgenesis. Clinical and hormonal findings correlated strongly with cytogenetic patterns. Normal karyotype individuals showed etiologies including Müllerian agenesis and hypothalamic–pituitary dysfunction.

Conclusion: Cytogenetic assessment remains essential in the evaluation of primary amenorrhea, enabling accurate etiological classification and guiding fertility planning, hormonal therapy, and long-term follow-up.

Keywords: Primary amenorrhea; Cytogenetics; Gonadal dysgenesis; Chromosomal abnormalities.

Introduction

Primary amenorrhea (PA) represents a significant reproductive health concern, defined as the absence of menarche by age 14 in the absence of secondary sexual characteristics or by age 16 despite normal pubertal development [1]. It is not a disease itself, but rather a manifestation of diverse underlying causes including hormonal dysfunctions, anatomic abnormalities, gonadal dysgenesis, and genetic defects [2]. Among these, chromosomal abnormalities form one of the most critical etiological groups, accounting for a substantial proportion of cases globally [3].

Cytogenetic abnormalities play a crucial role in determining ovarian development, sexual differentiation, and hormonal function. Recent studies consistently show that 11–20% of females with PA exhibit abnormal karyotypes, with monosomy X and mosaic variants being the most frequently identified anomalies [4]. Turner syndrome (45,X) and its mosaic forms often present with classical stigmata such as short stature, streak ovaries, and delayed sexual development, whereas structural X-chromosome aberrations may produce variable phenotypes depending on the segments affected [5]. Another significant group includes individuals with disorders of sex development (DSD), especially 46,XY karyotypes presenting phenotypically as females. These patients often show complete gonadal dysgenesis, absent puberty, and elevated gonadotropin levels [6]. The increasing availability of cytogenetic and advanced molecular techniques has improved the detection of such atypical chromosomal presentations in PA patients [7].

Recent literature also highlights correlations between chromosomal abnormalities, clinical phenotype, hormonal levels, and pelvic imaging findings. For example, patients with X-chromosome structural defects frequently exhibit uterine agenesis or hypoplasia, elevated gonadotropins, and absent ovarian activity [8]. Similarly, mosaic karyotypes may show milder phenotypes but still require careful endocrine and oncologic monitoring due to gonadal tumor risks [9]. Given the complexity and variable clinical manifestations associated with chromosomal anomalies, cytogenetic evaluation remains an indispensable tool in the diagnostic workup of primary amenorrhea. Establishing clinical-cytogenetic correlations not only aids in accurate

diagnosis but also guides individualized hormonal therapy, fertility counseling, and long-term follow-up planning [10]. Therefore, the present study aims to analyze the spectrum of chromosomal abnormalities in PA and correlate these findings with clinical and hormonal profiles to better understand their diagnostic and therapeutic implications.

Material and Methods

This hospital-based cross-sectional study was conducted in the Department of Obstetrics and Gynecology over a defined study period, and included a total of 120 patients presenting with primary amenorrhea. Primary amenorrhea was defined according to standard clinical criteria as absence of menarche by 14 years in the absence of secondary sexual characteristics, or by 16 years despite normal pubertal development. All patients fulfilling the diagnostic criteria and willing to participate were included after obtaining informed written consent from the patient or guardian. Individuals with secondary amenorrhea, previously diagnosed endocrine disorders, history of pelvic surgery, or incomplete clinical records were excluded.

Each participant underwent detailed evaluation beginning with a comprehensive clinical history that included age, developmental milestones, family history, menstrual history, symptoms related to puberty, and any associated systemic or syndromic features. This was followed by general, systemic, and gynecological examination with emphasis on secondary sexual characteristics assessed using Tanner staging, anthropometric measurements, and examination of external genitalia for ambiguity or developmental anomalies.

All subjects underwent baseline hormonal profiling, including serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), thyroid-stimulating hormone (TSH), and prolactin, using standard chemiluminescence assays. Additional hormonal tests such as anti-Müllerian hormone (AMH), testosterone, and dehydroepiandrosterone sulfate (DHEAS) were performed where clinically indicated. Pelvic ultrasonography was carried out in all cases to evaluate the presence, size, and morphology of the uterus and ovaries, and to identify Müllerian anomalies or gonadal dysgenesis.

