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PGS – Embryonic Mosaicism & Clinical Management

PGS - Embryonic Mosaicism & Clinical Management - Article Summaries

【Abstract】

Preimplantation genetic screening (PGS) testing platform has evolved through the years from FISH to aCGH and recently to Next-Generation Sequencing (NGS). With the increased sensitivity of NGS technology, chromosomal mosaicism in the biopsy samples of embryos is easier to be detected and the true chromosomal make-ups of the biopsy samples can be better reflected. However, this also presents new clinical challenges in counseling and management of these PGS results and embryos.

Preimplantation Genetic Diagnosis International Society (PGDIS) previously released a position statement discussing chromosome mosaicism in PGS testing. Sachdev et al. recently published a paper regarding diagnosis and clinical management of embryonic mosaicism. Both provide resources for clinicians in handling these challenges.

Euploid embryos remain the top priority in selecting embryos for transfer. If another IVF cycle to increase the chance of euploid embryos is not possible or wanted, transfer of embryos with chromosomal mosaicism may be considered after thorough counseling. Studies have suggested **embryos with chromosomal mosaicism may be associated with decreased potential for implantation and pregnancy development, and increased risks for fetal genetic abnormalities and adverse obstetric outcomes.** However, studies have also shown **these embryos have potential to result in healthy babies. Mosaicism involving trisomic or monosomic of *any* chromosome is associated with fetal and obstetric risks.** These authors suggest **transfer of embryos with mosaic trisomies 2, 7, 13, 14, 15, 16, 18 and 21 may pose *the most* risks for adverse outcome. Prenatal genetic diagnosis through invasive procedures remains the criterion standard for prenatal diagnosis of chromosomal abnormalities.**

【Article #1 Excerpts】

PGDIS Newsletter, July 19, 2016
PGDIS POSITION STATEMENT ON CHROMOSOME MOSAICISM AND PREIMPLANTATION ANEUPLOIDY TESTING AT THE BLASTOCYST STAGE

Preimplantation Genetic Diagnosis International Society (PGDIS) released a position statement regarding chromosome mosaicism and preimplantation aneuploidy testing in July of 2016. The following are excerpts taken from the position statement, which is posted on PGDIS official website: http://www.pgdis.org/docs/newsletter_071816.html.

Recommendations for the Clinician

1. Patients should continue to be advised that any genetic test based on sampling one or small number of cells biopsied from preimplantation embryos cannot be 100% accurate for a combination of technical and biological factors, including chromosome mosaicism.

2. The patient information and consent forms for aneuploidy testing (if used) should be modified to include the possibility of mosaic aneuploid results and any potential risks in the event of transfer and implantation. This needs to be explained to patients by the clinician recommending the aneuploidy testing.
3. Transfer of blastocysts with **a normal euploid result should always be prioritized over those with mosaic aneuploid results**.
4. In the event of considering the **transfer of a blastocyst with only mosaic aneuploidies, the following options should be discussed with the patient**:
    a. **further cycle of IVF** with aneuploidy testing to increase the chance of identifying a normal euploid blastocyst for transfer
    b. **Transfer of a blastocyst with mosaic aneuploidies for low risk chromosomes only**, after appropriate genetic counseling if available
    c. Appropriate monitoring and **prenatal diagnosis of any resulting pregnancy, preferably by early amniocentesis** (> 14 weeks gestation).

Suggested Guidelines to Prioritize Mosaic Embryos for Transfer

Based on our current knowledge of the reproductive outcomes of fetal and placental mosaicism from prenatal diagnosis, the following can be used as a guide by the clinician (or a genetic counselor if available) when a mosaic embryo is being considered for transfer:

1. Embryos showing **mosaic euploid/monosomy are preferable to euploid/trisomy,** given that monosomic embryos (excepting 45, X) are not viable
2. If a decision is made to transfer mosaic embryos trisomic for a single chromosome, one can **prioritize selection based on the level of mosaicism and the specific chromosome involved**
    a. The **preferable transfer category consists of mosaic embryos trisomic for chromosomes 1, 3, 4, 5, 6, 8, 9, 10, 11, 12, 17, 19, 20, 22, X, Y.** None of these chromosomes involve the adverse characteristics enumerated below
    b. Embryos mosaic for trisomies that are associated with potential for **uniparental disomy (14, 15) are of lesser priority**
    c. Embryos mosaic for trisomies that are associated with **intrauterine growth retardation (chromosomes 2, 7, 16) are of lesser priority**
    d. Embryos mosaic for trisomies capable of **liveborn viability (chromosomes 13, 18, 21) are of lowest priority**, for obvious reasons

Article reference: Preimplantation Genetic Diagnosis International Society. PGDIS position statement on chromosome mosaicism and preimplantation aneuploidy testing at the blastocyst stage. PGDIS Newsletter, July 19, 2016. Available at: http://www.pgdis.org/docs/newsletter_071816.html. Accessed March 27, 2017.

