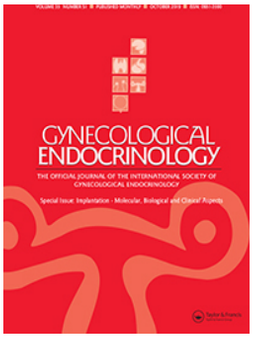

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ORIGINAL ARTICLE

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The application of PGT-A for carriers of balanced structural chromosomal rearrangements

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ABSTRACT

The aim of this study was to analyze differences in chromosomal aberrations and euploidy in embryos of each translocation type and gender of carrier in the case series of 10 couples with balanced translocations who underwent IVF with embryos trophectoderm (TE) biopsy and PGT-A to detect chromosomal aberrations. This is a Case Series (Retrospective study). In each case, controlled ovarian hyperstimulation, oocyte insemination with intracytoplasmic sperm injection (ICSI) and cultivation gave multiple blastocysts, that underwent trophectoderm (TE) biopsy with PGT-A analysis using aCGH and NGS. Number of total unbalanced translocations compared to the number of sporadic aneuploid embryos was 39.6% to 39.6% (50% to 50% of all 37 aneuploid embryos). The highest euploidy rate was in male carrier group – 26.7% and the lowest in the Robertsonian translocation carrier group – 18.2%. Sporadic aneuploidy – 68.2% was highest in Robertsonian translocation carrier group and lowest in female group – 11.1%. Chromosomal aberrations related to translocation were highest in female carrier group – 77.8% and lowest in Robertsonian translocation carrier group – 13.6%. Our study showed that expectancy of total embryo aneuploidy rates will be higher in carriers, than in people with normal karyotype. The prevalence of chromosomal aberrations related to translocation was 4.5 times higher in Reciprocal carrier group than in Robertsonian translocation carrier group. Among maternal and paternal carrier groups, the embryos from female carriers had the lowest euploidy rate, unbalanced translocation rate 4.7 times higher than in the male carrier group and higher total aneuploidy rates.

KEYWORDS

IVF; balanced chromosomal translocations; Robertsonian translocation; reciprocal translocation; embryo aneuploidy; PGT-A

Introduction

From population-based congenital anomaly registers in Europe more than 10,000 cases with a chromosomal abnormality are described, giving a total birth prevalence rate of 43.8/10,000 births [1]. This accounts for ∼15% of the major congenital anomalies diagnosed before the age of 1 year in Europe, and are associated with 25% of perinatal deaths [2]. It is known that patients with recurrent pregnancy loss, previous IVF failures, and prior aneuploid pregnancies have a significantly higher and age-independent aneuploidy rate compared to patients without infertility [3]. Abnormal karyotype in one of the parents is a serious additional problem on the way to a successful pregnancy. As described by S. Munne [4] among 1284 couples with recurrent miscarriage, 58 (4.5%) are carriers of translocations. In the next pregnancy couples carrying reciprocal translocations ($n = 47$) miscarries significantly more often (68%), compared to only 28% for couples without structural chromosomal abnormalities [4].

Together with development of molecular genetics IVF clinics use Preimplantation Genetic Testing for aneuploidies (PGT-A) to test embryos and select for transferring those without chromosomal abnormalities [5].

In the past, for an attempt to detect balanced and unbalanced chromosomal translocations, translocation breakpoint-specific and closely flanking fluorescence *in situ* hybridization (FISH) probes have been used to detect both structural and numerical aberrations in either interphase cells or in polar bodies [6,7].

Now abnormalities in embryos are measured with the new generation of methods, including comparative genomic hybridization (CGH), microarrays (aCGH and single nucleotide polymorphism arrays), quantitative polymerase chain reaction, and next-generation sequencing (NGS). These methodologies allow comprehensive chromosomal analysis, provide high accuracy, and have yielded encouraging preliminary clinical data [8]. Studies show, that the ongoing pregnancy rate per initiated cycle after array comparative genomic hybridization is significantly higher than after fluorescent *in-situ* hybridization in all translocation carriers (36.4% vs 9.0%; $p = .010$) [9].

Balanced rearrangements represent one of the most common forms of genetic abnormality affecting ∼1 in every 500 (0.2%) individuals. Difficulties processing the abnormal chromosomes during meiosis lead to an elevated risk of chromosomally abnormal gametes, resulting in high rates of miscarriage and/or children with congenital abnormalities [10].

