

Chromosomal Studies in Individuals with Infertility

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ABSTRACT

Objective: To determine the chromosomal constitution of infertile individuals.

Methodology: A cross-sectional descriptive study was carried out based on the results of the karyotypes in peripheral blood in infertile individuals. The sample consisted of infertile patients of both sexes, from the province of Villa Clara who were studied in the Cytogenetics Laboratory of the Provincial Center of Genetics, between the years 1991 and 2017. We analyzed the chromosome formulas obtained and the age of the subjects at the time of diagnosis.

Results: 232 individuals were studied, of which 97 were males and 135 females. 27.15% of the karyotypes were positive and in all, the sex chromosomes were involved. We found numerical chromosomal aberrations in thirty-one men (32%) in relation to Klinefelter Syndrome and variants. Thirty-two women (23.7%) had positive karyotype, where structural aberrations of the X chromosome and mosaicism predominated. The diagnosis of seven women with karyotype 46, XY (Androgen insensitivity Syndrome) and two 45,X/46,XY (Mixed gonadal dysgenesis) was significant. The average age at diagnosis in men was 31 years and in women 22 years.

Conclusions: Karyotyping is an essential study in infertility. The detailed clinical examination of this type of patients would facilitate early diagnosis and adequate therapeutics.

Key words: Infertility, Karyotype, Chromosomal aberration, Aneuploidy, Klinefelter Syndrome, Turner Syndrome.

INTRODUCTION

Infertility is a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner. The permanent state of infertility is named sterility.⁽¹⁾

It has been estimated that 15 % of couples seek medical assistance for infertility, and the origins of the problem seem to be equally distributed between male and female partners.⁽²⁾ The prevalence of infertility overall is difficult to establish because multiple definitions are being used.⁽³⁾ The great heterogeneity of criteria used by investigators to define infertility and critical differences between demographic and epidemiological definitions show ranges of prevalence between 1.8% and 47.4%⁽⁴⁾

Genetic disorders can lead to infertility in men by altering spermatogenesis and sperm function. About 10% of infertile men have severe defects in sperm production, and many of the cytogenetic disorders are concentrated in this group. Klinefelter syndrome was the first sex chromosome disorder to be described and its cytogenetic cause identified, and is the most common cause of hypogonadism and infertility in males. It is found in approximately 1 in 575-1,000 newborn males, although only 25% are ever diagnosed.^(2,5)

The majority of cytogenetic abnormalities in infertile women are related with ovulation disorders, which include hypothalamic, pituitary, and ovarian causes, in relation with primary amenorrhea. Turner Syndrome and its variants, Trisomy X and balanced X-autosome translocation are the most frequently chromosome aberrations observed in karyotypes from infertile women.⁽⁵⁾

The objective of these investigation is to determine the chromosomal constitution of infertile individuals.

MATERIALS AND METHODS

A cross-sectional descriptive study was carried out based on the results of the karyotypes in peripheral blood in infertile individuals. The sample consisted of infertile patients of both sexes, from the province of Villa Clara who were studied in the Cytogenetics Laboratory of the Provincial Center of Genetics, between the years 1991 and 2017.

All patients were referred to laboratory from endocrinology, gynecology and clinical genetics specialties because infertility or sterility and the suspicion of chromosomal aberration. Chromosome preparations were obtained from lymphocyte cultures and analyzed after G banding.

Records from the laboratory were analyzed in order to obtain chromosome formulas and the age of the subjects at the time of karyotyping.

RESULTS

A total of 232 individuals were studied, in which 97 were males and 135 females.

27.15% of the karyotypes were positive, and in all, sex chromosomes were involved. In table 1 are shown all positive Karyotypes in both genders.

Table 1. Chromosomal aberrations in infertile patients

Sex	1- Chromosomal aberrations	Karyotype	Total
Female	Numerical	45,X	1
	Structural	46,X,del(X)(q21)	2
		46,X,del(X)(q21.2)	1
		46,X,del(X)(q24)	1
		46,X,del(Xq) *	1
		46,X,del(X)(p11.2)	1
		46,X,i(X)(q10)	3
		46,X,t(X;14)(q24;q22)	1
	Numerical mosaicism	mos 45,X[42]/46,XX[8]	1
		mos 45,X[25]/46,XX[5]	1
		mos 45,X[3]/46,XX[97]	1
		mos 45,X[2]/46,XX[48]	1
		mos 45,X[2]/46,XX[58]	1
		mos 47,XXX[3]/46,XX[98]	1
		mos 47,XXX[3]/46,XX[59]	1
	Structural mosaicism	mos 45,X[87]/46,X,i(X)(q10)[8]	1
		mos 45,X/46,X,i(X)(q10) **	1
		mos 45,X[78]/46,X,r(X)[24]	1
		mos 45,X[77]/46,X,dup(X)(q28p22)[23]	1
		mos 46,X,i(Xq)/45,X/46,XX	1
	Mixed gonadal dysgenesis	mos 45,X[20]/46,XY[21]	1
		mos 45,X[10]/46,XY[40]	1
	2- Androgen insensitivity Syndrome	46,XY	7
Male	Numerical	47,XXY	29
	Numerical mosaicism	mos 47,XXY[83]/48,XXXY[6]/46,XY[11]	1
		mos 47,XXY[84]/46,XY[16]	1

Legend: * Break points were not recorded ** Metaphase number were not recorded

Numerical aberrations were diagnosed in thirty-one men (32%) in relation with Klinefelter Syndrome and variants. Thirty-two women (23.7%) had positive karyotype, structural aberrations of the X chromosome predominated in these gender, followed by numerical mosaicism and structural mosaicism, with a greater variety of chromosomal alterations in relation to cytogenetic variants of Turner Syndrome. The diagnosis of seven women with karyotype 46,XY (Androgen insensitivity Syndrome) and two 45,X/46,XY (Mixed gonadal dysgenesis) was relevant. A single patient with monosomy X was diagnosed.

