European Acedemy of Andrology (EAA) GUIDELINES ON KLINEFELTER SYNDROME - Endorsing Organisation: European Society of Endocrinology

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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.

1. Introduction

Klinefelter Syndrome (KS) is the most frequent chromosome disorder in men, yet many doctors have little information about KS diagnosis and treatment. While symptoms of KS are highly variable, common characteristics include:

- Small testes
- Azoospermia
- Hypergonadotropic hypogonadism
- Neuro-cognitive and psychosocial manifestations
- Cardiovascular conditions
- Metabolic conditions
- Bone-related conditions

Currently, there are no specific guidelines or recommendations about the care of patients with KS, and this study aims to provide a list of suggestions and recommendations to care for patients from the prenatal period through adulthood. The study was created by the European Academy of Andrology (EAA) and endorsed by the European Society of Endocrinology.

2. The GRADE SYSTEM

In order to create the list of suggestions and recommendations, the EAA gathered a task force of andrology experts from various backgrounds, including urology, genetics, pediatrics, and endocrinology. They searched PubMed for articles written in English between 1942-2020 that included the word “Klinefelter” and evaluated the evidence from this published literature. They created the GRADE system (Grading of Recommendations, Assessment, Development, and Evaluation).

The Cause and Prevalence of Klinefelter Syndrome

The additional X of KS originates when the sex chromosomes fail to seperate evenly during meiosis I (the period in which the sperm and egg cells divide to create the 23 chromosomes to create an egg with 46 total). When there is an abnormal distribution of chromosomes from either the sperm or egg, an extra chromosome may be formed.

According to studies from the 1960s-1970s, KS can happen in 1-2/1000 male newborns. 80-90% of the cases identified are the classic 47,XXY form, but 10-20% of cases may present as higher-grade aneuploidies (the presence of one or more extra chromosome) like 48,XXXY, 49, XXXXY, 48,XXYY or mosaicisms (having 2 or more genetically different sets of cells) such as 47,XXY and 46,XY. A small number of cases have structurally abnormal X chromosomes such as 47, iXq, Y.

The prevalence of 47,XXY when studied during the early stages of pregnancy was reported as 0.9%, which appeared to have a significant connection with maternal age. This suggests 47,XXY blastocysts (the early form of an embryo) might have lower rates of implantation (when the blastocyst attaches to the uterus' wall), or a higher early miscarriage rate. It's also thought embryos fertilized using IVF result in a higher rate of 47,XXY blastocysts.

It is estimated that 50-75% of males with KS are never diagnosed because there's such a variety of symptoms and presentation of the disorder. In order to increase the diagnosis rate, all male newborns should be screened for KS, potentially through dried blood spot samples. A correct and early diagnosis will enable better management and prevention of diseases related to KS. Many men are not even diagnosed with KS until they undergo an infertility evaluation.

3. Diagnostic Steps and Therapy

3.1 Genetics

Recommendations

1. A prenatal diagnosis of KS should be confirmed with a chromosome analysis on a postnatal peripheral blood sample.
2. Patients should have conventional karyotyping on peripheral blood cells for diagnosis of KS.
3. Patients with KS and/or their parents should be offered genetic counselling; prenatal counselling should be non-directive (do not tell parents to keep or abort child, just provide facts).
4. Men with non-obstructive azoospermia or (severe) oligozoospermia (total sperm count < 10 x 106/ejaculate or sperm concentration <5 x106/ml should undergo karyotyping to detect KS.
5. Men with primary hypogonadism (low serum levels of testosterone) and elevated serum levels of gonadotropins (LH and FSH) combined with small testicular volumes (<5 ml per testis) should undergo karyotype analysis to detect KS.

Evidence

KS is diagnosed based on the karyotype. KS affects 3-4% of infertile males; a majority of KS males are azoospermic (an absence of sperm in semen), while about 10% of men present with oligozoospermia (low sperm count) or cryptozoospermia (sperm can be found after extended microscopic search).

While about 50% of adults with KS experience low testosterone levels, nearly all patients have elevated LH levels which reflects the primary testicular damage in these patients. Hypogonadism is a hallmark symptom of KS, and present in most men with KS.

