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Advances in the Interdisciplinary Care of Children with Klinefelter Syndrome

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Keywords

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Key points

- Klinefelter syndrome is a common but underdiagnosed genetic condition with significant phenotypic variability in childhood.
- The pediatrician needs to be aware of the increased risk for neurodevelopmental, psychological, and medical conditions that are associated with an additional X-chromosome.
- Over the next decade, we anticipate a sharp increase in diagnosis rates with advances in genetics, particularly prenatal and neonatal diagnoses.

Klinefelter syndrome (KS) is a common genetic disorder characterized by an additional X-chromosome in male individuals leading to a karyotype of 47,XXY. The clinical syndrome was first described nearly 75 years ago in several male individuals with small testes, tall stature, gynecomastia, and azoospermia [1]. Our construct of what KS entails has greatly changed

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since then with identification of the genetic etiology in 1959, epidemiologic studies of birth cohorts in the 1980s, the development of rodent models, and many observational and interventional clinical studies in boys and men with KS [2–4]. Characterization of the neuropsychological profile, along with earlier diagnosis, facilitates earlier developmental evaluation and intervention services [5]. Optimizing testosterone treatment may prevent some of the physical manifestations of the "classic KS phenotype" [6]. Advanced reproductive technology (ART) has made it possible for nearly half of men with KS previously deemed infertile to have an opportunity to have a biological child [7,8]. Despite these scientific advances, the underlying molecular mechanisms underlying primary testicular failure and the phenotypic heterogeneity of physical and neurocognitive features observed in KS remains elusive. In this review, we will provide the pediatrician with an update on what is known about the clinical manifestations and current treatment recommendations for boys and men with KS. Table 1 provides a summary of current treatment recommendations.

EPIDEMIOLOGY AND DIAGNOSIS

KS is the most common sex chromosomal aneuploidy, with estimated prevalence rates ranging between 1 in 448 to 1 in 917 male births [9–14]. A comparative analysis of newborn karyotyping studies published in the 1960s to 1970s and studies published in the 1970s to 1980s reported an increase in the prevalence of KS [14]. An increasing prevalence of KS could theoretically be explained by increasing maternal age, environmentally derived increase of errors in paternal meiosis I, and decreasing rate of elective termination for prenatally diagnosed KS, although this increasing prevalence needs to be confirmed and further evaluated [12,14,15]. Epidemiologic studies of sex chromosome aneuploidies have been limited to industrialized nationals, and to our knowledge, there have been no reports of ethnic differences in KS prevalence.

Currently, there is a significant discrepancy between the known prevalence of KS based on newborn screening studies and the rate of clinical diagnosis. It is estimated that only 25% to 35% of male individuals with KS are diagnosed in their lifetime, with the remaining 65% to 75% left undiagnosed. A study in the United Kingdom estimated that of all expected cases, approximately 10% of diagnoses are made in the prenatal period, 6% in childhood or adolescence, and 19% in adulthood [16]. The small number of children who are diagnosed before puberty are typically identified due to underdeveloped genitalia, hypotonia, developmental delays, or learning and behavior problems. Diagnoses made in adolescence are secondary to small testicular size, gynecomastia, or rarely, incomplete puberty. Adults are most commonly diagnosed for infertility; however, may present for symptoms of hypogonadism [13]. The low rate of diagnosis in the pediatric population is due to a combination of factors, including subtle or underrecognized features that overlap with typical children and genetic testing practices of most pediatricians that do not cover the most common neurodevelopmental features in KS, such as reading disabilities or