

# **KLINEFELTER SYNDROME:**

## Clinical evaluation and intervention

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## **INTRODUCTION**

In 1942, Harry Klinefelter described a small group of males who presented with gynecomastia, small testes, Leydig cell dysfunction, and infertility (Klinefelter, Reinfenstein, Albright, 1942). Shortly thereafter this association of clinical features (Klinefelters syndrome or KS) was identified as being caused by an extra X chromosome, giving a sex chromosome pattern of XXY. This condition occurs in 1:500 to 1:1000 live births, (Hamerton et al., 1975) making it one of the most common of all forms of genetic conditions. However, Klinefelter Syndrome (KS) is under appreciated and often unrecognized, particularly in pediatrics (Bojesen, Juul, Gravholt, 2003). Children with KS and their families deal with significant problems, but because they are subtle and not immediately life threatening, the diagnosis is frequently missed (Hagenas, 1998). This under-recognition leads to less than optimal care, lost opportunities to intervene, and significant long-term consequences (Samango-Sprouse, 2001; Schmid & Widmer, 1983). Many children with KS present with learning disabilities and are frequently labeled as Attention Deficit Disorder (ADD). Later in life, individuals with KS are sometimes diagnosed when they request infertility evaluation. If the individual does not seek out this level of evaluation, the diagnosis will likely be overlooked. During the past decade, increased interest and need for more information on this condition has developed due to the expanded use of fetal testing for genetic disorders. Earlier diagnosis of KS requires more knowledgeable pediatric healthcare specialists to manage the special problems of these boys as they grow and mature. This chapter will present a review of KS, associated medical and psychological problems, and interventions that should be considered.

## **TYPES**

All types of KS are a form of "aneuploidy," where there is an extra or missing sex chromosome. The classic form of KS is the polyploidy (extra chromosome) condition of 47,XXY, which characterizes 80% of Klinefelter cases. Another 15% of the cases are mosaic types (46,XY / 47,XXY, 46,XY / 48,XXYY, 45,X0 / 46,XY / 47,XXY and 46XX / 47,XXY). The other 5% are XX forms with the SRY gene (testes determining factor) translocated to an X chromosome, Poly X + Y forms, or combined mosaic and poly X + Y forms (Paulsen et al., 1968).

## ETIOLOGY

Non-disjunction is the most common cause in the classic type of KS, where the chromosomes fail to disjoin normally during meiosis I or II. At fertilization there is an extra X chromosome in the cell that is usually maternal in origin (56% versus 46%). The incidence is greater with increasing maternal age (Carothers and Fillippi, 1988), but in most KS individuals maternal age is not advanced. With the XX forms, there is a crossover between the tip of the short arm of the Y chromosome and the short arm of the X chromosome. The incidence of these types is not related to maternal age as in the classic form. At least half of 47,XXY conceptions are spontaneously aborted.

