The nature of embryonic mosaicism across female age spectrum: an analysis of 21,345 preimplantation genetic testing for aneuploidy cycles

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Objective: To understand how mosaicism varies across patient-specific variables and clinics.
Design: Cross-sectional cohort.
Setting: Genetic testing laboratory.
Patients: A total of 86,208 embryos from 17,366 patients underwent preimplantation genetic testing for aneuploidy using next-generation sequencing.
Intervention(s): Mosaic embryos were classified as either low-level (20%–40%) or high-level (40%–80%) and by type of mosaic error: single segmental, complex segmental, single chromosome, or complex abnormal mosaic. The rate of mosaicism was stratified by the Society for Assisted Reproductive Technology age categories: <35 years, 35–37 years, 38–40 years, 41–42 years, and >42 years.
Main Outcome Measure(s): Distribution of chromosomal findings and prevalence of mosaicism type by age. Probability of creating mosaic embryos in a subsequent cycle.
Result(s): Among all embryos, 44% were euploid, 40.2% were aneuploid, and 15.8% were mosaic. Both low-level and high-level mosaicism were more prevalent among younger patients. Of all mosaic embryos, the youngest age cohort <35 years had the highest proportions of single and complex segmental mosaicism (37.9% and 6.8%, respectively), whereas those aged >42 years had the highest single whole chromosome and complex abnormal mosaicism (37.1% and 34.0%, respectively). Although there was variability in mosaic rates across clinics, the median mosaic rate over 3 years ranged from 14.48% to 17.72%. A diagnosis of a mosaic embryo in a previous cycle did not increase a patient's odds for having a mosaic embryo in a subsequent cycle.
Conclusion(s): Mosaicism is overall higher in younger patients, but the complexity of mosaic errors increases with age. A history of mosaicism was not associated with mosaicism in subsequent cycles. Additional research is needed to understand the etiologies of the various subtypes of mosaic embryos and clinical outcomes associated with their transfer. (Fertil Steril Rep® 2023;4:256–61. ©2023 by American Society for Reproductive Medicine.)
Key Words: Mosaic rates, segmental, whole chromosome, mosaicism types

Preimplantation genetic testing for aneuploidy (PGT-A) was developed to prevent transferring embryos with chromosomal abnormalities (1). Although studies have demonstrated that use of PGT-A over embryo morphology alone improves live birth rates per transfer in women aged >35 years, the value of PGT-A in unselected patients has not been demonstrated clearly (1, 2). In fact, studies have shown no difference in implantation or miscarriage rates for women aged <35 years old (1–3). Despite this, PGT-A has become the most frequently used adjunct for in vitro fertilization (IVF) (4), and many physicians advocate using PGT-A even in patients with good prognosis as an embryo selection tool (2). To successfully counsel patients on the use of PGT-A, the benefits of embryo screening must be weighed against the risks, including false positive PGT-A results and the complexities surrounding a mosaic result on trophectoderm biopsy (5).

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Given the resolution of next-generation sequencing (NGS), current genetic testing is sensitive enough to detect nonuniform chromosomal copy number differences within a subset of trophectoderm cells (3, 4). Thus, NGS technology has established mosaicism as a new group of diagnostic results without a clear consensus on clinical implications (4). The etiology of mosaicism on blastocyst biopsy is also uncertain. Although mosaic samples may be because of postfertilization errors of mitosis secondary to anaphase lag or nondisjunction of chromosomes (6), it is also possible that intermediate copy number results may not be a true biologic finding but rather a consequence of statistical artifacts, technique variation, or laboratory conditions (7, 8). Furthermore, determining the true prevalence of mosaicism is difficult given the variation in cell sampling numbers, genetic platforms, and laboratory techniques (9).

