

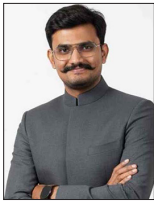


Review Article

# Klinefelter Syndrome: An Integrative Review of Clinical Features, Diagnosis, and Management

Arunkumar Ramjibhai Vaghela<sup>1</sup>

<sup>1</sup>Department of Pharmacology, Shree Aryatej Institute of Pharmacy, Morbi, Gujarat, India.



**\*Corresponding author:**  
Arunkumar Ramjibhai Vaghela,  
Department of Pharmacology,  
Shree Aryatej Institute of  
Pharmacy, Morbi, Gujarat,  
India.

[vaghelaarun56975@gmail.com](mailto:vaghelaarun56975@gmail.com)

Received: 11 July 2025  
Accepted: 29 September 2025  
Published: 15 November 2025

DOI  
10.25259/FSR\_40\_2025

Quick Response Code:



## ABSTRACT

Klinefelter syndrome (KS), characterised by the presence of an extra X chromosome in males (47, XXY), is the most common sex chromosome aneuploidy, affecting approximately 1 in 600 live male births. Despite its prevalence, KS remains underdiagnosed due to its variable clinical presentation, including hypogonadism, infertility, and neurocognitive challenges. This review summarises current understanding of KS epidemiology, pathophysiology, clinical features, diagnosis, and management, highlighting the importance of early identification and multidisciplinary care to improve patient outcomes.

**Keywords:** Cognitive impairment, Hypogonadism, Infertility, Klinefelter syndrome, Testosterone therapy, XXY

## INTRODUCTION

Klinefelter Syndrome (KS) is a common chromosomal disorder that occurs in males due to the presence of one or more extra X chromosomes. The most frequent karyotype associated with this condition is 47, XXY, although variants with additional X chromosomes (e.g., 48, XXXY or 49, XXXXY) can also occur. First described by Dr Harry Klinefelter in 1942, KS is recognised as the most prevalent sex chromosome aneuploidy, affecting approximately 1 in every 600 live male births worldwide.<sup>[1]</sup> This genetic condition results from a meiotic nondisjunction event, typically occurring during gametogenesis, which leads to the presence of an extra X chromosome in each cell. The additional X chromosome interferes with typical male sexual development and results in a constellation of clinical features that can vary significantly in severity and presentation.<sup>[1]</sup>

Core clinical characteristics of KS include:

- **Testicular dysgenesis:** The testes are typically small and firm, with histological findings showing fibrosis and hyalinisation of seminiferous tubules.
- **Hypogonadism:** A hallmark of the syndrome, characterised by low serum testosterone levels, often leading to reduced secondary sexual characteristics such as decreased facial and body hair, gynaecomastia (development of breast tissue), and decreased muscle mass.
- **Infertility:** Due to impaired spermatogenesis, most individuals with KS are azoospermic and unable to father children without assisted reproductive technologies (ART).

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, transform, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.  
©2025 Published by Scientific Scholar on behalf of Fertility Science and Research

- Neurodevelopmental and cognitive issues: These may include delayed speech and language development, learning difficulties, executive dysfunction, and social and emotional challenges. The degree of neurodevelopmental impairment varies widely and can sometimes go unrecognised.

Despite its relatively high prevalence, KS is often underdiagnosed or diagnosed later in life, frequently during infertility workups or evaluations for delayed puberty. This delay in diagnosis is largely due to the heterogeneous and often subtle clinical presentation, especially during childhood and adolescence. Many affected boys do not display overt physical signs, and cognitive symptoms may be misattributed to other causes.

Early diagnosis is crucial, as timely intervention—including testosterone replacement therapy (TRT), educational support, speech and occupational therapy, and psychological counselling—can significantly improve quality of life and long-term outcomes. Increased awareness among healthcare providers and improved genetic screening practices can help in identifying KS earlier and managing it more effectively.

## EPIDEMIOLOGY AND GENETICS

KS affects an estimated 1 in 500 to 1,000 males, making it one of the most common chromosomal abnormalities in humans. Despite this relatively high prevalence, diagnosis rates remain disproportionately low, with studies indicating that only 25%–50% of individuals with KS are ever formally diagnosed during their lifetime.<sup>[2]</sup> This significant underdiagnosis is primarily attributed to the variable and often subtle clinical presentation, which can delay recognition by both patients and healthcare providers.

