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The normal menstrual cycle in women☆

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ABSTRACT

The menstrual cycle in women is characterised by high variability in cycle length (26–35 days), 5-day menses, a fertile phase from 5 days before to the day of ovulation, and low fertility which is dependent on cycle length and age. All women show an FSH rise at the luteal–follicular transition, stimulating a cohort of follicular growth and inhibin B secretion in the early follicular phase. The ovulatory dominant follicle (DF) is selected in the mid-follicular phase, and as this DF grows it increasingly secretes oestradiol and inhibin A for a week before ovulation. Gonadotrophin responsiveness, IGF binding protein expression and degradation, and vascularisation have been identified to be crucial for DF selection and progression. Two-thirds of women show two follicle waves and 1/3 show 3 follicle waves per cycle. Three-wave women have longer cycles, and a later oestradiol rise and LH surge. The corpus luteum secretes progesterone, oestradiol and inhibin A in response to LH pulses, and reaches its peak in terms of size, secretions, and vascularization 6–7 days after ovulation. Luteal regression is passive and independent of the uterus, but can be prevented by hCG, the luteotrophic signal from the trophoblast, from 8 days after conception. Reductions in systemic steroid and protein hormone concentrations may be responsible for the FSH rise characteristic of premenopausal women. The functional layer of the endometrium shows steroid hormone-dependent proliferation, differentiation, and shedding in the absence of the trophoblast. Menstruation is initiated by progesterone responsive decidual cells, and executed by PGE and PGF2α, vasoconstriction and matrix metalloprotease secretion by leukocytes. Ovarian function and also hormone fluctuations during the menstrual cycle are similar to oestrous cycles of cows and mares, justifying research into comparative aspects of menstrual and oestrous cycles in monovulatory species.

1. Introduction

The menstrual cycle of women is tightly controlled by endocrine, autocrine and paracrine factors regulating ovarian follicular development, ovulation, luteinisation, luteolysis, and remodelling of the endometrium. While fundamental reproductive processes are clearly shared between women and our large domestic animals, cycle characteristics, regulatory aspects and research focus can differ widely. For example, cycle irregularities and lack of ovulation are very common in the postpubertal adolescent woman (Golden and Carlson, 2008), but would not have been acceptable in breeding animals, and reduced fertility during reproductive aging is a major research focus in women but not in domestic animals, which are not usually bred late in life.

However, human and animal reproductive physiologists have common interests: (1) the precise detection of the time of ovulation, and (2) understanding determinants

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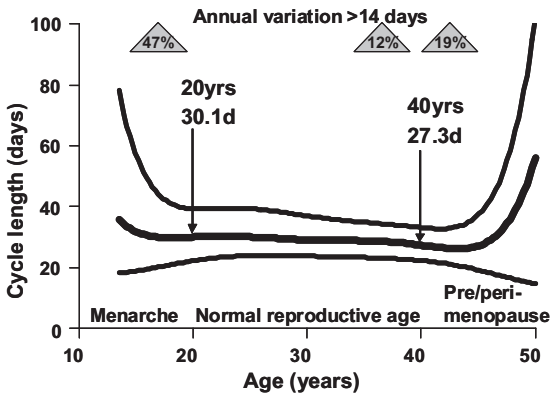

Fig. 1. Variation of menstrual cycle length as a function of age in the woman. This graph shows mean cycle length and the range (5th and 95th percentile) reported in 4 studies summarised by Harlow (2000). yrs = years, d = days. Triangles indicate the age group in which the indicated percentage of women shows more than 14 days variation in cycle length annually.

of fertility. The first is a challenge to human reproductive medicine, as in menstrual cycles of higher primates ovulation appears 'hidden', and menstrual flow does not necessarily indicate normality of cyclicity (Buffet et al., 1998; Harlow, 2000). The second is crucial to achieving economic return from domestic or for conserving wild animal species, but in humans a psychological dimension is added, when couples planning a pregnancy are faced with infertility. Because understanding the menstrual cycle of women will help identify conserved mechanisms underlying ovarian and uterine function, the aim of this review is to discuss what is a normal menstrual cycle, oestrus and fertility; summarise the underlying follicular and luteal function; address the steroid-dependent dynamics of endometrial growth, differentiation and shedding during menstruation; and describe the impact of normal 'aging'.