In addition to differences in laboratory conditions and techniques, fertility clinics and genetic testing companies have varying thresholds for designating an embryo mosaic and for stratifying the trophectoderm biopsy results in low- and high-level mosaicism (6, 10, 11). Given that an absolute threshold for clinically significant mosaicism remains poorly defined, clinics differ in their clinical management of mosaic biopsy results. As of 2021, the Preimplantation Genetic Diagnosis International Society recommends 20%–80% thresholds for mosaicism reporting (12). However, due to differences in both technology and philosophy, laboratories may vary significantly in their thresholds for defining an embryo with mosaic results (12). Although these thresholds are suggestions, ultimately, physicians, laboratories, and clinics bear the responsibility of making decisions regarding both the reporting and transferring of these embryos (10, 11). In addition, the variation in thresholds for mosaicism reporting and clinic acceptance or refusal of mosaic transfers also adds a burden to the patient and genetic counselors.

Thousands of mosaic blastocysts have been transferred, resulting in healthy infants with normal karyotypes (6). One prospective study has also shown that low- and medium-grade mosaic embryos have the same live birth potential as euploid embryos (13). Therefore, even when mosaic embryos are the result of technological artifacts, excluding them from transfer may result in discarding embryos with reproductive potential and increasing treatment failure (6, 9, 14). Given the ability of NGS to detect mosaicism, it is prudent to understand how the relative level of aneuploidy (mosaicism %), the size of the mosaic findings, and the number of impacted chromosomes vary within individuals and across embryology laboratories. The objective of this present study was to uncover clinically relevant features of mosaicism via an in-depth analysis of an international database.

MATERIALS AND METHODS

All PGT-A cycles from women aged 18–46 years at a single genetics laboratory from January 2019 to March 2021 were analyzed. Data received from the laboratory were de-identified and, thus, exemption from institutional review board review was granted. Preimplantation genetic testing for aneuploidy was performed using NGS on trophectoderm biopsies. Patients were stratified by the Society for Assisted Reproductive Technology age categories: <35 years, 35–37 years, 38–40 years, 41–42 years, and >42 years old. Exclusion criteria included oocyte donors, embryos with biopsy insufficient for interpretation, haploid, and polyploid embryos.

Preimplantation genetic testing for aneuploidy was performed by CooperSurgical, Inc. (Livingston, NJ). All trophectoderm biopsies were lysed and amplified using the SurePlexTM DNA Amplification System according to the manufacturer's instructions (Illumina, Inc.; San Diego, CA); successfully amplified samples were then processed for sequencing library preparation. Sequencing data were analyzed using the artificial intelligence algorithm PGTaiSM 2.0 (CooperSurgical, Inc.), which interprets sequencing data with an algorithm stack. The PGTai 2.0 pipeline calls any region that statistically deviates from the baseline reference population and flags regions that are automatically classified as 0–20% euploid, 20%–<40% and >40%–80% as mosaic, and >80% aneuploid (15, 16).

Mosaic level was defined by the fraction of aneuploid cells in a trophectoderm sample such that embryo biopsies were categorized as euploid if copy number counts were <20%; low-level mosaic if 20%–40%; high-level mosaic if 41%–80%; and aneuploid if copy number counts were >80%.

Mosaic samples were classified as single segmental if one chromosome segment was involved or complex segmental if two or more chromosome segments were involved. These samples were defined as a single chromosome when they involved a single whole chromosome, or as a complex abnormal mosaic when they included one whole chromosome and one segment or more than one numerical whole chromosomal abnormality. Mosaic trophectoderm biopsies with concurrent whole chromosome aneuploidies were categorized as aneuploid.