The genetic basis of KS lies in the presence of an extra X chromosome, typically resulting from meiotic nondisjunction—an error in chromosomal segregation that occurs during gamete formation (either in the sperm or the egg). This leads to a karyotype of 47, XXY, which disrupts normal testicular development and hormonal regulation.

In addition to the classic 47, XXY karyotype, mosaic forms of KS are also observed. The most common mosaic variant is 46, XY/47, XXY, in which some cells in the body have a normal male karyotype (46, XY), while others carry the extra X chromosome (47, XXY). Mosaicism accounts for approximately 10%–20% of KS cases.<sup>[3]</sup> Individuals with mosaic KS generally present with a milder clinical phenotype, which may include partially preserved spermatogenesis, less pronounced physical features, and more subtle neurocognitive impairments. As a result, mosaic cases are even more likely to remain undiagnosed, further contributing to the underestimation of the true prevalence.

Prenatal screening techniques, including non-invasive prenatal testing (NIPT) and amniocentesis, have significantly enhanced early detection of sex chromosome aneuploidies such as KS. These methods allow for the identification of affected fetuses during pregnancy, enabling early counselling and planning. However, despite advances in prenatal diagnostics, a substantial proportion of KS cases are still not diagnosed until adolescence or adulthood, often during evaluations for pubertal delay, infertility, or gynecomastia.<sup>[3]</sup>

Early diagnosis is critical for optimising health outcomes. Identification during infancy or early childhood allows for timely intervention, including TRT, developmental support, and fertility counselling, all of which can improve physical, cognitive, and psychosocial functioning. Therefore, raising awareness among healthcare providers and expanding screening efforts remain key priorities in the management of KS.<sup>[3]</sup>

## PATHOPHYSIOLOGY

The presence of an additional X chromosome in individuals with KS profoundly disrupts normal testicular development, primarily through the dysregulation of Sertoli and Leydig cell function. Sertoli cells, responsible for supporting spermatogenesis, and Leydig cells, which produce testosterone, are both adversely affected by the chromosomal imbalance. Over time, this leads to progressive testicular fibrosis, hyalinisation of seminiferous tubules, and germ cell loss, often beginning in early puberty.<sup>[4]</sup>

As a result, individuals with KS develop hypergonadotropic hypogonadism, a condition characterised by insufficient testosterone production and a compensatory increase in gonadotropin levels—specifically luteinising hormone (LH) and follicle-stimulating hormone (FSH). These elevated gonadotropins reflect the pituitary gland's attempt to stimulate a failing testicular response. Clinically, this endocrine imbalance contributes to several hallmark features of KS, including<sup>[5]</sup>:

- Reduced facial and body hair
- Decreased muscle mass
- Gynaecomastia (male breast tissue development)
- Small, firm testes
- Infertility, usually due to azoospermia (absence of sperm)

Beyond the endocrine and reproductive manifestations, neurological and cognitive deficits are also a significant and often unrecognised component of KS. These issues are believed to stem from gene dosage effects, where the presence of an extra X chromosome leads to overexpression of certain X-linked genes that escape normal X-inactivation. These genes can interfere with the development and function of specific brain regions, particularly those involved in language processing, executive function, and social cognition.

Common neurocognitive and behavioural features include:

- Delayed speech and language acquisition, often noticeable in early childhood
- Learning disabilities, especially related to reading (dyslexia) and verbal memory
- Executive dysfunction, affecting planning, impulse control, and organisation
- Social difficulties, including shyness, social anxiety, and challenges with peer interactions

Neuroimaging studies have shown structural differences in the brains of individuals with KS, including reduced volumes in the temporal lobes, amygdala, and frontal cortex, all of which are regions implicated in language and emotional regulation. These neurological impacts can vary widely among individuals, with some experiencing only mild impairments, while others may require comprehensive educational and psychological support. Importantly, early identification and intervention, such as speech therapy, cognitive behavioural therapy (CBT), and individualised educational plans (IEPs), can greatly improve developmental trajectories and quality of life.<sup>[5]</sup>

## CLINICAL PRESENTATION OF KS

KS presents with a broad spectrum of physical, endocrine, neurocognitive, and reproductive features. The variability in clinical expression often contributes to delayed diagnosis, with many individuals remaining undiagnosed until adulthood.

