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REVIEW

To transfer or not to transfer: the dilemma of mosaic embryos – a narrative review

BIOGRAPHY

Elkin Muñoz obtained his specialist degree in obstetrics and gynaecology at the University of Cauca, Colombia. He received training in reproduction, endocrinology and infertility at Valencia University, Spain. He is current MD and Professor at the Obstetrics and Gynecology Department of the University of Cauca, and Medical Director at IVIRMA Vigo, Spain.

Elkin Muñoz[a,b], Fernando Bronet[c], Belen Lledo[d], Gabriela Palacios-Verdú[e], Lorena Martinez-Rocca[f], Signe Altmäe[g,h,i], Josep Pla[j,*], representing the Special Interest Group in Reproductive Genetics of the Spanish Society of Fertility

KEY MESSAGE

This narrative review covers the aetiology, classification and diagnosis of human embryonic mosaicism, as well as clinical outcomes and genetic counselling when transferring mosaic embryos. It is intended to serve as a reference for practitioners in assisted reproduction.

ABSTRACT

A frequent finding after preimplantation genetic diagnostic testing for aneuploidies using next-generation sequencing is an embryo that is putatively mosaic. The prevalence of this outcome remains unclear and varies with technical and external factors. Mosaic embryos can be classified by the percentage of cells affected, type of chromosome involvement (whole or segmental), number of affected chromosomes or affected cell type (inner mass cell, trophectoderm or both). The origin of mosaicism seems to be intrinsic as a post-zygotic mitotic error, but some external factors can play a role. As experience has increased with the transfer of mosaic embryos, clinical practice has gradually become more flexible in recent years. Nevertheless, clinical results show lower implantation, pregnancy and clinical pregnancy rates and higher miscarriage rates with mosaic embryo transfer when compared with the transfer of euploid embryos. Prenatal diagnosis is highly recommended after the transfer of mosaic embryos. This narrative review is intended to serve as reference material for practitioners in reproductive medicine who must manage a mosaic embryo result after preimplantation genetic testing for aneuploidies.

INTRODUCTION

Embryo mosaicism can be defined as the existence of two or more cell populations with different genotypes in an embryo (*Schattman et al., 2018*). Next-generation sequencing (NGS) in preimplantation genetic testing for aneuploidies (PGT-A) facilitates the evaluation of chromosome number in each trophectoderm biopsy. This approach allows for the identification of potential numerical chromosome alterations by quantifying copy-number reads across a selection of markers spread throughout the whole genome. Embryos with an intermediate result after PGT-A, between the range of euploidy and the range of aneuploidy, have historically been designated as 'mosaic embryos'. Embryo mosaicism was viewed as the most plausible explanation for these results, probably arising from post-zygotic mitotic errors (*Taylor et al., 2014*). Embryos with

[a] Reproductive Medicine, IVIRMA Vigo, Vigo, Spain
[b] Department of Obstetrics and Gynecology, University of Cauca, Popayan, Colombia
[c] IVF Laboratory, IVIRMA Madrid, Madrid, Spain
[d] Instituto Bernabeu, Alicante, Spain
[e] Unit of Genomic Medicine, Department of Obstetrics, Gynecology and Reproductive Medicine, Institut Universitari Quirón Dexeus, Barcelona, Spain
[f] Research Department, IVIRMA Vigo, Vigo, Spain
[g] Department of Biochemistry and Molecular Biology, Faculty of Sciences, University of Granada, Granada, Spain
[h] Instituto de Investigación Biosanitaria ibs, Granada, Granada, Spain
[i] Division of Obstetrics and Gynecology, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden
[j] Reproductive Genetics Unit, IVIRMA Global, Barcelona, Spain

KEYWORDS

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*Corresponding author. E-mail address: Josep.pla@ivirma.com (J. Pla). https://doi.org/10.1016/j.rbmo.2023.103664 1472-6483/
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mosaicism can implant, and these pregnancies can end in healthy babies, so mosaic embryo transfers should be considered as a possibility for patients undergoing an assisted reproduction cycle.

A recent and increasing rise in embryo mosaicism after PGT-A can be explained by the high sensitivity and resolution of NGS. The latest NGS protocols offer more advantages than array comparative genomic hybridization (aCGH), the technique previously used with embryos. One advantage of NGS is the higher resolution, which allows the identification of different chromosomal abnormalities, such as segmental aneuploidy. NGS also offers a better balance between cost and benefits, and lower noise in the analysis. A recent study showed a mosaic embryo rate of 2–13% with NGS analysis in trophectoderm cells (*Popovic et al., 2020*), and this incidence seems to decrease throughout embryo development and pregnancy. When chorionic villus biopsy is performed, the mosaic rate is around 2.1% in embryos (*Malvestiti et al., 2015*), but it is less than 0.2% in newborn infants (*Hansteen et al., 1982*). Thus, ascertaining the real incidence of mosaic blastocysts as well as factors leading to mosaicism remains exceptionally challenging.

The reasons for the variable prevalence of embryo mosaicism could be biological (*Li et al., 2020*) or technical, depending on many factors, including ovarian stimulation (*Baart et al., 2007*), day of embryo cleavage, fertilization technique, culture conditions and technical platforms (*Fragouli et al., 2019*). This variety of candidate factors contributes to the lack of clarity about the exact prevalence of chromosomal mosaicism.

Embryonic mosaicism can be classified using different parameters: grade of mosaicism (based on the percentage of aneuploidy), number of chromosomes involved (simple mosaic or complex mosaic) or type of abnormality (whole-chromosome mosaic or segmental mosaic) (*Lee et al., 2020*; *Munné et al., 2017*; *Spinella et al., 2018*). Currently, more than 2700 mosaic embryos have been transferred (*Treff and Marin, 2021*). Evidence increasingly points to lower implantation, pregnancy and clinical pregnancy rates and a higher miscarriage rate when mosaic embryos are transferred (*Capalbo et al., 2021*; *Tiegs et al., 2021*). No differences in neonatal outcomes between euploid or mosaic embryo transfers have been reported (*Yakovlev et al., 2022*). It should also be noted that a few cases of mosaicism or aneuploidy persistence have been reported (*Greco et al., 2023*; *Kahraman et al., 2020*; *Schlade-Bartusiak et al., 2022*); however, the incidence appears to be equal to that seen in unassisted conception.

