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# Human antral folliculogenesis: what we have learned from the bovine and equine models

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## Abstract

The study of ovarian folliculogenesis has been of great interest to scientists and clinicians in the human and veterinary health fields for more than 20 centuries. Initial studies of the ovarian follicle were based on anatomical descriptions post-mortem, followed by histologic and endocrinologic evaluation of ovarian status. The introduction of high resolution ultrasonography in the 1980s provided a long-awaited tool to image the reproductive tissues in situ in both animal and human species. The bovine and equine species have been established as models for the study of human ovarian folliculogenesis. Profound similarities in the dynamics of follicle development exist between the menstrual cycle in humans and the estrous cycle in cattle and horses. Disparities between species appear specific rather than general. Research performed in women thus far has led to the concepts that: 1) follicle development occurs in a wave-like manner during the menstrual cycle, 2) the number of waves per cycle correlates positively with the length of the cycle, 3) the emergence of follicle waves in women are preceded by a rise in circulating FSH, 4) selection of a dominant follicle may occur in each wave of the cycle, and 5) a decline in circulating FSH and increase in follicular estradiol, inhibin A, and IGF-II act collectively to enable the dominant follicle to continue to grow in an endocrine environment of decreasing FSH and increasing LH, while subordinate follicles undergo regression. The goal of continued research using animal models for studying human ovarian function is to provide the hypothetical basis for further studies in women, which will ultimately lead to the development of safer and more efficacious infertility and contraceptive therapies.

**Keywords**: antral, bovine, equine, follicle, human.

## Introduction

We have come a long way in our understanding of the structure and function of the ovary over the past 2500 years. The earliest documented descriptions of reproduction came from Hippocrates in the 5th century BC who argued that generation of life occurred through the joining of male semen (ejaculate) and female semen (menstrual blood; Cobb, 2006). A century later, Aristotle attested that the female provided the matter that would constitute the fetus while the male's semen contributed to the form and shaping of the embryo (Cobb, 2006). In the early 17th century, the phrase 'ex ovo omnia' emerged from William Harvey, which translates as 'all things come from eggs'. Two decades later in 1672, Regnier de Graaf described the ovarian follicle in rabbits (Cobb, 2006). However, de Graaf mistakenly believed the follicle to be the egg itself. In the 19th century, von Baer provided the first accurate descriptions of the mammalian egg within the ovarian follicle (Cobb, 2006). It was not until the 20th century, that the human egg was first discovered and the dynamics of antral ovarian follicular growth were described.

Initial studies to characterize antral follicular dynamics, using histologic and later endocrinologic evaluation of ovarian status, were reported in mice (Bullough, 1946), rats (Mandle and Zuckerman, 1950), women (Block, 1951), monkeys (Green and Zuckerman, 1951), cows (Rajakoski, 1960), sheep (Brand and de Jong, 1973) and pigs (Clark *et al.*, 1975). The advent of high resolution ultrasonography in the 1980s provided a long-awaited tool to image the human reproductive tissues in situ in a number of different species. The initial studies of ovarian folliculogenesis have since been expanded upon and follicular dynamics have been further characterized in other animal species including, but not limited to horses (Ginther and Pierson, 1984), camelids (Adams *et al.*, 1989), wapiti (McCorkell *et al.*, 2006) and deer (Asher *et al.*, 1997).

The objective of this mini-review is to summarize some of the comparative aspects of ovarian antral follicular development during the bovine and equine estrous cycles and the human menstrual cycle. This article is intended for scientists and clinicians in both the human and veterinary disciplines of reproductive biology. Cattle, horses and humans exhibit similarities in patterns of antral follicular dynamics (Ginther *et al.*, 2001a). Thus, the bovine and equine species are appropriate models for studying follicular development in women (Adams and Pierson, 1995; Ginther *et al.*, 2004).

## Comparative reproductive cyclicity

Similarities in the dynamics of antral follicular growth and regression have been observed among the bovine, equine and human species, despite differences in reproductive cyclicity. The bovine and human species are similar in that they undergo estrous/menstrual cycles all year round, in contrast to the equine species which

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exhibits distinct ovulatory and anovulatory seasons.

