

FOLLICULOGENESIS IN CATTLE

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PRENATAL FOLLICULAR GROWTH

Development of oocytes and follicles begins in utero. Primordial germ cells proliferate by mitosis to form primary oocytes; the first meiotic prophase starts between Days 75 and 80 of pregnancy (Erickson, 1966). At the diplotene stage of meiosis (approximately Day 170) a primordial follicle forms; the oocyte is surrounded by a single layer of 4–8 pre-granulosa cells. The oocytes of these primordial follicles remain in the resting phase until they are stimulated to grow (Erickson, 1966). Factors regulating formation of primordial follicles are not well known (Fair, 2003).

Primordial, primary and secondary follicles appear in the fetal ovary on Days 90, 140 and 210, respectively (Russe, 1983). Activation of follicle growth is characterized by the acquisition of a complete layer of 11–20 cuboidal granulosa cells around the oocyte, forming the primary follicle (Hulshof et al, 1992). A secondary follicle is characterized by the addition of a second layer of granulosa cells (Driancourt, 1991), the initial deposition of zona pellucida material, formation of cortical granules within the oocyte cytoplasm (Fair et al, 1997a), onset of oocyte RNA synthesis (Fair et al, 1997b), and gonadotrophin responsiveness (Fair, 2003). The transition to the tertiary follicle includes development of the theca interna and externa, the basal lamina and cumulus cells, as well as the formation of a fluid-filled antral cavity (Driancourt, 1991).

POSTNATAL FOLLICULAR GROWTH AND PUBERTY

Follicular growth in prepubertal heifers occurs in waves; each wave is preceded by a peak in serum FSH concentrations (Adams et al, 1992; Adams et al, 1994; Fortune, 2004). Waves are present in heifers at 2 weeks of age (Evans et al, 1994). Numbers of small, medium and large follicles (3–5, 6–8 and ≥ 9 mm in diameter, respectively) and diameter of the largest follicle all increase from 2 to 14 weeks of age. Between 6 and 24 weeks of age, there is a marked but transient increase in blood concentrations of both LH and FSH (Evans et al, 1992; Evans et al, 1994; Honaramooz et al, 1999). The release of LH is pulsatile; the early increase is attributed to increased LH pulse amplitude. Thereafter, serum concentrations of LH and FSH decrease. However, 30–80 days before the first ovulation (Evans et al, 1994; Melvin et al, 1999), increases in LH pulse frequency result in increases in follicle diameter and serum estradiol concentrations, culminating with the first ovulation. Conversely, serum FSH remains relatively stable (Evans et al, 1994). Heifers usually do not express estrus prior to their first ovulation, the corpus luteum is small, and may be short-lived (Berardinelli et al, 1979). This short cycle is usually followed by estrus and a normal, full-length luteal phase.

Although growth of ovarian follicles in the young calf is apparently stimulated by gonadotropins, mechanisms controlling gonadotropins are not well understood (Rawlings et al, 2003). Early increases in gonadotropins seem to be subsequently suppressed by negative feedback until the heifer is able to successfully reproduce. Although estradiol appears to be the primary negative feedback agent on LH secretion (acting indirectly through other neuronal systems) in the adult, the initial suppression of

the early post-natal increase in LH secretion may not involve estradiol (Moseley et al, 1984; Day and Anderson, 1998), but rather an estrogen-dependent opioidergic mechanism (Wolfe et al, 1991). From 40–80 days prior to the first ovulation, the sensitivity of LH secretion to negative feedback suppression decreases, allowing LH secretion to increase (increased LH pulse frequency) and enhancing antral follicle development and estrogen secretion. Increasing estrogen concentrations eventually cause a preovulatory LH surge.

GROWTH PHASES

Cattle have two stages of ovarian antral follicle development, a 'slow' and a 'fast' growth phase, respectively (Fair, 2003). The first (slow) phase takes >30 days from antrum acquisition (approximately 300 µm) to the 'small' follicle stage (3–5 mm in diameter; Lussier et al, 1987). The second phase usually takes approximately 5–7 days, and includes emergence of a wave of follicles, follicle growth, selection of a dominant follicle, and a variable dominance period, followed by ovulation or regression.

FOLLICULAR WAVES AND DEVIATION

Follicles develop in waves; on average, 7–11 follicles (4 mm in diameter) are present at follicular wave emergence in cattle. Emergence of a new follicular wave is preceded by a rise in FSH, with wave emergence concurrent with the peak (Adams et al, 1992). Suppression of FSH prevents further growth of 3-5 mm follicles (Turzillo and Fortune, 1990), whereas treatment with exogenous FSH stimulates wave emergence (Bergfelt et al, 1994a). Treatment with FSH (without steroids or LH) results in follicles with limited capacity to produce steroids and lack of selection of a dominant follicle (Crowe et al, 2001). The transient FSH rise stimulates all antral follicles that have completed their 'slow' growth phase; they not only respond, but subsequently depend on elevated FSH for continued cell proliferation and enhanced steroidogenesis. Following emergence of a new wave, follicles grow (common-growth phase) for approximately 3 days; the end of the common-growth phase and the beginning of deviation are synonymous. The future dominant follicle emerges 6 h earlier than other follicles in the wave and is larger than the other follicles at the end of the common-growth phase (Ginther et al, 2003a).

