

# Klinefelter syndrome and fertility preservation

## Abstract

In this mini-review pathophysiology, symptoms, diagnosis and management of Klinefelter syndrome (KS) patients are discussed, including fertility preservation. The real complete spectrum of KS phenotypes remain still to be fully elucidated. Hypogonadism and infertility are almost invariably present. Almost all organs of KS patients are associated with increased risk of morbidity and mortality. Treatment is multidisciplinary for associated speech, language, learning and neurocognitive difficulties. Pharmacologic treatment is by topical or i.m administration of testosterone replacement therapy (TTR). The effect of TTR on compromised spermatogenesis is not well known. In this millennium fertility preservation by testes sperm extraction (TESE) via biopsies and fathering by subsequent intra cytoplasmic sperm injection (ICSI) has become possible with some 60% success rate in small studies. However, offspring data of KS patients are lacking and many knowledge gaps still exist.

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**Michael AB Naafs**

Naafs Health Consultancy, Netherlands

**Correspondence:** Michael AB Naafs, Naafs Health Consultancy, Address Rhodoslaan 20, 7577KN, Oldenzaal, Netherlands, Tel +31681589079, Email naafs.healthconsultancy@gmail.com

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## Introduction

Male factor infertility is responsible for about 50% of all causes of infertility and thus carries significant medical, financial and psychological implications for the couples struggling with conception. Klinefelter syndrome (KS) is the most common chromosomal male anomaly associated with infertility. KS is characterized by an extreme heterogeneity in its clinical and genetic presentation. The relationship between clinical phenotype and genetic background is only partially understood. Azoospermia and infertility are almost invariably present.<sup>1</sup> In this mini-review pathophysiology, symptoms, diagnosis, and treatment including fertility preservation are discussed.

## Pathophysiology

Klinefelter syndrome 47, XXY was first described in 1942.<sup>2</sup> With an incidence of 0,1% to 0,2% of male neonates (i.e. 1-2 per 1000). KS is one of the commonest congenital chromosome disorders resulting in hypogonadism and infertility.<sup>3,4</sup> The disease pattern is caused by congenital aneuploidy of the sex chromosomes. Eighty percent of patients have the 47, XXY karyotype. The remaining 20% have either mosaic 47, XXY/46XY (i.e different karyotypes in different cells), supernumery X-chromosome aneuploidy (48XXY;49XXXXY), one or several additional Y chromosomes (e.g. 48XXYY) or structural abnormal additional X-chromosomes.<sup>5,6</sup> These numerical chromosome abnormalities are the result of non disjunction in maternal oogenesis in approximately two-thirds of cases, and in paternal spermatogenesis in the remaining third. Although primordial germ cells (stem cells) are present in the testes of patients with KS, they degenerate unusually quickly, with the result that by puberty there are a few or no remaining seminiferous tubules with complete spermatogenesis.<sup>7,8</sup> The hyperplastic Leydig cells are unable to produce sufficient testosterone. This leads to testosterone deficiency, which can be modified by androgen receptor (AR) polymorphism and the severity of which varies between individual patients.<sup>9</sup> The real complete spectrum of different KS phenotypes remain still to be fully elucidated. Probably, the phenotype depends on the severity of the expression of the genetic defect, androgen deficiency and AR sensitivity (i.e. CAG repeats polymorphism)-(9). The more the genetic expression, androgen deficiency and AR sensitivity are worse, the more the phenotype will be severe.<sup>10</sup> Less severe forms of genetic abnormalities, such as mosaicism, generally result in both

less severe clinical symptoms and endocrine abnormalities.<sup>11</sup> The phenotype progressively worsens with the severity of polysomy (e.g. 49XXXXY).<sup>12</sup> Language and speech disabilities increases with the increase of supernumery X-chromosomes and seem to contribute decreasing some 15 points of intelligence quotient (IQ) per each extra X-chromosome.<sup>13</sup> KS patients have a phenotype, which is extremely variable, but without any obviously facial dysmorphism, making them indistinguishable from boys with a normal karyotype. The diagnosis KS is therefore frequently overlooked.<sup>3</sup> Almost all organ systems are associated with an elevated risk of morbidity and mortality in KS patients. Gynecomastia, which is common in KS, is accompanied by slightly higher incidence of breast cancer compared to normal men, who account for 1% of all breast cancers.<sup>14,15</sup> In addition to increased frequency of breast cancer, mediastinal non seminomatous germ cell tumors are also more common, mostly between the ages of 15-30 years. Osteoporosis results in an increased incidence of bone fractures and femoral fractures are associated with a high mortality rate. KS patients suffer from vascular diseases, particularly varicose veins and thromboembolism, often pulmonary embolism. Central obesity with reduced glucose tolerance is often observed and can lead to metabolic syndrome and type 2 diabetes.<sup>16</sup>

