J Assist Reprod Genet (2016) 33:821–822
DOI 10.1007/s10815-016-0758-5

EDITOR'S COMMENTARY

On the dichotomy (im)posed by developmental autonomy during early human embryogenesis

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Published online: 17 June 2016

Not since the seminal investigations of early human development known as the Carnegie Series generated by the infamous "egg hunts of Hertig and Rock" has the characterization of mechanisms driving the human conceptus remained such a well-kept secret. Granted, the introduction of human ARTs and the application of continually emerging technologies aimed primarily at the identification of embryos with live birth potential has yielded an impressive litany of properties which, when weighed against strictly associative outcomes, have fostered the belief that embryo selection strategies have a place in the management of human infertility. But has this newly acquired body of information (*sic* knowledge) truly afforded insight into the nature and causes of pregnancy loss? And what do we know with a measure of certainty about the relative contributions of the conceptus and endometrium during the earliest stages of implantation?

This dichotomy between the conceptus and its primal interactions with the maternal environment has fascinated students of human reproduction for decades, leaving many to subscribe to the seasoned adage that the more we know, the less we know. That immune recognition and tolerance are recognized as critical determinants for the establishment and maintenance of pregnancy is well appreciated, and the myriad potential genetic factors linked to recurrent pregnancy loss are the subject of a review this month by Grimstad and Krieg (Immunogenetic contributions to recurrent pregnancy loss, 10.1007/s10815-016-0720-6). As has become fashionable in the era of embryo selection technology, placing the blame for implantation failure on the embryo due to the high frequency of aneuploidy has derived from foundational studies that informed us of the link between miscarriages and chromosomal abnormalities in the human conceptus. Preimplantation genetic screening (PGS) in its various iterations over the past decade has provided tempered insights into the gametic and/or embryonic origins of aneuploidy and will continue to play a prominent role in human ARTs as the underlying technologies mature into the diagnostic platforms of tomorrow.

To assist our readership interested in engaging the world of PGS, we are fortunate to extend our educational mission this month by providing a scholarly treatment of this subject intended to bring all up to speed with current PGS applications as well as a glimpse of what lies ahead (Kearns and Brezina 740, "Preimplantation genetic testing for aneuploidy: what technology should you use and what are the differences?" DOI 10.1007/s10815-016-0740-2). As the authors clearly articulate in their concluding remarks, decision-making for patients, genetic counselors, and their physicians is assuming a character of greater complexity that will require all to recognize and remain cognizant of the moving target that is PGS (see also in this issue: "Discrepant diagnosis rate of array comparative genomic hybridization in thawed euploid blastocysts," 10.1007/s10815-016-0695-3, and "Clinical application of next-generation sequencing in preimplantation genetic diagnosis cycles for Robertsonian and reciprocal translocations," 10.1007/s10815-016-0724-2).

Along with the application of PGS has come a measure of clarity on the relative genetic contributions that blastomeres make to the first pair of cell lineages derived from the zygote. There is an increasing awareness of the proclivity human

Capsule Two recent publications illustrate the inherent developmental potential of human embryos when cultured under relatively simple conditions for up to 13 days after fertilization evidencing for the first time a degree of autonomy not previously appreciated.

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embryos display for errors in chromosome segregation during the initial cleavage divisions, not too surprising given the seasoned notion that cytokinesis is somewhat challenged—apparently in parallel with the process of karyokinesis. While discernible as an aneuploidy by PGS or fragmentation variants impacting an overall grading score, it remains peculiar and "out-of-character" that so many of the embryos generated by IVF or ICSI apparently launch their initial journey to implantation in such a seemingly precarious style.

While we know the developmental competence of human oocytes is very low, by nearly all measures of "success" (see paper by Ziebe and colleagues, "The total pregnancy potential per oocyte aspiration after assisted reproduction—in how many cycles are biologically competent oocytes available?" 10.1007/s10815-016-0707-3), just how much developmental autonomy a human embryo could exhibit in an ex vivo environment is not known—at least until now. Two notable contributions to the field of human embryology appeared in print last month, both demonstrating that under rather simple conditions of culture, a subset of frozen embryos upon thawing developed up to an equivalent of 13 days post-fertilization based on the Carnegie Staging system, and did so autonomously, without a maternal influence!

The first of these reports comes from the Laboratory of Stem Cell Biology and Molecular Embryology at the Rockefeller University in New York City (Deglincerti et al., "Self-organization on the in vitro attached human embryo," *Nature* 2016 DOI:10.1038/nature17948). Among the remarkable features of early development beyond the blastocyst stage, these investigators document an intrinsic capacity to generate diverse products of the trophectoderm, cavitation of both the yolk sac and amnion, as well as lineage expansion and determination of the inner cell mass with the attendant emergence of the bilaminar disc. These findings were based on the use of high-resolution confocal imaging and 3D rendition and analysis of complete serial sections, not unlike the meticulous reconstructions generated by Hertig and Rock over 75 years earlier. Two important distinctions must be made between the samples in the Carnegie Collection and those used in the present studies. First, the Carnegie Collection is based on histological preparations of concepti retrieved from healthy women of proven fertility for which menstrual cycle status and time of insemination were known; the present samples were as alluded to above generated from ART materials that had been frozen. Second, the data obtained in the *Nature* paper relied on the clever use of multiple specific antibody labeling steps that permitted the unequivocal detection and localization of cell lineage biomarkers at various stages of development between days 6 and 13 following the known "time" of fertilization. The remarkable congruence in organization and morphogenesis observed between the embryos used in this paper and those derived from the Hertig and Rock samples attests to the extraordinary autonomy and adaptability of the human conceptus to evolve in a manner indistinct from what had been our only true developmental roadmap for the human embryo!

From the Mammalian Embryo and Stem Cell group led by Professor Zernicka-Goetz and her colleagues comes an equally astonishing and evocative study that defines the culture conditions needed to support such advanced stages of development in human embryos ("Self-organization of the human embryo in the absence of maternal tissues," *Nature Cell Biology*, 2016; DOI 10.1038/ncb3347). Key parameters including choice of culture media, protein supplements, and oxygen tension were evaluated with respect to sequential environmental conditions that in the end are shown to support the morphogenetic events leading to the segregation and differentiation of embryonic and extraembryonic lineages elaborated upon in the studies noted above, and convincingly illustrating the existence of self-organizing principles within the human embryo.

Taken together, these reports usher in a new age for research on early human development that makes tractable investigations into the dichotomous origins of pregnancy loss from either a maternal or embryonic perspective and establish a new platform for elucidating and manipulating the fate of stem cells and their progenitor byproducts that will serve as a point of departure for the field of regenerative medicine.

In closing, we would like to welcome to the editorial board our new members, Rita Vassena, Navid Esfandiari, Bill Roudebush, and Dan Rappolee, and give thanks to those board members who are ending their period of dedicated service to the mission of *JARG*. To Anil Dubey, Outi Hovatta, David Reichman, and Armand Zini, we extend our gratitude for their support and involvement in establishing *JARG* during this most recent phase of maturation.