Putting early human development into the 4th dimension

David F. Albertini

Published online: 22 September 2012
© Springer Science+Business Media New York 2012

On a recent trip to Japan, I had the opportunity to visit an IVF clinic engaged in several fascinating lines of research. The breadth of human ARTs reached from psyches to cells as I passed from the pastels of the clinic to the quiet solitude of the research laboratories. In the case of the latter, room after room was occupied by one kind of microscope after another, until we reached the end of the hall, where I suspected something special was looming. There was, and hardly did the device of interest bear any resemblance to a microscope. Instead, deep within this unassuming cuboid was an experiment in progress, recording the very beginnings of human development with uncanny precision and resolution, so as to make the quest to understand this fundamental process as accessible to specialists in reproductive medicine as would be a midfield seat at a soccer match for football enthusiasts.

Human ARTs, as we know it today, continues to rely on the “observables” that make babies. Grading sperm, oocytes, cumulus and embryos is the daily task of the embryologists charged to make the decisions that will determine, in many cases, what are the chances of a patient having a baby. While the literature abounds with study after study asserting adequate predictability for our grading systems, two gaps remain: First, the skill set obtained while observing gametes and embryos retains the elements of subjectivity constrained by our senses and perceptions in a two-dimensional world. Second, even as we track a zygote's fate day after day, imposing along the way the threat of environmental disruption unavoidably linked to the need to move from incubator to benchtop at regular intervals, the perception of human development in the fourth

dimension of time has thus far escaped the armamentarium of human ARTs. Truth be known, few scientists or clinicians have ever had the luxury of experiencing the dynamics of cell behavior in the human embryo—at least until now.

So it was during my visit to the aforementioned clinic that I witnessed development of a human embryo in not one; not two; not three, but *four* dimensions! While the technology to do this routinely remains under development and is not likely to gain acceptance as a clinically safe grading tool (it involves inserting fluorescent proteins for the nucleus and cytoskeleton), our perceptions of human development in the fourth dimension are not only within reach, but are fast becoming a means to embryo selection that will likely result in editing some of our long held notions in ARTs. This issue of JARG takes two steps forward in the basic science and clinical application of time-lapse digital imaging as it pertains to the biology and manipulation of human embryos in a fourth dimension.

In the paper by Mio and colleagues (*Possible mechanism of polyspermy block in human oocytes observed by time-lapse cinematography*), high spatial and temporal resolution was obtained using a closed and environmentally regulated system to analyze the relative behavior of neighboring sperm, where the moment of fertilization of the lead spermatozoon could be documented in real time. Astonishingly, membrane fusion by the lead sperm was followed within 10 s by an immediate and abrupt cessation of penetration by the companion laggard. Because this reaction was followed successfully in three oocytes during the process of fertilization, the authors contend that a signal must have been generated rapidly upon membrane fusion, resulting in inactivation of any remaining sperm that may have been in the vicinity of the lead sperm. While their findings beg for further inquiry into the identification of putative factors acting on nearby sperm and validation of an inactivating stimulus being received by supernumerary sperm lodged in the zona pellucida, perivitelline space or cumulus mass, this high resolution analysis offers new insights into the

---

Capsule Time-lapse imaging is providing a glimpse into the fourth dimension of early human development that is apt contribute to our basic understanding of fertilization and the optimization of ARTs.

D. F. Albertini (✉)
University of Kansas Medical Center,
Kansas City, KS 66160, USA
e-mail: dalbertini@kumc.edu

fundamental biology of human fertilization yet to be fully appreciated.

The key to a discovery of such proportions is, not surprisingly, in the technology. Mio and colleagues developed an imaging system capable of recording the events of human fertilization at a rate of 240 frames per second! Aficionados of real-time imaging will immediately recognize that this kind of temporal resolution exceeds that of conventional capture rates by a factor of 8—surely placing this study among the first of its kind to lend insights into a dynamic process that could not have been detected using traditional technology. So much for microscopic imaging in the realm of basic science and a fourth dimension—What about clinical practice?

The second material advance evidenced in the pages of JARG this month builds upon the growing utilization of time-lapse imaging to monitor cellular activity in developing human embryos. Ciray and colleagues exploit the use of commercial systems being availed to clinics for tracking embryo behavior (Time-lapse evaluation of human embryo development in single versus sequential culture media—a sibling oocyte study). They adopt this approach for addressing an important and oft-asked question regarding strategies for culturing embryos—Is a single or sequential medium strategy best, in terms of clinical outcome? By comparing

sibling oocytes, the overall conclusion is that either strategy is equally efficient in terms of pregnancy rates, but that in the presence of a single medium, there is a tendency for embryos to develop more quickly from the pronuclear to 5-cell stage. So, maybe the speed of those initial cell cycles is not so reliable an indicator of developmental potential as has been suggested by other studies. Too soon to make a call on this one, but stay tuned as the more widespread adoption of time-lapse imaging is likely to result in many more reports that will provide proof of the pudding as to whether or not having access to the fourth dimension will improve and enhance our ability to make babies.

Adding the fourth dimension of time to our perceptual tool kit is a good thing, in that it adds a level of discrimination between embryos, patients, treatment protocols and the like, for making informed and objective decisions as optimized and more consistent outcomes continue to be sought. The field of human ARTs moves forward on the heels of technical innovation, as it has in the past. Whether such glimpses into the dynamics of human development, as revealed by time-lapse imaging, will offer patients improved success will await the test of time. But one thing is clear—our grasp of the biological underpinnings of early human development is getting firmer!