These rearrangements in embryos may occur as a *de novo* event or can be the product of abnormal karyotype of one of the parents. Carriers of balanced translocations are most often identified by karyotyping or by genetic analysis of products of conception after embryonic demise with subsequent karyotyping of parents [11]. Two types of balanced structural chromosomal

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Table 1. Patients data of karyotype, number and grade of obtained blastocysts with PGT-A results.

No.	Gender	Age	Karyotype	Blastocysts analyzed	Blastocysts grade	PGT-A results
1	Female	35	46,XX,t(1;6) (p22;p25)	4	1) BC3BB	1) arr1p36.331p22.1(102664–92589017)x1, 6p25.3p24.3(103351–8874411)x3;
					2) BC3BB	2) arr1p36.331p22.1(102664–92589017)x3,6p25.3p24.3(103351–8874411)x1;
					3) BC4AA	3) arr(1–22)x2,(XY)x1;
					4) BC3AB	4) arr1p36.331p22.1(102664–92589017)x1,6p25.3p24.3(103351–8874411)x3
2	Male	46	46, XY,t(4;12) (q31;q13)	4	1) BC3BB	1) arr4q32.3q35.2(169102980–190815481)x1,12q21.1–q24.33(72408753–133435933)x3
					2) BC3BA	2) arr16p13.3p12.2(137326–23760229)x3
					3) BC2BB	3) arr(1–22,X)x2
					4) BC3AB	4) arr(1–22,X)x2
3	Female	34	46,XX,t(9;17) (p10;p10)	3	1) BC2BB/3/D	1) arr9p24.3q13(104476–66534426)x1, 17p13.3p11.2(556474–20230594)x1
					2) BC2BB/2/A	2) arr(9)x1
					3) BC2BB/5/A	3) arr(1–22)x2, (XY)x1
4	Female	32	46,XX,t(6;10) (p21.3;q22.3)	1	1) BC3BB	1) arr(2)x1?2,6p25.3p21.32(672168–3233433100)x1, 10p23.1q26.3(82574455–135336967)x3,(12–22,X)cx
5	Male	28	46,XY,t(1;3) (q12;q29)[4]/ 46,XY[15]	4	1) BC2BB/4/A	1) seq[GRCh37]dup(4)(p16.3q31.21)chr4:g. 602,531_144,926,382 del(4)(q31.21q35.2)chr4:g.146,137,523_190,874,077
					2) BC3BB/4/A	2) seq[GRCh37](1–22)x2, (XY)x1
					3) BC3BB/4/B	3) seq[GRCh37](1–22)cx (21)x1?2
					4) BC3AB/5/D	4) seq[GRCh37] (1–22,X)x2
6	Female	31	46,XX,t(13;20) (q34q13)	6	1) BC2BC/5/A	1) seq[GRCh37](1–22)cx dup(13)(q12.11q33.3) chr13:g.19,812,720_108, 833, 167 del(13) (q34q34)chr13:g. 110,994,782_114, 494, 829 del(20) (p13q13.2) chr20:g. 621, 362_52, 103, 980 dup(20) (q13.2q13.33) chr20:g. 53,221,087_62,715,666
					2) BC2BB/5/A	2) seq[GRCh37] (1–22,X)cx dup(13) (q12.11q 33.3) chr13:g. 19,812,720_108,833,167 del(13) (q34q34) chr13:g. 110,994,782_114,494, 829 del(20) (q13.2q13.33) chr20:g. 53,221,087_62,715,666
					3) BC2AB/5/A	3) seq[GRCh37]dup(13) (q12.11q33.3) chr13:g. 19,812, 720_108, 833, 167 del(13) (q34q34) chr13:g. 110,994, 782_114,494,829 del(20)(p13q13.2) chr20:g. 621, 362_52, 103,980 dup(20)(q13.2q13.33) chr20:g.53,221,087_62,715,666
					4) BC2AB/4/A	4) seq[GRCh37](1)x1del(13) (q34q34) chr13:g. 110,994,782_114,494,829(17)x1 dup(20) (q13.2q13.33) chr20:g. 53,221,087_62,715,666 del(20) (q13.2q13.33) chr20:g. 53,221,087_62,715,666
					5) BC3BB/5/BG	5) seq[GRCh37]dup(13)(q12.11q33.3) chr13:g. 19,812,720_108, 833,167 del(13) (q34q34) chr13:g.110,994, 782_114,494,829
					6) BC2BB/5/A	6) seq[GRCh37]del(13)(q34q34) chr13:g. 110,994,782_114,494,829 dup(20) (q13.2q13.33) chr20:g.53,221,087_62,715,666
7	Female	36	46,XX,t(8;11) (p23;p15)	4	1) BC2AB/5/A	1) seq[GRCh37]del(8)(p23.3p23.1) chr8:g.663,894_9,478,357, dup(11)(p15.5p15.4) chr11:g.721,142_6,682,406,(13)x1, (14)x1
					2) BC2BC/CC/5/A	2) seq[GRCh37]dup(X)(p22.33p22.12)chrX:g.3,354,528_21,343,697
					3) BC5BC/CC/1/D	3) seq[GRCh37] dup(8)(p23.3p23.1) chr8:g.663,894_9,478,357, del(11) (p15.5p15.4)chr11:g.663,894_6, 682,406
					4) BC3AB/2/A	4) seq[GRCh37]del(6) (q26q27)chr(6):g.161, 462,989_170,976,006,cxmos

