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ASSISTED REPRODUCTION TECHNOLOGIES

Reproductive success of assisted reproductive technology in couples with chromosomal abnormalities

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Abstract

Purpose Infertility is estimated to affect 15% of couples, having chromosome abnormalities an important role in its etiology. The main objective of this work was to access the reproductive success of ART in infertile couples with chromosomal abnormalities comparing to a control group with normal karyotype.

Methods A 7-year retrospective karyotype analysis of infertile couples was done. Data regarding type of infertility, couples' ages, ART performed, and their reproductive success were obtained. Adjusted odds ratio (OR) were used to estimate magnitude of association between the reproductive success and the different groups.

Results We found a prevalence of 7.83% of chromosome abnormalities in our population (233 couples out of 2989). Chromosomal anomalies were found in 82 men (34.75%) and 154 women (65.25%), with low-grade mosaicism being the most prevalent (50.85%), followed by autosomal translocations (17.37%) and sex chromosomes abnormalities (13.56%). Only 2359 couples were treated with ART. There was a non-significant lower reproductive success rate in the cases (OR = 0.899, p = 0.530) with IVF providing the higher success rate. In general, female carriers of chromosome anomalies had a higher success rate, although not significant.

Conclusion Although the differences regarding success rate between groups were not found statistically significant, we still advocate that cytogenetic analysis should be performed routinely in all infertile couples namely before ART. This might help deciding the best treatment options including Preimplantation Genetic Testing for aneuploidies or structural rearrangements and minimize the risk of transmission of anomalies to the offspring.

Keywords Infertility · Chromosome abnormalities · Assisted reproduction technology · Karyotype

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Introduction

Infertility is defined by the World Health Organization (WHO) and by the International Committee for Monitoring Assisted Reproductive Technology (ICMART) as a disease of the reproductive system in which there is failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [1]. Infertility is of high prevalence around the world, especially among developing countries, being estimated that 1 out of 4 couples are infertile [2], a tendency that appears to be increasing [2, 3]. Among the several causes of human infertility, genetic abnormalities take an important part [4], with some estimates pointing to being the main factor in up to 50% of infertility cases [5]. Despite the difficulty in studying the genetic implications on fertility, some specific genetic anomalies have been associated with this problem, among which several chromosomal abnormalities [4] that may affect only one or both couple's members.

In this context, an increasing amount of couples has turned to assisted reproductive technology (ART) to find an answer to their reproductive needs [6], using techniques such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and intrauterine insemination (IUI) [7]. This includes those couples that present chromosomal abnormalities as well. However, there are not many studies regarding the success of these techniques in carriers of a chromosome anomaly, especially considering both the female and the male contribution, and the impact of those anomalies in the outcome. Furthermore, such studies usually use small series which make it difficult to draw definite conclusions.

In this context, we aimed to assess the reproductive success of ART in infertile couples with chromosomal abnormalities comparing to a control group also submitted to ART but with normal karyotype.

Methods

A retrospective cohort of all karyotypes performed in the Genetics Department of Faculty of Medicine, University of Porto (FMUP) with the clinical indication of infertility, was done. For this study, a 7-year period was considered, from January 2010 to February 2017. The Ethics Committee for Health of Centro Hospitalar Universitário São João (CHUSJ) approved this study, and all data was irreversibly anonymized, assuring protection of all patients' information.

To perform the karyotypes, cell culture and standard cytogenetic methods were used. Preparation of chromosome slides and high resolution G banding using Leishman stain were performed according to standard protocols [8]. At least 20 metaphases were counted, all performed according to the laboratory protocol for karyotype analysis [8]. The International System for Human Cytogenetic Nomenclature (ISCN, 2016), was followed for defining the chromosomal aberrations. Information regarding type and prevalence of chromosomal abnormalities was recorded.

