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Ovarian antral folliculogenesis during the human menstrual cycle: a review

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BACKGROUND: Ovarian follicles undergo dynamic morphologic and endocrinologic changes during the human menstrual cycle. The physiologic mechanisms underlying recruitment and selection of antral follicles in women are not fully elucidated.

METHODS: A comprehensive review of >200 studies was conducted using PubMed. The objective was to compare and contrast different perspectives on human antral folliculogenesis.

RESULTS: Antral folliculogenesis has been studied using histologic, endocrinologic and/or ultrasonographic techniques. Different theories of antral follicle recruitment include: (i) continuous recruitment throughout the menstrual cycle; (ii) recruitment of a 'cohort' of antral follicles once in the late-luteal phase or early-follicular phase of each cycle and (iii) recruitment of two or three 'cohorts' or 'waves' during each cycle. Generally, a single dominant follicle is selected in the mid-follicular phase of each cycle and this follicle ovulates at mid-cycle. However, a dominant follicle may also be selected during anovulatory waves that precede the ovulatory wave in some women.

CONCLUSIONS: There is increasing evidence to indicate that multiple waves of antral follicles develop during the human menstrual cycle. Ovarian follicular waves in women are comparable with those documented in several animal species; however, species-specific differences exist. Enhancing our understanding of the endocrine and paracrine mechanisms underlying antral follicular wave dynamics has clinical implications for understanding age-related changes in reproductive function, optimizing hormonal contraceptive and ovarian stimulation regimens and identifying non-invasive markers of the physiologic status of follicles which are predictive of oocyte competence and assisted reproduction outcomes.

Key words: antral / follicle / menstrual cycle / ovary

Introduction

The earliest descriptions of reproduction came from Hippocrates in the fifth century BC who attested that 'generation' occurred through the joining of the male ejaculate and female menstrual blood (Short, 1977; Cobb, 2006). Over 2 millennia later, William Harvey proclaimed '*ex ovo omnia*'—all things come from the egg (Cobb, 2006). In the late-1600s, a period that heralded the age of enlightenment, Regnier de Graaf recognized the ovary for what it is—the producer of eggs (Cobb, 2006). These early modern scientists, however, held the mistaken belief that the follicle itself was the egg. It was Karl Ernst von Baer, in 1827, who discovered that the mammalian

oocyte was enclosed within the ovarian follicle (Cobb, 2006). It was not until the twentieth century that the human oocyte was discovered and the first descriptions of human ovarian follicular development were made (Block, 1951; Short, 1977).

Much of the current knowledge on ovarian function in women has been extrapolated from studies performed in non-human primates, farm animals and rodents. However technologic advances over the past 60 years have provided non-invasive tools for evaluating ovarian function in women. Early studies to evaluate human folliculogenesis and menstrual cyclicity in the 1950–1970s were based on histologic and/or endocrinologic evaluation of ovarian function (Block, 1951, 1952; Baker, 1963; Bjersing, 1967; Mikhail, 1970; Ross *et al.*, 1970; Baird and Fraser, 1974; Lintern-Moore *et al.*, 1974; Ross, 1974; Baird *et al.*, 1975; Sherman and Korenman, 1975; Gougeon, 1977, 1979; McNatty, 1978; McNatty *et al.*, 1979, 1981a). Histologic assessment of the ovaries provides precise microscopic information about the structural and functional status of follicles at a given point in time. Serum endocrine profiling provides information about folliculogenesis at any given point or over multiple days during the cycle, albeit indirectly. Conceptual models for understanding ovarian function over the menstrual cycle were developed from data obtained using a combination of anatomical and endocrinologic techniques. However, it was not until the development of transabdominal ultrasonography in the late-1970s that the serial growth and regression of follicles could be visualized (Hackeloer and Robinson, 1978; Hackeloer *et al.*, 1979; Hall *et al.*, 1979; O'Herlihy, 1980; Queenan *et al.*, 1980; Renaud *et al.*, 1980; Kerin *et al.*, 1981; Zegers-Hochschild *et al.*, 1984; Lenz, 1985). High-resolution transvaginal ultrasonography, first used in the late-1980s, dramatically improved our ability to visualize ovarian structures *in situ*. Antral follicles as small as 2 mm can now be detected and the growth dynamics of individually identified follicles have been described (Andreotti *et al.*, 1989; Pache *et al.*, 1990; Pierson *et al.*, 1990; Pierson and Chizen, 1991; Martinuk *et al.*, 1992; Bakos *et al.*, 1994; Gore *et al.*, 1995). The resolving power of conventional ultrasonographic imaging is still much less than that of histology, and measurements of follicle size (i.e. diameter, volume) alone provide limited information about ovarian function. However, Doppler ultrasonographic measurements of blood flow (Jokubkiene *et al.*, 2006) and computer-assisted image analyses (Singh *et al.*, 1997, 1998; Rezaei *et al.*, 2009) can provide information about some physiologic aspects of ovarian function. It is the synergistic use of histologic, endocrinologic and ultrasonographic approaches that has been invaluable for elucidating our understanding of antral follicular development during the menstrual cycle.

The objective of the present review is to provide a comprehensive discussion of the different perspectives on antral folliculogenesis during the human menstrual cycle. The patterns and mechanisms of follicular recruitment, selection and ovulation in women are deliberated. Knowledge gleaned from the study of antral folliculogenesis during the estrous cycles of other mammals are considered where human data are not available and for comparative purposes.

Methods

Literature search

A comprehensive review was conducted on ovarian antral follicle dynamics using PubMed. The search criteria used were: antral, antrum, atresia, corpus, cycle, dynamics, endocrine, follicle, follicular, folliculogenesis, histologic, hormonal, hormone, luteal, luteum, menstrual, morphologic, ovary, ovarian, ovulation, paracrine, recruitment, regression, selection, ultrasonographic, ultrasound and/or wave. Searches were limited to the female gender and criteria were identified in the title and/or abstract of the publications. Literature available from 1950 to 2010 was included. Searches were conducted by the primary author and two trained research assistants. Additional journal articles were identified from the bibliographies of studies included as well as textbooks and hand searches of other source materials. No registration number for this review is available.

Study selection process

Approximately 4100 journal articles, case reports and reviews were initially identified. Articles written in English in the field of human medicine were selected first. A separate search was conducted using the same criteria indicated above to include results of research conducted in animals. Duplicated studies were removed. Articles written in a language other than English without available translations were excluded from our review. The titles were first reviewed for relevance to the study of ovarian follicular dynamics. The abstracts of ~610 English and non-English (translated) articles were reviewed. Research conducted to exclusively characterize antral follicle development during ovarian stimulation cycles or hormonal contraception cycles were excluded. Only review articles describing pre-antral follicular development were included. The full-text articles of ~320 studies were further examined. Of these, 246 were deemed relevant and included in our review.

Setting the stage: pre-antral and early antral follicle development

Early descriptions of ovarian follicular development in women were made using histologic evaluation of ovaries postmortem or following oophorectomy. From these studies, the entire duration of human folliculogenesis, from the primordial phase to the pre-ovulatory phase, has been estimated to span >175 days (Gougeon, 1986). Follicular development begins as early as the fourth month of fetal life (Baker, 1963). The primordial germ cells at this time have migrated from the yolk sac endoderm to the gonadal ridge, undergoing mitotic divisions. Once arriving at the gonadal ridge, the oogonia enter the first meiotic division and become primary oocytes. Somatic cells originating from the primitive gonad (i.e. surface epithelial cells, follicular granulosa and theca cells, interstitial cells, fibroblasts) surround the oogonia, forming rudimentary ovarian follicles (<0.1 mm in diameter) (Gougeon, 1979). Follicles containing oocytes arrested in the dictyate stage of meiosis I constitute the ovarian follicular reserve, which provides a woman with reproductive potential for her entire lifetime. The number of follicles occupying the follicular reserve is estimated to be ~7 million at 20 weeks gestation (Baker, 1963). Depletion of the ovarian follicular reserve begins during fetal life and continues throughout a woman's lifetime (Block, 1952; Baker, 1963; Gougeon *et al.*, 1994; Hansen *et al.*, 2008).

The mechanisms underlying the developmental progression of human primordial follicles from the resting to growing state are not fully understood, and are not the focus of the present review. Briefly, currently available evidence is broadly interpreted to mean that the destiny of each follicle is dependent on a delicate balance between the expression and action of factors promoting follicular cell proliferation, growth and differentiation and those promoting

apoptosis; some primordial follicles initiate growth while others remain quiescent for months or years [reviewed by: (Roy and Greenwald, 1996; Fortune, 2003; Aerts and Bols, 2010; Gougeon, epub ahead of print)]. Pre-antral follicles (~0.1–0.2 mm) develop independent of gonadotrophin support [reviewed in Gougeon (1979) and Craig et al., (2007)]. At a diameter of ~0.2–0.4 mm, a fluid-filled cavity (i.e. antrum) begins to develop, and follicles become responsive to gonadotrophins (Gougeon, 1979; Craig et al., 2007). Follicles may develop to the early antral stage throughout fetal life, infancy and childhood, but regress (Peters, 1979; Gougeon, 1996). At puberty, maturation of the hypothalamo-pituitary-gonadal axis results in pulsatile release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary which culminates in the cyclic development of antral follicles ≥2 mm, onset of ovulation and menstrual cyclicity [reviewed in Gougeon (2004) and Messinis (2006)].

Terminology used in describing folliculogenesis

Differing terminology used to describe antral follicular development among studies and among species has led to considerable confusion. For example, in the human literature, the term 'recruitment' has been used to describe three important, but distinctly different, physiologic events: (i) the initial transition of primordial follicles from the resting pool into the pre-antral growth phase, (ii) the cyclic recruitment of a cohort of antral follicles (2–5 mm) during the menstrual cycle following puberty and (iii) the preferential growth of the dominant ovulatory follicle. Follicles comprising a recruited cohort of 2–5 mm follicles have been referred to as 'selectable' follicles (Gougeon, 1996).

