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The Clinical Outcomes of Mosaic Embryo Transfer in Preimplantation Genetic Testing Cycles

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Abstract

Purpose: We aimed to analyze the pregnancy outcomes and perinatal follow-up of mosaic embryo transfer in the preimplantation genetic testing (PGT) cycles. **Method:** We retrospectively selected 27 mosaic embryo transfer cycles as the study group and 97 euploid embryo transfer cycles as the control group after propensity score matching, which were performed in the reproductive medicine center of the Sixth Affiliated Hospital, Sun Yat-sen University, from March 2019 to September 2023. The biopsy cells from blastocyst were undertaken next generation sequencing (NGS). **Results:** No significant difference in pregnancy outcomes compared between the two groups. According to the size of aneuploid, fragment the level of mosaicism or blastocyst morphological gradings, there were no significant difference in mosaic embryo transfers. **Conclusion:** Mosaic embryo detected in the PGT cycle can lead to clinical pregnancy and live birth of healthy offspring, which can be considerate suitable for transfer.

Keywords

Mosaic Embryo, PGT, Pregnancy Outcomes, Perinatal Follow-Up

1. Introduction

Mosaicism is a biological phenomenon, which describes a tissue or individual containing two or more different genomes. In human assisted reproductive, mosaicism has been found in cleavage or blastocyst stage embryo when biopsies were

performed for preimplantation genetic testing (PGT). There are three types of PGT. Preimplantation genetic testing for aneuploidy (PGT-A) is performed for couples who suffered advanced maternal age (AMA), recurrent miscarriage (RM), or repeated implantation failure (RIF). Preimplantation genetic testing for monogenic (PGT-M) is performed to prevent vertical transmission of the pathogenic variants to next generation [1], which always combined with PGT-A. Preimplantation genetic testing for chromosomal structural rearrangements (PGT-SR) is performed for patients who carrying chromosome translocation or inversion [2]. Nowadays, next generation sequencing (NGS) performed in PGT-A has a common resolution at 5 to 10 Mb and a detection limit of the mosaic level at 20% or 30% [3] [4] [5]. In PGT-SR, resolution can be promoted to 1 Mb, also with the same limit of mosaic level [6]. Mitotic errors with chromosomal mis-segregation in early embryo development can result in mosaicism. According to the statement which the Preimplantation Genetic Diagnosis International Society (PGDIS) announced in 2019, mosaic embryo with mosaic level of less than 50% was considerate to be transferred [7].

2. Method

2.1. Study Design

This single-center, retrospective cohort study was conducted to analyze the pregnancy outcomes and perinatal follow-up of mosaic embryo transfer in the preimplantation genetic testing (PGT) cycles. All the cycles were performed in the reproductive medicine center of the Sixth Affiliated Hospital, Sun Yat-sen University, from March 2019 to September 2023.

2.2. Patients

The inclusion criteria were cycles only transferring single mosaic embryo. The exclusion criteria were: 1) embryo morphology score worse than 4CC; 2) embryos not underwent PGT. Consequently, a total of 27 mosaic embryo transfer cycles were selected as the study group. After propensity score matching according to female age, female body mass index (BMI), infertility types (primary or secondary), clinical indications, and embryo morphology, 108 euploid embryo transfer cycles were matched as the control group in a ratio of 1:4. The general clinical data and pregnancy outcomes were reviewed and compared between groups. The human data were performed in accordance with the Declaration of Helsinki. And data collection in this study were approved by the ethics committee at the Center for Reproductive Medicine, the Sixth Affiliated Hospital of Sun Yat-Sen University (Program No.2017ZSLYEC-016S).

2.3. Ovarian Stimulation, Embryo Culture and Blastocyst Biopsy

Ovarian stimulation was performed as previously described (Guo *et al.*, 2019), and oocyte retrieval was performed 36 - 38 h after human chorionic gonadotro-

phin administration. All mature oocytes were fertilized by intracytoplasmic sperm injection (ICSI). Embryos were cultured in G1/G2 sequential media (Vitrolife, Sweden) at 37˚C in incubators with 6% CO_2.

