Gonadal dysfunction and beyond: Clinical challenges in children, adolescents, and adults with 47,XXY Klinefelter syndrome

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Abstract
Klinefelter syndrome (KS) is the most frequent sex chromosomal aneuploidy. The karyotype 47,XXY originates from either paternal or maternal meiotic nondisjunction during gametogenesis. KS males are very likely to exhibit marked gonadal dysfunctions, presenting both in severely attenuated spermatogenesis as well as hypergonadotropic hypogonadism. In addition, neurocognitive and psychosocial impairments, as well as cardiovascular, metabolic and bone disorders are often found in KS and might explain for an increased morbidity/mortality. All conditions in KS are likely to be induced by both gene overdosage effects resulting from supernumerary X-chromosomal genes as well as testosterone deficiency. Notwithstanding, the clinical features are highly variable between KS men. Symptoms can become obvious at infancy, childhood, or adolescence. However, the majority of KS subjects is diagnosed during adulthood. KS adolescents require specific attention regarding pubertal development, in order to exploit their remaining fertility potential and allow for timely and tailored testosterone replacement. The chances for sperm retrieval might decline with age and could be hampered by testosterone replacement; therefore, cryostorage of spermatozoa is an option during adolescence, before the decompensation of endocrine and exocrine testicular functions becomes more overt. Sperm from semen or surgically retrieved, in combination with intracytoplasmic sperm injection enables KS males to become biological fathers of healthy children. The aim of this article is to present the current knowledge on KS, to guide clinical care and to highlight research needs.

KEYWORDS
47,XXY, children with Klinefelter syndrome, fertility in Klinefelter syndrome, hypogonadism in Klinefelter syndrome, Klinefelter syndrome

1 | INTRODUCTION

Klinefelter syndrome (KS) is the most frequent sex chromosomal anomaly in males and denotes a karyotype 47,XXY.
The first clinical description of men presenting with bilateral gynecomastia, small testes, aspermogenesis, reduced Leydig cell function and increased excretion of follicle-stimulating hormone (FSH) by Dr Harry Klinefelter dates back to 1942 (Klinefelter, 1942), while the genetic origin of the condition, namely a supernumerary X chromosome was identified in 1959 (Jacobs & Strong, 1959).

The aim of this article is to present “the state of the art” regarding the clinical aspects of KS, to guide care and to highlight research needs.

1.1.1. Etiology of KS

Nonmosaic 47,XXY KS originates from paternal or maternal meiotic nondisjunction during gametogenesis. As a result, a supernumerary X-chromosome is present in putatively all body cells. While the maternally inherited karyotype 47,XXY is caused by nondisjunction during the first or second meiotic divisions of oocyte development or from nondisjunction during early postzygotic mitotic divisions in the developing zygote, a paternalally induced 47,XXY karyotype arises solely from meiosis I errors during spermatogenesis (Lanfranco, Kamischke, Zitzmann, & Nieschlag, 2004; Tuttelmann & Gromoll, 2010). The prevalence of KS seems to be related to maternal age, an observation that has been attributed to an increase of maternal meiosis I errors with aging. Whether there is an association with paternal age, is as yet unclear (Tuttelmann & Gromoll, 2010; Zitzmann et al., 2015).

The prevalence of KS in males, based on large newborn screening studies, is 1–2/1,000 (0.1–0.2%). By contrast, it is estimated that only 20–30% of all males with KS are ever diagnosed during lifetime (Hamerton, Canning, Ray, & Smith, 1975; Herlihy, Halliday, Cock, & McLachlan, 2011; Lanfranco et al., 2004; Maclean, Harnden, Brown, Bond, & Mantle, 1964; Nielsen & Wohlet, 1991).

