At the crossroads of bench and bedside: how gonadotropins do their thing!

David F. Albertini

Published online: 28 June 2014
© Springer Science+Business Media New York 2014

No single sentinel better captures the reproductive fitness of organisms than the gonadotropic hormones. Whether alluding to the sustaining forces of spermatogenesis or the cascade of events ushering in ovulation, this remarkable duo of glycoproteins, FSH and LH, purposely and heroically serve as the centerpiece of the reproductive axis for those multicellular organisms whose survival and propagation lie in the waiting. So it is after a protracted period of neglect that we draw attention in this issue of JARG to tales of FSH and LH of immediate clinical and experimental import. First to the bedside!

In one of those rare case reports, suffused with implications rather than speculations, the group at the Toronto Centre for Advanced Reproductive Technology of the University of Toronto and the Mount Sinai Hospital have discovered a mutation in the LH/HCG receptor that is certain to raise more questions than it answers regarding that age-old problem of how do we get from the LH surge to ovulation of a developmentally competent oocyte. The black box that is the Graafian follicle before and after the LH surge retains a mystical quality thus continuing the saga of bemusement and wonder that so much of human ART is centered around. Readers are encouraged to follow the case history in detail (Mitri et al., A novel compound heterozygous mutation of the luteinizing hormone receptor: implications for fertility, DOI10.1007/s10815-014-0249-5). Those whose interest has been piqued by the genetic underpinnings of this case should see the accompanying

commentary by our Senior Editor Professor T. Raj Kumar (“Been Hit Twice”: a novel bi-allelic heterozygous mutation LHCGR).

As is often the case when managing difficult cases, Mitri and colleagues were presented with a confounding initial result when oocyte retrieval following conventional COH yielded mostly immature oocytes. Not to be stonewalled, the group next extended their strategy for treating this patient within the purview of recent advances in ovarian follicle physiology. Accordingly, they reasoned that deficiencies in the signaling pathway for LH likely to contribute to the phenotype observed could be based in either a failure to propagate sufficient prostaglandins or a defect in what had become a central tenet of ovulation biology—the cascade of events mediated by EGF-like molecules as exemplified by a number of studies on mammalian oocytes and follicles. Would the application of conventional wisdom derived from studies on animals provide the long-awaited coup de grâce for the bench to bedside paradigm? As reported, things are never as straightforward as one would like when it comes to solving problems of this kind. Prostaglandin treatments did little to encourage or ameliorate the suspected defect in LH signaling. They next attempted in vitro maturation using amphiregulin, one of those EGF look-alikes that has worked so well on animal cumulus complexes; this strategy did result in maturation of a fraction of the retrieved GV oocytes to metaphase-2, but following ICSI, the resultant embryos failed to develop to the blastocyst stage. Clearly, patients of this ilk will continue to seek treatment for their infertility, and the case at hand is illustrative of how challenging resolutions will be in genetically complex cases. Never fear, however, as the human ART repertoire was brought to bear on this problem as oocyte donation has resulted in a live birth for this couple, interestingly validating the initiation and sustainment of a pregnancy while lacking functional LH receptor! Our readers are also encouraged to view another case, this time affecting males,

Capsule The underpinnings of gonadotropin receptors and the consequences of their activation on gonadal target cell signaling are revealed through a case report demonstrating a novel mutation in the LHCGR and the tenuous but critical link between bench discovery and bedside manner.

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

where the need for treatment for Leydig cell hypoplasia (LCH) could have its origins in a similar genetic disorder (see Successful testicular sperm recovery and IVF treatment in a man with Leydig cell hypoplasia, DOI [10.1007/s10815-014-0241-0](https://doi.org/10.1007/s10815-014-0241-0)).

No matter the gender, so many cases of unexplained infertility continue to escape detection and/or explanation with our present armament of technology. Our continuing reliance on

the evolution of deep-sequencing approaches stands as an example of what will come to pass in the coming years, bringing patients and physicians a step closer to achieving the level of satisfaction and success they so deserve. JARG will continue to bring advances in molecular genetics to our readership as we serve your needs as educators aimed at understanding and applying the new technologies taking residence in the field of human ARTs.