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EDITOR'S COMMENTARY

Vanishing returns on the investment that is the ovarian reserve

David F. Albertini

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Among the wishes and dreams of an aging human population is the optimism that this freight train to finality could be forestalled or delayed so as to enjoy the benefits of youth. And, for more than a decade now, we have heard through the media that a virtual fountain of youth may be just around the corner. Pronouncements that the molecular and genetic bases for aging are becoming better understood (and implicitly treatable or manageable by drugs or lifestyle) allay the concerns of some. For those who had hoped for a time when replacement parts would be proffered from the likes of regenerative medicine, aspirations have been dampened by the fateful realization that we know less the more we discover and maybe it will not be so straightforward to simply cut and paste our way to eternal health.

One of the most serious obstacles to grasping the essence of the aging problem is the lack of a tractable definition upon which good science can be based. Redefining and repurposing the discipline presently known as systems biology may help clarify matters. To the aged among us, systems biology is simply what the discipline of physiology has been for years. And in light of the aging problem, the gradual demise of organ systems as integrated entities reminds us that an extreme reductionist viewpoint may cause us to lose sight of the real problem-the whole organism. Accordingly we have come to appreciate that our bodies age not simply as a result of changes intrinsic to your favorite molecule, cell, tissue, or organ, but because the orchestration of our organ systems with one another breaks down. Without a doubt, and the focus of this issue of JARG, the most striking case for system disintegration upon advancing age is the female reproductive system.

Depletion of the ovarian follicle reserve is a major public health problem. And what causes the inevitable and periodic decline in follicles has been a lingering mystery in human biology since it was first recognized in animals and shown to be the irreversible course of action during the reproductive lifespan of women. If only the process could be delayed, then preservation of cardiovascular and musculoskeletal health for some additional decades might be achieved. And, with such an extended warranty, it follows that the ability to menstruate and bear children into a ripe old age would be a necessary (albeit controversial) consequence. Of course, extending a woman's reproductive lifespan would require a way to maintain the genetic integrity of those follicle-enclosed oocytes that, instead of hanging around for 5 decades losing their potential to support pregnancy, must be maintained in a healthy state for those wishing to delay childbearing.

So the matter of ovarian aging continues to preoccupy the synaptic circuitry of those amongst us interested in motherhood and parenting, or bringing the basic science of this problem into the realm of clinical practice. That same decade of hope which brought promise and pessimism to the broader question of aging has delivered significant advances in our understanding of the ovarian reserve and provided the impetus for a recent meeting seeking consensus on where we are, and where we need to go in the future.

Jointly sponsored by the NICHD and the ASRM, this full-day program grappled with the topic of the ovarian reserve with presentations from leading experts spanning topics from the clinical management of infertility through to the genetics, molecular mechanisms, and future treatment strategies for ovarian aging during normal and disease states.

We are privileged to share with our readership the proceedings for this long awaited meeting that begins to

Capsule Proceedings from a recent workshop on the ovarian reserve raise interesting and important questions about the state of the field and future directions. Two recent studies shed new light on the mechanisms underlying follicle loss that could have therapeutic implications.

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

forecast and inform, in 2013 terms, the problem of vanishing returns implicit to ovarian aging. Whether natural in occurrence, or a result of receiving treatment for diseases like cancer, the loss of ovarian function profoundly illustrates how the aging of one organ system (the human ovary) impacts a woman's overall physiology as she approaches and passes through the menopause.

From the enclosed proceedings, our readership will come to appreciate how clinical and basic science advances over the past 10 years have brought a small measure of clarity to our understanding of the problem of ovarian aging. As we discuss below, this backdrop and two recent breakthrough papers, begin to describe a pathway to discovery that if prioritized accordingly, will materially contribute to an improvement in women's health. Among the highlights from the meeting were (1) widespread recognition of the shortcomings of current ovarian reserve biomarkers, especially for PCOS patients or those seeking ARTs at an advanced age; (2) identification of gene sets implicated in the onset of menopause that interestingly point to both DNA repair and immunological targets for future research; (3) resolution of how signaling pathways in the primordial follicle regulate both the maintenance of quiescence and the process of follicle activation. At the end of the day, the crux of the ovarian aging problem reduces to the follicle reserve and its changing dynamics over the course of the reproductive lifespan. Two recent studies have added momentum and depth towards our understanding of the factors that contribute to the life and death of the ovarian follicle.

