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Full Length Research Paper

Does female with chromosome translocation have a normal response to controlled ovarian hyperstimulation?

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ABSTRACT

Patients with chromosomal translocation have been reported to have high risk of reproductive failure, lower ovarian response, recurrent pregnancy loss and implantation failure. The literature is not conclusive, and our objective is to study if female balanced translocation (BT) does affect the controlled ovarian stimulation (COS). We carried out a retrospective analysis of 3249 karyotypes between 2008 and 2016, including 2276 females and 973 males. 12 women (0.5%) with BT were compared with 93 control normal karyotype group (CN) in both female and male partner. An equivalent control group (EQc) of 12 patients was additionally selected to be accurate with the BT statistical contrast. Cycle, oocyte and embryo outcomes were analysed. We concluded that female BT carriers have no diminished response to COS than infertile females with normal karyotype. This is an important information for counselling couples previous to COS and preimplantational genetic testing (PGT).

Keywords: Chromosomal translocation, reciprocal, Robertsonian, controlled ovarian stimulation.

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INTRODUCTION

The incidence of balanced chromosomal rearrangements in the general population is 1/500 individuals (0.2%), but this frequency is increased in infertile patients. Chromosomal aberrations are involved in reproductive failures, chromosomal translocations, abnormal gametogenesis, implantation failure and recurrent pregnancy loss (RPL). Reciprocal translocation is produced when two non-homologous chromosomes exchange segments and, if no genetic material is gained or lost and no truncation of a gene occurs, patients can be phenotypically normal, but they will have a higher risk of recurrent pregnancy loss. In the Robertsonian translocation, two acrocentric chromosomes as 13, 14, 15, 21 and 22 fuse at the centromere (Scott et al., 2017), having low impact on cell function, but when meiosis happens can produce gametes nullisomic or disomic and if fertilization takes place, originates monosomic or trisomic zygotes (Munné et al., 2000). The imbalance can be caused by the duplication of a chromosome segment and the other chromosome deleted. In addition, the carriers of a translocation may have an increased risk of having descendant with physical or mental anomalies (Gardner and Sutherland, 2003). The great genetic imbalances produced by unbalanced combinations are responsible for early pregnancy loss or even for implantation failure and if the imbalances are moderate, can conduce to recognizable miscarriage or stillbirth.

Besides that, we take into account the inter-chromosomal effect (ICE) that will increase the rate of aneuploidy in gametes (Alfawati et al., 2012). Only those conceptuses with lesser imbalances may result in the birth of a normal child or a normal carrier.

It is of major importance to proceed with those patients to have an IVF treatment and a preimplantational genetic

testing for structural rearrangements (PGT-SR) as the safer technique to screen against embryos with unbalanced translocation and select only normal embryos to be transferred (Chow et al., 2019; Mardesić et al., 2011; Tulay et al., 2016). That strategy significantly reduces pregnancy losses and increase the number of viable pregnancies, being a safer method for conceiving a live birth child, at least for translocation carriers with recurrent pregnancy loss and no previous live births (Otani et al., 2006; Munné et al., 2005), in fact, the chance of having a normal pregnancy with a healthy live birth is higher than reported previously with FISH-PGT-SR (Huang et al., 2019).

Furthermore, some studies (Chen et al., 2005; Mayeur et al., 2020) suggest that translocation carriers may have an increased risk for poor response to controlled ovarian stimulation (COS), which would make embryo selection difficult, as it is needed a large number of embryos for biopsy to be able to select a healthy embryo and have a safer transfer. On the other hand, the study conducted by Dechanet et al. (2011), sustains that chromosomal translocation in female does not affect ovarian stimulation response. This point can be decisive to obtain enough embryos to select the healthy ones, prior to transfer to the uterus.

The objective of the present study is to determine the relation among translocation carriers and COS as well as oocytes quality, fertilization rate and embryo development, to give appropriate counsel to patients affected with a chromosomic translocation.