In nonmosaic KS subjects, a supernumerary sex chromosome, thus a 47,XXY karyotype, is most likely found in all cells, as demonstrated by analysis of peripheral lymphocytes. This may lead to X-chromosomal gene overdosage originating from both, genes located on the pseudo-autosomal regions at the very tips of each sex chromosome that regularly do not undergo Lyonization, as well as from so-called “escapee genes,” dispersed all over the X-chromosome. The latter are, by unknown mechanisms, not fully submitted to inactivation (Zitzmann et al., 2015; Zitzmann, Depenbusch, Gromoll, & Nieschlag, 2004). The vast phenotypic spectrum encountered in KS results from a variety of further genetic mechanisms, among which tissue mosaicism might be a potential contributor. In addition, differential expression of parental alleles, due to differential imprinting (Zitzmann et al., 2015), differential methylation patterns or other epigenetic regulatory mechanisms may be involved, as well as differential expression of RNA and noncoding RNA and differential protein–protein interactions (Skakkebaek et al., 2018). Finally, the individual sensitivity of the human androgen receptor may modulate the phenotype (Zitzmann et al., 2004).

2 | DIAGNOSIS OF KS

2.1 | Genetic diagnosis of KS

As the phenotypic spectrum of KS is extremely wide, this contributes to delay in diagnosis. Population studies have demonstrated that 20% of identified cases of 47,XXY are diagnosed prenatally, 12% during childhood, and additional 16% during puberty (Herlihy et al., 2011).

While detection of an extra Barr body in cells from buccal mucosa has been used in the past to evidence the presence of the supernumerary X-chromosome, karyotyping performed in peripheral blood cells is at current the well-established standard procedure for diagnosing chromosomal aneuploidies. A 47,XXY karyotype is present in 80–90% of subjects with KS, while sex chromosomal mosaicsisms (mainly 46,XY/47,XXY) and structural abnormalities of the X-chromosome (e.g., 47,iXq,Y) account for the remaining 10% (Bonomi et al., 2017; Tartaglia, Ayari, Howell, D'Epagnier, & Zeitler, 2011). High grade sex chromosomal aneuploidies (48,XXXXY, 49,XXXXY, or 48,XXYY) have also been resumed as “KS variants”; however, individuals with such karyotypes have severe additional problems regarding psychomotor development and their conditions may thus be considered as clinically different entities (Gravholt et al., 2018; Lanfranco et al., 2004).

In modern societies, KS is to an increasing extent diagnosed prenatally by amniocentesis or chorion villus biopsies, using conventional karyotyping. During recent years, parallel sequencing of circulating cell-free fetal DNA in maternal plasma has allowed for noninvasive prenatal testing (NIPT) for autosomal aneuploidies (specifically Chromosome 13, 18, and 21 aneuploidies). However, data on sensitivity and specificity of NIPT regarding detection of sex chromosome aneuploidies are a yet sparse (Gil, Accurti, Santacruz, Plana, & Nicolaides, 2017). Array-comparative genomic hybridization is available for additional diagnostic work-up in 47,XXY KS subjects with dysmorphic features (Gravholt et al., 2018).

2.2 | Clinical diagnosis of KS

KS can clinically be recognized from puberty onward through the presence of testicular dysfunction: The observation of reduced pubertal testicular growth arouses clinical suspicion toward a sex chromosomal aneuploidy, of which KS is the most frequent in males. As a rule with very rare exceptions, testicular volumes in KS adolescents increase to a maximum of 5–8 (−10) ml each side during mid-puberty (Aksglaede, Skakkebaek, Almstrup, & Juul, 2011; Rohayem, Nieschlag, Zitzmann, & Kliesch, 2016). With increasing age, degenerative processes within the testicles lead to gonadal shrinkage, with final singular volumes ranging around 1 ml.

