Preimplantation genetic diagnosis and screening as an assessment of embryo integrity

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Patients suffering from infertility receive reproductive medicine designed to give birth to healthy children. Although nearly 40 years have passed since the first success of assisted reproductive technology, the clinical pregnancy and live birth rates still do not meet the expectation of patients. As women age, especially women over 40 years, the chances of a successful pregnancy are low.

Despite advances in embryo culture systems, such as time-lapse embryo monitoring and improved culture media, noninvasive diagnostic methods fail to provide adequate information on embryo chromosome abnormalities. These abnormalities, which occur frequently in not only cleavage embryos but also blastocysts, decrease the implantation ability of embryos and lead pregnancies to miscarriages. The only methods of learning the chromosomal status of embryos are preimplantation genetic screening (PGS) for aneuploidy occurring by chance and preimplantation genetic diagnosis (PGD) for unbalanced chromosomes derived from couples with chromosomal structural abnormalities.

PGS initially analyzed chromosomes by fluorescence in situ hybridization (FISH). However, FISH PGS failed to improve the live birth rate due to mosaicism (a mixture of two or more cells with different chromosome compositions) of cleaved embryos, embryo damage biopsy, and poor methodological accuracy of the FISH method. At present, PGS using a trophectoderm biopsy to collect multiple cells from blastocysts, and comprehensive chromosome analysis, results in a higher pregnancy rate of about 70% per embryo transfer, and a lower miscarriage rate of about 10%. Comprehensive chromosome screening methods are shifting from array comparative genomic hybridization (aCGH) to the next generation sequencing (NGS) method because of its accuracy. NGS has a high analytical ability compared to aCGH because it can directly count DNA fragments produced by whole genome amplification from biopsy samples. Thus, with NGS, it is becoming possible to diagnose embryo mosaicism.

The incidence of mosaicism in blastocysts is 20-30% lower than that in cleavage embryos. The Preimplantation Genetic International Society issued a statement in which embryos with 20-80% of aneuploid cells are treated as having mosaicism. The implantation rate of blastocysts with mosaicism is low compared to that of normal blastocysts. The statement also suggested how to prioritize the transfer of mosaic

embryos, but treatment using such embryos is currently controversial. At the present time, when data on mosaicism is insufficient, additional genetic counseling is necessary for a decision for mosaic embryos to be transferred.

In Japan, the Japan Society of Obstetrics and Gynecology approves PGD in habitual cases of miscarriage with balanced chromosomal structural rearrangement, but does not allow PGS which is now widely practiced worldwide. However, a clinical study using PGS is under consideration. Immediately after confirmation of its validity, an environment for patients to undertake PGS should be created while carefully considering the ethical issues peculiar to Japan.