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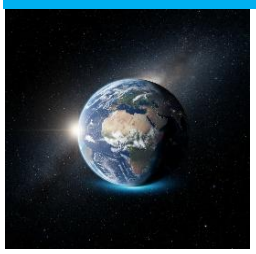

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Klinefelter Syndrome – Etiology, Clinical Presentation and Modern Approaches to the Diagnosis and Treatment: A Literature Review

Katarzyna Kupczyk

ORCID ID: 0009-0004-7532-7769

kasia25021@gmail.com

Warsaw Southern Hospital

Rotmistrza Witolda Pileckiego 99, 02-781 Warszawa, Poland

Mikhail Kazachok

ORCID ID: 0009-0006-2764-3710

mikimashrik@gmail.com

District Hospital in Sochaczew

Batalionów Chłopskich 3/7, 96-500, Sochaczew, Poland

Szymon Paruszewski
ORCID ID: 0009-0005-1822-244X
paruszewskiszymon@gmail.com
Mazovian Bródno Hospital
Ludwika Kondratowicza 8, 03-242 Warsaw, Poland
Aleksandra Dybcio
ORCID ID: 0009-0006-7840-3290
dybcio.aleksandra@gmail.com
Independent Public Health Care Complex in Wyszków
Komisji Edukacji Narodowej 1, 07–200 Wyszków, Poland
Mikołaj Jońca
ORCID ID: 0009-0006-4435-1138
joncamikolaj@gmail.com
Pomeranian Medical University
Rybacka 1, 70-204 Szczecin, Poland
Natasza Kurys
ORCID ID: 0009-0005-7090-259X
natasza.dzieza@gmail.com
Medical University of Lodz,
T. Kościuszki 4, 90-419 Łódź, Poland
Dorota Szydłowska
ORCID ID: 0000-0001-6763-6124
dorotaszydlowska1008@gmail.com
County Medical Center in Nowy Dwór Mazowiecki
Miodowa 2, 05-100 Nowy Dwór Mazowiecki, Poland
Adam Kubisa
ORCID ID: 0009-0003-1320-9890
adam.kubisa183@gmail.com
District Hospital in Sochaczew
Batalionów Chłopskich 3/7, 96-500 Sochaczew, Poland

Mateusz Miluski
ORCID ID: 0009-0003-5744-3291
mateusz.miluski@gmail.com
Szczecińska Szkoła Wyższa Collegium Balticum
Mieszka I 61 c, 71-011 Szczecin, Poland
Julia Kupczak
ORCID ID: 0009-0002-3423-8685
klodzinskaj00@gmail.com
District Hospital in Sochaczew
Batalionów Chłopskich 3/7, 96-500, Sochaczew, Poland
Corresponding Author
Katarzyna Kupczyk
ORCID ID: 0009-0004-7532-7769
kasia25021@gmail.com
Warsaw Southern Hospital
Rotmistrza Witolda Pileckiego 99, 02-781 Warszawa, Poland

Abstract

Introduction: Klinefelter syndrome is the most common chromosomal abnormality in males, characterized by the presence of an extra X chromosome, resulting in 47, XXY karyotype. Its prevalence is approximately 1 in 500 to 1 in 1,000 live-born males. The phenotypic expression is highly variable and includes hypogonadism, infertility, and an increased risk of metabolic complications and neurocognitive disorders.

Purpose: The aim of this review is to provide a comprehensive synthesis of the current state of knowledge on Klinefelter syndrome, with particular emphasis on modern diagnostic and therapeutic approaches.

Material and methods: This article is a narrative literature review and was conducted using international databases. Publications were selected based on their scientific value, relevance, and relation to the topic.

Results: Current evidence indicates that patients benefit from an interdisciplinary approach, involving coordinated care among multiple specialists, including andrologists, endocrinologists, geneticists, psychologists, and experts in infertility treatment. Despite its relatively high

prevalence, a significant proportion of affected individuals remain undiagnosed until adulthood, resulting in delayed initiation of therapeutic interventions.