Given the lack of knowledge about the impacts related to different degrees or types of mosaicism, clinical decisions around transferring this type of embryo can be challenging, particularly when no chromosomally normal embryo is available. Indeed, the question of when to transfer embryos with chromosomal mosaicism has attracted much attention (*Besser et al., 2019*; *Fragouli et al., 2019*; *Garvin et al., 2019*; *Luo et al., 2019*; *Popovic et al., 2018*). The initial proposal was that transferring mosaic embryos should depend on the type of abnormality and the involved chromosome. In recent years, different guidelines and position statements from international societies have been published, each with its own set of recommendations regarding transfer priority (*Cram et al., 2019*; *Grati et al., 2018*). A debate about transferring mosaic embryos (*Gleicher et al., 2020*) was followed by a committee opinion from international societies, such as the American Society for Reproductive Medicine (ASRM) and the Preimplantation Genetic Diagnosis International Society (PGDIS), about how to manage mosaic embryos (*Practice Committee and Genetic Counseling Professional Group (GCPG) of the American Society for Reproductive Medicine, 2020*; *Leigh et al., 2022*).

Another interesting debate has recently emerged. Some authors have suggested using 'intermediate copy number' instead of 'mosaic' as the applicable term (*Paulson and Treff, 2020*). The designation of 'mosaic' could be inaccurate, given that thousands of babies have been born without mosaicism after the transfer of embryos identified as mosaic (*Viotti et al., 2021*). In addition, applying the category 'mosaic' for embryos based on an arbitrary chromosomal copy-number threshold from NGS data could lead to an overestimation of chromosomal abnormalities (*Treff, 2021*). Throughout this review, the term 'mosaic' is used, reflecting its common use by professionals in assisted reproduction and an assumption that the term eases the reading of the text.

This narrative review summarizes current knowledge about mosaic embryos in the field of assisted reproduction techniques. The authors conducted a literature search and this review is intended to serve as reference material for practitioners in reproductive medicine who must manage a mosaic embryo result after PGT-A.

ORIGIN AND CLASSIFICATION OF EMBRYO MOSAICISM

Embryo mosaicism is a post-zygotic event that arises from an error during embryonic mitosis. Mitotic chromosomal errors most frequently occur during the first divisions of embryonic development, particularly in the first three cleavages (*Fragouli et al., 2019*; *Munné et al., 1994*; *Munné et al., 2002*). Chromosomal misalignment results in aneuploid cells during the second division (*Munné et al., 1994*). The frequency of mosaic blastocysts is reported to be 6.1% (*Capalbo and Rienzi, 2017*), although the post-implantation frequency of mosaicism is lower, at about 2% (*Huang et al., 2009*; *Malvestiti et al., 2015*). However, studies show a huge range of mosaicism in trophectoderm biopsies, from 2– 40% (*Fragouli et al., 2019*; *Katz-Jaffe et al., 2017*; *Ruttanajit et al., 2016*; *Stankewicz et al., 2017*).

The most common causes proposed for these mitotic errors are anaphase lagging (the chromatid does not migrate during anaphase) and non-disjunction (sister chromatids do not separate properly) (*Mantikou et al., 2012*; *Vazquez-Diez et al., 2019*). Less frequent mitotic errors that can cause embryo mosaicism include endoreplication, formation of micronuclei, and centriole/centrosome dysregulation (*Viotti et al., 2021*).

Embryo mosaicism can be classified using different parameters, as follows:

1. Number of chromosomes related to the abnormality (*Coonen et al., 2004*):
   a. Simple mosaic: one chromosome involved
   b. Complex mosaic: more than one chromosome involved
   c. Chaotic mosaics: four or more chromosomes involved
2. Cell lines affected (*McCoy, 2017*; *Taylor et al., 2020*):
   a. Total mosaic: chromosomally abnormal; normal cells are present

in both the inner cell mass (ICM) and trophectoderm.
   b. ICM mosaic: aneuploid and euploid cells are present only in the ICM, and all cells from the trophectoderm are euploids.
   c. Trophectoderm mosaic: aneuploid and euploid cells are present only in the trophectoderm, and all cells from the ICM are euploid.
   d. ICM/trophectoderm mosaic: the ICM shows 100% chromosomally abnormal cells, and 100% of trophectoderm cells are chromosomally normal, or vice versa.
3. Percentage of cells affected by the abnormality: embryos can present with a high or low degree of mosaicism based on the mosaic rate detected in a trophectoderm biopsy (*Lee et al., 2020*; *Munné et al., 2017*; *Spinella et al., 2018*):
   a. Low level: mosaicism rate <40%–50% (no consensus on the percentage threshold)
   b. High level: mosaicism rate >40–50%.
4. Type of aneuploidy (*Victor et al., 2019*; *Zore et al., 2019*):
   a. Whole-chromosome mosaic: the mosaic result involves the whole chromosome.
   b. Segmental mosaic: the mosaic result involves only a fragment of a chromosome.

In addition to natural factors and considering mosaicism as an intrinsic condition arising during the human preimplantation period, extrinsic factors could contribute to embryonic mosaicism. As noted, these factors could be biological (laboratory conditions affecting mosaicism rates) or technical (*Popovic et al., 2020*). Some studies suggest that culture conditions or hormonal stimulation protocols can explain some differences in mosaicism rates among IVF clinics (*Munne et al., 1997*; *Sachdeva et al., 2018*).

Fertilization methods may also affect the mosaicism rate. Some data indicate an increase in mosaicism rate with conventional IVF (*Palmerola et al., 2022*). A possible explanation is an increased presence of cumulus cells or sperm cells that contaminate the biopsy sample, so that the 'mosaic' result is a technical artefact.

The high sensitivity of NGS has been proposed as a factor in high false-positive rates, which could imply that many mosaic embryos detected by NGS in trophectoderm biopsies are non-mosaic (*Capalbo and Rienzi, 2017*; *Popovic et al., 2020*). The level of differentiation between biological signal and technical noise is another potential source of diagnostic error. This type of error is associated with the biopsy of only a few cells or fragmented cells, the incomplete lysis of trophectoderm cells before amplification, or even the biopsy and IVF protocols used (*Bean et al., 2002*; *Palmerola et al., 2019*; *Xiong et al., 2021*).

