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Pregnancy is influenced by more than just embryo ploidy: a retrospective study on preimplantation genetic testing

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Abstract

Background Assisted reproductive technology (ART) has been widely used to treat infertility for more than four decades, but its efficacy is still lower than expected. Therefore, further exploration of the factors that affect the pregnancy outcome of ART treatment is necessary.

Materials and methods A retrospective study of chromosome rearrangement carrier couples who requested preimplantation genetic testing (PGT) for structural rearrangements at the Fourth Hospital of Shijiazhuang was conducted between February 2019 and December 2022. Multivariate logistic regression analysis was performed to determine the risk factors for pregnancy.

Results In total, 113 couples were transferred with a single euploid blastocyst, and 77 couples achieved pregnancy. Women with good-quality embryos transferred had a higher probability of pregnancy than women with poor-quality embryos transferred (OR 6.149, 95% CI 2.026–18.658). The chance of pregnancy was higher in women with a pregnancy history than in women without a pregnancy history (OR 3.181, 95% CI 1.157–8.747). The progesterone level on the day of trigger was positively associated with pregnancy (OR 2.605, 95% CI 1.226–5.538).

Conclusion Embryo quality is significantly associated with the pregnancy rate in patients treated with PGT. Embryo ploidy is just one of the factors affecting embryo development. Future studies should focus on the molecular mechanisms of embryo development and develop corresponding detection methods.

Keywords Chromosomal structural rearrangements, Preimplantation genetic testing, Embryo quality, Pregnancy outcome

Background

Chromosomal structural rearrangements, which mainly include balanced translocation, Robertsonian translocation and inversion, are abnormalities in chromosome structure. They can induce chromosomal aberrations in gametes and seriously harm fertility, resulting in miscarriage or birth defects and enormous physiological and psychological burdens on patients [1]. For example, balanced translocation (also known as reciprocal translocation) is a condition in which DNA segments on one chromosome break off and switch places with a section on another nonhomologous chromosome [2]. A carrier with balanced translocation usually has all the genetic

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material necessary for normal development—a piece of a chromosome is merely broken off and attached to another one. However, when the carrier's germ cells divide to create oocyte or sperm cells for reproduction, the oocyte or sperm cells may end up with extra or missing genetic material because of abnormal chromosome segregation induced by balanced translocations, which could lead to miscarriage or other fertility issues. People usually do not know that they have this condition until they experience miscarriage or infertility when a balanced translocation is diagnosed through a karyotype cytogenetic test [3]. As balanced translocations cannot be corrected with today's technology, the main treatment strategy for translocation carriers who want to conceive is to screen the chromosome copy number of their embryos (in vitro fertilization) or fetuses (natural conception) and select those with normal chromosome copy numbers for transfer or for continuing with pregnancy [4, 5].

Preimplantation genetic testing (PGT), which is a well-established alternative to prenatal diagnosis, is performed for couples at high risk of transmitting known genetic conditions to their offspring [6, 7]. It involves the biopsy and genetic testing of single or multiple cells from in vitro-obtained oocytes or preimplantation embryos. As only embryos shown to be unaffected by the genetic condition in question are selected for transfer to the patient's uterus, PGT can block the transmission of the genetic condition to offspring, offering the patient the advantages of circumventing an invasive prenatal diagnosis and therapeutic abortion [8]. Preimplantation genetic testing comprises three types of tests performed on embryos. PGT for aneuploidy (PGT-A) is an analysis of embryo cells to screen for aneuploidy (an abnormal number of chromosomes). PGT for monogenic disease (PGT-M) searches for specific gene mutations that one or both of the couples are known to carry. To test embryos that are at risk for chromosome gains and losses related to parental structural chromosomal abnormalities (e.g., translocations, inversions, deletions, and insertions), PGT for structural rearrangements (PGT-SR) is used [9].

Since PGT-SR can identify chromosomal aberrations in embryos, it is assumed that it may improve pregnancy outcomes and reduce the abortion rate through the selection of euploid embryos for patients with chromosomal structural rearrangements [10–12]. This study seeks to answer the following question: for patients with chromosomal rearrangement to achieve a successful pregnancy, is a euploid embryo enough?

Materials and methods

Study population

This retrospective study was carried out at a university-affiliated reproductive medicine center between February 2019 and December 2022. Patients who were referred for preimplantation genetic testing for chromosomal structural rearrangements because of balanced translocations, Robertsonian translocations or inversions were included. At least one embryo with normal chromosomes was obtained, and the first transfer of a euploid embryo was completed. For repeated transfers, only the data from the first transfer were included. The exclusion criteria were as follows: abnormal uterine anatomy; endometriosis; polycystic ovary syndrome; adenomyosis; premature ovarian insufficiency; hyperprolactinemia; intrauterine adhesion; hydrosalpinx; and uterine myoma (multiple, submucous, or intramural myoma > 3 cm).

