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OPINIONs

Independent Voices on Reproductive Endocrinology, Medicine and Society

On the possibility of selectively transferring embryos, by preimplantation genetic diagnosis (PGD/PGS) determined to be chromosomally abnormal

Summary

If embryos are investigated for chromosomal abnormalities, CHR and other IVF centers transfer currently only embryos confirmed to be chromosomally normal. We in this *OPINION*, however, discuss the rationale why, under carefully considered exceptional circumstances, embryos, by preimplantation genetic diagnosis (PGD, also called preimplantation genetic screening, PGS) determined to be chromosomally abnormal, may still be transferrable. Since the risk of all embryos being chromosomally abnormal (aneuploid) increases with declining embryo numbers, such circumstances may mostly present in women with low functional ovarian reserve (LFOR) who routinely produce only small egg/embryo numbers. Whether embryos are correctly diagnosed as aneuploid, in such patients, therefore, is of particular importance because any "false-positive" diagnosis of an embryo may be the difference between having or not having an embryo transfer and between having or not having a pregnancy chance. Women with large embryo numbers usually do not face this problem since they still have many other normal embryos left for transfer even if they lose an embryo because of a "false-positive" diagnosis. As previously discussed in *OPINION* 002, CHR usually does not support the concept of PGD/PGS to improve IVF outcomes in women with LFOR, but once a patient has undergone a full IVF cycle with PGD/PGS and faces the option of having no chromosomally normal embryos available for transfer, the question arises whether the PGD/PGS diagnosis of aneuploidy in all tested embryos was correct. As we discuss in detail in this *OPINION*, new evidence suggests that PGD/PGS, whether performed at cleavage (day-3) or blastocyst stage (days 5/6), results in a significant number of "false-positive" diagnoses of aneuploidy. We in this *OPINION* argue that in so-affected patients it is ethical to consider transfer of embryos, which by PGD/PGS were reported as aneuploid, as long as reported aneuploidies are known to be lethal. Potentially non-lethal aneuploidies should never be transferred. Moreover, patients have to receive careful counseling prior to giving informed consent to such transfers about the small but relevant risk of establishing an ongoing aneuploid pregnancy, which may require medical termination.

Practically all IVF centers, CHR included, currently maintain a policy of transferring embryos after genetic testing (PGD/PGS) *only* if testing reveals the embryos to be chromosomally normal. Such testing has in principle three potential outcomes: An embryo can be normal, can be unequivocally abnormal or cannot be determined with certainty in its normality. Generally accepted standards of care currently require that only normal embryos be transferred and unequivocally abnormal as well as undeterminable embryos not be transferred.

As the recent literature suggests, a diagnosis of "abnormal" is not always correct.[1-3] In fact, recent research suggests that current PGD methods for testing for chromosomal abnormalities may not be as reliable as once thought. These tests, while highly accurate in determining normal and clearly abnormal embryos, are prone to a still to be determined degree of "false-positive" diagnoses.

A principal reason for misdiagnoses is that embryos are often "mosaic," meaning that they are made up of more than one line of cells. However, developing embryos grow from only one line of cells and often segregate out the line(s) of abnormal cells. Those cells are usually segregated into the so-called trophectoderm of the embryo, and away from the core of the embryo. The trophectoderm later develops into the placenta, and if the placenta later contains an abnormal cell line, it is of little consequence, as long as the embryo/fetus contains only cells from an initially normal cell line.

Determinations of chromosomal abnormalities of an embryo can be performed at one of two stages during embryo development: at 6-8 cells, the so-called cleavage-stage (three days after fertilization) or on days-5/6, the so-called blastocyst stage, when the embryo already has more cells than can be counted.

Day-3 embryos usually have only one cell removed and tested. If this cell is chromosomally abnormal and the other cells of the embryo are normal, the embryo as a whole would be classified as "abnormal." Mosaic embryos, however, frequently self-correct. This is often the consequence of the embryo "segregating" all daughter cells from abnormal cells toward the trophectoderm. If this occurs, this normal embryo would therefore be inaccurately diagnosed as abnormal and discarded for no reason, creating a so-called "false-positive" diagnosis.

Increasingly, embryos are tested on day-5/6 because biopsies at this stage allow for the removal of multiple cells from the trophectoderm and are considered more accurate than single cell biopsies on day-3. In these cases, however, biopsies are made from the trophectoderm where embryos segregate their abnormal cell lines. Therefore, the chance of biopsying a segregated abnormal cell line is higher. This would result in the embryo being discarded even though the embryo may be normal.

In a recent study by colleagues in Toronto, Canada, physicians took trophectoderm biopsies from consenting patients' embryos and sent them to different genetic laboratories for analysis. Though all three were highly reputable genetic laboratories that utilized state-of-the-art technologies, the results demonstrated significant differences,[4] supporting the concept that where the trophectoderm is biopsied matters.