Day 5/6 blastocysts were graded according to Gardner's criteria (Gardner and Schoolcraft, 1999). AA/AB/BA were defined as good quality; BB was defined as fair quality; and AC/BC/CB defined as poor quality. Such blastocysts were considered suitable for biopsy and transfer. According to the standard operating procedure in our library, biopsy of 5 to ten trophectoderm (TE) cells was performed, and blastocysts were frozen by vitrification (Kitazato, Japan).

2.4. Preimplantation Genetic Testing and Embryo Transfer

The single-cell whole genome amplification (WGA) of TE cells was performed by MALBAC (Yikon, China). Next generation sequencing (NGS) (Illumina, USA) was applied to detect copy number variants. According to CNV results, embryos were diagnosed as euploid, mosaic, or aneuploidy. Embryos were classified as mosaic if the level of mosaicism ranged from 30% to 70%, whereas a level of less than 30% was labeled as euploid and more than 70% as aneuploid. Mosaic embryos with a level less than 50% and only affecting one chromosome were considered suitable for single blastocyst transfer, as well as euploid embryos.

2.5. Prenatal Diagnosis

Anomaly scan by ultrasonic examination was performed for gravidas at 20 to 24 weeks of gestation. Amniocentesis was performed to extract amniotic fluid cells from gravidas who were at 18 - 26 weeks of gestation. Karyotype analysis and chromosomal microarray analysis (CMA) were performed to test DNA from amniotic fluid cells according to the manufacturer's instructions.

2.6. Outcome Measures

Women's peripheral blood was detected for β-HCG at two weeks after embryo transfer. The negative ones were judged as nonpregnant. The positive ones would perform abdominal ultrasound examination after three weeks. If there was a gestational sac in the uterine cavity, it was considered as clinical pregnancy; otherwise, it was considered as biochemical pregnancy. Ongoing pregnancy was pregnant longer than 12 weeks, unless miscarriage happened.

2.7. Statistical Analysis

Propensity score matching was performed using R 4.3.0 (Lucent, USA) to match the study group and the control group. SPSS 22.0 (IBM, USA) was used to analyze all the data. The measurement data were presented as mean and standard deviation ($\bar{x} \pm s$). The comparison of the mean between groups was performed by Mann-Whitney U test. And the enumeration data were presented as rate, using Pearson's chi-squared test or Fisher's Exact Test. Differences were considered significant at $P < 0.05$.

3. Results

3.1. General Clinical Data of Patients

There was no significant difference between the study group (mosaic embryo transfer) and the control group (euploid embryo transfer) in female age, female BMI, infertility type, clinical Indications, PGT types and embryo morphology (P > 0.05) (Table 1).

3.2. Pregnancy Outcomes of Mosaic Embryo Transfer

The specific clinical data of mosaic embryo transfer are shown in Table 2.

Among the 27 mosaic embryos transferred, 18 embryos were successfully implanted with biochemistry pregnancy rate of 66.67%, which is the same as that of euploid control group (66.67%, 72/108). Embryos with mosaicism could reach similar clinical pregnancy, ongoing pregnancy and live birth to the euploid embryos, and had lower miscarriage rate (P > 0.05) (Table 3).

According to the size of aneuploid fragment, no difference was observed in biochemistry pregnancy (4 numerical vs. 14 segmental, P = 0.375), clinical pregnancies (4 numerical vs. 13 segmental, P = 0.415) and ongoing pregnancies/live births (4 numerical vs. 13 segmental, P = 0.415) between embryos carrying numerical (8 embryos) and segmental (19 embryos) chromosomal abnormalities (Table 4).

Table 1. Clinical information of studied cohorts.

