In this issue, Fragouli et al. report the results obtained by examining a total of 1213 embryos by combining comprehensive chromosome analysis with a systematic assessment of embryo morphology. At the cleavage stage, chromosome abnormalities were common even amongst embryos assigned the best morphological scores, indicating that aneuploidy has little effect on microscopic appearance during the first days of development. At the blastocyst stage on the other hand, aneuploidies were found to be significantly less common among embryos of optimal morphological quality, while such abnormalities were overrepresented amongst embryos considered to be of poor morphology. However, many blastocysts affected by forms of aneuploidy with the greatest capacity to produce clinical pregnancies, such as trisomy 21, were indistinguishable from euploid embryos. Therefore this large study illustrates that embryo selection based on morphological criteria is not efficient enough.

The aim of selection during the preimplantation stage is to improve the success rate of ART. However, success can be defined in many different ways: as an increase of the implantation rate, as a decrease of the miscarriage rate, as an increase of the clinical pregnancy rate, as an increase of the live birth rate, as the prevention of chromosomally abnormal newborns and as a decrease of the time to pregnancy. This means that, at least in theory, an efficient selection system might have a lot of success. However, it should be based on aneuploidy detection, since chromosome abnormalities are the predominant cause of all these clinical problems, both in natural conceptions as well as after assisted reproduction (Macklon et al., 2002). About 42% of all oocytes exposed to natural fertilization survive until implantation, and only 31% will lead to a live birth. The miscarriage rate causing the difference between both figures mainly depends on the maternal age because of aneuploidy oocytes originating at maternal meiosis I. Recently a meta-study was performed to obtain a more precise evaluation of the risk of embryonic chromosomal abnormalities in first-trimester miscarriage after ART in which a total of 15 studies were included. No statistical difference was found in risk of chromosomally abnormal miscarriage compared with natural conception and the different types of ART utilized, whereas the risk of fetal aneuploidy significantly increased with maternal age ≥35 (Qin et al., 2013).

Already during preimplantation development the potential of human embryos depends on their chromosomal constitution. The majority of all normal embryos reach the blastocyst stage, while this is the case in only a minority of chromosomally abnormal embryos (Sandalinas et al., 2001). Since trisomies and triploidies are much more viable than monosomies and more complex aneuploidies, human miscarriage in the first trimester mainly results from embryos with extra chromosomes (Simpson, 2007). However, during the first trimester the behaviour of individual human autosomal trisomies is very variable. Trisomy 1 has hardly ever been observed in a clinically recognized pregnancy. Trisomy 16 on the other hand is the most frequently occurring abnormality. From the start, the survival of the latter does not seem to be compromised but before fetal development starts the loss of these embryos is complete. A minority of the autosomal trisomies 13, 18 and 21 only are compatible with post-natal life. They undergo a continuous and differential pre-natal loss as was shown for trisomies 18 and 21 by a Kaplan–Meier analysis (Won et al., 2005). Therefore, the finding of Fragouli and colleagues that it is difficult to prevent the transfer of these abnormalities on the basis of morphology is not surprising, although this has been the selection method of choice since the introduction of assisted reproduction.

It is clear that a more proper selection system should be based on other aspects than morphology or better than morphology only. However, which other selection methods should be considered? In general one can make a distinction between molecular methods and time-lapse systems. In all cases conclusions about the potential use of these should be based on RCT results, which are hardly available. Genomic, transcriptomic and proteomic analysis can only be based on embryonic material obtained by invasive procedures such as polar body, cleavage stage or trophectoderm biopsy. As an alternative for non-invasive molecular studies, it has also been suggested that the use of differential metabolomic markers found in spent media from preimplantation embryos could be a feasible method for the detection of aneuploidies before embryo transfer (Sanchez-Ribes et al., 2012). The most promising non-invasive strategy at present seems to be the combined evaluation of morphology and developmental kinetics using time-lapse imaging (Montag et al., 2013). Promising supplementary models of embryo selection based on time-dependent markers have been proposed and are currently being verified in prospective trials (Herrera and Meseguer, 2013). Until the results of the on-going RCTs available selection for aneuploidy will remain obscure.
References


