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The Puzzle of Mosaicism: Mechanisms and Clinical Implications in Preimplantation Genetic Testing

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ABSTRACT: Chromosomal mosaicism in preimplantation embryos, characterized by cells with varying genotypes, arises due to mitotic errors after fertilization. These errors, including anaphase lag, mitotic nondisjunction, or cytokinesis failure, typically occur during early embryonic divisions when maternal factors predominantly regulate development. The impact of mosaicism on embryonic viability varies based on the stage and nature of the chromosomal errors, potentially reducing implantation rates and increasing miscarriage risks. However, mosaic embryos can occasionally self-correct through apoptosis of abnormal cells or selective growth of euploid cells, enabling the development of healthy blastocysts.

Advancements in genetic screening, particularly next-generation sequencing (NGS), have improved mosaicism detection, although challenges remain in accurately interpreting its clinical significance. NGS identifies mosaicism with higher sensitivity than previous methods like fluorescence in situ hybridization (FISH) or array comparative genomic hybridization (aCGH). Nonetheless, discrepancies in detection rates and sampling errors complicate clinical decision-making.

Patients undergoing preimplantation genetic testing must be counseled on the potential outcomes of transferring mosaic embryos, especially when euploid options are unavailable. While mosaic embryos offer a chance for pregnancy, they carry an increased risk of miscarriage and uncertain long-term outcomes. Personalized genetic counseling and improved screening methodologies are essential for refining patient care and optimizing in vitro fertilization (IVF) outcomes. Further research is needed to understand the mechanisms and implications of mosaicism, ensuring evidence-based practices in embryo selection and transfer.

KEYWORDS: Chromosomal Mosaicism, In Vitro Fertilization (IVF), Preimplantation Embryos, Preimplantation Genetic Screening (PGS), Next-Generation Sequencing (NGS).

INTRODUCTION

Mosaicism within an embryo is defined as the presence of two or more cell populations with different genotypes. Early studies demonstrated mosaicism within preimplantation human embryos at the cleavage stage using fluorescence in situ hybridization (FISH) of sex Mosaicism in preimplantation embryos is a result of errors in chromosome segregation chromosomes[1]. after fertilization, which can occur during mitosis. These errors typically happen during the early cleavages when the embryo is still highly dependent on maternal factors, as the embryo's genome is not fully activated until later stages [2]. Because of this, the early embryo is particularly vulnerable to chromosomal errors such as anaphase lag, mitotic nondisjunction, or premature cell division. These errors can result in embryos with a mix of normal and abnormal cells, a condition known as mosaicism[3].

The impact of mosaicism on embryonic development depends on when and how the chromosomal error occurs. For instance, errors in the second cleavage stage tend to lead to a higher proportion of abnormal cells compared to errors in later stages, such as the third cleavage. These variations in the distribution of abnormal cells can affect the viability and development of the embryo and may influence its potential to implant and lead to a successful pregnancy. While mosaic embryos are generally considered to have a lower implantation potential and a higher risk of miscarriage compared to euploid embryos, some studies suggest that certain mosaic embryos may still result in a healthy pregnancy [4].

Interestingly, mosaic embryos can self-correct in some cases, especially when cultured for extended periods. Studies have shown that up to 50% of mosaic embryos may develop into euploid blastocysts after being left in culture, highlighting the potential for some embryos to overcome chromosomal imbalances. Self-correction mechanisms include increased apoptosis of the abnormal cells, selective suppression of abnormal cell division, or the preferential development of euploid cells within the inner cell mass

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(ICM). These processes help restore a more balanced chromosomal makeup, which may improve the chances of a successful pregnancy[5].

Another mechanism that may contribute to self-correction in mosaic embryos is the loss of the extra chromosome in trisomic cells. This can happen through anaphase lag or nondisjunction, where the extra chromosome is lost during cell division. However, this correction is not always successful, and mosaic embryos with multiple abnormalities are less likely to self-correct completely[6]. This phenomenon also suggests that not all mosaic embryos are equally capable of self-correction, and the likelihood of success may vary depending on the extent and type of chromosomal abnormalities present [7].

Understanding mosaicism in embryos is crucial for improving the outcomes of preimplantation genetic screening (PGS) and in vitro fertilization (IVF) procedures. As the detection of mosaicism has become more common due to advanced screening techniques, it is essential to refine counseling strategies for patients undergoing IVF [8]. Patients should be informed of the potential risks and uncertainties associated with transferring mosaic embryos, as the clinical implications of mosaicism are still not fully understood. Some patients may opt to transfer mosaic embryos if no euploid embryos are available, but they must be made aware of the potential risks, including lower implantation rates and higher chances of miscarriage. Ultimately, a personalized approach, informed by genetic counselling and patient preferences, will help guide decision-making in cases involving mosaic embryos [9].

