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Pregnancy Outcomes and Postnatal Health From Transferred Mosaic Embryos Following Preimplantation Genetic Testing for Aneuploidy

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ABSTRACT

Next-generation sequencing (NGS) has increased the detection of mosaic embryos during preimplantation genetic testing for aneuploidy (PGT-A). However, evidence regarding the postnatal and childhood health outcomes following mosaic embryo transfer remains limited especially in the Chinese mainland population. This retrospective study analyzed 123 mosaic embryo transfer cycles performed on 112 patients between January 2019 and May 2024. These cycles were matched to 130 euploid embryo transfer cycles based on the preimplantation genetic testing (PGT) indications. Statistical methods including differential analysis and multivariable logistic regression were employed to compare pregnancy outcomes and postnatal health status. Outcomes assessed included pregnancy results, prenatal ultrasound findings, amniocentesis results, neonatal outcomes, maternal complications, pediatric hospitalizations, the length and reasons for hospital stay, and cognitive development at 1 and 3 years of age. Results demonstrated that both clinical pregnancy rates and live birth rates were significantly lower in the mosaic embryo transfer group compared to the euploid group (both $p < 0.001$), and the miscarriage rate (typically in early pregnancy) rate was higher. Despite these differences, no significant association was observed between mosaic embryo transfer and adverse pregnancy complications, preterm birth, low birth weight, pediatric hospitalization rates, the length or cause of hospitalization, or cognitive development at 1 and 3 years of age. Notably, in ongoing pregnancies resulting from mosaic embryo transfer, persistent mosaicism was observed in 2 cases (4.2%, 2/47). Subgroup analyses revealed no significant differences between segmental mosaic embryos and monosomy/trisomy mosaic embryos in biochemical, clinical, or ongoing pregnancy rates. In contrast, low-level mosaic embryos demonstrated higher ongoing pregnancy rates ($p = 0.007$) and live birth rates ($p = 0.004$), alongside lower miscarriage rates ($p = 0.002$). These findings indicate that although mosaic embryo transfer may reduce pregnancy and live birth rates, healthy offspring can still be achieved.

1 | Introduction

Mosaic embryos are defined as embryos containing two or more distinct cell line karyotypes within a single individual [1]. The mosaicism rates in preimplantation embryos can range from 4% to 90% [2]. Post-zygotic mitotic errors occurring during cell division contribute to the prevalence of aneuploidy in human embryos [3, 4]. Accordingly, this can result in the formation of not only diploid–aneuploid mosaic embryos but also aneuploid, polyploid, and chaotic mosaic embryos.

It has been reported that chromosomal mosaicism may significantly predispose individuals to recurrent implantation failure, spontaneous abortion, stillbirth, and the birth of offspring with severe genetic disorders [5–7]. It may also be associated with cancer and aging [8, 9]. Historically, euploid embryos were regarded as possessing higher implantation potential, whereas aneuploid and mosaic embryos were generally considered unsuitable for transfer.

Clinical observations have demonstrated that although mosaic embryos tend to have lower pregnancy potential compared to euploid embryos [10, 11], ongoing pregnancies often result in healthy neonates [11–13]. However, long-term follow-up data on these neonates are scarce. Currently PGT has become a key strategy to enhance clinical pregnancy rates and reduce miscarriage risks. However, some scholars remain cautious and raise several concerns. First, there are still differences in the diagnostic criteria for mosaicism [11, 14], and the different approaches of clinical geneticists in counseling on mosaic embryos lead to different fates for these embryos [15, 16]. Second, the detection rate of mosaic embryos varies significantly, influenced by factors such as the testing platform, biopsy technique, contamination by cumulus cells, storage conditions, computational software, and operator differences [17]. Consequently, some embryos classified as mosaic may actually be euploid. Third, the potential adverse consequences of transferring mosaic embryos, including fetal growth restriction, neurodevelopmental delay, and certain genetic disorders, are a concern [6, 7]. However, the exact association between these adverse outcomes and the chromosomal mosaic state remains unclear as current detection of mosaicism does not typically involve the inner cell mass that develops into the fetus.

To avoid embryo wastage, especially for older couples who are unable or unwilling to continue with oocyte retrieval, mosaic embryos may offer a means to preserve the opportunity for fertility. Therefore, the safety of mosaic embryo transfer (particularly long-term safety) still requires continuous review and analysis. This retrospective study evaluated the karyotypes of amniotic fluid, morphological abnormalities, neonatal outcomes, and postnatal health assessment results of offspring from mosaic and euploid embryo transfers. These research results aim to improve the existing dataset, especially regarding long-term follow-up data and are expected to fill a gap in the safety and long-term follow-up data for mosaic embryo transfer in the mainland Chinese population.

2 | Materials and Methods

2.1 | Participant Selection, Ethical Review, and Patient Counseling

Participants were from 112 couples who underwent mosaic embryo transfer after preimplantation genetic testing at the Reproductive Centre of the First Affiliated Hospital of Anhui Medical University, China, between January 2019 and May 2024. A total of 123 mosaic embryo transfer cycles were included. The mosaic embryo group comprised cycles in which embryos were biopsied for PGT-A alone as well as cycles in which PGT-M or PGT-SR was performed first because of known monogenic diseases or chromosomal structural rearrangements. Embryos with normal PGT-M/PGT-SR results that were classified as mosaic by PGT-A were included in the mosaic group. These cycles (the mosaic group) were matched with 130 transfer cycles involving euploid embryos identified by PGT-A during the same period, forming the euploid group (see Figure S1 for matching details).

Indications for PGT included female patients aged ≥ 38 years (AMA), those with unexplained recurrent pregnancy loss (≥ 2 events) (RPL), unexplained recurrent implantation failure (≥ 3 frozen transfers with high-quality embryos) (RIF), or individuals requiring PGT for aneuploidy combined with PGT-M/SR. The exclusion criteria were as follows: (1) cycles with sperm and oocyte donors; (2) Infertile patients with endometriosis, submucosal fibroids, or uterine malformations; and (3) infertile patients with endocrine or metabolic diseases.

