Chapter 18
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How a Chromosome Translocation Affects Gametogenesis in Human Male and Female? A Clinical Study Approach

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ABSTRACT

Purpose: To study if females with balanced translocation (BT) have a normal ovarian response compared to normal karyotype XX women. And in male with BT, to determine if spermiogram is affected compared to normal XY karyotype men.
Methods: A retrospective analysis in a public IVF centre of 3249 karyotyped patients between 2008 and 2016, 2276 women, and 973 men. Cycle parameters, oocytes and embryo outcomes were examined. Spermiogram of 19 males with BT were compared with 93 normal XY patients. And 12 women with BT were compared with 93 control normal karyotype XX group (CN). An equivalent control group (EQc) of 12 patients was also selected to be accurate with the BT statistical contrast with normal karyotype in both members of the couple. Results of all cycles were compared.
Results: 19 males (1.9%) and 12 women (0.5%) had BT. Men with BT were older than CN group (37.86 ±5.62 vs. 40.26 ± 4.18; t57,590 = -3,169, p = 0.02). Motility (A+B) in fresh was not different (44.8 ± 17.96 vs. 42,28 ± 16.60 in control vs. pathologic; p=0.423) but had a significant lower concentration of spermatozoa (37.69 ± 37.36 vs. 23.49 ± 22.75 mill/ml; t65,04 = 3,191, p = 0.002). After capacitation, progressive motility (A + B) MSR (motile spermatozoa recovery) (70.86 ± 20.57 vs. 80.25 ± 18.94 control vs. pathologic; t292 = -2,589, p = 0.010). Women BT were older than CN (36.55±4.06 vs. 33.96±3.70; p<0.001), FSH was not different (6.54±1.30 vs. 6.39±1.72; p=0.618). BMI (body mass index) was higher in BT (26.73+5.36 vs. 24.32+3.98; p=0.011). Mature MII oocytes obtained was slightly higher in BT with no statistical difference (11.28±4.51 vs. 9.68±6.13; p=0.135), similar maturation rate (90.38% vs. 89.20%; p=0.602) and higher number of divided embryos with no statistical difference (9.03±3.53 vs. 7.28±5.25; p=0.09). Comparison with EQc to avoid differences with age, BMI and FSH values, showed no statistical differences in any of the studied parameters.
Conclusions: Men with a BT have poorer factors affecting sperm quality than control normal XY males. It is recommended to provide a karyotype in males with pathologic spermiogram prior to reproductive treatment. Women carriers of a BT do not have a diminished response pattern to COS (controlled ovarian stimulation) than CN of infertile women with normal karyotype XX. In both cases, an ICSI cycle with PGT and adequate genetic counseling are highly recommended.

Keywords: Translocations; robertsonian; reciprocal; gametogenesis; fertility; ovarian response.

1. INTRODUCTION

The incidence of balanced chromosomal rearrangements in the general population is 1/500 individuals (0.2%), but in infertile patients this percentage is higher than in general population.

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Chromosomal aberrations are involved in reproductive failures, chromosomal translocations, abnormal gametogenesis, implantation failure and recurrent pregnancy loss. Chromosomal traslocations are rearrangements involving the exchange of segments between chromosomes and a significant proportion of rearrangements include additional complexity that is not visible by conventional karyotype analysis.

There are two types of translocations: Reciprocal and Robertsonian translocations. Balanced translocations are typically benign, but meiosis in germ cells with balanced translocations may result in meiotic arrest and subsequent infertility, or in unbalanced gametes, with attendant risks of miscarriage and unbalanced progeny.

Reciprocal translocations (RT) are the most common chromosomal rearrangements in humans, with a prevalence of 1 every 500-625 born in the general population [1]. 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 (ROT) two acrocentric chromosomes as 13, 14, 15, 21 and 22 fuse at the centromere [2], ROT have low impact on cell function, but when meiosis happens can produce nullisomic or disomic gametes and if fertilization takes place, originates monosomic or trisomic zygotes. The imbalance can be caused by the duplication of a chromosome segment and the other chromosome deleted. In addition, translocation carriers may have an increased risk of having descendants with physical or mental anomalies [3]. 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. Those translocations can be originated by a reciprocal exchange between two non-homologous chromosomes [4], being inherited from one of the progenitors or produced *de novo* [5]. Robertsonian translocations can be formed *de novo* (can occur in 50% of cases) or inherited from a progenitor [6,7]. The prevalence of ROT in the general population is 1.2 every 1000 people, 1.8% in couples with recurrent abortions and 2-3% of infertile men [8,9]. When this junction occurs, extremes are lost and the two chromosomes are linked giving rise to a metacentric or submetacentric chromosome [10].