The FSH surge peaks, on average, when the largest follicle is about 5 mm; mean concentrations then decrease, with about a 3-day interval between peak concentrations and the beginning of deviation. Deviation is a distinctive change in growth rates between the developing dominant follicle and the remaining follicles (subordinates). Deviation in individual waves is defined as beginning at the examination before the first examination with an apparent change in the differences in diameter between the two largest follicles. Mean diameters of the two largest follicles at the beginning of deviation were 8.5 and 7.7 mm in heifers (Ginther et al, 2003b). Apparently, when the largest follicle reaches a decisive developmental stage, rapid development of the deviation mechanism blocks development of the second-largest follicle before it reaches a similar diameter. Thus, rather than selection of a dominant follicle, selection involves an action against the other follicles in the wave (Ginther et al, 2003a). It is noteworthy that the destiny of the follicles (dominant versus subordinate) must be established, on average, in <8 hours in cattle (equivalent to a diameter difference of 0.5 mm). All follicles of the common-growth phase have the potential for future dominance. A subordinate follicle

remains viable for at least 1 day after deviation starts; it can become the new dominant follicle if the existing dominant follicle fails or is removed.

During the dominance period, antral follicles completing their first 'slow' growth phase are prevented from embarking on their second FSH-dependent growth phase by the dominant follicle. Loss of dominance during the luteal phase or induced atresia of a dominant follicle that was artificially maintained is followed by increased FSH concentrations and emergence of a new wave (Sunderland et al, 1994). It is noteworthy that administration of FSH when a dominant follicle is present does not consistently hasten emergence of the next wave (Adams et al, 1993). In this regard, superovulatory responses are suppressed when cattle are given exogenous FSH during dominance (Bungartz and Niemann, 1994).

Between the peak FSH surge and the start of deviation, all follicles of the wave continue to require FSH and more than one follicle contributes to the FSH decrease. In association with the onset of deviation, the FSH/follicle relationship changes; instead of several follicles requiring FSH, only the dominant follicle continues to grow, despite low FSH concentrations. The FSH decline is necessary for the establishment of deviation; increasing endogenous FSH or administering FSH early in a wave induces several follicles to become dominant. With decreasing serum FSH concentrations, follicles begin to undergo changes, including reduced production of estrogens, reduced levels of higher molecular weight (MW) inhibins and increased amounts of lower MW insulin-like growth factor (IGF)-binding proteins, culminating in granulosa cell apoptosis (Sunderland et al, 1996; Mihm et al, 1997). In this environment, only the dominant follicle is able to continue to grow and produce steroids. FSH stimulates the production of estradiol, activin-A and inhibin-A (Glister et al, 2001). These FSH-stimulated factors have intrafollicular roles in deviation. Both estradiol and inhibin act alone (as well as synergistically) to suppress blood FSH concentrations. Blood estradiol concentrations begin to increase at the beginning of deviation in cattle (Ginther et al, 2003a). Inhibin (probably inhibin-A) is produced by multiple follicles before deviation and by the developing dominant follicle after the start of deviation and suppresses FSH during the entire FSH decline. The largest and the second-largest follicles at similar diameters had similar follicular-fluid estradiol concentrations during the common-growth phase; increasing concentrations were detected beginning at 7.6–7.7 mm in heifers (Ginther et al, 2003). Estradiol began to increase differentially in the largest follicle 4 h before diameter deviation (Ginther et al, 2003). The differential estradiol increase in the future dominant follicle increases blood estradiol concentrations; these increase the expression of genes for aromatase, 3-beta-HSD, and receptors for FSH and LH in granulosa cells (Bao and Garverick, 1998). Furthermore, estradiol increases its synthesis by upregulating thecal synthesis of androgens in vitro (Wrathal and Knight, 1995).