The study protocol was approved by the Ethics Committee of this hospital (Ethics No.: 2017002, Date: February 24, 2017). All couples underwent comprehensive counseling with genetic counselors and clinical specialists concerning the potential risks associated with mosaic embryo transfer before the procedure, including the possibility of miscarriage. In the event of a miscarriage, karyotyping of the tissue was recommended. Mid-pregnancy prenatal diagnosis was recommended to all patients who received PGT, and couples were briefed on the available prenatal screening and diagnostic methods, including their respective benefits and limitations. All participants underwent single blastocyst transfer after providing written informed consent.

2.2 | Standardized In Vitro Fertilization Procedure

Different controlled ovarian hyperstimulation (COH) protocols may affect egg quality [18]. All patients received a standardized ovarian stimulation protocol, oocyte retrieval, ICSI fertilization, embryo transfer, and luteal support subsequently. For a detailed description of these protocols, please refer to our previous publication [19]. To minimize DNA contamination from residual cumulus cells and sperm adherent to the zona pellucida, all PGT procedures at our center utilize ICSI for fertilization. The quality of blastocysts (Day 5 or Day 6) was assessed based on the Gardner and Schoolcraft grading system [20]. High-quality

blastocysts including grades AA, AB, BA, and BB blastocysts were chosen for PGT.

2.3 | PGT-A and Mosaic Classification

DNA extracted from blastocyst TE samples cultured to Day 5 or 6 underwent whole genome amplification (WGA) using SurePlex (Illumina). A portion of the amplified products was utilized for PGT-M/SR detection using the same platform as PGT-A (Illumina), with the detection process detailed in previous publications [21]. The remaining amplified products were subjected to NGS on the NextSeq550 (Illumina) system. Reads were aligned to the NCBI GRCh37 human reference genome using integrated analysis software and converted to BAM files. Levels of mosaicism > 80% or < 20% could not be distinguished from technical noise. Accordingly, based on the PGDIS guidelines [22], mosaicism > 80% was classified as aneuploid, mosaicism < 20% as euploid, and mosaicism between 20% and 80% as a putative mosaic embryo. A cutoff of 50% was applied, with ≥ 50% considered high-level mosaicism and < 50% low-level mosaicism. Putative mosaic embryos were further classified into segmental aneuploidy (single segment), whole chromosome aneuploidy (monosomy or trisomy), double mosaicism (involving two chromosomes), and complex aneuploidy (involving three or more chromosomes) [11].

2.4 | Outcome Measures

Clinical pregnancy was established when a gestational sac was visualized via transvaginal ultrasound 35 days after embryo transfer. For ongoing pregnancies, amniocentesis was recommended between 18 and 24 weeks to assess chromosomal karyotyping via standard G-banding and chromosomal microarray analysis (CMA) alongside fetal ultrasound to evaluate development and detect structural abnormalities. Live birth was defined as a delivery at or after 22 weeks of gestation or later [23]. This study tracked the pregnancy outcomes after embryo thawing and transfer, including prenatal and perinatal outcomes such as fetal ultrasound findings, amniotic fluid testing, and maternal complications. Postnatal outcomes included newborn measures, physical and intellectual development of the child, congenital anomalies, surgical intervention, as well as the reasons and duration of hospitalization for the child. Data were collected through the clinical reproductive medicine management system, prenatal diagnosis center, obstetric electronic medical record system, and telephone follow-ups. All information was up to February 10, 2025.

2.5 | Statistical Methods

The data were analyzed using SPSS 26.0 or GraphPad Prism 10.0. The Shapiro–Wilk test assessed the normality of continuous variables. Normally distributed measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$), whereas non-normally distributed data were represented by the median and interquartile range. Categorical data were reported as percentages or composition ratios. Comparisons of categorical data were made using the χ^2 test or Fisher's exact test, whereas measurement data were analyzed with the *t*-test or Mann–Whitney *U* test as appropriate. Binary logistic regression (with multivariable analysis accounting for confounding) was used for categorical variables associated with postpartum outcomes, including neonatal measures. Confounding factors used in these analyses included parental age, BMI, number of previous transfers, days of embryo development, maternal complications of pregnancy, and type of delivery. Statistical significance was defined as $p < 0.05$, with differences considered highly significant at $p < 0.001$.

3 | Results

3.1 | Baseline Characteristics, Pre-Transfer Clinical Indicators, and Clinical Outcomes

The mosaic group had a significantly higher number of previous transfer attempts than the euploid group ($p = 0.009$). In terms of embryo development stage, the euploid group had a greater proportion of day-5 (D5) embryos, with a statistically significant difference between groups ($p = 0.031$). Other baseline characteristics and pre-transfer clinical indicators did not differ significantly between the two groups. In clinical outcomes, the mosaic group showed a lower clinical pregnancy rate compared with the euploid group (51.22%, 63/123 vs. 75.38%, 98/130; $p < 0.001$) and a higher miscarriage rate (20.63%, 13/63 vs. 11.22%, 11/98). The live birth rate per transfer cycle was also significantly lower in the mosaic group (40.65%, 50/123 vs. 66.92%, 87/130; $p < 0.001$). These outcomes are summarized in Tables 1 and 2.

3.2 | Amniotic Fluid Testing and Ultrasound Analysis of Pregnancies

As detailed in the study flow chart (Figures S2A,B), some patients in both groups did not undergo amniotic fluid testing either due to low-risk results of noninvasive prenatal testing (NIPT) or the coronavirus disease 2019 (COVID-19) pandemic (Table 3).

In the mosaic group (classified as mosaic by PGT-A), two cases were excluded from the obstetric and postnatal health analyses. In Case no. 65 of Table S1, amniotic fluid testing revealed a novel mosaic karyotype [47, XNN (60%)/46, XN (40%)], where N denotes X or Y. After counseling regarding the probable risk of clinical symptoms suggestive of Klinefelter syndrome (47, XXY), including a high risk of severe intellectual disability and other health problems, the patient opted to terminate the pregnancy at 26 weeks. In Case no. 99, amniotic fluid testing showed a low-level duplication at 22q11.23 [46, XN; CNV (hg19) dup (22)(q11.23q11.23)] (details provided in Figure 1), which was deemed benign. No abnormalities were detected during prenatal ultrasound. However, intrauterine fetal death occurred at 38 weeks, prompting labor induction. Severe umbilical cord twisting was identified as a potential cause. In neither case of pregnancy termination was parental consent obtained for chromosomal testing of the fetal tissue.