Treatment procedure

The gonadotropin-releasing hormone agonist (GnRH-a) or antagonist (GnRH-ant) protocol was selected on the basis of patient age, serum anti-Mullerian hormone levels, antral follicle counts, and prior response to gonadotropins and was carried out according to established standard protocols. The human chorionic gonadotropin, Ovidrel (Merck-Serono) was administered when there were two or more follicles with maximal diameters of 18 mm or greater in the ovaries. Transvaginal ultrasound-guided oocyte retrieval under deep conscious sedation was performed 36 h later.

Oocytes were fertilized via conventional ICSI procedures. The embryos were cultured individually in pre-equilibrated media drops (Vitrolife) covered with mineral oil and maintained in an incubator at 37 °C, 6% CO_2 and 5% O_2.

Blastocysts were graded before biopsy according to the stratification recommended by Gardner et al. [13] and were divided into two groups: good (4AA, 4AB and 4BA) and poor (≥ 4 BC and < 4BA).

Trophectoderm biopsy was performed via a laser pulse on day 5 [14], and 4–6 cells were retrieved for PGT. Biopsy samples were transferred into RNase- and DNase-free PCR tubes containing 5 μL of cell lysis buffer (Yikon Genomics). Blastocysts were vitrified after biopsy.

After cell lysis, the samples were amplified via multiple annealing and looping-based amplification cycles. With an Illumina HiSeq 2500 platform (Illumina, Inc.), we sequenced the amplified genome of each sample. The sequencing yielded reproducible copy number variation (CNV) results with approximately 1 Mb resolution to detect variation and aneuploidy.

Chromosomally normal blastocysts were selected for transfer. Embryo thawing and transfer were performed on the basis of the routine of the center. Clinical pregnancy was defined as the presence of a gestational sac with fetal heart activity by ultrasound at 4–6 weeks after embryo transfer.

Statistical analysis

Continuous data are presented as mean and standard deviation, and categorical variables are presented as absolute and percentage frequency. Student's t-test or non-parametric test was used to examine the differences in continuous variables between groups, whereas Chi-square test was used to assess categorical variables. Multivariate logistic regression analysis was performed to evaluate the risk factors for pregnancy. $P<0.05$ was considered statistically significant. All the statistical analyses were performed using SPSS 16.0.

Results

In this study, we analyzed the data of 113 couples with balanced chromosomal rearrangements, including 65 reciprocal translocations, 32 Robertsonian translocations, and 9 inversions. Every woman had been transferred with a single euploid blastocyst. Among the 113 transfer cycles, 77 cycles led to pregnancy.

Table 1 summarizes the baseline demographics of each group. Compared with nonpregnant women, pregnant women had significantly higher antral follicle counts (AFCs) with comparable ages and BMIs ($P=0.011$). The baseline hormone levels were similar between the two groups. The two groups differed significantly in terms of the nulligravid rate ($P=0.009$) and severe oligoasthenoteratozoospermia (OAT) ($P=0.035$). Notably, prior miscarriage had no effect on the pregnancy rate.

The controlled ovarian hyperstimulation (COH) parameters and embryologic data are presented in Table 2. There were no differences between the two groups with respect to the ovarian stimulation protocol, days of gonadotropin use or cumulative gonadotropin dose. Among sex hormones, the estradiol and progesterone levels on the trigger day in the pregnant group were significantly higher than those in the nonpregnant group ($P=0.025$; $P=0.011$). The numbers of aspirated oocytes, metaphase II (MII) oocytes, two pronuclei (2PN) zygotes and blastocysts were significantly higher in the pregnant group than in the nonpregnant group ($P=0.004$, 0.001, 0.001, 0.017, respectively). PGT-SR results revealed that there was no difference in the number of euploid embryos between the two groups.

During the embryo transfer stage, euploid embryos were selected for transfer. Women who were transferred with good-quality embryos were more likely to conceive than women who were transferred with poor-quality embryos ($P=0.003$) (Table 3). Low-level mosaicism, as a potential factor affecting pregnancy outcome, was also detected in the present study, and no difference between the two groups was noted. The endometrial thickness on the transfer day was comparable between the two groups (Table 3).