Translocations will affect or not depending on the pattern of segregation in meiosis. Whether the translocation is Robertsonian or reciprocal, the only mode of segregation that will provide normal balanced gametes is alternate segregation. A study published by Zhang el al. [11] showed that the proportion of alternate segregation was lower in female than in male carriers. Although the sex of the translocation carrier does affect the segregation pattern, it does not affect the stability of non translocated chromosomes during meiosis [12].

It is known that men with ROT, even if they are phenotypically normal, present fertility problems producing an increase in the number of spermatozoa with unbalanced genetic loading ranging between 3.4% and 40% and resulting in infertility, oligozoospermia, azoospermia, oligoastenozoospermia, recurrent pregnancy loss and offspring chromosomally unbalanced [13,14,15]. On the other hand, men carriers of balanced RT present an unbalanced sperm frequency between 18.6% and 80.7% [16]. Ultimately, it is well known that infertile men with non-obstructive semen pathologies have a higher frequency of chromosomal abnormalities compared to fertile men with normal semen [17].

Besides that, we must also consider the inter-chromosomal effect (ICE) that will increase the rate of aneuploidies in gametes [18]. Only those conceptuses with minor imbalances may result in the birth of a normal child or a normal carrier.

The objective of this study is to assess possible repercussions and effects in the seminal quality when the male is the carrier of a chromosomal translocation compared to a control group of infertile patients but with normal karyotype 46 XY. In addition, to determine the relationship among female translocation carriers and controlled ovarian stimulation (COS) as well as oocytes quality, fertilization rate and embryo development at the University Hospital Complex of Canary Islands Hospital

Universitario de Canarias (CHUC), to give appropriate counselling to patients affected with a chromosomal translocation.

The main objective is to lay the foundations for the implementation of a treatment plan in a Human Reproduction unit when it comes to couples in which the male has a pathological spermiogram or a chromosomal translocation is diagnosed and when the female is the diagnosed carrier with chromosomal translocation.

It is of major importance to proceed with those patients to have an IVF treatment and a preimplantation genetic testing (PGT) to select only normal euploid embryos to transfer. 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 [19].

Furthermore, there are studies [19,20] suggesting that women carriers of a translocation may have an increased risk for poor response to COS and that it could be decisive to obtain enough embryos to select the healthy ones, before transfering to the uterus. We want to determine if the response to oocyte stimulation is lower than that of a control XX women or if it does not affect the ovarian response.

In addition, when the carrier of a chromosomal translocation is the male partner, we want to assess how it affects sperm quality and guide them to perform an Intracytoplasmatic sperm injection (ICSI) with PGT.

2. MATERIALS AND METHODS

2.1 Patients Groups

2.1.1 Female study

A retrospective study was performed in 3249 karyotyped patients, 2276 female and 973 males, attending at the Reproductive Unit of CHUC, 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 karyotype determination and other pathologies out of this study. A total of 12 female were diagnosed as chromosomal translocation carriers.

We compared age, body mass index (BMI) and female 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 female pathological patients in three items: age, BMI and FSH (Fig. 1).

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

2.1.2 Male study

A total of 19 males were diagnosed as carriers of translocations, both reciprocal and Robertsonian (pathological group) and it was randomly chosen as control group a total of 93 patients with 46 XY normal karyotype. The cycles in which we do not know the karyotype of any of the members of the couple and those cases in which had other alterations than translocation, were excluded from the control group (Fig. 1).

The variables collected were: male age, spermiogram diagnosis and seminal features (volume in fresh, fresh concentration, progressive sperm motility (A + B) in fresh, motile sperm recovery (MSR)

and spermatic progressive motility (A + B). For the diagnosis of the seminogram, the samples were evaluated following recommendations and standards of the World Health Organization [21] where the standards are classified as: Normozoospermia: Concentration ≥ 15 million / ml and ≥32% of progressive motile spermatozoa or also more than 39 million total concentration and 40% progressive motiles. Oligozoospermia: Concentration <15 million / ml. Astenozoospermia: progressive motile <32%. Oligoastenozoospermia: concentration <15 million / ml and <32% progressive motiles. Severe oligozoospermia: concentration <5 million / ml. Cryptozoospermia: Absence of sperm in the sample in fresh, but after centrifugation recovery of few spermatozoa. Azoospermia: There is a total absence of spermatozoa both from the sample in fresh and in the pellet after centrifugation.