Cytogenetic evaluation was performed for all 120 patients. Peripheral venous blood samples were collected under aseptic precautions, and lymphocyte culture was carried out using standard short-term phytohemagglutinin-stimulated culture techniques. Metaphase chromosome spreads were prepared and G-banding was performed. A minimum of 20 metaphases were analyzed per patient, and in suspected mosaic cases up to 50 metaphases were examined. Karyotypes were interpreted in accordance with the International System for Human Cytogenomic Nomenclature (ISCN). (Figure 1 and 2)

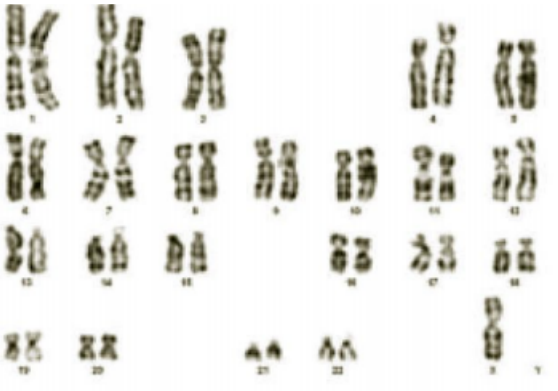

Figure 1: Karyotype showing Monosomy X

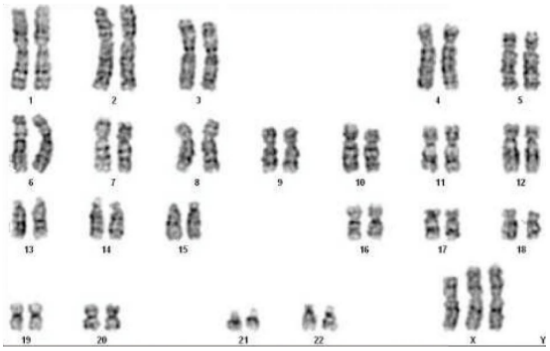

Figure 2: Karyotype showing iso(Xq)

The clinical, hormonal, and imaging findings were correlated with cytogenetic results to determine the association between chromosomal abnormalities and the phenotypic presentation of primary amenorrhea. All data were systematically recorded and analyzed using appropriate descriptive and inferential statistical methods. Ethical clearance for the study was obtained from the institutional ethics committee prior to commencement.

Results

The present study included 120 patients with primary amenorrhea. The distribution of clinical features is shown in Table 1. Majority of the patients presented with poorly developed secondary sexual characteristics, and delayed puberty remained the most frequent clinical finding. Additionally, a significant proportion showed short stature, streak gonads, or ambiguous genitalia depending upon underlying chromosomal etiology. The distribution demonstrated that hypogonadism-related phenotypes were more common than anatomical abnormalities in this cohort.

The etiological profile of the study population is presented in Table 2. Gonadal dysgenesis emerged as the predominant cause of primary amenorrhea, followed by Müllerian agenesis and hypothalamic–pituitary disorders. Dysgenetic ovaries and chromosomal anomalies accounted for a large proportion of cases, reinforcing the significance of cytogenetic evaluation. Functional hypothalamic causes and endocrine disorders formed a smaller subset.

Cytogenetic findings are summarized in Table 3. Out of 120 patients, 48 were found to have chromosomal abnormalities, while 72 patients showed a normal 46,XX karyotype. The most frequent abnormality was 45,X, accounting for 21.4% of the abnormal cytogenetic group, followed by mosaic 45,X/46,XX. Structural X-chromosome abnormalities, including isochromosomes, deletions, and derivative translocations, were also noted. A notable proportion of cases presented with 46,XY gonadal dysgenesis. Mosaic forms and rare rearrangements such as inverted X and inv(9) were also identified. The distribution highlights that numerical X-chromosome abnormalities remained dominant among patients with cytogenetic defects.

