Advances in the Interdisciplinary Care of Children With Klinefelter Syndrome, - Davis et al

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Guide to reading this adaptation:

This is an adaptation of a research paper. It includes information pertaining to children and men with 47,XXY/Klinefelter Syndrome, and other sex chromosome trisomies. This is a shortened version of the original paper, edited for clarity, readability, and relevancy to the XXY community. Page numbers noted in this adaptation correspond to the research paper.

Introduction:

Klinefelter Syndrome (KS) is a common chromosome disorder. Males have an extra X chromosome, which creates a karyotype of 47,XXY. The syndrome was first described 75 years ago. At that time, it was noted men with this syndrome had smaller testicles, were tall, had excess breast tissue (gynecomastia), and didn't have viable sperm (azoospermia).

With further research, the understanding of Klinefelter Syndrome has advanced. Better understanding about the psychological and physical development of KS males led to increases in early intervention services, as well as testosterone replacement therapies. These treatments have helped minimize some of the symptoms of the disorder. Additionally, advances in fertility treatment have allowed many men with Klinefelter Syndrome to have biological children.

This paper was created to help pediatricians understand what's currently known about Klinefelter Syndrome, how its symptoms manifest, and the current recommended treatments for boys and men.

Epidemiology and diagnosis:

Klinefelter Syndrome is one of the most common chromosomal disorders, and it's estimated between 1 in 448 to 1 in 917 male births have it. There was an increase of KS diagnoses in the 1970s and 1980s, which might be attributed to women having children later in life, a rise in errors during paternal meiosis I (when the cells split), and a decrease in termination of pregnancies diagnosed with KS.

There's a large gap between the diagnosis of KS in newborns, and those diagnosed later in life. It's estimated that only 25% to 35% of males with KS are diagnosed, which leaves 65%-75% undiagnosed. A study from the United Kingdom indicated "approximately 10% of diagnoses are made in the prenatal period, 6% in childhood or adolescence, and 19% in adulthood" [p.2]. Those identified during childhood were noted to have smaller genitals, hypotonia low muscle tone (hypotonia), developmental delays, learning disabilities, or problems with behavior. In older children and teenagers, KS shows as small testicles, gynecomastia, and rarely, incomplete puberty. In adults, the syndrome shows as hypogonadism (delayed puberty, smaller genitals, decreased sex drive, lack of facial or body hair, longer limbs, decreased muscle mass, infertility, and depression).

Diagnosis can be delayed in children, because the symptoms of KS often mimic the symptoms of other disorders. Additionally, most pediatricians aren't evaluating patients for other signs of the syndrome, such as reading disorders, or speech delays. KS is a spectrum disorder. This means about a quarter of boys with KS won't experience noticeable symptoms, or will have them in a mild or moderate way.

There's frequently a delay from when parents express concerns about their child's development, and confirmation of the diagnosis. On average, it takes 4.8 years for a formal diagnosis after parents first bring their concerns to pediatricians about developmental delays. However, when parents express concerns about their child's development with puberty, microorchidism (small testicles), or gynecomastia (enlarged breast tissue), diagnosis generally takes place within 2 years. However, most men are diagnosed after age 20.

Parents can encourage pediatricians to be up to date on the symptoms of Klinefelter Syndrome, as this can help hasten a diagnosis, and get appropriate treatment started.

Diagnosis:

A diagnosis of KS is made with a prenatal or postnatal test. This is done by testing the karyotype (the number and appearance of chromosomes) or DNA microarray (when the DNA is studied to look at a set of genes).

Prenatal: KS can be diagnosed by noninvasive prenatal testing (NIPT) in the first trimester, which looks at the fetus' DNA in the mother's blood. NIPT is only about 67% accurate for detecting XXY disorders, such as KS. Additionally, it's thought up to 80% of positives from NIPT can be from the mother having an abnormal karyotype. Therefore, follow up testing is recommended. This can be done prenatally with an amniocentesis (amniotic fluid is removed from the uterus for testing), or postnatal blood testing (the baby gives a blood sample after birth for testing). Including NIPT in pregnancy screenings can help parents prepare for the arrival of

their KS baby. Including screening for Fragile X syndrome in routine postnatal testing helps identify KS infants.

Genetics:
Having an understanding of the genetics associated with KS can help pediatricians and parents better understand the syndrome. The syndrome was confirmed by doctors Jacob and Strong in 1959, when they noted the extra chromosomes resulted in a karyotype of 47,XXY.

