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Klinefelter syndrome and infertility: Prevalence and institutional experience

Horacio Méndez Serrano[1], Cintia María Sepúlveda Rivera[2*], Fela Vanesa Morales Hernández[3]
[1, 3] Department of Reproduction, Instituto Nacional de Perinatología, Calle Montes Urales, Lomas - Virreyes, Lomas de Chapultepec IV Secc, Mexico
[2] Department of obstetrics Instituto Nacional de Perinatología, Calle Montes Urales, Lomas - Virreyes, Lomas de Chapultepec IV Secc, Mexico

Abstract
Background: Klinefelter syndrome (KS) is the most frequent chromosomal abnormality caused by aneuploidies. It occurs in 1/660 male newborns and has a prevalence of 1-2% in infertile men; 0.6% with severe oligospermia (<5 million sperm/ml) and 10-12% in patients with azoospermia.
Objective: To determine the prevalence of KS in patients with male infertility at the National Institute of Perinatology (INPer) and the prevalence of the main clinical characteristics of the syndrome, the hormonal profile and the diagnostic karyotype they presented.
Methodology: Patients with male infertility were included between 2016 and 2018 that presented azoospermia or severe oligospermia in semen analysis (SA) and had a karyotype as part of the diagnostic approach. The clinical characteristics, somatometry and initial hormonal profile were analyzed.
Results: A total of 1,029 men with male infertility were found between 2016 and 2018 with a prevalence of 0.29%; 100% presented azoospermia on SA with a 47, XYY karyotype. The average age of KS diagnosis was at 30.3 years, with a height of 1.66 m and BMI of 24.98 kg/m^2 (normal). 100% presented testicular hypotrophy with an average volume of 2.68 cc and 2.49 cc (right and left respectively). Only one patient presented gynecomastia (33%) stage 3 in Tanner scale and one hypospadias (33%). The average on hormonal profile levels was 32.4 mIU/ml for FSH, 20.43 mIU/ml for LH, testosterone of 8.14 nmol/L and estradiol of 53.46 pg/ml. 100% had normal prolactin levels (8.27 ng/ml).
Conclusions: KS is one of the most common genetic causes of male infertility characterized by a 47, XXY karyotype. The main clinical manifestations are: tall stature, overweight and obesity, sparse hair, testicular hypotrophy (<4 cc), gynecomastia, and infertility. They are characterized by having abnormal concentrations of testosterone, FSH and LH and they can achieve pregnancy using TESE (Testicular Sperm Extraction) combined with ICSI.

Keywords: Klinefelter, Infertility, institutional, chromosomal

Introduction
Infertility is a relatively common health condition that affects about 15% of all couples. Clinically, it is a highly heterogeneous pathology with a complex etiology that includes environmental and genetic factors. It is estimated that approximately 15-30% of cases of male infertility are due to genetic defects [2].
Chromosomal abnormalities occur in approximately 15% of patients with azoospermia. Those with non-obstructive azoospermia have an increased incidence of aneuploidies, especially in sex chromosomes.

Klinefelter syndrome
Klinefelter syndrome (karyotype 47, XXY) is the main chromosomal abnormality caused by aneuploidies and the most common cause of primary testicular insufficiency. It occurs in 1/660 male newborns and has a prevalence of 1-2% in infertile men; 0.6% with severe oligospermia (<5 million sperm / ml) and 10-12% in patients with azoospermia [3].
Only 10% are diagnosed before puberty because of their poor phenotypic expression.
The 47, XXY karyotype occurs in approximately 90%, while other variants that include karyotype are rare. Usually, the extra X results from chromosomal non-disjunction in female or male meiosis. About 10% of patients with KS are mosaics 47, XXY / 46, XY [1].

Clinical characteristics
The most common clinical manifestations are: tall stature with a predominance of the lower segment, overweight or obesity, neuropsychological alterations (behavioral problems, language and learning delays), micropenis, testicular hypotrophy (<4 cc), gynecomastia, and infertility.