MECHANISMS LEADING TO CHROMOSOMAL MOSAICISM:

Mosaic aneuploidies arise through two main mechanisms: post-zygotic mitotic chromosome segregation errors and post-zygotic mitotic trisomy/monosomy rescue of an existing meiotic aneuploidy. Various mechanisms have been suggested to cause errors in chromosome segregation during embryonic divisions. One such mechanism, anaphase lag, occurs when chromosomes remain at the mid-pole after most sister chromatids have segregated. This typically affects only one or a few chromosomes and can result from under-replication, entanglement, or improper attachment of sister chromatids to both spindle poles. Anaphase lag is linked to increased segregation errors and nonreciprocal aneuploidy, where chromosome loss occurs without a corresponding gain [10].

In some cases, chromosomes may fail to be captured by the spindle, as shown in live cell imaging of human zygotes. The zygotic division, where the two parental genomes are captured on a single spindle, is highly error-prone. Abnormal tripolar spindles can also form in preimplantation embryos, leading to significant chromosome loss, known as chaotic mosaicism. This phenomenon may be influenced by a genetic variant in or near the centrosomal regulator PLK4, which, when maternally inherited, increases the likelihood of tripolar spindle formation. Maternal inheritance is important because the egg's mRNAs and proteins control the early embryonic divisions until embryonic genome activation [11].

Other mechanisms contributing to chromosomal instability include endoduplication (where chromosomes are re-replicated without cell division), failed cytokinesis, and centrosome overduplication, which can lead to tetraploid cells. Tetraploidy has been observed in human conceptuses but also induces chromosomal instability, aneuploidy, and tumorigenesis in mouse embryos. A combination of chromosome segregation errors can result in uniparental disomy (UPD), where two copies of a chromosome are inherited from one parent [12]. UPD can increase the risk of autosomal recessive diseases in homozygous regions and cause abnormal gene expression in imprinted regions on specific chromosomes (e.g., chromosomes 6, 7, 11, 14, 15, and 20)[13].

MOSAICISM IN HUMAN PREIMPLANTATION EMBRYOS:

Mosaicism in human preimplantation embryos is estimated to affect up to 70% of embryos. By the blastocyst stage, 2% to 50% of embryo biopsies are reported to be mosaic, with the variation reflecting both biological mechanisms and technological artefacts [14]. Typically, the inner cell mass and trophectoderm biopsies show high concordance in 95-98% of embryos, suggesting that significant mosaicism is rare by this stage [15].

The 2015 report by Greco and colleagues, which showed the birth of healthy babies from mosaic aneuploid embryos, sparked debate about how to manage mosaicism in preimplantation embryos [16]. While some studies indicate that transferring mosaic embryos reduces clinical pregnancy rates, increases the chance of miscarriage, and lowers live birth rates compared to euploid embryos, other studies have found no significant differences in pregnancy outcomes, even when mosaicism is present up to 50%. Factors such as the proportion of abnormal cells in trophectoderm biopsies also influence outcomes, with lower mosaicism levels generally showing better clinical results. However, the degree of mosaicism is not always a reliable predictor of pregnancy success [17].

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One challenge in detecting mosaicism is that random sampling from 5 to 10 cells may not fully reflect the embryo's genomic makeup. Additionally, next-generation sequencing (NGS) used in preimplantation genetic testing (PGT-A) may be affected by various factors such as assay noise, amplification bias, and biopsy technique. Studies have shown that the concordance of mosaic results in blastocyst reanalysis is low, highlighting the unreliability of using mosaic levels as predictors of embryo viability [18].

Mosaic segmental aneuploidies (SAs), reported more frequently with NGS technologies, add further complexity to clinical assessments. While some studies show reduced implantation rates for mosaic SAs, others report no difference. Mosaic SAs generally have lower miscarriage rates compared to whole chromosome aneuploidies. However, some embryos with mosaic SAs also display whole chromosome aneuploidy in other parts of the embryo, complicating their clinical interpretation [19].

For patients with no euploid embryos, transferring mosaic embryos may be the only option to achieve pregnancy. The likelihood of success depends on the specific chromosomes involved and the distribution of normal and abnormal cells. Models have been proposed to prioritize mosaic embryos based on factors like the incidence of mosaic aneuploidies in CVS and amniocentesis samples, but these tools still need validation [20]. Genetic counseling is essential to help patients understand the risks and outcomes of transferring mosaic embryos, and prenatal diagnosis laboratories should be informed of prior mosaic PGT-A results for further analysis [21].

