CAN INDIVIDUALS WITH KLINEFELTER SYNDROME HAVE OFFSPRING?

INDIVÍDUOS COM SÍNDROME DE KLINEFELTER PODEM TER FILHOS?

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ABSTRACT

Klinefelter syndrome (KS) is the most common genetic cause of male infertility. The frequencies of infertility and azoospermia amongst the KS individuals are >99% and >95%, respectively. However, in extremely rare cases, KS patients will have offspring. This study aims to present the results of five scientific articles (3 case reports and 2 original articles) on individuals with KS who had children. Our results indicate that there are relative paucity of data on this topic published in the literature, highlighting that biological parenthood in the SK individuals is exceedingly rare.
KEYWORD: Klinefelter Syndrome; Infertility; Karyotype.

RESUMO

A síndrome de Klinefelter (SK) é a causa genética mais comum de infertilidade masculina. As frequências de infertilidade e azoospermia entre indivíduos com SK são >99% e >95%, respectivamente. No entanto, em casos extremamente raros, pacientes com SK terão filhos. Este estudo tem como objetivo apresentar os resultados de cinco artigos científicos (3 relatos de caso e 2 artigos originais) sobre indivíduos com SK que tiveram filhos. Nossos resultados indicam que há relativa escassez de dados publicados sobre este tema na literatura, destacando que a parentalidade biológica em indivíduos com SK é extremamente rara.
PALAVRAS-CHAVE: Síndrome de Klinefelter; Infertilidade; Cariótipo.

NOTE

Klinefelter syndrome (KS) is characterized by the presence of one or more extra “X” chromosome in a male patient and lead to hypogonadism and infertility. It is often under-diagnosed due to significant phenotypic variability with a large proportion of patients not expressing the “classical” features, that include tall

stature, gynaecomastia, androgen deficiency, small testes, infertility, hypergonadothropic hypogonadism and cognitive impairment[1,2].

KS is the most common genetic cause of male infertility. The bulk of KS patients are diagnosed during adulthood, typically in the course of a fertility workup. The frequencies of infertility and azoospermia amongst the KS individuals are >99% and >95%, respectively[1,2]. Furthermore, >95% of patients exibit decreased bitesticular testis volume (4–8 mL; normal range: 25–60 mL)[1].

However, in extremely rare cases, KS patients will have offspring. A recent case report described a KS patient (47,XXY) and the semen analysis showed normal motile sperm (total motility of 57.66% and progressive motility of 46.19%) but low sperm concentration (1.7×10^6 cells/mL). According to testicular ultrasonography, the volumes of the left and right testes are calculated to be 6.6 ml and 7 ml, respectively. He had a son by intracytoplasmic sperm injection (ICSI) using his ejaculated sperm[3]. Another study present an exceptional case of a 45-year-old man with mosaic KS (46,XY/47,XXY) and severe oligozoospermia who successfully achieved pregnancy utilizing ICSI with freshly ejaculated sperm[4]. This patient was advised to cryopreserve his sperm as a precautionary measure for future ICSI procedures due to severity of oligozoospermia. Semen analyses were performed according to the World Health Organization 2010 guidelines indicating a semen volume of 5 mL, a concentration of 3.7 $X10^6$/ml, 42% forward progressive motility, and 0% normal morphology. According to the authors, the diagnosis of the patient was initially made during infertility investigations and is the first report of the oldest man with mosaic KS to father his offspring using ejaculated spermatozoa[4]. These data underscores the critical importance of exhausting all possibilities to facilitate biological parenthood in men with KS before considering alternative options such as sperm donation or adoption[4].

A retrospective study was carried out with 51 patients diagnosed with KS from Jan/2010 to Dec/2019, being that 44 (86.3%) presented a classical karyotype (47,XXY) and 7 (13.7%) showed evidence of mosaicism[5]. Most cases were aged 30-39 years at diagnosis, with more than 50% of the patients being diagnosed during

the 3rd and 4th decades of life. KS was diagnosed in the context of infertility in most patients (54.2%), followed by complains related with hypogonadism (18.7%) and gynecomastia (8.3%). Biological paternity was achieved in 10 out of 42 patients (23.8%), although in 8 of these 10 cases this was the result of assisted reproductive techniques. With regards the question of fertility, assisted reproductive techniques were used in 39.6% of the studied subjects (N=48), with a success rate (a take home baby) of 57.9% (11/19), 2 with donor sperm and 9 with the patients' own gametes. A spermogram revealed azoospermia in more than 90% of patients (28 out of 31)[5].

Regarding assisted reproduction techniques, a Brazilian study[6] described a 40-year-old azoospermic man (sperm result: 8 units per milliliter) with KS (47,XXY) and his wife (46,XX) who resorted to in vitro fertilization and had four offspring, three boys (46,XY) and one girl (46,XX), all with no chromosomal alterations according to the karyotype exam. The patient undergoes regular follow-up with an urologist and his azoospermia has intensified, becoming severe[6].

Another recent search[7], conducted in Denmark, performed surgery in 93 men with KS and obtained testicular sperm in 42%. More than ten children are now born, and several couples still have sperm and embryos cryopreserved with the potential to increase the live birth rate further[7].

Our results indicate that there are relative paucity of data on this topic published in the literature, highlighting that biological parenthood in the SK individuals is exceedingly rare. This is because most KS patients are azoospermic or rarely having detectable spermatozoa in their ejaculate. In most cases described above assisted reproductive technology was necessary for conception.

It is worth noting that the etiology of infertility in KS remains incompletely understood, encompassing a complex interplay of genetic, molecular and cellular factors. Physiologically, the additional sex chromosome also alters testicular endocrinology and metabolism by dysregulating interstitial and Sertoli cell function, collectively impairing normal sperm development[8]. In addition, men with KS develop some degree of seminiferous tubule degeneration, hyalinization, and fibrosis by adulthood. However, the specific triggering factors of hyalinization and

fibrosis of the seminiferous tubules and the propagation mechanisms unique to KS remain unidentified[9].

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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