	Mosaic embryo transfer (n = 27)	Euploid-control (n = 108)	P
Age ($\bar{x}$ ± s)	32.70 ± 4.63	32.56 ± 4.80	0.906
BMI ($\bar{x}$ ± s)	21.75 ± 2.07	21.70 ± 3.00	0.775
Clinical Indications			0.999
Combined with PGT-M	8 (29.63%)	32 (29.63%)	
Translocation Carriers	11 (40.74%)	44 (40.74%)	
AMA	3 (11.11%)	14 (12.96%)	
RM	3 (11.11%)	11 (10.19%)	
RIF	2 (7.41%)	7 (6.48%)	
Type of PGT			1.000
PGT-A	8 (29.63%)	32 (29.63%)	
PGT-M	8 (29.63%)	32 (29.63%)	
PGT-SR	11 (40.74%)	44 (40.74%)	
Morphology			0.932
Good	9 (33.33%)	40 (37.04%)	
Fair	9 (33.33%)	33 (30.56%)	
Poor	9 (33.33%)	35 (32.41%)	

Note: P > 0.05. There is no significant difference.

Table 2. Clinical data of mosaic blastocyst transfers.

No.	Female age	Type of PGT	Results of NGS	Embyo Score	Pregnancy outcome	Clinical Outcome	Results of prenatal diagnosis (CMA)
1	37	PGT-A	dup (mosaic) (19) (q11q13.12) (11 Mb) (30%)	4BB	Clinical pregnancy	Live Birth	Euploid
2	38	PGT-A	del (mosaic) (8) (q12.1q21.11) (22 Mb) (34%)	4AB	Clinical pregnancy	Live Birth	Euploid
3	42	PGT-A	dup (mosaic) (15) (q24.1q25.2) (10 Mb) (32%)	4BA	Clinical pregnancy	Live Birth	Euploid
4	28	PGT-SR	del (mosaic) (7) (q31.31q36) (41 Mb) (48%)	6BC	Biochemical pregnancy	/	
5	36	PGT-SR	dup (mosaic) (15) (40%)	4BB	Nonpregnant	/	
6	29	PGT-M	dup (mosaic) (11) (p15.5p15) (11 Mb) (50%)	4BB	Clinical pregnancy	Live Birth	Euploid
7	29	PGT-M	dup (mosaic) (9) (q21.2q22.31) (14 Mb) (33%)	4BC	Clinical pregnancy	Miscarriage	Euploid
8	32	PGT-M	del (mosaic) (1) (p36.33p34) (36 Mb) (50%)	4AA	Clinical pregnancy	Live Birth	dup (9) (p24.1p23) (2.31 Mb), uncertain significance
9	44	PGT-A	del (mosaic) (5) (pterp15.31) (~10 Mb) (32%)	4AB	nonpregnant	/	
10	35	PGT-SR	del (mosaic) (13) (q12.13q14.11) (18 Mb) (30%)	4AA	clinical pregnancy	Live Birth	Euploid
11	38	PGT-A	del (mosaic) (5) (35%)	4CB	clinical pregnancy	Live Birth	Euploid
12	29	PGT-SR	del (mosaic) (8) (q24.21q24) (14 Mb) (45%)	4BC	nonpregnant	/	
13	32	PGT-SR	dup (mosaic) (10) (41%)	4BB	clinical pregnancy	Live Birth	del (4) (q28.1q28.2) (1.18 Mb), likely pathogenic
14	36	PGT-SR	del (mosaic) (9) (33%)	4BB	nonpregnant	/	
15	29	PGT-SR	dup (mosaic) (12) (q13.11q13) (11 Mb) (36%)	4AC	clinical pregnancy	Ongoing Pregnant	
16	32	PGT-M	del (mosaic) (14) (38%)	4BC	nonpregnant	/	
17	32	PGT-SR	del (mosaic) (6) (36%)	4AB	clinical pregnancy	Ongoing Pregnant	
18	34	PGT-A	del (mosaic) (20) (q13.2q13.33) (10.00 Mb) (50%)	4AA	clinical pregnancy	Ongoing Pregnant	
19	28	PGT-SR	dup (mosaic) (2) (50%)	4AB	clinical pregnancy	Ongoing Pregnant	