Multivariate logistic regression was used to assess the associations between clinical characteristics and pregnancy rates. The results are shown in Table 4. Compared with women with poor-quality embryos, those with

Table 1 Baseline characteristics

	Pregnancy ***N*** **= 77** **Mean ± SD or *N* (%)**	**Nonpregnancy** ***N*** **= 36** **Mean ± SD or *N* (%)**	***P*-value**
Female age (years)	29.6 ± 3.7	31 ± 4.3	0.076
Male age (years)	30.2 ± 3.9	30.8 ± 3.6	0.465
Female BMI (kg/m^2)	22.8 ± 3.4	21.8 ± 2.4	0.069
AFC	20.1 ± 11.6	15.1 ± 8.2	0.011
Basal FSH (mIU/ml)	6.1 ± 2.6	5.9 ± 2.7	0.81
Basal LH (mIU/ml)	3.2 ± 2.1	3.4 ± 2.5	0.716
Basal E_2 (pg/ml)	36.1 ± 17.5	38.7 ± 32.5	0.654
Basal P (ng/ml)	1.2 ± 3.5	1.1 ± 2.9	0.954
Basal T (nmol/L)	1.0 ± 0.4	1.0 ± 0.3	0.958
Nulligravida	25 (32.5%)	21 (58.3%)	0.009
Number of prior miscarriages			0.303
1	18 (23.4%)	2 (5.6%)	
2	16 (20.8%)	7 (19.4%)	
3	7 (9.1%)	3 (8.3%)	
4	8 (10.4%)	2 (5.6%)	
Severe OAT	4 (5.2%)	7 (19.4%)	0.035

BMI, body mass index; *AFC*, antral follicle count; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; E_2 estradiol; *P*, progesterone; *T*, testosterone; *OAT*, oligoasthenoteratozoospermia; *SD*, standard deviation

Table 2 COH parameters and embryologic data

	Pregnancy ***N*** **= 77** **Mean ± SD or *N* (%)**	**Nonpregnancy** ***N*** **= 36** **Mean ± SD or *N* (%)**	***P*-value**
Ovarian stimulation protocol			0.256
Long-acting GnRH-a protocol	16 (20.8%)	11 (30.6%)	
GnRH-ant protocol	61 (79.2%)	25 (69.4%)	
Days of gonadotropins used	10.4 ± 1.8	10.5 ± 1.9	0.804
Gonadotropin cumulative dose (IU)	2520.3 ± 769.5	2720.1 ± 658.1	0.183
FSH on day of trigger (mIU/ml)	12.6 ± 4.8	15.0 ± 5.2	0.14
LH on day of trigger (mIU/ml)	1.8 ± 1.8	1.6 ± 1.5	0.608
E_2 on day of trigger (pg/ml)	3958.7 ± 1162.7	3382.1 ± 1309.5	0.025
P on day of trigger (ng/ml)	1.4 ± 1.0	1.0 ± 0.6	0.011
Oocytes retrieved	16.8 ± 6.8	12.9 ± 5.2	0.004
MII oocytes	14.4 ± 6.5	10.6 ± 4.9	0.001
2PN zygotes	12.9 ± 6.3	9.5 ± 4.6	0.001
Blastocysts	8.5 ± 4.8	6.3 ± 3.8	0.017
Euploid embryos	2.5 ± 1.4	2.4 ± 1.4	0.693

GnRH-a, gonadotropin-releasing hormone agonist; *GnRH-ant*, gonadotropin-releasing hormone antagonist; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; E_2 estradiol; *P*, progesterone; *MII*, metaphase II; *2PN*, two pronuclei; *SD*, standard deviation

Table 3 Characteristics of the embryos transferred

	Pregnancy ***N*** **= 77** **Mean ± SD or N (%)**	**Nonpregnancy** ***N*** **= 36** **Mean ± SD or N (%)**	***P*-value**
Ploidy of embryos transferred	Euploidy	Euploidy	–
Grading of embryos transferred			0.003
Good quality	40 (51.9%)	8 (22.2%)	
Poor quality	37 (48.1%)	28 (77.8%)	
Whether embryos transferred with low-level mosaicism			0.884
With	12 (15.6%)	6 (16.7%)	
Without	65 (84.4%)	30 (83.3%)	
Endometrial thickness at transfer (mm)	10.5 ± 1.9	11.0 ± 2.0	0.242

SD, standard deviation

Table 4 Association between clinical characteristics and pregnancy outcomes

	***P*-value**	**OR**	**95% CI**
Embryo grading	0.001	6.149	2.026–18.658
Gravidity	0.025	3.181	1.157–8.747
P on day of trigger (ng/ml)	0.013	2.605	1.226–5.538

P, progesterone

good-quality embryos transferred had an increased probability of pregnancy (OR 6.149, 95% CI 2.026–18.658). The chance of pregnancy was higher in women with a pregnancy history than in women without a pregnancy history (OR 3.181, 95% CI 1.157–8.747). The progesterone concentration on the day of trigger was positively associated with pregnancy (OR 2.605, 95% CI 1.226–5.538).

We compared primary infertility patients who became pregnant after reproductive assistance with those who did not and found that the proportion of good-quality embryos in the pregnant group was significantly higher than that in the nonpregnant group ($P = 0.049$) (Table 5).