The IGF system is involved in cell growth and differentiation and consists of IGF-1, IGF-2, IGF receptors, and a family of binding proteins (IGFBPs) and IGFBP proteases (Webb et al, 1999; Fortune et al., 2004). The proteases degrade the IGFBPs, liberating IGF from the IGFBP-IGF complex. Intrafollicular concentrations of IGFBP-2 and free IGF-1 and were lower and higher, respectively in the largest compared to the second largest follicle in heifers (Beg et al, 2001). It appears that an FSH-induced increase in pregnancy-associated-plasma protein-A (PAPP-A) is the earliest change detectable in the future dominant follicle (Fortune et al, 2004). PAPP-A is a protease that degrades IGFBP-4 and IGFBP-5, thereby increasing intrafollicular IGF-I concentrations. Increased IGF-I acts together with FSH to increase estradiol synthesis, thereby suppressing plasma FSH concentrations and preventing other (subordinate) follicles from acquiring PAPP-A (Fortune et al, 2004). It is noteworthy that estradiol stimulates

the production of IGF-1 and IGF-1 stimulates the production of estradiol (Ginther, 2003). Both estradiol and IGF-1 increase the gonadotropin responsiveness of the follicle; a mutual augmentation system for estradiol and IGF-1 are critical to increased gonadotropin responsiveness and deviation.

Although the mechanisms are not well known, it appears that LH stimulates intrafollicular steroid and growth-factor systems that are involved in selection (Ginther et al, 2003a). In that regard, granulosa cells of the future dominant follicle acquire LH receptors before selection is apparent, suppression of LH in heifers limited maximum follicle diameter to 7-9 mm in heifers, and a transient increase in blood LH occurs around the time of selection (Ginther et al, 2003a). In addition to FSH, LH is essential to stimulate theca cells to produce androgens (as precursors of estradiol). Reductions in plasma LH prior to selection reduced the growth and lifespan of the CL (Ginther et al, 2001); in that regard, LH was regarded as essential for antral follicles to grow beyond 9 mm in diameter (Gong et al, 1996). Following selection, growth, estrogen production and the lifespan of the dominant follicle are all controlled by the LH pulse pattern (Mihm and Bleach, 2003); atresia of the dominant follicle occurs if LH pulse frequency is <1 pulse/2 hours (Mihm and Bleach, 2003). This has important clinical implications. Treatment with progesterone, GnRH or estradiol result in apoptosis and atresia of the dominant follicle (Mihm and Bleach, 2003). Conversely, increased LH pulse frequency (due to low-dose progestin treatment) cause persistent follicles (Savio et al, 1993; Stock and Fortune, 1993).

DETECTION OF DEVIATION

Observed deviation for individuals is determined in retrospect by inspection of the sequential changes in diameters of the dominant and subordinate follicles. When follicles are grouped in diameter ranges with each animal in a separate group, deviation is indicated statistically by the group that precedes the first group with a significant increase in the differences in diameter between the two largest follicles. A segmented linear regression model has been developed to minimize bias and improve precision by calculating the beginning of deviation in individuals (Bergfelt et al, 2003).

EFFECTS OF CO-DOMINANCE

The occurrence of more than one dominant follicle during a follicular wave in animals that normally ovulate only a single follicle can be considered a defect in the deviation mechanism. Double ovulations are usually due to codominance, but occasionally the follicles originate from different waves. The incidence of double ovulation was much higher in dairy cows with high versus low milk production (20 versus 7%, respectively; Fricke and Wiltbank, 1999). Perhaps the normal increase in blood estradiol concentrations and decrease in blood FSH concentrations at deviation is partially suppressed in lactating cows with high milk production (Wiltbank et al, 2000); in that regard, high milk production increases the rate of steroid catabolism due to increased hepatic blood flow. Due to suppressed blood estradiol concentrations, blood FSH is increased long enough for > 1 follicle to become a dominant and ovulate.

FINAL GROWTH AND OVULATION

Dominant follicles continue to grow for a few days after selection. In the absence of an LH surge, the dominant follicle starts to regress and triggers the recruitment of a new wave of growing follicles. Ultrastructural changes in oocytes have been described (Hyttel et al, 1986; Hyttel et al, 1989). If there is an LH surge the dominant follicle continues to grow and the oocyte within undergoes final maturation, culminating in follicle rupture and ovulation. Final maturation includes expansion of the cumulus cover, disruption of the contact between the corona radiata cells and the oocyte membrane and perivitelline space formation. In the oocyte cytoplasm, lipid content increases but the Golgi compartment decreases. The cortical granules are aligned just inside the oocyte membrane, meiosis resumes and the oocyte nucleus membrane breaks down. The chromosomes condense and progress through the final stages of meiosis I and arrest at metaphase of meiosis II (Hyttel et al, 1986 and Hyttel et al, 1989).