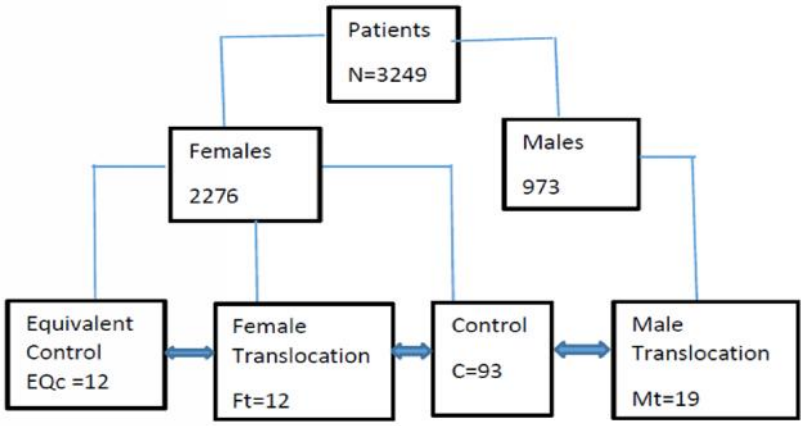

Fig. 1. Patient groups

2.2 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 of 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.

2.3 Cytogenetic Studies

Cytogenetic preparations were obtained from phytohaemaglutinin (PHA)-stimulated peripheral blood lymphocytes as described by Rooney and Czepulkowski [22]. Chromosome analysis was carried out on G-banded metaphases.

2.4 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) [23].

2.5 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.

3. RESULTS

3.1 Males

When analyzing the age of the men, we obtained for the control group and pathological group 37.86 ± 5,62 and 40,26 ± 4,18 years old respectively (t57,590 = -3,169, p = 0.02), therefore that age was significantly higher for the group of pathological males. In our infertile population, out of a total of 3249 karyotypes analyzed, 973 corresponded to males, and 19/973 (1.9%) of males presented a reciprocal or Robertsonian translocation. 11/19 (57.9%) men were carriers of reciprocal translocations and 8/19 (42.1 %) were carriers of Robertsonian translocations (Table 1).

Table 1. Male translocation diagnosed

Male Translocation
46XY, t(7;9)
45XY ,rob(13;14)
45,XY,rob(13;14)(q10;q10)
45,XY,rob(13;14)(q10;q10)
45,XY,rob(13;14)(q10;q10)
45,XY,rob(13;14)(q10;q10)
45,XY,rob(13;14)(q10;q10)
46,XY,t(14;21)(q12;q21)
46,XY,t(1;16)(q22;p13.2)
46,XY,t(3;8)(p21;p23)
46,XY,t(1;9)(q12;q12)
46,XY,der(21)t(Y;21)(q12;p11.1)
46,XY,t(X;6)(p22.3;p21.2)
46,XY,t(1;6)(q32;p23)
46,XY,t(5;11)(p10;p10)
46,XY,t(7;9)(p14;q34)
46,XY,t(4;12)(q28;q23)
46,XY,t(4,7)(p15;p15)
45,XY,rob(15;22)(q10;q10)

When comparing the parameters of the spermiogram of cycles from the two groups studied, we observe that in the group of 46 XY normal men there are 63.2% of normozoospermia (N), 10.9% of oligozoospermia (O), 6.8% of astenozoospermia (As), 13.5% of oligoastenozoospermia (OA), 2.3% of azoospermia (Az), 0.4% severe oligozoospermia (Os) and 3.0% of cryptozoospermia (Cr). Meanwhile in men carrying some translocation, we found 40.4% of normozoospermia, 12.8% oligozoospermia, 6.4% oligoastenozoospermia, 0.0% of severe oligozoospermia, 0.0% cryptozoospermia and 40.4% of azoospermia. There is a significant difference between both groups (χ21 = 8,582; p = 0.003) when the male has a translocation (Fig. 2).