The bovine and equine estrous cycles are divided into 4 phases: 1) proestrus, when an ovulatory follicle develops, 2) estrus, the period of 'sexual receptivity' during which time final follicular maturation and ovulation occur, 3) metestrus, when the corpus luteum (CL) forms, and 4) diestrus when the CL is actively producing progesterone. The follicular phase encompasses only about 1/5 of the estrous cycle in cows (~4 days) and about 1/3 of the cycle in horses (~7days). In comparison, the follicular phase in women encompasses about ½ of the menstrual cycle (~14 days). It is noteworthy that the lifespan of the dominant ovulatory follicle, defined as the time from emergence of the dominant follicle to ovulation, is comparable in all three species (i.e., ~11 days of the 21 day estrous cycle in cows, ~14 days of the 21 day estrous cycle in horses, and about 14 days of the 28 day menstrual cycle in women; Adams, 1999; Baerwald *et al.*, 2003a; Ginther *et al.*, 2004). The reproductive cycles of women are not overtly influenced by periods of sexual receptivity or 'estrus', but menstruation (cyclic shedding of the endometrial lining) is a clear and consistent characteristic. Therefore, onset of menstruation, rather than estrus, is used as a reference point for describing ovarian cyclicity in women. Menstruation occupies the first 5 days of the menstrual cycle and is the result of declining progesterone; i.e., it represents the beginning of the follicular phase. Hence, in contrast to that of animals, the classic illustration of the ovarian cycle in women begins with the follicular phase followed by ovulation at 'mid-cycle' and the luteal phase during the last part of the cycle. From a comparative standpoint, it is particularly important to appreciate the differences in sequence of follicular and luteal phases when referring to the menstrual and estrous cycles. In this regard, it has been useful to simply refer to the 'interovulatory interval' (IOI), in which the luteal phase occurs first followed by the follicular phase. The IOI has been used for evaluating ovarian follicular dynamics in domestic animals and women in attempt to reduce ambiguities in detection methods and definitions used to characterize follicle waves.

## Initiation of follicle development

The entire period of ovarian folliculogenesis, which includes the transition of primordial follicles into preovulatory follicles has been estimated to be more than 175 days in women (Gougeon, 1986). In cattle, the time required for a primordial follicle to develop to the tertiary stage has been estimated to be about 160 days (Russe, 1983), while the time required for a follicle to grow from the large pre-antral stage (secondary follicle) to a mature ovulatory size has been estimated to be about 42 days in cattle (Lussier *et al.*, 1987). In the human, bovine and equine species, the primordial follicles, which have become arrested at meiotic prophase I during embryonic development, begin to leave the resting pool and enter into the pre-antral growth phase. Movement of follicles from the ovarian reserve into the growing phase in women is thought to occur continuously during the reproductive years until exhaustion of the reserve at senescence. However, wave patterns of antral follicle development have been observed in cattle as early as 2 weeks of age (Evans *et al.*, 1994). Pre-antral follicles are believed to develop independent of gonadotropic support, but become more responsive to gonadotropins at the early-antral stages. With the onset of puberty, the cyclic growth of antral follicles occurs as a result of changes in hypothalamic and pituitary gonadotropin hormones (Craig *et al.*, 2007).

## Follicle recruitment

In the human literature, the term 'recruitment' has been used to describe two important but distinct physiologic stages of follicle development. Primordial follicles have been described as being 'recruited' from the resting pool of follicles following follicle formation at embryonic stages of development and continuing throughout a woman's reproductive lifetime (Baird, 1987; Adashi, 1994). In addition, a cohort of antral follicles is rescued from atresia and 'recruited' for continued growth at the onset of each menstrual cycle following puberty (Santbrink *et al.*, 1995; McGee and Hsueh, 2000). To provide consistency with animal data, 'recruitment' in this review will describe the cyclic growth of a cohort of antral follicles.

There are 3 different theories describing follicle recruitment during the human menstrual cycle. The earliest theory was based on histologic evaluation of ovaries in women undergoing oophorectomy. According to this early theory, follicle growth from the 2-5 mm stage occurred continuously, with privileged phases, especially in the late luteal phase (Gougeon, 1979). A second theory emerged to state that a cohort of antral follicles is recruited in the late luteal phase of each menstrual cycle, in response to the rise in GnRH and FSH following regression of the CL (Hodgen, 1982). Follicle development beyond 2 mm was thought to occur primarily in the follicular phase of the cycle, and luteal estrogen was believed to suppress gonadotropins to a level which was too low to initiate and maintain follicular growth during the luteal phase (Baird *et al.*, 1975).

