

Letter to the Editor

Preimplantation Genetic Diagnosis and Aneuploidy Screening

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Received: September 23, 2014; **Accepted:** October 10,
2014; **Published:** October 13, 2014

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The first baby after Preimplantation Genetic Diagnosis (PGD) technique with blastomere biopsy and sexing with DNA amplification 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 mosaicism declines 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].

References

1. Handyside AH, Kontogianni EH, Hardy K, Winston RM. Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. *Nature*. 1990; 344: 768-770.
2. Handyside AH, Lesko JG, Tarin JJ, Winston RM, Hughes MR. Birth of a normal girl after in vitro fertilization and preimplantation diagnostic testing for cystic fibrosis. *N Engl J Med*. 1992; 327: 905-909.
3. Shenfield F, Pennings G, Devroey P, Sureau C, Tarlatzis B, Cohen J; ESHRE Ethics Task Force. Taskforce 5: preimplantation genetic diagnosis. *Hum Reprod*. 2003; 18: 649-651.
4. Scott KL, Hong KH, Scott RT Jr. Selecting the optimal time to perform biopsy for preimplantation genetic testing. *Fertil Steril*. 2013; 100: 608-614.
5. Obradors A, Fernández E, Oliver-Bonet M, Rius M, de la Fuente A, Wells D, et al. Birth of a healthy boy after a double factor PGD in a couple carrying a genetic disease and at risk for aneuploidy: case report. *Human Reproduction*. 2008; 23: 1949-1956.
6. Obradors A, Fernández E, Rius M, Oliver-Bonet M, Martínez-Fresno M, Benet J, et al. Outcome of twin babies free of Von Hippel-Lindau disease after a double-factor preimplantation genetic diagnosis: monogenetic mutation analysis and comprehensive aneuploidy screening. *Fertility and sterility*. 2009; 91: 933 e1- e7.

7. Daina G, Ramos L, Obradors A, Rius M, Martinez-Pasarell O, Polo A, et al. First successful double-factor PGD for Lynch syndrome: monogenic analysis and comprehensive aneuploidy screening. *Clinical genetics*. 2013; 84: 70-73.
8. Geraedts J, Montag M, Magli MC, Repping S, Handyside A, Staessen C, et al. Polar body array CGH for prediction of the status of the corresponding oocyte. Part I: clinical results. *Human Reproduction*. 2011; 26: 3173-3180.
9. Magli MC, Montag M, Köster M, Muzi L, Geraedts J, Collins J, et al. Polar body array CGH for prediction of the status of the corresponding oocyte. Part II: technical aspects. *Human Reproduction*. 2011; 26: 3181-3185.
10. Levin I, Almog B, Shwartz T, Gold V, Ben-Yosef D, Shaubi M, et al. Effects of laser polar-body biopsy on embryo quality. *Fertil Steril*. 2012; 97: 1085-1088.
11. Harper JC, Wilton L, Traeger-Synodinos J, Goossens V, Moutou C, SenGupta SB, et al. The ESHRE PGD Consortium: 10 years of data collection. *Hum Reprod Update*. 2012; 18: 234-247.
12. Fragouli E, Alfarawati S, Daphnis DD, Goodall NN, Mania A, Griffiths T, et al. Cytogenetic analysis of human blastocysts with the use of FISH, CGH and aCGH: scientific data and technical evaluation. *Hum Reprod*. 2011; 26: 480-490.
13. Scott RT, Upham KM, Forman EJ, Zhao T, Treff NR. Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial. *Fertility and sterility*. 2013; 100: 624-630.
14. Franssen MTM, Musters AM, van der Veen F, Repping S, Leschot NJ, Bossuyt PMM, et al. Reproductive outcome after PGD in couples with recurrent miscarriage carrying a structural chromosome abnormality: a systematic review. *Human reproduction update*. 2011; 17: 467-475.
15. Mastenbroek S, Twisk M, van der Veen F, Repping S. Preimplantation genetic screening: a systematic review and meta-analysis of RCTs. *Hum Reprod Update*. 2011; 17: 454-466.
16. Harper J, Coonen E, De Rycke M, Fiorentino F, Geraedts J, Goossens V, et al. What next for preimplantation genetic screening (PGS)? A position statement from the ESHRE PGD Consortium Steering Committee. *Hum Reprod*. 2010; 25: 821-823.
17. Wells D, Alfarawati S, Fragouli E. Use of comprehensive chromosomal screening for embryo assessment: microarrays and CGH. *Mol Hum Reprod*. 2008; 14: 703-710.
18. Hodes-Wertz B, Grifo J, Ghadir S, Kaplan B, Laskin CA, Glassner M, et al. Idiopathic recurrent miscarriage is caused mostly by aneuploid embryos. *Fertil Steril*. 2012; 98: 675-680.
19. Gonzalez-Merino E, Emiliani S, Vassart G, Van den Bergh M, Vannin AS, Abramowicz M, et al. Incidence of chromosomal mosaicism in human embryos at different developmental stages analyzed by fluorescence in situ hybridization. *Genet Test*. 2003; 7: 85-95.
20. Bielanska M, Tan SL, Ao A. Chromosomal mosaicism throughout human preimplantation development in vitro: incidence, type, and relevance to embryo outcome. *Hum Reprod*. 2002; 17: 413-419.
21. Schoolcraft WB, Katz-Jaffe MG. Comprehensive chromosome screening of trophectoderm with vitrification facilitates elective single-embryo transfer for infertile women with advanced maternal age. *Fertil Steril*. 2013; 100: 615-619.
22. Rubio C, Rodrigo L, Mir P, Mateu E, Peinado V, Milán M, et al. Use of array comparative genomic hybridization (array-CGH) for embryo assessment: clinical results. *Fertil Steril*. 2013; 99: 1044-1048.
23. Lee VC, Chow JF, Lau EY, Yeung WS, Ng EH. Live birth following double-factor pre-implantation genetic diagnosis for both reciprocal translocation and alpha-thalassaemia. *Hong Kong Med J*. 2014; 20: 251-254.
24. Mastenbroek S, Repping S. Preimplantation genetic screening: back to the future. *Hum Reprod*. 2014; 29: 1846-1850.