Klinefelter Syndrome is a random, or spontaneous mutation. The extra X chromosome is added when chromosomes fail to separate while the cells are dividing (meiotic nondisjunction events). This can come from either the mother or father's genetic material. It can also happen when the embryo divides. It comes equally from the father or mother, indicating that it's a random event, and not genetic. It's not fully understood how or why Klinefelter Syndrome and its variants occur.

Mosaicism:
90% of the cases of KS are non mosaic, leaving 7% of mosaic cases, and 3% of other rare variants of KS. Males with mosaic KS have XXY cell lines in another cell line, such as 46,XY. There can be other karyotypes as well, such as 47,XYY or 47,XXX. Those with mosaic KS may have milder symptoms, which may be less noticeable. However, for those with the rare karyotype variations, symptoms may be more severe.

Variants:
Since the confirmation of 47,XXY, other variants that fall under the Klinefelter Syndrome definition have been identified. These "rare sex chromosome variations in male individuals have been identified and characterized by the presence of 2 or more extra X and Y chromosomes, including 48,XXYY, 48,XXXY, and 49,XXXXY syndromes," [p.9]. These variants occur in 1:18,000 to 1:100,000 male births, and generally have more severe symptoms, but can share some similar features to those with 47,XXY.

Genetic counseling:

Genetic counseling can be beneficial for those receiving a diagnosis of KS prenatally, in childhood/adolescence, as well as adults.

Prenatal/childhood and adolescence: Parents recieving a prenatal diagnosis of KS should know there's "no increased risk for miscarriage" [p. 12]. Parents should be given an explanation of their child's diagnosis, including:

- The wide range of symptoms, and how those symptoms manifest (phenotypic variability)

- Recommendations for developmental assessments and interventions, medical evaluations, neuropsychological assessments/academic supports, social and emotional assessments/supports [p.12].
- Referral to an endocrinologist to discuss options for testosterone replacement therapies, up to date reproductive options (for older teenagers and young adults)
- How to disclose the diagnosis to the child, and support groups, as well as informational websites, such as *livingwithxxy.org*.

Adult counseling: Advances in reproductive technology and research have made the possibility of fathering children biologically more possible. Research suggests "8% of men with KS have a small number of sperm in ejaculate," [p. 12] and there's a small number of recorded spontaneous pregnancies. There are several advanced techniques that have led to a 50% to 60% success rate of fathering children, including microtese (where sperm is removed from inside the testicle through dissection) which is followed with in vitro fertilization (the egg is fertilized by the sperm outside of the body, then implanted). The majority of children resulting from this technique have normal karyotypes, with a small percentage having KS or other abnormalities.

Men with KS should be counseled on options, risks, and possible outcomes for fertility interventions, as well as other options for parenthood, including sperm donation, and adoption.

Disclosure: Many parents wonder when to disclose their son's diagnosis, and how to do it. In other types of diagnoses, research has shown parents struggle with sharing a diagnosis with their child due to a lack of understanding about the diagnosis, their own emotions, and being unsure when/how to tell their child. It's recommended parents start by introducing the topic of the diagnosis, using age appropriate terms and language to help their child understand. Early disclosure is beneficial to children, creating an environment of understanding and support as they grow. This should occur before interventions are needed, so the child is prepared. Parents can help their child learn about and accept their diagnosis by:

- Focusing on their child's strengths.
- Telling their child the diagnosis is common.
- Encouraging questions, providing clear, age appropriate answers.
- Discussing future possibilities as science and research progresses.

Development, Behavior, and Psychology

While there's a wide range of development in boys with KS, there's a higher risk for mild to moderate developmental and learning delays. Parents should monitor their child and provide interventions as needed. Studies in infants with KS found 75% of children were delayed in speech and language after newborn screening, and 50% had motor skills delays. On average,

parents can expect their child with KS to achieve milestones 2-3 months later than their XY peers.

While delays can be mild, it's important to provide services to help resolve these delays. Early intervention is recommended if children are showing delays in more than one area of development (for example, the child is delayed in speech, and showing motor development delays). However, for 25%-50% of children with KS, development occurs without need for intervention.

For those with speech delays, there appears to be difficulty with promoter planning, meaning the child struggles with the formation of words, and speaking. While their receptive language (the ability to understand language) is fine, it can be hard for KS children to express themselves. Children with expressive language delays can become frustrated by their inability to communicate, which can lead to behavioral problems. Children with KS should have annual speech evaluations for their first 3 years, and this assessment should cover all aspects of speech development so interventions can be recommended.

