

# Klinefelter Syndrome

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Posted 2-14-05

## Key Points

### **Genetics**

- Klinefelter syndrome should be considered as a possible diagnosis among adult men with hypogonadism, infertility, and/or low libido.
- Testosterone replacement therapy can improve the health of men with Klinefelter syndrome.

### **Ethics**

- Almost all men with Klinefelter syndrome are infertile, which may raise questions of paternity if an affected male has a child.
- The implications of a genetic diagnosis should be discussed with the patient before ordering the test.

## Learning Objectives

Participants will be able to:

- Describe clinical indicators for workup of Klinefelter syndrome in adult males;
- Explain the appropriateness of pre-test counseling before ordering a karyotype in an adult male suspected of having Klinefelter syndrome;
- List the benefits of testosterone therapy in the treatment of an individual with Klinefelter syndrome.

## Family History Issues

Klinefelter syndrome (47,XXY) is a sporadically occurring chromosome abnormality occurring in approximately 1/500 males. Family history does not represent a risk factor for this condition.

## Red Flags



Klinefelter syndrome is suspected in males with developmental delay, hypogonadism, gynecomastia, or infertility. It is assumed that many males with 47,XXY are not karyotyped and remain undiagnosed.

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### Case 27. A 35-Year-Old Man with a New Diagnosis of Klinefelter Syndrome: Questions of Paternity

A resident presents a 35-year-old male patient with a five-year history of intermittent abdominal pain consistent with irritable bowel syndrome. The patient teaches mathematics in middle school; he is married and has a son. In the course of a full physical examination, small testes are noted. On questioning, the patient notes low sex drive. Initial workup reveals a low serum testosterone concentration. At the recommendation of an endocrinologist, a chromosomal study was ordered and reveals that the patient has a 47,XXY karyotype. He has an appointment to discuss his results.

### Clinical Care Issues

#### **Klinefelter syndrome**

The diagnosis of Klinefelter syndrome is based on the presence of at least one extra X chromosome, in the presence of a Y chromosome. The most common form of Klinefelter syndrome is due to a 47,XXY karyotype and is found in about 80% of cases, but can also be due to variant karyotypes, such as 48,XXXYY, 48,XXYY, 49,XXXXY, and 47,XXY/46,XY mosaicism [Lanfranco et al 2004]. The prognosis of individuals with variant karyotypes can be different from the prognosis of 47,XXY individuals. Some geneticists reserve the term "Klinefelter syndrome" for symptomatic adolescents and adults, and refer to fetuses, newborns, or children without symptoms as having 47,XXY.

**Medical findings in Klinefelter syndrome.** Klinefelter syndrome is associated with characteristic clinical findings but has substantial variability.

Some of the typical findings include tall stature, small testes after puberty, underdeveloped secondary sex characteristics, and learning disabilities, particularly in language development (see [Case 28](#)). Production of testosterone is deficient throughout adolescence and adulthood, resulting in less muscle development, reduced facial and body hair, and in some cases, gynecomastia. Affected men typically have azoospermia, resulting in infertility.

Treatment with testosterone can improve libido, increase muscle mass, and promote the development of facial and body hair. Additionally, it may assist with improved body image and mood enhancement.

In this case, the patient's presenting complaint seems compatible with a diagnosis of irritable bowel syndrome. This is unrelated to the diagnosis of Klinefelter syndrome.

### **Psychosocial adjustment in adults with Klinefelter syndrome.**

Although men with Klinefelter syndrome are more likely to have persistent language difficulties into adulthood, these deficits do not correlate with lack of achievement in education, employment, or socioeconomic status [[Manning & Hoyme 2002](#)]. Even without the benefit of early diagnosis, educational adjustment, and hormone treatment, men with Klinefelter syndrome do well as adults compared to hypogonadal 46,XY controls with respect to occupation, working capacity, social adjustment, and physical or psychological conditions [[Nielsen & Pelsen 1987](#)]. However, Klinefelter males tend to be more likely to remain single [[Nielsen & Pelsen 1987](#)]. Although some young men do go into vocational-type jobs, others have achieved advanced degrees and work in technical fields [[Manning & Hoyme 2002](#)].

**Infertility in Klinefelter syndrome.** The fact that Klinefelter syndrome is associated with infertility raises the possibility that this man may not be the biologic father of his son. In Klinefelter syndrome, approximately 95% of men are infertile because of azoospermia. However, some men with non-mosaic 47,XXY produce a small number of sperm, allowing for the use of assisted reproductive techniques with intracytoplasmic sperm insertion (ICSI) to achieve pregnancy. A few cases of naturally conceived offspring of proven paternity have been reported [[Tachdjian et al 2003](#)]. One hypothesis for fertility in Klinefelter syndrome is that some men have a mosaic (46,XY/47,XXY) karyotype; it is possible that fertile 47,XXY males who do not have mosaicism in leukocytes actually have a normal 46,XY cell line in their testes. A mosaic karyotype in the testes would not be detected by a blood karyotype analysis.