MATERIALS AND METHODS

Patients groups

A retrospective study was performed in 3249 karyotyped patients, 2276 female and 973 male patients, attending at the Reproductive Unit of the Hospital Universitario of Canarias (HUC), between January 2008 and December 2016. We analysed only reciprocal and Robertsonian translocations and a selected random group of 93 patients with normal karyotype for both members of the couple as a control, being excluded couples with no male karyotype determination and other pathologies out of this study.

We compared age, body mass index (BMI) and serum follicle stimulant hormone (FSH) on third day of cycle, number of oocytes obtained after COS, rate of mature oocytes (MII), fertilization rate and number of embryos obtained. A second control group was selected, that we denominated “equivalent control” (EQc) with 12 patients matching one by one with the pathological patients in three items: age, BMI and FSH (Figure 1).

Approval from the Ethical Committee of our institution was obtained for this study, and permission was obtained as all the research was performed according to the actual guidelines and regulations.

Controlled ovarian stimulation

Antagonist protocol used gonadotrophin stimulation starting from day 2 with the administration of a variable dose of 225-300 mg of rFSH (Puregon®, Organon, France or Gonal-F®, Merck Serono, France) associated or not with urinary gonadotrophin (Menopur®). Antagonist is added subcutaneously diary starting when the leading follicle achieved 14 mm. diameter, 0.1 mg of ganirelix or cetrorelix (Ganirelix, Orgalutran®, Organon, France; Cetrorelix, Cetrotide®, Serono, France). Additionally, Ovitrelle® 250 micrograms of solution for injection in pre-filled pen **(**Coriogonadotrophin alpha, Merck Serono, Bari, Italy) was administered when follicles had at least 17 mm. Egg retrieval was performed 36 hours after hCG administration.

Cytogenetic studies

Cytogenetic preparations were obtained from phytohaemaglutinin (PHA)-stimulated peripheral blood lymphocytes as described by Rooney and Czepulkowski (1992). Chromosome analysis was carried out on G-banded metaphases.

Embryo quality

The embryo quality of the obtained embryos was determined following the parameters marked by ASEBIR (Association for the Study of the Biology of Reproduction; 2015).

Statistical analysis

A frequency analysis of translocations was carried out. Therefore, data were compared with analysis of media differences for independent samples for numerical data, and a chi-square was applied for categorical factors. Also, ANCOVA test was used to neutralize a variable effect. For comparison of gonadotrophin doses administered, a comparison of media was applied. Statistical analysis was performed using the SPSS vs.21 statistic package and p value <0.05 was considered statistically significant.

RESULTS

Patients

Female with pathological karyotype had a mean age of (36.55 years; TD = 4.06 years), while the control group was (33.96 years; TD = 3.70 years) (t307 = -3.990; $p < 0.001$), a significant difference was obtained in the age between control and pathological groups. Female age of pathological group was statistically higher than control group ($p < 0.001$).

The mean BMI in pathological female was (26.73 kg/m^2; TD = 5.36 kg/m^2), compared with the control group (24.32 kg/m^2; TD = 3.98 kg/m^2) (t307 = -3.333; p = 0.011) showed a significant difference, greater in pathological patients. The pathological group had a significantly higher BMI value than the control group ($p = 0.011$).

The mean serum FSH in pathological female was (6.54 mIU/ml; TD=1.30 mUI/ml; Cv = 19.88%) compared with those in the control group (6.39 mIU/ml; TD=1.72 mUI/ml; Cv = 26.92%) (t-0.499 = -3.169; p = 0.618). FSH did not show significant differences between both groups (Table 1).

In our infertile population of a total of 3246 karyotypes we found that 12/2276 women (0.5%) were carriers of a chromosomal translocation. Translocations detected