Both, spermatogenic and endocrine testicular function, are compromised in KS. Azoospermia is a constant finding present already in late pubescent KS adolescents. Rarely, that is, in around 7% of KS males, very few spermatozoa are detected in semen (Aksglaede, Jorgensen, Skakkebaek, & Juul, 2009; Kitamura et al., 2000; Rohayem et al., 2016). Testosterone secretion is more robust than
spermatogenesis: Around 60% of KS boys experience normal spontaneous pubertal maturation, with serum testosterone concentrations within the normal range for age and Tanner stage (Rohayem et al., 2016; Salbenblatt et al., 1985). However, from early puberty onward, continuously increasing serum concentrations of FSH, followed by LH, indicate latent endocrine gonadal dysfunction. Decompensation of primary hypogonadism, with symptoms of androgen deficiency usually occurs either during late adolescence or at an undefined time point during adulthood (Aksglaede, Petersen, Main, Skakkebaek, & Juul, 2007; Gravholt et al., 2018; Lanfranco et al., 2004).

Tall stature and gynecomastia may additionally guide the diagnosis toward KS in adolescents. Further, a history of delayed speech acquisition, problems in reading and writing, attention deficits, psychological problems, autistic behavior, muscular hypotonia, or deficits in motor coordination may contribute to the clinical suspicion of KS.

3 | POTENTIAL CLINICAL CHALLENGES IN PREPUBERTAL BOYS WITH KS

3.1 | Testicular function in prepubertal KS boys

The majority of newborn boys with KS have normal genitalia. Exceptionally, clinical signs of intrauterine testosterone deficiency, such as decreased penile length are observed (Ratcliffe, 1982). The frequency of undescended testicles at birth in KS boys ranges around 13–16%, compared to 1–4% in full-term euploid newborns (Aksglaede, Christiansen, et al., 2011; Rohayem et al., 2015).

During “mini puberty,” the phase of postnatal physiologic activity of the hypothalamo–pituitary–gonadal (HPG) axis, normal serum testosterone levels have been documented (Cabröl et al., 2011; Johanssen et al., 2018).

During infancy and childhood, which is the “quiescent” phase of HPG axis activity, normal prepubescent serum concentrations of FSH, LH, testosterone, estradiol, anti-Müllerian hormone (AMH), Inhibin B, and insulin-like factor 3 have been demonstrated (Bastida et al., 2007; Christiansen, Andersson, & Skakkebaek, 2003; Salbenblatt et al., 1985; Topper et al., 1982; Wikstrom et al., 2004; Wikstrom, Dunkel, et al., 2006; Wikstrom, Bay, Hero, Andersson, & Dunkel, 2006).

Nevertheless, it is believed that subclinical testicular degeneration already starts during fetal life and worsens with age (Aksglaede et al., 2006; Braye, Tournaire, & Goossens, 2019; Davis, Rogol, & Ross, 2015; Rey et al., 2011; Wikstrom & Dunkel, 2008).

3.2 | Growth and body composition in prepubertal KS boys

During early infancy, growth of KS boys is usually within normal range, but by the age of 3–6 years onward, growth velocity may accelerate, resulting in significantly taller stature than expected from mid-parental target height (Ottesen et al., 2010; Ratcliffe, 1999; Ratcliffe, Butler, & Jones, 1990; Schibler, Brook, Kind, Zachmann, & Prader, 1974; Stewart, Netley, & Park, 1982; Tanner, Whitehouse, Hughes, & Carter, 1976). Increased leg length has been reported by several authors in KS boys (Schibler et al., 1974; Stewart et al., 1982; Tanner et al., 1976; Zupparinger, Engel, Forbes, Mantooth, & Claffey, 1967).

An altered body composition with increased body fat mass, fat accumulating around the hips, despite normal lean body mass has been evidenced by whole body DEXA scan (Aksglaede, Molgaard, Skakkebaek, & Juul, 2008) and by measurement of subscapular and triceps skinfolds (Ratcliffe et al., 1990).

The question whether early testosterone treatment could attenuate this phenotype has yet to be addressed by future randomized controlled trials. There are reports about the use of the anabolic steroid oxandrolone, which was applied over 2 years to prepubertal boys with KS. A decrease in body fat and triglycerides was observed, but also an unfavorable decrease in HDL cholesterol (Davis et al., 2017). In addition, an increased risk of significantly earlier gonadarche (on average 2 years) limits the utility of such a therapeutic regimen (Davis et al., 2018).

