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Letter to the Editor

Preimplantation Genetic Diagnosis and Aneuploidy Screening

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Letter to the Editor

The first baby after Preimplantation Genetic Diagnosis (PGD) technique with blastomere biopsy and sexing with DNA amplication of Y-chromosome specific repeat sequence was born in 90s [1]. It was followed by another baby girl, who was delivered after PGD with blastomere biopsy and Polymerase Chain Reaction (PCR) for cystic fibrosis [2]. In recent decades, the indications for PGD extended from severe lethal congenital diseases to adult-onset ones with variable penetrance, like Huntington chorea and hereditary cancer syndromes [3] (www.hfea.gov.uk). Not only the indications, the technique of PGD also revolutionised, with the advances of polar bodies and trophectoderm biopsies [4], using Comprehensive Chromosome Screening (CCS) with array comparative genomic hybridisation (aCGH) or Next Generation Sequencing (NGS) to replace Fluorescent In-Situ Hybridisation (FISH) for translocations and aneuploidy screening (PGS), and the combination of PGD for monogenetic diseases with PGS [5-7].

Polar body biopsy empowers the study on preimplantation human embryos in those countries with strict legislation on the manipulation of embryos, but it only allows the testing on maternal genetic material and the cost is higher for two polar bodies to be tested [8,9]. Polar body biopsy may also jeopardise the implantation of embryos, like blastomere biopsy [10]. Blastomere biopsy allows testing of both paternal and maternal genetic material; however, there is only one blastomere for testing, which creates problems, like allele dropout, predisposing to misdiagnosis [11]. Also cleavage stage embryos are well-known to have greatest proportion of mosaicism compared with oocytes or blastocysts [12] and blastomere biopsy may jeopardise the implantation potential of the cleavage stage embryos [4,13]. Trophectoderm biopsy allows more cells to be biopsied and it seems to be less harmful to the embryos with comparable implantation rate and pregnancy rate with those embryos without biopsy [4].

FISH was used for translocation carriers and Aneuploidy screening. However, for both purposes, it failed to show any benefit [14-16]. The technique of FISH carries its own pitfalls, including technical problem with fixation and spreading, and limited number of fluorescent DNA probes available. Usually the technique can test up to 5 chromosomes in one round. The number of chromosomes tested can be increased with repeated rounds after washing, but the diagnostic accuracy decreases with repeated rounds [17]. Another reason for its failure in improving the pregnancy rate is that FISH only tests for the translocated segments in translocation carriers. Due to the interchromosomal effect, the probability of aneuploidies unrelated to the translocation is increased, which is not being tested by FISH. As mentioned before, cleavage stage embryos have the highest proportion of mosaic genetic makeup, compared with oocytes or blastocysts. Mosaicism would be a reason for misdiagnosis and also Aneuploidy embryos may cause failure of implantation or clinical miscarriages [18]. CCS with various techniques including array CGH or Single Nucleotide Polymorphism (SNP) array can overcome the first two factors with all 24 chromosomes tested in one goal. The use of trophectoderm biopsy can overcome the problem of mosaicism partially as the level of mosaicismdeclines in the blastocyst stage [19,20]. Within the use of CCS, PGS is preliminarily showed to be beneficial in idiopathic recurrent pregnancy loss and advanced maternal age [21,22].

For couple with two genetic diseases, such as translocation together with monogenetic disease, in the past, the only option would be biopsy of two blastomeres or two biopsy procedures for polar bodies followed by blastomere, for FISH and PCR separately [5,23]. With the use of Whole Genome Amplification (WGA) and the emerge of use of NGS with targeted sequence in PGD and PGS, the possibility of using one cell for both tests including CCS and PCR would be feasible [23].

There are a few ongoing randomized trials on the use of PGS in various conditions now. Before the beneficial effect can be shown by these trials, PGS using new technique should not be offered as routine practice, otherwise, the same pitfall in the past using PGS with FISH may occur again [24].

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