2. The menstrual cycle

Women have a long reproductive lifespan of an average 36 years, from menarche at 8.5 to 13 years to menopause (defined as 1 year of anovulation) at around 51 years (Fig. 1; Aydos et al., 2005; Harlow, 2000; Park et al., 2002). Puberty takes 2.3 years, beginning with breast development followed by pubic hair development and axillary hair growth, and concluding with menarche, the first menstrual period (Park et al., 2002). The 'textbook' menstrual cycle (interval from first day of menses to begin of next menses) in young healthy women with proven fertility is 28 days, and ultrasound and hormonal studies show that women aged 19–42 years have follicular phases of 14.6-day durations and luteal phases of 13.6-day durations (Ecochard and Gougeon 2000). However, the accurate prediction of the stage of the cycle or ovulation is very difficult in individual women, because a) menstrual cycle length is highly variable, even between similarly aged young women, ranging from 25 to 34 days (Bakos et al., 1994; Harlow, 2000); (b) it changes from menarche to menopause, noticeably shortening from 35 years of age, with high variability, long cycle lengths and bleeding irregularities in the 5 years following menarche and preceding menopause (Fig. 1; Golden and Carlson, 2008; Harlow, 2000); (c) wide ranges in the follicular (10–23 days) and the luteal phase (7–19 days) are reported, and only 10% of women with a 28-day cycle show a 14-day follicular and luteal phase (Harlow, 2000; Wilcox et al., 2000). Most of the cycle length variability is due to variability of the follicular phase (Waller et al., 1998), which shortens by 3–7 days over time (Harlow, 2000; Wilcox et al., 2000); and (d) anovulation affects up to 7% of women aged 25–39 with normal length cycles, but occurs more frequently in shorter or longer cycles, particularly in postmenarcheal girls and premenopausal women (60% of 10–14-year old girls and 34% of women over age 50 are anovulatory; Harlow, 2000).

Menstrual bleeding is the external symptom of cyclicity in women and occurs at the end of the luteal and the beginning of the follicular phase. In 80% of ovulatory women menstrual bleeding occurs over 3–6 days (range: 2–12 days) with the heaviest flow on Day 2, and blood loss averages 33.2 ml (10–84 ml). An age-dependent decline of half a day is seen in women from the age of 35 years, and 50-year old women lose 6 ml more than younger women (Harlow, 2000). Interestingly, regional, ethnic and even socioeconomic differences in follicular and luteal phase length, the duration of bleeding and amount of blood loss may exist (Harlow, 2000).

3. Oestrus

Women have 'fertile sexuality' (equated to oestrus) associated with the end of the follicular phase and rising oestradiol before ovulation, which is distinct from 'extended sexuality' after ovulation (Gangestad and Thornhill, 2008). During the fertile phase in women features indicative of masculinity and genetic benefit show increased ratings, attraction to extra-pair men increases, while attraction to men who appear sexually faithful decreases. Women's ratings of features indicative of long-term mateship compatibility including financial success are not influenced by cycle phase (Gangestad and Thornhill, 2008).

Men can detect oestrus in women using physiological (fertile-phase scent) or behavioural cues (Gangestad and Thornhill, 2008; Miller et al., 2007). Scent cues are not just detected by men: young women in dormitories, sisters, and mothers-daughters can synchronize their menstrual cycles to each other (Weller and Weller, 1993). This may be due to the olfactory detection of 5alpha-androst-16-en-3alpha-ol, which is secreted during the fertile phase and decreases LH pulsatility (Morofushi et al., 2000; Shinohara et al., 2000). Whether social regulation of menstrual cyclicity is then due to delayed ovulation needs to be confirmed using parallel pheromone, hormone and ultrasound measurements.