3.3 | Neurodevelopmental issues in boys and adolescents with KS

Early developmental delays are usually mild in KS infants, with delays in speech acquisition prevailing above motor delay. In primary school, difficulties with reading may appear. As a consequence, academic difficulties due to language-based acquisition of knowledge are frequent. Deficits in higher aspects of expressive language are also common, associated with more difficulties in identifying and verbalizing emotions (van Rijn et al., 2007). An increased risk for psychosocial problems has been reported (Ratcliffe, 1999; van Rijn, Aleman, Swaab, & Kahn, 2006), some of which may be associated with hyperactivity and attention problems (Money, Annecillo, Van Orman, & Borgiaonkar, 1974; Ross et al., 2008; Walzer, Bashir, & Silbert, 1990). Impaired motor function, executive function and coordination, decreased visual–spatial and visual–motor function may cause additional problems (Cohen & Durham, 1985; Girardin et al., 2009; Nielsen, 1990; Nielsen & Pelsen, 1987; Ross et al., 2008; Ross, Zeger, Kushner, Zinn, & Roeltgen, 2009; Rovet, Netley, Bailey, Keenan, & Stewart, 1995; Rovet, Netley, Keenan, Bailey, & Stewart, 1996; Sorensen, 1992).

However, the intellectual and psychological, as well as the motor features observed in KS boys are highly variable and may also be influenced by the family’s socioeconomic status and its support. There is, to our knowledge, no study investigating this putative impact.

There are suggestions that very early testosterone treatment may improve the neurodevelopmental outcome of KS boys (Samango-Sprouse et al., 2013; Samango-Sprouse et al., 2015). However, these studies were retrospective chart reviews, without any assessment at baseline and therefore do not provide evidence for benefits of testosterone therapy in very young KS boys (Fennoy, 2011). One study evaluated the effects of the orally applied anabolic steroid
oxandrolone in 5–10 year old boys and reported improved visual motor performance, along with positive effects on anxiety/depression and social functioning, however, with no effects on cognition (Ross et al., 2008).

4 | POTENTIAL CLINICAL CHALLENGES IN ADOLESCENTS WITH KS

4.1 | Endocrine testicular function in pubertal KS boys—When should testosterone be started?

Adolescents with KS experience timely hypothalamic GnRH activation during puberty, with spontaneous pituitary LH and FSH secretion around 12 years of age. LH-stimulated testosterone secretion by Leydig cells induces spontaneous pubertal virilization. As a consequence, a pubertal Tanner stage IV–V is achieved in a high proportion of adolescents with KS, without any need for hormone replacement. These young males experience normal penile growth, pubertal body hair growth, beard growth, voice mutation, and awakening of libido with regular ejaculations. However, a steep rise in LH, occurring in the first or second year of puberty is indicative of latent, but progressive Leydig cell failure. Initially, enhanced LH-levels compensate for this deficiency, resulting in normal serum testosterone levels for age and pubertal stage (Aksglaede, Andersson, et al., 2007; Bastida et al., 2007; Christiansen et al., 2003; Rohayem et al., 2016; Salbenblatt et al., 1985; Topper et al., 1982; Wikstrom, Bay, et al., 2006; Wikstrom, Hoelt-Hansen, Dunkel, & Rajpert-De Meyts, 2007; Wikstrom et al., 2004).

Decompensation of endocrine gonadal function, thus Leydig cell exhaustion variably occurs during late puberty or adulthood. It is marked by a stagnation of the pubertal increase in serum testosterone concentrations, at a level well below the age-related reference range or a progressive decrease in serum testosterone, despite enhanced LH serum concentrations. At this point, testosterone substitution is indicated in most cases. One might speculate, that Leydig cell functionality will never be restored in patients with KS and that these patients will remain hypogonadal for the rest of their life, once a hypogonadal state has been reached. However, this remains an assumption. It could be possible that there is also a functional component to the hypogonadism, especially in obese men with KS. In this case, some of them might not require treatment after the underlying morbidity (here obesity) has been attenuated. One might also speculate that rather old patients with KS (without being able to give an age threshold here) are not necessarily requiring testosterone substitution. This should be a matter of individual case management and also studies in older patients with KS and hypogonadism are required.