### Physical and Endocrine Features

One of the hallmark features of KS is a tall stature with disproportionately long limbs, particularly noticeable in the legs. This is thought to result from delayed epiphyseal closure due to testosterone deficiency during adolescence. Other common physical findings include:

- Small, firm testes (typically less than 4 ml in volume)
- Gynaecomastia, which occurs in up to 40% of affected individuals and can lead to social discomfort or increased risk of breast cancer
- Sparse facial and body hair, especially in the axillary and pubic regions
- Decreased muscle mass and strength, contributing to reduced athletic performance
- Osteopenia or osteoporosis, often due to chronic testosterone deficiency and resulting in increased fracture risk<sup>[6]</sup>

Testosterone deficiency typically becomes evident during puberty. While many boys with KS enter puberty at a normal age, their development may stall or progress incompletely.

Features such as a lack of voice deepening, poor muscle development, and failure to develop secondary sexual characteristics are common indicators. Without testosterone replacement, affected individuals are at increased risk for metabolic syndrome, type 2 diabetes, and cardiovascular disease.

### Neurocognitive and Psychological Features

Neurodevelopmental challenges are frequently observed in KS and may be present as early as infancy or early childhood. One of the most consistent findings is a discrepancy between verbal and nonverbal IQ, with verbal IQ typically being lower. Common neurocognitive features include:

- Language delays, including late onset of speech, difficulty with expressive language, and problems with reading and writing
- Learning disabilities, especially in verbal comprehension and academic performance
- Executive dysfunction, involving deficits in attention, planning, memory, and impulse control<sup>[7]</sup>

In addition to cognitive deficits, psychological and behavioural difficulties are prevalent. Individuals with KS have higher rates of:

- Attention Deficit Hyperactivity Disorder (ADHD)
- Anxiety disorders and depressive symptoms
- Social difficulties, including poor peer relationships and low self-esteem
- Autism spectrum disorder traits, such as social withdrawal, rigidity, or sensory sensitivities<sup>[8]</sup>

### Fertility and Reproductive Health

Infertility is a defining characteristic of KS, with the vast majority of affected men exhibiting azoospermia, or absence of sperm in the ejaculate, due to seminiferous tubule dysgenesis. However, advances in ART have revolutionised fertility options for men with KS.

Specifically, microdissection testicular sperm extraction (micro-TESE), a surgical procedure that identifies focal areas of sperm production in the testes, has enabled sperm retrieval in up to 40%–50% of non-mosaic KS patients. When viable sperm are retrieved, intracytoplasmic sperm injection (ICSI) can be used to fertilise an egg, offering the possibility of biological fatherhood.<sup>[9]</sup>

## DIAGNOSIS

### Diagnosis of KS

The diagnosis of KS is established through cytogenetic testing, most commonly via karyotype analysis, which detects

the presence of one or more extra X chromosomes. The classic karyotype in KS is 47, XXY, but other variants, including higher-grade aneuploidies (e.g., 48, XXXY; 49, XXXXY) or mosaic forms (e.g., 46, XY/47, XXY), can also be identified through this method. Karyotyping remains the gold standard for confirming the diagnosis.<sup>[10]</sup>

In some cases, especially when low-level mosaicism is suspected or when higher-resolution analysis is needed, fluorescence in situ hybridisation or chromosomal microarray may be used as supplementary techniques to detect sex chromosome aneuploidies with greater sensitivity.