Motor delays were noted in 50% of children with KS, including:

- hypotonia (low muscle tone).
- They may also be able to extend their joints (hypermobility), have flat feet (pes planus), and knock knees (genu valgum), which can impact mobility.
- They may be delayed in coordination, dexterity, and self care skills, like "dressing, tying shoes, and eating" [p. 14].

Cognitive, language and learning profiles:

Studies indicate the IQ of children with KS "ranges from 90 to 100" [p. 14]. These children will most likely not have significant cognitive concerns, and can be successful academically, personally, and professionally.

Some children with KS have shown IQs that are 5-10 points less than those of their siblings, or other members of the general population. In these studies, the Verbal IQ scores tend to be lower than the Performance/Nonverbal IQ scores. The lower Verbal IQ score cause the overall IQ score to be lower. However, boys with KS tend to have higher "nonverbal, visual perceptual, and spatial reasoning abilities" [p.14].

As children with KS age, they may experience difficulties with higher-level language skills. They may struggle to: grasp verbal concepts, have verbal processing difficulties, process verbal information more slowly, have word retrieval problems, and find it difficult to communicate with peers. It's important for caregivers and educators to understand these difficulties in regards to

their KS child or student. Children with KS may have a harder time keeping up in highly verbal environments, such as classrooms, and may be slower to respond to questions from peers or educators. Children with KS should have speech therapy throughout their development, and all children/teens with KS showing social, educational, or behavioral difficulties should have annual speech evaluations.

Boys with KS in their school years may be at higher risk for "language-based learning disabilities, including dyslexia" [p. 15]. Learning disabilities occur between 50%-80% of the time, and if the child has a family member with a learning disability, this increases their risk. 80% of boys with KS will need support in school for reading or language. These services are generally provided with an individualized education plan (IEP), or a 504 plan. Caregivers are encouraged to strongly advocate for their children, as lapses in services can create more significant delays. Children with KS should have regular neuropsychological evaluations, which can help catch and address any early learning difficulties.

As children get older, assessment every 3 years can help continue managing any learning disabilities that may arise as learning becomes harder, and more complex. Evaluations of KS students have noted increased risk for deficits in executive function (EF), including:

- Attention.
- Working memory.
- Cognitive flexibility.
- Task initiation.
- Inhibition.

Executive function difficulties can impact children academically, and at home. Those with KS who have executive functioning difficulties can exhibit behavioral issues such as aggression, acting out, and thought problems. Caregivers and educators should be taught about the behaviors, as well as appropriate responses and support strategies.

Boys with KS are at an increased risk for attention deficit disorders, including attention-deficit/ hyperactivity disorder (ADHD). It's more likely KS boys with this diagnosis will experience distractibility and inattentiveness. Approximately 75% of KS patients with ADHD responded positively to medication. Medications should be started at a low dose, and side effects closely monitored.

Behavior/social-emotional development:

Some studies have indicated boys with KS might experience some of the following:

- Behavioral difficulties.
- Social-emotional immaturity.

- Low frustration tolerance.
- Decreased self-esteem.
- Emotional sensitivity.
- Increased risk of depression and anxiety.

Like other KS symptoms, there's a broad array of symptoms, and the severity through which a child could be impacted. Children should be monitored and screened for behavioral difficulties regularly, and provided with appropriate referrals for intervention services as needed. Therapists may need to adjust their practice to help children with KS, so a therapist familiar with delays and disabilities may be helpful.

Children may also benefit from occupational therapy approaches that help them self-regulate through sensory interactions, with less focus on verbal communication. Parents can consider medication if behavioral issues, depression, or anxiety symptoms begin to impact the child's life.

Autism Spectrum Disorder and KS:
Some studies noted autism symptoms in children with KS. Most of the studies focused on autism symptoms, noting " decreased social attention, decreased empathic skills, difficulty interpreting facial expressions, and social communication difficulties," [p.17]. While there are some similarities between autistic and KS individuals, there are also differences. Children with KS can be candidates for autism screening if symptoms are noted. An evaluation for ASD can help guide treatment for individuals who fall on the spectrum while also having KS.

Psychiatric conditions:

Studies from clinical settings have indicated an increased risk for more complex psychiatric conditions in individuals with KS. These conditions include:

- Bipolar disorder
- Psychotic spectrum disorders, including symptoms of:
    - Paranoia
    - Delusional thinking
    - Hallucinations

The range of symptoms for individuals with KS is varied. It's important to identify and encourage the strengths and talents of each individual. Even though a child might need interventions, parents should also focus on encouraging their child to develop strong self-esteem and coping skills. Children should have playtime, recreational activities, involvement in clubs, sports, and activities.