Characterization of ovarian follicular waves in domestic animals, in particular cattle (Rajakoski, 1960; Pierson and Ginther, 1987; Sirois and Fortune, 1988; Ginther *et al.*, 1989a; Knopf *et al.*, 1989), led to continued studies in women from which a third theory of follicle recruitment emerged. It is well-documented that 2 or 3 waves of follicles develop during the bovine estrous cycle (Rajakoski, 1960; Pierson and Ginther, 1987; Sirois and Fortune, 1988; Knopf *et al.*, 1989). The wave pattern of follicular development refers to the periodic, synchronous, growth of a group of antral follicles (Adams, 1999). Similarly, 2 or 3 waves of antral follicular growth were reported during an IOI in women (Baerwald *et al.*, 2003a, b). Characteristics of follicle wave emergence (i.e., days of wave emergence, number of follicles per wave, positive correlation between cycle length and number of waves) in women markedly resemble those previously reported during the bovine estrous cycle. By comparison, the emergence of 2 follicular waves has been detected during the equine estrous cycle (Sirois *et al.*, 1990; Ginther, 1993).

The emergence of each follicle wave is preceded by a rise in circulating FSH during the bovine (Adams *et al.*, 1992) and equine (Bergfelt and Ginther, 1992) IOIs. During the human menstrual cycle, the first wave (anovulatory) of the IOI emerges in association with the preovulatory FSH surge in women with both 2 and 3 waves of follicle development. The second wave (ovulatory) in women with 2 waves and second wave (anovulatory) in women with 3 waves occurs in association with the rise in FSH coinciding with regression of the CL in the late luteal phase. A rise in FSH, however, was not detected in association with emergence of the 3rd wave (ovulatory) in women with 3 waves, possibly due to infrequent blood sampling.

It has been shown in the bovine estrous cycle that periodic development of anovulatory waves continues after ovulation, and the viable dominant follicle present at the time of luteolysis becomes selected for continued growth and ovulation (Ginther *et al.*, 1989c). Luteal regression thus occurs later in cows with 3 versus 2 waves. In contrast, no differences in the day of onset of luteal regression, maximum luteal area, or luteal phase progesterone were detected between women with 2 versus 3 follicular waves (Baerwald *et al.*, 2005). Continued investigations in women and domestic animals are required to determine the role of the CL in regulating follicle wave dynamics. Morphologic and endocrinologic characterizations of follicle wave dynamics during the IOI in cattle and women are shown in Fig. 1 and 2. Individual follicle profiles during the equine IOI are shown in Fig. 3.

## Selection of the dominant follicle

Follicle selection in women, cattle and mares is the process in which a single follicle from the recruited cohort undergoes preferential growth, while all other follicles in the cohort fail to develop and undergo atresia. The follicle that is selected is referred to as the 'dominant' (Hodgen, 1982) or 'privileged' (Gougeon, 1986) follicle. Atretic follicles have been termed 'ordinary' (Gougeon, 1986), 'challenger' (Gore *et al.*, 1997), 'subdominant' (Gore *et al.*, 1994), or 'subordinate' (Knopf *et al.*, 1989) follicles.

Studies have been performed to compare the process of follicle selection in cattle, horses and women (Ginther *et al.*, 2001a, 2004, 2005; Gastal *et al.*, 2004). All three species are monovular, which means that a single follicle from the pair of ovaries (as compared to multiple follicles) is selected for continued growth and ovulation. Follicles from the recruited cohort undergo a common growth phase prior to selection (Ginther *et al.*, 2001a; Gastal *et al.*, 2004). The term ‘deviation’ describes the point at which divergence in the growth of the dominant and subordinate follicles occurs (Ginther *et al.*, 1997). Deviation of the dominant follicle from the largest subordinate follicle occurs at a diameter of 9 mm in heifers, 10 mm in women and 23 mm in mares (Gastal *et al.*, 1997; Ginther *et al.*, 2001a; Baerwald *et al.*, 2003a). Deviation in the ovulatory wave occurs, on average, 4 days after emergence of the largest follicle at 13 mm in mares and at 6 mm in women (Ginther *et al.*, 2004), compared to 3 days after emergence of the largest follicle at 4 mm in cattle (Ginther *et al.*, 1997). The dominant follicle maintains a constant growth rate throughout the deviation process, while the subordinate follicles exhibit a reduction in growth rates (Gastal *et al.*, 1997; Ginther *et al.*, 2001a). There is evidence in women, mares and heifers, that the dominant follicle exhibits an early size advantage over other follicles in the cohort, enabling it to establish dominance before the subordinate follicles reach a similar diameter (Ginther *et al.*, 2001a; Ginther *et al.*, 2004). A schematic model, comparing deviation of the dominant from the largest subordinate follicle in the human, bovine and equine species is shown in Fig. 4. The side of selection of the dominant follicle and subsequent ovulation (i.e., right versus left ovary) in women is not dependent on the side of the previous ovulation (Check *et al.*, 1991; Echochard and Gougeon, 2000; Ojha *et al.*, 2000; Baerwald *et al.*, 2003a), consistent with reports in heifers (Ginther *et al.*, 1989b).

