Preimplantation genetic screening using comprehensive chromosome screening: evidence and remaining challenges

Sir,

We read with great interest a recent systematic review by Lee et al. published in your journal evaluating the clinical effectiveness of preimplantation genetic diagnosis for aneuploidy in all 24 chromosomes (PGD-A) (Lee et al., 2015). The authors conclude that, for the time being, the role for PGD-A remains uncertain regarding its clinical- and cost- effectiveness. In our opinion, a number of observations need to be addressed with regards to the implication of their findings. First, in order to ensure standard nomenclature in preimplantation genetics, it must be made clear that what the authors refer to as PGD-A is otherwise known as preimplantation genetic screening (PGS). The term ‘PGD’ should be reserved for patients carrying specific genetic disorders in which a preimplantation diagnosis for the abnormality in question is desired.

Secondly, the authors reach their conclusion through a systematic review of studies with varied levels of evidence including both randomized control trials (RCTs) and observational studies. In the presence of level I evidence from RCTs, the inclusion of lower level evidence in a systematic review may induce erroneous conclusions and adversely impact clinical practice. A recent systematic review by our team (Dahdouh et al., 2015) restricted only to RCTs dealing with PGS using comprehensive chromosome screening (CCS) technology (Yang et al., 2012; Forman et al., 2013; Scott et al., 2013a) concluded that the use of PGS-CCS for the purpose of embryo selection in good-prognosis patients with normal ovarian reserve was favourable. Implantation rates (IR) were improved in the three RCTs with PGS-CCS following blastocyst biopsy. Using this approach, elective single embryo transfer (eSET) is optimized by improving the chance of delivering a healthy term singleton. With the high IR reported using PGS-CCS, eSET practice should be the standard of care. According to our review, the minimal standard for the success of this technology in today’s practice should be having enough experience with embryo biopsy and extended embryo culture, and validating the genetic platforms for CCS in order not to discard normal euploid embryos.

We agree that the use of PGS with fluorescence in situ hybridization (FISH) following cleavage-stage biopsy did not confer any advantageous results in IVF practice. However, in our opinion, the reason was not primarily related to the FISH technology, where up to 80% of embryonic aneuploidy can be diagnosed using 12 probes, but rather to the combination of FISH and day-3 embryo biopsy. Cleavage-stage biopsy might have been deleterious on embryo development under certain circumstances (e.g. retrieving two blastomeres, biopsy on poor quality embryos). In level I evidence data comparing day-3 to day-5 embryo biopsies (Scott et al., 2013b), cleavage-stage biopsy was associated with a 39% decrease in implantation potential, whereas no impact on embryo development was observed following blastocyst biopsy. A valid criticism regarding this paper was that IR in both day-3 and day-5 embryos were surprisingly equivalent. However, some investigators reported positive clinical outcomes from RCTs on PGS applied on day-3 embryo biopsy, both with FISH (Rubio et al., 2013) and with array comparative genomic hybridization (aCGH) (preliminary results, ClinicalTrials.gov NCT01571076). Therefore, embryo culture conditions and biopsy media and technique, are key laboratory aspects to consider for the ideal PGS practice.

In addition, the authors claim that there are no reports on subsequent embryo transfer cycles following PGS-CCS. However, some authors recently reported increased IR with subsequent euploid blastocyst transfers (Yang et al., 2013). With regards to cost-effectiveness, we agree with the authors that studies performed on the cost of PGS-CCS following at least two embryo transfer cycles compared with control groups will be needed to resolve this matter.

Future RCTs on PGS-CCS should be conducted on a multicentre basis, including different geographic locations, different patient populations (e.g. decreased ovarian reserve, advanced maternal age) and different embryo stage biopsy (e.g. day-3 versus day-5). We are witnessing the early days of the development of this new form of PGS; robust evidence is still needed from ongoing RCTs before it is applied on a regular basis.

References

Reply: Preimplantation genetic screening using comprehensive chromosome screening: evidence and remaining challenges

Sir,

We thank Dr Dahdouh and colleagues for their interest on our systematic review on the clinical effectiveness of preimplantation genetic diagnosis for aneuploidy (PGD-A) (Lee et al., 2015). We are pleased that in essence they concur with our conclusions, and that they also call for more robust evidence from randomized controlled trials (RCTs) before PGD-A is applied on a regular basis.

We chose to use the terminology PGD for aneuploidy (PGD-A) instead of preimplantation genetic screening (PGS) as we believe it better reflects that this type of testing is diagnostic for the individual embryos and is not a screening test. Other key authors (Bisignano et al., 2011; Handside, 2011; Munné 2012) in this field also recognize that either terminology can be used.

We chose to include both intervention and observational studies in our systematic review to provide a synopsis of the quality of available evidence on the topic and to draw objective conclusions where possible on the effectiveness of PGD-A based on patient-centred outcomes. We also concur with Dahdouh et al.’s systematic review (Dahdouh et al., 2014) that current evidence based from published RCTs demonstrates improved implantation and pregnancy rates in young good-prognosis patients following PGD-A and that such an approach advances the adoption of single embryo transfer (Yang et al., 2012; Forman et al., 2013; Scott et al., 2013). However, good quality evidence is lacking in other patient groups.

We did not claim that there were no reports on subsequent embryo transfer cycles following PGD-A, and in fact included the cumulative success rates following one thaw cycle reported in Forman’s RCT (Forman et al., 2014). However, we did not include the results of Yang et al.’s (Yang et al., 2013) follow-up thaw cycles because they were reported as a separate result of 15 patients and therefore did not fit our inclusion criteria of at least 20 patients.

We can also only concur with Dr Dahdouh and colleagues that laboratory quality and experience are key aspects for a successful PGD-A program, and is why we dedicated some text to describing the minimal requirements for conducting high-quality studies in this area. Furthermore, it is also important that RCTs are correctly designed and analysed according to intention-to-treat principles that minimize bias and report success in terms of cumulative live birth rates from fresh and subsequent frozen cycles.

References


Evelyn Lee 1,*, Peter Illingworth 2, Leeanda Wilton 3 and Georgina Mary Chambers 1

1National Perinatal Epidemiology and Statistics Unit, School of Women’s and Children’s Health, University of New South Wales (UNSW), Level 2, McNevin Dickson Building, Randwick Hospitals Campus, Sydney 2031, Australia

2IVF Australia Pty Ltd, 176 Pacific Highway, Greenwich, Sydney 2065 Australia

3Melbourne IVF, Victoria Parade, East Melbourne, VIC 3002, Australia

*Correspondence address. Tel: +61-293821014; E-mail: evelyn.lee@unsw.edu.au

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