Notably, amniotic fluid testing revealed persistent mosaicism in two cases (Case Nos. 11 and 50, Table S1), with mosaic patterns consistent with the embryo PGT-A results. The karyotype of

TABLE 1 | Comparison of baseline characteristics between the two groups M [Q1, Q3] *n* (%).

Variable	Mosaic group ($n = 123$)	Euploid group ($n = 130$)	Z value/x^2 value	p value
Female age (y), (M [Q1, Q3])	32.00 [29.00, 35.00]	31.00 [28.00, 34.00]	$Z = -1.873$	0.061
Male age (y), (M [Q1, Q3])	33.00 [30.00, 37.00]	32.00 [29.00, 35.00]	$Z = -1.678$	0.093
BMI (kg/m^2), (M [Q1, Q3])	22.30 [20.50, 23.90]	21.60 [19.90, 23.60]	$Z = -1.944$	0.052
FSH (mIU/mL), (M [Q1, Q3])	6.97 [5.77, 8.13]	6.81 [5.83, 7.88]	$Z = -0.153$	0.878
E2 (pmol/mL), (M [Q1, Q3])	132.00 [94.52, 221.00]	126.99 [81.65, 185.00]	$Z = -1.216$	0.224
LH (mIU/mL), (M [Q1, Q3])	4.87 [3.66, 6.35]	4.40 [3.23, 5.64]	$Z = -1.120$	0.263
Bilateral AFC (n), (M [Q1, Q3])	7.00 [5.00, 10.00]	7.00 [5.00, 10.00]	$Z = -0.326$	0.745
Infertility type, *n* (%)			$x^2 = 1.327$	0.249
Primary infertility, *n* (%)	29 (23.58%)	39 (30.00%)		
Secondary infertility, *n* (%)	94 (76.42%)	91 (70.00%)		
PGT indications, *n* (%)			$x^2 = 1.788$	0.618
RPL	30 (24.40%)	26 (20.00%)		
RIF	15 (12.20%)	12 (9.20%)		
AMA	13 (10.60%)	13 (10.00%)		
Chromosome-related (n)%	65 (52.80%)	79 (60.80%)		
Previous miscarriages, (M [Q1, Q3])	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)	$Z = -0.070$	0.994
Previous transfers, (M [Q1, Q3])	1.00 (0.00, 2.00)	0.00 (0.00, 1.00)	$Z = -2.608$	0.009

TABLE 2 | Comparison of pre-transfer clinical indicators and pregnancy outcomes between the two groups M [Q1, Q3] *n* (%).

Variable	Mosaic group ($n = 123$)	Euploid group ($n = 130$)	Z value/x^2 value	p value
Days of embryo development, *n* (%)			$x^2 = 4.670$	0.031
D5	69 (56.10%)	90 (69.23%)		
D6	54 (43.90%)	40 (30.77%)		
High-quality embryo, *n* (%)			$x^2 = 0.000$	0.989
Yes	104 (84.55%)	110 (84.62%)		
No	19 (15.45%)	20 (15.39%)		
Endometrial thickness on transformation day (mm), (M [Q1, Q3])	9.80 [9.00, 10.70]	10.00 [9.00, 11.00]	$Z = -0.230$	0.818
Endometrial preparation regimen, *n* (%)			$x^2 = 0.180$	0.671
HRT	118 (95.94%)	126 (96.92%)		
NC	5 (4.07%)	4 (3.08%)		
Clinical pregnancy rate, *n* (%)	63 (51.22%)	98 (75.38%)	$x^2 = 15.949$	0.000
Miscarriage Rate, *n* (%)	13 (20.63%)	11 (11.20%)	$x^2 = 2.677$	0.102
Live birth rate, *n* (%)	50 (40.65%)	87 (66.92%)	$x^2 = 17.571$	0.000

Note: High-quality embryo: grades AA, AB, BA, and BB blastocysts assessed based on Gardner and Schoolcraft grading system.
Abbreviations: HRT, hormone replacement therapy; mm, millimeter; NC, natural cycle.

embryo No. 11 was mos (+11) (q14.1q11.2) (19.80 Mb) (30%). Literature [24] indicates that a deletion of the q arm of chromosome 11 is associated with Jacobsen syndrome, which manifests as growth retardation, cardiac defects, thrombocytopenia, and other symptoms, with severity depending on the proportion of mosaicism. For the pregnancy resulting from this mosaic embryo, amniotic fluid testing at mid-pregnancy also revealed the duplication of a chromosome 11 fragment (karyotype: 46, XN, CNV duplication of Chr11, 1.2 Mb) (Figure 2). Systematic ultrasound examination of the fetus revealed no abnormalities, and the outcome was a healthy live birth. As of the follow-up deadline, the child was approaching 4 years of age, with no observed abnormalities in daily life, academic performance, or physical development. Embryo No. 50 had a karyotype of mos (+6) (33%). While normal amniotic fluid testing results for standard karyotyping and CMA, fluorescence in situ hybridization (FISH) results indicated a mosaic carrier of chromosome 6. Complete trisomy of chromosome 6 is typically associated with early miscarriage, whereas mosaic embryos may survive and carry tumor-related genes, potentially leading to

TABLE 3 | Comparison of prenatal and perinatal outcomes between the two groups who achieved live births (*n*%).