Diagnosis
KS can be diagnosed in the postnatal period by karyotype, the presence of Barr body inbuccal mucosa cells, fluorescence in situ hybridization (FISH) and molecular techniques. The karyotype is the gold standard in KS diagnosis, but this test is expensive and

takes time to obtain the result; it has a relatively low sensitivity for mosaicism 47, XXY / 46, XY[16]; however, the tests currently used are too expensive to offer initially.
Recently, the presence of Barr body has been proposed as a cheap test with a specificity of 95% and a sensitivity of 82% for diagnosis [9].

Hormonal profile
Children with KS are characterized by having normal concentrations of testosterone, FSH, LH, antimüllerian hormone (AMH), inhibin B and insulin-like factor 3 (INSL3). At the onset of puberty a decrease in inhibin B levels is observed. The physiological decrease in serum AMH is also observed in the KS, although this occurs later than in healthy children. During puberty, relative hypogonadism is observed by increasing gonadotropin concentrations at the expense of FSH.
Adults with KS show a decrease in testosterone levels in 65-85% of cases (<12nmol / L), elevation of follicle stimulating hormone (FSH) and luteinizing hormone (LH) with a variable sensitivity in the androgen receptor. Inhibit B is below the detection limit in the vast majority of adults with KS that reflects the absence of spermatogenesis, while circulating concentrations of AMH and INSL3 are significantly reduced compared to healthy men. In many cases estradiol levels are elevated.

Histology
In testicular biopsy, these patients present degeneration of testicular germ cells, arrest in spermatogenesis in the primary spermatocyte stage, extensive fibrosis and hyalinization of the seminiferous tubules and interstitial hyperplasia. Testicular germ cell degeneration begins at late stages of fetal life, progresses during childhood and more quickly in mid-puberty.

Spermatogenesis
Although the sperm of men with Klinefelter have a normal haploid genome 23, X or 23, Y, an increased rate of autosomal aneuploidies and sex chromosomes has been reported in the offspring of these patients. It is estimated that 25% of patients with non-mosaic KS have sperm in the ejaculate [10]; those with mosaicism may have residual spermatogenesis in the seminiferous tubules. Several studies have investigated the molecular mechanisms of spermatogenesis loss, like the intratesticular hormonal imbalance characterized by hypersensitivity in the intratesticular testosterone and estradiol concentration, the dysfunction of the Sertoli cells and defects in the stem cell renewal.

Reproductive options
Patients with KS can achieve pregnancy using TESE (Testicular Sperm Extraction) combined with ICSI (intracytoplasmic sperm injection), with a success that reaches 40%. It is reported that the presence of sperm is found only in 23% of biopsies with different stages of differentiation (from spermatogonias, to maturation arrest and hypoespermatogenesis) up to 59% [8].
There are new techniques (TESE microdissection) that has demonstrated a 66% in sperm recovery (euploid in the vast majority), and 45% of these cases they can reach a fertilization of an egg [11].
There is no hormonal factor or image that predicts the result of the technique. Over time, cryopreservation of semen samples has been suggested for children with KS before starting testosterone therapy, however there is new evidence that reports that sperm recovery rate for adolescents under 16 is 0-20% compared to the rate in adolescents and young adults between 16 and 30 years ranging from 40-70%, so children and adolescents with KS should be informed that early fertility preservation before 16 years cannot guarantee later fertility and even reduce the chances of offspring by eliminating germ cells [10].
It is recommended to offer a preimplantation genetic diagnosis (PGD) before performing any reproduction technique since biological paternity in patients with KS can associate with chromosomal abnormalities in gonosomes or autosomes 13, 18 and 21 in 6.3% of the cases [6].

Objectives
To determine the prevalence of KS in patients with male infertility at the National Institute of Perinatology (INPer), and the prevalence of the main clinical characteristics of the syndrome, the hormonal profile and the diagnostic karyotype they presented.

Methodology
All patients with male infertility of the National Institute of Perinatology (INPer) who entered to the infertility and reproductive consultation between 2016 and 2018 were included. Those who presented azoospermia or severe oligospermia in seminal analysis (SA) were analyzed.
We conducted an electronic search for those patients who were diagnosed with KS by karyotype as part of the diagnostic approach of azoospermia and severe oligospermia.
The clinical characteristics and somatometry reported in the medical history were analyzed. The body mass index (BMI) was classified as normal, overweight and obese according to the WHO criteria. The presence or absence of gynecomastia was described according to the Tanner scale, the testicular volume was reported by ultrasound considering normal values of 15-30 cc and the presence or absence of hypospadias by physical examination.
Likewise, the hormonal profile of admission (FSH, LH, testosterone, prolactin and estradiol) was analyzed considering the normal ranges established by the Institute's laboratory, as well as the average of their reported values.