Selection of a dominant follicle in women was initially thought to occur once during the menstrual cycle in the mid-follicular phase at a diameter of 10 mm (Baird and Fraser, 1975; Pache *et al.*, 1990). However, we have recently demonstrated that selection of a dominant follicle can occur 1-3 times during an IOI in women (Baerwald *et al.*, 2003a), consistent with observations in the bovine and equine species. Major and minor waves of follicle growth have been characterized in women and mares (Ginther, 1993; Baerwald *et al.*, 2003b). Major waves are defined as those in which a dominant follicle is selected for preferential growth, and minor waves are those in which dominance is not manifest. In the bovine species, all waves during the IOI are major waves. The last wave of the bovine IOI is characterized by the development of the dominant ovulatory follicle, and is therefore termed the ‘ovulatory wave’. A dominant follicle develops in all preceding waves but undergoes regression, resulting in ‘anovulatory waves’ (Sirois and Fortune, 1988; Ginther *et al.*, 1989c). By contrast, women and mares exhibit major and/or minor waves during the IOI (Ginther, 1993; Baerwald *et al.*, 2003a; Ginther *et al.*, 2004). In both species, the final wave of the IOI is a major ovulatory wave. In women, waves preceding the ovulatory wave are either major anovulatory waves or minor waves (Baerwald *et al.*, 2003a). In mares, the preceding wave is usually an anovulatory minor or major wave; however, ovulation of the preceding wave has been reported (Ginther, 1990; Bergfelt and Ginther, 1993). Similarities in the development of major and minor follicular waves in women and mares have provided rationale for using the equine species as an additional model for studying ovarian follicular development in women (Ginther *et al.*, 2004).