Variable	Classification	Mosaic group (n = 50)	Euploid group (n = 87)	x^2 value/ Z value/ t value	p value
Ultrasound screen, *n* (%)	Not done	2 (4.00%)	1 (1.15%)		
	Normal	37 (74.00%)	77 (88.50%)		
	Positive finding	11 (22.00%)	9 (10.30%)		
Amniocentesis fluid test, *n* (%)	Not done	5 (10.00%)	28 (32.30%)		
	Normal	34 (68.00%)	51 (58.62%)		
	Positive finding	11 (22.00%)	8 (9.20%)		
Gestational age (wk), (M [Q1, Q3])		38.71 [38.04, 39.43]	37.79 [0.00, 39.29]	$Z = -2.90$	< 0.01
	Prematurity	3 (6.00%)	14 (16.10%)	$x^2 = 2.975$	0.085
	Full-term	47 (94.00%)	73 (83.90%)		
Maternal age at birth (y) (mean ± SD)		33.23 ± 4.71	32.21 ± 4.60	$t = 1.24$	0.22
Delivery type, *n* (%)				$x^2 = 0.088$	0.767
	Cesarean section	34 (68.0%)	16 (32.0%)		
	Vaginal birth	57 (65.5%)	30 (34.5%)		
Maternal complications, *n* (%)				$x^2 = 2.382$	0.666
	Hypertension	5 (10.00%)	8 (6.85%)		
	GDM	7 (14.00%)	13 (14.90%)		
	Placental abnormalities	1 (2.78%)	5 (5.48%)		
	Others[a]	0 (0.00%)	3 (4.11%)		
	No complications	37 (74.00%)	59 (67.80%)		

Abbreviations: GDM, gestational diabetes mellitus; wk, week.
[a]Others, include hypothyroidism, placenta previa, liver function lesion.

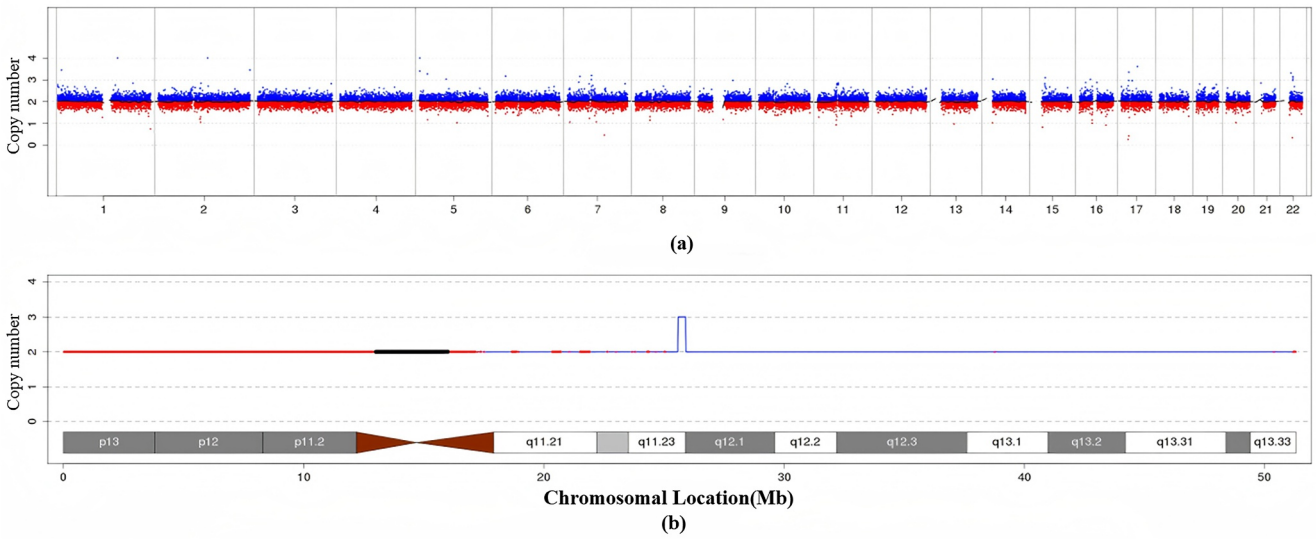

FIGURE 1 | Amniotic fluid sequencing results of No. 99 in Table S1. (a) Comprehensive Genomic Analysis Results; (b) Results of Chromosome 22 Detection (CNV):seq [hg19]dup (22) (q11.23q11.23) chr22:g.25580000_25900000dup. A 0.32 Mb duplication at chromosome 22 q11.23, encompassing three protein-coding genes (1A, 0 points; 3A, 0 points), was identified. A comprehensive search of public databases including DGV, DECIPHER, OMIM, ClinGen, UCSC, gnomAD, and PubMed revealed no additional definitive pathogenic information or case reports associated with this segment. Combining the population proportions from DGV and gnomAD databases (40, −1 point), the region's total score was ≤ −0.99 points, classifying it as a benign variant. The population frequency in DGV and gnomAD databases was 40 (−1 point). The total score for this region is ≤ −0.99 points, classifying it as a benign variant.