Conclusions: Klinefelter syndrome is a genetic condition with numerous somatic, reproductive, and psychosocial consequences. Early diagnosis, individualized therapeutic strategies, and multidisciplinary care significantly improve long-term prognosis and quality of life in patients. Future research should prioritize the refinement of diagnostic approaches, elucidation of the long-term effects of hormone therapy, and investigation of the molecular mechanisms underlying phenotypic variability.

Keywords: Klinefelter Syndrome; hypogonadism; infertility; 47, XXY; testosterone supplementation; TESE

1. Introduction

Klinefelter syndrome is the most common chromosomal abnormality in males and results from the presence of an extra X chromosome, most commonly manifesting as the 47, XXY karyotype. The syndrome was first described in 1942 by the American physician Harry Klinefelter et al., who reported a group of 9 men with enlarged breasts, sparse facial and body hair, small testicles, and infertility [1,3].

The prevalence of Klinefelter syndrome is estimated at approximately 1 in 500 to 1 in 1,000 live-born boys. The phenotypic expression of the syndrome is highly variable and encompasses not only tall stature, hypergonadotropic hypogonadism, and infertility, but also a range of metabolic and somatic comorbidities, such as an increased risk of osteoporosis, metabolic syndrome, breast cancer, and autoimmune disorders [2]. Since the second half of the 20th century, attention has increasingly been drawn to the co-occurrence of neurocognitive, psychosocial, and emotional disorders, which can significantly impair patients' quality of life. Individuals with Klinefelter syndrome frequently exhibit attention deficits, as well as impairments in speech, language, and social functioning. Consequently, affected individuals may demonstrate reduced academic achievement and occupational performance relative to peers of comparable socioeconomic status [2,3].

The considerable phenotypic variability and the relatively small proportion of patients presenting with the classical features of the Klinefelter syndrome contribute to its underdiagnosis, with many cases identified only at a later stage [4,5]. This review aims to enhance understanding of the clinical presentation, diagnosis, and management of patients with Klinefelter syndrome, as early detection and comprehensive care - including hormone

replacement therapy and psychosocial support - can facilitate favorable long-term outcomes and significantly improve patients' quality of life [2].

2. Purpose

The aim of this review is to synthesize current knowledge on Klinefelter syndrome - discussing its etiology, clinical presentation, epidemiology, as well as contemporary diagnostic and therapeutic approaches. This study aims to integrate the recent scientific findings and recommendations from the European Academy of Andrology to provide a comprehensive overview of the disease course and evidence-based management strategies across different stages of the patient's life. The review also addresses key clinical challenges, including diagnostic difficulties, endocrine dysfunction, reproductive impairments, and metabolic and psychosocial comorbidities.

3. Materials and methods

This article is a narrative literature review and is based on the available scientific literature on Klinefelter syndrome. All data presented here were derived from publicly accessible sources. The literature review was conducted using international databases: PubMed, Cochrane Library, and Wiley Online Library. The search encompassed publications from 2010 to 2025, in both English and Polish. Publications were selected based on their scientific value, relevance, and relation to the topic. The following keywords were used in the search: Klinefelter syndrome, hypogonadism, 47, XXY, testosterone supplementation, TESE.

4. Etiology

The "classic" karyotype in Klinefelter syndrome, representing the most prevalent form and accounting for approximately 90% of cases, is 47, XXY. The remaining 10% of cases include structural abnormalities of the X chromosome, higher-order aneuploidies (e.g., 48, XXXY or 48, XXYY), and mosaic karyotypes such as 46, XY/47, XXY [1].

Individuals with 48, XXXY and 48, XXYY karyotypes typically exhibit a more severe clinical phenotype compared to those with the classic 47,XXY karyotype. A higher prevalence of congenital anomalies, including inguinal hernia or cardiac defects, has been reported in these patients (56%) relative to individuals with the classic karyotype (18%). In contrast, mosaic karyotypes are generally associated with a milder phenotypic expression [4,6].

The presence of an extra chromosome is most commonly the result of meiotic nondisjunction or postzygotic nondisjunction [2].