Additionally, normal stem cells have been obtained from embryos even when trophectoderm biopsies defined the embryos as "abnormal" (Shoukhrat Mitalipov, PhD, personal communications). Finally, we are aware of at least two healthy births in infertile women who had only embryos transferred, which after PGD/PGS were classified as monosomies (Barad DH, Vidali A, Kushnir VA, Gleicher N; unpublished data).

All of this is of little consequence for women with large numbers of embryos. Because such women, even after losses of "false-positive" embryos, will still have "normal" embryos available for transfer, their "false-positive" losses will not significantly affect their pregnancy chances with IVF. For women with small embryo numbers, loss of one or two "false-positive" embryos can mean the difference between having or not having an embryo transfer and, therefore, between having or not having a pregnancy chance in their IVF cycle.

It therefore appears ethically appropriate to offer patients with LFOR and apparently no chromosomally normal embryos in an IVF cycle in carefully selected circumstances the opportunity to transfer PGD/PGS defined chromosomally abnormal embryos under the assumption that some of them may have been ”false-positively” designated as “abnormal.” Offering such an option is, however, ethically contingent upon absence of “non-lethal” chromosomal abnormalities in so transferred embryos, which would have the potential of implantation and delivery. These “non-lethal” chromosomal abnormalities can lead to genetic disorders like Down’s syndrome and Turner’s syndrome (and others) if delivered. Therefore, only reported aneuploidies known to be “lethal” should be transferred in such circumstances.

Most chromosomally abnormal embryos do not implant, and if they do, they frequently result in early miscarriages. Chromosomal abnormalities, which never result in live births, are therefore considered “lethal.” Ongoing pregnancies with “lethal” chromosomal abnormalities are almost impossible. The transfer of embryos with “lethal” chromosomal abnormalities can, therefore, be performed under the assumption that either a normal cell line will take over during further growth of the embryos or that if the “lethal” cell line becomes dominant, the embryo will with great likelihood either fail to implant or be quickly miscarried.

Because of the obvious complexities of here outlined ethical process, comprehensive counseling of patients is essential prior to obtaining written informed consent from patients for the transfer of embryos, by PGD/PGS reported to be aneuploid. Aside from above outlined considerations, such counseling also has to discuss the possibility that, though highly unlikely, the establishment of an ongoing chromosomally abnormal pregnancy can never completely be ruled out. Therefore, patients who are considering transfer of such embryos should be advised that all pregnancies established from such embryos should undergo early prenatal genetic testing, and that in chromosomally abnormal pregnancies a medically induced pregnancy termination may become necessary.

Considering all in this *OPINION* outlined issues, CHR has developed a policy, which allows for individualized transfer of embryos, by PGD/PGS reported to be aneuploid. CHR will make this policy gladly available to colleagues and IVF centers.

References

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2. Van Echten-Arends J, Mastenbroek S, Sikkema-Raddatz B, Korevaar JC, Heineman MJ, van der Veen F, Repping S. Chromosomal mosaicism in human preimplantation embryos: a systemic review. Hum Reprod Update 2011;17:620-627
3. Bazrgar M, Gourabi H, Valojerdi MR, Yazdi PE, Beharvand H. Self-correction of chromosomal abnormalities in human preimplantation embryos and embryonic stem cells. Stem Cells Dev 2013; 22:2449-2456
4. Esfandiari N, Bentov Y, Casper RF. Trophectoderm biopsy for aneuploidy screening using different platforms and conflicting test results. ESHRE O-034, Munich, Germany, June 29-July 2, 2014.

Comments

Comment Author	Comment
Jeffrey Braverman, MD, FACOG	I have transferred a Monsomy 22 as patient wanted a boy and this was the only male. It was a Grade A Blast , patient was counseled and she is now currently 32 weeks pregnant with all testing Amnio and Sonogram showing no genetic abnormalities. This is the second case by doctors in my practice where a monosomy was transferred and the baby was

	normal.
Dr Joel Batzofin	Great commentary on a very challenging and difficult topic. I am wondering if you would consider it ethically acceptable to transfer even non lethal abnormal embryos, if the intended parent(s) consented to further testing of the pregnancy if established, and termination of said pregnancy if it proved to be anything but normal? Again, the thought is that normal cell lines may take over, as you have discussed above. Thanks
The CHR	We have considered the transfer of embryos with potentially viable chromosomal abnormalities but, after lengthy in-house discussions and outside consultations, agreed on a policy that prohibits such transfers. A main reason for this decision was medical literature, which suggests that even women who prior to pregnancy in case of an abnormal prenatal genetic test plan on a therapeutic abortion, once it no longer represents only a theoretical consideration, often wrestle with the decision to terminate their pregnancy. Transfer of a presumed lethal aneuploidy will create such circumstances in only extremely rare circumstances; with transfer of embryos with non-lethal aneuploidies, we, however, would create this quagmire for patients on a regular basis. In CHR's opinion, transfer of embryos with non-lethal aneuploidies, therefore, would contradict the first tenet for the practice of medicine, "to do no harm," and be unethical.