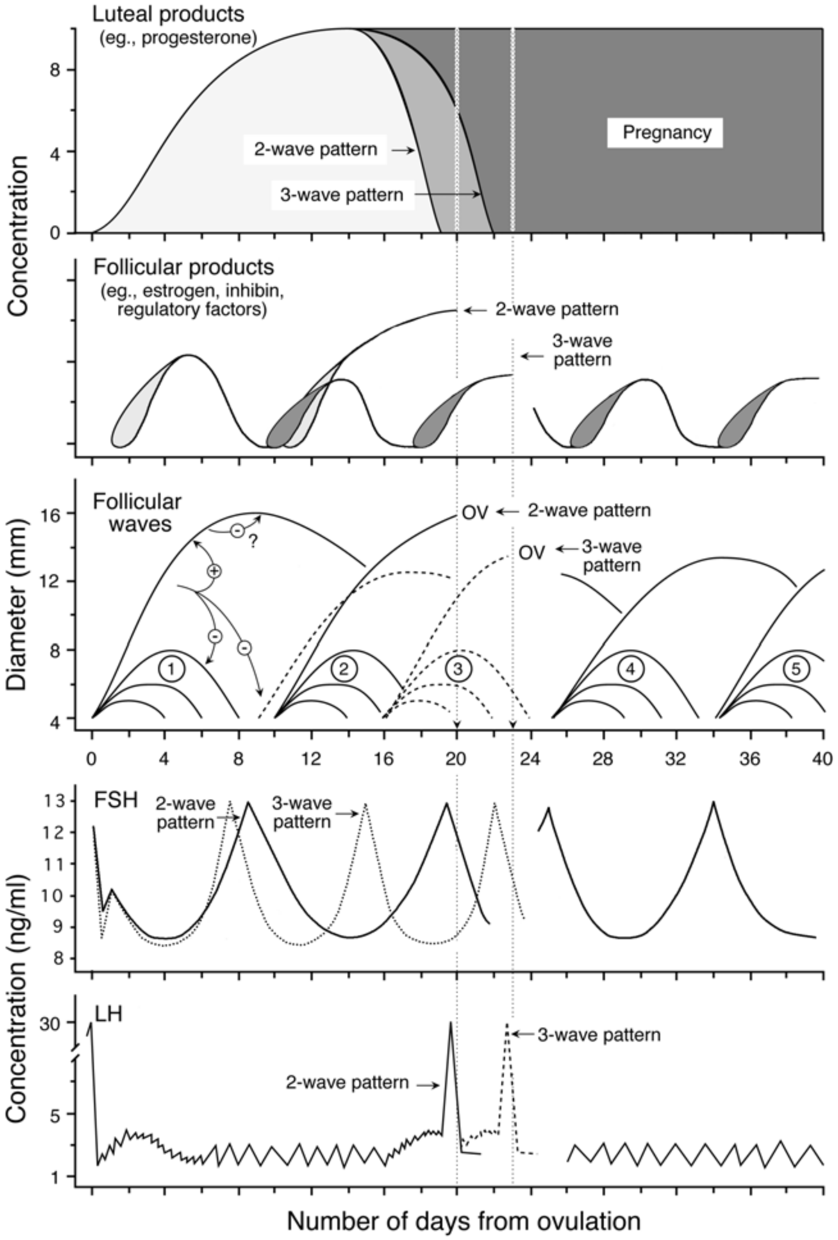

Figure 1. Proposed model of bovine ovarian follicular wave dynamics during 2-wave (solid lines) and 3-wave (dashed lines) interovulatory intervals (OV = ovulation), and early pregnancy (anovulatory; waves 4, 5 etc.). Follicle diameter profiles are represented in the middle panel, luteal and follicular products are represented in the upper panels, and gonadotropin profiles are depicted in the lower panels. Shapes drawn for follicular products represent the relative number of follicles contributing to the pool at a given time. Shapes taper as subordinate follicles regress, leaving only the dominant follicle as the main producer. Episodic pulses of LH are schematic and do not represent actual pulse frequency and amplitude. Hypotheses indicated by arrows in the middle panel are 1) the dominant follicle suppresses its subordinates and emergence of the next follicular wave, and 2) the dominant follicle contributes to self-growth and self-demise. (Reproduced with permission, Adams GP. 1998. *J Reprod Fertil Suppl,* 54:17-32).