Table 1: Distribution of clinical features in Primary Amenorrhea (N = 120)

Clinical Feature	Number of Cases	Percentage
Delayed puberty / absent secondary sexual characteristics	68	56.7%
Short stature	28	23.3%
Primary infertility presentation	10	8.3%
Ambiguous genitalia	6	5%
Cyclical abdominal pain	5	4.2%
Others (fatigue, generalized weakness, incidental findings)	3	2.5%

Table 2: Distribution of etiological factors in Primary Amenorrhea (N = 120)

Etiological Category	Number of Cases	Percentage
Gonadal dysgenesis	52	43.3%
Müllerian agenesis (MRKH syndrome)	26	21.7%
Hypothalamic–pituitary disorders	16	13.3%
Chromosomal DSD (46, XY)	8	6.7%
Constitutional delay of puberty	10	8.3%
Thyroid / endocrine disorders	4	3.3%
Others	4	3.3%

Table 3: Distribution of chromosomal abnormalities in Primary Amenorrhea (N = 120)

Karyotype	No. of Cases	Percentage
45, X	12	10%
45, X/46, XX	6	5%
46, X, i(Xq) & 47, X, i(q), i(q)	5	4.2%
46, X, del(X)	3	2.5%
46, X, der(X)t(X;10) (q11; q11)	2	1.7%
46, X, X, inv9 (p11; q13)	2	1.7%
46, XY	8	6.7%
46, XX (Normal)	72	60%

Discussion

The present study demonstrates a diverse spectrum of clinical, hormonal, and cytogenetic patterns among individuals with primary amenorrhea (PA), consistent with global literature. The high frequency of chromosomal abnormalities observed reinforces the essential role of cytogenetic evaluation in the diagnostic algorithm. Chromosomal defects, particularly X-chromosome monosomy, mosaicism, and structural abnormalities, continue to represent a major etiological category in PA and remain clinically significant due to their influence on gonadal development, pubertal progression, and fertility potential. Similar findings have been emphasized in recent studies, which affirm that cytogenetic alterations correlate strongly with diminished ovarian reserve, streak gonads, and elevated gonadotropins, highlighting the biological impact of chromosomal dosage imbalance on ovarian differentiation [11].

A notable observation in the present study is the considerable proportion of mosaic karyotypes, such as 45,X/46,XX, which demonstrated heterogenous phenotypic expressions. Mosaicism has been shown to produce variable ovarian function

depending on the proportion of normal cell lines, and such patients may retain partial follicular activity, thus influencing treatment counseling and fertility outcomes [12]. Furthermore, structural X-chromosomal abnormalities including deletions, isochromosomes, or derivative translocations were identified in a subset of patients. Recent cytogenomic reports indicate that structural aberrations may disrupt critical genes involved in ovarian development, such as those located in the pseudoautosomal regions, thereby contributing to clinical manifestations of PA even in the presence of a second intact X chromosome [13].

The presence of 46,XY gonadal dysgenesis in a significant proportion of participants underscores the need for early karyotyping in individuals presenting with absent puberty and elevated gonadotropins. Contemporary investigations show that individuals with 46,XY PA require prompt diagnosis due to risks of gonadoblastoma arising from dysgenetic gonads and the need for timely prophylactic gonadectomy [14]. The identification of such cases is crucial in guiding gender-affirming counseling, hormonal therapy planning, and long-term psychological support.

Finally, the sizeable fraction of patients with a normal 46,XX karyotype indicates that non-genetic mechanisms, such as Müllerian agenesis, hypothalamic dysfunction, and endocrine disorders, continue to constitute important etiologies. Recent endocrinologic studies stress the importance of integrating hormonal markers, pelvic imaging, and molecular diagnostics in evaluating 46,XX PA, particularly because subtle mutations in ovarian differentiation pathways or gonadotropin signaling may occur even with a normal karyotype [15]. Taken together, the findings of this study support a multidisciplinary diagnostic framework integrating clinical assessment, endocrinology, imaging, and cytogenetics for comprehensive evaluation of primary amenorrhea.

Conclusion

The study highlights that chromosomal abnormalities constitute a major contributing factor in primary amenorrhea, with monosomy X, mosaicism, 46,XY gonadal dysgenesis, and structural X-chromosome aberrations being the most frequently observed defects.

Correlation of cytogenetic patterns with clinical and hormonal characteristics enables precise etiological classification, timely intervention, and optimized counseling for fertility and long-term health.

Normal karyotype individuals also demonstrate diverse etiologies, reinforcing the need for integrated hormonal and anatomical evaluation. Comprehensive cytogenetic assessment remains indispensable for accurate diagnosis and management of primary amenorrhea.

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