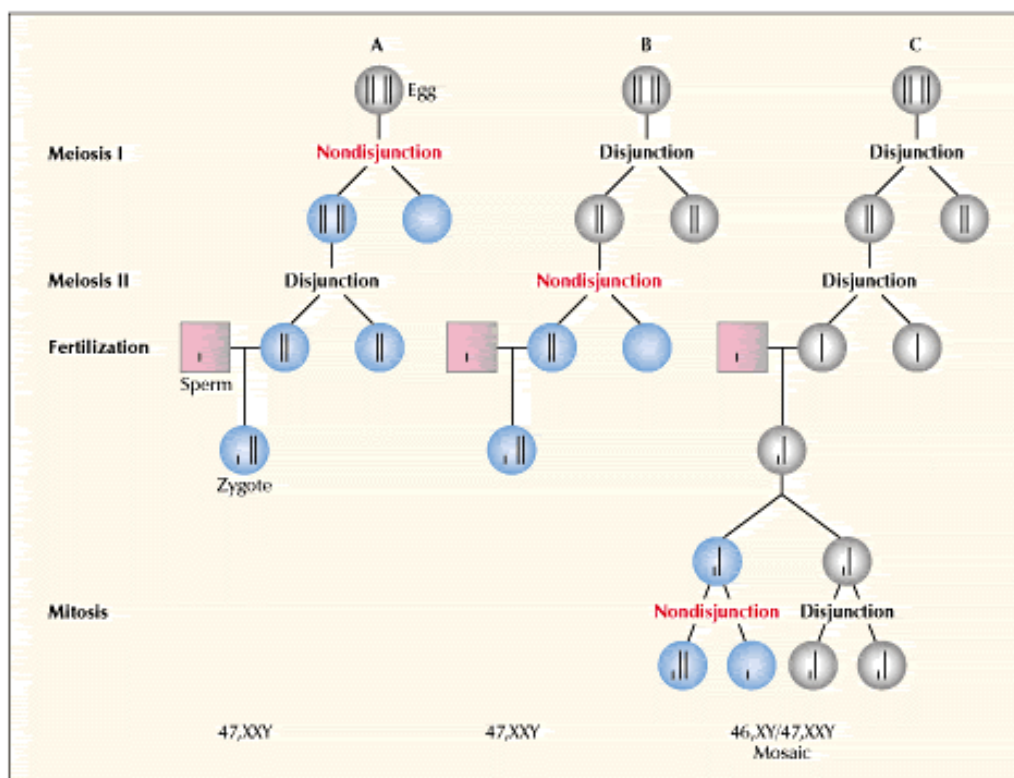


Figure 1. The 47,XXY karyotype of Klinefelter syndrome arises spontaneously when paired chromosomes fail to separate (nondisjunction) in the first (A) or second (B) stage of meiosis, either during oogenesis (44%) or spermatogenesis (53%). A similar failure occurring in the fertilized egg during

mitosis (3%) results in a mosaic karyotype (C). The most common form of mosaicism is 46,XY/47,XXY, but many other forms have been reported. The severity of the syndrome in these cases depends on the proportion of normal (gray) and abnormal (blue) cells.

[From: Smyth CS: Diagnosis and Treatment of Klinefelter Syndrome. Hosp Pract (Off Ed) 1999;34(10):111-112, 115-116, 119-120]

## CLINICAL CHARACTERISTICS

As mentioned, the diagnosis of KS is rarely made before puberty due to the subtleness of childhood clinical manifestations (Manning & Hoyme, 2002) and under-recognition by healthcare practitioners. The learning disabilities and school adjustment problems seen in KS boys are often viewed as “part of growing up” or Attention Deficit Disorder (ADD). As such, further evaluation for an underlying disorder is typically not pursued in childhood. It may not be until puberty or later when the typical clinical characteristics of tall stature, hypogonadism, gynecomastia, and low testosterone (see Table 1) are brought to the attention of the healthcare specialist.

<b>Table 1. Clinical Signs of Klinefelter Syndrome</b>	
<b>Sign</b>	<b>Affected Patients (%)</b>
Elevated gonadotropin levels	95
Infertility	95
Small testes	95
Decreased testosterone level	75
Decreased facial hair	70
Gynecomastia	62
Decreased pubic hair	45
Small penis	18

From Smyth and Bremner, 1998

Recognition and identification of the early clinical characteristics are very important (Mandoki & Sumner, 1991; Visootsak et al, 2001). In the infant, these include features of smaller-than-average head circumference, mild hypotonia, small external genitalia, and possibly the presence of hypospadias, microphallus, or cryptorchidism. Testicular development may be poor with small, firm testes but frequently they are not indistinguishable from normal at this age. Later, in the first few years of life, a significant delay in onset of normal motor milestones and/or a delay in speech development with persistent mild hypotonia are common (Bancroft et al, 1982).

During childhood, boys with KS will carry the history as described above and often begin to exhibit mild learning disabilities and behavior problems that can be misdiagnosed as ADD (Rovet et al., 1996). Boys with KS generally do not develop sport- and ball-handling skills and are sometimes thought to be excessively clumsy or accident-prone.