(*continued*)

Table 1. Continued.

No.	Gender	Age	Karyotype	Blastocysts analyzed	Blastocysts grade	PGT-A results
8	Male	46	45,XY,der(13;14)(q10;q10)	1 cikls-2 2 cikls-12	1) BC2BB/5/D 2) BC2BB/5/A 3) BC2BB/5/A 4) BC2BB/4/A 1) BC2BB/5/A 2) BC2BB/2/A 3) BC3BB/4/A 4) BC3AB/5/A 5) BC3AA/5/A 6) BC3BC/3/D 7) BC3AB/1/C 8) BC3AA/1/C 9) BC3BB/5/A 10) BC3BB/5/A 11) BC2BB + cells/2/A 12) BC3BB/2/A	1) arrmos(2)x1, 11q23.2q25(114304322–134564974)x1 2) arr(15)x1,(16)x3 3) arr(16)x1 4) arr(13)x1,(16)x1 1) arr(16)x1 2) arr18q21.2q23(49776191–77856022)x1 ~ 2 3) arr2q12.2q37.3(10656227–242058943)x1 ~ 2,6q23.3q27(138010907–170931603)x1 ~ 2; 4) arr(1–22),(XY)x1 5) arr(1–22),(XY)x1 6) arr(22)x1 7) arr(1–22,X)x2 8) arr(16)x3 9) arr(4)x3,(16)x3 10) arr(1–22)x2,(XY)x1 11) arr(4)x1, (19)x3 12) arr(16)x3
9	Male	40	45,XY,der(13;14)(q10;q10)	1 cikls-2 2 cikls-0	1) BC2AB 2) BC3BB	1) seq[GRCh37]6q13q27 (75,871,171–170,976,006)x1 2) seq[GRCh37](1–22)cx
10	Male	35	45,XY,der(13;14)(q10;q10)	4	1) BC2BB 2) BC3AB 3) BC3BB 4) BC3BB	1) seq[GRCh37](1–22,X)cx(13)x1,(21)x3 2) seq[GRCh37](1–22)cx (21)x23 3) seq[GRCh37]del(12)(q12q24.33) chr12:g. 44, 629,644_133,380,179 4) seq[GRCh37](1–22)cx(13)x12,(16)x1

rearrangements are known – Robertsonian translocations and reciprocal translocations.

Robertsonian translocations (ROBs) are chromosomal rearrangements that result from the fusion of the entire long arms of two acrocentric chromosomes. Robertsonian translocations are one of the most frequent reorganizations in humans. Most of the cases analyzed correspond to rearrangements with chromosomes from the D-group (chromosomes 13, 14 and 15), whereas some rare Robertsonian translocations are scarcely found in the literature, mainly those with both chromosomes from the G-group (chromosomes 21 and 22) and those involving chromosomes from both groups (D;G translocations) [10,12,13].