Typically, in Klinefelter syndrome, the chromosomal aberration arises de novo as a random error during cell division rather than through inheritance; however, familial cases have also been reported [2]. One of the major challenges in current research on Klinefelter syndrome is

elucidating the mechanisms underlying the considerable variability in clinical presentation observed among individuals with the same chromosomal aneuploidy. Among the mechanisms proposed to date, incomplete X-chromosome inactivation is one of the best characterized. This process, which involves multiple heterochromatin-mediated pathways, does not always occur uniformly, leading to incomplete silencing of the extra X chromosome and consequent expression of the unsilenced genes [4].

5. Epidemiology

Klinefelter syndrome represents the most prevalent chromosomal aberration in males, with an estimated incidence of 1:500 to 1:1,000 live-born male infants. It also constitutes the most common form of sex chromosome aneuploidy in the male population. In contrast, the most frequently observed sex chromosome aneuploidies in females include Trisomy X Syndrome (47, XXX) and Turner Syndrome (45, XO) [7]. Due to marked phenotypic variability and the substantial proportion of individuals exhibiting mild or nonspecific clinical features, it is estimated that up to 60–70% cases remain undiagnosed [8]. Consequently, the condition is frequently identified at a relatively late stage; the mean age at diagnosis is approximately 30 years, and fewer than 10% of affected individuals are diagnosed prior to the onset of puberty. Klinefelter syndrome is also recognized as the most common genetic cause of male infertility, accounting for approximately 3% of men undergoing evaluation for infertility [2].

6. Clinical presentation

The principal clinical features of Klinefelter syndrome have already been well described in the earliest reports on the condition published in the mid-20th century. Traditionally, affected individuals are characterized by tall stature with disproportionately long limbs, narrow shoulders, and relatively broader hips, accompanied by gynecomastia, small and firm testes, and sparse facial and body hair. These physical characteristics are frequently associated with increased body weight, often reflected by body mass index (BMI) values within the overweight or obese range, as well as reduced muscle mass and decreased bone mineral density. In some neonates with Klinefelter syndrome, abnormalities of genital development or congenital anomalies, such as inguinal hernia or cleft palate, may also be observed [1,4,9].

Individuals with Klinefelter syndrome are typically characterized by androgen deficiency and reduced serum testosterone levels accompanied by elevated concentrations of gonadotropins. Histopathological changes in the testes commonly include sclerosis and fibrosis of the seminiferous tubules, frequently leading to azoospermia. Consequently, a substantial proportion of affected individuals experience infertility as well as various forms of sexual dysfunction, including erectile dysfunction or decreased libido [1].

Neurocognitive, psychosocial, and emotional disturbances also represent important components of the clinical spectrum of Klinefelter syndrome [2,3].

The phenotypic manifestations of Klinefelter syndrome can generally be categorized into three developmental stages: childhood, adolescence, and adulthood.

Most boys with Klinefelter syndrome are born with normal birth height and weight [11]. Although some individuals demonstrate accelerated growth within the first months of life, in most cases growth acceleration becomes evident later in childhood, ultimately resulting in adult stature exceeding the mid-parental height [12].

With regard to developmental milestones, studies indicate that up to approximately 75% of boys with Klinefelter syndrome experience delays in speech and language development, and a proportion of these individuals require speech and language therapy. Early initiation of such interventions is recommended in order to improve long-term developmental outcomes. Furthermore, approximately 50% of boys with Klinefelter syndrome exhibit motor developmental abnormalities, including hypotonia, joint hypermobility, or flat feet [10]. Children with Klinefelter syndrome may also experience delays in psychosocial development, which can contribute to social difficulties, including peer isolation, reduced self-esteem, or an increased risk of depressive symptoms. Furthermore, studies suggest that boys with Klinefelter syndrome should be screened for neurodevelopmental disorders such as autism spectrum disorder and attention deficit hyperactivity disorder (ADHD), as an increased prevalence of these conditions has been observed in this population, with up to a sixfold higher risk of ADHD compared with age-matched control population [10,13,14].

Available evidence indicates that the onset of puberty in adolescents with Klinefelter syndrome is generally not delayed [15]. During early puberty, Leydig cells function is relatively preserved, allowing for initially normal testicular development, as high gonadotropin levels stimulate testosterone production. However, by mid-puberty, testosterone concentrations in individuals with Klinefelter syndrome tend to plateau, and the progressive increase in testosterone levels typically observed in healthy male adolescents is not seen [16].

