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Primary Amenorrhea in Females with Emphasis on Genetic Causes, Cytogenetic Evaluation and Clinical Management

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Abstract

Primary amenorrhea is an important gynecological and endocrine disorder characterized by the absence of menarche by the age of 15 years in females with normal secondary sexual characteristics or by 13 years in the absence of secondary sexual development. Although endocrine, anatomical, nutritional, and systemic disorders contribute to its etiology, genetic abnormalities represent a significant proportion of cases, particularly those involving chromosomal abnormalities, disorders of sex development (DSDs), and mutations affecting gonadal differentiation and reproductive hormone regulation. Advances in cytogenetics and molecular genetics have considerably improved the diagnosis and classification of genetic causes of primary amenorrhea through conventional karyotyping, fluorescence in situ hybridization (FISH), chromosomal microarray analysis (CMA), and next-generation sequencing (NGS). Early identification of the underlying genetic abnormalities facilitates appropriate clinical management, hormonal therapy, fertility counseling, and psychological support while reducing long-term complications such as osteoporosis, cardiovascular disease, and infertility. This review discusses the epidemiology, genetic mechanisms, cytogenetic evaluation, diagnostic approaches, clinical management, recent advances, and future perspectives in the management of primary amenorrhea with special emphasis on chromosomal disorders and molecular diagnostics.

Keywords: *Primary amenorrhea, Cytogenetics, Turner syndrome, Disorders of sex development, Karyotyping, Genetic counseling, Chromosomal abnormalities.*

1. Introduction

Primary amenorrhea is one of the most significant disorders encountered in adolescent gynecology and reproductive endocrinology. It represents the failure to attain menarche within the expected age range and often reflects underlying abnormalities affecting the hypothalamic-pituitary-ovarian axis, gonadal development, reproductive tract anatomy, or genetic regulation of sexual differentiation. Although relatively uncommon, primary amenorrhea has considerable clinical importance because it frequently serves as the initial manifestation of complex genetic and endocrine disorders requiring multidisciplinary evaluation and long-term management. The prevalence of primary amenorrhea is estimated to be less than 1% among adolescent females, but its incidence varies across populations depending on nutritional status, socioeconomic conditions, healthcare access, and genetic background. Delayed diagnosis may adversely affect physical growth, bone mineralization, reproductive potential, and psychological well-being [1]. Therefore, comprehensive clinical evaluation is essential to identify the underlying etiology and initiate appropriate treatment.

Genetic factors account for a substantial proportion of primary amenorrhea cases. Chromosomal abnormalities, particularly Turner syndrome (45,X), mosaic Turner syndrome, structural X chromosome abnormalities, Swyer syndrome (46,XY complete gonadal dysgenesis), and other disorders of sex development constitute the most common genetic causes. Additionally, mutations in genes involved in gonadal differentiation, hormone biosynthesis, receptor signaling, and follicular development have increasingly been recognized with advances in molecular genetics [2]. Cytogenetic analysis remains an indispensable diagnostic tool in patients with primary amenorrhea. Conventional G-banded karyotyping allows identification of numerical and structural chromosomal abnormalities, whereas molecular cytogenetic techniques including FISH, chromosomal microarray analysis, multiplex ligation-dependent probe amplification (MLPA), and next-generation sequencing provide high-resolution genomic information that improves diagnostic accuracy. Integration of cytogenetic findings with clinical, hormonal, radiological, and molecular investigations enables personalized patient management and informed reproductive counselling [3]. Recent progress in genomic medicine, assisted reproductive technologies, hormone replacement therapy, fertility preservation, and precision medicine has significantly improved the prognosis and quality of life of individuals affected by genetic forms of primary amenorrhea.

2. Etiology and Genetic Basis of Primary Amenorrhea

Primary amenorrhea results from a wide spectrum of congenital and acquired disorders affecting normal reproductive development. Etiological factors may be broadly categorized into chromosomal abnormalities, disorders of sex development, endocrine dysfunction, hypothalamic-pituitary disorders, Müllerian anomalies, systemic diseases, and environmental influences. Among these, genetic abnormalities constitute one of the most important categories because they frequently influence gonadal differentiation, sexual development, hormone production, and reproductive function. Chromosomal abnormalities account for approximately one-third of patients presenting with primary amenorrhea. Turner syndrome, caused by complete or partial monosomy of the X chromosome, remains the most common chromosomal cause. Individuals typically exhibit short stature, gonadal dysgenesis, delayed puberty, primary ovarian insufficiency, infertility, and characteristic somatic features.