4. Fertility

Fertility (clinically diagnosed pregnancy) per menstrual cycle in young women (mean age of 31 years) planning a pregnancy is low (25–30% in the first two cycles) with a high percentage (31%) of subclinical (transient human chorionic gonadotrophin, hCG, rise) and clinical (follow-

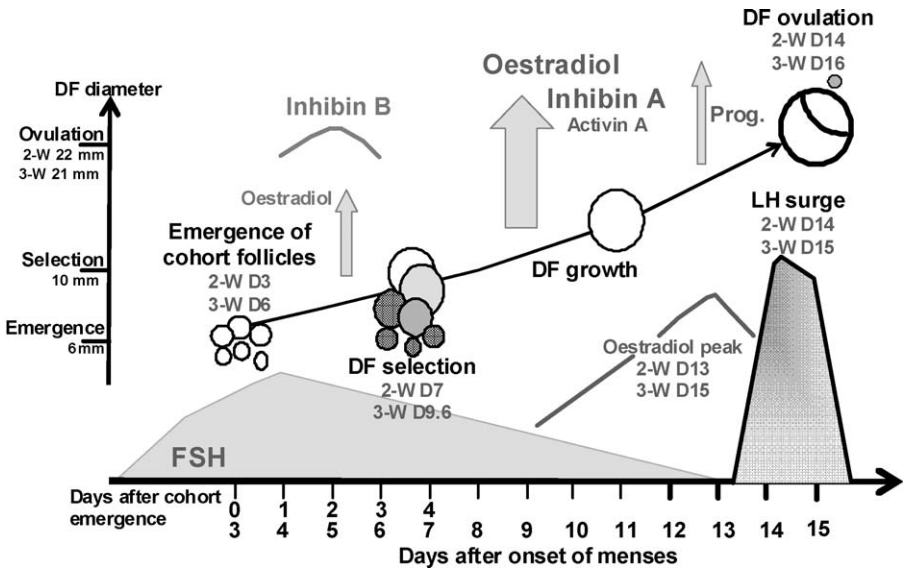

Fig. 2. Composite schematic of follicle wave dynamics and alterations in systemic gonadotrophins, steroids and inhibins during the follicular phase of the woman menstrual cycle. 2-W = 2-wave women, 3-W = 3-wave women. Prog. = progesterone. Cohort follicles undergoing atresia during the DF selection process are shaded.

ing a medical diagnosis) spontaneous abortions (Small et al., 2006). The maximum probability of conception to intercourse during the follicular phase is one day before ovulation, however, the fertile-phase spans six potentially fertile days in which pregnancies have been achieved, specifically 5 days before and the day of ovulation (Wilcox et al., 1995). Women can become pregnant following intercourse on Day 4 of the cycle or as late as 3 weeks after last menses due to the high variability of follicular phases. Pregnancy is not possible during the luteal phase. Interestingly, previous cycles of 30 and 31 days, and bleed lengths of 5 days in the current cycle are linked with highest probability of pregnancy, possibly related to influences on the quality of the ovulatory DF before and after its selection, and subsequent luteal and endometrial function (Small et al., 2006).

The low fertility per cycle may be due to almost 40% of regularly menstruating women aged 20–40 years showing luteal phase defects coupled with lowered preovulatory oestradiol concentrations (25%), or anovulation with (11%) or without (3%) luteinisation (Dal et al., 2005). Early pregnancy wastage following conception has been estimated as 22% based on transient rises in urine hCG (Small et al., 2006), and may be due to the reported luteal deficits and associated compromised blood flow to ovaries and uterus before and after ovulation (Dal et al., 2005). A shorter cycle length than 30 days is seen in reproductively older women (Fig. 1), and this combined with the increased incidence of luteal phase defects may contribute to the declining fertility from 37 years in women (van Zonneveld et al., 2003).