Examining the seminal values, we found significant differences in the seminal volume between the groups (t292 = -6,152, p = 0.000) with average in the control group (M = 2.95 ± 1.51 ml) and in the pathological group of (M = 4.64 ± 1.67 ml). Patients with translocations present greater seminal volume. We also found significant differences between the control and the pathological group in the fresh concentration (t65,04 = 3,191, p = 0.002) with an average of (m = 37.69 ± 37.36 mill/cc) and (m = 23.49 ± 22.75 mill/cc) respectively. The concentration per milliliter in fresh is lower in pathological patients (Table 2).

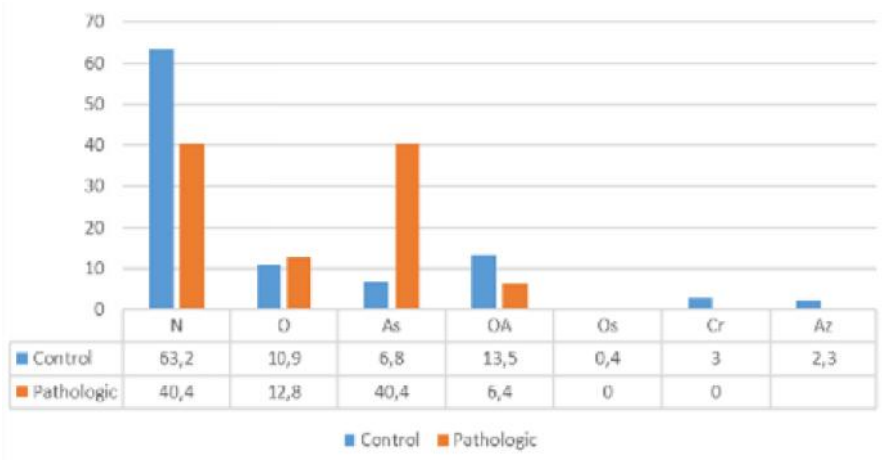

Fig. 2. Spermiogram diagnosis of pathologic vs. control group

Table 2. Spermiogram of pathologic group, (36 cycles from 19 patients) vs. control group (258 cycles from 93 patients)

SPERMIOGRAM	Group 0=Control 1=Pathologic	N	Media	SD
Volume (cc)	0	258	2.95	1.51
	1	36	4.63	1.67
Concentration	0	258	37.69	37.36
In fresh (mil/cc)	1	36	23.49	22.75
Mot (a+b) fresh	0	258	44.52	17.96
	1	36	42.26	16.60
Conc.REM (mill/cc)	0	258	30.35	30.22
	1	36	28.61	20.69
Mot. REM (a+b)	0	258	70.86	20.57
	1	36	80.25	18.94

We did not find significant differences in motility (A + B) in fresh (t292 = 0.803, p = 0.423) with a mean in the control group of (M = 44.8 ± 17.96 %) and in the pathological group (M = 42.28 ± 16.60 %). We obtained significance after capacitation in motility (A + B) MSR (t292 = -2,589, p = 0.010) with a mean in the control group of (M = 70.86 ± 20.57 %) and in the pathological group (M = 80.25 ± 18.94 %). We also did not find significant differences in the concentration in MSR (t292 = 0.314; p = 0.754) with one average in the control group of (M = 30.35 ± 30.22 mill/cc) and in the pathological group of (M = 28,67 ± 28.69 mill/cc), being slightly lower in the pathological group.

3.2 Female

Female with pathological karyotypes 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. The mean BMI in pathological female was (26.73 kg/m2; TD = 5.36 kg/m2), compared to the control group (24.32 kg/m2; TD = 3.98 kg/m2) (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 concentration in pathological females 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 any significant differences between both groups (Table 3).

Table 3. Comparison of age, BMI and FSH between pathological and control group

P vs C	Age (years)	BMI (Kg/m2)	FSH (mIU/ml)
Control (N=93)	33.96±3.70	24.32±3.98	6.39±1.72
Pathologic (N=12)	36.55±4.08	26.73±5.36	6.54±1.30
p	0.001	0.011	0.618

The Control Equivalent group (EQc) was selected to avoid any difference on those parameters and the results are showed in Table 4.

Table 4. Comparison of age, BMI and FSH between pathological and control equivalent group

P vs EQc	Age (years)	BMI (Kg/m2)	FSH (mIU/ml)
Control EQc (N=12)	33.83+5.18	26.58+4.28	6.18+1.85
Pathologic (N=12)	35.17+5.20	26.88+5.43	6.33+1.50
p	0.536 (NS)	0.883 (NS)	0.825 (NS)

In our infertile population, out of a total of 3249 karyotypes we found that 12/2276 women (0.5%) were carriers of a chromosomal translocation. Translocations detected included 10/12 reciprocal translocations (83.33%) and 2/12 (16.67%) Robertsonian translocations (Table 5).