Another possible technical issue is sample contamination, usually of maternal origin. If cumulus cells are present around the embryo, they could be included in the trophectoderm sample and amplified, leading to a misdiagnosis (*Palmerola et al., 2019*; *Xiong et al., 2021*). Some authors have suggested that human factors related to the embryologist could affect the mosaicism rate (*Ai et al., 2022*).

On the other hand, embryo quality also has been associated with mosaic rates. Some authors have shown reduced embryo quality or higher mosaicism rates among day 6 blastocysts (*Ai et al., 2022*; *Viotti et al., 2021*). Clearly, embryos with high levels of mosaicism have the lowest chances of reaching the blastocyst stage (*Bielanska et al., 2002*).

In summary, embryo mosaicism has different effects depending on the number of chromosomes involved, cell lines affected, percentage of affected cells and type of aneuploidy. Intrinsic and extrinsic factors, including laboratory conditions and fertilization methods, have differential effects on embryo mosaicism. Technical issues such as sample contamination and high false-positive rates with NGS also can lead to a diagnosis of mosaicism.

MOSAIC EMBRYO DIAGNOSIS

Embryo mosaicism was first reported in 1993, when it was identified using the fluorescence in-situ hybridization of blastomeres (*Delhanty et al., 1993*) and whole preimplantation cleavage stage embryos (*Munne et al., 1993*), and later in blastocysts (*Evsikov and Verlinsky, 1998*). Subsequent studies using aCGH and high-throughput sequencing approaches on trophectoderm biopsies have revealed a huge range of prevalence (*Chow et al., 2014*; *Lledó et al., 2017*; *Mourad et al., 2021*).

The detection of mosaicism is now possible in blastocyst biopsies containing 4–10 cells. A diagnosis of mosaicism is based on the presence of an intermediate chromosome copy number in a profile derived using NGS or aCGH. The diagnostic accuracy for mosaicism may be affected by the biopsy technique, NGS platform, cut-off applied for mosaicism, threshold established for data interpretation and chromosome involved in the mosaicism. Other intrinsic factors generating mosaicism have been highlighted (*Sachdev et al., 2016*). Proper validation to avoid the overdiagnosis of mosaicism because of technical artefacts is a priority. NGS may detect mosaic anomalies with accuracy rates of 20–80% using cell-mixing experiments (*Goodrich et al., 2016*), although some authors have posited that background noise could easily be confused with low-grade mosaicism because cell mixing may not properly represent a trophectoderm biopsy (*Treff and Franasiak, 2017*).

The biopsy procedure also seems to influence mosaicism (*Munné and Wells, 2017*). Two studies have yielded contradictory results regarding the biopsy operator. The first study evaluated possible factors influencing mosaicism in 1708 blastocysts from 482 PGT-A cycles and showed that, within the same set-up, the biopsy operator did not seem to influence the mosaicism rate (*Coll et al., 2021*). Another study of 5718 blastocysts from 1198 PGT-A cycles concluded, however, that the person conducting the biopsy might have contributed to artefactual mosaicism as an extrinsic factor (*Ai et al., 2022*). Regardless of these mixed findings, continuous operator learning and evaluation are necessary to avoid false-positive results.

In addition, specific biopsy parameters such as the number of laser impacts, flicking versus pulling, or number of cells biopsied might be related to false-positive results for mosaicism. Regarding other procedural influences, two studies evaluated the effect on artefactual mosaicism of different factors related to the trophectoderm biopsy technique and sample handling (*Coll et al., 2022*; *Mizobe et al., 2022*). In both studies, no analysed variable showed an association with mosaicism. The number of laser pulses, technique used for embryo biopsy, time elapsed from biopsy to tubing, and time of sample storage from tubing to genetic analysis did not appear to contribute to labelling the sample as mosaic.

A recent report described the mosaic blastocyst incidence with two different biopsy protocols according to zona pellucida drilling (day 3 versus day 5 or 6). The results indicated that zona pellucida opening on day 3 might be associated with an increased incidence of mosaic blastocysts (*Xiong et al., 2021*). Mosaic blastocyst rates were higher with zona pellucida opening on day 3 compared with day 5 or 6 (19.58% versus 8.12%, respectively; $P < 0.05$). Nevertheless, the relation between the number of collected cells and the mosaicism rate showed that a lower number of cells in the biopsy was related to increased artefactual mosaicism. In summary, with a standardized, high-quality embryo biopsy procedure, the generation of artefactual mosaicism should be ruled out.

For all of the above, mosaicism detection in trophectoderm biopsies is technically challenging and could be one reason for the discrepancies between laboratories (*Popovic et al., 2020*). Another important reason is the heterogeneity in definitions of mosaicism thresholds among different laboratories. The most common lower cut-off value ranges from 20% to 30%, and the upper value ranges from 50% to 80% (*Lledo et al., 2017*; *Spinella et al., 2018*). Therefore, specific cut-offs are not clearly defined, and these differences can lead to varying percentages of mosaic embryos being reported. Lower threshold values can lead to mosaicism over-diagnosis, i.e. false-positive results. A higher cut-off, in contrast, could reduce the sensitivity of detection for full aneuploidy in embryos, resulting in false-negative findings.

Although NGS can accurately detect abnormal cells even when their proportion is as low as 20% in a mixed cell sample, it is important to conduct experiments combining euploid and aneuploid cell lines in various ratios to confirm platform accuracy and avoid misdiagnosis. Trophectoderm biopsies are less stable than cell-line mixing models, so that the extrapolation of cell-line-derived cut-offs for the diagnosis of mosaicism could be inappropriate.

Algorithms used for normalizing background noise and inherent sample background noise could affect the mosaicism diagnosis, mainly in segmental mosaicism. A recent cross-validation study compared two commercially available platforms for PGT-A — MiSeq VeriSeq (Illumina, San Diego, CA, USA) and Ion Torrent Personal Genome Machine PGM ReproSeq (Thermo Fisher, Waltham, MA, USA) — for their detection of segmental mosaic aneuploidies (*Biricik et al., 2021*). It was found that VeriSeq NGS had a higher accuracy at a 20% level of mosaicism and a slightly higher resolution for segmental aneuploidies compared with ReproSeq. These results are concordant with those of an earlier study demonstrating different sensitivity values among platforms (*Goodrich et al., 2017*); however, that earlier study showed no difference in cell combinations with over 50% mosaicism for any of the platforms. These findings together demonstrate the importance of carefully considering a balance between sensitivity and specificity to prevent an over-diagnosis of mosaicism.

