Perhaps only those embryos graded in the Modest to Medium groupings should be considered for genetic screening. Blastocysts categorized in the High group and Top groups will not benefit from screening as the chance of a healthy live birth is not improved.

**References**


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**Reply: Which blastocysts should be considered for genetic screening?**

Sir,

We thank the authors for their interest in our paper (Fiorentino et al., 2014a). We welcome the opportunity to discuss the advantages of Pre-implantation Genetic Screening (PGS) versus morphological assessment of blastocysts and further stimulate the discussion on this important topic.

The authors claim that the transfer of embryos graded 4AA/5AA based on morphological criteria can provide an implantation rate equivalent to that achieved with the transfer of chromosomally screened embryos. However, they did not provide data on the cohort of patients involved in their study. As a consequence the results may be biased from the comparison of different groups of patients.

Our study included poor prognosis patients, for which embryo transfer has often involved the unique euploid blastocyst available, regardless of its morphological score. Despite so, the live birth rate obtained with blastocysts graded 4AA/5AA reported by the authors (54%) is lower than the overall live birth rate achieved in our study (62%). This value increases to 64% if considering embryos graded 4AA/5AA only (data not shown). Therefore, the concern raised by Yovich and colleagues appears unsupported.

Our study provided evidence that morphological and developmental embryo characteristics are weakly correlated with their viability. In fact, a high rate (55%) of aneuploid embryos has been detected, including those graded AA. Similarly, other studies involving comprehensive chromosome screening (CCS) and well-established criteria for the assessment of embryo morphology demonstrated that chromosome aneuploidies are common among embryos of optimal morphological score (40%), while overrepresented in embryos considered to be of poor morphology (60%) (Alfarawati et al., 2011; Fragnoli et al., 2013, 2014). Furthermore, in our center we performed a study evaluating the correlation between standard morphology and ploidy status of 1036 blastocysts; 378 of them (36.5%) were classified as top quality blastocysts (4AA, 5AA or 6AA). In this group with high potential of implantation, 217 (57.4%) were found to be aneuploid blastocysts (unpublished data). These data demonstrate that morphologic analysis cannot be relied on to ensure transfer of chromosomally normal embryos.

Recently, several randomized controlled trials (RCTs) have also demonstrated the clinical efficacy of PGS technology versus morphological assessment (Yang et al., 2012; Forman et al., 2013; Scott et al., 2013). For example, Yang et al. (2012) investigated the usefulness of PGS in young and good prognosis patients, demonstrating beneficial effect of PGS in terms of enhanced implantation and delivery rates in this group of patients. The ongoing pregnancy rate was significantly higher in the PGS group compared with the morphologically selected embryos group (69.1 versus 41.7%, respectively). Scott et al. (2013) investigated PGS usefulness in patients younger than 43 years old, demonstrating significantly higher sustained implantation rates per transfer (66.4 versus 47.9%) and higher delivery rates per cycle (84.7 versus 67.5%) in the PGS group compared with the control group.

A point to note is that, inevitably, aneuploid embryos fail to implant, and those that do implant will generally result in pregnancy loss or in live birth of children with chromosomal aberrations. As a consequence, PGS not only has the potential to improve the clinical outcome of IVF techniques, but the enhanced selection empowered by PGS may also provide a practical way to substantially lower the risk of adverse reproductive outcomes related with the transfer of chromosomally abnormal embryos without compromising clinical outcomes.

The benefit of PGS in terms of cost effectiveness may be more difficult to assess, as this question inevitably involves a subjective decision taken by patients after counseling with the clinicians. Although an additional cost is associated with CCS, it would be lower compared with the cost of repeated ART cycles. Moreover, the emerging CCS technologies, such as Next Generation Sequencing (NGS), allow simultaneous evaluation of multiple samples from different patients in the same sequencing run (Fiorentino et al., 2014a,b). This feature holds the potential to substantially lower the costs associated with PGS.

To conclude, in view of current knowledge, it is our opinion that CCS may be beneficial even if performed by testing all blastocysts, and not only those with the lower morphological scores. This approach may provide (i) improved IVF clinical outcome, (ii) no impact on developmental potential of the embryos and (iii) a cost-effective approach for the patients.


CDC analysis of ICSI/autism: association is not causation

Sir,

We read with interest the recent manuscript published in Human Reproduction by Kissin et al., which associated ICSI with autism risk (Kissin et al., 2015). We are concerned that, taken out of context, this publication may be misleading to the reproductive medicine community.

Autism is a serious neurodegenerative condition with largely unknown etiologies. According to the United States Centers for Disease Control (CDC), the prevalence of autism in the USA appears to have rapidly risen from approximately 6.7 per 1000 in 2002 to 14.7 per 1000 in 2010 (MMWR, 2012). According to the same CDC report, Caucasian children are 30% more likely to be diagnosed with autism than children of African descent (MMWR, 2012).

This discrepancy has been attributed to varying diagnostic practices in different socioeconomic settings and not to race or ethnicity (Durkin et al., 2010; Hoffman et al., 2012; Pedersen et al., 2012; Zuckerman et al., 2013). It seems likely that the same socioeconomic factors biasing the diagnosis of autism may also affect which patients utilize assisted reproductive technologies (ART) (Bitler and Schmidt, 2006; Jain, 2006; Chandra and Stephen, 2010; Duwe et al., 2010). Since ICSI adds significant expense to an already expensive procedure, one can surmise that socio-economically advantaged patients would utilize ICSI to a higher degree, especially during the years covered in the CDC study when ICSI was still an emerging technology (Palermo et al., 1995).

Statistical models used by Kissin et al. (2015) adjusted for infant gender, gestational age, birthweight, multiple pregnancy, birth year, parental age at delivery, number of previous births, mode of delivery, and fertility diagnosis, but do not appear to adjust for race/ethnicity and/or socioeconomic status. While direct indicators of socioeconomic status are not available on birth certificates, birth certificate information has been utilized by other investigators in similar epidemiologic studies to reconstruct socioeconomic status (Moceri et al., 2001). The authors did note that ART cycles associated with ICSI increased from 33% in 1996 to 60% in 2006 (an 81.82% increase), and that during the same time period the incidence of autism among ART patients remained steady around 1%, with an expected higher incidence among multiple pregnancies compared with singleton pregnancies (Kissin et al., 2015). If ICSI did indeed increase the risk of autism as suggested by Kissin et al. (adjusted hazard risk ratio 1.65; 1.08–2.52), it stands to reason that, commensurate with this increased proportion of ICSI cycles, there should have been a concomitant increase in autism among ART patients. Such an increase was, however, not observed.

Recognizing this fact as a potential contradiction, Kissin et al. suggested that absence of such an observed increase in autism among all ART patients might have been the consequence of decreasing multiple gestations due to fewer embryos being transferred. However, multiple gestation was a factor the authors adjusted for in their analysis (Kissin et al., 2015).

This study’s conclusion that the utilization of ICSI in California between 1997 and 2006 was associated with an increased adjusted hazard risk for autism, therefore, appears incorrect.

References