### Hormonal Evaluation

A hormonal profile is a key component in the clinical assessment and often supports the diagnosis, particularly in adolescents and adults. The characteristic pattern in KS is consistent with hypergonadotropic hypogonadism, which includes:

- Elevated LH
- Elevated FSH
- Low total and free serum testosterone levels

This hormonal profile reflects the impaired function of the Leydig and Sertoli cells within the testes, leading to decreased androgen production and impaired spermatogenesis. These endocrine abnormalities usually become evident during or after puberty and can provide an important clue for diagnosis in patients presenting with delayed or incomplete pubertal development, gynaecomastia, or infertility.<sup>[10]</sup>

### Imaging and Supportive Tests

While a testicular ultrasound is not diagnostic for KS, it can provide useful supportive information, particularly in the evaluation of testicular volume and architecture. Typical sonographic findings in KS include:

- Small testicular volume (usually < 4 ml)
- Homogeneous echotexture
- Occasionally, microcalcifications, which may warrant further monitoring due to a slightly increased risk of germ cell tumours, although this risk remains low.

Ultrasound may also be helpful in evaluating gynaecomastia to rule out underlying masses or in guiding sperm retrieval procedures such as micro-TESE.

In select cases, additional assessments may be used:

- Bone density scans (DEXA) to evaluate for osteopenia or osteoporosis
- Neuropsychological testing, particularly in children and adolescents with learning or behavioural concerns

- Semen analysis, which often reveals azoospermia but helps confirm the extent of spermatogenic failure<sup>[10]</sup>

### Prenatal Diagnosis

With the growing use of NIPT, KS can also be diagnosed prenatally through the detection of sex chromosome aneuploidies in cell-free foetal DNA from maternal blood. Confirmatory testing through amniocentesis or chorionic villus sampling is necessary following a positive NIPT result.<sup>[10]</sup>

## MANAGEMENT

### TRT

TRT is the cornerstone of medical management in individuals with KS and is essential for addressing the clinical consequences of testicular failure and testosterone deficiency. As most individuals with KS develop hypergonadotropic hypogonadism, particularly during or after puberty, TRT plays a critical role in optimising physical, psychological, and metabolic health.

### Timing and Initiation

TRT is generally initiated during adolescence or early adulthood, around the time when endogenous testosterone production would typically rise. The exact timing of initiation should be individualised, based on clinical signs of pubertal delay or incomplete pubertal progression, as well as biochemical evidence of low serum testosterone with elevated LH and FSH levels.

Early initiation of TRT allows for:

- Development of secondary sexual characteristics (e.g., increased facial and body hair, deepening of the voice, increased muscle mass)
- Prevention of gynaecomastia and feminised body habitus
- Psychosocial benefits, including improved mood, self-esteem, and social confidence
- Improved bone mineralisation, thereby reducing the risk of osteopenia and osteoporosis later in life
- Enhanced body composition, including increased lean muscle mass and reduced central adiposity

### Physiological Benefits of TRT

TRT offers a wide range of benefits in KS patients, many of whom experience multi-system effects of androgen deficiency. These include:

- Musculoskeletal: Increased bone mineral density and prevention of osteoporosis, along with increased muscle strength and mass.

- **Metabolic:** Improved insulin sensitivity and lipid profile, which helps reduce the risk of metabolic syndrome and type 2 diabetes.
- **Neuropsychiatric:** Positive effects on mood, cognitive performance, and energy levels; may reduce symptoms of depression and anxiety.
- **Sexual health:** Enhances libido, erectile function, and overall sexual satisfaction.
- **Quality of life:** Numerous studies show significant improvements in general well-being, social functioning, and self-perception following TRT.

### Forms of Testosterone Replacement

Several formulations of testosterone are available and can be tailored to patient preference and clinical context:

- Intramuscular injections (e.g., testosterone enanthate or cypionate every 2–4 weeks)
- Transdermal gels or patches, offering more stable serum testosterone levels
- Long-acting injectable formulations (e.g., every 10–12 weeks)

Regular monitoring of serum testosterone levels, haematocrit, lipids, liver function, and prostate health (in adult patients) is recommended during TRT to ensure efficacy and safety.

### Considerations and Limitations

While TRT addresses many systemic effects of hypogonadism, it does not restore fertility. In fact, exogenous testosterone may suppress the hypothalamic-pituitary-gonadal axis, further reducing intratesticular testosterone and spermatogenesis. Therefore, in men desiring biological fatherhood, fertility preservation strategies or referral to a reproductive endocrinologist should be considered before starting TRT.<sup>[11]</sup>

### Fertility Preservation

#### *Fertility in KS: Micro-TESE and ART*

For decades, infertility was considered an irreversible consequence of KS due to the high prevalence of azoospermia, the absence of sperm in the ejaculate resulting from severe testicular dysfunction. However, advances in microsurgical techniques and ART have significantly transformed the fertility outlook for men with KS, making biological paternity a realistic option in many cases.