The main challenge with PGT-A is the low quantity and quality of DNA material available for analysis. A single cell contains about 7 pg of genomic DNA, which is insufficient for routine genetic tests. Consequently, whole-genome amplification (WGA) is often used to generate enough DNA for testing (*Handyside et al., 2004*). A main limitation of WGA is amplification bias, which results in an incorrect representation of the original genome (*Sabina et al., 2015*). The nature, magnitude and conditions of the bias differ depending on the WGA method employed and the specific characteristics of the template DNA. A suboptimal number of trophectoderm cells analysed or poor-quality starting DNA because of inadequate biopsy or incomplete lysis could lead to the under- or over-representation of chromosomes (whole-chromosome mosaicism) or subchromosomal regions (segmental mosaicism).

In short, having too many cells risks amplification saturation before quantification, and having too few cells risks not reaching the linear phase of amplification (*Treff and Marin, 2021*). Both phenomena can lead to an underestimation of the relative quantity of DNA, resulting in a false-positive mosaic profile. Thus, using inadequate and unvalidated methods can lead to unfavourable outcomes by incorrectly categorizing embryos.

Regarding chromosomes affected by the mosaicism, which specific chromosomes exhibit higher frequencies of mosaicism remains unclear. Despite a known uneven distribution of mitotic errors among chromosomes, conflicting data are reported. Munné and colleagues (*Munné et al., 2017*) found no elevated rates of mitotic errors in larger chromosomes within day 5 blastocysts. This result is in line with previous studies showing no increase in mitotic errors in association with chromosome size (*Coll et al., 2021*; *McCoy et al., 2015*). In contrast, Chuang and co-workers (*Chuang et al., 2021*) reported that mosaicism more frequently involved larger chromosomes. Considering these discrepancies, further studies are needed to investigate the association between mosaicism frequency and individual chromosome structure. Regarding segmental mosaicism, however, all of these studies have demonstrated that larger chromosomes tend to be more affected than smaller ones. This difference suggests that larger chromosomes may be more susceptible to breaks that result in segmental aneuploidies.

In summary, several factors seem to affect the accuracy of labelling embryos as mosaic, including the biopsy technique, NGS platform, threshold established for data interpretation, cut-off applied for mosaicism and chromosomes involved in the mosaicism. Further studies with disaggregated embryos and different approaches for embryo diagnosis would add more data about true embryo mosaicism and the biases arising from an intermediate copy number in an NGS profile. Using genotyping data for embryo diagnosis may be a more rigorous method for predicting mosaicism within a biopsy by increasing the specificity of mosaicism predictions. All of these limitations in the diagnosis of mosaicism necessarily affect the interpretation of clinical results.

CLINICAL RESULTS

As noted, more than 2700 instances of mosaic embryo transfer have been documented to date. However, only a limited number of cases have officially been reported of live newborns exhibiting confirmed mosaicism after such transfers (*Greco et al., 2023*; *Kahraman et al., 2020*; *Schlade-Bartusiak et al., 2022*). The first case was the birth of a healthy child with mosaicism (2%, monosomy 2 by peripheral blood karyotyping and confirmation by fluorescence in-situ hybridization), previously detected by PGT-A (35%, monosomy 2). This case involved prenatal testing through amniocentesis, which detected mosaicism (2%, trisomy 2). With the absence of any pathological findings on detailed ultrasonography and normal fetal growth,

the couple made the decision not to terminate the pregnancy (*Kahraman et al., 2020*).

In another report, a baby was born with a diagnosis of syndromic partial trisomy 15 and maternal uniparental disomy 15. This aneuploidy occurred after a double-embryo transfer involving two mosaic embryos – one with high-level mosaic trisomy 15 and a high-level mosaic deletion of chromosome 20, and the other with high-level mosaic monosomy 21 and X monosomy (*Schlade-Bartusiak et al., 2022*). Only one gestational sac was observed. The couple declined invasive prenatal testing, and non-invasive prenatal testing showed no increased risk of viable aneuploidies.

In their recent publication, Greco and collaborators (*Greco et al., 2023*) documented two cases of confirmed mosaicism. In the first case, the mosaicism was observed as a low-level segmental loss in chromosome 1 that was confirmed through both amniocentesis and examination of tissue from the products of conception. In the second case, a low-level mosaic trisomy 21 was identified and confirmed through chorionic villus sampling and amniocentesis. This pregnancy was also terminated.

One limitation of analyses of outcomes after a putative mosaic embryo has been transferred is the adoption of an unsuitable study design. The three options are cohort studies, randomized clinical trials and non-selection trials to assess the predictive value of PGT-A (*Capalbo et al., 2021*). Each option yields different evidence about reproductive outcomes. In some unsuitable studies, patients with a poor prognosis received mosaic embryos or genuine aneuploid embryos that were misreported as mosaic and that were compared with unscreened or euploid embryos (Capalbo et al., 2022).

LITERATURE SEARCH

To develop an overview of relevant studies, an exhaustive search of the literature was performed; the collated information on case-control studies of mosaic and euploid embryo transfers is summarized in TABLE 1. A systematic search was conducted using the following Medical Subject Heading terms: preimplantation genetic testing for aneuploidies (PGT-A), mosaic embryo transfer (MET); mosaic embryo transfer human; mosaicism, preimplantation genetic testing; mosaicism AND genetic counselling (with US spelling); mosaic embryo transfer and clinical pregnancy rate; mosaic embryo transfer and live birth rate; mosaic embryo transfer and miscarriage rate; mosaic embryo transfer and outcome analysis; and mosaic embryo transfer and pregnancy outcomes. Of 2316 hits returned from these searches, duplicates, case reports, descriptive studies, reviews and those with incomplete information were excluded. Considering only comparative studies reporting euploid embryo transfers as the control group, 14 studies of reproductive outcomes were identified (FIGURE 1).