Value and Remarks
Conventional karyotyping should be completed to confirm clinical suspicion of KS in patients so further counseling, diagnostics, and treatment may be provided. "Karyotyping should also be considered in cases of low testicular volume (<5ml), which may be present without primary hypogonadism, apart from non-obstructive azoospermia or severe oligozoospermia (which must be confirmed in more than one semen analysis). Other possible causes of non-obstructive azoospermia or severe oligospermia must be considered. Especially cases with central hypogonadism might present with small testes, non-obstructive azoospermia or severe oligozoospermia and not all of them are candidates for karyotype analysis" [p.16].

KS may be diagnosed prenatally by conventional karyotyping of chorion villus tissue or amniotic fluid. Non-invasive prenatal testing (NIPT) is widely used for screening for autosomal trisomies, such as trisomy 13, 18, and 21, however the data from that screening may not be fully accurate and provide false positive results; therefore cytogenetic confirmation is required.

In cases of prenatal diagnosis of KS, genetic counseling is strongly recommended, and in fact is mandatory by law in some countries. The counseling is non-directive and will inform parents about the potential risks for patients with KS, and modern treatment options available. Information about KS patient and parent groups may be provided. Any decision the parents make regarding the child should be absolutely individual.

It may be recommended to perform additional screenings for mosaicism or higher number metaphases.

3.2 Developmental issues in infants and pre-pubertal children
3.2.1 Testicular development and the function of the hypothalamic-pituitary-testicular axis
Recommendations
6. Karyotype analysis should be used to detect KS in boys born with cryptorchidism (when the testicles don't descend from the abdomen), especially the bilateral forms, who don't experience spontaneous descent of the testes at the first year.

7. Children with KS should receive treatment for cryptorchidism according to the current treatment guidelines for children without KS.
8. Pre-pubertal boys with KS should receive a general physical examination including a testicular evaluation. These should be performed biennially or as deemed as appropriate. Suspected neurological or psychiatric deficits should be examined by respective specialists.
9. Determination of LH and testosterone during the first 2-3 months after birth in children with prenatal diagnosis of KS is required, as it might have a therapeutic consequence (i.e. diagnosis of micro-penis).
10. It's not recommended to perform cryopreservation of testicular tissue or spermatogonial stem cells retrieved from pre-pubertal children with KS.
11. It's not recommended that children with KS receive testosterone supplementation except in cases of micro-penis.

Evidence
In men with KS, testicular degeneration and abnormal testicular function may begin during the fetal period of life, and worsen with age. Some boys may have cryptorchidism (undescended testicles), reduced penile length and testicular volume. Boys with KS rarely fulfill the criteria for a micropenis, though one study found it may affect up to 17% of patients with KS.

3-4% of patients with cryptorchidism have chromosomal anomalies, with KS representing the most frequent alteration. Patients with KS are more likely to have bilateral cryptorchidism (both testes undescended), with potentially 27-37% of KS patients experiencing undescended testes. Testicular function, in particular sperm production, is linked with descended testes. As KS impairs testicular function, "these patients require high attention to the management of their undescended testes as early as possible" [p.19]. The EAA doesn't recommend testicular tissue cryopreservation or spermatogonial stem cell retrieval in children with KS.

There is conflicting data on the testosterone levels in newborns during the first 3 months after birth (mini-puberty) and there's been no significant differences found in the height, weight, testicular volume, or penile length of babies with KS. Some studies show some boys with KS may already be androgen deficient before puberty. The EAA recommends against testosterone treatment during early childhood for patients with KS as it has no justification, however in the cases of micro-penis, a short term low-dose of testosterone could be justified. This period of "mini-puberty" is a good time for evaluating the hypothalamic-pituitary-testicular axis in infancy through endocrine evaluation.

3.2.2. Growth

Recommendations

12. Pre-pubertal children with KS should have their height measured according to centiles or standard deviation scores (SDS), as well as body proportions and determinations of bone age based on their individual growth pattern.

Evidence
During infancy KS boys usually grow within the normal range, but by age 5-6 years their rate of growth may accelerate, resulting in them being significantly taller than expected based on parental target height. Additionally, some research suggests they may have significantly increased leg length before they reach puberty.

Value and Remarks
The height and weight of boys with KS should be monitored and assessed based on the SDS and bone age should be determined. Testosterone supplementation should be considered if there is excessive growth or abnormal body proportions; it may have significant physical or psychological side effects. High dose testosterone treatment is required to stop over-tall growth, but its effects on testicular functions are unknown, and is discouraged.