Data regarding type of infertility, couples' ages, ART techniques performed, and success of those techniques were obtained afterwards from paper registers at a tertiary hospital (Centro Hospitalar Universitário São João - CHUSJ) and from the electronic medical database of a private ART center. We excluded from comparison all couples that did not engage in any ART technique, either for choice or for any medical reasons (e.g., due to advanced maternal age or spontaneous pregnancy). Medical history including sperm parameters or oocyte count, although relevant for the reproductive success of the infertile couple, was not analyzed in this study as it was not the main purpose.

Infertility was classified into primary and secondary. Primary infertility was defined as inability to become pregnant or the inability to carry a pregnancy to a live birth, whereas secondary infertility was defined as inability to become pregnant or the inability to carry a pregnancy to a live birth after a previous pregnancy, according to the definition by the WHO [2]. Ovulation induction (OI), in vitro fertilization (IVF), intra cytoplasmic sperm injection (ICSI), intrauterine insemination (IUI), and frozen or vitrified embryo transfer (FET), performed either with material from the infertile individual or from a donor, were the techniques performed in both reproductive centers. FET was considered as an independent technique to differentiate multiple transfers of embryos resulting from a previous technique.

To conduct a comparative analysis, two groups were established attending the presence or absence of chromosomal abnormalities (cases and controls). Success was defined as pregnancy with delivery of a healthy baby (baby take home rate). The statistical analysis of the data was performed using the program IBM SPSS Statistics 25. Chi-square test and exact Fisher's test were performed for proportions comparison between groups. Adjusted odds ratio (OR) were used to estimate magnitude of association between the success and the different groups. Conditional logistic regression was used to estimate the odds ratio (OR) and the respective 95% confidence intervals (CI). Statistical significance level was established at 0.05.

Results

From a 7-year period, 2989 couples were tested for chromosomal anomalies as standard evaluation for infertility study in the Genetics Department of Faculty of Medicine of Porto. Chromosomal abnormalities were identified in 233 couples, accounting for 7.80% (233/2989) of total. Type and frequency of such anomalies are listed on Table 1. Both members were affected in 3 couples, accounting for a total of 236 (3.95%) individuals with abnormal karyotype. Chromosomal anomalies were found in 82 men (82/236, 34.75%) and 154 women (154/236, 65.25%). Low-grade mosaicism was the most prevalent anomaly, affecting 50.85% of individuals, followed by autosomal translocations (17.37%), and sex chromosomes abnormalities (13.56%). Low-grade mosaicism was defined according to criteria established by Madan and Lundberg [9]. It should be noted that the type of anomaly varied between genders. Sex chromosome abnormalities were more prevalent in the male partner (32.93% of males vs. 3.25% of females). Klinefelter syndrome was the most common sex chromosome abnormality, being found in 19/82 (23.17%) of males. Mosaicism, on the other hand, was much more prevalent among women than men (67.53% of females vs. 19.51% of males). Mosaic Turner syndrome was found in 92/154 women (59.74%), accounting for the large majority. Autosomal structural abnormalities were found in 32.63% individuals (77/

Table 1 Types and frequencies of chromosome anomalies in couples with infertility