A review of these studies indicates that although the live birth rate after transferring whole-chromosome aneuploid embryos is 2% or less, the results have been less clear for the transfer of putative mosaic embryos. The option to report intermediate chromosome copy numbers as mosaic leads to a high prevalence of false-positive calls (Capalbo, 2022; *Popovic et al., 2020*). Furthermore, reproductive outcomes can vary because of, for instance, different mosaicism classifications, and when the threshold for considering intermediate copy numbers is up to 50% as mosaic, outcomes have not been worse than for uniformly euploid embryos (*Capalbo et al., 2021*).

In general, compared with transfers of euploid embryos, there is a lower implantation rate after the transfer of mosaic embryos, along with a lower pregnancy rate and higher miscarriage rate. Many studies also included prenatal diagnosis testing after the transfer of mosaic embryos.

The largest study to date presented the results for transfers of 1000 mosaic embryos (*Viotti et al., 2021*). These authors reported that the risk of an affected pregnancy or newborn was low, whereas the transfer of mosaic embryos was associated with lower implantation rates and higher spontaneous miscarriage rates (most occurring early in pregnancy). Based on their evidence, the authors established criteria for the prioritization of embryo transfer, considering only the level of mosaicism (low level > high level) and type of mosaicism (segmental > one whole chromosome > two whole chromosomes > complex). The authors did not consider the chromosome involved in the mosaic because it has been reported that this variable does not modify the outcome (*Viotti et al., 2021*).

The results from another study, a prospective non-selection clinical trial involving 897 embryo transfers, revealed comparable rates of live birth and miscarriage, regardless of whether euploid embryos or embryos with low-level and medium-level mosaicism were transferred (*Capalbo et al., 2021*). Another study (*Lin et al., 2020*) evaluated the impact of mosaicism grade on clinical results, concluding that high-level mosaic embryos were associated with a live birth rate similar to that for low-level mosaics, but with a higher miscarriage rate.

Factors that could influence reproductive outcomes include the level of mosaicism, type of mosaicism and chromosome involved in the mosaic. However, other groups have found that reporting intermediate chromosome copy numbers as mosaic is linked to a high prevalence of false-positive results. For better diagnostic accuracy, single-nucleotide polymorphism microarray technology has been reported as successful (*Rana et al., 2023*). The chance of a persistence of mosaicism during pregnancy appears to be low, but a few cases have been reported, and detailed follow-up of mosaic embryo transfers should be performed to determine whether this incidence is significantly greater than that observed in non-PGT-A embryos or even with unassisted conceptions. A selection bias in these cases of mosaicism persistence is possible, as it is likely that follow-up is lacking for a large number of pregnancies and births. Moreover, an accurate report should include the rate of mosaicism in pregnancies derived from euploid embryo transfers, so that the values can be equitably compared (Capalbo et al., 2022).

Given several limitations in the diagnosis and the misidentification of mosaic embryos because of false-positive results, embryos should not be discarded, as doing so unavoidably impacts the cumulative pregnancy rate.

THE EVOLUTION OF SCIENTIFIC SOCIETY STATEMENTS CONCERNING THE TRANSFER AND PRIORITIZATION OF MOSAIC EMBRYOS

Since the first publication describing the birth of healthy children after the transfer

TABLE 1 SUMMARY OF COMPARATIVE STUDIES OF MOSAIC EMBRYO TRANSFER AND THEIR REPRODUCTIVE OUTCOME

Publication	Positive pregnancy test rate		Implantation rate		Biochemical pregnancy loss		Clinical pregnancy rate		Ongoing rate		Live birth rate		Miscarriage rate	
	Mosaic	Euploid	Mosaic	Euploid	Mosaic	Euploid	Mosaic	Euploid	Mosaic	Euploid	Mosaic	Euploid	Mosaic	Euploid
Yakovlev et al. (2022)	47.5 (56)[a]	55.2 (283)[a]	39.0 (46)[a]	47.0 (241)[a]							28.8 (34)[a]	40.7 (209)[a]	26.1 (12)[a]	12.0 (29)[a]
Tiegs et al. (2021)					12.5 (2)[a]	9 (28)[a]					68.8 (11)[a]	64.7 (202)[a]	12.5 (2)[a]	7.4 (23)[a]
Capalbo et al. (2021)	55.0 (155)[a]	55.8 (270)[a]			12.3 (19)[a]	10.7 (29)[a]					42.9 (121)[a]	43.4 (210)[a]	11 (15)[a]	12 (29)[a]
Viotti et al. (2021)			41.8 (517)[a]	57.2 (5561)[a]			35.4 (1000)[a]	52.3 (5561)[a]	31.3 (517)[a]	52.3 (5561)[a]			25.0 (517)[a]	8.6 (5561)[a]
Zhang et al. (2020)							40.0 (137)[a]	59.1 (476)[a]	27.1 (36)[a]	47.0 (210)[a]	27.1 (36)[a]	47.0 (210)[a]	33.3 (18)[a]	20.5 (54)[a]
Lee et al. (2020)			51.8 (43)	65.7 (142)					47.0 (39)	64.8 (140)			5.1 (2)	12.9 (18)
Munné et al. (2020)			49	83			49	92	37	77	37.5 (95)[a]		25	7
Victor et al. (2019)			38.0	49.6			42.2	45	30 (15)[a]	47.1 (225)[a]				
Zhang et al. (2019)	65.7 (67)[a]	76.1 (204)[a]			11.9 (8)[a]	11.3 (23)[a]	57.8 (59)[a]	67.5 (181)[a]	46.6 (47)[a]	59.1 (159)[a]	46.6 (47)[a]	59.1 (159)[a]	20.3 (12)[a]	12.7 (23)[a]
Zore et al. (2019)							40 (8)[a]	60 (215)[a]			30.0 (6)[a]	53.8 (192)[a]	40.0 (8)[a]	18.2 (65)[a]
Spinella et al. (2018)	48.1 (37)	64 (160)	38.5 (30)[a]	54.6 (137)[a]	7.8 (6)	8 (20)	30 (23)	46.4 (116)	30 (23)	46.4 (116)	30.8 (24)	46.6 (117)	7.8 (6)	8.0 (20)
Fragouli et al. (2017)			30.1	55.8					15.4	46.2	27.8 (10)	47.0	55.6	17.2
Lledó et al. (2017)	48.1	52.5	26.9	37.2	21.2	12.3	26.9	40.2			25 (13)[a]		7.1	18.1
Munné et al. (2017)			53 (57)[a]	71 (661)[a]					41 (76)[a]	63 (736)[a]			24 (19)[a]	10 (75)[a]

Data are given as percentage (*n*).