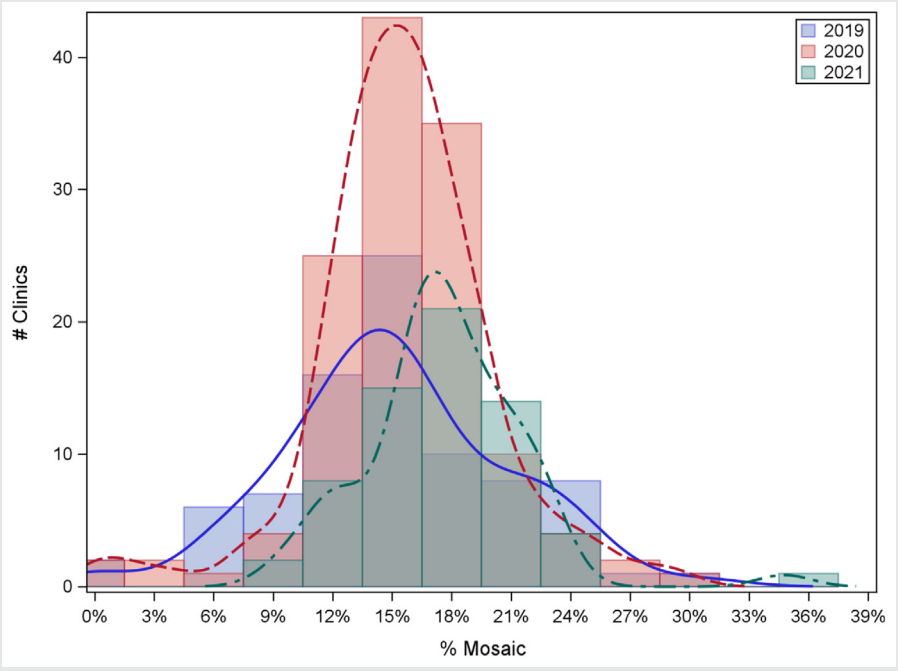
The main outcome measures were distribution of chromosomal findings and prevalence of mosaicism type by age. The secondary outcome was the probability of having a mosaic biopsy result in a subsequent cycle. Rates of mosaicism were compared across clinics, with at least 10 patients contributing biopsies for testing. The rates were evaluated over the study period and stratified by an age cohort. The number of embryos available for transfer, both when mosaic embryos were included and when they were excluded, was calculated for each age group. The fractional percentage increase in the number of available embryos when mosaic embryos were included for transfer was calculated by adding low- and high-level mosaic embryos divided by the number of euploid embryos for each age group.

Comparative analyses were performed with Chi-square tests and Mantel–Haenszel Chi-square for tests of linear trends. Logistic regression evaluating whether mosaicism in a patient's recorded index cycle was associated with mosaicism in their subsequent treatment was conducted with adjustment for the following covariates: patient age, clinic, and geographical region of the clinic. All analyses were conducted in SAS 9.4 (Cary, NC).

RESULTS

A total of 21,345 IVF stimulation cycles from 17,366 patients were included in the analysis, averaging 1.23 cycles

FIGURE 1



Mosaic percentage rates across clinics in 2019, 2020, and 2021.

Armstrong. Embryonic mosaicism across age. Fertil Steril Rep 2023.

(range, 1–8 cycles) per patient and a total of 86,208 embryos. Among the entire cohort, 82% (14,197) of patients had one PGT-A cycle at CooperSurgical during the study period, 14% (2,479) of patients had 2 cycles, and 4% (623) of patients had 3 or more cycles. The patients represented 233 United States clinics and 56 international clinics.

Mosaicism rates were analyzed by clinic as well as over time. In analyzing mosaic biopsy results across clinics, we found a range of mosaicism rates across clinics; rates were reported as low as 0% to as high as 36% in 2019, 33% in 2020, and 38% in 2021 in clinics that sent samples from at least 10 patients in a given year (Fig. 1). Although there was variation within a given clinic over time, the overall median mosaicism rates were very similar in 2019 (14.48% [interquartile range {IQR}, 10.10%–18.19%]), 2020 (15.95% [IQR, 13.11%–18.87%]), and 2021 (17.72% [IQR, 13.33%–21.64%]) (Fig. 1). Mosaicism rates vary from year to year, even within a single clinic. Overall, however, there is a banding between 10%–20% over the years, meaning that most clinics fall within this range of mosaicism, which is demonstrated by the relatively flat lines in Supplemental Figure 1 (available online). However, it did not appear that the same clinics were producing consistently low or high mosaicism rates (Supplemental Fig. 1).

