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Short Communication

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Preimplantation Genetic Testing for Couples with Balanced Chromosomal Rearrangements

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Abstract

Background: Chromosomal rearrangements play an important role in infertility. Carriers of chromosomal rearrangements have a lower chance of producing normal or balanced gametes due to abnormal segregation of chromosomes at meiosis, which leads to recurrent spontaneous abortions and infertility. Preimplantation genetic testing for structural chromosome rearrangements (PGT-SR) is offered to couples who have balanced chromosomal rearrangements in order to select embryos with a balanced karyotype prior to implantation, thereby increasing the chances of pregnancy. The purpose of the current study was to assess the outcomes of PGT-SR in patients carrying various balanced chromosomal rearrangements and to assess their clinical pregnancy outcome after in vitro fertilization (IVF).

Methods: In this study, infertile couples with balanced chromosomal abnormalities undergoing PGT-SR were retrospectively analyzed at a single fertility center from January 2016 to December 2019.

Results: PGT-SR was performed on 87 embryos from 22 couples in whom one partner carried a balanced translocation or an inversion. Fifty-seven (65.5%) of these embryos had unbalanced or sporadic aneuploidies, 30 (34.5%) embryos were normal or chromosomally balanced, which were then transferred in 18 couples. A higher rate of unbalanced translocations in comparison to sporadic aneuploidies was observed in couples with reciprocal translocation. The live birth rate per embryo transfer was found to be 66.6% (12/18).

Conclusion: PGT-SR is a useful tool in selecting normal or balanced embryos for transfer in IVF, which could lead to a pregnancy by reducing the chance of miscarriages due to chromosome aneuploidy in couples with balanced chromosomal rearrangements.

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Introduction

Reproductive genetic risk and infertility have become a global problem that affects both men and women with almost equal frequency. In fact, nearly 50% of infertility cases are due to genetic defects (1). The genetic causes of infertility are various, ranging from severe chromoso-

mal abnormalities to single-gene disorders. The results of cytogenetic studies have shown that 2-4% of infertile patients carry chromosomal abnormalities (2-4). Balanced chromosomal abnormalities are one of the causes of infertility and although carriers are phenotypically normal, they have a 50% risk of spontaneous abortions and a 20% risk of having offspring with abnormal karyotypes (5). Most IVF centers now routinely perform karyotyping of couples with infertility issues before beginning the IVF cycles. Guidelines have also been drawn up to help standardize protocols internationally (6). Therefore, karyotyping has become an obligatory biological examination in the management of all patients with infertility. Apart from reduced reproductive potential, carriers of chromosomal abnormalities increase the risk of pregnancy with a chromosomally unbalanced foetus leading to a miscarriage or the live birth of a child with congenital anomalies (7, 8).

PGT-SR is a technique applied in couples with balanced chromosomal rearrangements for the selection and transfer of chromosomally balanced or euploid embryos in an IVF cycle to improve the pregnancy outcome. There has been rapid improvement in the methodology used for PGT-SR, from traditional FISH to microarray (9) and most recently, next-generation sequencing (NGS), which has improved accuracy and reliability of methodologies; it has been proved to be the method of choice for performing chromosome screening of embryos (10, 11). The purpose of the current study was assessing the aneuploidy rate in a cohort of patients who were carriers of balanced chromosomal rearrangements. The current article details the karyotype abnormalities that were observed in couples undergoing IVF, outcomes of the chromosomal screening of embryos, and the result of performed embryo transfers.

Methods

Study subjects: This retrospective analysis included 22 patients in whom chromosomal abnormality was apparent in either of the couple and they had opted for PGT-SR from January 2016 to December 2019 in Gunasheela Surgical and Maternity Hospital, Bangalore, India. All couples were evaluated and counselled by infertility specialists and medical geneticists. The procedure and limitations of PGT-SR were explained to the couples. The study was approved by the institutional ethics committee and informed consent was obtained from all the participants.

Cytogenetic analysis: Karyotyping was carried out using cultured peripheral lymphocytes by the GTG-banding technique (12). For each case, ten high level-G banded metaphases (resolution ranging from 400-550) were analyzed following the International System for Human Cytogenetic Nomenclature (ISCN, 2013) (13). In cases of suspected mosaicism, ≥50 metaphases were examined. The chromosome polymorphism such as pericentric inversion of chromosome 9 was considered a normal variant (14).