Table 5. Description of female chromosomal translocations

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

3.3 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 $p \leq 0.000$. 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 analyze the COS response, and for the analysis of the number of oocytes in mature oocytes (MII) we take the number of oocytes as covariant (F 1.300 = 1173.808; $p \leq 0.000$), 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 6).

Control group had a mean number of MII oocytes (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 is 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.

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 6).

Table 6. Mature oocytes recovery, maturation rate and divided embryos comparing pathologic vs EQc group

P vs EQc	N Oocytes	N MII	% MII	% Fertilization	N Embryos
Control EQc (N=22)	9.00±5.49	7.86±5.82	82.58±22.71	81.93±25.19	5.68±3.68
Pathologic (N=19)	11.11±5.59	10.05±5.77	88.37±16.96	80.74±25.16	7.89±4.54
p	0.23	0.24	0.38	0.89	0.09

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 6; Figs. 3 and 4).

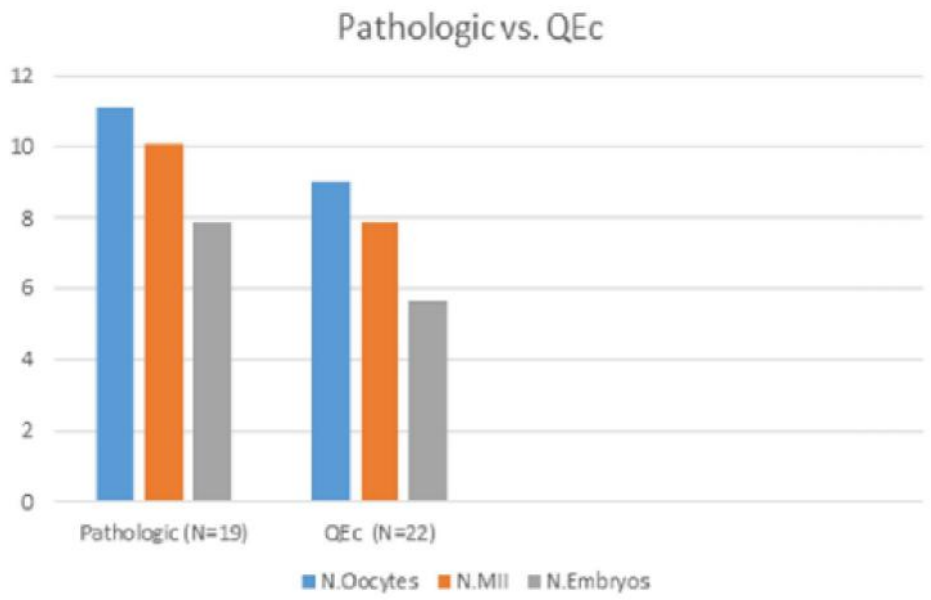

Fig. 3. Comparison of N. of oocytes, N. of MII and N. of embryos between pathologic group and QEc group

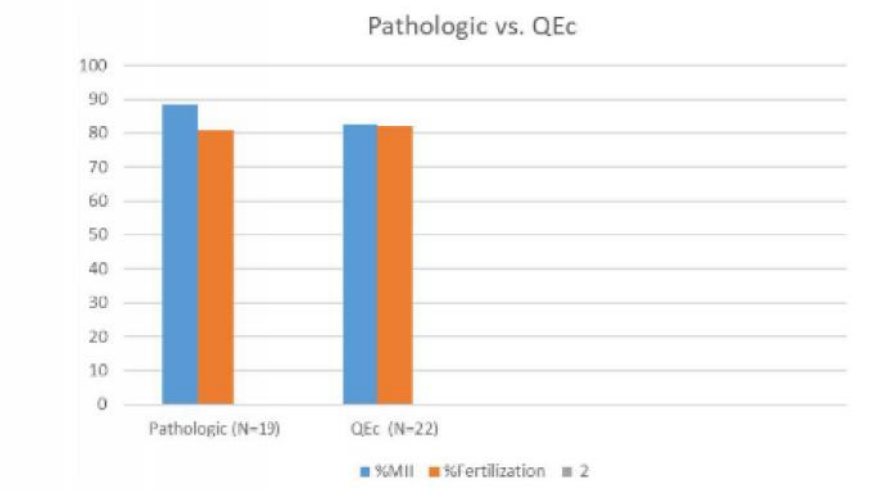

Fig. 4. Results of maturation rate and fertilization rate between pathologic group and EQc group