Mosaic forms such as 45,X/46,XX often demonstrate milder clinical manifestations depending on the proportion of normal cell lines [4]. Structural abnormalities involving the X chromosome, including deletions, isochromosomes, ring chromosomes, and balanced translocations, may also disrupt ovarian development and folliculogenesis. In contrast, Swyer syndrome (46,XY complete gonadal dysgenesis) results from mutations affecting testis-determining genes such as *SRY*, leading to female external genitalia despite the presence of a Y chromosome. These patients require early diagnosis because dysgenetic gonads possess a high risk of malignant transformation.

Single-gene disorders have become increasingly recognized due to advances in molecular genetics. Mutations in genes including FSHR, LHCGR, BMP15, FOXL2, NR5A1, WNT4, SOX9, DAX1, GNRHR, KISS1R, and TACR3 may impair hypothalamic-pituitary-gonadal function or ovarian development, resulting in primary amenorrhea. Disorders affecting steroid hormone biosynthesis, such as congenital adrenal hyperplasia and aromatase deficiency, further contribute to reproductive dysfunction. Non-genetic causes include Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome), imperforate hymen, transverse vaginal septum, pituitary tumors, hyperprolactinemia, hypothyroidism, chronic systemic diseases, eating disorders, excessive physical exercise, and severe psychological stress [5]. Distinguishing genetic from non-genetic etiologies is essential because management strategies and reproductive outcomes differ substantially.

Table 1: Major Causes of Primary Amenorrhea

Category	Examples	Clinical Features
Chromosomal abnormalities	Turner syndrome, Mosaic Turner syndrome	Gonadal dysgenesis, delayed puberty
Disorders of sex development	Swyer syndrome, Androgen insensitivity syndrome	Abnormal gonadal development
Single-gene disorders	FSHR, BMP15, FOXL2 mutations	Ovarian insufficiency
Müllerian anomalies	MRKH syndrome	Absent uterus with normal ovaries
Endocrine disorders	Hyperprolactinemia, Hypothyroidism	Hormonal imbalance
Hypothalamic disorders	Functional hypothalamic amenorrhea	Low gonadotropin secretion
Pituitary disorders	Pituitary adenoma	Reduced gonadotropin production

3. Cytogenetic Evaluation and Diagnostic Approaches

Accurate diagnosis of primary amenorrhea requires a systematic multidisciplinary approach integrating detailed clinical history, physical examination, hormonal investigations, imaging studies, cytogenetic analysis, and molecular genetic testing. Cytogenetic evaluation is particularly important because chromosomal abnormalities are frequently responsible for ovarian dysgenesis, disorders of sex development, and reproductive failure. Conventional G-banded karyotyping remains the first-line cytogenetic investigation in females presenting with primary amenorrhea, especially when accompanied by delayed puberty, short stature, dysmorphic features, or elevated gonadotropin concentrations.

Karyotyping accurately identifies numerical abnormalities such as monosomy X (45,X), mosaicism, sex chromosome aneuploidies, and structural rearrangements involving the X chromosome. Fluorescence in situ hybridization (FISH) provides rapid confirmation of suspected chromosomal abnormalities and enables detection of cryptic Y chromosome material in Turner syndrome or gonadal dysgenesis. Identification of Y chromosome sequences is clinically important because affected individuals have an increased risk of gonadoblastoma and often require prophylactic gonadectomy. Chromosomal microarray analysis has become increasingly valuable for detecting submicroscopic deletions, duplications, and copy number variations that cannot be identified by conventional cytogenetics [6].

In patients with unexplained primary amenorrhea and normal karyotypes, chromosomal microarray provides additional diagnostic yield by identifying clinically significant genomic imbalances.

Next-generation sequencing has revolutionized molecular diagnosis by enabling simultaneous analysis of numerous genes associated with ovarian development, hormone biosynthesis, gonadal differentiation, and hypothalamic-pituitary function. Targeted gene panels, whole-exome sequencing, and whole-genome sequencing have substantially increased diagnostic accuracy in genetically heterogeneous cases. Hormonal evaluation complements cytogenetic findings by measuring serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin, thyroid-stimulating hormone (TSH), testosterone, anti-Müllerian hormone (AMH), and cortisol. Pelvic ultrasonography and magnetic resonance imaging (MRI) further assess uterine development, ovarian morphology, and associated reproductive tract anomalies [7]. The integration of cytogenetic, molecular, endocrine, and radiological investigations provides comprehensive diagnostic information that guides individualized treatment and reproductive counseling.