3.2.3. Bone mineralization

Recommendations
13. Pre-pubertal children with KS should have their vitamin D blood levels determined and provided with adequate vitamin D and calcium supplementation.
14. Pre-pubertal children should have their bone mineral status assessed biennially in case of vitamin D deficiency (DXA scan, size-corrected determinations using a three-step-method are required).

Evidence
The risk of osteopenia/osteoporosis may not be present in boys with KS until after puberty. A study found higher parathyroid hormone levels and low vitamin D concentrations in boys.

Values and Remarks
There are no uniform studies of bone status and metabolism of boys with KS. It's recommended to check vitamin D levels and supplement if needed to maintain healthy bones. It's moderately recommended to assess bone mineral status because it's important to diagnose and treat osteopenia/osteoporosis as soon as possible. It's likely less than 20% of children with KS will suffer from osteopenia/osteoporosis.

3.2.4. Body Composition

Recommendations
15. Pre-pubertal children should have their weight measured based on centiles or standard deviation scores.

16. It's not recommended to treat infants and pre-pubertal boys with KS with testosterone treatments.

Evidence
Aside from low testosterone, boys with KS may experience other genetic causes or psychosocial environments that may cause elevated body fat mass; further studies will need to be conducted.

"Testosterone supplementation in early childhood was proposed, particularly in the USA" [p.22], and the studies claimed improved neurodevelopmental outcomes in boys with KS, however; the studies were not properly conducted and the evidence may not be conclusive. In one study, 20 infants with KS (ages 6 to 15 weeks) randomly received testosterone injections, or no treatment. The infants with no treatment presented a significant accumulation of fat tissue as compared to the 46, XY control group.

In a second study, prepubertal boys (ages 4 to 12 years old) were given a low-dose synthetic oral androgan (oxandrolone). "The authors reported improvements in areas of visual-motor performance, anxiety/depression, and social functioning, but no effect on cognition or attention. Furthermore, a significant reduction in body fat, triglycerides and high-density lipoprotein was found. Importantly, the oxandrolone treated boys had an increased risk of early gonadarche and pubarche, as well as advanced bone age, although no significant differences in T and gonadotropin concentrations between treated and untreated boys were found" [p. 22].

Values and Remarks
The EAA recommends assessing weight and possibly fat/lean proportions and suggests keeping them within normal ranges, as they're important for metabolic equilibrium. Waist circumference, and triceps/subscapular skinfolds can be assessed.

More research needs to be conducted on the positive short and long term effects of testosterone treatment in infants and pre-pubertal boys with KS.

3.2.5. Physiological Aspects

Recommendations
17. It's highly recommended children with KS see a speech therapist, and are monitored for learning disabilities. They should be provided with social training and psychological support if needed.

Evidence
"Boys with KS are known to have increased risk for psychosocial and educational problems" [p.23]. Their verbal abilities may be decreased, and they may have lower general cognitive abilities, and lower attention and executive dysfunction. This may present as impaired

performance on language development assessments, and measures of visuospatial and academic abilities. In younger boys with KS, delays in speech development may occur, and in adolescents possible significant deficits in aspects of expressive language.

Boys with KS may struggle to identify and verbalize emotions, be more easily aroused, and may have increased distractibility and increased hyperactivity.

Values and Remarks
Speech development and learning abilities should be monitored, as well as psychosocial problems, and support should be provided. Early testosterone treatment may improve psychological development, however there's not sufficient data to validate the treatment.

4.1. Developmental Issues in puberty and Adolescence
4.1.1. Spermatogenesis
Recommendations
18. Information on fertility issues should be given to adolescent patients with KS and, if appropriate, his parents.
19. Patients with KS should receive testicular ultrasound evaluation, and regular follow up visits during puberty.
20. Semen collection and cryopreservation of motile sperm (if present) in adolescents with KS should only be done after careful information is provided.
21. Adolescents with KS might undergo a testicular biopsy for testicular sperm extraction (TESE) either using multifocal (standard TESE) or microdissection-TESE (mTESE) and consequent sperm cryopreservation in selected cases only after specific counselling has been provided, and they're physically and emotional mature enough.

Evidence
Puberty generally occurs at the normal age for boys with KS. The testes grow to a minor extent, and then shrink. As this is happening, gonadotropin levels (the group of hormones secreted by the pituitary which stimulate the activity of the gonads) rise to the highly elevated levels seen in adults with KS.

