

## **PGS MAY BE SUITABLE FOR CERTAIN PATIENTS TO SELECT EMBRYOS**

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Proponents as well as critics of preimplantation genetic screening (PGS) are in agreement that the number of chromosomal anomalies in human embryos correlates with maternal age, and that PGS on biopsied blastomeres with fluorescence in situ hybridization (FISH) does not provide an advantage in patients of younger age and those with repeated implantation failure. Where opinions become starkly opposed is when PGS using FISH is used to predict embryonic viability and when it is applied prospectively prior to transfer in reproductively older women and couples at high risk of having a repeated miscarriage. Proponents of such clinical PGS procedures have argued that in experienced hands the method using FISH with 9-12 probes, may improve the chance of implantation and ongoing pregnancy, although this may only be attained in a relatively narrow sub-population of patients. They base this assumption on a number of retrospective and comparative studies in patients with advanced maternal age and good follicular response and others who are considered to suffer from repeated pregnancy loss (RPL). Opponents of PGS by FISH argue that the retrospective studies are perhaps interesting, but are not conclusive because the studies did not involve prospective randomization. About half a dozen randomized clinical trials (RCT) have been used in which FISH was applied in day 3 embryos with no measure of success. In the largest RCT the results of PGS were very disappointing. Pregnancy rates appeared even diminished when control group patients whose embryos were biopsied without FISH assay results were compared to a subset of patients whose embryos were not subjected to biopsy. A clear warning that embryo biopsy may be detrimental in the hands of some. It is not surprising that a typical evidence based medicine analysis would now argue that PGS by FISH is ineffective.

Although the RCT is considered the cornerstone of evidence based medicine, it is surprising that this relatively new notion has such a massive following among medical specialists, without much debate. The RCT was developed 60 years ago in order to reliably assess the effectiveness of newly developed drugs using the simple platform of the two-armed study; drug versus placebo. Its application in complicated technical areas requiring specific technical expertise such as surgery has been questioned. ART in combination with embryo biopsy, cell fixation and assays for PGD/PGS is a highly complicated model. The custom to apply the RCT to this model has never been challenged. The breakdown of this system has been profound in some of the PGS trials. Optimization of methodologies, not just patient selection and randomization, has failed more than once. The hardcore acceptance of evidence-based medicine will limit inclusion into the formula only to those prospective studies that have been randomized. In spite of the excellent title of the new field of evidence-based medicine, the accepted formula is based on a simple concept. It is not an exact science. It remains largely unchallenged because of the bandwagon effect even though it has distinct aspects of being authoritarian. The current debate about PGS, though appealing for some has caused much disappointment and fatigue among colleagues. Several practice committees of professional organizations have cautioned regarding the current application of PGS. However, new data related to the application of micro-array and Comparative Genome Hybridization (CGH) technology on trophectodermal cells of blastocysts may render the discussion soon out of date. Recent PGS data has shown promising results of embryo selection applied to the blastocyst stage using trophectoderm biopsy followed by vitrification. Interestingly, both FISH and CGH data sets provided positive information. The study by Wells and co-workers using CGH indicates pregnancy rates above 80% in women of relatively advanced maternal age (average 37 years) with at least one previous IVF implantation failure and a doubling of implantation. These and other studies may shed a different light on the current debate, because the question is not whether chromosomally abnormal embryos should be removed, but whether they can be removed safely with limited downside to the embryos that are considered viable, while applying the highest measure of accuracy and yielding the finest and most complete set of information. The recent improvements of prolonging embryo culture, and reducing the rate of loss after freezing and vitrification may allow a more in-depth study of the blastocyst. This is of interest because the blastocyst is quite ideal for the purposes of PGD and PGS. A larger sample of cells may be removed which could allow for a more robust analysis of DNA or even combine different methods applied to the same sample. Also, at least in principal, it should reduce error and 'no result' rates simply because dubious assays can be repeated. Finally, it would allow for transfer of embryos in a non-stimulated cycle. All this is of course dependent on a high rate of success of both prolonged culture and freezing or vitrification.