Discussion

In this study, each of the 113 couples who were treated with PGT-SR just because of chromosomal structural rearrangements without other infertility factors was transferred with a single euploid embryo. Although 77

Table 5 Pregnancy outcomes in women with primary infertility after the transfer of euploid embryos

	Women with primary infertility		
	Pregnancy *N* = 26 *N* (%)	Nonpregnancy *N* = 20 *N* (%)	*P*-value
Grading of embryos transferred			0.049
Good quality	14 (53.8%)	5 (25%)	
Poor quality	12 (46.2%)	15 (75%)	

of the 113 transfer cycles achieved pregnancy, 36 cycles failed to achieve pregnancy after the transfer of euploid embryos. In addition to ploidy, embryo quality, pregnancy history and progesterone on the trigger day were strongly associated with achieving pregnancy in patients who underwent treatment with PGT-SR. The most important factor was embryo quality.

For women transferred with euploid embryos, the adjusted odds ratio for comparing embryos of good quality with those of poor quality was 6.149, demonstrating that embryo quality is significantly associated with the pregnancy rate in patients after the impact of aneuploidy on pregnancy is excluded. That is, only the transfer of embryos that are both euploid and of good quality can improve pregnancy outcomes, whereas the transfer of euploid embryos of poor quality has a lower chance of pregnancy.

The results revealed that embryo quality was associated with the pregnancy rate; thus, ploidy cannot fully represent the quality of embryos and is not the only factor involved in successful embryonic development. Embryo quality and development are affected by many factors in addition to chromosome variations, including gene variation, epigenetics, mitochondria, cell metabolism, and endometrial receptivity [15–19]. However, there are no direct detection methods for these factors, and only morphological grading methods can be used to indirectly observe embryos.

The morphological grading method used to determine the quality of embryos is currently the mainstream method for embryo screening in assisted reproductive technology. It is a grading method based on cell morphology and development speed, which can better reflect the developmental ability of embryos [20]. The disadvantage of this morphological grading method is that it cannot directly reflect the molecular situation of embryonic cells [21]. For example, the chromosomes of an embryo with a morphological rating of excellence may be aneuploid, and selecting such an embryo may result in abortion after transfer. Therefore, the existing methods for chromosome and morphological grading of embryos cannot replace each other, and the combination of the two methods can most accurately reflect the development of embryos [22].

We found that women with primary infertility had a higher risk of pregnancy failure than those with a history of pregnancy (OR 3.181). Why was the pregnancy rate lower in women with primary infertility? This finding might be related to uncertain potential idiopathic diseases associated with primary infertility patients. Alternatively, this finding might be related to embryo quality, since all the women with or without a pregnancy history were without female infertility factors, and their baseline characteristics were comparable. To assess this hypothesis, the grading of embryos transferred was compared between primary infertility patients who became pregnant after reproductive assistance and those who did not and we found that the proportion of good-quality embryos in the pregnant group was significantly higher than that in the nonpregnant group, indicating that embryo quality may be an important potential cause of primary infertility [20].

Another significant finding of this study is that a high level of progesterone on the trigger day was associated with pregnancy (OR 2.605). Progesterone is secreted by the granulosa cells of mature follicles during controlled ovarian hyperstimulation [23]. A higher progesterone level might reflect a higher ovarian response [24], and more follicles might be recruited and well developed, which means that more eggs could be retrieved [25], good-quality embryos would be more likely to be produced, and pregnancy outcomes could be improved. Although elevated progesterone on the day of human chorionic gonadotropin (hCG) administration may be associated with impaired early embryo implantation [26], there seems to be no adverse effect of elevated progesterone during frozen-thawed cycles [27].

Our study has strengths and limitations. The main strength of this study is that we selected a specific population as the research subjects—patients with chromosomal rearrangements treated with PGT. The characteristics of the population are that these patients and their spouses generally do not have infertility factors themselves and that the embryos transferred are all euploid embryos screened by PGT. Thus, it can further identify other possible factors that may affect pregnancy, excluding the influences of patients' own infertility factors and embryonic aneuploidy. This study has several limitations. One limitation is that this is a retrospective study, and heterogeneity among the included patients is inevitable. Another limitation is that patients in the study only received frozen embryo transfer, but whether the results could apply to fresh embryo transfer is unclear. Therefore, caution should be taken when extrapolating the results, and further

multicenter randomized clinical trials are needed for confirmation.

Good-quality embryos are positively correlated with the clinical pregnancy rate and depend on good ovarian function. Chromosome screening combined with morphological grading is currently the most effective evaluation method. In the future, we expect that technological advancements will lead to more targeted molecular evaluation methods, which will help us effectively screen for embryos with developmental potential.

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Author contributions
Conception and design of study: S-BM and C-PG; acquisition of data: GT and Z-CZ; analysis and/or interpretation of data: JZ and X-WW; drafting the manuscript: S-BM; revising the manuscript: C-PG. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Approval was obtained from the Ethics Committee of Shijiazhuang Fourth Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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