Reproductive BioMedicine Online (2016) **32**, 337–338

www.sciencedirect.com
www.rbmonline.com

EDITORIAL

Preimplantation genetic screening – what a wonderful world it would be!

When IVF was first described, it challenged the biological dogma that embryos were to be created only inside the human body. It took some time before IVF was accepted by the scientific community and for it to truly revolutionize human reproduction. Not only would women with blocked Fallopian tubes benefit, but also very many others, to the extent that contemporary use now encompasses many non-medical indications.

Embryo quality and selection is key to successful IVF. However, morphologic assessment of embryos is highly inaccurate. Even with modern time-lapse evaluations, much information is missing when deciding which embryo to transfer, with implantation rates varying from 20 to 40% in the best scenarios. In fact, human fecundability is not very high. Only around 25% of menstrual cycles result in a pregnancy, so it is likely that many embryos created *in vivo* never develop to produce a healthy baby (Macklon et al., 2002).

With the advent of embryo biopsy and single-cell chromosomal analysis, first reported in 1990 (Handyside et al., 1990), a new era in assisted reproduction was initiated and an animated debate has since ensued regarding possible indications for preimplantation genetic screening (PGS) technology (Wiessman et al., 2016). Although initial fluorescent in situ hybridization (FISH) analyses were not very reliable, new technologies such as array-comparative genomic hybridization (aCGH), or the recently adopted next generation sequencing (NGS), seem to produce highly reproducible and more accurate results than previous techniques. Including the full chromosomal spectrum provides a tremendous amount of additional information which may help to improve embryo selection. However, chromosomes do not explain everything, and some women still do not achieve a pregnancy even when euploid embryos are transferred.

Moreover, many questions need to be answered before PGS can be advocated as the preferred universal screening method for IVF embryos.

First of all, diagnostic accuracy is not flawless: all diagnostic tests have an error rate. Can we be absolutely sure that discarded embryos do not have the potential to become newborns, or that transferred embryos are always healthy? How accurate and robust is the technique? The risk of overdiagnosing chromosomal abnormalities to avoid transferring abnormal embryos has to be balanced against the risk of discarding healthy embryos that may carry limited anomalies of uncertain significance. This error rate per pregnancy is 0.13% (Werner et al., 2014). The implications of mosaicism in embryos (the presence of two or more distinct cells lines in the same embryo) are still unknown and have generated vigorous debate (Scott and Galiano, 2016; Taylor et al., 2014). Recent data reporting monosomic mosaic embryos implanting and becoming healthy newborns (Greco et al., 2015) challenges the concept of discarding all mosaic embryos. Not all groups agree that mosaicism might be lower when embryo biopsy is performed at the blastocyst stage (Taylor et al., 2014). What should be the minimum number of abnormal cells determining that an embryo be discarded?

The risk of interpreting as abnormal "noisy" profiles when DNA is degraded also needs to be investigated further. Still an open question is whether the biopsy procedure itself may physically compromise the embryo. Current data do not seem to suggest such damage (Rubio et al., 2014), especially at the blastocyst stage (Scott et al., 2013), but this possibility should be discussed with the patients. Additionally, if biopsy is performed not at the cleavage stage but on the trophectoderm, most of the centres throughout the world may need to freeze all of the biopsied embryos, wait for the results and then perform the transfer of frozen embryos in a subsequent thaw cycle. Although blastocyst vitrification provides excellent results, a new procedure being incorporated into the process will increase complexity, cost and time to pregnancy, alongside the hypothetical additional risk of late-onset disorders.

Analyzing the cost-effectiveness of PGS is not a simple task. Even though new molecular technologies are becoming cheaper, they remain expensive procedures and are not available at every centre. On the other hand, reducing the number of abnormal embryos transferred, especially in cases of advanced maternal age, may reduce the costs associated with repeatedly failed IVF cycles, as well as reducing the frustration experienced after a negative pregnancy test or a miscarriage. Another relevant benefit of PGS is that, by enhancing embryo selection, it allows liberal application of elective single

http://dx.doi.org/10.1016/j.rbmo.2016.02.007

embryo transfer (eSET) without compromising delivery rates; with increased numbers of eSET, multiple pregnancies are reduced, diminishing the risk of preterm delivery, low birthweight and neonatal intensive-care unit admission (Dadouh et al., 2015). The cost savings made by reducing multiple pregnancies may outweigh additional PGS expenses.

