

The craft of ART: infertility strategies in 2002 and 2022

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Over the last decade, novel methods of assisted reproductive have revolutionized treatments for overcoming infertility. Surprisingly, many of these ART techniques were introduced prior to any preclinical trials so that the fundamental research necessary to understand the cellular and molecular events of ART still lags behind. One of the problems facing researchers has been to identify relevant animal models. Working with non-human primates gametes, we have developed pre-clinical primate models for understanding the biological basis of ICSI and other ARTs. This work has revealed several unusual deviations in mitochondrial, centrosomal and cytoplasmic trafficking during ART including: i) the variable position of the second meiotic spindle within the oocyte; ii) abnormal sperm decondensation results in the unusual retention of membrane VAMP and the perinuclear theca; iii) NuMA, typically trafficked into the nuclear matrix, is apically excluded; iv) male pronuclear remodeling of either parental genomes is required prior to DNA replication, indicating a unique G1-S phase checkpoint; v) the ability to introduce transgenic DNA into rhesus oocytes by ICSI, but not by IVF, raises the concern that the ICSI procedure could unknowingly transmit infectious material and vi) cytoplasmic transfer may lead to a heterogeneous population of mitochondrial DNA (mtDNA) derived from the donor oocyte, as have been found in the few babies born by this technique.

Before new infertility strategies can be designed, studies assessing the developmental and reproductive consequences of ARTs must be undertaken. These studies should encompass pediatric and adult health, reproduction and genetics outcomes; implantation (leading to single embryo transfers); fetal development (imaged non-invasively *in utero*); extranuclear transmissions (e.g. mitochondrial DNA, centrosomes, foreign DNA or RNA); cytoplasmic transfer and mitochondrial heteroplasmy; genomic imprinting and cryopreservation (for unfertilized eggs, immature oocytes, ovaries and testes). When combined with the benefits of non-human primate ART models, these clinical studies can evaluate the risks and benefits of sophisticated methods in molecular medicine including gene and cell therapies, as well as the potential utility of embryonic stem cell lines and therapeutic cloning. Only then can new strategies be developed for managing reproduction and treating infertility.