Table 2: Diagnostic Investigations for Primary Amenorrhea

Investigation	Purpose	Major Findings
Karyotyping	Chromosome analysis	Turner syndrome, mosaicism
FISH	Detection of Y chromosome material	Gonadal dysgenesis
Chromosomal Microarray	Copy number variations	Microdeletions and duplications
Next-Generation Sequencing	Gene mutation analysis	Single-gene disorders
Hormonal Profile	Endocrine assessment	Ovarian and pituitary function
Pelvic Ultrasound	Reproductive anatomy	Uterus and ovarian evaluation
MRI	Detailed pelvic imaging	Müllerian anomalies

4. Clinical Management of Primary Amenorrhea

The management of primary amenorrhea depends on the underlying etiology and requires a multidisciplinary approach involving gynecologists, endocrinologists, clinical geneticists, reproductive medicine specialists, psychologists, nutritionists, and genetic counselors. The primary goals of treatment include induction of puberty, establishment of normal secondary sexual characteristics, optimization of reproductive health, prevention of long-term complications, and improvement of psychological well-being and quality of life. Hormone replacement therapy (HRT) remains the cornerstone of treatment in patients with ovarian insufficiency and gonadal dysgenesis, particularly those with Turner syndrome or premature ovarian failure. Low-dose estrogen therapy is initiated to promote breast development, uterine growth, and bone mineralization, followed by the addition of cyclic progesterone after adequate estrogenization to establish regular withdrawal bleeding and protect the endometrium. Appropriate hormone replacement also reduces the risk of osteoporosis, cardiovascular disease, and metabolic complications associated with prolonged estrogen deficiency. Patients with hypothalamic or pituitary disorders require treatment directed toward the underlying endocrine abnormalities [8]. Functional hypothalamic amenorrhea associated with malnutrition, excessive physical activity, or psychological stress is managed through nutritional rehabilitation, lifestyle modification, stress reduction, and psychological counseling.

Hyperprolactinemia is treated using dopamine agonists such as bromocriptine or cabergoline, whereas hypothyroidism requires thyroid hormone replacement therapy. Congenital adrenal hyperplasia is managed with glucocorticoid replacement to suppress excessive adrenal androgen production and restore hormonal balance.

Management of anatomical abnormalities depends on the specific structural defect. Imperforate hymen, transverse vaginal septum, and obstructive Müllerian anomalies generally require corrective surgery to restore normal menstrual outflow. Patients with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome benefit from vaginal reconstruction when indicated, along with psychological counseling and fertility counseling regarding assisted reproductive options such as gestational surrogacy where legally permitted. Individuals with disorders of sex development require highly individualized management. Patients with complete androgen insensitivity syndrome generally undergo gonadectomy after completion of puberty because of the increased risk of gonadal malignancy [9]. Similarly, individuals with Swyer syndrome require prophylactic removal of dysgenetic gonads owing to the significant risk of gonadoblastoma. Hormone replacement therapy is subsequently initiated to maintain secondary sexual characteristics and bone health. Fertility preservation and assisted reproductive technologies have substantially improved reproductive outcomes in selected patients. Women with Turner syndrome may achieve pregnancy through donor oocyte in vitro fertilization following comprehensive cardiovascular evaluation, whereas fertility preservation techniques such as oocyte cryopreservation may be considered in selected individuals with declining ovarian reserve. Advances in reproductive medicine continue to expand fertility options for patients with genetic causes of primary amenorrhea.

Table 3: Clinical Management According to Etiology

Etiology	Primary Treatment	Long-Term Management
Turner syndrome	Estrogen and progesterone replacement	Bone health, cardiovascular monitoring, fertility counseling
Premature ovarian insufficiency	Hormone replacement therapy	Osteoporosis prevention
Hyperprolactinemia	Dopamine agonists	Endocrine follow-up
Hypothyroidism	Levothyroxine	Thyroid function monitoring
MRKH syndrome	Surgical correction if required	Psychological and reproductive counseling
Swyer syndrome	Gonadectomy and hormone replacement	Long-term endocrine care
Functional hypothalamic amenorrhea	Nutritional and lifestyle modification	Psychological support

5. Genetic Counseling and Reproductive Considerations

Genetic counseling is a fundamental component of the comprehensive evaluation and management of females with primary amenorrhea, particularly when chromosomal abnormalities or inherited genetic disorders are identified. Counseling enables patients and their families to understand the genetic basis of the condition, inheritance patterns, recurrence risks, available diagnostic tests, reproductive options, and long-term health implications. It also provides psychological support during diagnosis and treatment planning. Individuals diagnosed with Turner syndrome, Swyer syndrome, or other chromosomal disorders require counseling regarding fertility potential, pregnancy-associated risks, and available reproductive technologies. Although spontaneous fertility is uncommon in classical Turner syndrome, women with mosaic forms may retain limited ovarian function [10]. Because pregnancy carries increased cardiovascular risks in Turner syndrome, comprehensive preconception evaluation is essential before assisted reproductive procedures are considered. Carrier detection and family studies may be recommended when inherited gene mutations are identified. Molecular genetic testing allows accurate risk assessment for family members and facilitates informed reproductive decision-making. Prenatal diagnosis using chorionic villus sampling, amniocentesis, or non-invasive prenatal testing (NIPT) may be offered in pregnancies at increased genetic risk.