Some other limitations to the technique need to be discussed, to avoid the risk of misdiagnosis. The ideal day for the embryo biopsy has shifted from day 3 to day 5/6, as most (but not all) groups have shown that not only does this shift reduce the risk of damage to the embryo but it also makes more cells available for diagnosis, allowing even a double diagnosis of aneuploidies and single gene defects, if necessary. One of the paramount issues is the quality of the laboratory and the professionals involved in the process of embryo biopsy and genetic analysis. Lab to lab variation in IVF is a significant contributing factor to differences in implantation rates, and a similar consideration applies to genetic testing results. The possibility of human error or technology failure during the process – including embryo biopsy and handling, DNA amplification, hybridization, and contamination – requires continuous and strict quality control.

However, recent retrospective data show that IVF results after PGS almost eliminate the impact of aging – the main cause of aneuploidies – on embryo quality (Rodrigo et al., 2014). We agree that the live birth rate per initiated IVF cycle cannot be improved with PGS, as the risk of cycle cancellation and not reaching embryo transfer increases dramatically with age. But providing this information to our patients, even if all embryos are abnormal, will help the decision-making process to move to other options, including gamete donation, adoption or ceasing further treatment.

Doctors discussing PGS with their patients need to be aware of the potential benefits as well as the current limitations of this diagnostic technique.

References

Dadouh, E.M., Balayla, J., Garcia-Velasco, J.A., 2015. Impact of blastocyst biopsy and comprehensive chromosome screening technology on preimplantation genetic screening: a systematic review of randomized controlled trials. Reprod. Biomed. Online 30, 281–289.

Greco, E., Minasi, M., Fiorentino, F., 2015. Healthy babies after intrauterine transfer of mosaic aneuploidy blastocysts. N. Engl. J. Med. 373, 2089–2090.

Handyside, A.H., Kontogianni, E.H., Hardy, K., Winston, R.M., 1990. Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. Nature 344, 768–770.

Macklon, N.S., Geraedts, J.P., Fauser, B.C., 2002. Conception to ongoing pregnancy: the "black box" of early pregnancy loss. Hum. Reprod. Update 8, 333–343.

Rodrigo, L., Mateu, E., Mercader, A., Cobo, A., Peinado, V., Milan, M., Al-Asmar, N., Campos-Galindo, I., Garcia-Herrero, S., Mir, P., Simon, C., Rubio, C., 2014. New tools for embryo selection: comprehensive chromosome screening by array comparative genomic hybridization. Biomed Res. Int. 2014, Article ID 517125.

Rubio, C., Bellver, J., Castillon, G., Rodrigo, L., Guillen, A., Remohi, J., Pellicer, A., Simon, C., 2014. RCST study in advanced maternal age patients using array-CGH: interim analysis. Hum. Reprod. 29 (Suppl. 1).

Scott, R.T., Jr., Galiano, D., 2016. The challenge of embryonic mosaicism in preimplantation genetic screening. Fertil. Steril. doi:10.1016/j.fertnstert.2016.01.007; (in press).

Scott, R.T., Jr., Upham, K.M., Forman, E.J., Zhao, T., Treff, N.R., 2013. Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial. Fertil. Steril. 100, 624–630.

Taylor, T.H., Gitlin, S., Patrick, J., Crain, J., Wilson, M., Griffin, D., 2014. Hum. Reprod. Update 20, 571–581.

Werner, M., Leondires, M., Schoolcraft, W., Miller, B., Copperman, A., Robins, E., Arredondo, F., Hickman, T.N., Gutmann, J., Schillings, W.J., Levy, B., Taylor, D., Treff, T.R., Scott, R.T., Jr., 2014. Clinically recognizable error rate after the transfer of comprehensive chromosomal screened euploid embryos is low. Fertil. Steril. 102, 1613–1618.

Wiessman, A., Yaron, Y., Fishel, S., 2016. <http://www.ivf-worldwide.com/survey/preimplantation-genetic-screening-pgs-what-is-my-opinion/results-preimplantation-genetic-screening-pgs-what-is-my-opinion.html> (accessed 13.02.16).

Juan A. Garcia-Velasco, Bart C.J.M. Fauser
E-mail addresses: juan.garcia.velasco@ivi.es; b.c.fauser@umcutrecht.nl