[a] The number given is the same as the number of embryos transferred.

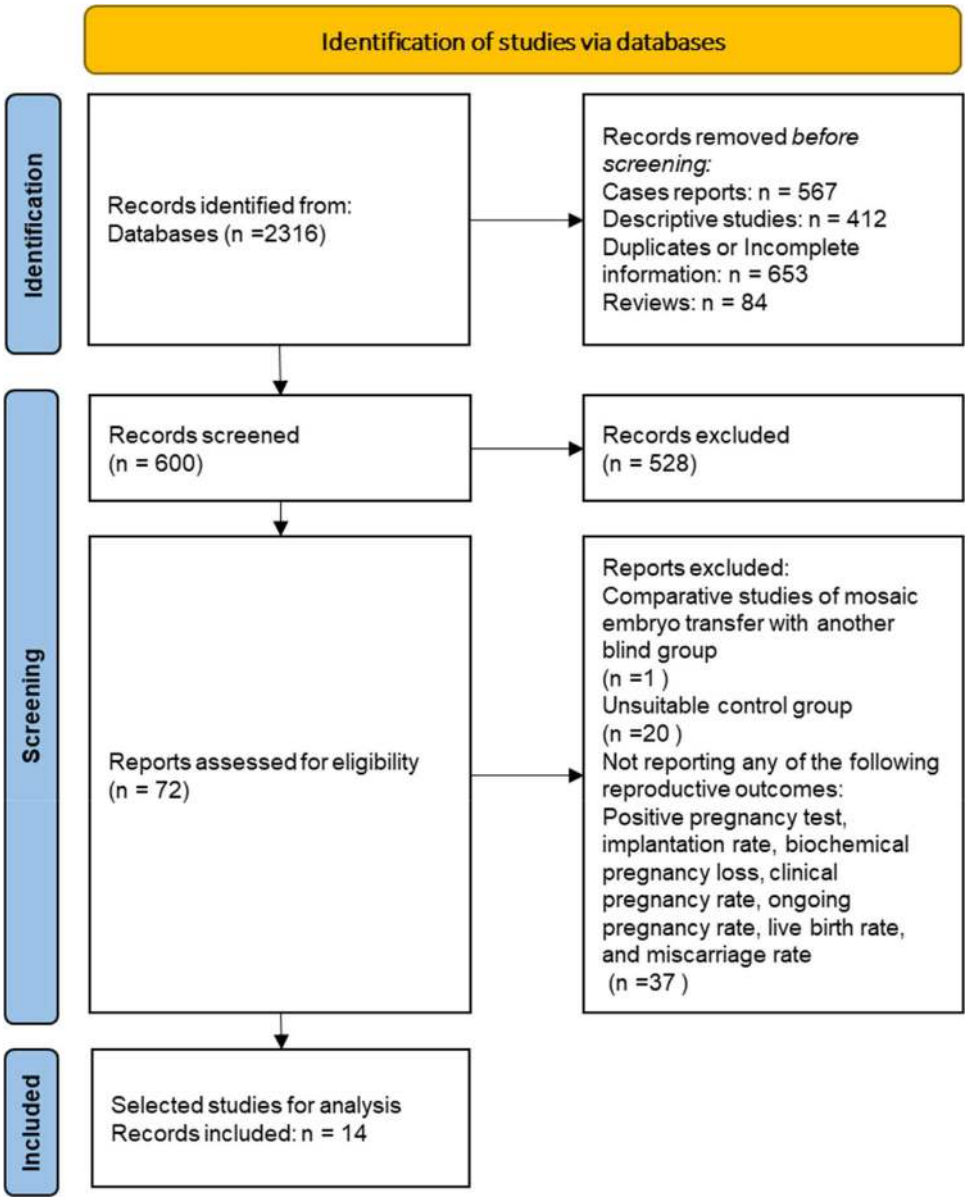

FIGURE 1 PRISMA flow diagram of the systematic search.

of embryos classified as mosaic after PGT-A (*Greco et al., 2015*), different scientific societies have published guidelines or position statements regarding their recommendations on management and prioritization criteria for couples considering the transfer of a mosaic embryo (**TABLE 2**).

The first organization to release a position statement was PGDIS. In this 2016 statement, they shared recommendations for both laboratories (how to report mosaicism) and clinicians (to discuss with patients the option of a further IVF cycle and prenatal screening and diagnostic confirmation by amniocentesis). Regarding the criteria for prioritization, the Society proposed that mosaic euploid/monosomy mosaicism should be prioritized over euploid/trisomy mosaicism, a low mosaicism level should be prioritized over high-level mosaicism, and the theoretical implications of the chromosome(s) involved should be considered (chromosomes not associated with a known chromosomal disorder should be favoured over chromosomes associated with uniparental disomy, intrauterine growth restriction or a viable chromosomal syndrome) (*PGDIS, 2016*).

In 2017, the World Congress on Controversies in Preconception, Preimplantation and Prenatal Diagnosis (COGEN; *COGEN, 2017*) released their initial position statement on this issue. Their prioritization criteria were similar to those of PGDIS (2016), with a modification to prioritize monosomy mosaicism over trisomy mosaicism. Their rationale was that both types of mosaic embryo seem to present similar implantation rates and that euploid/monosomy mosaicism might also contain trisomic cell lines. In this statement, the mosaicism range was defined as low-level mosaic at values of 20–40% and high-level mosaic at 40–70% (*COGEN, 2017*).