Chromosomal abnormality		Karyotype			
		Males (n = 82)	*N* (%)	Females (n = 154)	*N* (%)
Autosomal abnormalities	(inv) inversion	46,XY,inv(1)(q21.3q32.1)	1	46,XX,inv(2)(p11q13)	1
		46,XY,inv(1)(p23.3q32.1)	1	46,XX,inv(7)(p11.2q11.2)	1
		46,XY, inv(4)(p12q12)	1	46,XX,inv(7)(p15.3q11.23)	1
		46,XY, inv(7)(p11.2q11.2)	1	46,XX,inv(8)(p11.1q11.23)	1
		46,XY,inv(8)(q21.2q22.1)	1	46,XX,inv(8)(p12q21.1)	1
		46,XY,inv(21)(p11.1,q11.1)	1	46,XX,inv(11)(p15.2q23.3)	1
		46,XY,inv(12)(q13.1q15) t(2;12)(q36;q15)	1	46,XX,inv(21)(p11.1q11.1)	1
				46,XX,inv(22)(p11.1q11.1)	1
		Total males	7 (8.54)	Total females	8 (5.20)
		Total inversions	15/236 (6.36)		
	(t) translocation	46,XY,t(1;7)(p13.3;p15.2)	1	46,XX,t(1;6)(q42.1;q25.1)	1
		46,XY,t(2;2)(p23;q21.2)	1	46,XX,t(1;20)(p36.1;q13.3)	1
		46,XY,t(2;6)(q35;q13)	1	46,XX,t(2;11)(q33;q13.3)	1
		46,XY,t(4;8)(q31.23;q13.2)	1	46,XX,t(2;16)(p15;p11.2)	1
		46,XY,t(5;6)(p12;q16.3)	1	46,XX,t(3;22)(q24;q11.1)	1
		46,XY,t(7;10)(q11.2;q26)	1	46,XX,t(4;16)(q35;q22)	1
		46,XY,t(8;9)(q21.2;q22.3)	2	46,XX,t(4;19)(p16.1;q13.13)	1
		46,XY,t(8;10)(q24.1;p11.2)	1	46,XX,t(5;7;6)(q15;q36;p24)	1
		46,XY,t(8;15)(p23.1;q12)	1	46,XX,t(5;9)(p13.3;q34.1)	1
		46,XY,t(9;14)(q31;q21)	1	46,XX,t(5;20)(q13.1;q13.1)	1
		46,XY,t(10;21)(q24.1;q11.2)	1	46,XX,t(6;8)(q13;p23)	1
		46,XY,t(11;22)(q23;q11)	2	46,XX,t(6;9)(p23;p24.1)	1
		46,XY,t(13;18)(q22;p11.31)	1	46,XX,t(7;12)(q22;q24.32)	1
		46,XY,t(20;22)	1	46,XX,t(7;13)(p13;q14.1)	1
				46,XX,t(7;21)(p11.2;q11.2)	1
				46,XX,t(8;11)(q13;q21)	1
				46,XX,t(8;13)(q22.3;q14.3)	1
				46,XX,t(9;16)(p13;q22)	1
				46,XX,t(10;12)(q23.2;q23)	1
				46,XX,t(11;20)(p11.2;p11.2)	1
				46,XX,t(11;22)(q23;q11)	3
				46,XX,t(12;14)(q15;q32.1)	1
				46,XX,t(16;19)(q22;q13.3)	1
		Total males	16 (19.51)	Total females	25 (16.23)
		Total translocations	41/236 (17.37)		
	(rob) Robertsonian translocations	45,XY,rob(13;14)(q10;q10)	10	45,XX,rob(13;14)(q10;q10)	7
		45,XY,rob(15;21)(q10;q10)	1	45,XX,rob(14;21)(q10;q10)	1
		44,XY,rob(21;22)(q10;q10)×2	1	45,XX,rob(15;22)(q10;q10)	1
		Total males	12 (14.63)	Total females	9 (5.84)
		Total Robertsonian translocations	21/236 (8.89)		
Sex abnormalities		47,XYY	1	47,XXX	3
		47,XXY	19	46,X,der(X)del(X)(q26)add(Xqs)	1
		46,X,inv(Y)(p11;q11)	5	46X,t(X;1)(q21.2;p34)	1
		46,Y,der(X)	1		
		46,Y,del(X)(p22.3)ps	1		
		Total males	27 (32.93)	Total females	5 (3.25)
		Total sex abnormalities	33/236 (13.98)		
Mosaic		46,XX[29]/46,XY[1]	1	45,X[3]/46,XX[27] or 45,X[3]/46,XX[55] or 45,X[4]/46,XX[54] or 45,X[5]/46,XX[53] or 45,X[6]/46,XX[52] or 45,X[10]/46,XX[48]	33
		45,X[3]/46,XY[55] or 45,X[4]/46,XY[54]	2	47,XXX[2]/46,XX[28] or 47,XXX[2]/46,XX[56] or 47,XXX[3]/46,XX[27]	10
		47,XXY[2]/46,XY[28] or 47,XXY[3]/46,XY[27] or 47,XXY[4]/46,XY[26]	5	47,XXX[2]/45,X[1]/46,XX[55] or 47,XXX[2]/45,X[1]/46,XX[27] or 47,XXX[3]/45,X[2]/46,XX[53] or 47,XXX[4]/45,X[1]46,XX[53] or 47,XXX[4]/45,X[2]/46,XX[52] or	50