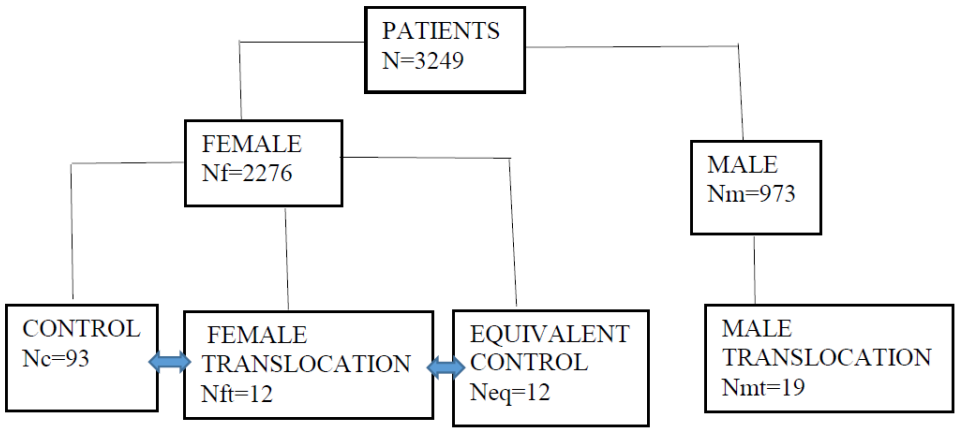

Figure 1. Patients groups.

Table 1. Comparison of age, BMI and FSH.

	Age (years)	BMI (kg/m^2)	FSH (mIU/ml)
Control (N = 93)	33.96 ± 3.70	24.32 ± 3.98	6.39 ± 1.72
Pathologic (N = 12)	36.55 ± 4.06	26.73 ± 5.36	6.54 ± 1.30
P	0.001	0.011	0.618

Table 2. Description of chromosomal translocations.

Translocation in female (N = 12)	
45, XX, rob(13;14)	46, XX, t(2;8)(q31; q22)
45, XX, rob(13;14) (q11;q11)	46, XX, t(1;19)(q1.2; q13.1)
46, XX, t(3;10)(p22;q26)	46, XX, t(5;19)(p13; p12)
46, XX, t(3;10)(p24;q26)	46, XX, t(2;10)(p22; p14)
46, XX, t(7;9)	46, XX, t(2;8)
46, XX, t(1;19)(q32;q13.3)	46, XX, t(2;12)

included 10/12 reciprocal translocations (83.33%) and 2/12 (16.67%) of Robertsonian translocations (Table 2).

Controlled ovarian stimulation

We measured total gonadotrophin administered to each patient in every cycle and the results were: 4201.39 ± 1332.14 IU for EQc, and 2532.05 ± 742.33 IU for the pathological group, with significant difference p ≤ 0.000. This confirms that the stimulation response is not affected by a higher dose of gonadotrophin administration in the translocated group, given the same results were obtained even with lower gonadotrophin dose administration.

We analysed COS response. For the analysis of the number of oocytes in MII we take the number of oocytes as covariant (F 1.300 = 1173.808; p ≤ 0.000), the latter being a significant variable. The effect of the group on the number of oocytes in MII was not significant (F 1.300 = 2.250; P = 0.135). The mean was greater in the group of patients with translocation (11.28 MII; TD = 4 51) compared to those who did not have translocation (9.68 MII; TD = 6 13) (Table 3). Control group had a mean number of mature oocytes in metaphase II (MII) (8.85 MII; TD = 5.73), while in translocation group was (11.00 MII; TD= 4.8) (F1.38 = 12,164; p = 0.01), being greater in women with translocation. When a comparison was made for both groups neutralizing the effect of the oocytes with the inter-subject effects test (not taking into account the number of oocytes extracted but only those that were in MII) we saw that there was a significant statistical difference. Regarding the maturation rate of the oocytes, control group had (87.54%; TD = 19.12) in contrast, in women with translocation it was (92.39%; TD = 13.34) (F1.38 = 1.594; p = 0.214) (t360 = -0.521; p = 0.602). When performing the intra-subject effects test for both groups, we found that there was no significant difference between the groups studied.

Table 3. Mature oocytes recovery (MII), maturation rate and embryos obtained.

Group	N cycles	MII	Maturation Rate (%)	Divided embryos
Control	264	9.68 ± 6.13	90.38	7.28 ± 5.25
Pathologic	39	11.28 ± 4.51	89.20	9.03 ± 3.53
P		0.135	0.602	0.09

When comparing the study group with the "equivalent control" (EQc), the three factors measured were compared one by one to reveal no significant differences (Table 4).