#### *Micro-TESE: A Breakthrough in Sperm Retrieval*

micro-TESE is a specialised surgical procedure developed to identify and extract rare sperm from the testes of men with

non-obstructive azoospermia, including those with KS. It involves the use of an operating microscope to selectively examine seminiferous tubules under high magnification, allowing the surgeon to pinpoint areas where focal spermatogenesis may still be occurring.

Key benefits of micro-TESE include:

- Higher sperm retrieval rates compared to conventional testicular biopsy or needle aspiration
- Minimised tissue damage, preserving testicular function
- Improved outcomes when paired with ART

In non-mosaic KS patients, sperm retrieval success rates with micro-TESE range from 30% to 50%, though they may vary depending on patient age, hormonal profile, testicular volume, and surgical expertise.

### ICSI

Once viable sperm are retrieved via micro-TESE, ICSI is used for fertilisation. In ICSI, a single sperm is directly injected into an oocyte (egg), bypassing the need for sperm motility or high numbers. This method has been highly successful in men with very low sperm counts, including those with KS.

Studies show that:

- Fertilisation and pregnancy rates in KS patients using micro-TESE–ICSI are comparable to other causes of male infertility.
- There is no significant increase in birth defects or chromosomal abnormalities in children born to KS fathers using ART, though genetic counselling and preimplantation genetic testing are often recommended to assess risk.

### *Patient Counselling and Ethical Considerations*

Despite promising outcomes, the success of micro-TESE and ART is not guaranteed, and patients must be thoroughly counselled about:

- Variability in sperm retrieval success and potential need for multiple procedures
- The emotional, financial, and physical demands of ART
- The possible need to consider donor sperm or adoption if retrieval fails
- The low (but present) risk of transmitting sex chromosome abnormalities to offspring, particularly in mosaic KS or higher-order aneuploidies

Furthermore, hormonal suppression (from exogenous testosterone therapy) may impair residual spermatogenesis. For men considering fertility, testosterone therapy should be

paused or avoided during the sperm retrieval process, and management should involve an andrologist or reproductive endocrinologist.

### **Early Fertility Planning**

Emerging research suggests that early identification and proactive fertility planning, especially in adolescents and young adults, may improve outcomes. Some centres are exploring sperm or testicular tissue cryopreservation in peripubertal boys with KS, though this remains experimental and ethically debated.<sup>[12]</sup>

### **Psychosocial Support**

#### **Supportive Interventions in KS: Cognitive, Behavioural, and Educational Management**

In addition to endocrine and reproductive issues, individuals with KS frequently experience neurodevelopmental, cognitive, and psychosocial challenges that significantly impact their quality of life. These challenges often emerge in early childhood and may persist into adulthood if not properly addressed. As such, early, individualised, and multidisciplinary interventions are critical to promoting optimal development.

#### **Speech and Language Therapy**

Language delays are among the most consistent neurodevelopmental features of KS. Affected children often experience:

- Delayed speech acquisition
- Difficulty with expressive and receptive language
- Problems with articulation, vocabulary, and sentence structure
- Impaired reading comprehension and verbal fluency

Speech and language therapy should begin as early as possible—often in preschool—once delays are identified. Key goals include:

- Enhancing communication skills
- Supporting academic performance
- Improving social interactions and self-confidence

Early intervention can prevent compounding effects on literacy, learning, and peer relationships and may reduce frustration and behavioural issues associated with communication difficulties.

#### **Psychological Counselling and Behavioural Support**

Children, adolescents, and adults with KS are at increased risk for emotional and behavioural difficulties, including:

- Anxiety and depression
- Social withdrawal
- Low self-esteem
- Increased rates of ADHD
- Traits associated with the autism spectrum, such as rigidity, poor eye contact, or difficulty interpreting social cues

Psychological counselling, particularly CBT, can be instrumental in:

- Managing mood and anxiety disorders
- Improving coping strategies
- Enhancing self-awareness and social skills
- Supporting identity development, especially during adolescence

Family counselling can also be beneficial, helping carers understand the unique challenges associated with KS and how best to provide support.