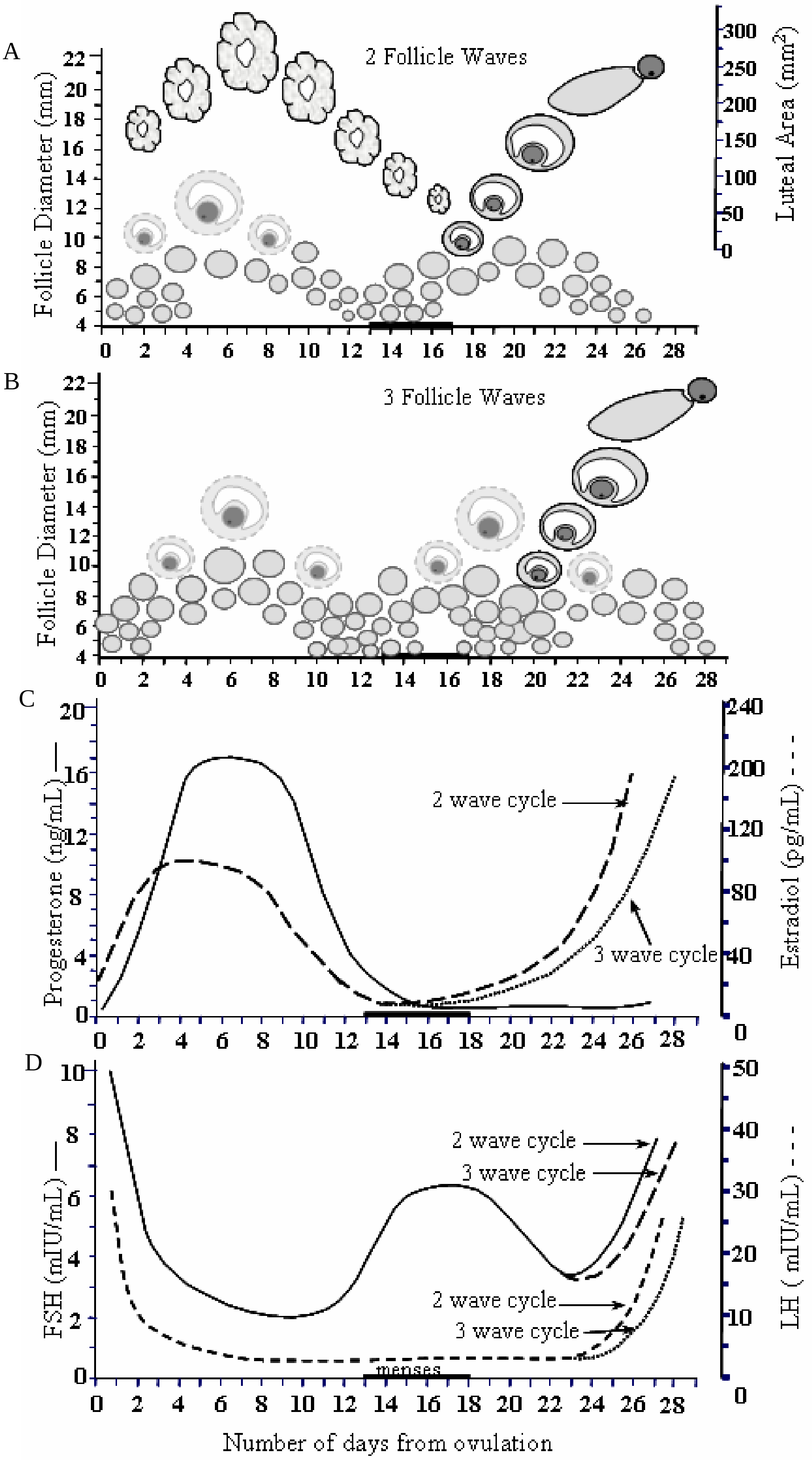

Figure 2. Morphologic and endocrinologic characteristics of ovarian follicular wave dynamics in women. Follicle and luteal dynamics are illustrated in women with 2 (A) and 3 (B) follicle waves during an IOI. Follicles outlined with dashed lines represent major waves that were present in some, but not all women. Serum concentrations of Estradiol and Progesterone in women with 2 and 3 waves are shown (C). Serum concentrations of FSH and LH in women with 2 versus 3 follicle waves during an IOI are shown (D).

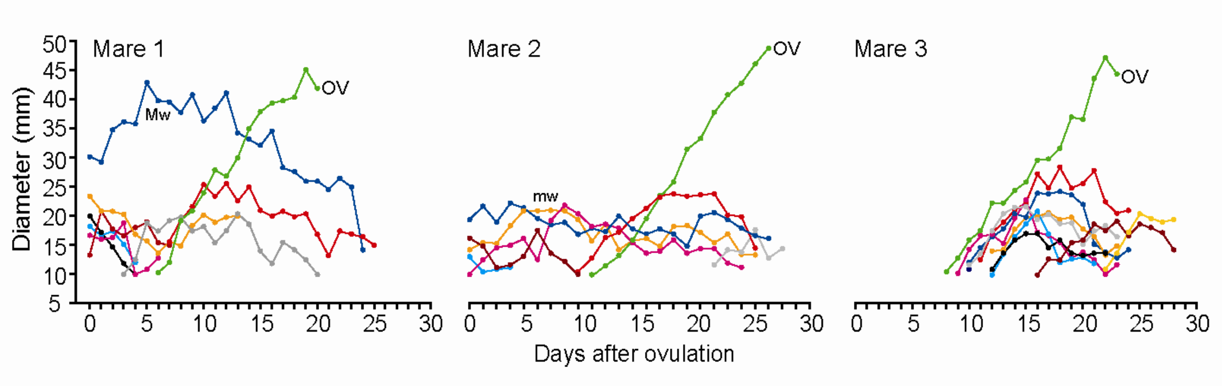

Figure 3. Profiles of individual identified follicles for 3 horse mares during the estrous cycle, starting on the day of the first ovulation and ending 4 days after the second ovulation (OV). Follicles smaller than 10 mm were omitted. A dominant anovulatory follicle of a major wave (Mw) and a minor wave (mw) are shown preceding the ovulatory waves of Mares 1 and 2, respectively. Mare 3 had no significant follicles growing during the first days after ovulation. (Figure courtesy of EL Gastal).