However, the decision for replacement needs to take the time of spontaneous pubertal onset into consideration: In KS boys with constitutionally delayed spontaneous puberty, peak serum testosterone levels may be physiologically achieved only at the age of 19 years (Kelsey et al., 2014). Stagnating or declining serum testosterone concentrations have to be evidenced by repeated morning measurements. The decision for testosterone supplementation also has to consider that pituitary gonadotropin secretion will subsequently be suppressed. This is especially true for KS adolescents that have recently entered puberty. As low LH and FSH-concentrations potentially mitigate remnant spermatogenesis, this is relevant for fertility issues (see below).

One preparation licensed for testosterone substitution below the age of 18 years is the testosterone ester testosterone enanthate. It has to be injected intramuscularly at three to four weekly intervals. The initial dosage has to be adapted according to the degree of the spontaneously achieved pubertal maturation. In several European countries and the United States, testosterone gels are available for an age below 18 years, and in the United States, transdermal patches are also available. And even if it is not licensed, such forms of testosterone application can be used on compassionate care grounds. Testosterone gels have the advantage of self-administration and dose titration.

Whether physical and psychological development, educational achievements and social integration could be positively influenced by early exogenous testosterone in adolescents with KS, remains to be investigated by controlled trials.

4.2 | Spermatogenetic testicular function in adolescents with KS—When should fertility issues be addressed?

Spermatogonia carrying a supernumerary X-chromosome undergo apoptosis. The testicular germ cell loss is believed to start very early in life (Aksglaede et al., 2006; Coerdt, Rehder, Gausmann, Johannisson, & Gropp, 1985). However, it becomes clinically apparent only during puberty: At pubertal onset, impairment of Sertoli cell function is denoted by a continuous decrease of the Sertoli cell's secretory product Inhibin B to undetectable levels in serum (Christiansen et al., 2003; Rey et al., 2011; Wikstrom & Dunkel, 2008). Interestingly, the pubertal decline of serum AMH concentrations during puberty is normal in KS (Rohayem et al., 2015). A rise of FSH well above the normal adult range during mid-puberty is another clinical indicator of disturbed spermatogenetic function.

Histologically, degeneration of seminiferous tubules with “Sertoli cell only syndrome” is observed during puberty, followed by extensive hyalinization of the tubules. This is accompanied by hyperplasia of Leydig cells, clustering in the interstitial space (Aksglaede et al., 2006; Davis et al., 2015; Rey et al., 2011; Wikstrom & Dunkel, 2008). Nevertheless, a small subset of euploid spermatogonia can variably be distributed in the testis, even in nonmosaic 47,XXY KS subjects, and allow for remnant spermatogenesis. Foci containing intact spermatogonia may exist in up to 50% of young KS males. In subjects with a history of undescended testes, the chances are reduced to around 30%. (Ragab et al., 2018). Nevertheless, the chances to find spermatooza in semen of KS adolescents only range around 7% (Aksglaede et al., 2009; Rohayem et al., 2016), substantiating the rationale for surgical procedures to attempt testicular sperm extraction (TESE or micro-TESE) (Dabaja & Schlegel, 2013; Tournaye et al., 1996).

In most adolescents, endocrine testicular function is sufficient to support meiotic divisions of residual gonocytes. However, if serum
testosterone concentrations are too low to support spermatogenesis, the chances for successful sperm retrieval seem to be reduced (Rohayem et al., 2015). Patients at a younger age (i.e., ≥15 and <25 years) with simultaneously preserved Leydig cell function seem to have better chances of successful surgical sperm retrieval than older patients (Rohayem et al., 2015). If spermatozoa are found in semen or testicular samples, they can be cryopreserved for future use in assisted reproductive techniques, primarily intracytoplasmic sperm injection (ICSI).