Similarly, the term 'selection' has been used to describe two different phenomena: (i) the recruitment of a cohort of 2–5-mm antral follicles and (ii) the preferential growth of a species-specific number of large antral follicles from the recruited cohort. The follicle that is selected from the recruited cohort has been referred to as the 'dominant' (Hodgen, 1982) or 'privileged' (Gougeon, 1986) follicle, while all other follicles of the cohort which undergo atresia have been termed 'ordinary' (Gougeon, 1986), 'challenger' (Gore et al., 1997), 'subdominant' (Gore et al., 1994), or 'subordinate' (Adams, 1999).

In the present review, the terms follicle 'recruitment' and 'selection' are used to represent two different physiologic events. Follicle 'recruitment' refers to the emergence of a group or cohort of medium-size (2–5 mm) antral follicles. 'Selection' refers to the preferential growth of the dominant follicle from the cohort of recruited antral follicles. 'Subordinate' follicles comprise all follicles of the recruited cohort, excluding the dominant follicle. The term 'cohort' is used interchangeably with 'wave'. The term 'recruitment' is used interchangeably with 'emergence'. The term 'interovulatory interval' (IOI) is used to define the time period between successive ovulations (Douglas and Ginther, 1975; Pierson and Ginther, 1987b; Knopf et al., 1989; Baerwald et al., 2003b). In this way, we have attempted to maintain consistency with terminologies used in the human and animal literature.

Antral follicle recruitment

Antral follicles 2–5 mm in diameter have been detected histologically and ultrasonographically throughout the human menstrual cycle (Gougeon and Lefevre, 1983; Chikazawa et al., 1986; Pache et al., 1990; Baerwald et al., 2003a). The pattern of emergence of 2–5 mm follicles, however, is a matter of long-standing debate. Several studies have been conducted to characterize changes in the diameters and numbers of antral follicles during the menstrual cycle. Some investigators have suggested that antral follicles 2–5 mm develop continuously, while others have proposed that 'cohorts' or 'waves' of antral follicles develop in a cyclic manner during the menstrual cycle. Three separate theories of follicular recruitment have been proposed and are presented in detail below.

Continuous recruitment (Theory 1)

Early histological studies in rats (Mandle and Zuckerman, 1950), monkeys (Green and Zuckerman, 1951) and sheep (Turnbull et al., 1977) led investigators to conclude that early antral follicle growth occurred continuously throughout the estrous/menstrual cycle. From these studies in animals, the theory of continuous follicular recruitment evolved for the human menstrual cycle. According to this theory, small antral follicles ≤4–6 mm are recruited to grow continuously, at all stages of reproductive life, independent of gonadotrophins (McNatty, 1981a; Westergaard et al., 1986; Baird, 1987). The follicle destined to ovulate is said to be selected, by chance, from the continuous supply of antral follicles by virtue of being at the right stage of maturity to respond to the rise in FSH (and subsequently LH) that occurs following luteal regression (Wiele et al., 1970; Baird, 1983, 1987) (Fig. 1a).

Cyclic recruitment

Cyclic increases in the number of antral follicles, referred to as 'recruitment of a follicular cohort' or 'follicle wave emergence', have been observed at regular intervals during the menstrual cycle in women (Block, 1951; Gougeon and Lefevre, 1983; McNatty et al., 1983; Baerwald et al., 2003b) and non-human primates (Dizerega and Hodgen, 1981). There is inconsistency in the literature, however, regarding the number of recruitment episodes that occur during the human menstrual cycle.

Single recruitment episode (Theory 2)

Histologic, endocrinologic and early ultrasonographic investigations demonstrated that a cohort of 2–5 mm follicles is recruited from a continuous supply of antral follicles once during each menstrual cycle (Gougeon, 1979; O'Herlihy, 1980; Chikazawa et al., 1986; Pache et al., 1990) (Figs 1b, 2a and b). The single increase in the number of follicles 2–5 mm, detected after regression of the CL in the late-luteal phase or early follicular phase of the menstrual cycle, has been referred to as a 'privileged' phase of follicle development (Gougeon, 1979). It is thought that the recruited cohort represents a group of follicles at comparable, but not identical, stages of development (Fauser and Van Heusden, 1997). Follicles of the recruited cohort are believed to leave the pool of resting primordial follicles around the same period of time several months before (Fauser and Van Heusden, 1997).
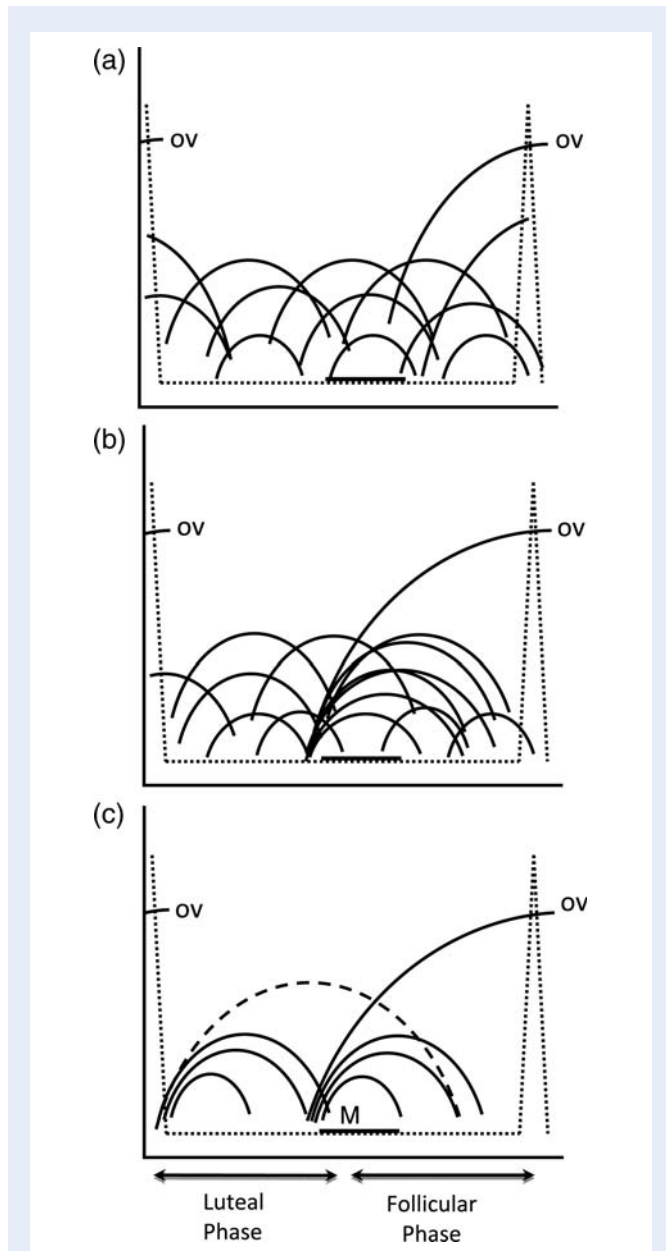
Figure 1 Schematic illustrations of the three different theories of ovarian follicular recruitment during the menstrual/estrous cycle. The theory of continuous recruitment (**a**) suggests that small antral follicles grow and regress constantly throughout the interovulatory interval and the dominant ovulatory follicle is selected, by chance, from the pool following luteal regression. The theory of a single recruitment episode (**b**) suggests that an ovulatory follicle is selected from a single follicular cohort that emerges following luteal regression. The wave theory of follicle recruitment (**c**) suggests that two or more cohorts (i.e. waves) of antral follicles are recruited (i.e. emerge) during the ovarian cycle. The dominant follicle that develops in the final wave of the IOI ovulates while preceding waves are anovulatory; dominant follicles develop in a minority of anovulatory waves (dotted line). M, menses.

Following regression of the CL, luteal estradiol and inhibin fall resulting in a rise in circulating concentrations of FSH (Roseff *et al.*, 1989; Le Nestour *et al.*, 1993). The rise in FSH following luteolysis is

thought to be responsible for preventing atresia of a cohort of 2−5 mm antral follicles in each ovary (Koering, 1969; Hodgen, 1982; McNatty *et al.*, 1983; Gougeon, 1984; Pache *et al.*, 1990; Van Santbrink *et al.*, 1995). The corollary to the notion of preventing atresia is the concept that recruitment is induced by rising FSH; it has been postulated that each follicle and/or woman has a threshold requirement for FSH below which follicle recruitment does not occur (Brown, 1978; Fauser and Van Heusden, 1997). Thus, recruitment of the follicular cohort (through stimulation of growth or prevention of atresia) rather than selection of the dominant follicle occurs in response to a transient elevation in circulating FSH.

Antral fluid from follicles of the recruited cohort contains low concentrations of estradiol but relatively high concentrations of androgens (Gougeon, 1996). Inhibin B produced by granulosa cells in follicles of the recruited cohort (Groome *et al.*, 1996; Fraser *et al.*, 1999; Laven and Fauser, 2004) acts in an endocrine manner to inhibit continued FSH secretion in the mid-follicular phase (Van Santbrink *et al.*, 1995; Groome *et al.*, 1996). By comparison, inhibin A concentrations are low during the follicular phase and maximal during the midluteal phase (Groome *et al.*, 1996), suggesting that the CL is a source of inhibin A.

In the luteal phase of the menstrual cycle in women and non-human primates, estradiol and inhibin A production by the CL is thought to suppress FSH and thereby prevent the development of healthy follicles >4 mm (Savard *et al.*, 1965; Mikhail, 1970; Gougeon and Lefevre, 1983; McNatty *et al.*, 1983; Baird *et al.*, 1984; Chikazawa *et al.*, 1986; McLachlan *et al.*, 1987; Sasano *et al.*, 1989; Basseti *et al.*, 1990; Smith *et al.*, 1990; Roberts *et al.*, 1993; Groome *et al.*, 1996; Sanders and Stouffer, 1997; Devoto *et al.*, 2008). Most antral follicles observed histologically during the luteal phase in women were atretic, leading to the conclusion that there is a limited number of healthy antral follicles that can develop under the influence of the corpus luteum (McNatty *et al.*, 1983). In addition, the development of healthy follicles in the luteal phase has been demonstrated when the CL was enucleated or when exogenous gonadotrophins were administered (Nilsson *et al.*, 1982; Baird *et al.*, 1984; Baird, 1987).