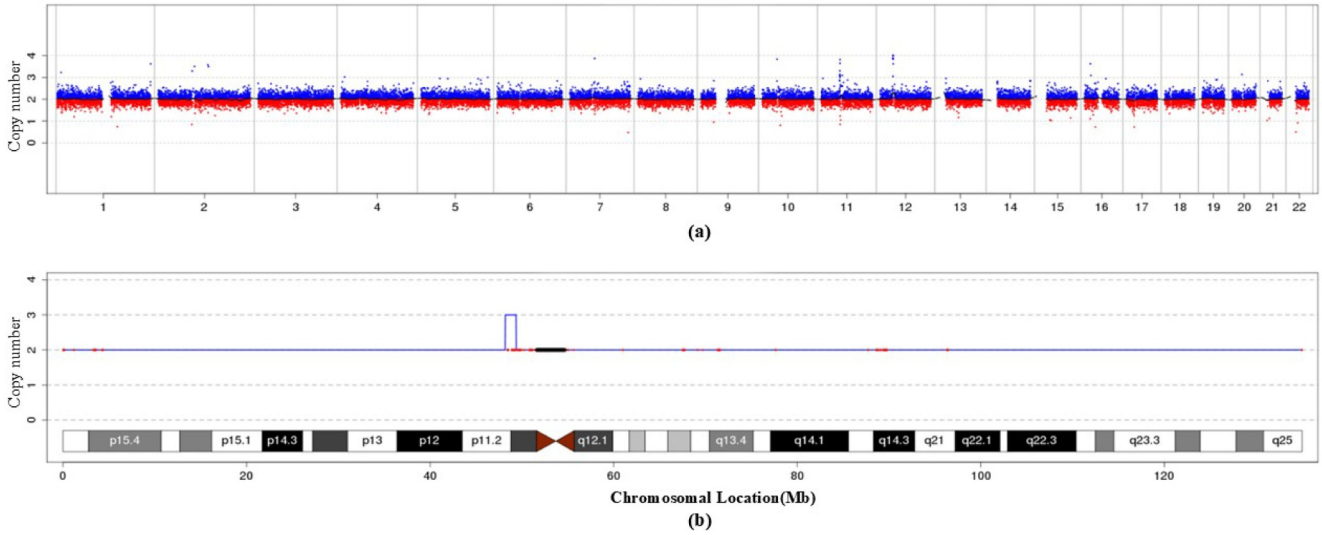

FIGURE 2 | Amniotic fluid sequencing results of No. 11 in Table S1. (a) Comprehensive Genomic Analysis Results; (b) Results of CNV:seq [hg19] dup (11) (p11.2p11.12) chr11:g.48180000_49380000dupdup (11) (p11.2p11.12). A 1.20 Mb duplication at chromosome 11 p11.2-p11.12 was identified. A search of public databases including DECIPHER, OMIM, ClinGen, UCSC, gnomAD, and PubMed revealed no definitive pathogenic information or literature reports associated with this segment. The DGV database identified one normal carrier of this duplicate segment among 3017 samples carrying this duplicated segment.

hematologic malignancies. Systemic ultrasound screening results for this patient at mid-pregnancy were normal. A healthy infant was delivered naturally after a full-term pregnancy, and as of the follow-up deadline, the infant was 1 month old with no abnormalities detected, though further follow-up was required. Although these two cases exhibited persistent mosaicism, the copy number variation (CNV) results suggested a benign possibility, and no abnormalities were observed in the postpartum outcomes.

The abnormal findings of amniotic and relevant ultrasound results of the two groups are presented in Table S2. The types of abnormal ultrasound screening findings in the mosaic group ($n = 123$) included small defects near the ventricular septum (1 case), a small gallbladder (1 case), persistent left superior vena cava (1 case), bright spots in the left ventricle (2 cases), mild tricuspid valve regurgitation (7 cases), and polydactyly with amniotic band syndrome (1 case). Findings in the euploid group ($n = 130$) included echogenic bowel (1 case), mild tricuspid valve regurgitation (5 cases), a velamentous placenta (1 case), and a persistent right umbilical vein (1 case). All identified abnormalities were isolated, as detailed in Table S1.

3.3 | Follow-Up Outcomes up to 3 Years

No significant differences were observed between the mosaic and euploid groups in terms of premature birth (6.00% vs. 16.10%), low birth weight (2.00% vs. 9.20%), average newborn weight (3353.90 vs. 3262.76 g), or age of the child at the time of follow-up (all $p > 0.05$). Similarly, the hospitalization rates at 1 year (12.00% vs. 8.00%) and 3 years after birth (8.00% vs. 11.50%), as well as the total number of hospitalization days, showed no significant differences between the groups (all $p > 0.05$). A significant difference was found in the hospitalization rate during the neonatal period (2.00% vs. 14.90%, $p = 0.016$), though no significant differences were noted in the causes of hospitalization ($p = 0.96$). As of the follow-up date, the primary postnatal conditions in the mosaic group comprised neonatal pulmonary adaptation (5 cases), neonatal fever (1 case), and neonatal jaundice (3 cases). In contrast, the primary postnatal conditions in the euploid group comprised neonatal pulmonary adaptation (10 cases), neonatal fever (3 cases), neonatal jaundice (6 cases), preterm birth (3 cases), and necrotizing enterocolitis (1 case). Within the euploid group, one case underwent inguinal hernia repair and currently presents with cryptorchidism. One case underwent tongue frenotomy. No surgical cases were recorded in the mosaic group.

Three cases in the mosaic group exhibited postnatal structural or body surface abnormalities. As shown in Table S1, In Case No. 27 a mosaic embryo with mos (-7) (q31.1-q36.3) (47.72Mb) (43%) was transferred; the amniocentesis results were 45, XN, der (14:21) (q10q10), and the ultrasound showed a perventricular septal defect. A female infant was delivered via cesarean section at full term, weighing 3500 g. At 10 months, the infant presented with a persistent patent foramen ovale during physical examination and is currently under regular follow-up at the Children's Hospital. In Case No. 28, a mosaic embryo with mos (+20)[35%] transferred, which had normal amniocentesis results, Ultrasound screening identified a persistent left superior vena cava and a significant echogenic focus in the left ventricle. The infant was delivered by cesarean section at 38 + 5 weeks, weighing 4450 g, and is currently 16 months old. Physical examination at the Children's Hospital revealed a patent foramen ovale, a 3.6 mm ventricular septal defect, mild pulmonary hypertension, and mild mitral regurgitation. This case still requires ongoing follow-up as there are currently no obvious symptoms. Case No. 44 involved a transferred mosaic blastocyst mos (+22)[30%], with normal NIPT during pregnancy and no

amniocentesis performed. Fetal ultrasound screening indicated polydactyly with amniotic band syndrome, and a right thumb polydactyly was detected at birth. No intellectual abnormalities were found in the physical examination.

Parental reports via telephone follow-up indicated that no intellectual or mental deficiencies have been detected so far in either the mosaic group or the euploid group, and school-aged children were all attending mainstream classes. Physical examinations in the community have also shown no growth retardation, as shown in Table 4.

Multivariable logistic regression analyses were performed separately for major postnatal outcomes. Embryo type (mosaic vs. euploid) was included as the primary exposure. Previous transfers, days of embryo development, maternal complications, maternal complications, maternal age at birth, and delivery type were adjusted as potential confounders. The results showed that embryo type was not significantly associated with any postnatal outcomes up to a mean child age of approximately 3 years (Table S3).