In cases with more severe behavioural or psychiatric symptoms, referral to a child psychiatrist may be necessary for diagnostic evaluation and, when appropriate, pharmacologic management (e.g., for ADHD or anxiety disorders).

#### **IEPs**

Many individuals with KS benefit from tailored educational support, especially those with learning disabilities or executive function deficits. While general intelligence in KS is usually within the average range, there is often a discrepancy between verbal and performance IQ, with verbal skills being relatively weaker.

Common academic difficulties include:

- Reading and language-based learning disorders
- Poor attention and concentration
- Organisational challenges
- Difficulty with abstract reasoning and problem-solving

An IEP or 504 Plan developed through collaboration between teachers, school psychologists, special educators, and the family can provide targeted accommodations such as:

- Extra time on tests
- Speech-language therapy during school hours
- Resource room support or tutoring
- Behavioural interventions and social skills training

These supports are often critical to academic success, emotional regulation, and social integration.

### **Multidisciplinary Approach**

The best outcomes for individuals with KS are achieved through ongoing collaboration among:

- Endocrinologists
- Paediatricians and developmental specialists
- Speech-language pathologists
- Psychologists and psychiatrists
- Educators and school-based support staff
- Genetic counsellors and social workers<sup>[13]</sup>

## **FUTURE DIRECTIONS**

### **Emerging Research and Future Directions in KS**

While current treatment for KS focuses on managing symptoms, particularly testosterone deficiency, infertility, and neurodevelopmental challenges, ongoing research in genetics, epigenetics, and neurobiology is paving the way for innovative therapeutic approaches. These advances have the potential to shift the paradigm from symptomatic management toward targeted, disease-modifying treatments.<sup>[14]</sup>

### **Epigenetics: Understanding the Molecular Impact of the Extra X Chromosome**

One of the most exciting frontiers in KS research lies in the field of epigenetics, the study of how gene expression is regulated without changes to the DNA sequence itself. In KS, the additional X chromosome introduces a gene dosage imbalance, especially from X-linked genes that escape inactivation. Unlike females, who naturally inactivate one of their two X chromosomes through a process called X-inactivation (lyonisation), KS individuals often exhibit incomplete silencing of the extra X chromosome. This leads to overexpression of certain genes, which is believed to contribute to<sup>[14]</sup>:

- Impaired testicular development
- Neurodevelopmental abnormalities
- Dysregulated immune responses

Research is currently exploring how epigenetic modifiers such as DNA methylation patterns and histone modifications contribute to these phenotypes. This deeper understanding may eventually enable the development of epigenetic therapies to selectively silence or regulate the overactive genes, potentially mitigating the effects of the extra X chromosome.

### **Gene Therapy: A Future Possibility**

Although still in its early stages, gene therapy holds promise as a potential long-term intervention. Theoretically, techniques such as

- CRISPR-Cas9 gene editing
- RNA interference
- Chromosome silencing technologies

Could 1 day be used to either silence the extra X chromosome or correct gene expression imbalances? A proof-of-concept study in mice has demonstrated that it is possible to silence an entire extra chromosome using epigenetic reprogramming tools, raising the possibility of functional monosomy restoration in trisomic conditions like KS.

However, translating this approach into clinical practice poses major technical and ethical challenges, including:

- Ensuring safety and specificity
- Avoiding off-target effects
- Navigating germline vs. somatic gene therapy implications

At present, gene therapy for KS remains speculative, but as technologies mature, it may become a viable component of future treatment strategies.