In contrast to primates, large antral follicles develop in some domestic animals throughout the luteal phase (i.e. sheep, cows) (Baird *et al.*, 1975, 1984; Pierson and Ginther, 1987b; Sirois and Fortune, 1988). Estradiol and inhibin production by the CL was thought to be unique to primates (Savard *et al.*, 1965; Mikhail, 1970; Baird *et al.*, 1975; Basseti *et al.*, 1990). Thus, the development of luteal phase follicles and asymmetry in the lengths of the luteal and follicular phases observed in domestic animals (in particular, sheep) were attributed to the absence of estradiol production (and possibly inhibin) by the CL (Short, 1964; Kaltenbach *et al.*, 1967; Baird *et al.*, 1973, 1975). However, a more recent documentation of luteal aromatase activity in mares (Albrecht *et al.*, 1997) has challenged the notion that luteal estradiol production is unique to primates.

Contrary to early histologic and ultrasonographic studies in which a single increase in the number of 2−5 mm follicles was detected in the late-luteal or early-follicular phase (reviewed above), the results of other studies indicated no clear change in the number of antral follicles across the menstrual cycle. In one study, the mean number of antral follicles (referred to as the antral follicle count—AFC) were not different in the early-follicular, late-follicular and luteal phases (Pache *et al.*, 1990). In another study, the numbers of antral follicles 2−5 and
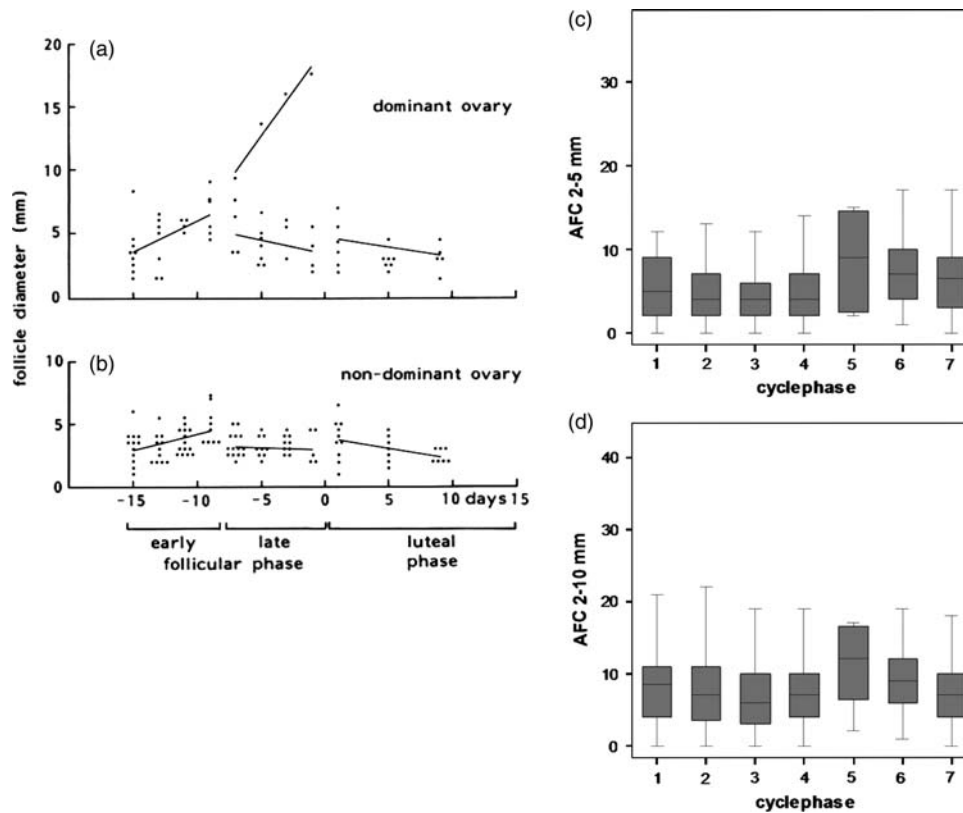
Figure 2 Data regarding the single recruitment episode theory of antral follicle development during the human menstrual cycle. Morphologic changes associated with the selection of a single dominant follicle from the recruited cohort in the mid-follicular phase, followed by ovulation at mid-cycle and limited luteal phase follicle development; data represent a single woman [**a** and **b**; *Reproduced by permission from the American Society for Reproductive Medicine, Pache et al., 1990 Fertil Steril, 54(4):638–42*]. The number of antral follicles 2–5 and 2–10 mm in diameter at different phases of the menstrual cycle [**c** and **d**; *Reproduced with permission from Oxford Journals, Disseldorp et al., 2010, Hum Reprod 25(1): 221–7*].

2–10 mm were not different between the early-, mid- and late-follicular, pre-ovulatory and early-, mid- and late-luteal phases of the cycle (van Disseldorp et al., 2010) (Fig. 2c and d). Non-significant but observable increases in the mean number of antral follicles in the early-luteal phase of the cycle were attributed to inter-individual differences and were considered to be of limited biological importance (van Disseldorp et al., 2010).

Anti-Mullerian hormone (AMH) is produced from the granulosa cells of primary, secondary, pre-antral and early antral follicles (≤ 4 mm). AMH inhibits the initiation of primordial follicle growth from the ovarian reserve (Weenen et al., 2004; Nilsson et al., 2007). Furthermore, in mice, AMH decreases the sensitivity of follicles to FSH thereby inhibiting FSH-induced antral follicle growth (Durlinger et al., 2002). Although not fully understood, AMH may play a role in regulating recruitment of the antral follicular cohort (Visser and Themmen, 2005; Visser et al., 2006).

Follicular waves (Theory 3)

In contrast to the notion of a single recruitment episode during the menstrual cycle in women, multiple cohorts or 'waves' of antral follicle recruitment have been described (Block, 1951; Hackeloer et al., 1979; Dervain, 1980; Queenan et al., 1980; Baerwald et al., 2003a, b)

(Fig. 1c). A 'wave' of follicular development is defined as the synchronous growth of a group of antral follicles that occurs at regular intervals during the menstrual/estrous cycle; follicles in each wave are of similar, but not identical, diameters (Pierson and Ginther, 1987b; Ginther et al., 1989a; Baerwald et al., 2003a; Ginther et al., 2004).

The earliest studies of human follicular dynamics involved histologic evaluations of excised ovaries (Block, 1951; McNatty, 1978, 1981a; McNatty et al., 1983). Two waves of follicle growth >1 mm were detected during the menstrual cycle (Block, 1951). The first wave occurred in the follicular phase and a second wave occurred in the luteal phase. The number of antral follicles >4 mm increased in the late-follicular and late-luteal phases (McNatty, 1978). However, luteal phase follicles had fewer granulosa cells and produced less estradiol compared with those in the follicular phase (McNatty, 1978, 1981a). In another study, antral follicles 1–10 mm were detected in the luteal phase (McNatty et al., 1983). Most follicles were atretic; however, an increase in the number of non-atretic antral follicles >1 mm was reported in the early-luteal versus mid-luteal and late-follicular phases.

Waves of follicle development have been documented in healthy women using transabdominal ultrasonography (Hackeloer et al., 1979; Dervain, 1980). Two waves were detected in women with regular 30–35 day cycles compared with one follicular wave in

women with 26–30 day cycles. Results of a more recent study using serial transvaginal ultrasonography and concurrent endocrine profiling further supported a wave theory of antral folliculogenesis in women (Baerwald *et al.*, 2003b). Emergence of a wave of 4–14 follicles ≥4–5 mm was detected either two or three times during the IOI in a large population of healthy women. Most women (68%) exhibited two waves of follicle recruitment during the IOI, while the remaining women (32%) exhibited three waves. Women with three follicular waves had a mean IOI of 29 days, which was significantly longer than the mean IOI of 27 days in women with two waves. In women with two follicular waves, an anovulatory wave emerged at the time of ovulation (i.e. early-luteal phase) followed by emergence of the ovulatory wave during the early-follicular phase. In women with three waves, an anovulatory wave emerged at the time of ovulation, a second anovulatory wave emerged during the mid- to late-luteal phase and a third wave (the ovulatory wave) emerged in the early- to mid-follicular phase (Baerwald *et al.*, 2003b).

An elevation in circulating FSH appears to precede the recruitment of each follicular wave during the IOI in women (Baerwald *et al.*, 2003a), consistent with previous reports in domestic animals (Adams *et al.*, 1992b; Ginther *et al.*, 1995; Adams, 1999; Gastal *et al.*, 2000; Baerwald *et al.*, 2003a). In cows, the wave-eliciting surge in circulating FSH spans a period of ∼3–4 days and is of similar magnitude among waves (Adams *et al.*, 2008). In contrast to initial expectations, the height of the peak in circulating FSH in cows is inversely related to the number of follicles recruited into a wave (Singh *et al.*, 2004; Burns *et al.*, 2005). The inverse association between circulating FSH and number of follicles in a wave cannot be directly explained by alterations in the secretion of estradiol, inhibin, or insulin-like growth factor (IGF)-I (Burns *et al.*, 2005), but is consistent with the age-related decrease in AFC and elevated serum FSH in women (Klein *et al.*, 1996a; Gougeon, 1998), cattle (Malhi *et al.*, 2005) and sheep (De Souza *et al.*, 1998).

Inhibin B from the granulosa cells of the recruited cohort (Groome *et al.*, 1996; Fraser *et al.*, 1999; Laven and Fauser, 2004) inhibits continued FSH secretion in the mid-follicular phase (Van Santbrink *et al.*, 1995; Groome *et al.*, 1996). A second short-lived peak in inhibin B has been documented 2 days after the mid-cycle LH surge (Groome *et al.*, 1996), providing evidence of a luteal phase wave of follicular growth in women. The precise roles of inhibin A, inhibin B and AMH in regulating the emergence of multiple follicular waves in women are not understood; investigations are currently underway (Baerwald *et al.*, unpublished data).