5. Follicle dynamics

Women ovulate a single DF similar to cows and mares (Fig. 2; Ginther et al., 2001). In reproductive-age women the ovulatory DF emerges at 6 mm diameter on Day 3 of the cycle, 11–12 days before the next ovulation (Ginther et al., 2004), in a cohort of small antral follicles (a follicle wave undergoing 'cyclic recruitment', McGee and Hsueh, 2000). Deviation (the time-point from when on DF are morphologically larger than the remaining cohort follicles which will become atretic) occurs 3–4 days later at a size of 10 mm, 1 week before ovulation (Baerwald et al., 2003b; Ginther et al., 2001, 2004). Asymmetrical secretion of oestradiol into the ovarian veins as a marker of functional DF selection is observed from Day 5 of the menstrual cycle (Chikazawa et al., 1986). There is no predominance of ovulations from one ovary and no alternate DF ovulation from the right and left ovary in successive cycles. Corpus luteum location also does not influence DF growth or steroid hormone secretions (Baerwald et al., 2003a; Ecochard and Gougeon, 2000).

Detailed ultrasound studies show, that, similar to cows and mares, other follicle waves than the one giving rise to the ovulatory DF can emerge and even select a DF during the luteal or early follicular phase (Fig. 3; Baerwald et al., 2003a,b). Follicular wave dynamics in women are similar to mares, where major waves leading to DF selection in addition to minor waves, not leading to DF selection or largest follicle growth $\geq$9 mm, are described (Ginther et al., 2001, 2004). Thus, in the majority of normal ovulatory women (68%) two follicle waves emerge on the day of ovulation (Day 0) and Day 14 after ovulation, respectively, while in the remaining 32% three waves emerge on Days 0, 12 and 18 after ovulation. The overall majority of non-ovulatory waves are minor waves; only 15% of 2-wave women and 38% of 3-wave women select anovulatory DF (Baerwald et al., 2003b). Only the last wave leads to the selection of the ovulatory DF on Days 19 (2-waves) and 22 (3-waves) after ovulation, ovulating at 22 mm (2-waves) or 21 mm (3-waves) in diameter (Fig. 2; Baerwald et al., 2003b). Women showing 3 follicle waves per cycle have 2-

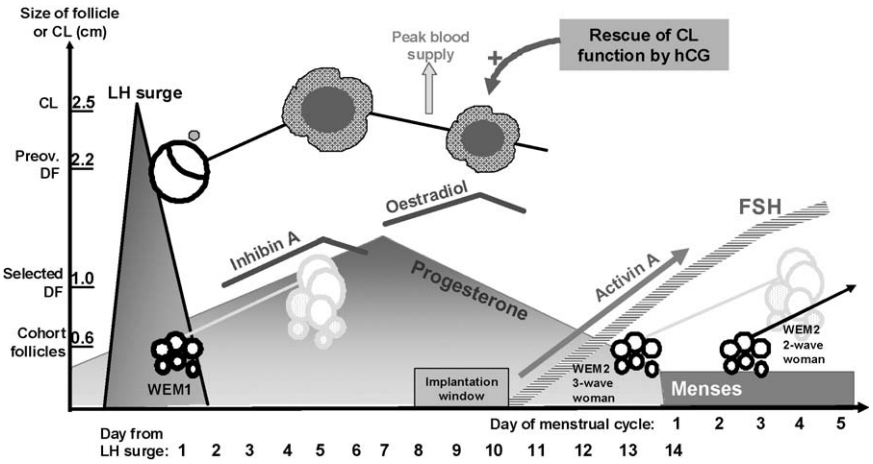

Fig. 3. Composite schematic showing luteal, follicular and hormonal events during the luteal phase of the woman cycle. CL = corpus luteum; DF = dominant follicle; WEM1–3 = wave emergence 1, 2 or 3 in the cycle; light grey lined follicle waves indicate the low frequency of major waves (DF selection) during the luteal or early follicular phase in 2- or 3-wave women.

day longer interovulatory intervals (29 days) than 2-wave women, but both have similar luteal phases (Baerwald et al., 2003b, 2005). So far, it has not been established whether follicular wave dynamics are consistent within individual women, are related with fertility, or change with age.

Most normally cycling adolescent girls (17 years) have 29.5-day cycles, and show DF selection on Day 9 after onset of menses about 5 days before ovulation, with follicular phases of <16 days (Cabral and de Medeiros, 2007). In reproductively older women, an earlier wave emergence and selection of the ovulatory DF in the luteal phase, and a shortened growth period achieving smaller preovulatory sizes during an overall shortened follicular phase are described (Ecochard and Gougeon 2000; Klein et al., 2002; Santoro et al., 2003; van Zonneveld et al., 2003).