The number of zygotes with 2 pronuclei did not show significant differences (t 362 1.046; p = 0.296) between the two groups. In the study group, it was (6.34 zygotes; TD = 3.64) versus the control group (5.82 zygotes; TD = 4.42) and was higher in patients with translocations.

Comparing our results in all stimulation cycles in both groups of patients we confirmed previous results, no differences were observed in number of oocytes, division rate, fertilization rate or number of embryos obtained (Table 5; Figures 2 and 3).

Table 4. Comparison of pathological (P) and equivalent control (EQc) group.

	0=EQc 1=P	N	X ± SD	*p*
Age (years)	0	12	33.83 ± 5.18	0.536
	1	12	35.17 ± 5.20	
BMI (kg/m^2)	0	12	26.58 ± 4.28	0.883
	1	12	26.88 ± 5.43	
FSH (mIU/ml)	0	12	6.18 ± 1.85	0.825
	1	12	6.33 ± 1.50	

Table 5. Mature oocytes recovery (MII), maturation rate and number of embryos obtained.

0 = QEc. 1 = P	N	X ± SD	*p*
Number of Oocytes			
0	22	9.00 ± 5.49	
1	19	11.11 ± 5.59	0.232
Number MII			
0	22	7.86 ± 5.82	
1	19	10.05 ± 5.77	0.235
% MII			
0	22	82.58 ± 22.71	
1	19	88.37 ± 16.96	0.376
% Fertilization			
0	22	81.93 ± 25.19	
1	17	80.74 ± 25.16	0.885
Number of Embryos			
0	22	5.68 ± 3.68	
1	19	7.89 ± 4.54	0.093

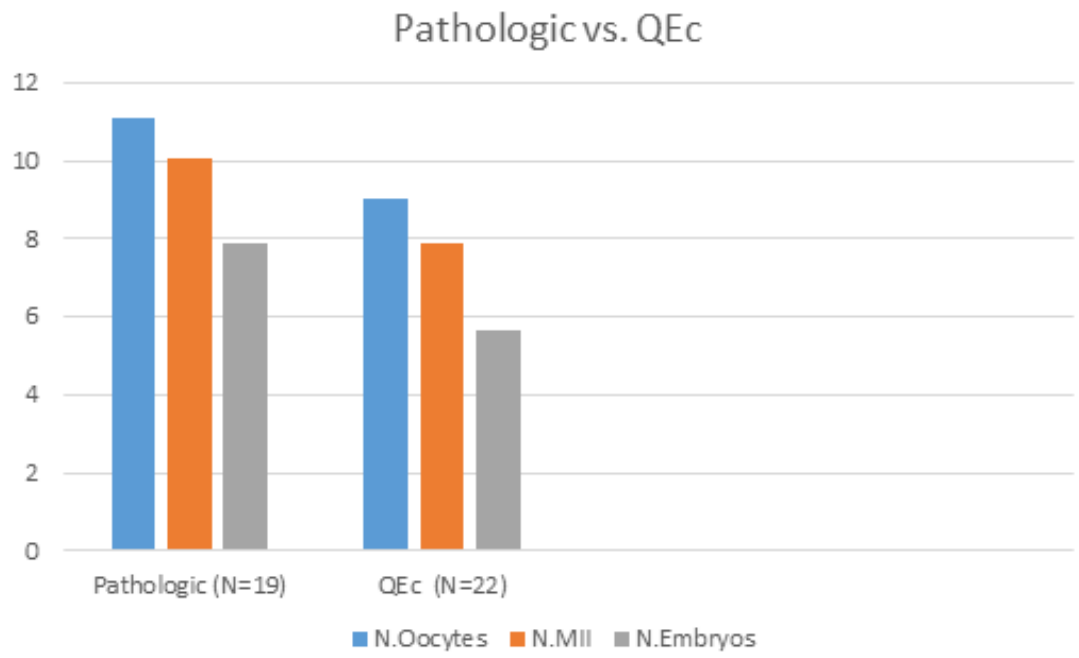

Figure 2. Results of N.Oocytes, N.MII and N. Embryos of Pathologic vs. QEc groups.