### **Neurodevelopmental Research: Toward Targeted Interventions**

Another area of active research involves better defining the neurodevelopmental profile of KS and identifying the biological underpinnings of its cognitive and behavioural symptoms. Neuroimaging and functional MRI studies have revealed alterations in brain structure and connectivity in KS individuals, particularly in regions involved in:

- Language processing
- Executive function
- Social cognition

By mapping these brain-behaviour relationships and linking them to specific genetic or epigenetic patterns, researchers hope to:

- Develop predictive models for neurodevelopmental outcomes
- Guide the creation of precision interventions tailored to a child's specific cognitive and emotional profile
- Explore pharmacological agents that modulate neurotransmitter systems affected in KS (e.g., dopaminergic or serotonergic pathways)<sup>[14]</sup>

## **CONCLUSION**

KS is common, multisystemic, and often unrecognised, but it is also highly manageable with the right interventions. Early diagnosis, personalised care, and coordinated multidisciplinary management can significantly improve the clinical trajectory,

psychosocial functioning, and overall quality of life for individuals with KS. Increasing awareness and vigilance among healthcare providers is not only necessary, but it is essential to ensure that patients receive the timely, comprehensive care they deserve.

**Author contribution:** ARV: Concept, design, definition and intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and review.

**Ethical approval:** Institutional Review Board approval is not required.

**Declaration of patient consent:** Patient's consent not required as there are no patients in this study.

**Financial support and sponsorship:** Nil.

**Conflicts of interest:** There are no conflicts of interest.

**Use of artificial intelligence (AI)-assisted technology for manuscript preparation:** The authors confirm that they have used artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript or image creations.

## REFERENCES

1. Klinefelter HF, Reifenstein EC Jr, Albright F. Syndrome Characterized by Gynecomastia, Aspermatogenesis Without Aleydigism, and Increased Excretion of Follicle-Stimulating Hormone. *J Clin Endocrinol Metab* 1942;2:615–27.
2. Bonomi M, Rochira V, Pasquali D, Balercia G, Jannini EA, Ferlin A. Klinefelter Syndrome (KS): Genetics, Clinical Phenotype and Hypogonadism. *J Endocrinol Invest* 2017;40:123–34.
3. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's Syndrome. *Lancet* 2004;364:273–83.
4. Zitzmann M. Testosterone Deficiency, Insulin Resistance and the Metabolic Syndrome. *Nat Rev Endocrinol* 2009;5:673–81.
5. Skakkebaek A, Nielsen MM, Kjaergaard S, Bojesen A, Hertz JM, Østergaard JR, *et al.* Neuropsychological Characteristics of Klinefelter Syndrome in Children and Adolescents: A Review. *Horm Behav* 2017;94:46–54.
6. Bojesen A, Juul S, Gravholt CH. Prenatal and Postnatal Prevalence of Klinefelter Syndrome: A National Registry Study. *J Clin Endocrinol Metab* 2003;88:622–6.
7. Bender BG, Linden MG, Robinson A. Language Development in Klinefelter Syndrome. *J Speech Hear Disord* 1986;51:13–9.
8. Bruining H, Swaab H, Kas M, van Engeland H. Psychiatric Characteristics in a Self-Selected Sample of Boys with Klinefelter Syndrome. *Pediatrics* 2009;123:e865–70.
9. Palermo GD, Neri QV, Schlegel PN. Sperm Recovery and Assisted Reproductive Technologies in Men with Klinefelter Syndrome. *J Urol* 2012;187:898–903.
10. Tüttelmann F, Gromoll J. Genetic Causes of Spermatogenic Failure. *Asian J Androl* 2015;17:5–10.
11. Samplaski MK, Grober ED, Dimitromanolakis A, Lo KC, Grober E. Testosterone Replacement Therapy in Klinefelter Syndrome: A Review. *Asian J Androl* 2015;17:703–9.
12. Okada H, Kamidono S. Recent Advances in the Diagnosis and Management of Male Infertility Caused by Klinefelter Syndrome. *Int J Urol* 2018;25:732–9.
13. Bruining H, Swaab H, Kas MJ, van Rijn S. The Cognitive and Behavioral Phenotype in Klinefelter Syndrome. *J Clin Endocrinol Metab* 2009;94:2530–9.
14. Lanfranco F, Bonomi M, Balercia G, Rochira V. Future Perspectives in Klinefelter Syndrome: Molecular and Genetic Therapies. *Endocrine* 2020;68:457–65.

**How to cite this article:** Vaghela AR. Klinefelter Syndrome: An Integrative Review of Clinical Features, Diagnosis, and Management. *Fertil Sci Res.* 2025;12:33. doi: 10.25259/FSR\_40\_2025