Graduate Studies

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The Role of the Ovarian Reserve in Fertility

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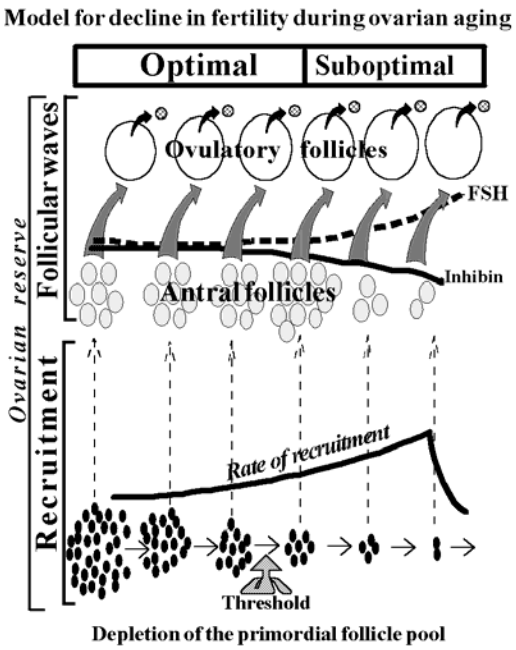
Fertility begins to decline at 28 to 30 years of age in women, which is nearly two decades before menopause! In addition, fertility plummets 50% in 2-year old dairy cows after birth of their first calf! The causes of the relatively rapid age-related onset of infertility in these species are poorly understood.



At birth, ovaries of humans or cattle contain a non-replenishable, but highly variable number (10,000 to 800,000) of primordial follicles (dark circles in model). Each primordial follicle contains an immature oocyte arrested in meiosis I and surrounded by a single layer of granulosa cells. Once primordial follicles begin growth (recruitment), they must progress through a series of developmental stages (primordial→ primary→ preantral, represented by dotted arrows in model) before they become antral follicles (gray circles in model). Antral follicles grow and undergo atresia in a wave-like fashion every 7 to 10 days, but only a single dominant ovulatory follicle develops from one wave per menstrual or estrous cycle (dark arrows in model) and ovulates. Surprisingly, as humans and cattle age, < 0.1% of the tens of thousands of follicles in ovaries (ovarian reserve) ever ovulate while 99.9% die via atresia! While the causes of age-related onset of infertility are unknown, the chronic, permanent loss of follicles via atresia as ovaries age may be a major contributing factor. The model also shows that fertility becomes suboptimal in humans or cattle as their ovaries age, despite the continued wave-like growth of non-ovulatory antral follicles and ovulation of a single dominant follicle from a follicular wave during each menstrual or estrous cycle. Also, ovarian aging is associated with increased secretion of follicle stimulating hormone (FSH) from the pituitary gland, decreased secretion of inhibin from antral follicles, a transient increase followed by a decrease in numbers of antral follicles, increased rate of recruitment of primordial follicles (% of total number of primordial follicles beginning growth), which is necessary to maintain growth of a relatively constant number of antral follicles during follicular waves, and a permanent chronic decrease in numbers of primordial follicles in ovaries. Taken together, these observations support the general overall hypothesis that "once a threshold number of primordial follicles remaining in ovaries is reached as ovaries age, fertility begins to decline because the decreased number of antral follicles growing during follicular waves alters endocrine and intra-ovarian mechanisms that compromise both function of dominant ovulatory follicles and oocyte quality".

Numbers of the different follicle types in the ovarian reserve vary greatly among individual adult humans or cattle. However, despite high variability and chronic age-related depletion of the ovarian reserve, the physiological importance of the ovarian reserve to fertility is unknown. For example, it is unknown if the high variation in numbers of follicles in ovarian reserves among individuals causes a highly variable number of non-ovulatory antral follicles to grow during menstrual or estrous cycles. This simple question is especially important to resolve because relatively high numbers of antral follicles are positively associated with an increased responsiveness to gonadotropin treatments during superovulation, a larger number of oocytes recovered for *in vitro* fertilization, higher pregnancy rates following *in vitro* fertilization, and fecundity in cattle and humans. Collectively, these observations imply that variation in numbers of follicles that develop during menstrual or estrous cycles may have an important, albeit poorly understood role in regulation of fertility in humans and cattle. Novel data generated recently in my laboratory using ultrasound analysis to monitor follicular growth demonstrate that numbers of antral follicles growing during follicular waves in cattle varies more than 7-fold amongst animals, but is very highly repeatable (0.95) within individuals. For example, some animals have as few as 8 antral follicles growing repeatedly during each different follicular wave of an estrous cycle while others of the same age, breed and management scheme have as many as 58! Thus, ultrasound analysis can be used to reliably phenotypically classify animals based on numbers of antral follicles growing during follicular waves. My laboratory, therefore, will take advantage of this classification scheme to identify animals that consistently have low vs high numbers of antral follicles growing during follicular waves and use a combination of ultrasonography, ultrasound-guided intrafollicular injections/biopsy, molecular biology (DNA array, RT-PCR), protein chemistry, immunoassays, histology, and cell culture to address the following questions: Is the variation in antral follicle numbers growing during follicular waves associated with alterations in key hormones (such as estradiol, inhibin and FSH) or growth factors (such as IGF-1, activins, kit-ligand, and anti-mullerian hormone) known to regulate folliculogenesis? Do alterations in numbers of antral follicles per wave affect dominant follicle function? Is the variation in numbers of antral follicles during follicular waves reflective of numbers of primordial follicles in the ovarian reserve, oocyte quality, fertility and(or) reproductive lifespan? Could reliable morphological (numbers of antral follicles growing per wave, ovarian volume) and(or) biochemical markers (inhibin, anti-mullerian hormone) be identified to monitor depletion of the ovarian reserve during aging and thus be useful to predict an individual's "reproductive biological clock"? Could methods to slow depletion of the ovarian reserve and extend fertility be developed? Successful resolution of these questions using our novel animal model will provide new insight into the relevance of the ovarian reserve to fertility, which will have important implications for human clinical reproductive medicine and animal agriculture.