There are no controlled trials evaluating the putatively negative impact of previous exogenous testosterone treatment in KS adolescents on sperm retrieval or later reproductive outcomes. However, suppression of gonadotropin stimulation of gonads is observed if testosterone is replaced in males. This may hamper spermatogenesis in the residual euploid gonocytes and reduce the chances for sperm retrieval. Therefore, it seems reasonable to address fertility issues early in life (Slowikowska-Hilczer et al., 2017) and before initiation of testosterone replacement.

4.3 | Growth and bone health in pubertal KS boys

Tall stature is a common clinical feature in KS. Linear growth may be increased from early childhood onward and accelerate during puberty, resulting in a mean adult height of KS patients of around 4 cm above that of healthy males, ranging around 184 cm (Rohayem et al., 2016). In very rare cases with excessively tall stature, high-dose testosterone treatment may be considered during puberty, to induce premature fusion of growth plates. Importantly, this issue might be in opposition to the procedures necessary for sperm retrieval.

It is believed that the SHOX gene, due to its localization on the pseudoautosomal region 1 of the sex chromosomes, escaping X-inactivation, contributes to tall stature in KS. Present in three active copies, SHOX could exert a dosage effect, thereby enhancing linear growth (Ottesen et al., 2010; Rao, Weiss, Fukami, Mertz, et al., 1997; Rao, Weiss, Fukami, Rump, et al., 1997). Another hypothesis relates to latent hypogonadism in KS, with reduced aromatization of testosterone to estradiol, contributing to late epiphyseal closure in the long bones (Bastida et al., 2007).

Substantial data on bone health in adolescents with KS are missing. Randomized trials or at least large-scale registries are required to solve this issue.

5 | CLINICAL ISSUES IN ADULTS WITH KS

5.1 | Endocrine testicular function in adults with KS

Leydig cell capacity continuously declines during life of KS men. In adults without testosterone replacement, serum concentrations of gonadotropins (LH, FSH) in KS men levels are generally elevated, but not all men exhibit hypogonadal symptoms or low serum testosterone levels. Hypogonadism may remain at a compensated state (with elevated serum concentrations of LH and yet normal testosterone levels) until the fifth decade of life (Gravholt et al., 2018; Lanfranco et al., 2004). Therefore, previously undiagnosed men with KS are rather recognized within the context of an unfulfilled wish for fatherhood, during evaluation of their fertility status. In such situations, regular controls of LH and FSH, testosterone concentrations, as well as monitoring of indirect signs of androgen deficiency, such as such as hematocrit and PSA, are advisable. In KS men with compensated hypogonadism, transdermal testosterone preparations are licensed for use. The gel has to be applied every morning on the skin and the dose can be titrated according to individual needs. Physiological diurnal variations of serum testosterone can thereby be mimicked. Alternatively, the long-acting testosterone depot preparation testosterone undecanoate may be used for substitution in adult KS males. Intramuscular injections (in doses of 1,000 mg testosterone in 4 ml castor oil) administered every 10–14 weeks (with one primary loading dose after 6 weeks) results in stable serum testosterone within the normal adult range for 10–14 weeks.

Diagnosis, treatment, and surveillance of hypogonadism in adults should follow the respective general guidelines (Bhasin et al., 2018; Mirone et al., 2017; Salonia et al., 2019).