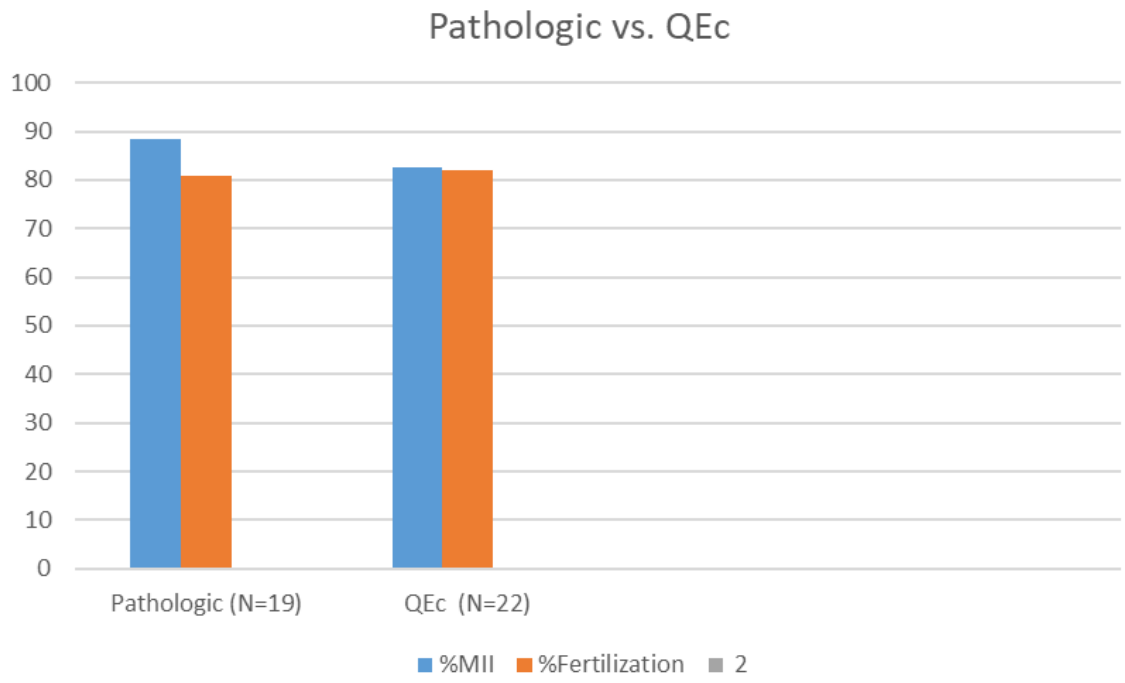

Figure 3. Maturation and fertilization rate of Pathologic vs. QEc groups.

DISCUSSION

It is known that the incidence of chromosomal translocations in general population is around 0.2%, (Jacobs et al., 1974), but this rate is increased at the infertile individuals, thus in our studied group of infertile female is 0.5%, according to expected. Patients with chromosomal translocation has been reported to have a higher risk of reproductive failure, including recurrent spontaneous miscarriage or implantation failure, and the

pattern of segregation at meiosis plays an important role on genetical inheritance of the embryos generated (Jacobs et al.,1999). It is also reported that female translocation carriers can have a lower follicular output rate than females with partner carrying the chromosomal translocation (Mayeur et al., 2020). Other studies reported that female carrier meiosis has an increased incidence of segregation type 3:1 and 4:0 compared to male carriers (Ko et al., 2010; Tease et al., 2002), meaning that female carriers present higher rates of unbalanced gametes than men carriers (Munne et al., 2000). Additionally, it is relevant to consider the known inter-chromosomal effect (ICE) that leads, especially in Robertsonian translocations, an increase in the risk of producing aneuploidy in gametes (Alfawati et al., 2012). When embryo chromosomal screenings are applied, abnormalities are revealed not only affecting the specific chromosomes involved in the translocation, but also are detected aneuploidies affecting other chromosomes as result of ICE effect (Fiorentino et al., 2011). This is a major concern to take under consideration when counselling patients about the risk of abnormal conception or probability of producing healthy embryos suitable for uterine transfer during cycles of IVF with PGT (Mardesić et al., 2011; Tulay et al., 2016). A concern we have for a successful PGT treatment is to know if balanced chromosomal translocated patients are candidates to have a diminished COS , because the better the response to drug is, the better PGT prognosis will be.