The germ and Sertoli cells rapidly degenerate during this time, as the seminiferous tubules (site where sperm is created) become fibrotic and deteriorate. The creation of sperm cannot be detected in a majority of the seminiferous tubules, however; there may be a few tubules capable of creating viable sperm.

In boys with KS ages 13-14 years who underwent TESE attempts, spermatozoa was only collected in 10%, while spermatozoa was collected in 45% of the TESE attempts made in

adolescents ages 15-19 years. Sperm retrieval rates by TESE in adolescents with KS were similar to the rates reported by young adults who are 20-30 years old.

Values and Remarks
The EAA highly recommends patients and caregivers of those with KS receive information on fertility status and treatment possibilities. Patients with KS, and his family should feel empowered to undertake further medical treatment.

The EAA does not suggest to collect semen or perform TESE on adolescents in puberty as they may not be "psychologically ready to focus on fertility, and because success rates are similar if these procedures are performed later" [p. 25]. Adolescents with KS may undergo a TESE provided they're able to demonstrate physical and mental maturity. The decision must come from them, and not caregivers. Not all patients are mature enough to talk about their fertility, but they should be fully informed on their fertility status, and the possibility of preservation. This information should be provided at the appropriate cognitive level for the patient to understand.

The EAA recommends performing a testicular ultrasound every year to assess testicular development.

4.1.2. Function of the hypothalamic-pituitary-testicular axis

Recommendations
22. Prior to the predicted start of puberty, boys with KS should undergo an assessment of Tanner stages, pubertal development, measurement of testosterone and gonadotropins, signs and symptoms of hypogonadism, height, weight, waist circumference and body proportions (the time-window for the start of puberty does not differ from boys with a karyotype of 46,XY).
23. Testosterone supplementation is recommended in case of delayed puberty and/or symptoms of hypogonadism associated with low-normal testosterone and supra-normal LH serum concentrations (LH > 2 SD according to age-related references), after fertility issues have been addressed (see above).
24. Testosterone therapy is not recommended for adolescents with KS who also experience compensated hypergonadotropic hypogonadism.

Evidence
Around mid-puberty most patients with KS will experience a plateau in their testosterone and INSL3 concentrations. Simultaneously, FSH and LH concentrations increase as testes fail to produce sufficient quantities of testosterone. Most patients with KS experience an undetectable amount of Inhibin B (the hormone associated with the production of sperm).

Most KS boys are able to spontaneously accomplish pubertal development, however about 25% of KS diagnoses are made because they have testosterone levels below normal levels, which

leads to a prolonged progression of pubertal development. This is not the same as delayed onset of puberty.

Values and Remarks
Exams should be done around the estimated time of pubertal onset, based on parents' pubertal history. Before hormone replacement therapy begins, fertility status should be assessed. It's highly recommended to treat patients with KS who have low testosterone levels with adequately dosed testosterone replacement. Testosterone supplementation will ensure improved physical and psychological development, educational achievements, and social integration [p. 28].

There are no studies evaluating the possible negative impacts of testosterone treatment on successful sperm retrieval, or its possible effects on reproductive outcomes in patients with KS. Testosterone treatment should be handled on a case by case basis with the provider, parents, and patient.

4.1.3. Cognitive and Psychological Aspects

Recommendations
25. Adolescents with KS should receive speech therapy, and should be monitored for educational problems; social training and psychological support should be provided.

Evidence
"Boys with KS might show deficits in verbal memory, verbal fluency, word retrieval, expressive/receptive vocabulary difficulties, as well as planning, organization, and decision-making problems' [p.29]. While this may be related to lower academic/school performance, boys with KS are not general learning disabled. These limitations may impact their development and personality, and their ability to adapt in social situations.

Value and Remarks
The EAA highly recommends caregivers of patients with KS monitor speech development, educational, social, psychosocial problems, and give support if necessary [p. 29]. Further studies are needed to evaluate how KS may impact men in adulthood in relation to their final education, socio-economic status, psychological well-being, and general quality of life in adulthood.

5.1. Pathophysiology and clinics in adults

5.1.1. Hypogonadism

Recommendations
26. Testosterone substitution should be initiated in patients with KS with hypogonadism as diagnosed according to established guidelines on hypogonadism, once fertility issues have been addressed.