Follicular waves have been recently detected in women during the perimenopausal transition (Hale *et al.*, 2007; Baerwald *et al.*, unpublished data) and in women undergoing ovarian stimulation therapy (Bentov *et al.*, 2010). Further support for the concept of multiple follicular waves is provided by clinical reports of successful luteal phase oocyte retrieval and *in vitro* maturation as an optional procedure for urgent fertility preservation (Demirtas *et al.*, 2008; Maman *et al.*, 2011). The existence of healthy antral follicles in the luteal phase was attributed to the emergence of a new wave of follicle development in the luteal phase.

Observations of antral follicular waves in women are consistent with those previously documented in several animal species, including cattle (Pierson and Ginther, 1987b, 1988; Sirois and Fortune, 1988; Ginther *et al.*, 1989a), mares (Pierson and Ginther, 1987a; Sirois *et al.*, 1990;

Ginther, 1993), sheep and goats (Ginther *et al.*, 1995; Evans *et al.*, 2000), llamas and alpacas (Adams *et al.*, 1990; Vaughan *et al.*, 2004), musk oxen (Hoare *et al.*, 1997), water buffalo (Taneja *et al.*, 1996), as well as deer and wapiti (Asher *et al.*, 1997; McCorkell *et al.*, 2006). Evidence of follicular waves has also been reported in sub-human primates (Lujan *et al.*, 2006; Bishop *et al.*, 2009). The day of follicular wave emergence is recognized ultrasonographically when the largest follicle of the cohort first attains a diameter of 4–6 mm in women (Baerwald *et al.*, 2003a; Ginther *et al.*, 2004), compared with 4–5 mm in cows (Sirois and Fortune, 1988; Ginther *et al.*, 1989b; Ginther, 2000), 4–5 mm in sheep (Evans *et al.*, 2000) and 13–15 mm in mares (Sirois *et al.*, 1990; Ginther *et al.*, 2004).

Follicle selection

Follicle 'selection' is the process by which a single 'dominant' follicle is chosen from the recruited cohort or wave for preferential growth (Block, 1951; Hodgen, 1982; Chikazawa *et al.*, 1986; Gougeon, 1986; Pache *et al.*, 1990; Van Santbrink *et al.*, 1995; Ginther *et al.*, 2001a; Baerwald *et al.*, 2003a). Follicle selection has generally been documented to occur once in the early- to mid- follicular phase of the menstrual cycle, leading to ovulation (Baird, 1990; Pache *et al.*, 1990; Zeleznik, 2004) (Fig. 2a and b).

Follicle divergence

The dominant and largest subordinate follicles of the ovulatory wave undergo a common growth phase in women, consistent with observations in mares and cows (Ginther *et al.*, 2001a). At the time of selection, the growth profile of the dominant follicle begins to 'diverge' as it continues to grow while the subordinate follicles undergo atresia (Adams *et al.*, 1993; Ginther *et al.*, 2001a). Divergence occurs when the dominant follicle reaches a diameter of ∼10 mm on Day 6–9 of the follicular phase in women (Pache *et al.*, 1990; Van Santbrink *et al.*, 1995; Ginther *et al.*, 2001a; Baerwald *et al.*, 2003a). Morphologic changes in the growth dynamics of dominant and first subordinate follicles in women are similar to that described in other monovular species (cows and mares; Fig. 3) (Adams and Pierson, 1995; Ginther *et al.*, 2001a).

Follicle dominance

Ablation of the dominant follicle in monkeys (Dizerega and Hodgen, 1981) and women (Nilsson *et al.*, 1982; Araki *et al.*, 1983) has been shown to cause a delay in the pre-ovulatory gonadotrophin surge and ovulation by ∼2 weeks. This delay was interpreted to mean that the dominant follicle had already been selected at the time of cautery and that no other follicle was competent to accommodate a timely ovulation. The delay reflected the period of time required for a new group of follicles to be recruited, out of which another dominant follicle was selected and ovulated. Similar follicle ablation studies in cattle have demonstrated that the dominant follicle suppresses the growth of subordinates of the same wave and suppressed emergence of the next follicular wave through an inhibitory effect on circulating FSH concentrations (Adams *et al.*, 1992b, 1993). Collectively, these findings from human and animal studies support the concept that the dominant follicle exerts both morphologic and functional dominance once selection has occurred.
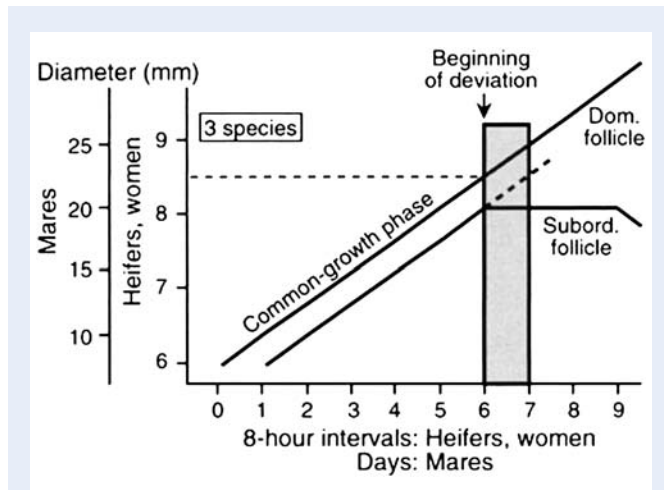
Figure 3 Comparative changes in the diameters of the dominant and first subordinate follicles during the process of follicle selection in women, mares/horses and heifers/cows (day 0 = follicle wave emergence). The dotted horizontal line indicates the diameter at which deviation in follicle growth rates between the dominant and first subordinate follicles occurs (*Reproduced with permission from Elsevier, Ginther et al., 2001, Biol Reprod, 65:648–647*).

Figure 4 Schematic representation of the FSH threshold (window) concept and follicle growth dynamics (recruitment, selection and dominance) during the follicular phase of the menstrual cycle. [*Reproduced with permission from Elsevier, Fauser and Van Heusden, 1997, Endocrine Reviews, 18(1): 71–105; Originally adapted from Baird et al., 1987, J Steroid Biochem, 71(1): 15–23*].

Follicle-stimulating hormone

While an increase in circulating concentrations of FSH is requisite for recruitment of the follicular cohort or wave (Roseff *et al.*, 1989; Adams *et al.*, 1992a; Le Nestour *et al.*, 1993; Van Santbrink *et al.*, 1995; Baerwald *et al.*, 2003a), the nature of the post-surge decline in FSH is a critical factor in selection of the dominant follicle (Adams *et al.*, 1992a, 1993). The duration of the rise in FSH above a critical threshold determines the number of dominant follicles selected from the recruited cohort for preferential growth (Gibbons *et al.*, 1997; Schipper *et al.*, 1998). This concept has been termed the 'FSH Threshold/Window/Gate Concept' (Brown, 1978; Baird, 1987; Schipper *et al.*, 1998) (Fig. 4). The duration that FSH is above the threshold is short for the development of a single dominant follicle. In contrast, widening the FSH window allows multiple follicles to be selected at the same time, as occurs in polyovular species and during ovarian stimulation therapy (Schipper *et al.*, 1998).

There is evidence in women and domestic animals that the dominant follicle has an early size advantage over subordinate follicles (Ginther *et al.*, 1997, 2004; Jaiswal *et al.*, 2004). It has been postulated that the future dominant follicle may contain more granulosa cells and FSH receptors, making it more sensitive to FSH, compared with the subordinate follicles (Fauser and Van Heusden, 1997). Subordinate follicles are not able to thrive in an environment of declining FSH and therefore succumb to atresia (Yamoto *et al.*, 1992a; Roberts *et al.*, 1993; Van Santbrink *et al.*, 1995; Magoffin and Jakimiuk, 1997; Schneyer *et al.*, 2000; Baerwald *et al.*, 2003a). Selection has been described as a phenomenon of avoiding atresia. That is, the selection process may be considered a hierarchical progression of follicle atresia over the period encompassing the rise and fall in FSH. The smallest follicles in the cohort are th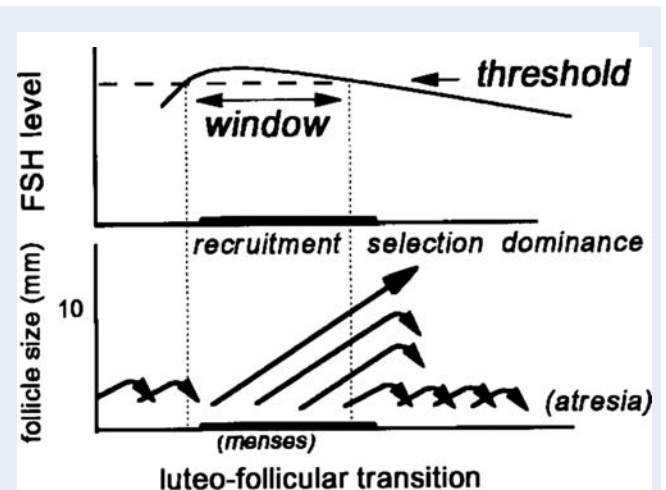e least capable of competing for diminishing levels of FSH and therefore undergo atresia first, followed by regression of progressively larger follicles in the wave until ultimately only one (dominant) follicle survives (Adams *et al.*, 1993; Jaiswal *et al.*, 2004).