The degree of pubertal development in boys with Klinefelter syndrome may vary considerably. Regardless of the extent of secondary and tertiary sexual characteristic development, testicular volume in this population remains consistently reduced, as the testes fail to undergo the progressive enlargement typically observed during puberty [17].

Puberty is also the period during which gynecomastia frequently begins clinically apparent in patients with Klinefelter syndrome. This phenomenon is thought to result from increased aromatase activity, leading to enhanced peripheral conversion of androgens to estrogens [18].

Some adolescents with Klinefelter syndrome may also experience emotional and psychosocial difficulties during this developmental stage. In addition, deficits in executive functions, including memory and attention, have been reported in this population. Nevertheless, most individuals with Klinefelter syndrome do not exhibit severe educational impairments and are capable of achieving academic outcomes comparable to those of the general population, as overall cognitive abilities are generally within the normal range [9].

In adulthood, approximately 80% of men with Klinefelter syndrome primarily present with manifestations of hypogonadism, including decreased libido, erectile dysfunction, irritability, mood disorders, reduced muscle mass and strength, and diminished facial and body hair [19]. Infertility is another significant concern in this population. Klinefelter syndrome represents the most common genetic cause of male infertility, with azoospermia observed in the vast majority of affected individuals and spermatozoa detectable in the ejaculate in only a small proportion of cases [4,23].

Azoospermia in men with Klinefelter syndrome results from progressive testicular dysfunction. Degenerative changes in the testes lead to infertility, with normal testicular architecture initially replaced by atrophy, sclerosis, and arrested maturation of the seminiferous tubules, ultimately culminating in fibrosis [24]. Several studies have demonstrated a reduced number of germ cells in testicular biopsies in fetuses with a 47, XXY karyotype as early as 18 and 22 weeks of gestation. The most critical period for dynamic deterioration of both germ cell populations and testicular histological architecture occurs during puberty [25].

Until the late 20th century, men with Klinefelter syndrome were generally considered irreversibly infertile. This perspective changed in 1998, when two cases were reported in which spermatozoa were successfully retrieved from testicular tissue, resulting in pregnancy following intracytoplasmic sperm injection (ICSI) [20, 21]. Subsequent studies have confirmed these findings, demonstrating that testicular sperm extraction (TESE) from residual foci of preserved spermatogenesis, in combination with assisted reproductive technologies, can enable men with Klinefelter syndrome to father biological children [20,21,22].

7. Diagnosis

Due to the considerable phenotypic heterogeneity and the often subtle presentation of characteristic clinical features, diagnosis of Klinefelter syndrome is frequently delayed. Patients are typically identified initially due to manifestations of hypogonadism, including small testes, sparse facial and body hair, gynecomastia, and/or infertility.

Both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels are elevated in these individuals, with FSH usually more prominently increased than LH. Serum testosterone

concentrations are generally decreased or at the lower limit of normal range. Additionally, levels of sex-hormone-binding globulin (SHBG) are often elevated, resulting in reduction of circulating free testosterone, even when total testosterone concentrations remain within the normal limits. Serum estradiol levels are frequently at the upper end of the reference range or elevated, and the estradiol-to-testosterone ratio remains consistently increased, contributing to the development of gynecomastia in patients [2,26].

In childhood, serum inhibin B levels in boys with Klinefelter syndrome typically remain within the normal range; however, following puberty, these levels decline markedly, often becoming low or undetectable. Similarly, anti-Müllerian hormone (AMH) levels remain normal during childhood but decrease after puberty. The reduction in both inhibin B and AMH concentrations reflects progressive testicular changes, including hyalinization of the seminiferous tubules and gradual deterioration of Sertoli cell function [2,27].

The definitive diagnosis of Klinefelter syndrome is typically established through karyotype analysis, most commonly performed on peripheral blood lymphocytes, or via chromosomal microarray testing (CMA). It is essential that these investigations be conducted in a specialized reference laboratories with expertise in cytogenetic and molecular diagnostic techniques [2].