4. DISCUSSION

It is known that the incidence of chromosomal translocations in general population is around 0.2% [24], but this rate is increased at the infertile individuals, so that in our studied group of infertile females is 0.5%, according to expected. Patients with chromosomal translocations 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 [25]. Additionally, it is relevant to consider the known inter-chromosomal effect (ICE) that leads, especially in Robertsonian translocations, to a generalised increase in the risk of producing aneuploidy in gametes [18]. 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 a result of the ICE effect [26]. 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. Another worry we have for a successful PGT treatment is to know if balanced chromosomal translocated female patients are candidates to have a diminished ovarian reserve and if will manifest a poor response in an ovarian controlled stimulation, because the better the response to drug is, the better the 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. One study reports gonadal dysgenesis in two patient's carriers of a balanced translocation [27], with no phenotype abnormality or malformation other than ovarian failure, but the authors do not mention wether it was a coincidental event or a consequence of the balanced translocation. Further, 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 [28]. Another case report shows 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 [29]. But most gonadal dysgenesis has been reported in association with chromosomal translocation between the X chromosome and an autosome 4, 6, 9, 12, 15 and 18 [30,31,32,33].

It was our concern to find out if balanced translocation patients may have a normal response to gonadotrophin stimulation or if there is a diminished ovarian response, compared to a control group with normal karyotype, to guide the process for couples to undergo an IVF treatment with PGT. The literature published on this subject is not conclusive; on one side there is the Chen et al. work [13]

concluding that female carriers of a balanced chromosomal translocation are at risk for a poor response to ovarian stimulation. On the other side, the work conducted by Dechanet et al. [34] sustains that those groups of patients had a normal pattern of response to ovarian stimulation and conclude that translocation did not influence the ovarian response in an IVF-PGT procedure. Both studies chose as a control group patients in whom the translocation carrier was the male partner. But we decided to compare our group of female carriers with a control group of infertile patients without chromosomal aberrations in any of the partners to compare the ovarian response to stimulation, and we found no differences between groups. 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 are encountered in stimulation results: number of oocytes, maturation rate, fertilization rate and embryo number. Our results are more coincident with Dechanet et al. conclusions. The purpose to achieve a large embryos number available for biopsy must be determinant to select the normal ones for transfer. Therefore, it is of utmost 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. But the results obtained in our study group conclude that there is no decrease in the ovarian response in chromosomal translocated patients, which confirms no different ovarian reserve, as well as no difference in the maturation rate, fertilization rate or number of embryos obtained.

Nevertheless, female translocated carriers are known to have a less stringent checkpoint of germline cells, compared to males, to repair and activate the apoptosis proceeding to eliminate abnormal oocytes from unbalanced meiotic segregation [35]. This is the reason for females to have a higher proportion of 3:1 segregation pattern and a diminished proportion of alternate segregation than males [12].

On the other side, when the carrier of the translocation is the male, the prevalence of chromosomal alterations is greater in infertile males, in fact, the probability of finding an altered karyotype is inversely proportional to the spermatic count. The carriers of a chromosomal translocation have an increased risk of having a reproductive failure or affecting the offspring due to producing unbalanced gametes.

In the general population, it is known according to the bibliography already published [8,36] that the percentage of reciprocal translocation is around 0.2% while the Robertsonian translocations is around 0.12%. It is known that this percentage is increased in infertile couples (0.6%) compared to the general population [37]. And it is greater this frequency in individuals with implantation failures (1.4%), and especially in individuals of couples with repeated abortions (4.1%) [38]. Studies of large series like that of Gekas J. et al. [39] get among a population of infertile patients a frequency of 1.23 % of males with RT and 0.82% with ROT. According to these publications, in our study we have found that monitoring a population of infertile patients, the index of translocations we have found is 1.9% in male carriers of chromosomal translocation, 1.13% RT and 0.82% of ROT, so we can say that our population of infertile males is adjusted to the expected frequencies of translocation carriers.