DETECTION OF MOSAICISM AND INTERPRETATION OF MOSAIC RESULTS:

The detection rate of mosaicism in preimplantation embryos depends on both the developmental stage of the embryo and the chromosomal detection technique used. Early PGS primarily utilized fluorescence in situ hybridization (FISH), which visualizes probes for a limited number of chromosomes, such as X, Y, 13, 18, and 21. However, FISH is restricted in its ability to detect mosaicism in the remaining autosomes, and its application in cleavage-stage embryos is limited due to the risks associated with multiple blastomere biopsies [22].

To address these limitations, comprehensive chromosome screening (CCS) emerged as a more advanced method. CCS, involving whole genome amplification and comparative genomic hybridization (CGH), allows for the detection of mosaicism across all 24 chromosomes. This method revealed significant mosaicism in cleavage-stage embryos, prompting the adoption of trophectoderm biopsy of blastocysts for mosaicism detection using CCS in clinical practices. TE biopsies, containing 4 to 10 cells, provide a sufficient sample for analysis [23].

Array CGH (aCGH) is commonly used for PGS and utilizes whole genome amplification followed by hybridization on a microarray. It detects whole chromosome aneuploidy but is not designed for structural chromosomal aberrations [24]. The detection rate of mosaicism in blastocysts with aCGH is estimated to range from 4.8% to 32%, varying depending on protocols [25]. The ability of aCGH to identify mosaicism depends on the proportion of aneuploid cells within the TE biopsy. Studies have shown that aCGH can detect mosaicism when more than 50% of the cells are abnormal, but interpreting borderline results remains challenging due to overlapping values between normal and abnormal copy numbers [26].

A study compared the results of array CGH (aCGH) screening of blastocyst embryos with FISH reanalysis of trophectoderm (TE) and inner cell mass (ICM) biopsy samples. They found that 2% of the embryos were diploid-aneuploid mosaic with more than 40% normal cells, as detected by both aCGH and FISH. However, aCGH was less accurate when fewer than 25% of cells in the trophectoderm biopsy were abnormal, failing to detect mosaicism in such cases. It performed better in detecting mosaicism when over 40% of cells in the TE biopsy were aneuploid. For medium-grade mosaicism (25–40% abnormal cells), aCGH correctly identified three cases but misdiagnosed two. Concordance between TE and ICM biopsies was 97% for all chromosomes [27].

Next-generation sequencing (NGS) has become a more advanced method for PGS, offering higher accuracy, greater throughput, and lower costs than aCGH. NGS platforms such as Illumina's MiSeq and Thermo-Fischer's Personal Genome Machine can analyse multiple DNA samples simultaneously, generating results within 13-16 hours. NGS is particularly useful for detecting whole chromosome aneuploidy, mitochondrial copy number, and mosaicism with different platforms having varying sensitivity. The MiSeq platform can detect mosaicism above 50%, while the Personal Genome Machine can identify mosaicism as low as 20%. A randomized blinded study showed that NGS could detect mosaicism when only 17% of cells were aneuploid, with 100% specificity. However, increasing sensitivity through custom analysis criteria also increased the false positive rate. Differences in analytical methods across laboratories may explain variability in mosaicism reporting from blastocyst biopsies [28].

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The increased detection of mosaicism using NGS has raised concerns about whether a single trophectoderm biopsy accurately reflects the chromosomal makeup of the entire embryo. A study by Garrisi et al. found that when multiple biopsies were taken from 43 mosaic embryos, 11.6% were normal across all rebiopsy samples, and 41.8% had a normal inner cell mass (ICM). The TE biopsy accurately predicted the chromosomal status of the ICM 83% of the time. The overall predictability of mosaicism from a single TE biopsy was 58.2% [29]. Similarly, Maxwell et al. confirmed mosaicism in only 48.3% of embryos after multiple biopsies, indicating that detecting low-grade mosaicism in embryos can be influenced by sampling error [30].

The higher rates of mosaicism detected by NGS compared to aCGH have raised questions about the clinical significance of these findings. While some studies suggest that transferring mosaic embryos may lead to healthy live births, others caution that mosaic embryos could have an increased risk of miscarriage or complications. A study found that some mosaic embryos led to healthy births, but others resulted in biochemical pregnancies or negative outcomes, implying that some mosaic embryos may "self-correct." However, the possibility of false positives, where embryos labelled as mosaic are euploid, complicates the interpretation. A retrospective study showed that some embryos initially identified as euploid by aCGH were later found to be mosaic by NGS, with varying outcomes, including miscarriages and live births. Despite these observations, the implantation potential of mosaic embryos remains unclear, though data suggests it may be lower [31].