TABLE 2 SUMMARY OF RECOMMENDATIONS ESTABLISHED BY DIFFERENT SCIENTIFIC SOCIETIES REGARDING THE PRIORITIZATION OF TRANSFER OF MOSAIC EMBRYOS AND PRENATAL MANAGEMENT

Source of recommendation	Monosomy > trisomy	Mosaicism level	Type of mosaicism	Chromosome involved	Prenatal diagnosis	New stimulation cycle
PGDIS (2016)	Yes	Yes; no threshold defined	Single chromosome	Yes Priority 1: 1, 3, 4, 5, 6, 8, 9, 10, 11, 12, 17, 19, 20, 22 Priority 2: 14, 15 (UPD risk) Priority 3: 2, 7, 16 (IUGR risk) and 13, 18, 21 (liveborn viability)	Yes (early amniocentesis >14 weeks)	Yes
COGEN (2017)	No	Yes; lower level (20–40%) > high level (40–70%)	Yes; transfer with complex mosaicism is not recommended	Yes Highest priority: 1, 3, 4, 5, 6, 8, 9, 10, 11, 12, 17, 19, 20 Low priority: 14, 15 (UPD) and 2, 7, 16 (IUGR) Lowest priority: 13, 18, 21, 22 (liveborn viability)	Yes; amniocentesis > CVS	Yes
Grati et al. (2018)	No	NR	NR	Yes Score 0: 1, 3, 10, 12, 19 Score 1: 4, 5, 47,XYY Score 2: 2, 7, 11, 17, 22 Score 3: 6, 9, 15 Score 4-5: 8, 20, 47,XXX, 47,XXY Transfer not recommended: 13, 14, 16, 18, 21, 45,X	Yes; amniocentesis	NR
Cram et al., 2019	No	Yes; no threshold defined	NR	Yes; Grati et al.'s criteria	Yes; amniocentesis >14 weeks	Yes
ASRM (2020)	No	It remains to be determined whether it can be applied to predict outcomes			Discussion of prenatal screening and diagnosis options	Yes
Viotti et al. (2021)	No	Yes Low level > high -level (threshold 50%)	Yes Segmental > one chromosome > two chromosomes > complex	No	NR	NR
Leigh et al., 2022	No	Yes; no threshold defined	Yes (segmental > whole chromosome)	No	Yes; no distinction between euploid and mosaic pregnancies	Yes
ESHRE (2022)	No	Yes No Recommendations in case of high-range mosaic	NR	No	Low-range mosaic: non-directive counselling	No (low-range mosaic)

CVS, chorionic villi sampling; IUGR, intrauterine growth restriction; NR, not reported; UPD, uniparental disomy.

A retrospective study of the cytogenetic and molecular data obtained from chorionic villus samples and products of conception led to a composite score for each distinct kind of mosaic aneuploidy. The authors produced a grading system to determine which mosaic embryo transfers should be prioritized (*Grati et al., 2018*). Based on their observations, they divided the chromosomes into five groups in accordance with the standards released by PGDIS (2016) and *COGEN (2017)*. Ultimately, this author group recommended avoiding the transfer of mosaic embryos involving chromosomes 13, 14, 16, 18, 21 or 45,X as they carried the greatest risk of an affected viable pregnancy. The group also highly recommended prenatal diagnosis by amniocentesis.

PGDIS published a second position statement in 2019 (*Cram et al., 2019*) that was similar to their first publication. In this statement, prioritization based on level of mosaicism was maintained, while the use of Grati and coworkers' prioritization system based on the chromosome involved was recommended. The authors firmly agreed that prenatal diagnosis by amniocentesis should be offered in the event of an ongoing pregnancy following the transfer of a mosaic embryo.

As a next step, in 2020, ASRM released a committee opinion document covering the clinical care of mosaic embryos and their transfer (ASRM, 2020). This publication reviewed the criteria that had previously been published for embryo stratification, including the percentage of mosaicism (mosaicism level), affected chromosome(s), presence of monosomy or trisomy, full chromosome mosaicism versus segmental mosaicism, and number of chromosomes involved in the mosaicism. However, the document shared a clear statement: no evidence-based criteria existed at that time for prioritizing mosaic embryos. It remained to be seen if the criteria based on prenatal and postnatal evidence could be applied to predict clinical outcomes after the transfer of mosaic embryos (ASRM, 2020).

In 2021, PGDIS published a third position statement (*Leigh et al., 2022*). Based on the abovementioned publications (*Capalbo et al., 2021*; *Viotti et al., 2021*), the following criteria were recommended for use in mosaic embryo prioritization: level of mosaicism (low-level mosaics were prioritized over high-level mosaics, cut-off threshold was not defined) and type of mosaicism (segmental mosaicism prioritized over whole-chromosome mosaicism). When two embryos have identical qualities, a preference could be established based on their morphology (*Leigh et al., 2022*). The authors also stated that prenatal diagnosis is advised in pregnancies following PGT-A, regardless of whether a euploid or a mosaic embryo has been transferred. They further wrote that prenatal diagnosis should be discussed and offered for every pregnancy regardless of the method of conception, in line with the recommendations of the American College of Obstetricians and Gynecologists and the American College of Medical Genetics and Genomics (*Leigh et al., 2022*).

Finally, in 2022, the European Society for Human Reproduction and Embryology released good-practice recommendations on embryo mosaicism, derived from data obtained from a PubMed search (*De Rycke et al., 2022*). They also used a web-based questionnaire to collect data on current practices regarding the management of embryo mosaicism. When considering the transfer of an embryo that was low-level mosaic, they suggested the following: (i) the results of PGT-A should be assessed alongside the embryo's morphology; (ii) no recommendations could be made regarding the prenatal confirmation of pregnancies following the transfer of a low-level mosaic embryo, as evidence was insufficient for the indication of an invasive diagnosis at the time of publication; (iii) non-directive genetic counselling is advised to discuss the different possibilities and limitations of each approach; and (iv) a new stimulation cycle is not advised when transferrable low-level mosaic embryos are available. The authors also stated that with the information available at the time of writing, they could not make any recommendations for cases of high-level mosaic embryos (*De Rycke et al., 2022*).

GENETIC COUNSELLING

Since the first position statement was published, all societies have stated that clients who have mosaic embryos suitable for transfer should receive genetic counselling. However, few publications have addressed the specific information that should be given to couples undergoing IVF with PGT-A (ASRM, 2020; *Besser and Mounts, 2017*).

Genetic counselling is a non-directive process that involves the communication of information and support to individuals or families who may be at risk of inherited disorders or genetic conditions (*Resta et al., 2006*). In the context of mosaic embryo transfer, genetic counselling aims to inform couples about known evidence regarding the implications so that they can make an informed decision (preservation, use or destruction).