Among all embryos, 44% were euploid, 40.2% were aneuploid, and 15.8% were mosaic, of which approximately half were low-level mosaic and half were high-level mosaic for all ages. A mosaic result of any level (low or high) was more common in younger patient groups, and this decreased with age, as high as 18.9% for patients aged <35 years and down to 8.5% for patients aged >42 years. The rates of both low- and high-level mosaicism decreased with age, whereas both mosaic complex abnormal and aneuploid results increased with age (Table 1). When considering only samples yielding a diagnosis of mosaicism and stratifying by mosaicism type, patients aged<35 years had the highest proportions of single segmental and complex segmental mosaicism (37.9% and 6.8%, respectively), whereas those aged >42 years had the highest single whole chromosome mosaicism and complex abnormal mosaicism (37.1% and 34%, respectively) (*P* Mantel–Haenszel Chi-square <.0001) (Table 2).

After adjusting for patient age, clinic, and clinic geographic region, we found that a diagnosis of a mosaic embryo in the first cycle did not increase the odds of a patient having a mosaic embryo in a subsequent cycle. This analysis was then performed stratifying by the number of embryos biopsied in the initial cycle (1 through 6+ embryos), and again demonstrated that a mosaic embryo in the first cycle did not increase the odds of a mosaic embryo in a subsequent cycle, regardless of the number of embryos biopsied (Fig. 2).

The number of cycles without a euploid embryo for transfer was calculated for each Society for Assisted Reproductive Technology age group (Supplemental Table 1, available online). The embryos available for transfer, including and excluding mosaic embryos were then calculated for each group, as well as the percent increase in available embryos when mosaic embryos were included (Supplemental Table 2,

TABLE 1

Distribution of chromosomal findings by SART age groups ($N_{embryos}$ = 86,208).

	Total N = 86,208 % (n)	SART age groups: < 35 y N = 23,442 % (n)	35–37 y N = 21,381 % (n)	38–40 y N = 21,487 % (n)	41–42 y N = 11,310 % (n)	> 42 y N = 8,588 % (n)	*P* value
Euploid	44% (37,889)	57.7% (13,522)	51.4% (10,996)	41.4% (8,890)	27.2% (3,077)	16.4% (1,404)	< .0001
Low -evel mosaic	8% (6,852)	10.4% (2,431)	9.1% (1,946)	7.5% (1,607)	5.4% (611)	3% (257)	
High-level mosaic	7.9% (6,790)	8.5% (2,000)	8.2% (1,762)	7.9% (1,701)	7.6% (857)	5.5% (470)	
Aneuploid	27.9% (24,039)	16.8% (3,946)	23% (4,910)	32% (6,867)	41.6% (4,708)	42% (3,608)	
Complex abnormal aneuploid	12.3% (10,638)	6.6% (1,543)	8.3% (1,767)	11.3% (2,422)	18.2% (2,057)	33.2% (2,849)	

SART = Society for Assisted Reproductive Technology.

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available online). Our data demonstrate that transferring embryos with mosaic biopsy results may provide up to 52% more embryos in patients older than 42 years old and 33% more embryos in patients who are younger than 35 years old. Overall, the fractional increase in transferrable embryos, when including mosaic embryos, increased with age.

DISCUSSION

Our data demonstrate an overall embryo mosaic prevalence rate of 15.8% among all cycles. We demonstrated that both low- and high-level mosaic results occurred more frequently in younger patients; however, the complexity of mosaic errors increased with age. The prevalence of single segmental and complex segmental mosaicism was the highest among the younger cohort and decreased with age. In contrast, the number of single whole chromosome or complex abnormal mosaicisms on trophectoderm biopsy was more common among older patients.

The observed decline in the mosaicism rate with age is consistent with prior research showing that younger patients are more likely to have mosaic embryos without a full chromosome aneuploidy, whereas older patients may have mosaicism concurrent with a whole chromosome aneuploidy (11, 17). Younger patients are more likely to have mosaic embryos without full chromosome aneuploidies, given the young oocytes are less likely to cause meiotic nondisjunction (17). It is possible that single whole chromosome and complex abnormal mosaic embryos are more common with increasing age because they originated as aneuploid embryos that underwent partial "self-correction" by aneuploid cell death or reduced cell division rate (18). However, there is limited direct evidence for corrective mechanisms during blastocyst growth (9).