There have been several works, mainly case reports, relating a diminished follicular production or excessive apoptosis related with long arm of X chromosome implicated in a chromosomal aberration. A work reported gonadal dysgenesis in two patient's carriers of a balanced translocation (Tupler et al., 1994), with no phenotype abnormality or malformation other than ovarian failure, but the authors did not refer if that was a coincidental fact or a consequence of the balanced translocation. A case report of a young woman 18 years old with amenorrhea had associated a balanced autosomal translocation between chromosomes 1 and 11 and a clinical suggestive of hyper gonadotrophic hypogonadism (Tullu et al., 2001), and in a later reported case, the authors informed of a poor ovarian response in a 34 years old female carrier of a translocation t(1;11)(q23; p11.2) (D´Íppolito et al., 2011), highlighting the relevance of chromosome 11 in the loci p11.2, where several relevant genes are related to ovarian function and involved in oogenesis, follicular atresia and early embryo development. Another case report showed a diminished ovarian reserve in a woman with a balanced translocation of chromosomes 13 and 21, but with a familiar history of early menopause, and no other case reported in the literature with this aberration associated to diminished ovarian reserve (Kummer et al., 2009). But most of the gonadal dysgenesis have been reported associated with chromosomal translocation between X chromosome and an autosome 4, 6, 9, 12, 15 and 18 (Center et al., 1994; Larizza et al., 1993; Ji et al., 1988; Fusco et al., 2011).

Mostly, a number of cases of premature ovarian failure has been related to balanced X chromosome rearrangements, focusing on the long arm between Xq13 and Xq25/q26 (Schlessinger et al., 2002).

It was our concern to found out if balanced translocated patients can have a normal response to gonadotrophin stimulation or if there is a diminished ovarian response, compared with a control group with normal karyotype, in order to counsel the couples to undergo an IVF treatment with PGT. The literature published on this subject is not conclusive; there is, Chen et al. (2005), concluding that female carriers of a balanced chromosomal translocation are at risk for a poor response to COS, more recently supported by Mayeur et al. (2020). On the other side, the work conducted by Dechanet et al. (2011) sustains that those groups of patients had a normal pattern of response to COS and conclude that translocation did not influence the ovarian response in an IVF-PGT procedure. All those works choose as a control group, patients whose male partners were the translocation carriers. But we decided to compare our group of female carriers with a control group of infertile patients with no chromosomal aberrations in any of the partners, to compare the ovarian response to stimulation, and we found no differences. Also, because our control group was significantly younger and with lower BMI, and knowing that ovarian reserve is related to woman´s age, we made the additional comparison with an equivalent control group with no differences in age, BMI or FSH, matching a control with a pathological patient one by one, to conclude that no differences were encountered in stimulation results: number of oocytes, maturation rate, fertilization rate and embryo number. Our results are more coincident with Dechanet et al. (2011). The purpose to achieve a large embryo number available for biopsy must be determinant to select the normal ones for transfer. So, it is of major importance to have a good ovarian response to gonadotrophin stimulation. Most case reports associate chromosome translocation with ovarian dysfunction implying X chromosome, and in our patient series there are not any case involving X chromosome, so the results obtained can be not accurate for those patients. In addition to it, we had no cases with the translocation 1;11 to compare with the case reported by D´Íppolito et al. (2011). But the results obtained in our studied group conclude that there is no diminished ovarian response in the autosomal chromosomal translocated patients, confirming no different ovarian reserve, as well as no difference in maturation rate, fertilization rate or number of embryos obtained.

In conclusion, patients with a balanced chromosomal translocation must be counselled to have IVF treatment with PGT to improve pregnancy rate and diminish the incidence of recurrent pregnancy loss, particularly to

patients with a previous history of recurrent pregnancy loss, being informed of no different COS pattern than normal karyotyped females.

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