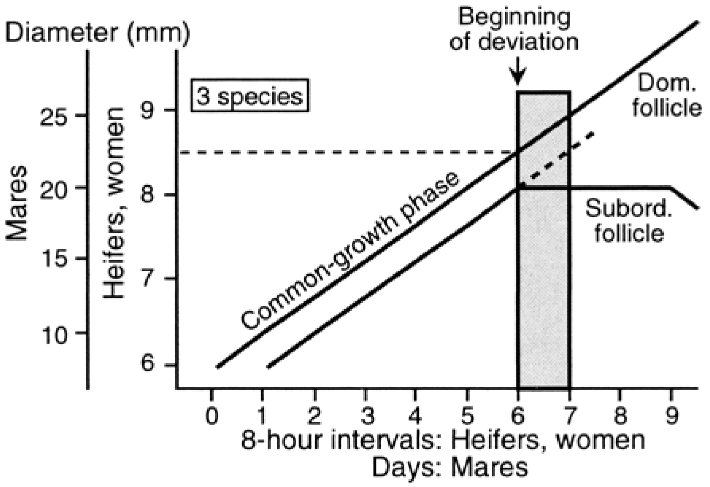

Figure 4. Schematic two-follicle model illustrating the size advantage of the future dominant follicle. Based on limited information, the diameter scale for women is speculated to be similar to the scale for heifers. The extent and duration of parallelism between the two follicles during the common-growth phase varies considerably among individuals and are exaggerated in the illustration. On average, the common-growth phase ends and deviation begins when the largest follicle reaches the indicated diameters. Deviation is established before the next largest follicle can reach a similar diameter, represented by the width of the vertical bar. (Reproduced with permission, Ginther OJ. 2001. *Biol Reprod*, 65:638-647).

## Physiologic mechanisms underling follicle dominance

Physiologic selection of a dominant follicle is a complex phenomenon, which is regulated by endocrine, autocrine and paracrine factors. Most research to characterize the precise mechanisms underlying selection thus far has been performed in animals. Results obtained in women appear consistent with those in domestic farm animals.

The rise in FSH responsible for stimulating follicle recruitment begins to decline in association with selection of the dominant follicle and atresia of subordinates (Santbrink *et al.*, 1995; Gastal *et al.*, 1997; Ginther *et al.*, 1997). The duration and magnitude of the FSH rise above a critical threshold has been shown to determine the number of follicles selected from the recruited cohort (Brown, 1978; Baird, 1987; Fauser and Heusden, 1997). Similar to FSH, heifers and mares exhibit a small but significant transient increase in circulating LH around the time of deviation (Ginther *et al.*, 1998, 2001c). A temporal LH increase associated with follicle selection in women has not been detected.

The dominant follicle exerts both morphologic and functional dominance over other follicles of the wave. Concentrations of circulating estradiol increase with continued growth of the dominant follicle in women, mares and cattle (McNatty, 1981; Baird, 1983;

Santbrink *et al.*, 1995; Gastal *et al.*, 1999; Ginther *et al.*, 2000a). The follicular fluid of dominant follicles in women contains greater estradiol and progesterone levels and lower androstenedione levels than subordinate follicles (McNatty, 1981; Schneyer *et al.*, 2000), consistent with findings in mares (Donadeu and Ginther, 2002). In heifers, however, estradiol and androgen concentrations increase in the developing dominant follicle (Beg *et al.*, 2002). Dominant follicle estradiol production is believed to provide negative feedback on FSH and induce the formation of granulosa cell LH receptors, which initiates a shift from FSH to LH dependency in the dominant follicle (Yamoto *et al.*, 1992b; Xu *et al.*, 1995; Bodensteiner *et al.*, 1996; Gastal *et al.*, 1999, 2000; Sullivan *et al.*, 1999; Ginther *et al.*, 2001b, c). The dominant follicle then becomes unique in its ability to thrive despite decreasing FSH, while the subordinate follicles regress.

Although the dominant follicle plays the major role, all follicles of an emerging wave contribute to suppression of the wave-eliciting surge in FSH in cattle (Ginther *et al.*, 2000b). Follicles within the recruited cohort produce inhibin which further acts to suppress FSH in women, mares and cows (Ginther *et al.*, 2001a). The selection process in women is accompanied by a decrease in circulating inhibin B and increase in inhibin A concentrations (Yamoto *et al.*, 1992a; Roberts *et al.*, 1993; Schneyer *et al.*, 2000). Distinct roles of inhibin A and inhibin B, however, during follicle deviation in the equine and bovine estrous cycle have not been shown (Beg and Ginther, 2006). The role of activin and follistatin in regulating follicle selection in human (Roberts *et al.*, 1993; Schneyer *et al.*, 2000) and domestic farm animals (Donadeu and Ginther, 2002; Glister *et al.*, 2006) has been evaluated. However, results are inconclusive and further investigations are necessary. An increase in free Insulin-like Growth Factor (IGF) in the follicular fluid of the dominant follicle, mediated by IGF binding protein proteases -4/-5 (the bovine equivalent of Pregnancy Associated Plasma Protein-A, PAPP-A) has also been implicated as a candidate for increasing the responsiveness to gonadotropins and thereby initiating follicle selection in cattle and horses (for reviews, see Fortune *et al.*, 2004; Beg and Ginther, 2006). Similarly, studies in women have reported an increase in IGF-II and IGFBP-4 protease (PAPP-A) in association with follicle selection (reviewed in Guidice, 1995).