Prenatal diagnosis is increasingly recognized as an important component in the identification of Klinefelter syndrome. A major advancement in the detection of sex chromosome aneuploidy has been the introduction of noninvasive prenatal testing (NIPT), which allows for the analysis of cell-free fetal DNA in the maternal blood [4]. The reported positive predictive value of NIPT for Klinefelter syndrome ranges from approximately 50% to 90% [4,28,34]. However, due to the limited number of studies, a recent Cochrane review was unable to definitively assess the reliability of NIPT-based predictions for Klinefelter syndrome predictions [35]. Consequently, pregnancies with NIPT results indicating an elevated risk for Klinefelter syndrome are typically offered confirmatory diagnostic procedures.

The first of these procedures is chorionic villus sampling (CVS), which can be performed between 10 and 14 weeks of gestation; a small amount of placental tissue is obtained for cytogenetic analysis, with an associated miscarriage risk of less than 1 in 450. The second procedure is amniocentesis, performed between 15 and 24 weeks of gestation, in which a small volume of amniotic fluid is collected for analysis. The procedure carries a miscarriage risk of less than 1 in 900 [36].

Recent research has also increasingly focused on prenatal phenotypic features that may be associated with Klinefelter syndrome. One study reported that 23% of fetuses with Klinefelter syndrome exhibited increased nuchal translucency ≥ 3 mm, while systemic anomalies -

including cerebral ventriculomegaly and nonspecific cardiac abnormalities - were observed in nearly one-third of cases [4,29]. These findings indicate that, although no definitive prenatal diagnostic criteria for Klinefelter syndrome currently exist, certain anomalies may occur with increased frequency in affected fetuses [4].

The European Academy of Andrology recommends that prenatally suspected cases of Klinefelter syndrome be confirmed postnatally through karyotype analysis of peripheral blood [33].

The Academy strongly advocates for genetic counseling in both prenatal and postnatal contexts. The purpose of such counseling is to inform parents about the potential clinical implications of Klinefelter syndrome, the most current therapeutic options, and the clinical experiences of healthcare professionals who manage patients with this condition [33].

8. Treatment

The management and treatment of individuals with Klinefelter syndrome can be addressed according to different stages of life: infancy and early childhood, prepubertal children, adolescents, and adulthood.

8.1 Infancy and early childhood

Hypogonadism in Klinefelter syndrome may manifest as early as the prenatal or infantile period. The European Academy of Andrology recommends assessing luteinizing hormone (LH) and testosterone levels in infants with a prenatal diagnosis of Klinefelter syndrome within the first 2–3 months of life, as this assessment may have therapeutic implications, such as in the evaluation of micropenis [33]. Current evidence does not support routine testosterone supplementation during early childhood in patients with Klinefelter syndrome [31,33]. An exception is made for individuals diagnosed with micropenis, who should be referred to a pediatric endocrinologist. The guidelines of the British Society for Pediatric Endocrinology and Diabetes recommend treatment with either intramuscular testosterone injections administered every three months or topical testosterone gel in such cases [32].

If cases of inguinal hernia or cryptorchidism, referral to a pediatric urologist is recommended [30].

Approximately 60–70% of boys with Klinefelter syndrome require speech and language therapy or either forms of developmental support. Early initiation of these interventions is critical to optimize outcomes. The type and intensity of support should be individualized according to the child’s specific needs and generally follow the same guidelines as for typically developing children, as no therapeutic protocols are specifically designed for individuals with Klinefelter syndrome [30].

8.2 Prepubertal children

In prepubertal children, the European Academy of Andrology (EAA) recommends a comprehensive physical examination every two years or as clinically indicated, including evaluation of testicular development. In addition to palpation, testicular ultrasonography may be employed to provide more detailed assessment.

Current guidelines advise against cryopreservation of spermatogonial stem cells or testicular tissue obtained from prepubertal boys with Klinefelter syndrome. Routine testosterone supplementation is also not recommended at this stage [33].

In prepubertal children, EAA recommends regular monitoring of body weight and height. During early childhood, stature in boys with Klinefelter syndrome generally remains within the upper limits of the normal range; however, by 5–6 years of age, the growth rate may accelerate, resulting in the final height that exceeds the mid-parental target height [33,48]. Additionally, it is recommended to assess serum vitamin D levels concentrations and consider supplementation if indicated [33].