Table 1 (continued)

Chromosomal abnormality	Karyotype			
	Males (n = 82)	*N* (%)	Females (n = 154)	*N* (%)
			45,X[2]/47,XXX[1]/46,XX[27] or 45,X[2]/47,XXX[2]/46,XX[26] or 45,X[2]/47,XXX[1]/46,XX[27] or 45,X[2]/47,XXX[1]/46,XX[55] or 45,X[2]/47,XXX[2]/46,XX[54] or 45,X[3]/47,XXX[1]/46,XX[26] or 45,X[3]/47,XXX[1]/46,XX[27] or 45,X[3]/47,XXX[1]/46,XX[52] or 45,X[3]/47,XXX[1]/46,XX[54] or 45,X[3]/47,XXX[2]/46,XX[53] or 45,X[3]/47,XXX[3]/46,XX[52] or 45,X[4]/47,XXX[1]/46,XX[25] or 45,X[4]/47,XXX[1]/46,XX[53] or 45,X[4]/47,XXX[4]/46,XX[50] or 45,X[5]/47,XXX[1]/46,XX[52] or 45,X[5]/47,XXX[1]/46,XX[24]	
	45,X[2]/47,XXY[1]/46,XY[55] or 47,XXY[2]/45,X[1]/46,XY[55] or 47,XXY[2]/45,X[2]/46,XY[54] or 45,X[2]/47,XXY[2]/46,XY[26]	4	45,X[4]/48,XXXX[1]/46,XX[53] or 45,X[2]/48,XXXX[1]/46,XX[55]	2
	47,XXY[54]/46,XX[2]/46,XY[2]	1	47,XXX[2]/45,X[1]/48,XXXX[1]/46,XX[54] or 47,XXX[4]/45,X[2]/48,XXXX[1]/46,XX[23] or 45,X[5]/47,XXX[1]/48,XXXX[1]/46,XX[23] or 45,X[4]/47,XXX[1]/48,XXXX[1]/46,XX[52]	5
	46,XY,del20(q11.2q13.1)[14]/46,XY[27]	1	45,X,t(3;14)(p12;q21)[4]/46,XX,t(3;14)(p12;q21)[54]	1
	46,XY,ins(17;6)(q23;q21q25.1)[6]/46,XY[24]	1	45,X[22]/46,X,del(X)(q25qter)[12]	1
	47,XY,+mar[6]/46,XY[24]	1	46,XX,fra(16)(q22.1)[6]/46,XX[24]	1
			47,XX,+mar[21]/46,XX[9]	1
	Total males	16 (19.51)	Total females	104 (67.53)
	Total Mosaic	120/236 (50.85)		
Others	46,X,idic(Y)(p)	1	46,X,+mar	1
	47,XY,+mar	2	46,XX,dup(15)(q12q13)	1
	47,XY,+idic(15)(q11.1)	1	46,XX,dup(22)(q11.2)	1
	Total males	4 (4.88)	Total females	3 (1.95)
	Total others	7/236 (2.97)		
Total cases		236 (100)		

236), the most frequent being translocations (62/77, 80.52%), in both genders.

Only 2359 couples proceeded with an ART technique, which included 161 cases and 2198 controls. Mean age was 38.87 years for women and 40.41 for men. There were no significant differences between cases and controls regarding age ($t = 1.467$, $p = 0.143$ for women and $t = .871$, $p = 0.061$ for men). Women with primary infertility were significantly more young than women with secondary infertility, with a medium of 38.48 years versus 40.44 years, respectively ($t = -8.212$, $p < 0.001$). Information regarding the type of infertility and success rate is summarized on Table 2 for both groups. A vast majority of 80.12% of couples has not had a previous pregnancy or has had a miscarriage before. We found a 49.55% success rate for all couples.