## Preovulatory follicular growth

The dominant follicle grows at a rate of approximately 1.2 mm/day in cattle, 2.7 mm/day in mares, and 1.8 mm/day in women following its selection until it ovulates at mid-cycle (Ginther *et al.*, 1989a; Gastal *et al.*, 1997; Ginther *et al.*, 2004). The percentage of diameter increase is similar between species, given differences in the size of the leading follicle at deviation. The dominant follicle in women ovulates at a diameter of approximately 20 mm (Pache *et al.*, 1990; Baerwald *et al.*, 2003a). In contrast, the preovulatory diameter of the dominant follicle in the cow is smaller (16 mm) while that in the mare is considerably larger (45 mm).

Growth of the ovulatory dominant follicle results in a rapid elevation of circulating estradiol in cattle, mares and women (McNatty, 1982; Sunderland *et al.*, 1994; Gastal *et al.*, 1999). Estradiol production from the dominant follicle peaks one day before the LH surge in women, three days before the LH surge in mares, and on the day of the LH surge in cattle. Dominant follicle estradiol provides positive feedback at the hypothalamus and pituitary to stimulate the release of LH necessary for inducing ovulation. The estradiol levels in the mid-late follicular phase increase earlier in women with 2 versus 3 follicular waves, and the preovulatory estradiol peak occurs 2 days earlier in women with 2 waves (Baerwald *et al.*, 2003a). Similarly, the preovulatory FSH and LH surges occur 1 day earlier in women with 2 versus 3 follicle waves in association with a shorter cycle length (Baerwald *et al.*, 2003a), similar to previous studies in cattle (Adams, 1999). As LH levels rise in the late follicular phase, the preovulatory follicle in all three species shifts from an estrogen-secreting state into a progesterone secreting state and transformation from follicular cells to luteal cells begins.

## Conclusions and future directions

Waves of antral follicular development have been well-documented in several animal species, including mares and cattle (Ginther, 1993; Fortune, 1994; Adams, 1999). Recent evidence supports the concept of wave patterns of antral follicular recruitment in women (Baerwald *et al.*, 2003a, b, 2005). Patterns of follicular wave emergence in women closely resemble those previously described during the bovine and equine estrous cycle. The number of waves observed depends upon the length of the cycle. Furthermore, the final wave of the IOI is ovulatory, while all preceding waves are anovulatory. Major and minor patterns of follicle waves in women are similar to those observed in the equine estrous cycle. The mechanisms underlying deviation of the dominant follicle from the subordinate follicles are similar in all three species. Thus, both the bovine and equine species have been established as models for studying human ovarian function (Adams and Pierson, 1995; Ginther *et al.*, 2004). Animal models are critical for increasing our understanding of the biologic mechanisms underlying ovarian folliculogenesis, given the practical and ethical limitations in studying human reproductive tissues. The goal of developing animal models for studying human ovarian function is to provide the hypothetical basis for continued research in women, which will ultimately lead to the development of safer and more efficacious infertility and contraceptive therapies. It is further anticipated that future research in women will provide insight into female reproductive function in animal species.

Future studies should be performed to determine the role of the CL in regulating the fate of follicular waves in women and domestic animals. A greater understanding of the roles of paracrine and autocrine factors in regulating ovarian follicular waves is needed. Repeatability of follicle wave patterns have recently been documented during the bovine estrous cycle (Jaiswal *et al.*, 2005) and several follicle endpoints in the equine (Jacob *et al.*, 2008). Currently, we are conducting studies in our laboratory to determine repeatability of follicle wave dynamics in women. The bovine and equine species have recently been established as models for studying reproductive aging in women (Malhi *et al.*, 2005, 2006, 2007; Carnevale, 2008; Ginther *et al.*, 2008a, b). Continued studies in this area may provide insight into age-related changes in human female reproductive potential as well as infertility associated with premature ovarian failure.

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