3.4 | Types and Levels of Mosaicism in the Mosaic Embryo Transfer Group

Among the 123 mosaic embryos, 50 (40.65%, 50/123) exhibited chromosomal segmental mosaicism, the most common type. Whole chromosome mosaicism was identified in 47 embryos (38.21%, 47/123), whereas 14 embryos (11.38%, 14/123) involved two chromosomes and complex mosaicism was observed in 12 embryos (9.76%, 12/123). Of the 50 live births, 49 were classified as low-level mosaicism and 1 as high-level mosaicism. No significant differences were found in the biochemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate, early miscarriage rate, or live birth rate across different mosaicism types. However, the miscarriage rate was higher for whole chromosome mosaicism compared to segmental mosaicism (33.3% vs. 3.7%). In the analysis of mosaicism levels, the biochemical pregnancy rate and the clinical pregnancy rate showed no significant differences (all $p > 0.05$). As pregnancy progressed, differences in pregnancy potential became more evident. The low-level mosaic group demonstrated significantly higher ongoing pregnancy ($p = 0.007$), lower early miscarriage

TABLE 4 | Comparison of postnatal outcomes and offspring health follow-up between the two groups who achieved live births (*n*)%.

Variable	Classification	Mosaic group ($n = 50$)	Euploid group ($n = 87$)	x^2 value/ Z value/ t value	p value
Neonatal birth length (cm) (mean ± SD)		50.64 ± 1.86	50.12 ± 2.21	$t = 14.652$	0.261
Neonatal birth weight (g) (mean ± SD)		3353.90 ± 471.85	3262.76 ± 509.85	$t = 1.04$	0.877
Birth weight < 2500 g, *n* (%)				$x^2 = 2.678$	0.102
	No	49 (98.00%)	79 (90.80%)		
	Yes	1 (2.00%)	8 (9.20%)		
Neonatal hospitalization rate, *n* (%)		1 (2.00%)	13 (14.90%)	$x^2 = 5.797$	0.016
Hospitalization rate before 1 year old, *n* (%)		6 (12.00%)	7 (8.05%)	$x^2 = 0.209$	0.647
Hospitalization rate before 3 years old, *n* (%)		4 (8.00%)	10 (11.50%)	$x^2 = 0.423$	0.516
Reason for hospitalization, *n* (%)				$x^2 = 0.341$	0.961
	Not hospitalized	25 (69.44%)	49 (67.12%)		
	Neonatal jaundice	1 (2.778%)	3 (4.110%)		
	Pneumonia, bronchitis	7 (19.44%)	13 (17.81%)		
	Others[a]	3 (8.33%)	8 (10.96%)		
Hospital length (d), M [Q1,Q3]		0.000 [0.000, 0.000]	0.000 [0.000, 6.000]	$Z = 1.389$	0.165
Congenital anomalies, *n* (%)		1 (2.00%)	0	—	
Surgical intervention, *n* (%)		0	2 (2.30%)	—	
Age of the child (y), M [Q1,Q3]		1.65 [0.70, 3.46]	1.87 [1.24, 3.45]	$Z = -1.15$	0.25
Intelligence defect, *n* (%)		0	0	—	
Growth restriction in childhood, *n* (%)		0	0	—	

Abbreviations: cm, centimeter; d, day; g, gram.
[a]Others, include fever, viral cold, parascarlatina, acute laryngitis, bubonocele, prematurity, lingual frenulum surgery, abnormal coagulation function.

TABLE 5 | Comparison of mosaic types and mosaic level classification in the mosaic embryo group (n = 123) (n%).

Variable	Segmental mosaicism n = 50	Monosomy/trisomy mosaicism n = 47	Two chromosomes n = 14	Complex mosaicism n = 12	x^2 value	p value	Low-level mosaicism n = 106	High-level mosaicism n = 17	x^2 value	p value
Biochemical pregnancy, n (%)	27 (54.00%)	29 (61.70%)	6 (42.86%)	5 (41.67%)	2.550	0.466	61 (57.50%)	6 (35.3%)	2.925	0.087
Clinical pregnancy, n (%)	27 (54.00%)	27 (57.40%)	4 (28.60%)	5 (41.67%)	4.197	0.241	58 (54.70%)	2 (29.41%)	3.755	0.053
Ongoing pregnancy, n (%)	26 (52.00%)	17 (36.17%)	4 (28.60%)	4 (33.33%)	4.115	0.249	49 (46.23%)	2 (11.76%)	7.169	0.007
Miscarriage, n (%)	1 (3.70%)	9 (33.33%)	1 (25.00%)	1 (20.00%)	7.791	0.051	9 (15.52%)	4 (80.00%)	8.081	0.004
Live birth, n (%)	25 (50.00%)	18 (38.30%)	3 (21.43%)	4 (33.33%)	4.330	0.228	49 (46.23%)	1 (5.90%)	9.884	0.002

(p = 0.004), and higher live birth rates (p = 0.002) compared to the high-level mosaic group, with statistically significant differences as shown in Table 5.

We further compared outcomes among the segmental mosaicism, the whole chromosome mosaicism, and the euploid embryo groups, as well as between the low-level mosaicism and the euploid groups. It was observed that pregnancy and live birth rates were lower in cases of segmental mosaicism, whole chromosome mosaicism, and low-level mosaicism compared to the euploid embryo group. However, there was no significant difference in these outcomes between the segmental and whole chromosome mosaicism groups (as shown in Figure 3).

4 | Discussion

In the present study, the number of prior transfer cycles was significantly higher in the mosaic group compared to the euploid group (p = 0.009), potentially due to the mosaic group undergoing more cycles following failed transfers of euploid embryos. Comparing embryo development days, the euploid group exhibited a higher proportion of D5 embryos, with a significant difference between groups (p = 0.031). Previous work [25] indicates that by Day 5, embryos forming blastocysts typically exhibit superior developmental potential and are more likely to be euploid, whereas embryos developing to the blastocyst stage on Day 6 demonstrate relatively higher rates of chromosomal abnormalities and mosaicism. The uneven distribution of embryonic development days between the two groups in this study suggests that embryos in the euploid group exhibited faster overall development and potentially superior quality. To account for this imbalance, we included both the number of previous transfers and the day of blastocyst development in the multivariable logistic regression when comparing pregnancy outcomes between the two groups, thereby reducing the impact of these confounding factors. Finally, the analysis revealed that postnatal outcomes did not differ based on the classification of the transferred embryo (mosaic or euploid) up to an average child age of approximately 3 years.