As they mature, many KS boys present with a clinical picture of being slim, underweight, and taller than expected for parental heights (average height 5 cm > mid-parental height). Others may be obese. In addition, they often have an arm span 5 cm more than height, and an upper-to-lower segment ratio <0.9. Pubertal development can be late, but may appear to be occurring normally as these boys will experience adrenarche with some androgen development leading to the appearance of axillary and pubic hair. Adrenal androgen secretion and minimal residual testicular testosterone secretion can allow for testosterone levels to reach the lowest levels of the reported normal ranges for adult men. In fact, 50% of KS adolescent or young adults have testosterone levels that are in the normal range. However, in general, pubertal development is frequently late, progresses more slowly than normal, and is not associated with the normal and expected growth in the testes.

Androgen levels are low for both chronologic and bone age, but can be near or low normal. Almost 50% of KS patients will have low normal testosterone levels, with the mean testosterone level as a group being approximately ½ expected normal values (300 ng/dL vs 600 ng/dL). In almost all adult men with KS, the gonadotropins LH and FSH are elevated. It has been reported that 97 percent of adolescents and men with KS present with elevated FSH and many (but less) will present with elevated LH even with “normal” testosterone levels. Estradiol levels are also two fold higher than normal, and this relates to the gynecomastia that generally occurs by late puberty in 50 to 75% of boys (Salenblatt et al., 1985). Microscopic exam of the breast tissue shows hyperplasia of tissue surrounding the mammary ducts, which is different from breast development in women. Gynecomastia does not regress spontaneously, and is associated with an increased incidence of breast cancer.

Other features of KS include IQ deficits, learning disabilities and personality abnormalities (Amory et al., 2000; Bender et al, 1995; Khalifa & Struthers, 2002; Ratcliffe et al., 1982; Robinson et al., 1991). The etiology of learning abnormalities has not been established, although current theories point to either effects of the extra X chromosome on the brain or hormone deficiency during fetal development. Personality abnormalities observed include low self-esteem, poor impulse control, anxiety, socially immature group skills, excessively shy behavior patterns, excessive aggressiveness, depression, difficult social skill development, and difficulty developing normal peer and female relationships (Nielsen et al, 1982; Sorensen, 1992; Stewart et al, 1986).

## TREATMENT

Early intervention with an established early intervention program beginning in infancy appears to have long lasting benefits. *Physical therapy* for truncal hypotonia and delayed motor development is recommend, if significant, until independent ambulation is accomplished. *Speech and language evaluation and therapy* beginning at 12 months is also essential to evaluate and treat possible receptive and/or expressive language problems. During the preschool and early school-age years, intervention with physical therapy and play therapy for the hypotonia and delayed motor skills are important not only for muscle development, but also to prevent and treat poor self-esteem associated behavioral and social development problems. Utilization of early intervention programs that incorporate reading readiness and speech therapy are also recommended and attention to anxiety issues should be addressed as well.

In the middle school years, continued attention to learning deficits and annual Individual Education Plans (IEP) should be implemented even if the child is doing "OK". Particular attention should be placed on the child's involvement with *physical activities* and *sports programs*. The natural process for the boy with KS is to become more sport and/or activity avoidant with increasing age. Physical activity has benefits beyond building muscle strength and endurance, including social skill development and the associated benefits of friendships with teammates. In most KS boys, it is expected that with advancing age, team sports will become more anxiety-producing at higher grade levels; therefore, consideration should be given to developing skill sets and interests in more individual activities, such as swimming, track, tennis, golf or martial arts. For some boys, continued participation and acquisition of benefits may require assistance with a personal trainer to help with the coordination components of the sport.

Initiation of *testosterone therapy* is generally considered between the ages of 11 and 12 years (Nielsen & Pelsen, 1987). There is an expanding body of published research showing possible cognitive benefits of early treatment (Patwardhan et al, 2000). While encouraging, carefully controlled interventional data are necessary to determine if the putative positive effects of testosterone treatment on cognition can be substantiated. Other very important benefits of hormone therapy include more normal pubertal development, improved self-esteem, attitude, and mood, mental function, school performance, physical strength, and decreased emotional problems.