Estradiol

By Day 5–8 of the menstrual cycle, aromatase activity begins in granulosa cells of follicles larger than 6–8 mm, with the dominant follicle producing more estradiol-17β than other follicles in the cohort (Mikhail, 1967; Lloyd *et al.*, 1971; Baird and Fraser, 1975; McNatty *et al.*, 1976; Hillier *et al.*, 1981; Chikazawa *et al.*, 1986). The follicular fluid of dominant follicles contains more estrogen and less androgen, while atretic subordinate follicles exhibit a greater androgen/estrogen ratio (Westergaard *et al.*, 1986; Mango *et al.*, 1988; Gougeon, 1996; Van Dessel *et al.*, 1996). LH-induced production of androgens in thecal cells provides the substrate for estradiol production in granulosa cells (Ryan, 1979; Baird, 1987; Adashi, 1994). Estradiol-17β produced from the dominant follicle provides negative feedback on pituitary FSH secretion which contributes, in part, to the mid-follicular phase decrease in circulating FSH and inhibition of subordinate follicle growth (Ginther *et al.*, 2000a). LH receptors form on granulosa cells of the dominant follicle following estradiol secretion (Zeleznik *et al.*, 1974; Bodensteiner *et al.*, 1996). The dominant follicle therefore becomes less dependent on FSH and more responsive to LH during the selection process (Yamoto *et al.*, 1992b; Sullivan *et al.*, 1999; Filicori *et al.*, 2002). Greater production of estradiol and a shift from FSH to LH sensitivity in the dominant follicle in women is consistent with observations in cows and mares (Bodensteiner *et al.*, 1996; Gastal *et al.*, 1999, 2000; Ginther *et al.*, 2000a, 2001b, c).

Transforming growth factor-β (TGF-β) superfamily

Bi-directional communication between the oocyte and cumulus cells regulates both folliculogenesis and oogenesis (Eppig, 2001; Senbon *et al.*, 2003). Oocyte and follicle-derived factors have stage-specific roles in regulating antral follicular development and oocyte competence. Members of the transforming growth factor-β (TGF-β) superfamily, including inhibin, activin, follistatin, TGF-β, bone morphogenic protein (BMP), growth differentiation factor (GDF) and AMH, are among the many growth factors which operate via paracrine and/or autocrine mechanisms to regulate follicular development and oocyte maturation.

All follicles of the cohort produce inhibin B, which contributes to the decrease in FSH that occurs prior to selection (Gibbons *et al.*, 1997; Fraser *et al.*, 1999; Ginther *et al.*, 2000b). However, the role of activin in dominant follicle selection in women is not well elucidated. Activin B is produced by the anterior pituitary and stimulates FSH production from the gonadotropes by autocrine/paracrine mechanisms [reviewed in Bilezikjian *et al.* (2004)]. Activins are also produced by the granulosa cells and have been shown to stimulate granulosa cell proliferation in large and small follicles in rats (Li *et al.*, 1995; Miro and Hillier, 1996). Activin A was shown to cause a time- and dose-dependent inhibitory effect on LH-induced production of progesterone and oxytocin production in bovine granulosa cells *in vitro*, indicating that activin A inhibits spontaneous luteinization in mature antral follicles (Findlay, 1993). Granulosa cell activin A in rats (Hsueh *et al.*, 1987) and humans (Hillier *et al.*, 1991a) was also shown to attenuate LH-dependent androgen production *in vitro* in thecal cells of small to medium size antral follicles, with this effect reversed by follistatin/activin-binding protein. Conversely, granulosa cell inhibin A of selected antral follicles in rodents (Hsueh *et al.*, 1987), domestic animals (Wrathall and Knight, 1995) and humans (Hillier *et al.*, 1991b) increased LH-induced thecal androgen production, which was then thought to serve as the substrate for dominant follicle estradiol production. In contrast to inhibin A, follicular fluid inhibin B peaks at a follicle diameter of 9–10 mm in women (Andersen *et al.*, 2010). Thus, it has been proposed that an orderly transition from an inhibin B/activin follicular environment to an inhibin A/follistatin environment is critical for dominant follicle development in women (Roberts *et al.*, 1993; Groome *et al.*, 1996; Schneyer *et al.*, 2000). Inhibin and activin are involved in regulating follicle selection in domestic animals; however, species-specific differences have been detected in the isoforms involved [reviewed in Ginther *et al.* (2001a) and Mihm and Evans (2008)]. Differences and similarities between the secretion of gonadotrophins, inhibin and estradiol during follicle selection in women, compared and contrasted to that in domestic farm animals, are illustrated in Fig. 5.

Intrafollicular AMH gradually decreases during antral follicular growth until 8–10 mm (i.e. approximate time of selection), when AMH profoundly decreases and remains low thereafter (Andersen *et al.*, 2010). The decrease in intrafollicular AMH during selection of the ovulatory follicle occurs in association with a rise in granulosa cell aromatase expression (Nielsen *et al.*, 2010); higher AMH concentrations have been detected in cumulus versus granulosa cells (Grondahl *et al.*, 2011). It is plausible that the decrease in AMH around the time of selection may release inhibition of aromatase expression; however, the precise roles of AMH in dominant follicle selection are not known.

Research conducted primarily in rodents suggests that granulosa-cell activin and BMP-6 act via autocrine/paracrine mechanisms while oocyte-derived GDF-9, BMP-15, BMP-6 act via paracrine routes to promote granulosa cell proliferation and modulate FSH-dependent follicle function [reviewed in Knight and Glister (2006)]. It is proposed that differential exposure to these signaling molecules may be one of the ways in which the dominant follicle is sensitized to FSH and thereby selected for preferential growth.

Insulin-like growth factor (IGF) system

The IGF system plays an important role in the intraovarian regulation of antral follicular development. Circulating levels of IGF-I and IGF-II have not been shown to differ during the human menstrual cycle (Jesionowska *et al.*, 1990). However, changes in follicular fluid IGF concentrations have been reported (Eden *et al.*, 1988). Both IGF-I and II have been shown *in vitro* to have effects on ovarian follicular function; however, IGF-II appears to be the primary IGF in primate ovaries. IGF-I and II mRNA have been detected in thecal cells from small antral follicles, but only IGF II mRNA has been detected in the granulosa cells of dominant follicles (El-Roeiy *et al.*, 1993).

IGF-II increases in the dominant follicle at the time of selection. Simultaneously, its bioavailability is increased via proteolysis of insulin-like growth factor-binding protein-4 (IGFBP-4) by IGFBP-4 protease (Poretsky *et al.*, 1999; Giudice, 2001). IGF II (and also IGF-I) stimulates aromatase activity, estradiol and progesterone production in human granulosa cells and promotes androgen production in the thecal cells of the growing dominant follicle. In subordinate follicles, IGF is sequestered by IGFBP-4, granulosa and thecal cell steroidogenesis is inhibited, and atresia ensues (Iwashita *et al.*, 1996; Mason *et al.*, 1998; Poretsky *et al.*, 1999; Hourvitz *et al.*, 2000). The role of IGF-I and II in regulating antral follicle development in women is similar to that described in rodent and domestic animal species (Poretsky *et al.*, 1999; Fortune *et al.*, 2004; Beg and Ginther, 2006). There is further evidence in rodents to suggest that follicular activin, GDF-9, AMH and BMPs may regulate dominant follicle selection by modulating granulosa cell IGF-dependent signaling pathways [reviewed in Knight and Glister (2006)].

Although current data on the role of paracrine and autocrine factors in regulating physiologic selection of the dominant follicle show general similarities among species, inconsistencies have been reported. Continued research is required to elucidate the precise roles of intraovarian factors in modulating antral folliculogenesis.