Co-dominance or double ovulations are seen less frequently in women (4%) than in mares (20%) or cows (<10%; Ginther et al., 2004; Baerwald et al., 2005; Mihm and Evans, 2008), and very rarely lead to twin pregnancies (1.6% in Western developed countries; www.doh.gov.uk/public/statlink.htm). While there are recognized nutritional, genetic and other factors (e.g. smoking, recent use of steroid contraceptives) which can increase the probability of dizygotic twinning, the increase seen since the 1970s has been related to an increase in maternal age and increased use of assisted reproductive technologies (Hoekstra et al., 2008).

6. Endocrine changes: the gonadotrophins FSH and LH

As described for cows and mares, a close functional coupling between follicle wave growth, DF selection and FSH exists also in women (Ginther et al., 2001). In regularly cycling women FSH increases at the luteal–follicular transition, beginning 4 days before menses (Figs. 2 and 3; Miro and Aspinall, 2005). Concentrations of FSH achieve maximum levels on the day of emergence of the ovulatory DF followed by a slow decline during the follicular phase (from Days 5 to 13), reaching nadir concentrations just before the surge preceding ovulation (Ginther et al., 2005; van Santbrink et al., 1995). In addition, small FSH rises appear linked with emergence of minor and major follicle waves (Baerwald et al., 2003b; Ginther et al., 2005).

In reproductively older women FSH is higher even at nadir concentrations, and the FSH rise occurs earlier during the luteal phase (van Zonneveld et al., 2003), associated with an earlier cohort emergence and DF selection (Klein et al., 2002; Santoro et al., 2003). Women with elevated FSH also have a shortened follicular phase (Miro and Aspinall, 2005). While a mutation of the FSH-receptor can alter FSH and cycle characteristics without changing the incidence of dizygotic twinning (Greb et al., 2005; Hoekstra et al., 2008), the effects of such mutations on follicle wave dynamics are unknown.

The maturation of the hypothalamo–pituitary–ovarian axis as demonstrated by induction of the LH surge in premenarcheal girls is only achieved by mid- to late puberty (Park et al., 2002). The gonadotrophin peak is induced by an acute preovulatory oestradiol rise only in the follicular phase, possibly requires progesterone and GnRH pulse priming, and occurs one day earlier in 2-wave versus 3-wave women (Fig. 2; Araki et al., 1985; Baerwald et al., 2003b; Hoff et al., 1983; Park et al., 2002; Taylor et al., 1995). The small progesterone rise seen 12–40 h before the LH peak is necessary for the onset of the gonadotrophin surge (Fig. 2; Buffet et al., 1998; Hoff et al., 1983; March et al., 1979; Park et al., 2002). The surge lasts 48–54 h, with peak concentrations reached in 14 h, and is associated with a decline in oestradiol and a continuous rise in progesterone (Fritz et al., 1992; Hoff et al., 1983). The interval from surge onset to ovulation is 38 h (Fritz et al., 1992), and because ovulation occurs reliably 24–36 h after the oestrogen peak (Park et al., 2002), urine oestradiol, progesterone and LH metabolite measurements are incorporated in ovulation predictor kits for women.

Pulsatile GnRH and thus LH patterns are essential to female reproduction, and, similar to our domestic animal species, LH pulse frequency in women is regulated by ovarian oestradiol and progesterone and varies with phase

of the cycle (Nippoldt et al., 1989). During the follicular phase LH pulse frequency is one pulse every 60–90 min (Nippoldt et al., 1989), the mid-cycle LH surge is a result of an increase in both LH pulse amplitude and frequency (up to one pulse every 15–20 min), and when progesterone reaches high levels during the mid-luteal phase of the cycle, LH pulsatile secretion is reduced to one pulse every 3–4 h with increased amplitude (Nippoldt et al., 1989; Park et al., 2002). Following the progesterone decline during the luteal–follicular transition, LH pulse frequency increases over 4-fold (Hall et al., 1992).