Since we know the existence of the apoptosis phenomenon, selective process that excludes the proportion of germinal cells unbalanced during spermatogenesis and that alters the spermatic parameters of these infertile men, we know that those patients who present translocations, theoretically must have a higher incidence of oligozoospermia and azoospermia due to this phenomenon [40,36], [41]. Following this principle, we check in the present study that effectively the population of males with a translocation have a sperm count significantly lower than the control group, highlighting the diagnosis of azoospermia with more prevalence even that of oligozoospermia. In addition, when we study the frequency of a sperm pathology due to genetic alteration, we observe that there is a higher incidence of males with azoospermia and severe oligozoospermia (according to guide 22 of SEF(Spanish Society of Fertility)) [42], which leads us to be able to affirm that in the cases in which couples are treated where male presents some of these sperm pathologies, it is indicated to

carry out the study of the karyotype as an initial test of the couple study to discard possible structural alterations such as reciprocal and Robertsonian translocations .

The condition of aneuploid / euploid of the gametes obtained after meiosis depends on the types of meiotic segregation (alternating, adjacent I, adjacent II, 3: 0, 3: 1 and 4: 0) predominant in each patient translocation carrier and the influence of the intercomosomal effect phenomenon (ICE). In studies like the one developed by Benet et al. [16], indicate a percentage of aneuploid gametes in male patients carriers of reciprocal translocation ranging between 18.6% and 80.7% while the percentage of Robertsonian translocations ranges between 3.4 % and 40% [14]. Since *a priori* in patients carriers of a translocations we do not know what kind of segregation is being dominant, it is recommended in those cases to perform a FISH in spermatozoa to determine what would be the probability of obtaining healthy embryos and later being able to provide a genetic advice to the couple [43].

Analyzing the results of our semen determinations we can state that the detection of a chromosomal rearrangement in the karyotype of a patient has a negative correlation on the sperm concentration [44,45], since patients carrying some translocation have a decrease in sperm concentration in fresh compared to control subjects, also observed by other authors [40]. Fresh concentration has greater rigor diagnosis that the concentration in MSR because it allows a seminal diagnosis of pathology, while concentration of MSR is variable depending on the volume of media used on resuspension and the training technique used, and that is the reason why in our study we have centered on the seminal parameters in fresh. In published studies of male chromosomal aberrations like the one performed by Van Assche et al., correlate these with a decline in sperm motility, fact that is not confirmed in our study in fresh samples, but observed significatively after sperm capacitation, what indicates that it would be interesting to expand the number of patients studied with this pathology to confirm this observation. When a male has a low sperm concentration or an increased anomalous morphology and present a normal karyotype, it is known to have an increased risk to have aneuploidies in the sperm, especially in sexual chromosomes. However this fact is not confirmed when he presents a decrease in motility [46]. Therefore, the results obtained in the present study regarding sperm motility does not determine when setting guidelines of clinical performance according to the Andrology Manual of the Spanish Society of Fertility [Brasesco et al., 2011]; [47], The study of male sterility should systematically include the karyotype and the study of aneuploidies in the spermatozoa using the technique of FISH, therefore, it is recommended that for patients with low motility or sperm concentration to perform a diagnostic test to make an estimate of the percentage of affected sperm and determine the probability of having a chromosomal alteration in the offspring and therefore in these cases recommend a preimplantation genetic test, PGT.

5. CONCLUSION

When a woman is carrier of a chromosomal translocation, has a normal ovarian response to a COS with no diminished obtention of oocytes and embryos than women with a normal XX karyotype.

And when in the study of the sterile couple the male is diagnosed with a pathologic finding with a reduced sperm concentration, asthenozoospermia, severe oligozoospermia or cryptozoospermia, a karyotype must first be performed to rule out possible chromosomal alterations. The realization of a FISH in spermatozoa is also indicated to those male patients who present severe oligozoospermia, in couples with idiopathic sterility, in implantation failures and males of couples with repeating abortions, since these could be carriers of a translocations.

In addition, 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 miscarriage, particularly to patients with a previous history of recurrent pregnancy loss, being informed the female carriers of no different COS pattern than normal karyotyped females.

Furthermore, in future, the issues of genetic counseling should be treated with an increasingly particular attention focused on fertility care, within the framework of the open coordination method with other health professionals in the field of human reproduction.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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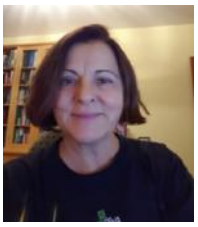

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