Important factors to consider when correcting testosterone deficiency include the biochemistry of the preparation, timing of onset of treatment, dosing plan over time, the method of administration and side effects. Because of hepatotoxic side effects, some testosterone preparations are not recommended. These include oral 17-alkylated androgens, such as methyl

testosterone. Timing of initial treatment and dosing patterns depend on the individual age and circumstances of the KS patient. One protocol recommended by the authors is to begin with a low intramuscular dose (50 mg/month) of testosterone (enanthate or cypionate), with 50-mg increments every 6-9 months until a maintenance dose for adults (200 mg/2 weeks) is achieved. At that time, testosterone gel patches (5.0 to 7.5 grams per day) may be substituted for the injections. For older boys, larger initial doses and increments can achieve more rapid virilization. Side effects of testosterone therapy should be monitored. These include fluid retention, hypertension, polycythemia, acne, transient and occasional permanent gynecomastia, sleep apnea and prostatic hypertrophy. Monitoring of therapy effectiveness includes measurement of testosterone and free testosterone levels, along with the patient's overall general well-being, muscle strength, libido, body hair growth and shaving frequency. In addition to pharmacological therapy, adolescents with KS should maintain their IEPs and physical activity programs.

## **EVALUATION AND TREATMENT OF COMMON COMORBIDITIES**

### Gynecomastia

Gynecomastia does not resolve spontaneously and may worsen with testosterone therapy. In severe cases (i.e. when it is cosmetically indicated), plastic surgery procedures for mastectomy can be considered. Breast cancer accounts for only about 0.5% of all cancers in men but is at least 20 times more frequent in KS patients than in the general population (Smyth & Bremner, 1998). Prophylactic mastectomy is not indicated to prevent cancer, but regular breast self-monitoring is important to monitor for changes suggestive of cancer, since 7.5% of male breast cancer occurs in KS.

### Hashimoto's Thyroiditis

Children with KS are at higher risk for chronic autoimmune thyroiditis (Hashimoto's thyroiditis), with thyroid enlargement and gradual loss of thyroid function. Therefore, an annual physical exam of the thyroid along with a directed history for thyroid-related symptoms and serum TSH evaluation is indicated. Synthroid therapy should be initiated if hypothyroidism occurs.

### Osteoporosis

In up to 50% of patients with KS, the bone mineral density is 12% to 15% lower than normal due to low testosterone and low calcitonin levels, necessitating a baseline measurement

of bone mineral density (BMD) in late adolescence. If the BMD becomes abnormally low, treatment including weight bearing exercises and calcium should be initiated, and bone mineral density studies should be repeated every 1 to 2 years. Regular testosterone replacement is effective in increasing BMD, and bisphosphonate treatment may be indicated in severe cases.

### Tumor Potential

Several other types of malignancies occur in KS men, including acute or chronic leukemia, lymphoma, and gonadal or extragonadal (mediastinal) germ cell tumors (Hasle et al., 1995). The highest risk for cancer occurs in the 15-30 year age group. Lab evaluations of tumor markers (beta hCG, alpha-fetoprotein) should be performed at least once before age 25.

### Rheumatoid Arthritis

Rheumatoid arthritis occurs in men with KS as a side effect of testosterone that decreases sedimentation rate and increases suppressor T cells. Standard therapy with anti-inflammatory agents is appropriate.

### Psychosocial Issues

Care of the individual with KS requires close monitoring of affect and thought, intellectual functioning and sexual adjustment. Appropriate counseling of parents and patient is appropriate as indicated.

## **NURSING MANAGEMENT**

Nursing management of the child and adolescent with KS is primarily educational and supportive. At the time of diagnosis, questions about etiology, treatment, and prognosis will be paramount in the parent's/teen's mind. Directing parents to relevant and reputable resources (see end of chapter) is a key nursing strategy, especially with the availability of information on the World Wide Web. In addition to information about KS, guidance about interacting with the healthcare and school systems will empower parents and assist them in moving forward. Armed with information and support, parents/patients can begin the process of adaptation to having a chronic disease.