27. Testosterone substitution in patients with KS should follow the established guidelines on hypogonadism using the suggested monitoring intervals for clinical assessment, safety parameters (haematocrit, PSA), and dose titration.
28. Adult patients with KS not on testosterone substitution should have an endocrine evaluation completed every 12 months.

Evidence
Most adults with KS have low-normal or subnormal serum testosterone levels, though some may have very low amounts, and others may present with normal amounts. In adults with KS, insulin-like-factor 3 (INSL3) and inhibin are decreased, while FSH and LH are highly elevated. Estradiol and SHBG are comparable to non-KS men. Testosterone replacement therapy should follow established guidelines on diagnosis and treatment of hypogonadism.

Value and Remarks
In order for patients with KS to understand their hypogonadism and fertility issues, assessment of serum concentrations and gonadotropins are necessary. These need to be monitored in order to tailor hormone replacement therapy to the patient in order to avoid side effects. Treatment should begin as soon as a diagnosis is made. Testosterone treatment in hypogonadal men with KS can improve body composition and bone mineral density, though its effects on lipid and glucose profiles may be less evident. More studies are needed in order to understand the benefits of testosterone treatment in KS.

5.1.2. Infertility

Recommendations

29. Adult patients with KS who wish for paternity should have a semen analysis and sperm cryopreservation.
30. All patients with KS and confirmed azoospermia, with a current or future wish for paternity undergo a testicular biopsy for testicular sperm extraction (TESE) either using multifocal (standard TESE) or microdissection-TESE (mTESE) and consequent sperm cryopreservation.
31. If a patient with KS has a TESE planned, it's suggested they delay starting testosterone replacement therapy, due to the possible suppression of gonadotropins and remnant spermatogenesis.

Evidence
Between 30-60% of men with KS have sperm, and the reported rate of live birth by assisted reproduction is about 16%. There have been no differences in sperm retrieval between a classic-TESE and a micro-TESE.

Values and Remarks
Semen sampling is a non-invasive procedure and can be offered after puberty as soon as the patient is able to provide a sample. Conventional TESE or micro-assisted TESE in azoospermic patients with KS the the next step to obtain sperm, and can be used for later methods of assisted reproduction.

Offspring of men with KS seem not be affected by the genetic condition of the father, so it's unclear whether offering prenatal genetic analysis is required. Genetic counseling is mandatory. It's unclear whether 47,XXY sperm are able to complete meiosis, or if during meiosis they're able to shed the extra X and become a normal 46,XY to continue through meiosis.

There's no data about whether the creation of sperm decreases with advancing age in KS. There's no evidence to suggest what may provide more or less of a chance to find sperm in men with KS. The EAA cannot recommend for or against stopping testosterone prior to TESE, but suggest against starting testosterone once a TESE is planned.

5.1.3. Metabolic disorders, body composition, cardiovascular risk and thrombosis

Recommendations
32. All patients with KS should receive education on lifestyle and yearly assessment of weight, waist circumference, blood pressure, fasting glucose, HbA1c and lipid profile, and adequate treatment.
33. Patients with KS should receive medication to prevent blood clots prior to long-term flights, or exposure to other risks to reduce the increased risk for deep vein thrombosis and/or pulmonary embolism.
34. All patients with KS should have their heart rate assessed based on their 12-lead ECG QTc time, at least once.

Evidence
Men with KS suffer from higher rates of various diseases, and may have a shortened lifespan (2-3 years shorter than average). Men with KS have increased fat mass and reduced lean mass, which limits their insulin resistance and may predispose them to a higher risk of developing type 2 diabetes. While cardiovascular issues may be attributed to hypogonadism, it doesn't fully explain why KS men are more likely to suffer from these diseases. Testosterone replacement therapy doesn't completely reduce the risk of cardiometabolic issues.

Men with KS may have reduced heart function or an irregular heartbeat, which may lead to sudden cardiac arrest. This may be related to the extra X-chromosome, and can be a life-threatening condition.

Men with KS are at a higher risk of developing deep vein thrombosis or pulmonary embolisms, compared to the general population; this may be attributed to lower testosterone levels and higher levels of PAI-1 (a protein which can cause clotting in the blood). While testosterone treatment may reduce the risk, there's little evidence yet to support this.