Given prior data showing more favorable outcomes with segmental mosaic embryos, which tend to occur more frequently in the younger population, transferring embryos with a mosaic result from younger patients in general may have increased success (6). As a result, we suspect that, although NGS detects mosaicism of all types, young patients may create more embryos with mosaic biopsy results that are more likely to lead to a live birth compared with older patients. Prior studies have also shown that in addition to segmental and single chromosome mosaics, mosaic transfers from younger patients have a significantly higher implantation rate (10, 19, 20). This aligns clinically with our data, given younger patients produce fewer embryos with complex mosaic diagnoses.

Ultimately, the clinical relevance of mosaicism likely increases with age because of its increasing complexity. Our

TABLE 2

Mosaicism type among all mosaic embryos by SART age group ($N_{mosaic\ embryos}$ = 26,745)

Mosaic type	Total N = 26,745 % (n)	SART age groups: < 35 y N = 6,681 % (n)	35-37 y N = 6,297 % (n)	38-40 y N = 6,685 % (n)	41-42 y N = 3,883 % (n)	> 42 y N = 3,199 % (n)	*P* value
Single segmental	33.4% (8,919)	37.9% (2,535)	36.9% (2,321)	32.4% (2,163)	29% (1,124)	24.3% (776)	< .0001*
Complex segmental	5.8% (1,561)	6.8% (439)	6% (380)	5.7% (379)	5.5% (215)	4.6% (148)	
Single chromosome	32.8% (8,760)	30% (2,003)	30.5% (1,920)	33.9% (2,269)	35.5% (1,380)	37.1% (1,188)	
Mosaic complex abnormal	28.1% (7,505)	25.5% (1,704)	26.6% (1,676)	28% (1,874)	30% (1,164)	34% (1,087)	

MH = Mantel–Haenszel; SART = Society for Assisted Reproductive Technology.
* Linear trend by age: P_{MH} < .0001

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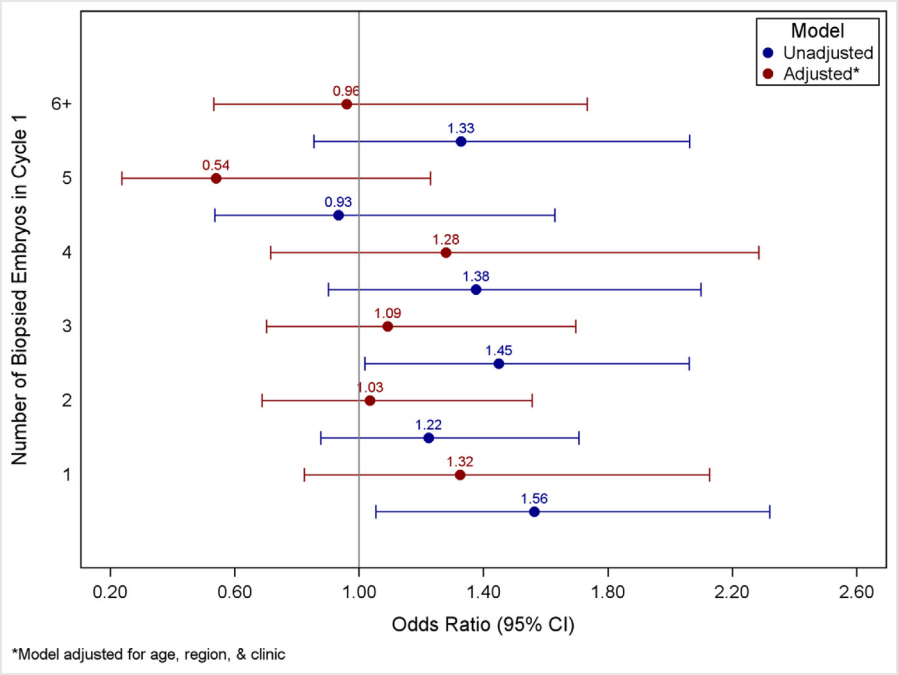
FIGURE 2



Prediction of mosaicism in subsequent cycle stratified by number of embryos biopsied in an unadjusted and adjusted model for age, region, and clinic.