Continued

20	38	PGT-M	del (mosaic) (11) (p15.4p13) (30 Mb) (33%)	4BB	nonpregnant	/
21	24	PGT-M	del (mosaic) (7) (p22.3p11.2) (56.28 Mb) (35%)	4AB	clinical pregnancy	Ongoing Pregnant
22	32	PGT-M	dup (mosaic) (9q) (37%)	4CB	nonpregnant	/
23	38	PGT-A	del (mosaic) (7) (q11.23q36.3) (86.34 Mb) (44%)	4BB	clinical pregnancy	Ongoing Pregnant
24	34	PGT-A	dup (mosaic) (11) (p15.5p11.2) (48.00 Mb) (43%)	4BB	clinical pregnancy	Ongoing Pregnant
25	32	PGT-M	del (mosaic) (5) (q22.3q35) (65 Mb) (44%)	4BC	nonpregnant	/
26	31	PGT-M	del (mosaic) (16) (q11.2q24.3) (43.20 Mb) (38%)	4BC	clinical pregnancy	Ongoing Pregnant
27	37	PGT-SR	dup (mosaic) (5) (q11.2q14) (30 Mb) (35%)	4BB	nonpregnant	/

Table 3. Comparison of clinical outcome between two groups.

	Number of cases	Biochemistry Pregnancy	Clinical Pregnancy	Ongoing Pregnancy/Live Birth	Miscarriage	Neonatal Weight (g)
Mosaic embryo transfer	27	18 (66.67%)	17 (59.26%)	16 (59.26%)	0 (0%)	3231.74 ± 496.90
Euploid Control	108	72 (66.67%)	65 (60.19%)	63 (58.33)	2 (3.08%)	3375.00 ± 543.32
X^2		<0.001	0.070	0.008	-	-
P		1.000	0.791	0.930	1.000	0.933

Note: P > 0.05. There is no significant difference.

Table 4. Outcome comparison according to the size of aneuploid fragment (Fisher's Exact Test).

Classification by Size of Mosaic Variant	Biochemistry Pregnancy	Clinical Pregnancy	Ongoing Pregnancy/Live Birth
Numerical	4 (50.00%)	4 (50.00%)	4 (50.00%)
Segmental	14 (73.68%)	13 (68.42%)	13 (68.42%)
P	0.375	0.415	0.415

According to the level of mosaicism, the number of embryos with a mosaic level of <40% that reached biochemistry pregnancy, clinical pregnancy and ongoing/live birth was similar to those with a mosaic level of 40% - 50%. No significant difference was found within different mosaic levels (Fisher's exact test, P > 0.05) (Table 5).

Table 5. Outcome comparison according to the level of mosaicism.

Mosaic level	Biochemistry Pregnancy	Clinical Pregnancy	Ongoing Pregnancy/Live Birth
<40%	9 (60.00%)	9 (60.00%)	9 (60.00%)
40% - 50%	9 (75.00%)	8 (66.67%)	8 (66.67%)
P	0.683	1.000	1.000

Pregnancy outcomes were compared with different blastocyst morphological gradings in mosaic embryo transfers. Embryos with "good" morphology showed better pregnancy outcome than those with "fair" and "poor" morphology, but with no significant difference (Table 6).

3.3. Perinatal Follow-Up of Mosaic Embryo Transfers

Sixteen live births in mosaic embryo transfers and 65 live births in the euploid control all had birth weight records. No difference was found in regard to birth weight between babies from mosaic transfers (3231.74 ± 496.90 g) and those in the control group (3375.00 ± 543.32 g, P = 0.933) (Table 3). Elven gravidas (68.75%) among the 16 ongoing pregnancy/live births in mosaic embryo transfers and 37 gravidas (58.73%) among 63 ongoing pregnancy/live births in euploid controls underwent anomaly scan. There was one fetus (9.09%) had congenital heart disease in mosaic transfers, while none in euploid controls. Nine gravidas (56.25%) in mosaic transfers and 35 gravidas (55.56%) in euploid controls underwent amniocentesis for karyotyping and CMA. All the karyotyping showed normal karyotype or inherited balanced translocation. Two results (22.22%) of 9 CMA results showed abnormal CNV in mosaic transfers (Table 2). Case 8 showed a small deletion: arr[GRCh37] 9p24.1p23 (7764226_10077962) × 3, 2.31 Mb, uncertain significance. And case 13 was detected a small deletion: del (4) (q28.1q28.2) (1.18 Mb), likely pathogenic. The two CNVs were not the same mosaic chromosome detected in embryos. There was no CNVs were detected in euploid control.

