

Maturitas *ex vivo*: the case for oocyte *in vitro* maturation in human ARTs

David F. Albertini

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This special issue of JARG is focused on the subject of *in vitro* maturation (IVM) of human oocytes. Of all the variations on the theme of ARTs, IVM is perhaps the most distinguished, from a historical perspective. Consider for a moment that the implementation of a new ART typically (with some exceptions) results from many years of testing in animal models to obtain a firm biological foundation upon which clinical trials are based. In the end, detailing conditions that work in the embryology laboratory are shared in the peer-reviewed scientific literature and assume a rightful place in the ART menu of patient options, when pregnancy rates and live births reach an acceptable level of safety and efficacy. In an ironic twist of fate, the case for human IVM remains enshrouded in controversy, despite it being perhaps one of the most thoroughly studied areas of modern reproductive medicine and biology. Why should this be the case?

Answers to this and other questions were the basis for a meeting held in Milan from December 2–4, 2010. Convened by Professor Rubens Fadini and his colleagues (Giovanni Cotichio, Mariabeatrice Dal Canto, and Mario Renzini), “**In Vitro maturation of human oocytes: Biological Foundations for a breakthrough**” attracted 35 expert speakers from around the world and some 200 scientists and clinicians. Many of the speakers graciously agreed to contribute to this special issue of JARG and their papers form the foundation for this contemporary statement on the status of human IVM.

The meeting began with an ESHRE perspective provided by past president Dr. Luca Gianaroli, who noted that since the initial reports by Trounson and colleagues, in 1994, of successful IVM, there remain relatively few papers per year dedicated to this topic. He emphasized that new technology and research must always remain secondary to the welfare of the child in ascertaining whether an ART such as IVM is, indeed, ready for widespread utilization. In this vein, he reminded the audience that following studies in small and large animals, the validation of IVM for use in humans will require studies on human materials procured through oocyte donation programs. These will form the basis for risk assessment and randomized clinical trials, including short- and long-term health evaluations of any resulting offspring. With this background, the first day was devoted to a clinical assessment of human IVM as practiced in leading centers throughout the world.

Subjects ranging from cost effectiveness (Fadini), patient selection (Childs), and clinical protocols (Lim) provided a launching pad for discussions on the benefits of IVM over conventional COH for treating PCOS patients, or those seeking fertility preservation (Tan). In closing with his assessment of the health of IVM children, Professor Sutcliffe cautioned optimistically that, while the initial studies are encouraging, establishment of a registry and system for tracking offspring health is an imperative at this time.

With this clinical backdrop, the stage was set for a full day of presentations dealing with the basic mechanisms of oocyte biology that underlie the process of meiotic maturation under *in vivo* or *in vitro* conditions. Discussions focused on the utility of animal models—especially with regard to those that offer an analysis of embryo quality and offspring health. While Professor Eppig noted that

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

all of his “patients” (mice) were no longer of the ranks of the living, the murine model stands alone for its experimental tractability and ability to track offspring health, following the generation of embryos from IVM. Advantages and disadvantages of large animal models such as the sheep (Ledda) and cow (Sirard) were detailed in the context of understanding the signals that cause escape from meiotic arrest and the role of the cumulus cells in conferring cytoplasmic quality sufficient to sustain the preimplantation stages of embryonic development. As the intrafollicular physiology continues to be explained in molecular and signaling terms, there was a uniform sense that tailoring new media and culture conditions could someday allow for the recapitulation of oocyte maturation not unlike that observed following a natural LH surge.

The final day of the meeting alerted the audience to the array of growth factors that modulate the metabolism of the oocyte and cumulus during the process of IVM. That many of these such as EGF-like molecules and those of the TGF

beta family already known to be pivotal to ovarian function (GDF9, BMP15) are subject to the gonadotropin responsiveness of the follicle was reviewed in the context of experimental paradigms designed to mimic what is believed to be the physiological course of events during natural ovulation. In this context, Dr. Gilchrist introduced deploying sequential media formulations that reminded most attendees of the pioneering studies of Bavister and Boatman, studies that paved the way for the birth of the first macaque IVF babies back in the early 1990s. Dr. Morimoto revealed new data on the impact of IVM on mitochondrial positioning in human oocytes, and the potential utility of oocyte cryopreservation in the context of human IVM was discussed by Dr. Cotichio.

This robust program was peppered by discussions that have set the stage for the next generation of research into the application of human oocyte IVM to the practice of ARTs. We hope the JARG readership will benefit from the contents of this issue, as the imperative to achieve better treatment options for our patients begs for advances in this field.