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Phase transitions in human ARTs: fertility preservation comes of age

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Nearly a decade has passed since the dawning of the movement of fertility preservation. At its inception, this nascent subdiscipline of human ARTs sought to address the needs of a particular class of patients whose future fertility stood to be compromised as a result of gonadotoxic treatments for various types of cancers. With survival rates for cancer patients on the rise, the impetus for preserving and/or restoring fertility for those yet to have built their families was clear.

Recognizing the pressing need for options to offer cancer patients, especially children posed with the threat of forever losing their reproductive potential, several groups launched programs taking the specific challenge faced by cancer patients to heart. Among these, the Oncofertility Consortium, based at Northwestern University in Chicago under the leadership of Professor Teresa Woodruff, sets standards of clinical care and prompted research initiatives complementary to those already being developed in other parts of the world. The importance of these developments cannot be underestimated, as illustrated in this month's issue.

Here at JARG, we have had the privilege of covering several of the meetings of the International Society for Fertility Preservation (ISFP) and have maintained a healthy dose of reporting over the past 10 years of advances in this evolving domain in reproductive medicine. We have brought our readership through a "phase transition" in human ARTs based in part by the increased awareness of patient needs and possible therapeutic approaches that now extend well beyond the original purview assumed by fertility preservation. From ovarian tissue cryopreservation and autologous transplantation to mechanisms of germ cell demise after chemotherapy, and potential stem cell-based applications, the field of fertility preservation has opened up windows of opportunity for reproductive medicine and biology that could not have been imagined even 10 years ago when these efforts commenced.

Consider the following. The struggle to connect the reproductive physiology of mammalian model systems to the human condition has been pervasive, mainly because of the limited access to human materials with which to test novel hypotheses. As a result of fertility preservation research efforts, the availability of human tissues, especially ovaries and testes, has enabled original research into the optimizing cryopreservation methods and development of cell and organ culture strategies with which to probe the molecular underpinnings of gametogenesis. These efforts have resulted in reports confirming future prospects for sustaining oogenesis ex vivo from tissue equivalents, such as cryopreserved ovarian cortical strips, opening new doors for drug or environmental chemical screening. As with all technological advances, core questions regarding safety, efficacy, access, and ethical implications need to be formulated and addressed before the translational utility can be established.

In addition to the scientific advances afforded by the fertility preservation movement, many of the core principles and practices enabled through such efforts have brought to the surface an expanded menu of ART options for a broader patient population than what has traditionally been serviced (the infertile or subfertile couple). As seen with the widespread adoption of "social" egg freezing for delaying family building, societal needs dictated by alternative lifestyles are accommodated with an array of ART options that are not without their own ethical dilemmas. In this context, we begin this issue with coverage of the Reproductive Ethics: Challenges, and Solutions meeting that was held at the New York University Langone Medical Center that includes a meeting summary and treatment of specific topics ranging from gamete donation, germline genetic modification, and providing an ethical foundation for the next generation of REIs. Among these contributions, the paper by Nahata and colleagues begins to address the ethical issues associated with ongoing and future research efforts in the pediatric cancer patient population (*Conducting reproductive research during a new childhood cancer diagnosis: ethical considerations and impact on participants* https://doi.org/10.1007/s10815-019-01546).

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Phase transitions, such as has been suggested here with reference to the impact of fertility preservation on the practice of human ARTs, imply changes of state or composition at least when used in the context of basic biological transformations in substance. Signs of this happening are well-illustrated in the collection of articles beginning with the report from the Meirow group on the potential therapeutic role AMH adjuvant treatment could play in regulating excessive follicle "burnout" in a mouse model of chemotherapy-induced ovarian toxicity (*Pharmacological administration of recombinant human AMH rescues ovarian reserve and preserves fertility in a mouse model of chemotherapy, without interfering with anti-tumoural effects* https://doi.org/10.1007/s10815-019-01507).