A majority of 68.16% of couples (66.67% of cases and 68.28% of controls) engaged in only 1 procedure to achieve live birth, 23.40% (20.37% of cases and 23.62% of controls) made 3 to 4 procedures, and only 8.44% (12.96% of cases and 8.10% of controls) performed 5 or more. On average, 2.21 fertility treatments (median = 2.00) were necessary to achieve reproductive success. A vast majority of pregnancies resulted in live birth (63.32% of total, 62.07% for cases, and 65.54% for controls). Miscarriages accounted for 12.46% of all pregnancies. Only 22.22% of all cases had 2 or more newborns per pregnancy.

Type and frequency of the last procedure performed, either having achieved a successful pregnancy or not, is shown on Table 3. ICSI was by far the most frequent, being the last technique offered to 50.74% of all couples. On the other hand,

Table 2 Type of infertility and reproductive outcome of couples treated with ART

Characteristic		Cases, *N* (%)	Controls, *N* (%)	Total N (%)
Type of infertility	Primary	125 (77.64)	1765 (80.30)	1890 (80.12)
	Secondary	36 (22.36)	433 (19.70)	469 (19.88)
	Total	161 (100.00)	2198 (100.00)	2359 (100.00)
Outcome	Successful	74 (45.96)	1095 (49.82)	1169 (49.55)
	Not successful	87 (54.04)	1103 (50.18)	1190 (50.45)
	Total	161 (100.00)	2198 (100.00)	2359 (100.00)

OI and treatment using donor gametes were much less frequent, accounting for only 2.67% and 0.72% of couples, respectively.

Table 4 presents the association between reproductive success and multiple variables considered in this study. There was a slightly lesser rate of reproductive success in the cases group, although not statistically significant (OR = 0.899, p = 0.530). IVF had a significantly superior reproductive success comparing to other ART techniques, with exception of procedures performed with donor gametes. Notwithstanding, ART using donor gametes was associated with a non-significant higher rate of success (OR = 1.194, p = 0.738). A probability of success was negatively associated with increasing age of female partner (OR = 0.937, p < 0.001). Secondary infertility was negatively associated with the probability of success (OR = 0.643, $p < 0.001$). An association between higher number of procedures and small rate of success was found, although not significant (OR = 0.970, p = 0.306).

Rate of success outcome according to type of anomaly and gender of the member affected is summarized on Fig. 1. There is a higher rate of success when the female is the carrier, with exception of sex chromosome anomalies. However, this differences were not significant (p = 0.810, for inversions; p = 0.314, for translocations; p = 0.232, for mosaics). A great disparity between genders regarding success was found in inversion's carriers, with all couples in which the female was the carrier having a 100% success rate (versus 37.5% for couples with male carriers).

Discussion

Infertility is a condition of increasing prevalence [2, 3] that has a multifactorial cause and therefore a complex treatment [10]. Comprehensive study of both members of the couple is essential to maximize the probability of pregnancy and minimize the transmission of genetic anomalies to the offspring. Chromosome abnormalities seem to play an important role in the etiology of infertility [4], making karyotype testing a useful tool to understand chromosomal anomalies and their impact on human reproduction. In this study, as part of the routine evaluation of the infertile couple, karyotype allowed the identification of chromosome abnormalities in 233 couples, which accounts for 7.80% (233/2990) of our population. This is consistent with recent studies [11–13] that reported a similar prevalence of chromosomal anomalies in the infertile population, a rate 2–3 times higher than the general population [14].

All individuals were evaluated by the same laboratory, which leave virtually no space for differences in interpretation of cytogenetic results. However, information regarding age, type of infertility, ART procedures performed, and outcome were collected from two different fertility centers, from paper and electronic registers. Some information bias may therefore distort these results. Diagnostic methods, techniques' protocols and success rates may also vary between centers. Nevertheless, no statistical differences were found comparing the successful outcome of both centers.