The EAA further recommends that boys with Klinefelter syndrome undergo regular monitoring and, when indicated, receive speech and language therapy during the prepubertal period. Additionally, interventions targeting social skills development and provision of psychological support should be considered as needed, given the elevated risk of educational and psychosocial challenges in this population [33].

8.3 Adolescents

Puberty, which typically occurs at a similar age in individuals with Klinefelter syndrome as in the general population, represents a critical period characterized by accelerated degeneration of germ cells and Sertoli cells. This process is accompanied by progressive fibrosis and hyalinization of the seminiferous tubules, as well as Leydig cell hyperplasia and interstitial fibrosis. In the majority of seminiferous tubules spermatogenesis is absent; however, isolated tubules with preserved spermatogenesis and limited numbers of spermatozoa may still be identified [20,21,22]. This residual spermatogenic activity provides the basis for the use of Testicular Sperm Extraction (TESE), which, in combination with assisted reproductive techniques, has enabled men with Klinefelter syndrome to father biological offspring. Consequently, Klinefelter syndrome is no longer regarded as an absolute cause of infertility, as was previously assumed.

As previously noted, puberty is associated with a marked acceleration in the degeneration of germ cells and Sertoli cells accelerates. From a theoretical perspective, this could suggest that

earlier sperm retrieval might yield more favorable outcomes. However, current evidence does not support this assumption. A study published in 2016 demonstrated that successful sperm retrieval in younger adolescents (13–14 years of age) was achieved in only 10% of TESE procedures, whereas the success rate increased to 45% in individuals aged 15 – 19 years [37]. Similarly, a study by S. Franik, Y. Hoeijmakers, K. D'Hauwers, et al. reported higher success rates of TESE in older adolescents, with sperm retrieval achieved in 40% to 70% of patients over 16 years of age, compared to approximately 0–20% in those younger than 16 years. Furthermore, available data indicate that sperm retrieval rates in adolescents aged 15–19 are comparable to those observed in young adults aged 20–30 years [39].

The European Academy of Andrology (EAA) strongly recommends that adolescents with Klinefelter syndrome who have entered puberty, as well as their parents, be provided with comprehensive information regarding fertility and available treatment options.

In adolescent males with Klinefelter syndrome, following an appropriate and thorough discussion of fertility preservation strategies, semen analysis may be considered. In cases where motile spermatozoa are identified, cryopreservation may be offered. Aa alternative approach involves testicular sperm extraction (TESE) or microdissection TESE (micro-TESE), provided that the patient demonstrates sufficient physical and psychological maturity, has a clear understanding of the proposed intervention, and independently consents to the procedure [4,33]. However, current EAA guidelines place less emphasis on routine semen collection or TESE in adolescent patients. This reflects the recognition that not all individuals of this stage possess the necessary psychological maturity to engage in decisions regarding future fertility, and the fertility preservation procedures performed at a later age yield comparable outcomes [33].

The EAA recommends that clinical assessment in adolescents with Klinefelter syndrome include Tanner stage, measurement of serum testosterone and gonadotropin levels, screening for symptoms of hypogonadism, and monitoring of height, weight, and body proportions. These assessments should be performed prior to the expected onset of puberty and subsequently at regular intervals throughout pubertal development, with the frequency individualized according to the patient’s clinical status. EAA guidelines further recommend initiation of testosterone therapy in individuals with delayed puberty and/or hypogonadism associated with low-normal testosterone levels and elevated luteinizing hormone (LH) concentrations. However, testosterone supplementation is not advised in adolescents with Klinefelter syndrome presenting with compensated hypergonadotropic hypogonadism [33, 49].

The available evidence regarding testosterone supplementation in adolescents with Klinefelter syndrome remains limited. To date, no randomized controlled trials have evaluated the effects

of testosterone therapy on subsequent sperm retrieval or reproductive outcomes in this population [33]. Testosterone therapy, through suppression of gonadotropin secretion, may theoretically contribute to further impairment of spermatogenesis. Therefore, consideration of fertility preservation strategies prior to the initiating of testosterone therapy is recommended [4].