Reciprocal translocation is a type of chromosome rearrangement that is involved in the exchange of chromosome segments between two chromosomes that do not belong to the same pair of chromosomes [14].

Materials and methods

Study subjects

From the 36 patients with changes in karyotypes that were found in IVF Riga clinic from period 2013–2018 10 patients undergoing IVF with TE biopsy for PGT-A and who signed informed consent were eligible for the study. Three patients were with the most frequent type of Robertsonian translocation from the D group (between 13 and 14 chromosomes) and seven patients with various reciprocal translocations. One hundred and eighty oocytes were collected, 140 fertilized normally, 90 embryos were frozen, 69 were biopsied, and 48 from those were analyzed with PGT-A.

Parental karyotype

Parental karyotyping was performed using classical G band cytogenetic approach. Peripheral blood cells (lymphocytes) were cultivated for 72 h in the PB-MAX^{TM} Karyotyping Medium. The colcemide solution was added and put to a thermostat to stop the cell division. Fixative, consisting of methanol and acetic acid, was added to each sample of cells. Processed cells in their metaphase state were fixated on the glass slide with chromosome staining using Giemsa stain. At least 15 metaphases analyzed for each patient with a microscope using Lucia Kario software program. Karyotype was analyzed based on the International System for Human Cytogenomic Nomenclature (ISCN 2016) criteria.

Ovarian stimulation, insemination, and embryo biopsy

Controlled ovarian stimulation was performed using recombinant follicle-stimulating hormone (Follitropin Alfa) and gonadotropin-releasing hormone antagonist (Ganirelix acetate injection or Cetrorelix acetate). All the dosages were used considering ovarian reserve and anti-mullerian hormone values in patients medical histories. When the lead follicle reached its mean diameter 18–20 mm, 6500 IU human chorionic gonadotropin agonist (hCG) were injected subcutaneously for ovulation induction. Oocyte retrieval was performed 35–36 h after hCG injection, and all metaphase II oocytes underwent intracytoplasmic sperm injection (ICSI). Before the procedure, the quality of sperm of 7 out of 10 men were analyzed with main semen analysis test, semen functional test, and semen fragmentation test.

Embryos were grown in Life Global cultivation media. On day five when embryos have reached the blastocyst stage, assisted hatching was performed with the creation of a circular opening

Table 2. The rates of embryo aneuploidy and euploidy in total, balanced translocation, and gender groups.

Population	No.of embryos	Unbalanced translocation rate, %	Sporadic aneuploidy rate, %	Total abnormality rate, %	Euploid rate, %
Total	48	39.6%	39.6%	79.2%	20.8%
Robertsonian translocation	22	13.6%	68.2%	81.8%	18.2%
Reciprocal translocation	26	61.5%	15.4%	76.9%	23.1%
Maternal	18	77.8%	11.1%	88.9%	11.1%
Paternal	30	16.67%	56.67%	73.3%	26.67%

in the zona pellucida for trophectoderm (TE) biopsy. Five to ten TE cells were aspirated with a biopsy pipette and the specimens were cleaved. Embryo vitrification was performed using Kitazato vitrification cryotop method.

Comprehensive chromosomal screening

Whole genome amplification from TE cells was done using SurePlex reagent kit, electrophoresis was done to confirm successful DNA amplification and exclude amplification in negative amplification controls. PGT-A was done using aCGH Illumina 24Sure arrays or using NGS – Illumina VeriSeq PGS kit. For analysis BlueFuse software was used for both approaches.

Statistical analysis with statistical significance level was not done due to small patient group.

Results

A total of 180 oocytes were collected, 140 (77.8%) fertilized normally, resulting in 90 (64%) embryos that reached the maturation stage on day 5. A biopsy was performed to 69 blastocysts and PGT-A was done for biopsies from 48 embryos (Table 1). Total abnormality rate from the 48 embryos were 79.2% (10 – euploid, 38 – with chromosomal structural aberrations or aneuploidies) (Table 2). Number of total unbalanced translocations compared to the number of sporadic aneuploid embryos was 39.6% to 39.6% (50% to 50% of all 37 abnormal embryos).

In 22 embryos, that were analyzed from the carriers of Robertsonian translocations the rate of unbalanced translocations was 81.8%, whereas from the Reciprocal translocation carrier group the unbalanced translocation rate in embryos was 76.9%.