【Article #2 Summary Points】

Journal: Fertility and Sterility
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Diagnosis and clinical management of embryonic mosaicism

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Mechanisms Causing and Correcting Chromosomal Mosaicism

Embryonic chromosomal mosaicism describes the presence of two or more types of cells with different chromosomal complements within the same embryo.

There are many mechanisms causing an originally diploid embryo to develop into a mosaic state, including “anaphase lag, mitotic nondisjunction, inadvertent chromosome demolition, or premature cell division before DNA duplication”. Because of these reasons, chromosomal mosaicism is commonly detected in cleavage-stage blastomere biopsies. One study has shown that nearly 50% of mosaic cleavage-stage embryos were self-corrected to euploid blastocysts when left in extended culture.

Mechanisms for self-correction of chromosomal aneuploidies include “increased apoptosis of aneuploidy cells, decreased division of aneuploidy cells in relation to euploid cells, preferential development of euploid cells within the inner cell mass”, and trisomy rescue.

Detection of Mosaicism and Interpretation of Mosaic Results

Technical platforms for PGS testing has evolved through the years from FISH technology focusing on selected chromosomes, to aCGH platform screening of entire chromosome set, and recently to NGS technology with improved accuracies and lower costs. With its greater sensitivity, detection of chromosomal mosaicism has been easier than before with this new NGS technology. This allows test results to better reflect the true chromosomal make-ups of the biopsy samples. With the increased reporting of chromosomal mosaicism, the issue of whether test results from a single trophectoderm biopsy is indicative of the chromosomal complement of the entire embryo is again a popular discussion topic.

Which Patient Population is at Risk for Mosaicism?

It is well known that advancing maternal age is associated with increased chances for aneuploidy. However, whether maternal age is a factor leading to chromosomal mosaicism is less clear. Sachdev et al. reviewed publications with maternal ages and PGS results, and **suggested that there are no correlations between advancing maternal ages and chances of chromosomal mosaicism**.

Results Interpretation and Patient Counseling

The authors suggest **pre-test counseling regarding PGS testing should include: "a discussion about the frequency of mosaic results, the challenges associated with interpretation of these results, the possibility of a false positive diagnosis of embryonic mosaicism, and the limited predictive data available"**. A thorough pre-test counseling help the patients understand the risks/benefits/limitations of PGS testing, and can therefore make an informed choice that is most suitable for their own needs.

Current knowledge supports preferential transfer of euploid embryos. However, sometimes there are no euploid embryos for selection. The authors suggest if there are no euploid embryos for consideration and another IVF cycle to collect more embryos to increase the chance of euploid embryos is not possible or wanted, then transfer of mosaic embryos can be considered after comprehensive counseling regarding possible obstetric and fetal risks.

Embryo Selection

Sachdev et al. referred to the position statement from PGDIS in discussing selection of mosaic embryos for transfer – embryos with mosaic trisomies involving chromosomes # 1, 3, 4, 5, 6, 8, 9, 10, 11, 12, 17, 19, 20, 22, X and Y, are preferred over those involving chromosomes # 2, 7, 13, 14, 15, 16, 18 and 21.

Most of the time, an embryo with pure aneuploidy (non-mosaic, all cells carry aneuploid chromosomes) is non-viable. However, mosaicisms involving almost all chromosomes have been reported to result in live-borns with clinical abnormalities. The clinical severity depends on the proportions and the distributions of abnormal cells. Therefore, **there are still risks of fetal abnormalities even with those chromosomes considered to be "safer" or "preferred" for transfer. Transfer of mosaic embryos involving *any* chromosome should be handled with cautions, and thorough patient counseling should be provided**.

Prenatal Testing after Transfer of Mosaic Embryos

With the advancement in genetic testing technology, options of prenatal genetic testing have expanded. However, to date, **genetic testing through invasive procedures, such as amniocentesis, remains the gold standard for prenatal diagnosis of fetal chromosomal abnormalities**.

Article reference: Sachdev NM, Maxwell SM, Besser AG, and Grifo JA. Diagnosis and clinical management of embryonic mosaicism. Fertil Steril. 2017 Jan;107(1):6-11. PubMed PMID: 27842993.

Do you have any questions related to genetic counseling?
What topics would you like the GGA Genetic Counseling Newsletter to discuss?
Your suggestions are greatly appreciated so we can further improve our newsletter!
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