Testicular development and function:

A common symptom of KS is testicular insufficiency, and abnormal testicular development. Normal testicles are made of "germ cells, Leydig cells, and Sertoli cells" [p.18]. Studies are limited regarding the testicular biology of men with KS, but those available indicate lower germ cells in infants, which also occurs throughout the individual's life.

Evaluation of the function of Leydig and Sertoli cells relies on "measurement of serum hormone concentrations," [p.17] Leydig cells are responsible for testosterone production, which is important for the overall health and development of males. However, assessment of these hormones don't always demonstrate an accurate amount of testosterone in the testicles.

Regulation of the gonadal function occurs in the hypothalamic-pituitary gonadal axis. Luteinizing hormone (LH), and follicle-stimulating hormone (FSH) stimulate Leydig and Sertoli cells. This is activated in boys during the first 2-3 months of life, known as a mini-puberty. The stimulation happens again during puberty, and then is active throughout the individual's life. Males with KS seem to have lower serum testosterone.

Infancy:
Symptoms of hypogonadism may occur in the fetus, and early infancy in children with KS. This is noted by underdeveloped genitals, and testicles that don't descend from the abdomen into the scrotum (cryptorchidism). There also appears to be less germ cells in testicular biopsies, smaller testicles, and a stunted mini-puberty. Some providers give testosterone during the mini-puberty period to support the process, but there isn't sufficient evidence to indicate this makes a difference in the child's development. Endocrinologists should evaluate the stretched length of the child's penis, and the descended testicles. Appropriate referrals should be made if the child has a micropenis. If the testicles have failed to descend after age six months, or there are signs of hernias in the groin (inguinal hernia), refer to a pediatric urologist.

Childhood:
Prior to puberty, boys with KS may experience decreased testicular volume, and slower penile growth. Since children aren't going through puberty, testing their testosterone levels won't provide a lot of useful information. Currently "there are no recommendations for prepubertal hormonal evaluation or treatment" [p.17].

Puberty:

Boys with KS are generally expected to go through puberty at the same time as their peers.

Their testes may begin to enlarge, with a volume of up to 10mL, but will decrease to a volume smaller than 4mL. While serum testosterone may appear to rise normally in KS boys, it plateaus,

or decreases. FSH levels are noted to rise to normal ranges one year after puberty onsets, and "LH approximately 2 years after pubertal onset" [p.17].

Young men with KS generally won't develop as much body or facial hair as family members, but will most likely experience penile enlargement, and grow pubic hair. Bones may not fuse at the appropriate time (epiphyses), which can result in longer limbs. While up to 50% of pubertal boys experience gynecomastia (enlarged breast tissue), it's more likely to persist in boys with KS. Therefore, healthcare providers should examine for breast tissue, and if found treat with testosterone. Surgery can be considered if the issue doesn't resolve.

Children with KS should be referred to an endocrinologist at age 10, or the onset of puberty. KS children should be monitored by their endocrinologist, with levels checked every 6 months. There's no specific guideline for when to start a child on androgen replacement therapy, so work with the parents and child to determine the best time to start.

Options for testosterone treatment for adolescents include injections of testosterone, or topical testosterone gel. Testosterone injections have been used extensively, so most endocrinologists are familiar with their use. Injections can be done at home, or at a healthcare provider's office. Doses are based upon the symptoms, and psychological examination. Injections can provide highs and lows in mood, as the testosterone works its way out of the individual's system, and can be painful or inconvenient to administer.

Topical testosterone gels are considered a newer treatment, and may not be covered by insurance. When starting gels, the smallest dosage is recommended. The goal is to achieve normal testosterone levels for the puberty stage of the child. The gel needs to be applied daily, and can cause skin irritation or sensory issues. The lowest dose can sometimes be too high for children, which can elevate testosterone levels, and lead to early fusion of growth plates.

Adulthood:

Adults with KS generally have smaller, firmer testicles, due to the significant reduction of the germ cells that would lead to fuller testicles. The male genitalia is normal in size and function. Untreated males with KS have higher FSH and LH levels, and low testosterone levels. Testosterone replacement therapy should be offered to all men with KS, as their symptoms of hypogonadism may or may not be apparent, but still need treatment.

While it's more likely Klinefelter Syndrome won't produce biological children without intervention, there are several techniques and procedures available. With the increased success of sperm retrieval and egg fertilization, individuals with KS should be told of promising outcomes,

and advances in reproductive technology. Referrals to reproductive specialists should be made as necessary to support and educate families.