Luteal influences on follicle selection

Numerous studies have been conducted to determine whether the presence of the CL influences selection of the dominant follicle. Seven out of eight dominant follicles were reported to develop contralateral to the CL from the previous ovulation in women (Chikazawa *et al.*, 1986). Dominant follicles which developed contralateral to the previous ovulation have been shown to exhibit higher estradiol/androstenedione ratios than dominant follicles that developed ipsilateral to the previous CL (Fukuda *et al.*, 1996). Furthermore, pregnancy rates in natural cycles following insemination and IVF were found to be higher when the ovulatory follicle developed contralateral to the CL
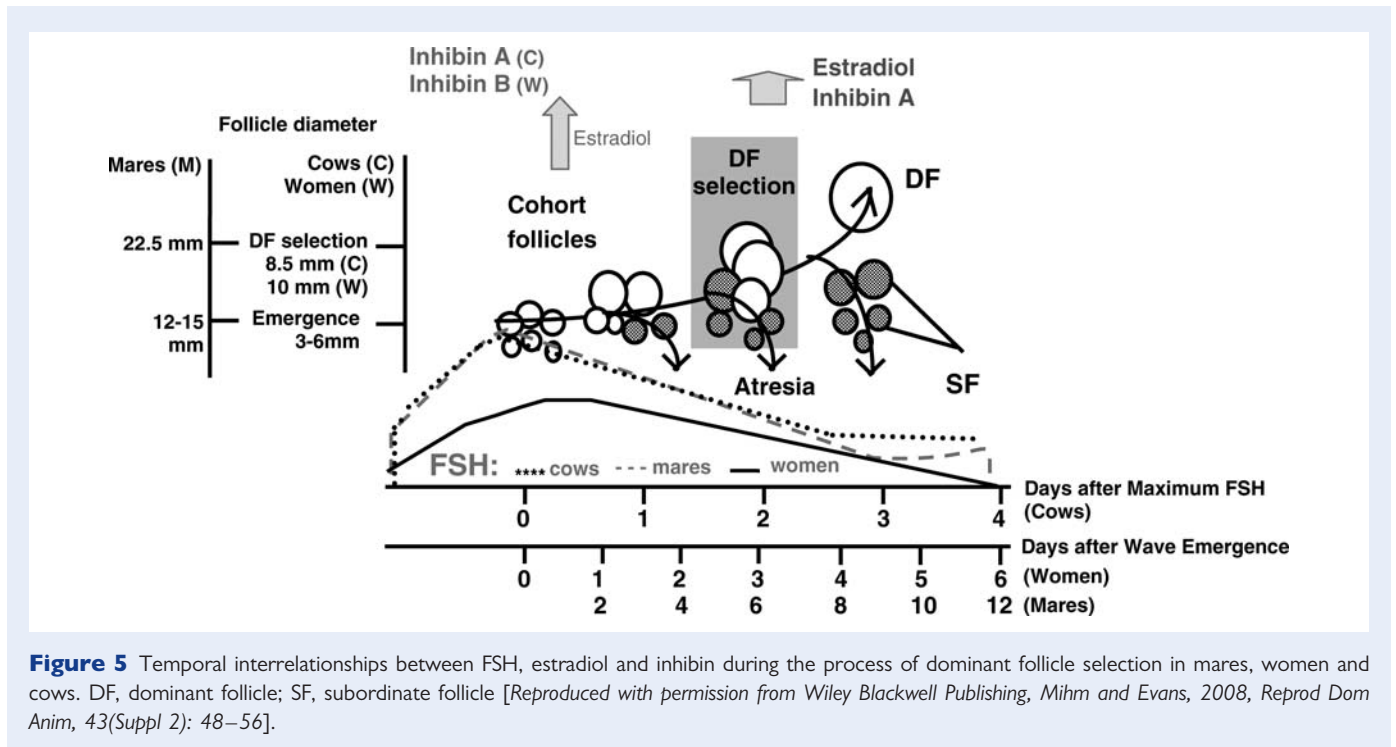
Figure 5 Temporal interrelationships between FSH, estradiol and inhibin during the process of dominant follicle selection in mares, women and cows. DF, dominant follicle; SF, subordinate follicle [*Reproduced with permission from Wiley Blackwell Publishing, Mihm and Evans, 2008, Reprod Dom Anim, 43(Suppl 2): 48–56*].
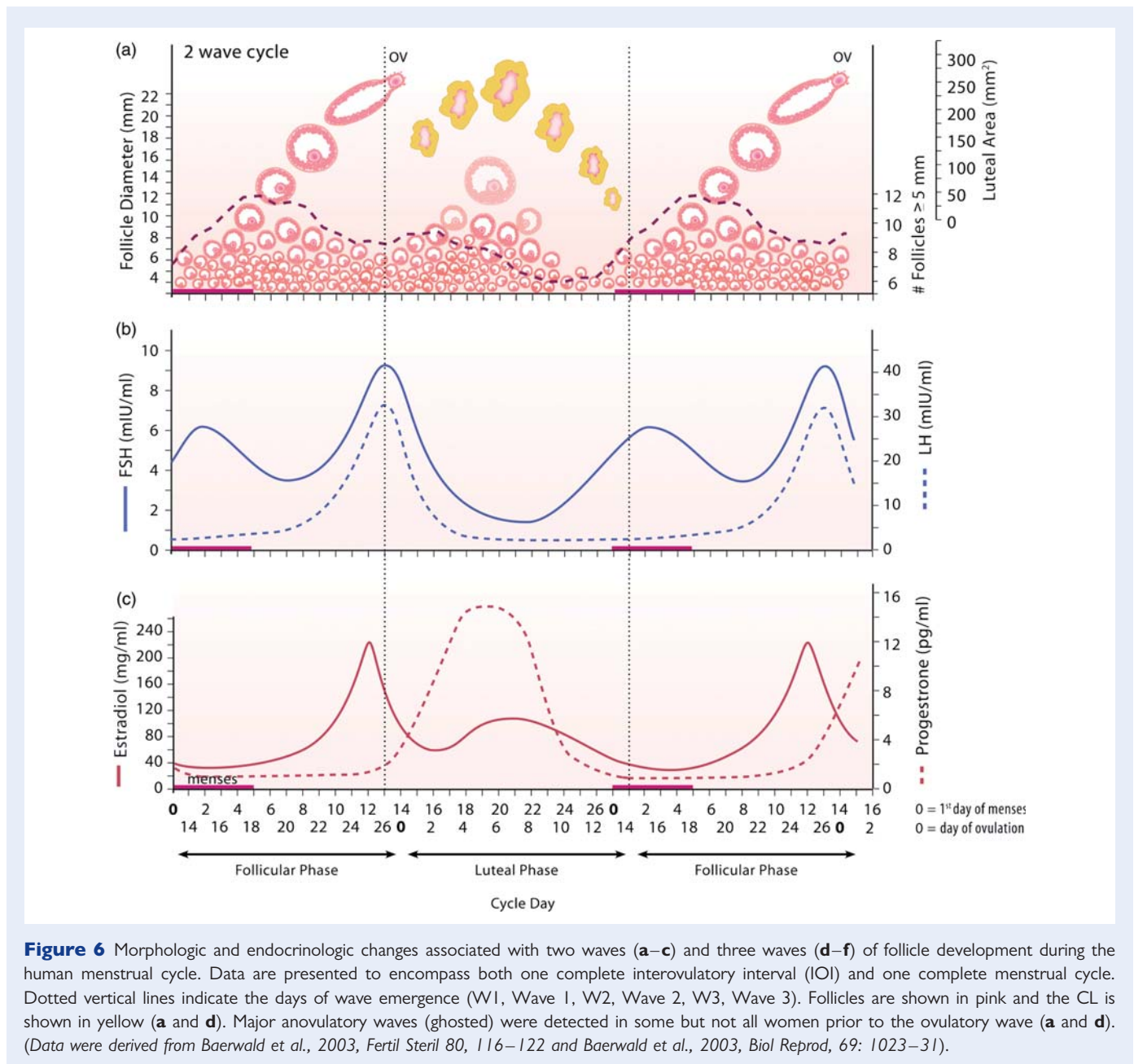
from the previous ovulation (Fukuda *et al.*, 1996). Evaluations of ovulation in both infertile and fertile women, however, support the notion that follicle selection and subsequent ovulation occurs randomly between the right and left ovaries (Baird, 1987; Check *et al.*, 1991; Ecochard and Gougeon, 2000; Ojha *et al.*, 2000; Baerwald *et al.*, 2003a), similar to findings in domestic animal species (Adams *et al.*, 2008).

Selection of a dominant follicle has been generally described to occur once in the early- to mid-follicular phase of the menstrual cycle (Gougeon and Lefevre, 1983; Baird, 1990). However, selection has been observed more than once during natural menstrual cycles in some healthy women (Baerwald *et al.*, 2003a). Major and minor waves of follicle growth were characterized in healthy women of reproductive age (Baerwald *et al.*, 2003a; Ginther *et al.*, 2004). Major waves were those in which a dominant follicle was selected, and minor waves were those in which dominance was not manifest. Most women developed a major ovulatory wave in the follicular phase and 1 or 2 minor anovulatory waves in the preceding luteal phase. However, 1 or 2 dominant follicles developed and subsequently regressed prior to selection of the ovulatory follicle in nearly a quarter of natural menstrual cycles (Baerwald *et al.*, 2003a). Reports of major anovulatory waves developing spontaneously prior to the ovulatory follicular wave in some, but not all, women are similar to follicular dynamics in mares (Ginther *et al.*, 2004), despite differences in luteal phase lengths between these species.

The role of the CL in regulating follicular wave dynamics has been studied in women and domestic farm animals. No differences in the size or lifespan of the CL, progesterone secretion or luteal phase estradiol secretion were detected in women with two versus three waves or in women with major versus minor waves preceding the ovulatory wave (Baerwald *et al.*, 2005). However, the presence of the CL appeared to influence dominant follicle selection in women

with three waves. When the second of three waves emerged in the mid-luteal phase, selection of a dominant follicle did not occur (i.e. a minor anovulatory wave developed) (Baerwald *et al.*, 2003a). By comparison, when the second wave emerged in the late-luteal or early-follicular phase, a dominant follicle was selected (i.e. a major anovulatory wave developed) (Baerwald *et al.*, 2003a). In contrast to women, one or two major anovulatory waves develop during the luteal phase of all estrous cycles in cows; minor waves have not been observed (Pierson and Ginther, 1987b; Ginther *et al.*, 1989a, 2004; Baerwald *et al.*, 2003a). Luteal regression and progesterone withdrawal occurs later in cows with three versus two follicular waves, at which time the viable dominant follicle present goes on to ovulate [reviewed in Adams *et al.* (2008)].

The functional status of dominant follicles that develop during anovulatory waves preceding the ovulatory wave in women is not fully understood. Estradiol levels have been shown to increase in association with the emergence of anovulatory follicle waves during the luteal and early-follicular phases of the cycle (Baerwald *et al.*, 2003a); however, the source of the estradiol (i.e. follicle versus corpus luteum) is not known. In a preliminary study, no differences in circulating estradiol concentrations were observed in the luteal phase of women with anovulatory major waves versus minor waves (Ginther *et al.*, 2005); however, data from a larger sample of women are required to either confirm or refute the preliminary inference. Ultrasonographic image attributes of dominant follicles have been found to differ between anovulatory and ovulatory waves (Rezaei *et al.*, 2009). Taken together, these data suggest that dominant follicles of anovulatory waves may exhibit different physiologic characteristics than dominant follicles of ovulatory waves in women. The morphologic and endocrinologic changes occurring in association with the development of follicle waves during the human menstrual cycle are illustrated in Fig. 6.

Figure 6 Morphologic and endocrinologic changes associated with two waves (**a**–**c**) and three waves (**d**–**f**) of follicle development during the human menstrual cycle. Data are presented to encompass both one complete interovulatory interval (IOI) and one complete menstrual cycle. Dotted vertical lines indicate the days of wave emergence (W1, Wave 1, W2, Wave 2, W3, Wave 3). Follicles are shown in pink and the CL is shown in yellow (**a** and **d**). Major anovulatory waves (ghosted) were detected in some but not all women prior to the ovulatory wave (**a** and **d**). (*Data were derived from Baerwald et al., 2003, Fertil Steril 80, 116–122 and Baerwald et al., 2003, Biol Reprod, 69: 1023–31*).

Pre-ovulatory follicle development

The dominant follicle of the final follicular phase wave continues to develop after it is selected and reaches pre-ovulatory status at a diameter of 16–29 mm in the late-follicular phase (Renaud *et al.*, 1980; Kerin *et al.*, 1981; Lenz, 1985; Gougeon, 1986; Pache *et al.*, 1990; Bakos *et al.*, 1994; Baerwald *et al.*, 2003b). The ovulatory follicle grows at a rate of 1–4 mm/day, with reports of increases, decreases or no change in growth rate in the few days leading up to ovulation (Hackeloer *et al.*, 1979; Renaud *et al.*, 1980; Gougeon and Lefevre, 1983; Bomsel-Helmreich, 1985; Rossavik and Gibbons, 1985; Doody *et al.*, 1987; Pache *et al.*, 1990; Bakos *et al.*, 1994; Baerwald *et al.*, 2009). The dominant ovulatory follicle

grows slightly faster after selection compared with before (Baerwald *et al.*, 2009).