Psychological counseling should accompany genetic counseling because delayed puberty, infertility, and altered sexual development frequently have profound emotional and social consequences. Anxiety, depression, reduced self-esteem, body image concerns, and impaired quality of life are commonly reported among affected individuals. Early psychosocial intervention significantly improves treatment adherence and overall well-being. Advances in reproductive medicine, including in vitro fertilization, donor oocytes, fertility preservation, and preimplantation genetic testing (PGT), have expanded reproductive opportunities for selected patients with genetic causes of primary amenorrhea. Appropriate counseling enables patients to make informed decisions regarding family planning while considering medical, ethical, and legal aspects.

Table 4: Role of Genetic Counseling in Primary Amenorrhea

Counseling Component	Clinical Importance
Interpretation of genetic diagnosis	Explains disease mechanism
Recurrence risk assessment	Guides family planning
Prenatal diagnostic options	Supports informed pregnancy decisions
Fertility counseling	Discusses assisted reproductive technologies
Psychological support	Improves emotional well-being
Family screening	Identifies at-risk relatives
Long-term follow-up	Supports lifelong healthcare planning

6. Recent Advances and Future Perspectives

The field of reproductive genetics has advanced rapidly with the introduction of high-resolution cytogenetic and genomic technologies. Chromosomal microarray analysis, next-generation sequencing, whole-exome sequencing, and whole-genome sequencing have substantially improved the identification of previously undiagnosed genetic causes of primary amenorrhea. These technologies facilitate the discovery of novel pathogenic variants and expand understanding of genes involved in ovarian development, gonadal differentiation, and endocrine regulation. Artificial intelligence and machine learning are increasingly being incorporated into clinical genetics by assisting in chromosome analysis, variant interpretation, phenotype prediction, and clinical decision support. Automated image analysis systems improve the efficiency and accuracy of cytogenetic laboratories while reducing observer variability. Gene editing technologies, particularly CRISPR-Cas systems, hold considerable promise for future therapeutic applications, although their clinical use in reproductive genetics remains experimental [11]. Stem cell research, ovarian tissue engineering, regenerative medicine, and in vitro gametogenesis also represent emerging areas that may eventually improve fertility options for women with genetic forms of ovarian insufficiency.

Precision medicine approaches integrating genomic, transcriptomic, proteomic, hormonal, and clinical data are expected to enable individualized diagnosis and treatment. Future research should also emphasize large multicenter studies, standardized diagnostic protocols, genotype-phenotype correlations, and long-term outcome evaluation to optimize patient care. Challenges remain regarding accessibility, affordability, ethical considerations, interpretation of variants of uncertain significance, and implementation of advanced genomic testing in resource-limited settings. Continued collaboration among clinicians, geneticists, reproductive specialists, and researchers will be essential for translating scientific advances into improved patient outcomes.

7. Conclusion

Primary amenorrhea is a clinically significant reproductive disorder with a diverse etiology in which genetic and chromosomal abnormalities play a central role. Conditions such as Turner syndrome, gonadal dysgenesis, sex chromosome abnormalities, and single-gene disorders account for a substantial proportion of affected individuals and frequently require specialized multidisciplinary management. Early recognition of these genetic causes is essential for timely intervention, prevention of complications, and appropriate reproductive counseling. Conventional cytogenetic techniques, particularly G-banded karyotyping, remain fundamental diagnostic tools, while modern molecular approaches including fluorescence in situ hybridization, chromosomal microarray analysis, and next-generation sequencing have greatly improved diagnostic precision by identifying subtle chromosomal abnormalities and pathogenic genetic variants. Integration of cytogenetic findings with hormonal evaluation, imaging studies, and molecular diagnostics enables accurate diagnosis and personalized treatment planning. Clinical management should be individualized according to the underlying cause and typically includes hormone replacement therapy, treatment of endocrine disorders, surgical correction of anatomical abnormalities, fertility counseling, psychological support, and long-term multidisciplinary follow-up. Genetic counseling is indispensable for explaining inheritance patterns, assessing recurrence risks, guiding reproductive decisions, and supporting affected individuals and their families.

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