And without belaboring the theme of this issue, over the years, a matter of much debate has been the topic of mitochondria and their genomes as sentinels, it has been hoped, for evaluating the quality of embryos destined for transfer contingent upon predictable readouts of the content of mtDNA available from a trophectoderm biopsy. We hope JARG followers will pay close attention to the series of papers proffered this month that take issue with the basis for the use of mtDNA assessment as a tool for embryo selection. We value your opinions and welcome your responses to this and other topics that will be considered in greater detail in an upcoming issue later this year.

Finally, and hardly a matter of happenstance, bringing ART into the context of a phase transition (*of sorts—editorial prerogative*) aligns well with fundamental changes in our thinking about how cells maintain a balance of protein functionality to achieve the ends their differentiation was indeed designed for. This story harkens back to the tale of the Balbiani body (BB), a structure unique to animal oocytes that have in the past been referred to in these pages as central to the maternal inheritance of the mitochondria [1]. Not only has the genomic and genetic basis of disease taken a rearward step in the current view of how personalized medicine will translate into future models of health care, but to the forefront has come a more critical look at protein stability and turnover as targets for future therapies and lifestyle changes take on a tractable character. Herein lies the subject of phase transitions as we seek a deeper understanding of topics like cryopreservation of gametes or tissues, or what really matters when it comes to evaluating gamete or embryo quality in ARTs. This ongoing renaissance in biology will eventually play into many aspects of ART practices [2] having to do with how proteins are managed at the subcellular level. Enter BB. First recognized to be comprised of amyloid-like proteins, whose storage and function would play out during the development of frog oocytes [3] there is now good reason to believe that a similar *modus operandi* may be shared by the oocytes of mammals including humans. At least this is what the paper by Pimentel and coworkers would like us to believe (*Amyloid-like substance in mice and human oocytes and embryos* https://doi.org/10.1007/s10815-019-01530).

When we think about that all-consuming subject of aging, not too surprisingly the matter of neurodegenerative diseases comes to mind, whether a loved one has been affected or you find yourself noticing changes in memory that you had hoped to avoid. Besides your aging neurons, which will accumulate amyloid-like substances on the road to pre-senility, oocytes and even embryos seem to contain similar materials in the BB. While this paper draws attention to the presence of such materials, it remains to be seen whether the aged oocyte or embryo derived thereof exhibits imbalances of protein homeostasis that could be linked to the many long-suspected causes of an age-related decline in fertility so uniquely ascribable to humans (versus other mammals) nor do we know at this point exactly what proteins are involved in processes that would be tangibly related to known impairments in oocyte or embryo functions. One thing that is clear, however, is proteins of the cytoskeleton are broadly implicated in the very dynamics that pull off the sophisticated processes of cell division, and control of the stability and turnover of these proteins are very much influenced by factors we are only beginning to understand [4].

It would thus not be too extreme to suggest that the heralded meiotic spindle in the oocyte, or for that matter, the mitotic one that directs the early cleavage divisions of the embryo, might have their suspected failures to perform somehow tied up in the phase transitions alluded to above. This is exactly what the group of Schuh now reports in a recent paper on mouse oocytes calling attention to a very different mechanism employed to assemble and direct the movement of chromosomes during the process of meiotic maturation (5). And the importance of phase transitions extends past that of the cytoskeleton to include protein–protein interactions regulating the translation of nascent mRNAs (6). Insights being gleaned from the tools of cell biology and contemporary imaging are advancing our thinking of how normal and cancer cells engage so many vital processes that are manifest in one form or another by the gametes and embryos handled each day in the infertility clinic.

In closing, the phase transition in human ARTs that has paralleled the emergence of fertility preservation as a formal discipline presents an opportunity to rethink how we diagnose and treat human infertility and the problem of aging. As an example, recent advances in the use of stem cells to generate germ cells provide animal models that are accessible to a wide array of technologies already making an impact in the field of ovarian aging that may someday be translatable to the human condition (7). Here at JARG, we remain committed to keeping our readership abreast of these developments and to track emergent technologies as they may approach utility in the expanding purview of reproductive medicine.

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