PATIENT POPULATIONS AT RISK FOR MOSAICISM:

The link between advanced maternal age and aneuploid embryos is well-established, but the connection to mosaicism remains unclear. A study by Daphnis et al. using FISH analysis on discarded embryos showed a high mosaicism rate of 90%, even in embryos from women with an average age of 34 years, suggesting that mosaicism may not be associated with maternal age [32]. Similarly, Turner et al.found no correlation between advancing maternal age and blastocyst mosaicism using 24-chromosome FISH analysis. Moreover, retrospective data from a large reference laboratory using NGS for PGS revealed a 33% mosaicism rate in embryos from donor oocytes of women aged 21-30, indicating that post-zygotic errors are common even in younger, fertile populations [33]. Additionally, laboratory factors may influence mosaicism rates, as a study of 192 donor oocyte cycles from various IVF centers showed mosaicism rates detected by NGS ranging from 17% to 47%, suggesting that different laboratory techniques may impact the detection of mosaicism. Further research is needed to understand the influence of laboratory methods on mosaicism rates [34].

RESULTS INTERPRETATION AND PATIENT COUNSELLING

The increasing identification of mosaicism in embryos has introduced new challenges in interpreting PGS results and counselling patients. Previously, embryos were categorized as either euploid or aneuploid, with only euploid embryos typically considered for transfer. However, as mosaic embryos now represent a third category, counseling strategies must adapt to address these changes [35].

While early data suggest that detecting mosaicism in embryos may offer clinical value, patients may have varying preferences about the uncertain information it provides. Pre-test counseling should include discussions on the frequency of mosaic results, the complexities in interpreting these results, the possibility of false positives, and the limited predictive data. For patients who are uncomfortable with uncertainty, this information may discourage them from pursuing PGS. For those who proceed with PGS, it is important to manage expectations regarding the type of information obtained.

Although current guidelines recommend preferential transfer of euploid embryos, many cycles do not produce euploid options. Since some mosaic embryos have the potential to result in healthy pregnancies, patients without euploid embryos may consider transferring a mosaic one. These patients should receive detailed genetic counseling about the risks and potential outcomes. While some patients may be willing to accept the lower implantation rates of mosaic embryos, they must be informed about the higher risk of miscarriage. Understanding these risks, along with the emotional and financial implications of pregnancy loss, is critical for informed decision-making [36].

CONCLUSION

One of the primary challenges in reproductive medicine is the presence of chromosomal mosaicism in preimplantation embryos. Advances in technology, such as next-generation sequencing (NGS) and comprehensive chromosomal screening (CCS), have

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heightened awareness of this issue by enabling more detailed analyses of embryonic development dynamics. Mosaic embryos, which contain both normal (euploid) and abnormal (aneuploid) cell populations, can have varying outcomes. Some studies suggest that certain mosaic embryos may self-correct over time, resulting in healthy pregnancies, while others indicate that mosaicism is associated with lower implantation rates and an increased risk of pregnancy loss. However, the mechanisms underlying this self-correction, such as the selective growth of euploid cells or the elimination of abnormal cells, remain unclear.

Mosaicism is sometimes clinically overdiagnosed, leading to false positives where euploid embryos are mistakenly identified as mosaic. This emphasizes the need for careful communication with patients to explain the risks and benefits of transferring mosaic embryos. While transferring true mosaic embryos is generally preferable to transferring normal euploid embryos when both options are available, personalized approaches are crucial. Although mosaic embryos are more likely to fail, they can, in some cases, result in healthy offspring.

Laboratory factors, including biopsy techniques, may influence the detection and variability of mosaicism, with inconsistencies noted across institutions. This underscores the need for standardized testing protocols and additional research into how mosaicism affects embryo viability and long-term health. Before transferring a mosaic embryo, genetic counseling and informed consent are essential. Patients should be fully informed about the risks of reduced implantation success and the increased likelihood of miscarriage. Some patients may choose to transfer mosaic embryos, particularly when euploid embryos are not available, but they must be well-advised about the potential outcomes.

Further research is critical to improve screening methods and to educate patients about optimal clinical strategies for addressing mosaicism in preimplantation embryos. As the volume of available data grows, so does the potential to enhance understanding and management of this complex issue.

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