5.2 | Fertility in adults with KS

Among males with nonobstructive azoospermia (NOS), KS is diagnosed in around 10–15% (Tournaye, Krausz, & Oates, 2017). Fertility issues should be addressed in a similar way to the procedure described for adolescents. Although the success to retrieve sperm from semen or testicular samples seems to decline with age, adult KS men may nevertheless undergo mTESE/TESE to clarify their chances for biological fatherhood (Bhasin & Oates, 2020; Deebel et al., 2020; Rohayem et al., 2015; Zganjar, Nangia, Sokol, Ryabets, & Samplaski, 2020). Reported success rates of sperm retrieval in men with KS varies between 30 and 66% (Bakircioglu et al., 2011; Dabaja & Schlegel, 2013; Frank et al., 2016; Okada et al., 2002; Ploton et al., 2015; Ramasamy et al., 2009; Vernaeve et al., 2004). Whether exogenous testosterone hampers a successful TESE in adults, is unclear to date, but presumably depends on the degree of gonadotropin suppression prior to surgery. Subcutaneous hCG injections or orally applied estrogen receptor blockers or aromatase inhibitors prior to TESE have been used off-label, with the intention to additionally stimulate Leydig cells a few months prior to surgery (Ramasamy et al., 2009; Shiraiishi, Ohmi, Shimabukuro, & Matsuyama, 2012). Whether there is a benefit of these procedures regarding sperm retrieval rates, has yet to be established.

Assisted reproductive techniques using cryopreserved spermatozoa for ICSI have enabled KS patients to father biological children (Aksglaede & Juul, 2013). A slightly enhanced risk for aneuploidies (Hennebicq, Pelletier, Bergues, & Rousseaux, 2001) or imprinting disorders (Greco et al., 2013) compared to healthy fathers has been reported; however, the risk seems similar to that of euploid men with NOS.
5.3 | Metabolic and cardiovascular risks in adults with KS

Men with KS suffer from higher rates in various diseases, which may result in a shortened lifespan (Bojesen, Juul, Birkebaek, & Gravholt, 2004; Groth, Skakkebaek, Host, Gravholt, & Bojesen, 2013; Salzano et al., 2016; Sverdlov et al., 2005). Increased amounts of truncal/visceral fat in KS may originate from both hypogonadism and from genetic causes (Gravholt, Jensen, Host, & Bojesen, 2011; Zitzmann et al., 2004; Zitzmann et al., 2015). Augmentation of visceral adipocytes promotes insulin resistance, potentially fostering Type 2 diabetes mellitus (Gravholt et al., 2011; Groth et al., 2013). Increased cardiovascular morbidity and mortality has been described in KS (Bojesen et al., 2004; Bojesen, Juul, Birkebaek, & Gravholt, 2006; Zoller, Ji, Sundquist, & Sundquist, 2016). Higher levels of the procoagulatory substance PAI-1, associated with the genetic setting in KS as well as with decreased testosterone levels (Zitzmann et al., 2015; Zollner et al., 1997) have been associated with an increased risk of deep vein thrombosis (Chang et al., 2020) and pulmonary embolism in KS. The overall risk is increase threefold to sixfold compared to the general population (Bojesen et al., 2006; Salzano et al., 2016; Sverdlov et al., 2005). Randomized controlled studies or meta-analyses are needed to elucidate the role of testosterone substitution in KS patients for the prevention of unfavorable metabolic and cardiovascular outcomes (Host et al., 2019).

5.4 | Psychosocial and intellectual issues in men with KS

Intellectual impairments as described above for young KS subjects may persist into adulthood (Boada, Janusz, Hutaff-Lee, & Tartaglia, 2009); specifically, deficits in language skills such as verbal processing speed, expressive grammar, and word retrieval may represent challenges for academic performance (Bruining, Swaab, Kas, & van Engeland, 2009). In addition, KS men may experience disadvantages by impairments of executive functions related to attention, flexibility and planning as well as response inhibition (Skakkebaek

### TABLE 1 Possible conditions and therapeutic approaches in KS

| Childhood                  | Therapeutic approach                                      |
|---------------------------|-----------------------------------------------------------|
| Undescended testes        | hCG i.m./intranasal GnRH                                   |
|                           | orchidopexia                                               |
| Unfavorable body composition | Optimized nutrition and physical activity                  |
|                           | Physiotherapy                                             |
| Psychosocial problems, ADHS, ASDs | Psychological/psychiatric support                          |
| Learning problems, legasthenia | Tailored assistance, choice of school, adapted to deficits |
| Articulation deficits, motor problems | Speech therapy, ergotherapy, physical training        |

