as facts harder than faith alone, before PGD (and this was the main subject of the debate) is systematically applied to older patients.

References

J. Egozcue
Department of Cell Biology
Universitat Autònoma de Barcelona
08193 Bellaterra, Spain

Dear Sir,
We read with interest the last part of the debate by Munné and Cohen (1997), and it is a great honour for us to be able to comment on the remarks made by these pioneers in the field of preimplantation genetic diagnosis (PGD).

Like Munné and Cohen we believe that PGD of aneuploidy in older in-vitro fertilization (IVF) patients is an evolving and promising clinical tool for the reduction of aneuploidy in this age group. This approach may serve as an alternative to invasive prenatal screening and therapeutic abortions, and may also increase the chances of an implanted embryo to arrive to term. However, we find that it is still uncertain whether this approach will significantly improve pregnancy rates.

Indeed, the data supporting the correlation between maternal age and the rate of chromosomal imbalance in oocytes and embryos is quite convincing (Angell et al., 1993; Munné et al., 1995; Dailey et al., 1996), and it is undeniable that the increase in aneuploidy with age is inversely correlated with assisted reproductive techniques (ART) success rates. Yet, do these facts guarantee that routine PGD in all women of advanced age will significantly improve pregnancy rates per cycle? Will it prove cost effective? It is our view that several issues have still to be investigated before the answer ‘Of course’ can be given. Some of these issues are as follows.

Firstly, at present there is no proof in humans that embryo biopsy does not reduce implantation rate. It is possible that such an adverse effect of embryo biopsy will counteract the benefits in terms of pregnancy rates which are expected following PGD.

Secondly, poor oocyte quality has a prominent role in the age related fertility decline. There is accumulating evidence that the decline in oocyte quality with age is a result of the degeneration and malfunction of multiple cellular components (Tárín, 1996). If these degenerative processes are not closely linked to chromosomal imbalance, the selection of the euploid embryos for transfer might have only a marginal effect on implantation rates, as failure of implantation could still result from other age related sequelae.

Thirdly, the decline in ART success rates is most pronounced in women aged >40 years. These women usually have a small cohort of embryos (Plachot et al., 1988), and even if four or more embryos are produced, in many units, all embryos will be transferred. Under such circumstances, the chromosomally balanced embryos of the cohort are transferred in any case, and it seems unlikely that their selection by PGD would increase pregnancy rates. The implementation of PGD could be more relevant in the age range of 35–40 years, where production of a large cohort of embryos is common. Yet, both the increase in aneuploidy and the decline in pregnancy rates are less pronounced in these women. Therefore, it is doubtful whether PGD would significantly increase pregnancy rates in this age group.

Fourthly, chromosomal mosaicism, a frequent phenomenon among IVF embryos, raises an additional uncertainty. The current approach is to discard mosaic embryos. However, the biological significance of mosaicism is uncertain. It was recently suggested that abnormal cells in the early mosaic embryo are subsequently eliminated or diverted to the trophoectoderm and thus do not impair normal development (James and West, 1994). Therefore, discarding mosaic embryos may lead to the loss of potentially normal embryos and hence hamper the expected beneficial effect of PGD on pregnancy rates.

Fifthly, false FISH results may also lead to an erroneous unwanted loss of normal embryos (although to a lesser extent). Finally, the issue of cost effectiveness is not yet clear. Although PGD of aneuploidy is expected to reduce the abortion rate, it does not necessarily imply an improved delivery rate per cycle. It will be possible to calculate the cost effectiveness of this process only when the extent to which PGD will improve the delivery rate per cycle is determined.

In conclusion, PGD of aneuploidy is undoubtedly an important step towards accurate assessment of embryo quality. This approach may prevent aneuploidy at birth while avoiding the moral and religious impediments of pregnancy termination. It may also reduce the rate of abortions which are highly related to chromosomal imbalance. Still, it is unclear whether routine implementation of PGD in patients aged >35 years will improve pregnancy rates per cycle and will prove to be financially effective. Hence, the question: ‘to biopsy or not to biopsy?’ all embryos of older IVF patients needs further study.

References

Benjamin E. Reubinoff and Asher Shushan
Department of Obstetrics and Gynecology, Hebrew University, Hadassah Ein-Karem Medical Center Jerusalem, Israel