Amniotic fluid testing showed that most chromosomal abnormalities detected at the blastocyst stage were no longer present as pregnancy progressed. This is consistent with previous reports. Studies have reported that the incidence of mosaicism during the cleavage stage ranges from 15% to 93% [2, 26, 27], whereas in the blastocyst stage, it is typically between 5% and 15% [28]. By the second trimester, amniotic fluid karyotyping reveals a reduced mosaicism rate, with mosaic cells potentially disappearing postnatally, as confirmed by blood or tissue testing [12, 29]. This observation suggests that chromosomal mosaicism can be self-corrected, as normal ploidy cells exhibit greater selective adaptability than aneuploid cells during pregnancy [30]. Another proposed theory is confined placental mosaicism (CPM), where mosaicism is generally restricted to trophectoderm cells and does not extend to the inner cell mass [31]. This may explain why the majority of mosaicism cases are no longer detectable in amniotic fluid testing.

However, this self-correction mechanism is not always complete. Mosaicism identified at the blastocyst stage persisted to amniotic

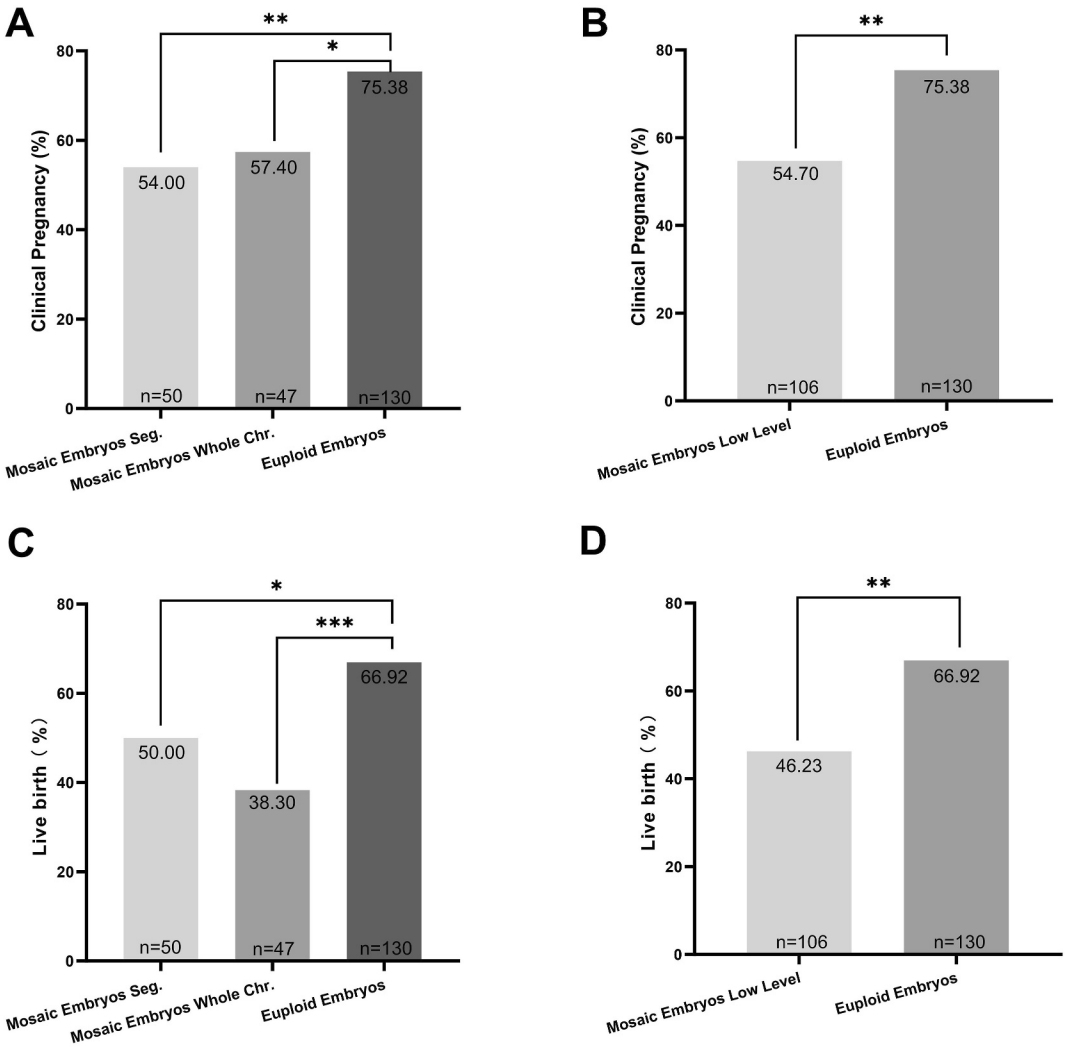

FIGURE 3 | Comparison of different mosaic types and mosaic levels of mosaic embryos with the euploid group. (A) Comparison of clinical pregnancy rates between different mosaic type groups and the euploid group. **$p < 0.01$ mosaic embryo Seg. versus euploid group. *: $p < 0.05$, mosaic embryo whole Chr. versus euploid group. Chr., chromosome; Seg., segmental. (B) Comparison of clinical pregnancy rates between mosaic low-level group and the euploid group. **: $p < 0.01$. (C) Comparison of live birth rates between different mosaic type groups and the euploid group. *: $p < 0.05$, mosaic embryo Seg. versus euploid group. ***: $p < 0.001$, mosaic embryo whole Chr. versus euploid group. Chr., chromosome; Seg., segmental. (D) Comparison of live birth rates between the mosaic low-level group and the euploid group. **: $p < 0.01$.

fluid testing in 2 cases (4.2%, 2/47) in our cohort. This rate is higher than in some previously reports [12], a finding that may be due to the limited sample size in our study. Nevertheless, both infants were born without apparent abnormalities and remained well during follow-up. This is in line with findings by Phillips et al. [32] who noted that although mosaicism typically remains limited to the placenta, fetal involvement occurs in about 10% of cases.