| Adolescence               | Therapeutic approach                                      |
|---------------------------|-----------------------------------------------------------|
| Decompensation of hypergonadotropic hypogonadism with pubertal arrest | Testosterone substitution after addressing fertility issues |
| Reduced sperm production (azoospermia, severe oligozoospermia) | Counseling + semen analysis  |
|                           | Surgical sperm extraction (mTESE)→Cryopreservation of spermatoza |
| Prognosis of very tall stature | Consideration of high dose testosterone treatment after addressing fertility issues |
| Unfavorable body composition | Optimized nutrition and physical activity                  |
| Psychosocial problems, ADHS, ASDs | Behavioral coaching/psychological/psychiatric support |
| Learning problems | Tailored assistance, choice of school and professional training, adapted according to skills/preferences |

| Adulthood                  | Therapeutic approach                                      |
|---------------------------|-----------------------------------------------------------|
| Decompensated hypergonadotropic hypogonadism with symptoms of androgen deficiency, sexual dysfunction, metabolic disorders | Testosterone substitution after addressing fertility issues |
| Infertility (azoospermia, severe oligozoospermia) | Counseling + semen analysis  |
|                           | Surgical sperm extraction (mTESE)→Cryopreservation of spermatoza |
| Psychosocial problems, ADHS, ASD | Psychological/psychiatric support                          |
| Back pain/fractures due to osteopenia/osteoporosis | Testosterone replacement                                    |
|                           | Vitamin-D supplementation                                  |
|                           | Osteoanabolic therapy                                      |
| DVT                       | Testosterone replacement tailored according to needs, avoiding erythrocytosis, anticoagulation prophylaxis |

Abbreviations: ADHS, attention deficit + hyperactivity; ASD, autism spectrum disorder; DVT, deep vein thrombosis.
et al., 2014). From population-based settings with matched population controls, it is concluded that the risks for psychiatric disorders are elevated (schizophrenia [odd ratio [OR]: 3.6], bipolar disorder [OR: 3.8], autism [OR: 6.2], and ADHD [OR: 5.6]) (Cederlof et al., 2014). Unfocused anxiety and depression also seem to be more frequent in KS subjects (Skakkebaek et al., 2018).

5.5 | Bone health

Osteopenia and osteoporosis is present in up to 40% of KS men, with a suspected increased risk of fractures (Ferlin et al., 2015; Ferlin, Schipilliti, & Foresta, 2011; Gravholt et al., 2018). Most likely, this is due to both reduced bone formation and higher bone resorption. No clear relation between testosterone plasma levels and bone mineral density has been found, and osteopenia/osteoporosis has been observed also in KS men with testosterone levels in the normal range (Bojesen et al., 2011; Rochira, Antonio, & Vanderschueren, 2018).

6 | OTHER ISSUES IN KS

There are reports on retinal dysfunction and impaired vision in KS (Brand et al., 2017; Karampelas, Gardner, Holder, Hardcastle, & Webster, 2013). Development of teeth may be affected, causing taurodontism (Giambrosio, Barile, & Giambrosio, 2019). Cardiovascular integrity of KS patients might be altered, resulting in a reduced QTc time, potentially leading to sudden cardiac arrest (Jorgensen et al., 2015; Zitzmann et al., 2015). However, the reports are still based on smaller numbers of KS patients and need validation.

7 | CONCLUSION

KS is the most common chromosome disorder in men. Affected males are regularly infertile and likely to be hypogonadal. Neurocognitive and psychosocial impairments as well as cardiovascular, metabolic and bone disorders may lead to increased morbidity and mortality. Clinical care in various phases of life, from childhood to adolescence and on to adulthood, has to be adapted according to individual needs, as summarized in Table 1.

Marked advances have been made regarding reproductive care, potentially enabling biological fatherhood and allowing for tailored testosterone substitution.

Nevertheless, further research is needed to clarify the impact of testosterone replacement on long-term outcomes, and to further elucidate the genetic and epigenetic factors that determine the phenotype.

CONFLICT OF INTEREST

None.

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