Pregnancy outcomes following 24-chromosome preimplantation genetic diagnosis in couples with balanced reciprocal or Robertsonian translocations

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Objective: To report live birth rates (LBR) and total aneuploidy rates in a series of patients with balanced translocations who pursued in vitro fertilization (IVF)–preimplantation genetic diagnosis (PGD) cycles.
Design: Retrospective cohort analysis.
Setting: Genetic testing reference laboratory.
Patient(s): Seventy-four couples who underwent IVF-PGD due to a parental translocation.
Intervention(s): IVF cycles and embryo biopsies were performed by referring clinics. Biopsy samples were sent to a single reference lab for PGD for the translocation plus 24-chromosome aneuploidy screening with the use of a single-nucleotide polymorphism (SNP) microarray.
Main Outcome Measure(s): LBR per biopsy cycle, aneuploidy rate, embryo transfer (ET) rate, miscarriage rate.
Result(s): The LBR per IVF biopsy cycle was 38%. LBR for patients reaching ET was 52%. Clinical miscarriage rate was 10%. Despite a mean age of 33.8 years and mean of 7 embryos biopsied, there was a 30% chance for no chromosomally normal embryos. Maternal age >35 years, day 3 biopsy, and having fewer than five embryos available for biopsy increased the risk of no ET.
Conclusion(s): IVF-PGD for translocation and aneuploidy screening had good clinical outcomes. Patients carrying a balanced translocation who are considering IVF-PGD should be aware of the high risk of no ET, particularly in women ≥35 years old. (Fertil Steril® 2015;103:1037–42. ©2015 by American Society for Reproductive Medicine.)
Key Words: Robertsonian translocation, reciprocal translocation, preimplantation genetic diagnosis (PGD), aneuploidy

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Balanced translocations can present as infertility, recurrent miscarriage, or the birth of a child with congenital anomalies as a result of inheriting an unbalanced chromosome rearrangement. Treatment options include expectant management, gamete donation, and in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD). Each treatment option has associated costs, risks, and success rates that couples must consider. Whereas expectant management has the lowest treatment-related costs, there is a higher risk of miscarriage, reaching 50% for most translocations (1, 2). Gamete or embryo donation can eliminate the risk associated with the translocation, but has higher costs of treatment and does not maintain a

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genetic link to both parents, which is extremely important to some couples. IVF-PGD is a treatment option often used for individuals with balanced translocations in an effort to improve the likelihood of achieving a healthy pregnancy (3, 4) while maintaining a genetic link to both parents. While initial studies of translocation carriers who pursued IVF-PGD using fluorescence in situ hybridization (FISH) have shown reduction in miscarriage rates compared to the expectant management population (5-12), reported live birth rates per cycle ranged from 12.7-22% (7,12-14). It should be noted that these early studies largely consisted of day 3 biopsies.

The accuracy and scope of PGD has improved with the ability to perform concurrent 24-chromosome aneuploidy screening in addition to testing for the specific unbalanced chromosome products expected to result from the parental translocation (15–18). The addition of 24-chromosome screening with PGD for translocations often decreases the number of embryos with "normal" (euploid) results to transfer, but has the potential to increase the implantation rate per normal embryo transferred and to reduce the risk of miscarriage due to chromosomal defects missed with targeted or limited testing.

The aim of the present study was to assess live birth outcomes in a cohort of patients with balanced translocations who pursued IVF with PGD using 24-chromosome SNP microarray analysis and a bioinformatics technique.

MATERIALS AND METHODS

This was a retrospective cohort study of 74 completed IVF-biopsy cycles. All PGD cases received from January 2010 to August 2012 for the indication of a parental translocation, as confirmed by standard karyotype analysis, were included in the study. All samples were analyzed at a single reference laboratory. Before embryo samples were accepted for testing, each parent's karyotype report was reviewed to determine whether there was adequate single-nucleotide polymorphism (SNP) coverage on the microarray to detect the potential combinations of unbalanced chromosome products that could result from the parent's balanced translocation. IVF cycles were performed by referring clinics. After fertilization, embryos underwent a single-cell biopsy on day 3, or a trophectoderm biopsy on day 5/6, according to each clinic's standard procedures. Embryo biopsies were shipped on dry ice, and parental blood or buccal samples were shipped at room temperature to the reference laboratory for analysis.

PGD for the parental translocation with concurrent 24-chromosome aneuploidy screening was performed with the use of Illumina Cyto12 SNP microarrays and Parental Support (19). This methodology incorporates parental SNP genotype information to predict the possible SNP genotypes for an embryo. For each chromosome, the algorithm compares the observed SNP data with each of the predicted allele distributions for each copy number hypothesis and identifies that with the maximum likelihood. Inclusion of parental genotypic information allows for identification of both chromosome content and parental source of chromosomes for each embryo biopsy sample. Thus, if there was a chromosome abnormality in an embryo sample that involved the chromosome of interest (given the translocation) but was of the wrong parent of origin (did not match with the parent who was the translocation carrier), we were able to determine that the chromosome error was sporadic and not related to the parental translocation. Therefore, inclusion of the parental genotypic information allowed for us to calculate the unbalanced chromosome rates in the embryo samples. This analysis did not allow us to differentiate euploid versus balanced. Accordingly, the embryo results were classified as "unbalanced" if the abnormal chromosome was involved in the parental translocation, "euploid" if normal and/or balanced without other aneuploidy, or "sporadic aneuploid" if other chromosomes were abnormal. Embryos affected by unbalanced structural rearrangements in addition to sporadic aneuploidy were classified as "combined abnormalities." Total abnormality rate was calculated as the sum of unbalanced translocation rates, sporadic aneuploidy rates, and combined abnormality rates.

Cycle outcomes were requested from clinics with the use of a defined data collection protocol for patients with at least one euploid embryo available for transfer. Outcomes obtained included number of euploid embryos transferred, chemical pregnancy according to positive hCG, clinical pregnancy according to fetal heart beat (FHB), and live birth (LB) data. Cycles were examined by type of translocation (reciprocal vs. Robertsonian), parent of origin, day of biopsy, and maternal age (<35 or ≥ 35 years). If multiple embryo transfers (ETs) were performed from a single biopsy cycle, outcomes were combined for the calculations per cycle but not for the calculations that were reported per ET. Clinical pregnancy loss was defined as the presence of a FHB with no subsequent LB. Overall miscarriage rate was defined as a positive chemical pregnancy with no resultant LB. Successful pregnancies were defined by a LB.

Statistical analyses were performed using a combination of the Welch *t* test, F test for variance, and chi-square test as indicated. The cycle data provided by the reference laboratory was deidentified for research purposes. As such, this study was determined to be exempt from Institutional Review Board review.

RESULTS

Of the 74 completed IVF-biopsy cycles in couples with balanced translocations, 52 (70.3%) resulted in one or more euploid embryos. We calculated the euploid versus aneuploid (unbalanced, sporadic, combined) rates based on the number of embryo samples with results. The number of embryo samples with no results on day 5 testing was 7 out of 109 (6%), and on day 3 testing was 29 out of 466 (6%). Two of the 52 cycles had two ETs, resulting in a total of 54 ETs. There were a total of 82 embryos transferred in this patient cohort, and the overall implantation rate was 49% (40/82).

Total chromosome abnormality rates for embryos were analyzed separately and are presented in Table 1. Rates for both unbalanced translocation and combined abnormality (unbalanced translocation with sporadic aneuploidy) were significantly higher for reciprocal translocation carriers