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EDITOR'S COMMENTARY

Luteinization desynchronized: the devil is in the details

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One of the marvels of the reproductive process of viviparous organisms like ourselves is the extraordinary synchronization of events driving everything from ovulation to implantation. There is no better case to make than the remarkable off-on switch triggered by the LH surge, the *raison d'être* for the resumption of meiosis, and maturation of the oocyte in parallel with an instantaneous transformation of granulosa cells into the progesterone secreting cells of the corpus luteum (CL). Simply put, the Graafian follicle is a time bomb holding in abeyance both the oocyte cell cycle and luteinization of the follicle.

While there is little doubt that mammals have together propelled this paradigm of synchronicity into an essential and well-tuned survival strategy, recapitulating such a strategy in the clinical setting, where controlled ovarian stimulation (COS) is deployed to obtain as many eggs as possible, continues to be an obstacle in the alleviation of infertility.

Default systems are *off* for a reason. And the factors that actively prevent luteinization of granulosa cells have been resistant to explanation since the pioneering work of Channing, Tsafriri, and others suggesting there was an intrafollicular force inhibiting this capability until ovulation. In a sense, letting go of de facto constraints (otherwise known to the masses as ACTIVATION) has been receiving the well-deserved attention it is getting in other spheres of reproductive medicine such as awakening follicles, or hyper-motivating sperm, or delimiting the embryo's potentially harmful metabolism ("keeping quiet") until implantation is well on its way under the guidance of a CL of pregnancy! When such constraints breakdown in the ovarian follicle, particularly in the presence of exogenous gonadotropins as during COS, the result is the all too familiar case of premature luteinization (PL).

As Kaponis and colleagues share with us this month in our lead article ("The curious case of premature luteinization," https://doi.org/10.1007/s10815-018-1264), this troublesome condition often determines the course of treatment for many patients. And despite attempts for many years by practitioners to come to grips with the predispositions, causes, and remedies for delimiting the occurrence and extent of PL, management strategies remain inadequate in some circumstances. Given the timely and broad-spectrum view they provide on PL in leading off this issue of *JARG*, tracing the history of this seemingly turnkey mechanism at the heart of fecundity for all mammals is deserving of a retrospective treatment.

Well before there were human ARTs, the importance of the CL in determining menstrual cycle length—and as a crucial determinant in the establishment of pregnancy—was appreciated by the classical work of Csapo and his collaborators [1]. It was a decade later, shortly after the birth of Louise Brown, that the consequences of disrupting follicle fate for the expressed purpose of laparoscopically removing an oocyte (referred to by some at the time as *ovectomy*) were noticed by Steptoe and Edwards as a rate-limiting factor in the early days of ARTs. Trepidation was evident at the time given questions about the activity of available progestins, the timing and route of administration if any hope of iatrogenically creating an operational luteal phase and beyond was to be achieved following embryo transfer [2]. With the adoption of more aggressive ovarian stimulation protocols and improvements in egg retrieval technology, the name of the game became one of obtaining as many oocytes as possible and in so doing, evacuate (sic eradicate) follicles of luteinizing potential—of course to various extents.

Somewhere along the way to establishing this standard of care, reproductive biologists were coming to grips with the enormous powers that oocytes seemed to exert on their surrounding companion granulosa cells. The tools of mouse genetics were brought to bear on genes essential for various aspects of reproduction, and one of the first stars of the show to emerge was a gene known as GDF9 [3]. This oocyte-specific gene yielded products that appeared to regulate the earliest stages of follicle development and would come to be the first of many factors to be identified in oocytes that would

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play various roles over the coming years, among them inhibiting luteinization.

For the vanishing breed of history buffs among us, it turns out that long before the discovery of GDF9 and its TGF-beta family members now at center stage as anti-luteinizing oocyte secreting factors (OSFs), a series of experiments was being conducted back in the 1960s that sheds light on the problem of PL today.

Nalbandov and his lab members came up with the notion that the oocyte itself was the gatekeeper for luteinization back in the 1960s. And true to form, their investigations were to be yet another illustrious case of the Krogh principle in action [4]. To test their hypothesis, the choice of an appropriate animal model was critical. Turns out their choice, rabbits, are among those animals that exhibit reflex ovulation—that is ovulation is triggered by coitus ensuring that the LH surge is precisely timed with the arrival of sperm. There is virtually no reproductive failure in species exercising the reproductive strategy of reflex ovulation; all ovulated eggs are fertilized and develop to term. Their experiment involved surgical removal of oocytes from each of the Graafian follicles and monitoring progesterone levels in "ovectomized" animals and comparing them to "non-ovectomized" controls. The results were startling and convincing! Robust luteinization was found in the ovaries of ovectomized, but not non-ovectomized, animals consistent with the notion of an oocyte-based anti-luteinization factor.

Against this backdrop, we invite our readership to take the problem of PL beyond the clinical entity encountered in infertility practices. The series of papers leading off this issue encompasses a review on current thinking regarding the central players of oocyte origin that dictate the fate of ovarian follicles and just how this new line of thinking could impact reproductive medicine in the future, especially in the context of reproductive aging ("GDF-9 and BMP-15 direct the follicle symphony," https://doi.org/10.1007/s10815-018-1268). We continue to the clinical perspective in the article by Ortega et al. ("Ovarian manipulation in ART: going beyond physiological standards to provide best clinical outcomes," https://doi.org/10.1007/s10815-018-1258). And finally, recent notions on signaling interactions that may be involved in the genesis of PCOS are given consideration by Maas and her colleagues ("Hippo signaling in the ovary and polycystic ovarian syndrome"; https://doi.org/10.1007/s10815-018-1235).

Synchrony between signaling systems linking ovulation to implantation reflects a continuum founded in precise spatial and temporal constraints. While we are in the midst of manipulating reproduction with the current-and-future toolkit that is human ARTs, we should remain mindful of just what a delicate balance exists in multicomponent systems that guarantee species survival. Whether constraining or liberating in nature, the elimination or addition of just one component within a network can and does have downstream consequences at many levels under conditions permissive for birth and survival of offspring [5]. The reproductive axis as we knew it even 40 years ago is becoming more complex and challenging to tease apart. As new details, genes, mechanisms, and omics emerge and become contextualized against ideas and biases old and new, ARTs and the many fruits of our efforts will hopefully lead to paradigm changes dictated by reason and not by chance alone.

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