Other medical issues:

Adults with KS may experience higher rates of "disorders related to insulin resistance, including type 2 diabetes mellitus, dyslipidemia, and fatty liver disease." 50% of men with KS experience metabolic syndrome, which includes large waist circumference, dyslipidemia (high cholesterol), elevated fasting blood glucose, and high blood pressure. They may be at higher risk for Type 2 diabetes, and cardiovascular diseases.

Less work has been done regarding other medical issues in children with KS. Recent studies noted higher levels of metabolic syndrome symptoms, and higher body fat percentages. These symptoms don't appear to correlate with body mass indexes (BMI). Children should have a healthy, active lifestyle to minimize these symptoms. Cholesterol screening with a fasting lipid panel should be performed from ages 9 to 11, after puberty is completed, and more frequently if there are any additional risk factors. The lipid panel should be repeated if there are abnormalities, or "additional risk factors are present, such as obesity, untreated hypogonadism, or atypical antipsychotic use" [p. 22].

Boys and men with KS are at increased risk for peripheral vascular disease (narrowing or tightening of blood vessels outside of the heart and brain), and thromboembolic disease (clots forming in the blood). They're at increased risk for venous stasis (wounds on the legs caused by abnormal veins), and recurrent leg ulcers. Healthcare providers should be alerted to these risk factors.

Bone health:

Men with KS are indicated to have lower bone mineral density, and are at higher risk for hip or spine fractures. There's not enough evidence to suggest what causes this, and routine bone mineral density tests are not advised. However, parents can support the bone health of their KS child by "ensuring adequate calcium and vitamin D intake, regular physical exercise, maintaining a normal BMI, and tobacco avoidance" [p.22]. For postpubertal boys, keeping testosterone levels regulated can help. Teens and men experiencing long term back pain should be evaluated for vertebral compression fractures.

Autoimmunity:

KS individuals tend to have higher rates of autoimmune disorders, such as rheumatoid arthritis, lupus, multiple sclerosis, Addison disease, Sjogren syndrome, autoimmune hypothyroidism, and

type 1 diabetes mellitus. There's no information indicating advanced risk to children with KS, but individuals should be monitored for symptoms.

Malignancy:

There are no studies currently indicating an increased risk of malignancies, or cancer, in children with KS. In adults, there are three cancers found to be more prevalent: breast cancer, extragonadal germ cell tumors, and non-Hodgkin lymphoma. Screening isn't recommended in children, but any symptoms noted should be immediately reported to their healthcare provider.

Breast cancer is 20 times more common for men with KS than men without, affecting 3% to 7% of the KS population, and is rare in adolescents. Men with KS are encouraged to perform regular breast exams, as should their healthcare providers. Any mass should be reported to their healthcare provider.

Extragonadal germ cell tumors are diagnosed in 0.1% of the KS population, a significant increase compared to the general population. Half of the reports occur in pediatrics, with an increase in adolescents. The most common symptom is precocious (early) puberty. In adolescents and adults, cough, dyspnea (difficulty breathing), or chest pain were common symptoms, with the tumors occurring under the mediastinum (lining between organs). If symptoms occur, an x-ray and blood work should be done.

While there isn't significant evidence that non-Hodgkin lymphoma occurs more frequently in men with KS, it was found in one study that boys with more than three extra sex chromosomes may be at a higher risk. As leukemia is the most common childhood cancer, boys with KS are still at risk for developing it, and any symptoms should be explored further.

Other medical conditions:
Congenital disorders are noted as being more prevelant in boys with KS, and higher in "boys with more than 3 sex chromosomes" [p. 24]. Abnormalities most noted are "inguinal hernia, congenital heart disease, cleft palate and velopharyngeal insufficiency, and kidney malformations," [p. 24] They also can have dental issues, so children should have regular dental checkups.

Seizures and tremors have been reported, particularly in boys with more than 3 extra sex chromosomes.

Conclusion:

Klinefelter Syndrome is a common, but little understood chromosomal disorder. Pediatricians need to be aware of "of the increased risk for neurodevelopmental, psychological, and medical conditions that are associated with an additional X-chromosome" [p. 25]. Due to the rising rates of prenatal testing, a sharp increase in the amount of diagnoses of KS is anticipated. More research is needed to thoroughly understand the variety of symptoms associated with KS, as well as their spectrum of severity. Finally, further research can help determine best courses of action for early intervention.