Table 3 Frequencies of the last procedure performed, independent of success

Assisted reproduction techniques		Cases, *N* (%)	Controls, *N* (%)	Total N (%)
	IVF	34 (21.12)	527 (23.98)	561 (23.78)
	ICSI	84 (52.18)	1113 (50.64)	1197 (50.74)
	OI	4 (2.48)	59 (2.68)	63 (2.67)
	FET	21 (13.04)	359 (16.33)	380 (16.11)
	IUI	10 (6.21)	131 (5.96)	141 (5.98)
	Donor	8 (4.97)	9 (0.41)	17 (0.72)
	Total	161 (100.00)	2198 (100.00)	2359 (100.00)

IVF, in vitro fertilization; *OI*, ovulation induction; *ICSI*, intra cytoplasmic sperm injection; *IUI*, intrauterine insemination; *FET*, frozen or vitrified embryo transfer; Donor is a technique using donor sperm or oocyte

Table 4 Association between reproductive success and multiple variables

	OR	Lower	Upper	Sig.
Chromosome abnormality				
Absent	Ref			
Present	0.899	0.644	1.254	0.530
Last technique performed				
IVF	Ref			
ICSI	0.606	0.492	0.745	< 0.001
OI	0.306	0.175	0.534	< 0.001
FET	0.682	0.515	0.903	0.008
Donor	1.194	0.423	3.369	0.738
IUI	0.487	0.332	0.716	< 0.001
Age of female partner (years)	0.937	0.918	0.955	< 0.001
Type of infertility				
Primary	Ref			
Secondary	0.643	0.519	0.796	< 0.001
Number of procedures performed	0.970	0.915	1.028	0.306

*adjusted for all variables and local

Ref, Reference; *IVF*, in vitro fertilization; *OI*, ovulation induction; *ICSI*, intra cytoplasmic sperm injection; *IUI*, intrauterine insemination; *FET*, frozen or vitrified embryo transfer

Chromosomal abnormalities were more frequent among women than men (65.25% vs. 34.75%). Mosaics were by far the most prevalent anomaly, accounting for 50.85% of affected individuals, and were mainly found in women, mosaic monosomy X being the most common. This represents an important cause of infertility, considering that primary amenorrhea and lack of pubertal development presents in 90% of women with 45,X or 45,X/46,XY, 45,X/46,XX or 45,X/47,XXX mosaicism [15], and is consistent with findings from similar studies [13]. Because it has been shown that the frequency of low-level X aneuploidy is correlated with age and gender but not with reproductive history [9], we conducted the same analysis performed in Table 4 for all couples but removing all the mosaic cases. The results obtained were not statistically different from those showed in Table 4, so we chose to keep all couples in the analysis.

Sex chromosome abnormalities were more frequent among infertile men, the most common being Klinefelter syndrome. Other studies have reported similar results [11, 13, 16]. The most common pericentric inversion of the Y chromosome, 46,X,inv(Y)(p11q11), was found in 5 men. For a long period of time, this chromosomal polymorphic variation was considered a normal variation but some recent studies have reported an association with poor spermatogenesis and production of unbalanced gametes [14, 17]. Although some controversy, this could be explained by the presence of Y microdeletion. As standard policy in our laboratory, all pericentric inversions of the Y chromosome detected by karyotype testing are tested for AZF deletions.

Autosomal translocations were the second most common anomaly found in our study, followed by sex chromosome anomalies and inversions. Balanced translocations and other autosomal abnormalities may have an impact in the fertility of an otherwise phenotypically normal individual, due to the production of unbalanced gametes with abnormal chromosome pairing and segregation at meiosis I [18, 19]. This increases the risk of miscarriage and birth of a child with abnormal karyotype [20].

A significant number of infertile couples decided not to initiate treatment or engage in any further ART procedure. This is demonstrative of the enormous financial burden and psychological exhaustion that infertile individuals are exposed [21].

The reproductive success rate of the overall population was 49.55%, which is similar to other studies [19, 22].