Ovarian stimulation, oocyte retrieval, embryo culture, and embryo biopsy: All the participants underwent controlled ovarian stimulation, using either the long agonist, antagonist or flare protocol depending on the clinical scenario of the patient (15). The follicular response was monitored at regular intervals by transvaginal ultrasound scan and ovulation was induced with IU hCG 250 *mcg* when at least two follicles had reached a diameter of 17 *mm*. Ultrasound-guided oocyte retrieval was performed 34-36 *hr* after hCG injection. The aspirated follicular fluid was screened under the microscope to identify and assess the cumulus oocyte complex (COC). The COC was mechanically denuded using 150 *µl* flexipet (Stripper tips, CooperSurgical, USA). Simultaneously, the semen sample obtained from the husband was processed using density gradient centrifugation or wash method in combination with the swim-up technique depending on the semen parameters. The intracytoplasmic sperm injection (ICSI), involving the injection of the matured oocyte with a single sperm was carried out using the standard protocol. The embryos were incubated in a Tri-gas incubator and cultured until day 5 in One-Step media (Vitromed, USA). In the PGT-SR group, the trophectoderm biopsy was performed using laser assisted hatching. Five to seven trophectoderm cells were dissected from each blastocyst and transferred into thin walled 0.2 *ml* PCR tubes containing 2 *µl* 1X phosphate buffer solution and sent to our in-house genetics laboratory.

PGT-SR using NGS: NGS methodology was used to test for structural rearrangements in biopsied embryo samples on the Ion PGM system (Thermo Fisher Scientific, USA). Once the samples were received in the genetics laboratory, whole genome amplification (WGA) was carried out using the Ion Reproseq™ PGS kit. The barcodes were assigned as per the Ion Reproseq™ PGS kit protocol (Thermo Fisher Scientific, USA). Libraries were

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pooled, purified using Agencourt Ampure XP beads, quantified, and templates were prepared with the Ion PGM™ Template IA 500 kit. This was followed by enriching the template-positive Ion Sphere particles. Samples were loaded on to Ion 316™ Chip Kit v2 and sequencing was carried out using the Ion PGM™ Hi-Q™ sequencing kit. The data was analyzed using Torrent Suite 5.0.4 for read filtering, base calling, barcode filtering, and alignment of reads to the human genome hg19 reference sequence. For data analysis, the samples were processed through the Ion Reporter™ Software version 5.10 using the Reproseq low-pass whole-genome aneuploidy workflow that can detect aneuploidies greater than around 10 MB in size. The decimal-level copy number gain or loss calls were enabled in the mosaic detection workflow. The Reproseq Mosaic PGS w1.1 v 5.10 workflow was used for mosaicism detection. Visualization of the analysis can be viewed in Integrative Genome Viewer (IGV) version 5.0, and the scoring of aneuploidies was based on visualization of the IGV profile indicating losses and gains of the whole chromosome coupled with confidence and precision metrics. Embryos were further evaluated and scored based on the Median Absolute Pairwise Difference (MAPD) value, the number of reads obtained, and the coverage value.

Results

The study consisted of a total of 357 couples who had opted for PGT in the years 2016-2019 and chromosomal abnormality was detected in 22 patients in either of partners. The frequency of the chromosomal abnormality was observed to be 2.3% (11/468) in both male and female partners. The various chromosomal abnormalities observed are summarised in table 1. The median age of females was 31.6 (range 22-43 years) and males was 34 (range 27-39). A total of 341 oocytes were retrieved; the maturation rate of oocytes was

Table 1. Karyotype findings of the couples undergoing PGT-SR

Karyotype	Number of subjects	Type	Origin	History
46,XX,t(10;14)(p13;q24)	1	Reciprocal translocation (n=16)	Maternal	Primary infertility
46,XX,t(8;12)(p11.2;q24.3)	1			3 miscarriages
46,XX,t(6;7)(q25;q22)	1			2 failed IVF cycles
46,XX,t(1;6)(p36.1;q13)	1			Primary infertility
46,XX,t(11;22)(q23;q11.2)	1			Primary infertility
46,XX,t(5;9)(q22;p22)	1			3 miscarriages
46,XX,t(5;8)(q31;p22)	1			2 failed IVF cycles
46,XX,t(7;13)(p13;q22)	1			2 failed IVF cycles
46,XY,t(2:17)(q31;p13)	1			Primary infertility
46,XY,t(7;17)(p22:p11)	1			2 miscarriages
46,XY,t(6;11)(p21;q23)	1			Primary infertility
46,XY,t(9;22)(q34;q11)	1			Primary infertility
46,XY,t(4;21)(q25;q22)	1		Paternal	1 biochemical pregnancy 3 failed IVF cycles
46,XY,t(4;18)(p12;q11.2)	1			3 miscarriages
46,XY,t(8;15)(q13;q24)	1			1 miscarriage
46,XY, t(14;21)(q22;q22.1)	1			Primary infertility
45,XX,der(13;14)(q10;q10)	2	Robertsonian translocation (n=3)	Maternal	Primary infertility
45,XY,der(13;14)(q10;q10)	1		Paternal	2 miscarriages
46,XX,inv(10)p11.2q21.2	1	Inversion (n=3)	Maternal	Primary infertility
46,XY,inv(5)(p15.1q31)	1		Paternal	1 miscarriage 2 biochemical pregnancies
46X,inv(Y)(p11.2;q11.23)	1			1 failed IVF cycle