## Symptoms and diagnosis

Most patients with KS will present with tall stature and long limbs, reflected in upper-lower segment ratio. Mean height is at the 75<sup>th</sup> percentile with weight and head circumference at the 50<sup>th</sup> percentile. In childhood, the phallus and testes may be relatively small. During adolescence there is discordant pubertal development with fairly normal phallus and pubic hair development, although testes volume rarely exceeds 4ml and testes are characteristically firm due to hyalinization and fibrosis. Testosterone levels are usually in the low to the low-normal range. Gynecomastia is common. Mean full-scale IQ is between 85-90. Verbal IO is higher than performance due to problems with expressive language and auditory processing. Behavioral difficulties including immaturity, insecurity, shyness, poor judgment, and the formation of meaningful peer relationships may be affected. Between 20% to 50% of individuals with KS have an intention tremor.<sup>8,17,18</sup>

Diagnosis of Klinefelter syndrome is often delayed because of substantial variations in clinical picture. It is estimated that 10%

of expected cases were identified prenatally by amniocentesis and chorionic villus sampling and 26% were diagnosed in adult life because of hypogonadism, gynecomastia or infertility, leaving 64% of cases undiagnosed.<sup>19</sup> Diagnosis of KS is typically made by prenatal or postnatal karyotype or chromosomal microarray. Non-invasive prenatal testing (NIPT) for cell-free DNA-testing can identify sex chromosome abnormalities. Published positive predictive values in the detection of KS via NIPT are 67%.<sup>20</sup> The initial evaluation of KS may include a workup for hypogonadism or infertility. In KS, gonadotropins are usually elevated when testicular hyalinization and fibrosis are present, though this may evolve during adolescence. The finding of hypogonadotropic hypogonadism indicates primary gonadal failure. FSH elevation typically predominates over LH, though both are elevated above normal. Testosterone concentrations are usually low or low-normal in both adolescents and adults. A minority of children may demonstrate low inhibin B and elevated AMH (anti-Müllerian hormone) reflecting Sertoli cell function, but it is unclear whether identifying these differences is predictive of future gonadal failure.<sup>21</sup>

### Therapy and management

Treatment and care of KS patients should be multidisciplinary and involve speech therapists, psychologists, general practitioners, paediatricians, endocrinologists, urologists and fertility specialists. Rarely, KS boys have micropenis, which can be treated successfully with topical testosterone cream or single i.m injections with testosterone.<sup>22</sup> The most serious problem in early childhood is the delay of speech development and learning problems affecting perhaps half of the boys with KS.<sup>23</sup> Early androgen therapy is recommended.<sup>24,25</sup> Flannegan et al.<sup>24</sup> performed a systematic review of early androgen therapy and KS using PubMed-Medline and Scopus databases. Relevant articles commenting on social behavior, cognition, and physical outcomes among infants, children and adolescents were included. Three retrospective articles and two randomized controlled trials (RCTs) were reviewed. The authors conclude that early androgen therapy in children with KS combined with specific educational, family and social support improves behavioral functioning. The optimal timing of hormonal therapy might require prospective studies, however.<sup>24</sup> In her PhD thesis Lauren Chen also concludes that the management of KS combines counseling, special education and early testosterone replacement therapy.<sup>25</sup> Androgens can induce the development of male secondary sex characteristics, eliminate gynecomastia, and improve general behavior and work performance. Testosterone replacement therapy (TRT) should begin at puberty and increase in dosage to maintain age-appropriate testosterone, estradiol, FSH, and LH serum concentrations. TRT normalizes body proportions and male secondary sex characteristics. Long-term benefits of TRT include reducing risk of osteoporosis, autoimmune disease, breast cancer, promoting male phenotype development, increasing penile size, improving cognition and decreasing gynecomastia and obesity. TRT is now mostly given as topical treatment for convenience and avoiding excessive testosterone levels after painful i.m administration, achieving more physiological levels with topical testosterone. However, TRT does not treat small testes and infertility.<sup>25</sup>