Value and Remarks

Men with KS should receive accurate information on lifestyle interventions (such as physical activity and diet) to reduce cardiovascular risk factors. They should be monitored regularly for cardiovascular risk factors, and treated for obesity, diabetes, and high cholesterol levels. Testosterone replacement may help make body composition more favorable, especially in aging men with KS, though it may not completely lower other cardiovascular risk factors. More research is needed to prove its effectiveness.

5.1.4. Bone Disorders

Recommendations

35. Patients with KS are at risk of low bone mineral density (BMD) and fractures, independently of their serum levels of testosterone, so it's recommended to follow the EAA clinical guidelines on management of bone health.
36. Adults with KS should receive a DXA analysis at the lumbar and femoral levels, and fracture risk assessment.
37. All adult patients with KS should have their vitamin D plasma levels evaluated, independently from their bone mineral density, and proper vitamin D and calcium supplementation should be provided when needed.

Evidence

Hypogonadism may reduce bone density and lead to osteopenia/osteoporosis, and up to 40% of patients with KS may experience fractures. There's not a clear relation between testosterone levels and bone mineral density (BMD). The rate of osteopenia/osteoporosis in patients with KS, may be subject to osteopenia/osteoporosis even when testosterone levels are within a normal range. Decrease in bone mass may be caused by the lack of peak bone mass at the end of puberty.

While hypogonadism and low bone mineral density may cause a risk of fractures, KS men are also at risk due to low vitamin D levels, their fat mass/lean mass ratio, other associated illnesses, low INSL3, X inactivation, and AR sensitivity. Testosterone replacement therapy may improve bone density. Vitamin D supplements should also be provided, as well as monitoring calcium levels in the blood.

Value and Remarks

Young boys with KS may have normal BMD, but the risk of lower bone mass starts mid-puberty when testicular function progressively declines, and they're unable to achieve optimal peak bone mass. "Lifestyle interventions (physical activity, smoking, diet, sun exposure), vitamin D and calcium supplementation and specific antiosteoporotic drugs are required based on individual assessments of both BMD and fracture risk" [p. 35]. The effects of anti-osteoprotic drugs on BMD and fracture risk in KS have not been studied.

5.1.5. Psychological and psychiatric conditions/ Gender incongruence

Recommendations

38. All adult patients with KS should be considered for psychosexual and psychiatric issues, and consult a specialist if required.

39. We suggest attention to the possible existence of gender incongruence (when an individual identifies as a gender other than the one assigned to them at birth) in patients with KS. The patient should be referred to a specialist as necessary.

Evidence

Men with KS don't generally have decreased intellectual ability, though may experience some impairment of language skills (verbal processing speed, expressive grammar, word retrieval). They may exhibit impairments in executive related functions like attention, flexibility, planning, and response inhibition. Patients with KS are at increased risk of developing psychiatric conditions such as schizophrenia, bipolar disorders, depression, anxiety, autism, and ADHD.

Values:

Parents and medical providers should pay attention to psychological, sexual, psychiatric, and gender incongruence aspects being experienced by an individual with KS. Individuals with KS may be more withdrawn, may not react strongly to feelings of anger or fear, may be more prone to experience anxiety, depression, and self-doubt. They may have a lower IQ.

Remarks:

The symptoms of KS are highly variable, meaning every individual won't experience the symptoms to the same level of severity. Many of the available studies have selection bias, meaning there wasn't enough randomization of participants in the study. Therefore, current understanding of KS, and its symptoms are primarily based on diagnosed cases. Non-diagnosed cases may have less severe symptoms.

Before starting testosterone therapy, patients with KS should determine if they are experiencing gender incongruence. If so, they may not wish to participate in testosterone replacement therapy. This should be determined after consulting with appropriate healthcare providers, so a correct course of treatment can be provided.

5.1.6. Risk of neoplasia (increased tissue)

Patients with KS should have regular breast exams, including mammary gland ultrasonography as needed to detect gynecomastia (excess breast tissue). This exam should be repeated as necessary to ensure the overall health of the patient.

Evidence:
Individuals with KS appear to have a higher mortality rate for cancers, particularly breast and lung cancers, as well as non-Hodgkin lymphoma. In a large cohort of KS patients, non-Hodgkin lymphoma, as well as various forms of leukemia were more likely to present. However, they have a lower rate of prostate cancer. While the overall risk of breast cancer remains low for 47,XXY individuals, it's still higher than the rate of 46,XY individuals.