Since fertility is occasionally possible in Klinefelter syndrome, men should not assume they are infertile without semen analysis.

## Risk Assessment

When using options such as ICSI to achieve pregnancy, the increased risk of transmitting a chromosome abnormality to the offspring of men with 47,XXY should be discussed, even though the precise risks are not known.

Chromosome analyses performed in sperm from individuals with 46,XY/ 47,XXY mosaicism and in rare sperm from non-mosaic 47,XXY individuals have shown an increased incidence of sperm cells with 24,XX or 24,XY karyotypes [[Tachdjian et al 2003](#)].

## Genetic Counseling and Testing

The psychosocial implications of 47,XXY may be significant for men diagnosed in adulthood. This underscores the need for pre-test counseling, which would involve explaining to the patient some of the implications of this condition prior to ordering the chromosome test, and allowing him to participate in the decision to test. In this case, a 47,XXY diagnosis can lead this patient to serious questions of paternity regarding his son. Since his initial workup already shows low testosterone levels, he can likely benefit from testosterone replacement therapy with or without the 47,XXY diagnosis. By discussing the implications of the test prior to ordering it, the patient can preserve his right to decline testing if he prefers to do so.

## Interventions

In Klinefelter syndrome, testosterone replacement therapy is recommended to treat or prevent sparse body and facial hair, breast development, and diminished libido. Hormone treatment is also helpful in stimulating energy level, muscle mass development, and general well-being, and may prevent osteoporosis. It may help with improved psychological adjustment through improved body image and mood. Because the most effective methods of androgen replacement are still being perfected and may vary between individuals, referral to an endocrinologist is recommended [[Manning & Hoyme 2002](#)].

Due to testosterone deficiency, men with Klinefelter syndrome are at increased risk for osteoporosis. Optimal calcium and vitamin D intake should

be encouraged. Screening for osteoporosis with bone mineral density studies can help determine if osteoporosis is present before medical complications occur.

Men with Klinefelter syndrome seem to have an increased risk of breast cancer [Hultborn et al 1997, Swerdlow et al 2001] and may benefit from instruction in breast self exam and from counseling to bring any breast abnormalities to medical attention. Screening mammography has no role in men because of the rarity of the disease and the small size of the male breast, which allows easy palpation of most masses [Giordano et al 2002].

Men with XXY are also at increased risk for autoimmune disorders such as diabetes mellitus and hypothyroidism. Additionally, men with this condition are prone to varicose veins and leg ulcers due to venous stasis. Although no formal guidelines have been established, an annual physical examination should include an assessment of signs and symptoms of these disorders [Robinson et al 2001].

Regardless of age at diagnosis, males with XXY should be evaluated for the presence of specific learning problems and for negative self-appraisal. Adults can be evaluated in hospital-based learning clinics or by psychologists and speech therapists in outpatient settings.

## Ethical/Legal/Social/Cultural Issues

### Genetic labeling

Genetic labeling often involves both benefits and burdens (see Table 1). The balance between these is often highly subjective.

**Table 1. Benefits and Burdens of Disease Labeling**

<b>Benefit</b>	<b>Burden</b>
Understanding	Stigmatization
Specific management or prevention options	Discrimination
Access to services	Helplessness

For this patient, the benefit of having a new diagnosis may outweigh the burdens. The diagnosis of Klinefelter syndrome may come as a relief because it provides an explanation of his symptoms and a basis for treatment with testosterone replacement therapy, which would be expected to lead to improved sex drive and sense of well-being. However, the burden of being labeled with a diagnosis may have adverse psychological consequences. Having the diagnosis may not significantly impact his medical care since he is likely to be a candidate for testosterone replacement therapy regardless of whether Klinefelter syndrome was the cause of his symptoms.

### **Question of paternity**

The fact that 95% of men with Klinefelter syndrome are infertile needs to be relayed to the patient. Further discussion of infertility or paternity testing should be addressed as brought up by the patient in the current or future visits. Like many other conversations between patient and physician, this discussion will benefit from sensitivity and established trust.

Although the initial assumption might be that raising the possibility of non-paternity would be disruptive to the patient, there are many possible situations in which he may already know he is not the biologic father of his son (perhaps he is the child's stepfather, the child was adopted, etc).

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### Resources

- [American Association for Klinefelter Syndrome and Support](#)
- [Klinefelter Syndrome Support Group Homepage](#)
- [National Library of Medicine Genetics Home Reference](#)  
[Klinefelter syndrome](#)
- [GeneTests Online Medical Genetics Information Resource](#)
- [GeneReviews, GeneTests Online Medical Genetics Information Resource](#)

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