The European Academy of Andrology further recommends annual periodic testicular ultrasonography during puberty to enable ongoing monitoring of testicular development in adolescents with Klinefelter syndrome. In addition, similarly to recommendations for younger children, the EAA advises the provision of speech and language therapy, monitoring of learning difficulties, social skills interventions, and psychological support, as indicated based on the individual needs of the patient [33].

8.4 Adults

Upon reaching adulthood, individuals with Klinefelter syndrome diagnosed with hypogonadism are recommended to initiate testosterone replacement therapy. When feasible, initiation of treatment should be preceded by appropriate evaluation and management of fertility-related issues [33]. Assessment of serum sex steroid and gonadotropin concentrations is essential in the evaluation of hypogonadism and reproductive function in this population. Regular monitoring of these parameters is critical for optimizing hormone replacement therapy, enabling dose adjustments that maximize therapeutic benefits while minimizing potential adverse effects [33].

Treatment of hypogonadism in individuals with Klinefelter syndrome should be initiated promptly, ideally soon after diagnosis. Current recommendations indicate that testosterone replacement therapy in this population should be conducted in accordance with established guidelines for the management of hypogonadism, including appropriate dose titration, regular monitoring of safety parameters – such as hematocrit and prostate-specific antigen (PSA) - and periodic clinical evaluation at recommended intervals [33, 40]. A meta-analysis published in 2020 demonstrated that untreated individuals with Klinefelter syndrome exhibited a less favorable metabolic profile, including higher fasting glucose levels, altered lipid parameters (HDL and LDL cholesterol), and increased body mass index (BMI), compared with control subjects [41]. However, further large-scale, long-term randomized placebo-controlled trials are required to more comprehensively evaluate the benefits of testosterone therapy in this population.

According to the European Academy of Andrology, adult individuals with Klinefelter syndrome who are not receiving testosterone replacement therapy should undergo annual

endocrine evaluation [33].

The European Academy of Andrology (EAA) further recommends that all patients with Klinefelter syndrome who express a desire for paternity undergo a semen analysis and, where appropriate, sperm cryopreservation. Motile spermatozoa can be identified in the ejaculate in approximately 10% of these individuals, allowing for cryopreservation. In patients with confirmed azoospermia who wish to achieve biological paternity, the EAA recommends testicular sperm retrieval via biopsy, including either conventional multifocal testicular sperm extraction (TESE) or microdissection TESE (micro-TESE), followed by sperm cryopreservation. Current evidence indicates no significant differences in sperm retrieval rates between conventional TESE and micro-TESE techniques [42]. Additionally, EAA guidelines advise against initiating testosterone replacement therapy in men scheduled for TESE, due to the potential suppression of gonadotropin secretion and consequent inhibition of residual spermatogenesis [33].

Individuals with Klinefelter syndrome are at increased risk of developing a range of comorbid conditions, including metabolic syndrome, osteoporosis, breast cancer, and autoimmune disorders. Elevated mortality rates have also been reported across several disease categories, contributing to a modest reduction in life expectancy of approximately 2–3 years [2,43]. Patients with Klinefelter syndrome frequently exhibit increased body weight, insulin resistance, and a higher prevalence of type 2 diabetes mellitus, all of which contribute to an elevated cardiovascular risk profile. Additionally, emerging evidence suggest a potential increased risk of cardiac arrhythmias, possibly related to QTc interval prolongation, which may predispose to sudden cardiac death. However, these findings are based on limited data derived from relatively small study populations and should therefore be interpreted with caution [44].

An increased risk of thromboembolic events has also been reported in men with Klinefelter syndrome, estimated to be three- to six-fold higher than in the general population. This elevated risk may be attributable to genetically determined higher levels of the procoagulant plasminogen activator inhibitor-1 (PAI-1), as well as reduced circulating testosterone concentrations [45].

The EAA recommends annual assessment of body weight, blood pressure, fasting plasma glucose, glycated hemoglobin (HbA1c), and lipid profile. Additionally, at least one 12-lead electrocardiogram (ECG) with QTc interval evaluation is advised. Prophylactic anticoagulation should be considered during long-haul flights or in the presence of additional thromboembolic risk factors [33].

