

Challenges of Genetic Screening of *In Vitro* Fertilized Human Embryos Using Current Technologies

Human is usually sub-fertile in comparison to other mammals; in other words, reproduction process of other mammals is more effective than human. Chromosomal anomalies of early embryos are the major reason for the low fecundity of human per cycle. Most of embryos with major genetic defects may be implanted and it can be followed with stopping of early development and early embryo loss with no tangible evidence of pregnancy. In addition, several studies have shown that more than 70% of embryos from assisted reproductive technologies have genetic anomalies. These anomalies lead to implantation failure or early embryo loss following implantation in IVF cycles (1).

According to the above evidence on *in vitro* produced embryos, different methods such as PGD and PGS were developed for choosing the best embryos without genetic defects. These methods are based on molecular techniques of Q-PCR, FISH, CGH and SNP microarray, NGS and many other advanced technologies. While several studies approved the efficiency of these techniques, they have different problems that put their effectiveness in doubt over time. For example, the FISH method on blastomeres of day three embryos was the choice in the two past decades, but recent evidence revealed that it failed to provide reliable result of PGS on cleavage embryos. Therefore, it has been replaced by the newer techniques such as CGH microarray and SNP microarray over time. However, though the newer techniques have higher degree of accuracy, they always have their own limitations and deficiencies as well (2).

Alternatively, the poor results of PDG and PGS on day three embryos lead to performing the embryo biopsy on blastocyst on day five after fertilization. Although the quantity and quality of biopsied cells are better than day three embryos, this area already raised issues such as suspicion about its limitations and deficiencies like epigenetic changes due to prolonged *in vitro* culture, self-correction potency for chromosomal anomalies of early embryo, different origins of biopsied cells from trophoectoderm against ICM and several other limitations. Furthermore, today in the scientific community and the media, application of the expensive technique of next generation of sequencing (NGS) is recommended for genetic screening of IVF embryos. Preliminary data using this technology reported the increase of ART outcomes up to %70-80. Based on these results, this technique may have high accuracy and reliability. However, its wide application in large portion of infertile couples, especially those with repeated IVF failure (RIF), repeated pregnancy loss (RPL) and the patients older than 40 years requires further investigation (3). Currently, application of this technique will impose huge cost on couples and if its accuracy and precision is in doubt, it may lead to loss of a large number of embryos that have the potential of implantation and live birth. In addition, the interpretation of the large volume of data from NGS is not very simple. Many of these findings may indicate normal variations or corrective potential of embryos may ameliorate most of them. So, as long as validation of the effectiveness of this technique or innovation of newer techniques with maximum sensitivity and specificity is required, care should be taken in prescribing these techniques to infertile couples.

References

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