In 18 embryos from 5 couples where female was a carrier of balanced translocation, with the mean age of 33.6 (ranged from 31 to 36 years), and 30 embryos from 5 couples where male was a carrier of balanced translocation, with the mean age of 39 (ranged from 28 to 46 years), the percentage of unbalanced translocation rate in embryos resulting from woman compared to men were 88.9% and 73.3%.

The highest euploidy rate was in male carrier group – 26.7% and the lowest in the Robertsonian translocation carrier group – 18.2%. Sporadic aneuploidy of 68.2% was highest in Robertsonian translocation carrier group and lowest in female carrier group – 11.1%. Unbalanced translocation rate in embryos was highest in female carrier group – 77.8% and lowest in Robertsonian group – 13.6%.

One female patient with a reciprocal translocation between 13 and 20 chromosomes had unbalanced chromosomal translocations inherited from mother in all six tested embryos. One male patient with type D Robertsonian translocation between 13 and 14 chromosomes had aneuploidy in 12 embryos from 16 tested and only one of them had aneuploidy associated with abnormal karyotype.

After PGT-A results were obtained, 5 of 10 female patients needed new stimulation as PGT-A showed 0 euploid embryos. In 1 female patient with reciprocal translocation, pregnancy did not occur after FET. 1 patient, whose husband was carrier of reciprocal translocation, naturally got pregnant. Two patients got pregnant after IVF with husbands being Robertsonian and reciprocal translocation carriers. One child was born from woman-reciprocal translocation carrier (Table 3).

Discussion

We have shown that additional whole chromosome aneuploidies detected by aCGH and NGS diagnosis on embryonic material from translocation carrier parents persist and are widespread in 79.2% of embryos. The 4 different publications had described the rate of abnormal embryos in their study. Mean percentage of chromosomal aberrations between four of them were 79.5%, (69.4% [15], 85.5% [16], 84% [17], 79% [18]), which makes it fairly close to our findings. In the comparison between the balanced translocation type, the difference in unbalanced chromosomal translocations in embryos between Robertsonian and Reciprocal translocation carriers are not that high – 81,8% to 76,9%, with a slight prevalence from the carriers of Robertsonian translocations. There are conflicting data about this aspect. For example in one study on 432 PGD of translocation cycles performed by 'Reprogenetics', indicated that on average 72% of embryos from Robertsonian translocation cycles and 82% of reciprocal translocation cycles are abnormal [4]. In the other article, patients with Robertsonian translocations produced a larger number of normal/balanced embryos than those with reciprocal translocations, 76% versus 33% [19].

If we look at the sporadic and unbalanced chromosomal aberration rates in embryos between Robertsonian and reciprocal translocation carriers we can see that prevalence of sporadic abnormality events is almost 5 times higher than unbalanced translocations in embryos in the Robertsonian translocation carrier group. Where the results in reciprocal translocation carrier group are opposite – unbalanced translocation rates are 4 times higher than sporadic aneuploidies. In one of the studies, the sporadic aneuploidy rates that were related to Robertsonian translocation was 31%, wherein reciprocal translocations was 6% [20]. More sporadic events in Robertsonian translocations carriers than in reciprocal translocation carriers were shown in the article of 122 informative sibships, where numbers were 74% and 25% [21]. This could lead to suggestion that despite the prevalence in abnormality from Robertsonian translocation carriers, in this group it is less likely to get translocation – related abnormality, thus increasing the probability of getting pregnant. There have been few studies that proved this statement. The incidence of spontaneous abortion is nearly 50% in balanced reciprocal translocation carriers and between 20 and 25% in carriers of balanced Robertsonian translocation families [22]. From the total number of 629 embryos, 21.9% were detected as normal or with balanced translocation – 25.2% in couples with balanced Robertsonian translocation and 16.4% with balanced reciprocal translocation. Embryo transfer was performed in 30 cycles

Table 3. All the patient's pregnancy history with data of ovarian stimulation, insemination, embryo biopsy with current results.