Preferential growth of the dominant follicle in the mid-late-follicular phase is associated with increased aromatase activity and a rapid elevation of circulating and follicular fluid estradiol-17β (Bomsel-Helmreich *et al.*, 1979; Hackeloer *et al.*, 1979; Kerin *et al.*, 1981; McNatty, 1981a; Chikazawa *et al.*, 1986; Bakos *et al.*, 1994; Van Dessel *et al.*, 1996; Baerwald *et al.*, 2003a). Greater gonadotrophin responsiveness in the dominant follicle, compared with subordinate follicles, is responsible for mediating dominant follicle granulosa cell estradiol production, LH receptor expression and continued pre-ovulatory growth (McNatty, 1981b; Baird, 1983; Yamoto *et al.*, 1992b; Van Santbrink *et al.*, 1995; Van Dessel *et al.*, 1996; Sullivan *et al.*, 1999; Ginther *et al.*, 2000a; Filicori, 2002). The dominant follicle
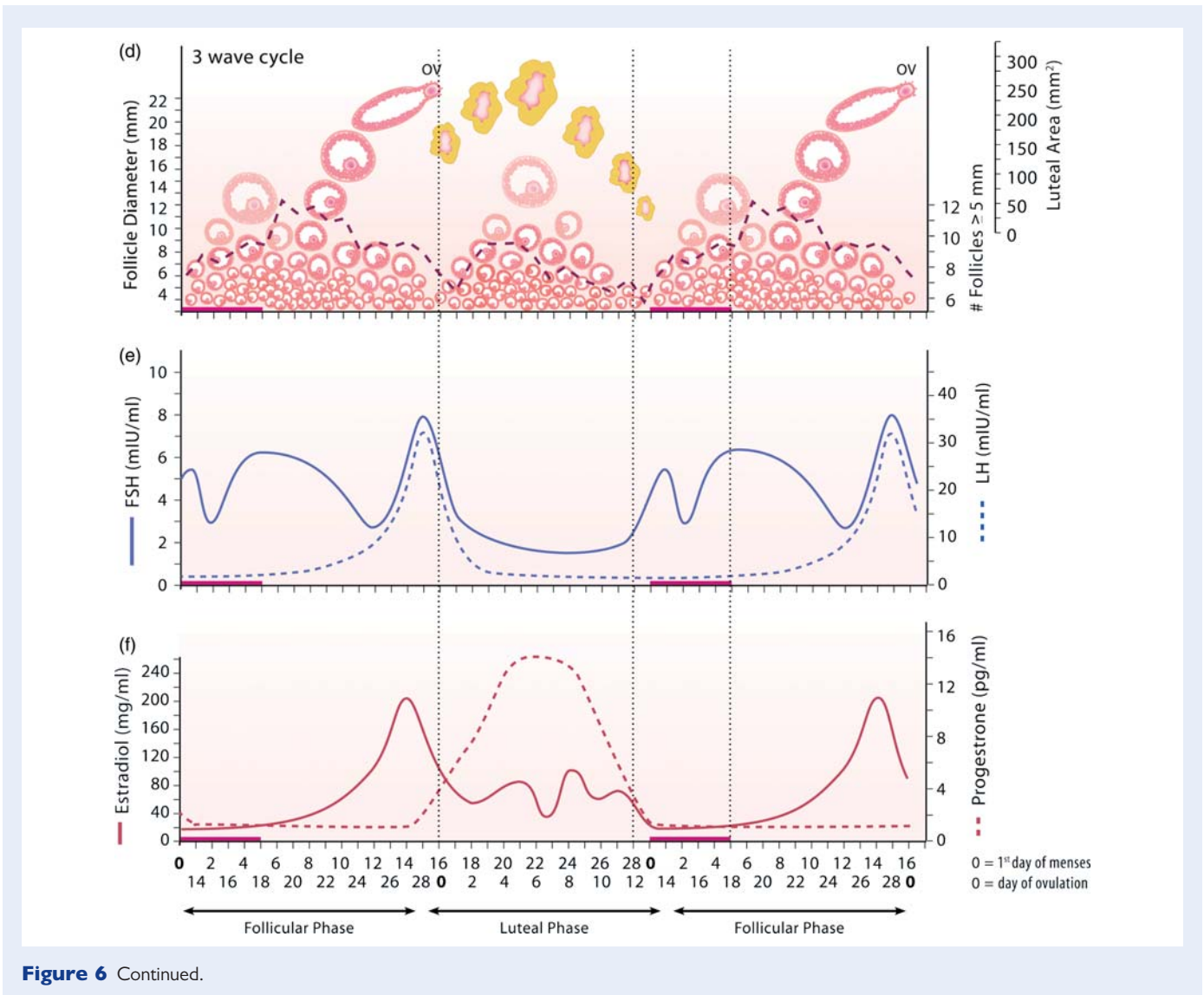
Figure 6 Continued.

is responsible for over 90% of the estrogen production in the pre-ovulatory period (Baird and Fraser, 1974).

Both intraovarian and endocrine factors contribute to pre-ovulatory follicle growth. The increase in granulosa cell aromatase mRNA expression in the dominant pre-ovulatory follicle is inversely related to follicular fluid AMH concentrations (Nielsen et al., 2010). Increasing levels of inhibin A stimulate thecal cell androgen production, which acts as the substrate for continued estradiol secretion (Hillier et al., 1991a; Roberts et al., 1993; Schneyer et al., 2000). IGF-II mRNA is abundantly expressed by granulosa cells of pre-ovulatory follicles (Geisthovel et al., 1989) and stimulates aromatase activity (Hernandez et al., 1992). Oocyte-derived GDF-9 and BMP-15 appear to be required for follicle development to the ovulatory stage (Juengel et al., 2002), and BMP-15 may be involved in cumulus expansion (Gueripel et al., 2006).

Estradiol production from the dominant follicle peaks the day before the LH surge (Wiele et al., 1970; Bomsel-Helmreich et al., 1979) providing positive feedback at the hypothalamus and pituitary to stimulate the surge of LH necessary for inducing ovulation. The highly vascularized pre-ovulatory follicle, which has acquired LH receptors, is now able to respond to the mid-cycle rise in LH (McNatty, 1978; Bomsel-Helmreich et al., 1979; Tsang et al., 1979). Ovulation occurs, on average, within 24 h of the LH peak (Kerin et al., 1981). Serum progesterone concentrations begin to rise after the pre-ovulatory estradiol peak but before the LH surge, and indicate the onset of follicular luteinization (McNatty, 1978; Bomsel-Helmreich et al., 1979; Brailly et al., 1981; Chikazawa et al., 1986; Westergaard et al., 1986). Interactions between LH and EGF in the granulosa cell cytoplasm stimulate expression of extracellular-regulated protein kinases 1 and 2, which are believed to mediate a decrease in granulosa cell proliferation and estrogen synthesis, an increase in cumulus expansion and progesterone secretion and ultimately ovulation (Duggavathi and Murphy, 2009).

Discussion

Research conducted over the past 60 years using histologic, endocrinologic and ultrasonographic techniques has profoundly increased our understanding of antral ovarian folliculogenesis in women.

Different theories have emerged regarding the patterns in which antral follicles develop during the human menstrual cycle. However, comprehensive review of the literature shows similar trends among studies and among species. The following sections highlight common themes among research and suggest areas where continued investigations are required.

Animal models for the study of antral follicular dynamics in women

The study of human ovarian function is limited by ethical and practical considerations. Therefore, non-human primate, rodent and domestic farm animal models have been used to make inferences about follicular dynamics in women (Mandle and Zuckerman, 1950; McNatty, 1981b; Hodgen, 1982; Adams and Pierson, 1995; Bartlewski et al., 1999; Menezo and Herubel, 2002; Ginther et al., 2004; Ginther et al., 2005; Baerwald, 2008). While the use of animal models has increased our understanding of antral follicular dynamics in women, it is important to recognize similarities and differences in physiologic function as well as differences in research methodologies employed between species. In women, the presence of endometrial shedding and symmetric luteal and follicular phases are different from that observed during the estrous cycles of domestic farm animals. Despite these differences, general similarities in antral follicular dynamics exist. It is important to note that a continuous pattern of antral follicle development was originally proposed in domestic livestock species, similar to that shown in Fig. 1a. However, the use of frequent serial high-resolution ultrasonography and simultaneous endocrine profiling in these animal species has resulted in a broad understanding of follicular wave dynamics (Fig. 1c). Follicular waves have now been described in every species (including humans) in which this approach has been used. The number of follicular waves that develop appears to be species-specific and is positively correlated with the length of the menstrual/estrous cycle. Furthermore, despite a proportionately longer luteal phase in cows and mares, the growth phase of the dominant ovulatory follicle (defined as the time period from wave emergence to ovulation) is comparable in the human, cow and mare (Adams, 1999; Baerwald et al., 2003a; Ginther et al., 2004).

Critical studies of the characteristics and control of ovarian follicular and luteal dynamics in domestic farm animals have involved frequent (i.e. daily or multiple times a day) blood sampling and ultrasonography (Pierson and Ginther, 1987b; Sirois and Fortune, 1988; Ginther et al., 1989b; Sirois et al., 1990; Adams et al., 1992a; Ginther et al., 1998, 2000a, 2001c; Adams et al., 2008). Studies of this nature in women are difficult, and often unethical, to conduct. Differences in antral folliculogenesis between humans and animals appear to be more in detail rather than in essence, and may reflect differences in intrinsic physiology and/or differences in our ability to detect changes in ovarian function. Future studies should be conducted to compare endocrinologic and morphologic aspects of antral follicular wave dynamics at focused periods of the menstrual and estrous cycles in women and domestic farm species. This approach will continue to provide valuable insight for hypothesis testing and experimental design.