Patients were grouped into 6 age groups, starting at age 15, with intervals of 5 years. In the last group, those older than 40 met, including six men between 45 and 49 years old and three over 50 years old.

The average age at the moment of karyotyping in men was 31 years and in women 22 years. In graphic 1 is represented the tendency in each gender group of the age at the moment of positive diagnosis. Women with positive karyotype predominated in the group between 15 and 19 years, while positive karyotypes in men were more frequent in the group between 25 and 29 years.

Spermogram data were recorded in 68 men. 55 had azoospermia and 13 oligospermia. No spermogram data were found in the remaining 29 subjects, but 11 had testicular atrophy. Chromosomal aberrations were found in 18 men with azoospermia, 5 with testicular atrophy and 8 infertile without other data collected in the laboratory files. No chromosomal aberrations were diagnosed in any man with oligospermia.

Primary amenorrhea was recorded in 87 women, secondary amenorrhea in 18, and in 30 there were no data in the registries that associated infertility with the presence of amenorrhea or other clinical data of interest. Positive karyotypes were diagnosed in 24 with primary amenorrhea, 3 with secondary amenorrhea, and 5 in the infertility group with no other data of interest.

Graphic 1: Age at the moment of positive karyotype in relation with gender.

DISCUSIÓN

Among men with infertility, the most frequent cytogenetic findings are 47,XXY and 47,XXY/46,XY. Men with this chromosome constitution commonly have the clinical features of Klinefelter syndrome, but some ones are not diagnosed until such time as they are seeking the cause for their infertility.⁽⁵⁾ In these investigation all men with chromosomal aberrations were Klinefelter Syndrome and variants. Pimentel report similar results, unless the sample collected is different.⁽⁶⁾

Several theories try to explain the impact of a supernumerary X chromosome on the phenotypic features of Klinefelter Syndrome. Inactivation of one X chromosome is responsible of mosaicism

and gene deregulations, including genes in autosomes. This fact implies that the presence of a supernumerary chromosome may affect the expression of several genes throughout the genome.^(6,7) There is a broad spectrum of phenotypes with subjects presenting more severe signs and symptoms and others who present a mild form of the syndrome that they can escape diagnosis and live an apparently normal life, that's why in several affected men diagnosis is after mid twenty. Nevertheless, testicular atrophy and dysfunction is reported as constant feature of Klinefelter Syndrome affecting the tubular compartment and spermatogenesis.^(5,7,8)

Early diagnosis is vital for treatment and minimize adverse manifestations. An important step in order of this direction would be if all physicians would examine the testes of their patients routinely, pointing the physician in the right direction. Therefore, physical examination of the testes should be part of graduate training.

Turner Syndrome is a complex, reproductive and development disorder with a distinctive phenotype. Although some patients may be diagnosed at birth due to the presence of dysmorphic findings, diagnosis is delayed until childhood, adolescence or later. Approximately half of all individuals have a 45,X karyotype and the remainder exhibit mosaicism and structural abnormalities of the X chromosome. In the present investigation, the most common form of mosaicism observed was 45,X/46,XX. These finding in infertile women are according with international and cuban researchs.^(6,9-11)

Deletions of Xq are less common associated with clinical features of Turner Syndrome phenotype, but terminal deletions originating at Xq13 are more likely to have complete ovarian failure, while terminal Xq24 deletions might have partial ovarian failure and infertility as seen in our series. The patient with Xp11.2 deletion had infertility with complete ovarian failure, just like literature reports.^(5,9) Duplications of X chromosome are not frequent, the patient we report had no dysmorphic signs, but was affected for infertility and amenorrhea, in relation with her mosaic condition.

Isochromosome with karyotype 46,X,i(Xq) is the most common structural abnormality of X chromosome, usually associated with mosaicism for a 45,X cell line. A ring X chromosome is generally found in mosaic. We report patients with those karyotypes whose phenotype was variable but in all accompanying for infertility.^(5,9)

Balanced reciprocal X;autosome translocations are rare, in females can be divided into four phenotypic categories: normal phenotype with or without history of recurrent miscarriage, gonadal dysfunction with primary amenorrhea or premature ovarian failure, a known X-linked disorder, or congenital abnormalities and developmental delay.⁽⁵⁾ The patient we report was searching for infertility, and posterior familiar karyotype showed maternal inheritance.

Karyotype 45,X/46,XY can be seen in 5-10% of the patients. Phenotype is variable and range from typical Turner Syndrome phenotype, normal male appearance, moderate masculinization,

male pseudohermaphroditism, and mixed gonadal dysgenesis which can be transformed into a malignant form patient.⁽⁹⁾ 46,XY females are usually diagnosed in puberty because amenorrhea and uterine agenesis. We suspect that the very late diagnosis of some women with Androgen Insensitive Syndrome is in relation with cultural aspects of population, someone hide the condition from their partner and even pretend to have menses.

Among infertile population is more frequent to found balanced autosomal abnormalities such as Robertsonian translocation, reciprocal translocations and inversions.^(5,12) The referral criteria of patients in the present investigation explain the absence of these aberrations. Karyotype was indicated in patients with clinical suspect of chromosomopathies, not as a routine study of infertile couples.

CONCLUSIONS

Karyotyping is an essential study in infertility. The detailed clinical examination of infertile patients would facilitate early diagnosis and adequate therapeutics.

LIMITATIONS

Molecular studies are helpful for determining break points, parental origin, and evaluate mosaicism, but are not available.

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