Morphology matters: are all euploid blastocysts created equal?

The current issue of *Fertility & Sterility* includes a retrospective study by Irani et al. (1) that investigates the relationship between blastocyst morphology and implantation among euploid embryos. Their finding that higher graded euploid embryos have more of a chance of implantation calls into question what seems like conventional wisdom in current assisted reproductive technology (ART) practice: that all euploid blastocysts are equally likely to implant provided a well-timed synchronous ET is performed, regardless of their appearance or the age of the couple who produced them. If morphology really does matter, this would have important clinical implications, for example, on the use of gender preference for embryo selection and with regard to how many frozen euploid embryos may be required to achieve a couple's desired family size.

The past few years has witnessed a tremendous increase in the application of new techniques in ART with many clinics routinely using extended culture, trophectoderm biopsy, vitrification, and comprehensive chromosome screening with subsequent frozen euploid single ET. This approach has demonstrated benefit in prospective trials (2), but roughly a third of euploid blastocysts still fail to implant despite optimal conditions. Significant effort is underway at present to elucidate the causes for why some euploid embryos fail to implant.

It has been well established that blastocyst morphology, although associated with ploidy status, is not accurate enough to reliably select euploid blastocysts for elective single ET. If increased use of elective single ET across age groups is our goal as a field, then improved selection methods are essential. Outside of a randomized control trial setting, it is impractical to expect patients to continue to undergo successive single ETs until they have a successful outcome as many will drop out from care or demand multiple ET. Achieving pregnancy on the first ET is, therefore, an important goal to optimize outcomes and prevent drop out from care.

When comprehensive chromosome screening is used, it alters selection for elective single ET a significant proportion of the time, especially with increasing maternal age (3). But once euploid embryos are available, does their morphological appearance impact success?

A prior study by Capalbo et al. (4) suggested that morphology was not associated with the chance for ongoing pregnancy; "poor" quality euploid blastocysts fared just as well as higher graded blastocysts. It is important to remember that even the "poor" quality blastocysts were of sufficient quality to undergo trophectoderm biopsy and survive vitrification and warming to be transferred. Another study by Harton et al. (5) found that euploid embryos implant equally well regardless of age up to 42 years.

In the current study (1) from the Weill Cornell Medical College Center for Reproductive Medicine on 417 euploid frozen ETs, the investigators found a significant difference in the chance for ongoing pregnancy based on the morphology of the transferred blastocyst(s). Similar to the Capalbo et al. (4) study, blastocysts were grouped into four categories (excellent, good, average, poor). Although only 38 excellent embryos were transferred, they resulted in ongoing pregnancies significantly more often than average and poor quality embryos (84.2% vs. 55.8% vs. 35.8%); good quality embryos performed significantly better than poor quality ones (61.8% vs. 35.8%). The investigators conclude that morphological grading should be used to guide selection among euploid embryos.

Although intriguing, it is important to acknowledge that this type of study cannot truly assess the impact of selection of euploid embyros based on morphology. That would require a prospective trial in which a single euploid embryo was randomly selected from a cohort of euploid embryos, regardless of morphology. An alternative study design would randomize patients to a euploid embryo selected by morphology versus one selected at random. These types of prospective trials admittedly are impractical and unlikely to be performed.

In the present study, patients who had average or poor quality embryos transferred did not have any excellent or good quality ones available from which to select. The appropriate conclusion here is that patients who can produce excellent and good quality embryos in a given IVF cycle have a better prognosis in their first frozen ET than those who only produce poor quality ones. Although the investigators were diligent at correcting for potential confounders (including maternal age, day of biopsy, and number of euploid embryos available), it is possible that some other underlying factor reflecting diminished oocyte and/or sperm quality or aspects of the stimulation may have contributed to the lower success rates with poor quality blastocysts.

At Reproductive Medicine Associates of New Jersey, most ETs are now frozen, euploid single ETs. A large cross-section of all euploid frozen single ETs year-to-date in 2016 reveals that the highest quality blastocysts also have a significantly higher implantation rate (unpublished data). The implantation rate of excellent embryos (4AA, 5AA, 6AA) was 80.9% (n = 429). Poor quality embryos (4BC, 4CB, 4CC, 5BC, 5CB, 5CC, 6BC, 6CB, 6CC) still had an excellent implantation rate of 56.3% (n = 325), supporting the continued transfer of these embryos, but this was significantly lower than excellent and good quality embryos. This retrospective review, however, is subject to the same limitations and cannot prove that selecting by morphology impacts outcomes.

Another factor not considered is the potential role of mosaicism or segmental imbalances. The current study (1) includes embryos transferred after testing with array comparative genomic hybridization, which is not as well validated for the detection of these embryonic abnormalities as next generation sequencing. With the increasing clinical use of next generation sequencing, it will be interesting to determine whether there is an association between mosaicism and morphology that could influence the performance of poorer graded blastocysts (or perhaps remove some of them from potential transfer).

Although near-universal application of elective single ET should remain our goal as a field, a significantly lower implantation rate with poor quality (but viable) euploid blastocysts may justify consideration of double embryo transfer in certain settings and with appropriate counseling related to the increased risk of twins and obstetric complications. Another important factor to consider is the inherent variability and subjectivity of blastocyst grading. A good quality blastocyst in one laboratory may be considered a poor quality one in another. As blastocyst stage comprehensive chromosome screening and euploid single ET become increasingly used by clinicians, it would be prudent for each program to assess its own implantation rates based on a variety of factors including morphology. They too may find that morphology matters.

Eric J. Forman, M.D., H.C.L.D./A.L.D.
Reproductive Medicine Associates of New Jersey and Sidney Kimmel Medical College at Thomas Jefferson University, Basking Ridge, New Jersey

http://dx.doi.org/10.1016/j.fertnstert.2016.12.002

You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/13830-23497.

REFERENCES

1. Irani M, Reichman D, Robles A, Melnick A, Davis O, Zaninovic N, et al. Morphologic grading of euploid blastocysts influences implantation and ongoing pregnancy rates. Fertil Steril 2017;107:664–70.
2. Dahdouh EM, Balayla J, Garcia-Velasco JA. Comprehensive chromosome screening improves embryo selection: a meta-analysis. Fertil Steril 2015; 104:1503–12.
3. Forman EJ, Upham KM, Cheng M, Zhao T, Hong KH, Treff NR, et al. Comprehensive chromosome screening alters traditional morphology-based embryo selection: a prospective study of 100 consecutive cycles of planned fresh euploid blastocyst transfer. Fertil Steril 2013;100:718–24.
4. Capalbo A, Rienzi L, Cimadomo D, Maggiulli R, Elliott T, Wright G, et al. Correlation between standard blastocyst morphology, euploidy and implantation: an observational study in two centers involving 956 screened blastocysts. Hum Reprod 2014;29:1173–81.
5. Harton G, Munne S, Surrey M, Grifo J, Kaplan B, McCulloh DH, et al. Diminished effect of maternal age on implantation after preimplantation genetic diagnosis with array comparative genomic hybridization. Fertil Steril 2013; 100:1695–703.