PairNo.	Karyotype	Pregnancy	Childbirth	Children	Pregnancy with fetal abnormality	Life-born child with pathology	Obtained oocytes	Fertilized oocytes	Obtained blastocysts	Biopsied blastocysts	Blastocysts analyzed	Euploidy	Aneuploidy	Results
1	46,XX,t(1;6) (p22;p25)	0	0	0	0	0	18	9	8	5	4	1	3	Pregnancy did not occur
	46,XY			0		0								
2	46,XX	1	0	0	0		8	8	5	4	4	2	2	Natural pregnancy
	46, XY,t(4;12) (q31;q13)			0		0								
3	46,XX	0	0	0	0	0	1 cycle-13 2 cycle-21	1 cycle-11 2 cycle-18	1 cycle-4 2 cycle-13	1 cycle-4 2 cycle-12	1 cycle-4 2 cycle-12	4	2	Pregnant after IVF
	45,XY,der(13;14) (q10;q10)			0		0								
4	46,XX,t(9;17) (p10;p10)	0	0	0	0	0	18	14	8	4	3	1	2	1 child after IVF
	46,XY			0		0								
5	46,XX,t(6;10) (p21.3;q22.3)	1	1	1	0	0	13	5	5	4	1	0	1	Needs new stimulation
	46,XY			0		0								
6	46,XX	1	1	1	0	0	1 cycle-11 2 cycle-4	1 cycle-9 2 cycle-3	1 cycle-9 2 cycle-0	1 cycle-2 2 cycle-0	1 cycle-2 2 cycle-0	0	2	Needs new stimulation
	45,XY,der(13;14) (q10;q10)			0		0								
7	46,XX	0	0	0	0	0	24	20	16	15	4	2	2	Pregnant after IVF
	46,XY,t(1;3) (q12;q29)[4]/46,XY[15]			0		0								
8	46,XX,t(13;20) (q34q13)	2	0	0	1	0	8	8	8	6	6	0	6	Needs new stimulation
	46,XY			0		0								
9	46,XX,t(8;11) (p23;p15)	3-5	1	1	0	0	25	18	5	4	4	0	4	Needs new stimulation
	46, XY			1										
10	46,XX	2	0	0	0	0	17	17	9	9	4	0	4	Needs new stimulation
	45,XY,der(13;14) (q10;q10)		0	0		0								

(68.2%) in couples with balanced Robertsonian translocation and 27 (54%) in couples with balanced reciprocal translocations [23]. Among the balanced reciprocal translocation group, the live delivery rate was 8.3% per ovum pick-up cycle and 18.2% per embryo transfer cycle and among the balanced Robertsonian translocation group, the live delivery rate was 14.3% per ovum pick-up cycle and 20.0% per embryo transfer cycle [24]. The percentage of embryos consistent with normal or balanced segregation (55.1% vs. 27.1%) and clinical pregnancy (62.5% vs. 19.2%) rates were higher in Robertsonian than the reciprocal translocation from male carriers [25]. A difference between carriers of reciprocal and Robertsonian translocations in terms of the proportion of abnormal embryos and structurally normal chromosomes was 63.3% vs. 27.5%, and 1.1% vs. 0.3%, respectively [26].

Between male and female carriers, it seems that not only total aneuploidy rates are higher in the maternal group, but the percentage of embryos related to translocation is 4.7 times higher than in the paternal group, even after taking into account maternal age. This also could lead to a thought, that if a mother is a carrier of translocation, the percentage of miscarriages and abnormalities in fetuses will be more frequent than from male carriers. Statistically significant difference in the rate of embryos with unbalanced translocations between male and female translocation carriers (12% vs. 24%; $p < .5$) has been described [27].

Studies, where patients with balanced translocations in all possible aspects are compared are not that many and we need to gain more proof for the purpose of more effective consultation and evaluation of patients with balanced chromosomal changes and prognostic accuracy of embryos that are aneuploid.

Our study showed that expectancy of total embryo aneuploidy rates will be higher in carriers, than in people with normal karyotype. The prevalence of aneuploidy related to translocation is 4.5 times higher in balanced reciprocal translocation carrier group, than in balanced Robertsonian translocation carrier group. Among maternal carrier and paternal carrier groups, the embryos from female carriers have the lowest euploidy rate; have unbalanced translocation rate 4.7 times higher than in the male group and higher total aneuploidy rates.

Compliance with an ethical standard

The study follows principles of the Declaration of Helsinki.

Disclosure statement

The authors declare that they have no conflict of interest.

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