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Table 2. PGT-SR results and the pregnancy outcome in the study group

PGT-SR	Frequency
Number of successfully biopsied embryos (mean±SD)	87 (3.7±1.3)
Chromosomally normal embryos	34.5% (30/87)
Aneuploid embryos (%)	65.5% (57/87)
Monosomy (%)	14% (8/57)
Trisomy (%)	17.5% (10/57)
Two chromosome abnormalities (%)	40.4% (23/57)
Multiple aneuploidies (%)	19.3% (11/57)
Sex chromosome abnormality (%)	3.5% (2/57)
Mosaicism (%)	5.3% (3/57)
Pregnancy outcome	
Number of embryo transfer (ET)	18
Clinical pregnancy per ET (%)	72.2% (13/18)
Live birth per ET (%)	66.6% (12/18)
Miscarriage per clinical pregnancy	7.7% (1/13)

70.9% (242/341) and 194 oocytes were fertilized with a fertilization rate of 80.1% (Supplementary table 1).

Eighty-seven embryos were successfully biopsied and PGT-SR was performed on the same. A total of 30 (34.5%) were observed to be chromosomally balanced or normal and 57 (65.5%) were aneuploid. The frequency and the types of aneuploidies are listed in table 2. Of the 22 patients, 18 had at least one healthy embryo for transfer. In three patients, all the embryos tested were chromosomally abnormal as a result of unbalanced translocations, sporadic aneuploidies or combined abnormalities, and one patient had 2 euploid/balanced embryos for transfer, but both embryos did not survive thawing process and consequently, there was no transfer. The clinical pregnancy rate per embryo transfer was observed to be 72.2% (13/18), live birth per embryo transfer was 66.6% (12/18), and miscarriage rate per pregnancy was 7.7% (1/13). Detailed profiles and ploidy status of the embryos based on PGT-SR and pregnancy rates are available in supplementary table 2.

Table 3 provides details of the unbalanced, sporadic aneuploidy and euploidy rates in the patients with three types of balanced chromosomal rearrangements which were observed in this study: reciprocal translocations (n=16), Robertsonian translocations (n=3), and inversions (n=3).

In subjects with reciprocal translocations, a total of 65 embryos were tested, of which 45 embryos were aneuploid, consisting of 30 (46.1%) embryos with inherited (unbalanced) translocation and 11 embryos (16.9%) with sporadic aneuploidies.

Table 3. Unbalanced translocation, sporadic aneuploidy, and euploidy rates

	Number of embryos	Unbalanced translocation rate, %	Sporadic aneuploidy rate, %	Total abnormality rate, % *	Euploidy rate, %
Total	87	39.1%	21.8%	65.5%	34.5%
Maternal	53	41.5%	24.5%	67.9%	32.1%
Paternal	34	38.3%	23.5%	61.8%	38.2%
Reciprocal translocation	65	46.1%	16.9%	69.2%	30.8%
Robertsonian translocation	13	23.1%	46.1%	69.2%	30.8%
Inversion	9	11.1%	22.2%	33.3%	66.7%

* Unbalanced translocation, sporadic aneuploidy and combined abnormality

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Among 13 embryos from patients with Robertsonian translocations, 9 abnormal embryos were identified, consisting of 3 embryos (23.1%) with inherited (unbalanced) translocations and 6 embryos (46.1%) with sporadic aneuploidies. In the inversion carrier group, 9 embryos were tested, of which 3 embryos were aneuploid (33.3%), consisting of 1 (11.1%) embryo with inherited (unbalanced) translocation and 2 embryos (22.2%) with sporadic aneuploidies. The percentages of normal and abnormal embryos were calculated based on whether the balanced chromosomal translocation was present maternally or paternally (Table 3).

Discussion

In a couple, even if one of the partners has a translocation or an inversion, they may have long-standing infertility or recurrent implantation failure (16, 17). Balanced translocation or inversion carriers increase the rate of aneuploid gametes as a result of unequal exchanges and improper pairing of chromosomes during meiosis (18, 19). Alfarawati et al. showed that the group of embryos with Robertsonian translocation carriers exhibited mitotic interchromosomal effect due to mal-segregation which could be the probable cause of sporadic aneuploidies (20).