### Fertility preservation

KS individuals typically initiate puberty at the same age as the general population, but they have delays in facial hair and muscle development compared with their siblings. Penile growth is not affected but the girth may be. Penile circumference can exceed the length. Scrotal development is normal, but as puberty progresses,

testicular size is significantly decreased. As previously stated many KS adolescents enter puberty around the same age as the general population, but testosterone concentrations decline at late adolescence and early adulthood. Because of decreased androgen production, characteristics such as facial, body and sexual hair do not develop, whereas features of eunuchoidism and gynecomastia can develop. As a result KS adolescents and KS men in their early twenties look much younger than chronological age. Although testosterone levels are low in KS adolescents, they start masturbating at a similar time to the general population. However, KS adolescents experience a significant delay in the age of first voluntary ejaculation. In healthy adolescents, the mean time difference from the age of first masturbation to the age of ejaculation is 2 months, but in KS adolescents the delay is 9 months. This delay may occur because the S2-S4 region of the spinal cord, which is responsible for ejaculation is sexually dimorphic and is highly dependent on adequate levels of testosterone.<sup>25</sup>

All KS patients are considered infertile, though there have been reports of pregnancy without assisted reproductive technology (ART). These cases are believed to have only occurred in mosaic KS men. With the introduction of new technology, such as intra cytoplasmic sperm injection (ICSI), some KS patients have an increased chance of fathering a child. A study done by Schiff et al.,<sup>26</sup> consisting of 42 KS men showed that the sperm retrieval rate was 72% for each testicular sperm extraction (TESE) biopsy attempt and that 69% of the patients achieved pregnancy using ICSI. Therefore, TESE and ICSI may be considered as a good alternative to reproduce.<sup>26</sup> According to Paduch et al.,<sup>27</sup> one should allow the patient to deliver semen samples by masturbation, to initially check for sperm in the ejaculate before proceeding to surgical treatment options.<sup>27</sup> Current evidence shows that fertility preservation should not be offered to adolescents with KS younger than 16 years because of lower retrieval rates for germ cells by TESE compared with retrieval rates between 16 and 30 years. Spermatozoa can be found by TESE in 50% of adults with KS despite severe testicular degeneration. Franik et al.<sup>28</sup> performed an extensive literature survey searching PubMed and Embase from 1942 to 2016.<sup>28</sup> In total 76 studies were included in this review. The presence of spermatozoa in the ejaculate of adolescents with KS is extremely rare. Using TESE, the retrieval rate for adolescents younger than 16 years are much lower (0%-20%) compared with those for adolescents and young adults between 16 and 30 years old (40%-70%). Although spermatozoa can be found by TESE in about half of the peri-pubertal adolescents, there are currently no clinically functional techniques for their future use. Early fertility preservation before the age of 16 cannot guarantee fertility later in life and may even reduce the chances for offspring by removing functional immature germ cells, which may possibly develop into spermatozoa after puberty. There are no reliable factors that can be used as a predictive marker for fertility preservation.<sup>28,29</sup> There are no data available for the offspring of KS patients, yet. Neither, it is known if KS patients have an increased prevalence of gender dysphoria.

### Conclusion

There are still many knowledge gaps in KS patients and fertility preservation.<sup>21,25,28,30</sup> Studies are small. The potential impact of prior testosterone therapy on sperm retrieval is not well documented.<sup>28</sup> Prospective studies have been limited due to the rarity of the disease.<sup>25</sup> Unanswered are questions about the viability and quality of sperm retrieved from this patient population after many years of freezing.<sup>30</sup> Data from offspring of KS patients are lacking. Although KS is not an inherited disease, these would be very interesting. Prenatal testing (NIPT) will likely increase early diagnosis of KS. Further research in

predictive markers for TESE is warranted. Anyway, progress has been made, as in the last century fathering was impossible for KS patients, except for some rare mosaic KS patients.

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## Conflicts of interest

Author declares that there is no conflicts of interest.

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