Results
A total of 1,029 men with infertility were found between 2016 and 2018; 3 cases of KS were reported in this period with a prevalence of 0.29%.
All patients were diagnosed during the infertility study approach; 100% presented azoospermia in the SA at admission and a 47, XYY karyotype. (Table 1)
The average age of diagnosis of patients with KS was 30.3 years, with a height of 1.66 m and BMI of 24.98 kg/m^2 (normal). 100% presented testicular hypotrophy with average values of 2.68 cc and 2.49 cc (right and left respectively). Only one patient presented gynecomastia (33%) stage 3 in Tanner scale and one hypospadias (33%). (Table 2)

The hormonal profile showed a hypergonadotrophic hypogonadism and hyperestrogenism with average levels of 32.4 mIU/ml for FSH, 20.43 mIU/ml for LH, testosterone of 8.14 nmol/L and estradiol of 53.46 pg/ml. The average value of prolactin was 8.27 ng/ml. Only one patient (33%) presented testosterone within normal ranges and 100% presented hyperestrogenism with normal prolactin levels. (Table 3)

Conclusions

KS is the most common X chromosome abnormality and genetic cause of male infertility. The genotype of these patients is variable, approximately 80-90% of KS men have a 47, XXY karyotype. The main clinical manifestations are: tall stature, overweight or obesity, sparse body hair, testicular hypotrophy (<4cc), gynecomastia, and infertility.

These patients are characterized by having abnormal concentrations of testosterone, FSH and LH in the hormonal profile.

In testicular biopsy, germ cell degeneration, extensive fibrosis, hyalinization of the seminiferous tubules and interstitial hyperplasia are observed.

Patients with KS can achieve pregnancy using TESE combined with ICSI, however it is recommended to perform a prior PGD since there are an increased number of chromosomal abnormalities reported.

Limitations

The number of patients in the study is limited since there are no records of patients with azoospermia and severe oligospermia prior to 2016. These patients were offered IVF with donor semen as an assisted reproductive technique.

Table 1: Karyotype and semen analysis

		SA						
N = 3	**Karyotype**	**Volume (ml)**	**Appearance**	**pH**	**Leukocytes**	**Bacteria**	**Erythrocytes**	**Observations**
1	47,XXY	3	gray opalescent	6.5	8	many	8	Azoospermia
2	47,XXY	2.5	yellow	8.0	1	Few	1	Azoospermia
3	47,XXY	3	yellow	8.5	4	moderate	3	Azoospermia

Table 2: Somatometry and clinical characteristics

N = 3	Age (years)	Height (m)	Weight (Kg)	BMI (18.5 – 24.9 Kg/m^2)	Right testicular volume (cc)	Left testicular volume (cc)
1	28	1.7	74.5	↑25.7	↓0.55	Absent
2	37	1.65	65	↑25.36	↓5.89	↓3.9
3	26	1.65	65	23.88	↓1.02	↓1.49
□	30.3	1.66	68.16	24.98	↓2.48	↓2.69

N = 3	Gynecomastia	Hypospadias
1	Tanner 3	Present
2	Absent	Absent
3	Absent	Absent

Table 3: Hormonal profile

N = 3	FSH (0.70-11.10 mIU/ml)	LH (0.80-7.60 mIU/ml)	Testosterone (9.90 - 52.40 nmol/L)	FAI (14.80 - 94.80 %)	Prolactin (1.9 - 25 ng/ml)	Estradiol (<20 pg/ml)
1	↑31.6	↑19.5	↓1.01	↓5.94	7.74	↑61.7
2	↑31.7	↑23.3	15.2	33.78	9.28	↑48.4
3	↑33.9	↑18.5	↓8.25	41.25	7.79	↑50.3
□	↑32.4	↑20.43	↓8.15	26.99	8.27	↑53.46

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