Armstrong. Embryonic mosaicism across age. Fertil Steril Rep 2023.

data show that complex mosaicism increases with age, possibly because of self-correction of meiotic nondisjunction. In older fertility patients with few euploid embryos, including embryos with mosaic diagnosis on trophectoderm biopsy significantly increases the number of embryos available for transfer by up to 50%. Although these embryos would have a lower yield per embryo, given the high proportion of whole chromosome and complex abnormal mosaicism, the inclusion of these embryos may have a clinically significant effect. In addition, prior studies of patients with no euploid embryos have shown that approximately one-third of patients will undergo mosaic embryo transfer after genetic counseling instead of pursuing further treatment cycles (10). Thus, transferring embryos with mosaicism may increase the overall odds for achieving pregnancy.

It does not appear that mosaicism repeats itself in subsequent cycles. After adjusting for age, clinic, and region, a history of having a mosaic embryo in a previous cycle was not associated with mosaicism in a subsequent cycle. Thus, our data demonstrate that the finding of mosaicism on trophectoderm biopsy is not inherent to an individual. This suggests that patients whose cycles result in large numbers of mosaic embryos can be encouraged to reattempt another cycle or consider the transfer of a mosaic embryo.

Although there was a wide range in the minimum and maximum mosaic rates across clinics, the median yearly mosaicism rate was similar for years 2019 (14.48%), 2020 (15.95%), and 2021 (17.72%). Given that our data demonstrated a fairly stable mosaicism rate across clinics, the variability in the mosaic rate may be introduced by patient-specific factors or variables that are unrelated to laboratory and biopsy techniques. Additionally, the clinics that produced the outlier mosaicism rates varied year to year, further pointing to mosaicism being unrelated to the specific laboratory. Our findings agree with prior studies that observed few differences in mosaicism rates across US clinics (21, 22). However, some previous studies have demonstrated higher mosaicism rates in certain laboratories, which may be attributable to a specific laboratory environment, embryologist technique, or embryo quality (23, 24). Rather than a true biological phenomenon, mosaic embryos may represent ultimately the limitations of our NGS testing, as several studies have shown that mosaic embryos have equivalent live birth rates to euploid embryos (13, 25). In comparison with these studies, our dataset represents a larger number of clinics, a more diverse patient population, and an analysis of all samples on a single, consistent genetics platform. Limitations of our study include only 3 years of data and a lack of information on stimulation protocol, patient demographics, infertility diagnosis, PGT-A indication, and specific chromosomal numbers. Given these limitations, we were unable to evaluate the potential causes of mosaicism. Overall, our data provide less plausibility for mosaicism to occur because of clinic-specific differences.

CONCLUSION

In this large international dataset, we demonstrated that age impacts the complexity of mosaic errors. Furthermore, a

history of mosaicism was not associated with future mosaicism. From our data, it does not appear that mosaicism on trophectoderm biopsy is inherent to an individual. Our field continues to grapple with the biologic importance and clinical use of detecting mosaicism. Although the clinical meaning behind mosaic embryos is controversial, mosaicism is disclosed on most reports, which ultimately impacts patients as some providers are not routinely transferring these embryos (26). A clinic policy of transferring mosaic blastocysts may improve the live birth rate by increasing the number of available embryos for transfer. However, further research is needed to understand the biologic etiologies of nonuniform chromosomal copy number differences in trophectoderm biopsy and clinical outcomes associated with this type of embryo transfer, particularly in older patients with more complex mosaicism. Our data is limited in that it is largely descriptive and does not assess mosaic transfer or live birth outcomes. Future work will be facilitated by assessing mosaic embryo transfer outcomes and uniformly accepted thresholds for mosaicism.

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