When looks are deceiving—the challenge facing embryo quality prognosticators

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The quest for biomarkers of embryo quality is as seasoned as the practice of human ARTs itself. Reaching back into the annals of IVF reminds us of the attempts of the late Bob Edwards and his progeny during the 1980s that placed the property of fragmentation at the disposal of budding embryologists charged with identifying those embryos most suitable to transfer—and, hopefully, endowed with the most potential to give rise to a term pregnancy. As Bob showed, not so reliable was this admittedly “ugly” identifier as a predictor of implantation, let alone pregnancy. And then there were the primordial and laudable efforts of Lucinda Veeck and her colleagues to catalogue the entire range of morphological variation in oocytes, sperm, and embryos proffered to prognosticators for the next decade of human ARTs, one that brought with it measurable advances in ovarian stimulation and ICSI, placing “in the dish” many more embryos to transfer to the delight of patients and clinicians than could have been anticipated 10 years before. But, truth be told, embryo selection remains a vague and frustrating exercise, heightening the need for something less subjective and more objective even in the face of an “embryonic embarrassment of riches.”

A turning point in this field of endeavor came from the pioneering efforts of the late Lynette Scott. Her passion and observational talents were harnessed through a series of papers describing the details of pronuclear development, and their attendant dynamics, providing to the ART

community yet another landscape with which to discriminate between those embryos most desirable for transfer. Bearing in mind that her insights came at a time when discussions as to the optimum stage for transfer presaged the introduction of media extending the developmental window to blastocyst, pronuclear staging filled an important gap in our understanding of the earliest stages of human development. She also was among the first to deploy time-lapse imaging, convinced that cellular behaviors at the one-cell stage might someday be linked to outcome measures consistent with a term pregnancy.

Now comes a report from the laboratory of Dr. Sangita Jindal taking aim at the utility of pronuclear scoring as a biomarker for pregnancy outcome (this issue JARG, Berger et al., 2014, “*Embryo quality but not pronuclear score is associated with clinical pregnancy following IVF*” DOI [10.1007/s10815-013-0162-3](https://doi.org/10.1007/s10815-013-0162-3)). Using more contemporary biomarkers of embryo quality such as cell number, fragmentation, and blastomere symmetry, the results clearly indicate that the application of pronuclear scoring offers no additional benefit over the use of the accepted measures cited above in terms of clinical pregnancy rates in Day 3 transfers. While putting to rest one approach to embryo scoring, and validating the use of criteria in Day 3 embryos firmly entrenched in the formative events of compaction and cavitation, this work also sets the stage for a new perspective on embryo quality assessment consonant with extending the culture period to Day 5 or 6 for embryo transfer.

Why? Because along with extended culture comes the opportunity to track and deconstruct the details of individual preimplantation embryos under the watchful “eyes” of time-lapse imaging while cohorts of concepti make their merry way to the day of transfer content in their isolation in microdrops of media designed to recapitulate the female reproductive tract. It is undeniable that the introduction of dynamic imaging brings an analytical array of benchmarks to the prognosticators’

Capsule The search for reliable measures of embryo quality continues, following decades of score sheets featuring as many criteria as were morphologically discernible with the human eye and a stereo microscope. With the advent of time-lapse microscopy, the next “goldrush” is upon us, and with it the hopes of many that the time has finally arrived for objective selection of embryos in the practice of human ARTs.

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playbook. It is far less apparent to what extent the “criteria under development” will indeed offer more reliable and accurate indices of embryo quality.

Here at JARG, we remain mindful of the historical traces of gamete and embryo evaluation that may at the time have satisfied the needs of embryo selection but in the end offer little more when it comes to predicting whether a clinically

significant event will ever take place. While as a community of clinicians and scientists eternally optimistic that the perspective of time-lapse imaging will bear fruit as a predictive tool, “proof of the pudding” has yet to be realized. We encourage our readership to maintain focus in the pages of JARG as this next phase of embryo quality assessment matures into what will hopefully become a useful tool.