There's an increased risk of extragonadal germ cell neoplasia (tumors) in individuals with KS. It's most commonly associated with ages 15-30. The tumors most frequently occur in the mediastinum (within the thorax) and are non-seminomas (type of cancer that begins in cells that form sperm or eggs). Tumors may present in younger boys who go through early puberty, or in older men under their thorax. There's no specific relationship between testicular germ cell tumours and KS. A higher rate of benign Leydig cell tumours has been reported in men with KS.

Values and Remarks
Patients with KS have a higher risk of growing extra tissue, particularly breast tissue. Physicians should be aware of this risk, and provide appropriate care.

5.1.7. Other disorders

Recommendations
41. Patients with KS should have breast and axilla (space between shoulder and armpit) exams every two years. For patients with a history of breast cancer, or suspicion of breast cancer, mammography and/or mammary gland ultrasonography is recommended.
42. Patients complaining of visual issues should have eye exams.
43. Patients with KS should have regular dental exams.
44. Physicians should evaluate KS patients for possible autoimmune disorders.

Evidence
Gynaecomastia (enlarged breast tissue) has been recognized as one of the primary symptoms of KS. Recently, studies have found it's less likely than previously believed, and present in only one third of adults with KS. It should be assessed by a healthcare provider if it appears in puberty. If the gynaecomastia becomes permanent during or after puberty, surgical correction can be considered.

There have been reports of retinal dysfunction, and issues with day/night vision in KS individuals. Dental issues such as adult teeth development, and tooth decay have been reported. Autoimmune disorders may be more frequent, but overall thyroid function seems to be fine.

Values and Remarks
Evaluation and treatment of gynaecomastia is important to maintain the overall self-esteem and positive body image of the individual with KS. The other mentioned conditions should be treated as necessary. The reports on eye issues, dental issues, and autoimmune disease come from a small number of individuals studied.

6. GENERAL DEMANDS
Recommendations
45. Centers that provide specific care to individuals with KS should be set up
46. There should be improved transitional care from pediatric to adult endocrinologists/andrologists for individuals with KS
47. There should be further education about KS for healthcare professionals and the general public by providing structured graduate and postgraduate education

Evidence:
Data indicates 21% of KS patients are diagnosed prenatally, 10-12% during childhood, 16% at puberty, and 51% during adulthood. KS infants generally present as normal, but may be noticed when their testicles fail to descend from the abdominal cavity (bilateral cryptorchidism), or as having a micro penis.

During childhood, excessive growth, speech and behavioral issues, and long limbs may indicate KS. “Delayed puberty, poor testicular development, gynaecomastia, excessive height, learning disabilities and psychosocial problems,” [p.40] should also raise suspicion of KS.

Early diagnosis is still considered rare, but increasing due to prenatal screening. This should be considered advantageous for the patient, as early intervention can help minimize symptoms later in life. Pediatricians should be aware of the increasing rate of early diagnosis, and be prepared to properly assist patients. Being prepared will increase parents’ confidence in provided care, as well as outcomes for their child.

Values and Remarks
It’s important to increase knowledge about KS in the medical community, and for the general public. “It is also paramount to provide patients with KS and their parents with specific information and support them psychologically as needed” [p.40]. The setup of multidisciplinary healthcare centers specifically for KS individuals is also critically important. “These should include all professionals involved (geneticists, paediatricians/paediatric endocrinologists,

psychologists, speech therapists, adult endocrinologists/andrologists, urologists, reproductive gynaecologists, sexologists, psychiatrists)" [p.40].

7. CONCLUSIONS AND FUTURE DIRECTIONS

"KS is the most common sex chromosome disorder in men" [p.41]. It impacts patients with hypogonadism, and infertility. Men with KS are at higher risk of having cardiovascular, metabolic, psychiatric, and other health issues. Providing the patient and parents with "suitable and balanced information as well as assistance for various aspects of his life after receiving the diagnosis is suggested," [p.41]. Prevention and treatment of symptoms associated with KS should be standardized. Interventions to minimize neurodevelopmental difficulties like speech and learning disabilities, as well as behavioral issues should be applied. When taken, these interventions can help improve the self-esteem of the KS individual, as well as assure his quality of life. Preserving semen for the option of egg fertilization later in life is a viable option.

KS is a vastly understudied and underdiagnosed condition. Therefore, in order to improve care and outcomes, "establishment of standard care in multidisciplinary networks is mandatory." [p.41].