The relatively large diameters of antral follicles in cows and mares, compared with monkeys, sheep and rodents provide greater feasibility for characterizing antral follicular dynamics ultrasonographically. Thus, at present, cows and mares may be the most appropriate models for the ultrasonographic study of antral follicular dynamics in women (Adams and Pierson, 1995; Ginther et al., 2004)

Continuous versus wave patterns of follicular recruitment

Discrepancies among studies about the continuous versus cyclic nature of antral follicular recruitment in women may, in part, be attributed to methodological challenges associated with serially monitoring follicles <6 mm. Serial ultrasonographic evaluation of antral follicle growth 2–5 mm is technically difficult due to the large quantity of these follicles present in the ovaries throughout the cycle. Follicle waves were most readily detected when follicles ≥5 mm were evaluated; waves were not as obvious when follicles <5 mm were analyzed (Baerwald et al., 2003a). Quantifying the growth of 2–3 mm follicles is near the detection limit of current ultrasound equipment, and there is a great deal of error in detecting these small follicles in women. It is interesting that 1–3 mm follicles have been shown to develop in a wave-like manner in association with surges in plasma concentrations of FSH waves in cattle (Jaiswal et al., 2004). Similar ultrasonographic studies in women have not been conducted. As non-invasive imaging technology improves, future research should be directed at carefully characterizing the dynamics of antral follicles <5 mm during the menstrual cycle. Further characterization of the endocrine and paracrine mechanisms underlying follicular waves in women is also required. Elucidation of a third subtle, but significant, FSH peak and fluctuations in luteal phase estradiol in women with three follicle waves is of particular interest (Baerwald et al., 2003a).

Comprehensive comparisons of data that describe continuous, single and multiple waves of antral follicular recruitment show similar trends. We believe that inconsistencies in descriptions of antral follicular growth are attributable to differences in study designs employed, statistical methods used and interpretations of data. For example, it is plausible that the data from one woman, interpreted as a single recruitment episode (Fig. 2a and b), may actually represent two follicle waves, a major ovulatory wave in the follicular phase followed by a minor anovulatory wave in the luteal phase. No differences in AFC were detected during the cycle in this study; however, AFC was compared at only the early-follicular, late-follicular and luteal phases of the cycle. The grouping of data into three categories versus daily data collection for the entire cycle could have masked changes in the number of antral follicles that occurred. Similarly, when AFC data were grouped into seven different phases of the cycle (Fig. 2c and d), no differences in AFC (2–5 or 2–10 mm) were detected. A non-significant increase in AFC in the early-luteal phase was observed, but was attributed to inter-individual differences and not considered to be biologically relevant. In contrast, significant changes in AFC during the cycle have been reported in other studies (Block, 1951; McNatty et al., 1983; Baerwald et al., 2003b). It therefore appears that evaluation of daily or more frequent changes in AFC, follicle size and/or hormone concentrations throughout the cycle may more readily enable the detection of follicle waves while data grouped into phases of the cycle may not.

Further characterization of the daily changes in AFC during the menstrual cycle has important implications for determining the most appropriate time to consistently measure AFC as a predictor of response to ovarian stimulation (Verhagen et al., 2008). Knowledge

of multiple follicular waves during the menstrual cycle provides a rationale for the notion that ovarian stimulation therapy can be initiated at different times during the cycle. The plausibility of initiating ovarian stimulation therapy during the luteal phase in women is supported by reports that multiple dominant follicles were induced to grow following FSH administration in the early-luteal phase of monkeys (Dizerega and Hodgen, 1980). Rationale for luteal phase ovarian stimulation protocols in women is further provided by knowledge of the routine early-luteal phase initiation of ovarian stimulation in domestic farm animals (Adams et al., 1994b). Synchronizing ovarian stimulation therapy with wave emergence has been shown to optimize follicular responses in both cattle (Nasser et al., 1993) and in women with a history of a poor response to treatment (Baerwald et al., 2010).

Follicle selection in anovulatory waves

It has been generally accepted that follicle selection occurs only once during the menstrual cycle (Gougeon and Lefevre, 1983; Baird, 1990; Pache et al., 1990). However, more recent research suggests that selection may occur more than once in approximately one-quarter of apparently healthy women (Baerwald et al., 2003a). These findings are similar to domestic farm animals; in particular, mares (Ginther, 1993; Ginther et al., 2004). It is plausible that follicular dynamics in women of reproductive age may be more variable than previously thought. The functional status and ovulatory potential of follicles comprising anovulatory follicular waves requires further evaluation, considering earlier evidence that the majority of luteal phase follicles in women were atretic (McNatty et al., 1983). In animals, antral follicle dynamics are influenced by environmental factors such as energy balance, temperature and exposure to endocrine disrupting chemicals (Frisch, 1985; Mackey et al., 2000; Armstrong et al., 2003; De et al., 2008; Kwintkiewicz and Giudice, 2009). However, the effects of environmental factors on human antral folliculogenesis are not well understood.

Role of the corpus luteum in regulating antral follicular development

Observations of multiple follicle waves during the menstrual cycle and the development of more than one dominant follicle in some women have challenged the notion of luteal inhibition of antral follicular development in primates. Therefore, future research should be conducted to confirm species-specific differences in luteal regulation of antral follicular dynamics. Evidence of aromatase activity in the mare CL (Albrecht et al., 1997) provides a rationale for research to confirm whether the CL of other domestic animals produces estradiol and to determine its potential roles in regulating antral folliculogenesis. It is important to clarify whether the estradiol increase that occurs in association with anovulatory waves in women is of follicular or luteal origin. Furthermore, the precise roles of luteal inhibin in regulating antral follicular wave dynamics in women are unknown.

Repeatability in the follicular wave pattern

Knowledge about the repeatability of follicular waves in women is fundamental for designing future studies to elucidate the mechanisms underlying follicular wave dynamics and to predict the number of waves that a woman may develop in a given cycle. The consistency, or lack thereof, in the number of waves that develop per cycle has

clinical implications for optimizing strategies which manipulate ovarian follicular development, such as hormonal contraceptive and ovarian stimulation regimens. Studies in cattle have revealed that the number of follicle waves per estrous cycle is fairly consistent within individuals (Singh et al., 2004; Jaiswal et al., 2009). Similar research in women is ongoing (Baerwald et al., unpublished data).

The pre-pubertal and pubertal period

Human follicular development occurs to the early antral stage during infancy and childhood (Peters et al., 1978). The first few menstrual cycles during puberty may be anovulatory due to incomplete maturation of the hypothalamo-pituitary-axis and the inability to adequately produce LH. In comparison, repeated anovulatory waves of antral follicle development have been documented in pre-pubertal calves, as early as 2 weeks of age (Adams et al., 1994a; Evans et al., 1994). Follicular dynamics in pre-pubertal and pubertal girls remain poorly understood due to ethical and technical constraints on conducting reproductive research in this population. Our understanding of pubertal disorders would be greatly enhanced by the elucidation of ovarian function during the prepubertal and pubertal phases of development.

Reproductive senescence

The age-related decrease in ovarian reserve correlates with a decrease in the number of antral follicles 2–10 mm in diameter (Scheffer et al., 1999). A decrease in the AFC in perimenopausal women results in a reduction in circulating inhibin B, AMH and IGF-I and a correspondent increase in FSH and cycle irregularity; estradiol levels remain the same or are elevated (Lee et al., 1988; Ahmed Ebbiary et al., 1994; Klein et al., 1996a, b, c; Scheffer et al., 1999; Klein et al., 2000; Erdem et al., 2002; Broekmans et al., 2004; Van Rooij et al., 2005; Visser et al., 2006). Continued depletion of the AFC results in a continued decline in inhibin B, increasing FSH and LH, decreasing estradiol and progesterone and loss of menstrual cyclicity culminating in menopause at ~51 years of age [reviewed in Broekmans et al. (2009)].

In women, increasing age has been associated with higher mitotic activity of granulosa cells in small antral follicles (Gougeon, 1998), earlier selection of the dominant follicle, a shorter follicular phase, shorter menstrual cycle, anovulation and an increased incidence of dizygotic twinning (Lenton et al., 1984; Klein et al., 1996a, 2002; Beemsterboer et al., 2006; Brodin et al., 2007). Earlier selection of the dominant ovulatory follicle in aging women has been attributed to a faster growth rate of the dominant follicle (Gougeon, 2005) or earlier emergence of the follicular cohort in the luteal phase of the preceding cycle (Van Zonneveld et al., 2003). Similar age-related changes in ovarian function have been reported in mares (Carnevale, 2008) and cows (Malhi et al., 2005, 2006, 2007).

Age-related changes in antral follicle dynamics are not fully understood. Research to characterize age-related changes in follicular wave dynamics may explain the earlier selection of the dominant follicle and shorter follicular phases (described above), as well as abnormal ovulation, estradiol secretion and cyclicity observed in women of advanced reproductive age (Santoro et al., 2003; Hale et al., 2009). It is plausible that women with more follicular waves during their cycles may undergo menopause earlier; however, research to test this hypothesis has not yet been conducted.

Summary

Theories of continuous versus cyclic antral follicle recruitment during the human menstrual cycle have been proposed. There is increasing evidence to suggest that multiple cohorts (also referred to as 'waves') of antral follicles are recruited (i.e. emerge) during the menstrual cycle. Observations of ovarian follicular waves in women are comparable with those documented in several animal species; however, some species-specific differences appear to exist. Enhancing our understanding of the physiologic, biochemical and molecular mechanisms underlying antral follicular wave dynamics is important for understanding age-related changes in reproductive function and will have clinical implications for the development of safer, more efficacious and patient-friendly hormonal contraceptive and ovarian stimulation regimens. Elucidation of endocrine and paracrine regulation of follicular wave dynamics in women is also important for understanding follicle−oocyte interactions and identifying non-invasive markers of the physiologic status of follicles, which are predictive of oocyte competence and assisted reproduction outcomes.

Authors' roles

All of the authors have made substantial contributions to the present review article in the following manner: (i) conception and design, acquisition of data or analysis and interpretation of data, (ii) drafting or revising the article and (iii) final approval of the version to be published.

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Conflict of interest

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