Given the reduced bone mineral density and elevated risk of osteoporosis in adult patients with

Klinefelter syndrome, dual-energy X-ray absorptiometry (DXA) of the lumbar spine and femoral regions, alongside fracture risk assessment, is recommended at the initial evaluation. Assessment of serum vitamin D3 levels and consideration of supplementation, if indicated, should also be performed [33].

In addition, clinical attention should be directed toward psychosexual and psychiatric health in all adult individuals with Klinefelter syndrome. Referral to an appropriate specialist is recommended when indicated. This population demonstrates an increased prevalence of neurodevelopmental and psychiatric conditions, including autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), as well as schizophrenia, bipolar disorders, depression, and anxiety [46, 47].

Individuals with Klinefelter syndrome exhibit a markedly increased risk of breast cancer, estimated to be four- to thirty-fold higher than in males with a 46, XY karyotype. Accordingly, annual clinical breast examination, supplemented with mammary gland ultrasonography when indicated, is recommended for this population. In addition, an elevated incidence of extragonadal germ cell tumors has been reported in patients with Klinefelter syndrome, most commonly between the ages of 15 and 30 years. These neoplasms predominantly arise within the mediastinum and may present clinically as precocious puberty due to human chorionic gonadotropin (hCG) secretion or with thoracic symptoms [33].

9. Conclusions

Klinefelter syndrome (47, XXY and its mosaic variants) represents the most common chromosomal aberration in males; however, it remains markedly underdiagnosed in clinical practice. Current evidence indicates that a significant proportion of cases are not identified until puberty or adulthood, resulting in delayed initiation of appropriate therapeutic interventions and psychosocial support. This diagnostic delay largely attributable to the pronounced phenotypic heterogeneity observed in Klinefelter syndrome, which ranges from asymptomatic mosaic forms to the classical clinical phenotype characterized by hypergonadotropic hypogonadism, tall stature, gynecomastia, infertility, and impairments in cognitive, language and psychosocial functioning.

A critical implication of this study is the necessity for an interdisciplinary approach to the management of individuals with Klinefelter syndrome. Optimal care requires coordinated involvement of multiple specialists, including andrologists, endocrinologists, clinical geneticists, and experts in infertility and assisted reproductive technologies. Equally essential is the provision of psychological, educational and social support from early childhood, tailored to the individual needs of each patient.

In conclusion, Klinefelter syndrome is a complex genetic disorder with multifaceted somatic, reproductive, and psychosocial consequences. Early diagnosis, individualized therapeutic strategies, and comprehensive long-term care can significantly improve clinical outcomes and overall quality of life in patients. Future research should prioritize the refinement of diagnostic methods, elucidation of the long-term effects of hormone replacement therapy, and identification of the molecular mechanisms underlying the extensive phenotypic variability observed in this population.

DISCLOSURE

Author's contribution Conceptualization: Katarzyna Kupczyk and Szymon Paruszewski Methodology: Mikchail Kazachok, Dorota Szydłowska Formal analysis: Adam Kubisa, Natasza Kurys Investigation: Julia Kupczak, Mateusz Mikulski, Mikołaj Jońca Resources: Katarzyna Kupczyk, Aleksandra Dybcio, Szymon Paruszewski Data curation: Natasza Kurys, Mikchail Kazachok Writing - original draft preparation: Mikchail Kazachok, Szymon Paruszewski, Adam Kubisa Writing - review and editing: Mikołaj Jońca, Aleksandra Dybcio, Natasza Kurys, Mateusz Miluski and Julia Kupczak Supervision: Katarzyna Kupczyk, Dorota Szydłowska Project administration: Katarzyna Kupczyk All authors have read and agreed to the published version of the manuscript.

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The authors declare no conflict of interest in relation to this study.

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Declaration of Generative AI and AI-Assisted Technologies

During the preparation of this work, the authors used ChatGPT (OpenAI) and DeepL to improve grammar and language clarity and to format a list of references according to AMA style. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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