When analyzing the last procedure performed, ICSI was by far the most frequent. This is not surprising since ICSI is a much more exigent technique. On the contrary, OI is usually more used as a first approach procedure, being less technically exigent, less time and money consuming, and less invasive. Procedures using donor gametes are viewed as an end of the line treatment, and as such were not performed frequently. We have to keep in mind that ART is not assigned randomly by the doctor, but chosen according to the characteristics of each individual, in order to maximize the chances of a successful outcome. Thus, karyotype results were considered when deciding which treatment to offer, and this may explain why procedures using donor gametes were more commonly used among cases than controls.

Success rate was higher in the control group, although this was not statistically significant. As chromosome abnormalities are a known cause of infertility, some differences regarding success rate might be expected between groups. However, studies reporting success rates of ICSI among couples with chromosomal abnormalities also found no significant differences from a control group [23, 24]. This might be explained by the fact that ovarian stimulation, required to perform any ART technique, may extend the process of natural selection thus increasing the rejection of abnormal oocytes and the probability of producing a normal embryo [25].

A significant lesser probability of success was associated with increasing age of female partner. Decreasing fertility with age is already a well-established relationship [26–28].

IVF had a significantly superior reproductive success comparing to other ART techniques, with exception of procedures performed with donor gametes. Donor treatments bypass the possible anomalies present in the couple, making unsurprising that they offer better results.

Secondary infertility was significant for lower probability of success. At first sight, this may seem counter-intuitive. However, couples that present secondary infertility were significantly older than couples with primary infertility, a factor

already established as an important element in decreasing fertility. Other important factors may be involved in the loss of fertility, including endocrine, metabolic, urologic, and gynecologic pathologies that may require other type of treatments and further decrease the probability of success. An association between higher number of procedures and small rate of success was found, although not significant. An explanation for this is the fact that these couples present infertility so severe that no matter the number of treatments performed, success could never be achieved.

Taking into account success according to type of chromosome anomaly, it is clear in Fig. 1 that the outcome was better when the carrier of a translocation, inversion or even a mosaic was a woman. This could be explained by the fact that gametogenesis in the male is more vulnerable to the stumbling block imposed by a chromosomal abnormality. According to literature, another important element is the impaired synapsis of homologous segments in the normal and the rearranged chromosomes, which itself could prevent further progress in gametogenesis. Spermatogenesis may be more sensitive to this obstacle than oogenesis [29–31].

In the case of a non-mosaic sexual chromosomal abnormality either structural or numerical, a success outcome was achieved in about 50% of cases with affected male individuals. This rate could be explained, at least partially, by the development of ICSI and testicular sperm extraction that could be applied to Klinefelter patients, allowing the possibility of fathering to be a reality for these individuals. A previous study from our group also concluded that there is no increased risk for aneuploidies in the offspring [32]. Regarding women with non-mosaic sexual chromosomal abnormality, only 5 cases were included and so no conclusion could be made.

Finally, some authors have argued that ART techniques, such as ICSI, may contribute to the propagation of chromosome abnormalities to the offspring, even when parents are not affected by any anomaly [33]. Studies are beginning to report on genetic and epigenetic impact of such techniques, with some reporting an increased risk of multiple pathologies [34, 35]. This furthers enhances the need for karyotype testing before engaging in any procedure. Reproductive counseling including the option of Preimplantation Genetic Test for