TWO VERSUS THREE WAVES OF FOLLICULAR DEVELOPMENT

Lactating Holstein dairy cows described in recent studies tend to have two-wave cycles (Townson et al, 2002), whereas beef and dairy heifers have discrete populations with a majority of cattle having either two- or three-wave cycles (Ginther et al, 1989). The peak and average plasma concentrations of FSH and inhibin A are lower in the two non-ovulatory waves of a three-wave cycle than in the ovulatory wave, but are similar in two-wave cycles (Parker et al, 2003). Holstein cows which had a three-wave cycle preceding insemination had higher conception rates than those with two waves (Townson et al, 2002), and beef cows with the equivalent of three waves in the cycle following insemination also had a higher conception rate (Ahmad et al, 1997). Higher fertility in three-wave cycles could be due to a shorter interval for development of the ovulatory follicle (Mihm et al, 1994 and Townson et al, 2002) and/or delayed regression of the corpus luteum in nonbred cattle with three versus two waves (Ginther et al, 1989), thereby providing more opportunity for maternal recognition of pregnancy.

OOCYTE RECOVERY FOR IN VITRO FERTILIZATION

Although IVM and IVF of bovine oocytes is highly successful (80%), only about 30% of oocytes develop to the blastocyst stage (Rizos et al, 2002). Oocytes matured in vivo are more competent than those matured in vitro (van de Leemput et al, 1999 and Rizos et al, 2002). Although various chemical approaches have also been used to artificially maintain meiotic arrest in bovine oocytes (Fair, 2003), pre-maturation culture may be more effective (Pavlok et al, 2000). In a recent study (Blondin et al, 2002), a cohort of large follicles was maintained on the ovary (coasting) for 2 days following final FSH treatment, allowing the oocyte cytoplasm to mature. LH was given 6 h before oocyte recovery (by ovum pick up). Up to 80% of oocytes developed to the blastocyst stage in vitro. Physiological methods of artificially maintaining meiotic arrest in bovine oocytes have involved co-culturing oocytes with different follicle constituents in vitro, with variable success (Sirard, 2001). The inhibitory factor(s) are not characterized but are probably from theca cells (Richard and Sirard, 1996).

B. INDICUS VERSUS B. TAURUS CATTLE

A comparison of ovarian function in *B. indicus* versus *B. taurus* cattle was recently reviewed (Bó et al, 2003). In general, follicular growth and dominance were similar in *B. indicus* versus *B. taurus* cattle. However, maximum diameter of the dominant follicle (10–12 mm) and the CL (17–21 mm) seemed smaller in *B. indicus* cattle seemed smaller than in *B. taurus* cattle (14–20 mm and 20–30 mm, respectively; Bo). Furthermore, blood progesterone concentrations were lower in *B. indicus* than in *B. taurus* cows (Segerson et al, 1984). The progesterone content of the CL was lower in *B. indicus* versus *B. taurus* cattle, perhaps due to a lower response to estrogen, smaller preovulatory LH-surge, and other endocrine differences (Randel, 1984).

In a recent study comparing *B. indicus* and *B. taurus* cattle (Bó et al, 2003), the mean maximum diameter of the dominant follicle of the third wave and the CL were significantly smaller in *B. indicus* versus *B. taurus* cows. Furthermore, there were significantly more four-wave interovulatory intervals in *B. indicus* versus *B. taurus* cows (4/25, 16% versus 0/17). Although four-wave interovulatory intervals have been reported in Brahman and Gyr cattle, they are rare in Nelore cattle (Bó et al, 2003). The mean length of the interovulatory interval was positively correlated to the number of follicular waves. Furthermore, the day of emergence of the second follicular wave tended to decrease as the number of waves per cycle increased (Rhodes et al, 1995a; Bó et al, 2003) and the third follicular wave tended to emerge earlier in *B. indicus* than in *B. taurus* cows (Bó et al, 2003). There was a significant interaction between season and subspecies in the growth rate of the dominant follicle of the third wave; the growth rate of the dominant follicle in *B. indicus* cows was slower in the fall than in the spring (1.1 versus 1.5 mm/day, respectively), whereas the dominant follicle in *B. taurus* cows tended to grow faster during the fall than in the spring (1.6 versus 1.4 mm/day). Although *B. indicus* cattle are apparently more influenced by photoperiod than *B. taurus* cattle, the confounding effects of nutrition must also be considered.

There appear to be more follicles < 5 mm in diameter in *B. indicus* versus *B. taurus* heifers (Segerson et al, 1984), as well as differences in ovarian insulin and insulin-like growth factor (IGF). In Nelore heifers (Buratini et al, 2000), although treatment with BST increased both plasma IGF-I concentrations and the number of small follicles (<5 mm), the rate of increase in follicle numbers were lower than those reported in *B. taurus*. Brahman cows had higher plasma IGF-I concentrations (Simpson et al, 1994, Alvarez et al, 2000) but lower FSH concentrations than Angus cows (Alvarez et al, 2000); perhaps these differences contribute to differences in the number of follicles and/or to the high sensitivity of *B. indicus* cattle to the dose of FSH used in superstimulation regimens (Barros and Nogueira, 2001).

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