Peer acceptance and independence are problematic for adolescents with KS. The physical characteristics that define KS (tall stature, sparse facial hair, etc) separate them out from their peers. In addition, as a group, they tend to be shy, somewhat passive, and unlikely to take a leadership role. Although they do make friends with other children, they tend to have only

a few friends at a time. As discussed earlier, directing the adolescent and parent to individual sports activities and social activities involving small groups will be more beneficial for the KS adolescent. Independence from parents and other authority figures is a related issue that the KS teen will confront. Adolescents want to be independent and separate from parents, but when confronted with a chronic illness such as KS, they recognize that they have a medical condition that requires dependence on parents and healthcare professionals. Helping boys with KS progress through these developmental issues is a key nursing strategy.

Parents of XXY boys are sometimes concerned that their sons may grow up to be homosexual. This concern is unfounded. There is no evidence that XXY males are any more inclined toward homosexuality than are other men. In fact, the only significant sexual difference between XXY men and teenagers and other males their age is that the XXY males may have less interest in sex. Supportive counseling about sexuality should be provided when the teenager and/or family indicates it to be an area of concern. For some adolescents and families, referral for mental health services may be appropriate.

A major area of nursing intervention relates to the school system. Teachers need alerted to learning problems associated with KS (i.e. verbal cognitive defects) and to specific strategies that assist the KS child in mastery of classroom content. For example, studies have shown that KS boys often do poorly in open classroom situations as compared to a structured environment centered on routines (Graham et al., 1988). Early intervention with the school system in cooperation with the parents will go a long way in assisting the boy with KS reach appropriate academic milestones.

## **CONCLUSIONS**

Males with KS are at increased risk for physical, metabolic, emotional, and behavioral disorders, yet most go through life undiagnosed. Missed and/or delayed diagnosis is in part due to lack of understanding by medical professionals. Many childcare specialists do not understand the importance of directed motor and learning early intervention programs, nor do they understand the importance of instituting testosterone treatment in pre-teen years. Furthermore, many healthcare professionals incorrectly believe that KS patients are always tall, mentally retarded, have very small testes, and have abnormal testosterone and elevated gonadotropins levels. Alerting healthcare professionals to key clinical characteristics at various developmental stages will assist in earlier identification and treatment. As infants, these features include hypotonia, smaller than average head circumference, hypospadias, microphallus and cryptorchidism. For the school-age individual with KS, these include learning disabilities (usually

mild), delayed language skill development, poor school performance, delayed emotional development, minor behavioral problems, and poorly developed gross motor control. As adolescents, KS males present with the classic features discussed earlier, as well as relative androgen deficiency, as evidenced by almost normal virilization, but smaller than average phallus, small and poorly-developed testes, and sparse facial hair. Adult KS men generally present with primarily infertility, gynecomastia and decreased libido.

Education of healthcare professionals toward more careful understanding of both the classic and variable presentation patterns, attention to all the known characteristics, and the need and benefit of early diagnosis may help to identify these patients in the pre-pubertal state when interventions can be very important. Early intervention with appropriate attention to hypotonia, delayed speech development, and behavior can have lasting positive effects. Early treatment with testosterone may modulate many aspects of the clinical course, attenuate or prevent complications, and provide patients with improved social skills and relationships.

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### VIDEOTAPE:

- <http://klinefeltersyndrome.org/videtape.htm> (\$10, 20minutes)

### WEB SITES:

- <http://www.47xxy.org/XXY.htm>
- <http://www.nichcy.org>
- <http://www.aaksis.org/> - American Association for Klinefelter Syndrome Information and Support
- <http://www.hosprract.com/issues/1999/0915/cesmyth.ht>
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<http://www.faculty.fairfield.edu/fleitas/contents.html> - a site about growing up with a chronic illness.