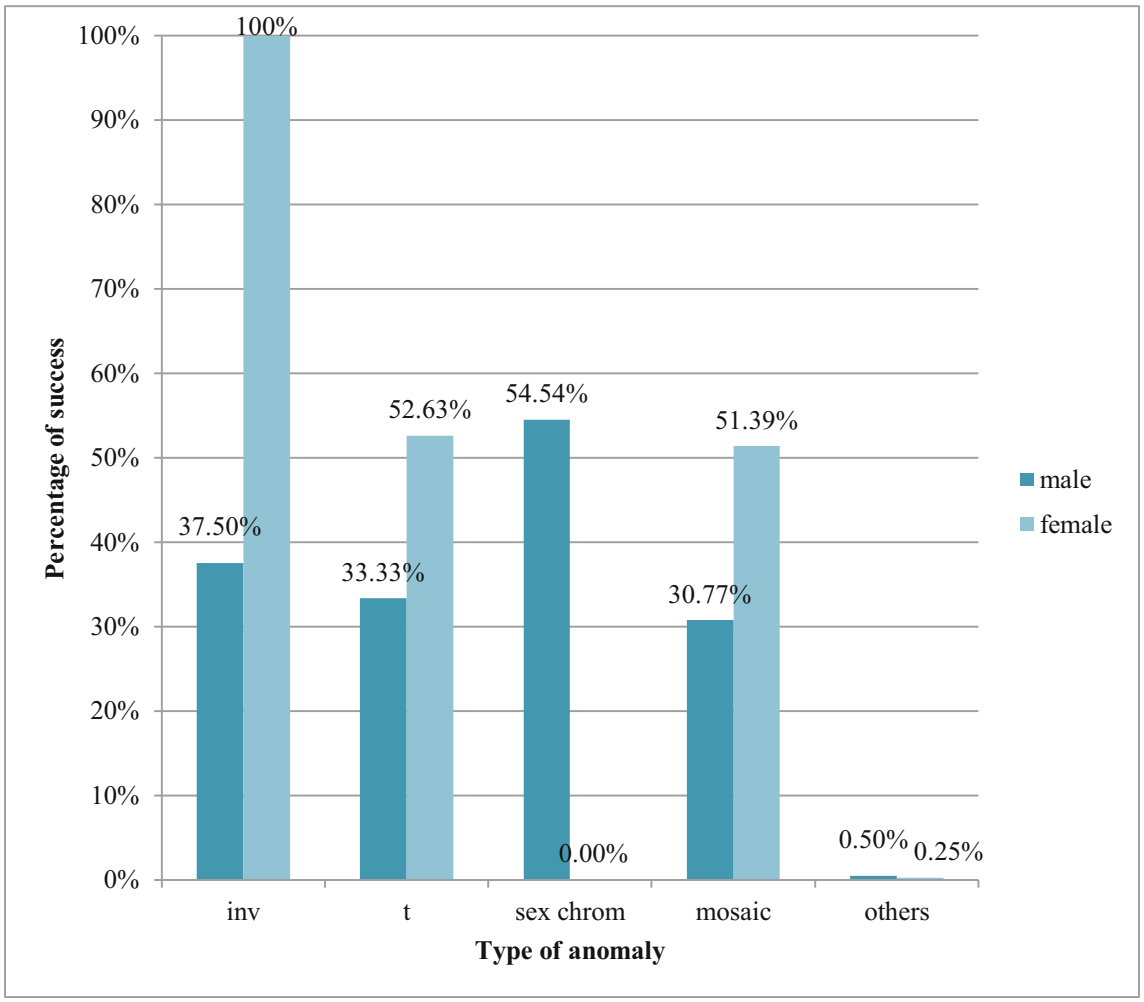

Fig. 1 Successful outcome according to type of chromosome anomaly. inv, inversion; t, translocation; sex chrom, Sex chromosomal structural/numerical abnormality

aneuploidies (PGT-A) or structural rearrangements (PGT-SR) should be given to the infertile couple to minimize the risk of transmission of anomalies to the offspring.

Conclusion

Chromosome abnormalities are an important cause of infertility, being found in a significant percentage of the infertile population. Although the differences regarding success rate between cases and controls were not found statistically significant, we still advocate that cytogenetic analysis should be performed routinely in all infertile men and women due to the fact that it might help deciding the best fertility treatment options to offer the couple. Furthermore, there are still questions regarding the risk of transmission of anomalies to the offspring and the impact of such anomalies in the future child. Genetic counseling and PGT-A/PGT-SR should therefore be offered to couples in this situation. Infertility is a very complex issue that is far from being completely understood. It is clear that more evidence is needed in order to make any definite conclusion about the impact of chromosome abnormalities on human infertility and usefulness of ART techniques in these individuals.

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Compliance with ethical standards

The Ethics Committee for Health of Centro Hospitalar Universitário São João (CHUSJ) approved this study, and all data was irreversibly anonymized, assuring protection of all patients' information.

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