4. Discussion

Embryo mosaicism was a normal biological phenomenon, but the incidences of mosaicism were different according to different developmental stages or different detection methods. Mosaicism incidence when biopsy was performed in blastocyst stage was 3% - 24%, which was lower than cleavage stage (15% - 90%). In the past, biopsy cells were detected by fluorescence *in situ* hybridization (FISH), single nucleotide polymorphism array (SNP array) or array comparative genome hybridization (aCGH), leading to different mosaicism incidences. Nowadays, most centers performed biopsy in blastocyst stage and applied NGS to detect cells, so that the identification and quantification of mosaicism were comparable between different centers.

Table 6. Outcome comparison by morphological grading in mosaic embryo transfers.

Morphological Grading	Biochemistry Pregnancy	Clinical Pregnancy	Ongoing Pregnancy/Live Birth
Good	8 (88.89.00%)	8 (88.89.00%)	8 (88.89.00%)
Fair	5 (55.56%)	5 (55.56%)	5 (55.56%)
Poor	5 (55.56%)	4 (44.44%)	4 (44.44%)
P	0.281	0.21	0.21

According to the latest statement PGDIS published in 2022, most studies about mosaic embryo transfer were conducted in the PGT-A cycle [8]. This study compared PGT-A, PGT-M and PGT-SR cycles, including different clinical indications, and there is no significant difference in pregnancy outcomes. It indicates that mosaic embryo in PGT-M and PGT-SR cycles can be considered for transfer, as well as in PGT-A cycles.

Embryo mosaicism can be typed according to mosaic level, the number of chromosomes involved, or the size of the fragment. It has been focused and discussed whether clinic outcomes of mosaic embryo transfer could be predicted by these indications in the current research. There is no consensus about these factors' influence on clinical outcomes. Some scholars believed that fragment mosaic embryos could obtain better pregnancy outcomes than the whole chromosome mosaic embryos [9] [10], while some did not observe this phenomenon in their studies [11] [12]. In our study, there was no significant difference of pregnancy outcome between different mosaic level (<40% VS 40% - 50%), or different size of fragment (fragment mosaic VS whole chromosome mosaic).

In this study, compared to euploid embryos, mosaic embryos reached similar clinical pregnancy rate and live birth/ongoing pregnancy rate, indicating mosaic embryos had good developmental and implantation potential. There were two theories to explain the phenomenon. One was that: biopsy samples were 5 - 8 cells of trophoblastic ectoderm instead of inner cell mass, so that it cannot accurately represent the fetus. Some studies found that some embryos diagnosed as mosaic were diagnosed as euploid embryos after secondary biopsy. Another one was that: mosaic embryos may have a mechanism of self-correction, which included: superiority growth of euploid cells, self-correction of abnormal cells, and euploid cells aggregating to the inner cell mass. Some studies found that aneuploid cells grow slowly, and gradually die in the process of apoptosis, which leading to the born of a healthy fetus.

In general, there was no significant difference the pregnancy outcomes when compared mosaic embryo transfers with euploid controls in our study. But when it comes to CMA analysis and anomaly scan, there were two cases of CNVs and one case of congenital heart disease, while none in euploid controls. And no difference was found in regard to birth weight between the two groups. The data showed mosaic embryo transfer may have worse outcome in prenatal diagnosis

and perinatal follow-up, but the sample size was too small to show significant difference.

However, our study was limited because the sample size was small. It is necessary to conduct a larger study on the clinical outcomes of mosaic embryo transfer and postpartum follow-up, so as to provide doctors with abundant data for clinic consultation.

5. Conclusions

Mosaic embryo detected in the PGT cycle can lead to clinical pregnancy and live birth of healthy offspring, which can be considerate suitable for transfer. Patients should take genetic counseling before transfer, and amniocentesis is recommended for prenatal diagnosis.

In the future, more mosaic embryos would be transferred, which would benefit patients, especially for those have limited number of embryos. And embryos with mosaic level > 50% or more than one chromosome mosaicism may have more chance to be transferred.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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