Besser and Mounts (2017) and the *Practice Committee and Genetic Counseling Professional Group (GCPG) of the American Society for Reproductive Medicine, 2020* describe the content that should be discussed with patients in genetic counselling sessions before and after PGT-A. Every individual who undergoes IVF with PGT-A should receive a pre-test genetic counselling session. In this initial session, the potential hazards, benefits and constraints of the technique should be addressed. Patients must be informed about the possible results, including the euploid, aneuploid, no diagnosis and mosaic reporting policy. Patients also should be adequately informed about the meaning of mosaicism and its biological mechanism, the origin of the embryonic cells analysed during PGT-A, the expected in-house rate of mosaicism, the technical and clinical limitations on the interpretation of results, the possible clinical outcomes after a mosaic embryo transfer (based on reliable and up-to-date information), the prenatal screening and diagnosis recommendations in the event of an ongoing pregnancy, and the embryo storage policy of the centre. Finally, couples should be informed that they have the option to decline PGT-A if desired (ASRM, 2020; *Besser and Mounts, 2017*).

After undergoing PGT-A, individuals contemplating mosaic embryo transfer should be referred for a post-test genetic counselling session (ASRM, 2020; *Besser and Mounts, 2017*). During this session, the information given during the pre-test should be updated. The possible explanations for the mosaic PGT-A result should be discussed, highlighting the potential clinical outcomes from the transfer of a mosaic embryo. It is crucial for the genetic counsellor to be up to date with the evidence and guidelines that are available at the time of a session.

Regarding the clinical outcomes, counsellors should note that most current

evidence suggests that mosaic embryos seem to have a reduced rate of implantation and an increased rate of miscarriage compared with the transfer of euploid embryos. The odds of a viable pregnancy appear to be low because few cases of a viable affected pregnancy have been described so far (*Greco et al., 2023*; *Kahraman et al., 2020*; *Schlade-Bartusiak et al., 2022*). However, data regarding the outcome for a specific type of mosaicism are still limited and should be interpreted with caution. Each mosaic embryo should be evaluated individually, and in cases involving more than one mosaic embryo available for transfer, prioritization should be based on the most current evidence.

The genetic counsellor should also discuss the different options for prenatal screening and diagnosis, including resolution, possible results, implications and limitations. In addition, the genetic counsellor needs to address the comfort level of the couple regarding uncertainty during the pregnancy (*Besser and Mounts, 2017*). Individuals who have difficulties deciding the fate of their mosaic embryos or who are anxious about the transfer and the progress of an ongoing pregnancy should be referred to a psychologist. Many patients might be surprised that they are pregnant after a mosaic embryo transfer because, based on current evidence, they might have expected no implantation, and many doubts regarding the risks may arise. A follow-up genetic counselling appointment should be offered on demand in these scenarios.

Few reports have addressed the decision making of couples who have mosaic embryos. Besser and colleagues (*Besser et al., 2019*) reported that more than a quarter of couples agreed to transfer their mosaic embryos and that couples who were more likely to accept this tended to be older or had undergone more egg retrieval cycles compared with those who chose not to transfer. Although most patients did not opt to transfer immediately, most chose to preserve the embryos in case of a future transfer (*Besser et al., 2019*).

Cheng and co-workers (*Cheng et al., 2022*) explored factors driving the decision-making process for patients and the impact of mosaic embryos. The authors found that religion was a factor in these decisions and in the termination of pregnancy in case of an adverse event. Patients highlighted their unmet needs regarding the information they had received from professionals and that the attitude of professionals significantly affected the decision-making process. The authors reflected on the importance of giving patients educational resources, of patient support groups and of professionals describing all the available options and explaining the benefits and constraints of each (*Cheng et al., 2022*).

Genetic counselling is indispensable in the decision-making process in mosaic embryo transfer. Further studies are needed to address the factors influencing patients' decisions and how to help them overcome the difficulties they face when deciding the fate of their mosaic embryos.

CONCLUSIONS

1. Embryo mosaicism is defined as the presence of two or more cell populations with different genotypes in an embryo. Mosaicism is usually inferred from the presence of an intermediate chromosome copy number on an NGS profile in a trophectoderm biopsy, and its prevalence varies from 2% to 40%.
2. Embryo mosaicism is a post-zygotic event that arises from errors in mitosis. These mitotic errors usually involve anaphase lagging and non-disjunction.
3. Mosaicism can be classified according to the number of chromosomes, type of cell line affected, percentage of affected cells or affected portion of a chromosome.
4. A mosaicism diagnosis is inferred from the presence of an intermediate chromosome copy number on an aCGH or NGS profile. Its accuracy depends on technical conditions including the presence of technical artefacts, background noises and operator skills.
5. Some studies show that the clinical results after mosaic embryo transfer involve lower implantation, pregnancy and clinical pregnancy rates and higher miscarriage rates compared with the transfer of euploid embryos. However, many studies have biases due to diagnostic limitations and unsuitable study design.
6. A few cases of mosaicism persistence in pregnancy have been reported. However, more consistent reports are required without reporting bias to confirm the persistence rate from pregnancies derived from mosaic embryos.
7. Prenatal diagnosis is highly advised after the transfer of mosaic embryos, and the only reasonable approach in case of mosaic transfer is amniocentesis. However, recommendations among scientific societies are conflicting regarding the methodology (non-invasive versus invasive techniques). Further research on this topic may support the development of more accurate recommendations.
8. All individuals undergoing IVF with PGT-A should receive a pre-test genetic counselling session. They should receive explanations about the potential risks, benefits and limitations of the technique.
9. Individuals considering the transfer of a mosaic embryo should be referred to a post-test genetic counselling session. The possible explanations for a mosaic PGT-A result should be discussed, highlighting the potential clinical outcomes of the transfer of a mosaic embryo.
10. Follow-up of clinical outcomes after mosaic embryo transfer should be continued to build a robust body of evidence regarding this PGT-A result.
11. Based on current evidence, embryos with a result within the mosaic range should not systematically be discarded or disregarded for transfer as this practice could negatively affect the cumulative live birth rate per cycle.

DATA AVAILABILITY

No data was used for the research described in the article.

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