The first of these studies appeared late in 2012 and comes from an Australian group publishing in Molecular Cell (Kerr et al., DNA Damage-Induced Primordial Follicle Oocyte Apoptosis and Loss of Fertility Require TAp63-MediatedInduction of Puma and Noxa, Molecular Cell (2012), http://dx.doi.org/10.1016/j.molcel.2012.08.017). Kerr and Hutt and their colleagues build upon the prevailing opinion that apoptosis in oocytes underscores the loss of follicles and hence fertility that has long been suspected. With the field of fertility preservation front and center, this group explores the role of TAp63 (a comrade in crime to the famous p53 tumor suppressor), a gene product known to be expressed in the nuclei of oocytes and previously implicated as a central player in oocyte apoptosis. Using several lines of knockout mice in which Tap63 or the genes for the pro-apoptotic factors PUMA and NOXA had been deleted, they begin to trace a pathway to oocyte demise that answers the following question: Since the follicle reserve is invariably damaged by gamma irradiation (IR), how is it that oocytes are eliminated after such a DNA-damaging insult? They report that in response to IR, the pro-apoptotic genes Puma and Noxa are induced but only in oocytes expressing TAp63. Strikingly, in Puma-less mice, even after IR, follicle loss did not occur and viable offspring were born despite having survived the initial rounds of radiation treatment. Besides closing several gaps in the apoptosis cascade for oocytes in an animal model system, this work raises the provocative prospect that if genes like Puma function in a similar way in humans, then drugs that block its pro-apoptotic actions might be used to protect and maintain the follicle reserve in the face of cancer treatments or other predisposing conditions that threaten ovarian function.

The second landmark paper has just appeared in Science Translational Medicine and comes from the laboratory of Oktay (Titus, S et. al., Impairment of BRCA1-Related DNA Double-Strand Break Repair Leads to Ovarian Aging in Mice and Humans. Sci Transl Med 13 February 2013 5:172ra21. DOI:10.1126/scitranslmed.3004925) As noted previously, one of the more remarkable features of oocytes resting within primordial follicles for many years is their ability to establish and maintain genetic integrity before being called into a developmental capacity at the time of fertilization. Given the propensity for oocyte quality to diminish with advancing age, and the fact that this tendency is often linked to an increase in meiotic aneuploidy detectable in older women undergoing ARTs, the mechanisms by which oocytes would look after their genetic stability have remained perplexing and enigmatic.

What brings the work of Oktay and his colleagues to the forefront is their discovery that human and mouse oocytes engage in an active and widely-conserved mechanism for the detection of DNA double strand breaks and their subsequent repair through the ATM-mediated signaling pathway. Most importantly, they show that the efficiency of the repair process deteriorates with advancing age, and such a deficiency is present in women carrying BRCA1 (but not BRCA2) mutations who often experience menopause at an earlier age than non-carriers of the mutations. That BRCA1 provides an essential link to the DNA repair process is also elegantly demonstrated in animal model experiments where the genes needed for repair are inhibited in isolated oocytes; moreover, BRCA1 deficient mice are also shown to be defective in repair, bolstering the human data. This is a telling case where the combination of research on human and animal materials has synergized to provide a fundamental insight into the ovarian aging problem.

The work of Menezo and colleagues some years ago recognized that human oocytes express many of the genes needed to effect repair of damaged DNA and that levels of these important mRNAs diminished with age. But a biological *raison d'etre* has escaped validation, until now. In this vein, it is of further interest to draw attention to the review of embryo metabolism by Menezo and colleagues as they highlight key factors that are required to maintain the DNA integrity of the conceptus. We hope you enjoy this issue of JARG and come to appreciate what the landscape of the problem of ovarian reserve will look like in future years.