In our dataset, the mosaicism detected at the blastocyst stage did not correlate with the findings from amniocentesis. New chromosomal variants can emerge in pregnancies originating from euploid embryos. One explanation for this phenomenon is that the initial blastocyst assay targets trophoblast ectodermal cells, which may not accurately represent the fetus, leading to discrepancies between the amniotic fluid assay and the karyotype at the time of embryo assessment. This perspective is supported by previous reports [33]. Another potential explanation is that due to sampling bias, mosaicism detected in one examination may be missed in another, highlighting a significant limitation in the detection of mosaicism. Technical factors must also be considered when interpreting mosaic or inconsistent results, as they can cause false-positive mosaicism. Beyond true biological mosaicism, errors introduced during whole-genome amplification (WGA) and subsequent copy-number analysis can create patterns that mimic low-level aneuploidy. Ou et al. showed that some blastocysts initially classified as abnormal or mosaic on trophectoderm (TE) biopsy were reclassified as euploid or non-mosaic when the whole blastocyst was reanalyzed, suggesting that part of the discordance may be technical [34]. In particular, multiple displacement amplification (MDA) can introduce uneven amplification and spurious copy-number changes, whereas the high sensitivity of next-generation sequencing (NGS) to small segmental imbalances makes it vulnerable to noise and algorithm-dependent calling thresholds. Together, these issues indicate that some mosaic calls may reflect methodological limitations rather than true embryonic mosaicism, underscoring

the need for cautious interpretation of TE-based PGT results and careful reporting of mosaic embryos.

Taken together, these observations suggest that many embryos classified as mosaic may actually be euploid or may normalize during development [33]. Such embryos should therefore not be discarded lightly, especially in older patients for whom each embryo has high clinical value. At the same time, the prioritization of different types of mosaic embryos for transplantation should be considered within the scope of evaluation.

Both the type and level of mosaicism are believed to influence an embryo's developmental potential [35]. More complex chromosomal mosaicism is generally associated with poorer pregnancy outcomes [36]. As is well established, embryos originate from a single fertilized oocyte, and abnormalities during the meiotic stage of gamete formation typically result in homogeneous aneuploidy across all cells. The incidence of such aneuploidy increases with maternal age. However, Munne [35] and Frumkin et al. [4] found that the incidence of early embryonic mosaicism did not increase with age, suggesting that mosaicism arises during the mitotic phase following fertilization.

In our study, embryos with segmental mosaicism and those with monosomy/trisomy mosaicism had similar biochemical, clinical, and ongoing pregnancy rates. These outcomes were better than those for embryos with double or complex mosaicism. Although these results were consistent with previous reports [35], differences among mosaic subtypes did not reach statistical significance, likely due to the limited sample size.

The level of mosaicism is also associated with outcomes, with higher levels generally predicting poorer prognosis. In a mouse model, Bolton et al. [37] identified the same proportion of aneuploid cells: embryos below this threshold can selectively eliminate aneuploid cells from the embryonic lineage, whereas embryos above the threshold often fail. Embryos below this threshold are preferentially removed from the embryonic lineage to dilute the aneuploid cell ratio, whereas embryos with an aneuploid cell ratio exceeding the threshold often fail to develop. Clinical data similarly indicate that low-level mosaic embryos can have outcomes comparable to euploid embryos [38, 39]. Clinically, a 50% threshold is commonly used to distinguish low- from high-level mosaic embryos [40]. Our analysis revealed that the difference in viability between low- and high-level mosaic embryos became more pronounced with advancing gestation, and the live birth rate was significantly higher in the low-level group than in the high-level group (46.20% vs. 5.90%, $p = 0.002$).

The safety of mosaic embryo transfer remains an area of active debate, and careful clinical management is essential. PGDIS [22] emphasizes that prenatal diagnosis holds significant importance for patients undergoing mosaic embryo transfer following PGT. Amniocentesis, by analyzing fetal cells in the amniotic fluid, provides a more direct assessment of the fetal chromosomal status. Furthermore, detailed mid-pregnancy anatomical assessment and long-term developmental follow-up are crucial to building a robust evidence base for counseling and managing patients considering or undergoing mosaic embryo transfer.

4.1 | Limitations

To our knowledge, our study represents the first comprehensive analysis of postnatal outcomes and childhood follow-up data for embryos classified as mosaic by PGT-A in the mainland Chinese population. It provides unique and valuable data and experience specific to this demographic. However, several limitations should be noted. First, differences in assessment criteria, follow-up duration, and data collection methods may affect the accuracy of the health information obtained. In particular, the health status of children aged 1–3 years was mainly assessed via telephone interviews with parents, which may be subject to recall bias, underreporting, or minor inaccuracies. Second, the retrospective and single-center nature of the study introduces potential selection and information bias and restricts the sample size. Longer-term follow-up into adolescence and adulthood will be needed to confirm and extend these findings.

5 | Conclusions

This study suggests that the transfer of mosaic embryos can yield healthy offspring without a significant increase in congenital anomalies. For couples lacking euploid embryos or experiencing limited oocyte yield, transferring a mosaic embryo may be a reasonable option, provided that potential risks and benefits are fully discussed and understood. Future work, especially large multicenter prospective studies, is essential to refine diagnostic criteria for mosaicism and to validate these results. In addition, robust long-term follow-up protocols, combined with genetic confirmation when appropriate, will be crucial for accurately assessing the safety of mosaic embryo transfer.

Author Contributions

Lili Chen: writing – original draft, writing – review and editing, investigation, data curation, methodology, software, conceptualization, visualization. **Dehuan Huang:** investigation, data curation. **Jingcheng Sang:** investigation, data curation. **Yiqi Yin:** investigation, data curation. **Caiyun Wu:** writing – review and editing. **Yan Hao:** validation, methodology, project administration. **Dawei Chen:** validation, methodology, project administration. **Zhiguo Zhang:** validation, methodology, project administration. **Yunxia Cao:** writing – review and editing. **Ri-Cheng Chian:** writing – review and editing. **Ping Zhou:** conceptualization, methodology, data curation, funding acquisition, project administration, resources, writing – review and editing, supervision.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Figure S1: Matching details of the mosaic embryo group and the control euploid embryo group. **Figure S2:** Study flow chart of the two groups. (A) Study flow chart of the mosaic group. IUFD, Intrauterine Fetal Death; NIPT, noninvasive prenatal testing. (B) Study flow chart of the euploid group. **Table S1:** Details of mosaic embryos results (n = 123). **Table S2:** Details of positive results of prenatal tests performed in pregnancies from two groups embryo transfers. **Table S3:** Adjusted association analysis of postnatal outcomes following mosaic embryo and euploid embryo transfer.