Studies have shown embryonic aneuploidy as one of the major reasons for failure of implantation and miscarriage. In cases where either the male or female partner is a carrier of a balanced translocation, about two thirds of the produced gametes will be genetically imbalanced and only one third will be balanced (either normal or balanced translocation) according to chromatid segregation during the first meiotic division (21). Thus, two thirds of the generated embryos following fertilization will be genetically abnormal which may either fail to implant or be aborted. Sugiura-Ogasawara et al. showed that frequencies of implantation failures and/or miscarriages in patients with reciprocal translocations (68.08%), Robertsonian translocations (36.4%) or inversions (42.9%) were much higher than in the normal population (28.3%) because of these scenarios (22).

The PGT-SR method has proven to be very effective and sensitive for the identification of whole chromosome and partial aneuploidies which can lead to miscarriages, implantation failures or live born infants with congenital anomalies. The method has been validated for unbalanced translocations using NGS based Ion Torrent™ platform and the recorded smallest detectable segmental aneuploidy was 5 *Mbp* in size (23). In our PGT-SR cycles, 39.1% of embryos contained unbalanced translocations and 21.8% contained sporadic aneuploidies. This resulted in an aneuploidy rate of 65.5% which is similar to the percentage observed in other PGT-SR studies (24-27). The percentage of aneuploid embryos in IVF patients without balanced chromosomal rearrangements was observed to be 22.7-35.5% (28).

The PGT-SR outcome of embryos of translocation and inversion carrier groups was compared to determine the rates of unbalanced and sporadic aneuploidy. The group with reciprocal translocation carrier had a higher percentage of embryos with unbalanced translocations (46.1%) compared to embryos with sporadic aneuploidies (16.9%). On the contrary, embryos with sporadic aneuploidies were observed to be higher in the Robertsonian translocation carrier group. Fodina et al. showed in their study that the reciprocal translocation carrier group had embryos with unbalanced translocations at a rate that was 4 times higher than embryos with sporadic aneuploidies, while the Robertsonian translocation group had 5 times more embryos with sporadic aneuploidies in comparison to embryos with unbalanced translocations (22, 29, 30). Our study showed similar patterns, with the translocation carrier group exhibiting three times higher unbalanced translocations compared to sporadic aneuploidies.

No differences in percentages of normal versus abnormal embryos were observed irrespective of maternal or paternal carrier of the balanced chromosomal translocation as shown in table 3. A study by Idowu et al. also showed a similar trend where embryonic aneuploidies were observed to be similar in both maternal and paternal carriers of balanced chromosomal rearrangements (27).

Generally, twenty-four embryos in eighteen couples were transferred in this study. Five patients had no clinical pregnancy and one patient had a miscarriage at 15.4 weeks. The rate of live births was 66.6% per embryo transfer which is similar to the study conducted by Idowu et al., demonstrating similar live birth rate (31). Moreover, it is important to note that miscarriages or implantation failures are also associated with factors such as abnormal uterine anatomy, abnormal immunological response, and the non-receptive endometrium and that these factors could also affect the chances of a successful pregnancy in spite of ensuring that

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only one euploid embryo was transferred (21). In such cases, these other factors also may need to be assessed and addressed.

Conclusion

The results of our study lead us to conclude that the number of euploid embryos in couples with a balanced translocation carrier is much lower than the normal population and that PGT-SR could increase the rate of clinical pregnancies and live births in such couples by enabling the transfer of chromosomally balanced or euploid embryos. This not only provides the couple with a high chance of having a normal child but can also reduce the chances of implantation failures and miscarriages which can be extremely traumatic.

Conflict of Interest

The authors declare no conflict of interest.

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Supplementary

Supplementary Table 1. General features of the studied population

	Female carriers	Male carriers	Total
Number of couples	11	11	22
Mean age of the carrier	31.6 (22-43)	34 (27-39)	
Type of infertility			
Primary (%)			9 (41%)
Secondary (%)			13 (59%)
Type of chromosomal abnormality			
Reciprocal translocation	8	8	16
Robertsonian translocation	2	1	3
Inversion	1	2	3
Number of oocytes retrieved (mean±SD)			341 (15.5±7.75)
Maturation rate of oocytes (%)			70.9% (242/341)
Fertilization rate (%)			80.1% (194/242)
Cleavage rate (%)			98.4% (191/194)

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Supplementary Table 2. Detailed profile and the ploidy status of the embryos based on PGT-SR and their pregnancy outcome

