The intra-follicular molecular biology mandating advancement of egg retrieval in some women

As is the case for many natural biological processes, oocytes have a peak moment when, if harvested, they can produce the best quality embryo. If harvested too soon an oocyte will be immature and cannot be inseminated, if harvested too late the oocyte may be atretic leading to abnormal fertilization, retention of polar bodies and poor embryo development.

The granulosa cell population of the graafian follicle can be divided in to two populations. The mural granulosa cells which line the inside of the follicle and the cumulus cells which surround the zona pellucida of the developing oocyte. The cumulus cells interact with the oocyte via intercellular transzonal projections and gap junctions. In addition, cell to cell interaction can occur via receptor tyrosine kinase, receptor/ligand interaction, cell/cell contact and autocrine/paracrine factors. Through these mechanisms there is bidirectional communication between the cumulus cells and the oocyte. Cumulus cells can control oocyte meiotic resumption, nuclear and cytoplasmic maturation and transcriptional activity. Meanwhile factors from the oocyte such as growth/differentiation factor 9 (GDF-9) and bone morphogenetic protein 15 (BMP-15) regulate growth and atresia of the granulosa cells, gene expression, and metabolism, differentiation, proliferation, apoptosis, and luteinization of granulosa cells. Breakdown in the communication between cumulus cells and the oocyte leads to onset of nuclear maturation.

Premature luteinization can occur more frequently among older women in part due to defects in cumulus cell/ oocyte communication. Premature follicular luteinization is associated with rapidly declining IVF pregnancy chances in older women and can be avoided by earlier oocyte retrieval. With advancing age FSH receptor (FSHR), aromatase (CYP19A1) and 17b-hydroxysteroid dehydrogenase (HSD17B) expression in mural granulosa cells are down regulated, while LH receptor (LHCGR), P450scc (CYP11A1) and progesterone receptor (PGR) are up regulated. In vitro cultured, mural GCs from older women exhibit evidence of lower proliferation and increased apoptosis. Taken together these observations suggest age-related functional decline of granulosa cell function with resulting premature luteinization.

As clinicians, we follow follicular development by monitoring serum estradiol and sonographically determined follicular diameter. In most young women, peak oocyte development is observed when a follicle is 18 to 20 mm diameter. However, for women over age 38, mature oocytes can be harvested from follicles 16 to 18 mm in diameter. Over the age of 42 years, an 18 mm follicle will often yield an atretic oocyte, thus forcing us to err on the side of immaturity to trigger at 14 to 16 mm follicle diameter. At CHR we found that

in women above age 42, by triggering ovulation at maximal leading follicle size of 16 mm (as opposed to routine 18–20 mm), we were able to avoid premature luteinization and atresia. Compared to normal cycles in women of similar age, earlier retrieved patients demonstrated only a marginal increase in oocyte prematurity yet exhibited improved embryo numbers as well as quality and respectable clinical pregnancy rates. Better to have a potentially viable MI oocyte than to have atretic oocytes.

Oocytes require the support of their cumulus granulosa cells to inhibit rapid maturation (and atresia) and to allow the attainment of some degree of competence. Currently, we address the problem of premature luteinization and rapid atresia by early retrieval and further maturation in the laboratory with continued exposure to granulosa cells. In the future we hope to be able to further improve in vitro maturation techniques. Alternatively, one could look for pharmacological ways to improve in vivo follicle performance to better maintain cumulus granulosa cell/ oocyte bidirectional communication.