Karyotype	Retrieved	MII	Fertilized	Cleaved	Biopsied	PGT-SR embryo status	Number of embryos transferred	Clinical pregnancy/ outcome
46,XX,t(10;14)(p13;q24)	8	8	7	7	3	2 x normal Unbalanced (-14, -22)	1	Positive/Aborted
46,XX,t(8;12)(p11.2;q24.3)	13	6	6	6	5	2 x normal Multiple aneuploidies Unbalanced (-8) Unbalanced (+8, -12)	2	Positive/Delivered
46,XX,t(6;7)(q25;q22)	23	12	10	10	5	2 x normal Unbalanced (-6 ,+7, -16) Unbalanced (-6 , +7) Unbalanced (-7)	1	Negative
46,XY,t(7;17)(p22;p11)	6	6	6	6	4	Normal 2 X multiple aneuploidies Unbalanced (-17)	1	Negative
46,XX, t(1;6)(p36.1;q13)	15	13	5	5	4	Unbalanced (-6) Mosaic trisomy 6 Multiple aneuploidies Unbalanced (+1, -6)	0	NA
46,XY,t(2;17)(q31;p13)	12	11	6	6	3	Unbalanced (-2) Unbalanced (+2) Normal	1	Positive/Delivered
46,XY,t(6;11)(p21;q23)	7	6	4	4	2	Normal Unbalanced (-6, +11)	1	Positive/Delivered
46,XX,t(11;22)(q23;q11.2)	27	22	19	19	6	Normal Sex chromosome aneuploidy Unbalanced (+11, -22) 2 X unbalanced (-11, +22) Unbalanced (+11)	1	Negative

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Contd. Supplementary Table 2. Detailed profile and the ploidy status of the embryos based on PGT-SR and their pregnancy outcome

Karyotype	Retrieved	MII	Fertilized	Cleaved	Biopsied	PGT-SR embryo status	Number of embryos transferred	Clinical pregnancy/ outcome
46,XY,t(9;22)(q34;q11)	21	19	16	15	4	3 X normal Mosaic partial trisomy 6 (25%)	2	Positive/Delivered
46,XX,t(5;9)(q22;p22)	19	10	8	8	7	2 X normal 3 X unbalanced (+5, -9) 2 X unbalanced (-5, +9)	2	Positive/Delivered
46,XX,t(5;8)(q31;p22)	16	10	10	10	4	2 X normal Trisomy 7 Sex chromosome aneuploidy	2	Positive/Delivered
46,XX,t(7;13)(p13;q22)	20	19	15	15	6	Normal 2 X unbalanced (+7, -13) Unbalanced (+7, -13, -11) Unbalanced (-7, +13) Multiple aneuploidies	1	Negative
46,XY,t(4;21)(q25;q22)	6	4	3	3	2	Unbalanced (+4, -21) Unbalanced (-4, +21)	0	NA
46,XY,t(4;18)(p12;q11.2)	11	8	6	6	3	Normal Multiple mosaic aneuploidies Unbalanced (-4, +8)	1	Positive/Delivered
46,XY,t(8;15)(q13;q24)	31	20	18	17	4	Normal Trisomy 6 Trisomy 3 Unbalanced (+8, -15)	1	Positive/Delivered
46,XY,t(14;21)(q22;q22.1)	8	4	3	3	3	Unbalanced (+3; +6) Unbalanced (+14; -21) Unbalanced (-14; +21)	0	NA
45,XX,der(13;14)(q10;q10)	27	2	1	1	3	2 X normal Multiple aneuploidies	0	NA
45,XY,der(13;14)(q10;q10)	12	12	9	9	3	Normal Multiple aneuploidies Unbalanced (+14)	1	Negative

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Contd. Supplementary Table 2. Detailed profile and the ploidy status of the embryos based on PGT-SR and their pregnancy outcome

Karyotype	Retrieved	MII	Fertilized	Cleaved	Biopsied	PGT-SR embryo status	Number of embryos transferred	Clinical pregnancy/ outcome
45,XX,der(13;14)(q10;q10)	16	15	12	12	7	Normal Unbalanced (-16) Unbalanced (+11) Unbalanced (+20) Unbalanced (+13) Unbalanced (-14) Unbalanced (-19)	1	Positive/Delivered
46,XY,inv(5)(p15.1q31)	5	4	4	4	3	Normal Multiple aneuploidies Unbalanced (+5)	1	Positive/Delivered
46,XX,inv(10)p11.2q21.2	11	6	5	4	3	2X normal Multiple aneuploidies	2	Positive/Delivered
46X,inv(Y)(p11.2;q11.23)	17	16	14	14	3	3X normal	2	Positive/Delivered

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