Cattle in chronic negative energy balance show a reduction in LH pulsatility, DF atresia and anovulation (Diskin et al., 2003), and amenorrhea in women suffering from cachexia or eating disorders may have the same pathophysiology. Reductions in LH pulses have indeed been associated with functional and reversible weight loss-related hypothalamic amenorrhea (Meczekalski et al., 2008). Conversely, increased LH pulsatility can be seen in irregularly cycling adolescent girls or in women with polycystic ovary syndrome, which is also associated with anovulation, but here DF selection is absent (Minan et al., 1999; Venturoli et al., 1986). In the ovulatory perimenopausal woman the initial characteristic increase in mean FSH concentrations is followed by an increase in mean LH during the late luteal phase, a lower LH pulse frequency during the mid-to late follicular phase and a reduced response to oestradiol induction of the surge (Park et al., 2002). Menopausal women have higher LH (due to high amplitude frequent LH pulses) than reproductive-age women (Park et al., 2002).

7. Ovarian endocrine function: follicular and luteal secretions

The oestradiol rise in the follicular phase begins after emergence of the ovulatory DF, becomes more rapid following DF selection, and occurs earlier in women with 2 versus 3 follicle waves per cycle (Fig. 2; Baerwald et al., 2003b; Ginther et al., 2005). After ovulation, oestradiol concentrations increase to the mid-luteal phase (Days 7–9 after ovulation) and then decline, and this is due to luteal oestradiol secretion and is unaffected by minor or major anovulatory waves (Fig. 3; Baerwald et al., 2005; Ginther et al., 2005; Muttukrishna et al., 1994, 2002).

Progesterone rises asymmetrically in ovarian veins from two days before the surge and ovulation, and thus clearly originates from the preovulatory DF (Fig. 2; Chikazawa et al., 1986). Ultrasound studies show that corpora lutea in most women have central fluid-filled cavities, with diameter and mean luteal tissue area increasing for 4 days after ovulation independent of follicle wave dynamics (Fig. 3; Baerwald et al., 2005). Equally, length of the luteal phase (13 days) or serum progesterone concentrations are not affected by number of follicle waves per cycle. Progesterone reaches peak levels 6 days after ovulation followed by a decline to preovulatory levels at the onset of menses. Mean luteal area is positively correlated with serum progesterone and oestradiol, and also with parameters of perfusion showing a maximum between Days 7 and 9 after the LH surge (Fig. 3; Baerwald et al., 2005; Bourne et al., 1996).

In addition to oestradiol, ovarian growth factors from the inhibin family of proteins also regulate FSH. Specifically, oestradiol and inhibins inhibit and activins stimulate pituitary FSH secretion (Muttukrishna et al., 2002). Inhibin A (the inhibin alpha and beta A subunit heterodimer) secretion from the DF in the follicular phase is LH-dependent and thus positively correlated with oestradiol, rising following selection of the preovulatory DF and reaching a peak coincident with the mid-cycle oestradiol peak (Fig. 2; Muttukrishna et al., 1994, 2000; Welt et al., 1999). After ovulation systemic inhibin A declines, but as the corpus luteum secretes inhibin A, concentrations rise again in parallel with progesterone to a peak on Days 4–6 after the gonadotrophin surge followed by a decline (Fig. 3; Muttukrishna et al., 1994, 2000, 2002). Interestingly, inhibin B (the inhibin alpha and beta B subunit heterodimer) secretion into circulation differs from that of inhibin A, and rising concentrations at the luteal–follicular transition with a peak on Day 5 after menses onset reflect the growing cohort follicles emerging in response to FSH (Fig. 2). Thus inhibin B is a good marker of the number and health of FSH-dependent cohort follicles (Laven and Fauser, 2004).

Concentrations of activin A, the homodimer of the inhibin beta A subunit secreted by follicles, rise in the second half of the luteal phase (Fig. 3; Muttukrishna et al., 1996), decline during the early follicular phase, then rise again during the mid-follicular phase in concert with oestradiol and inhibin A (Fig. 2; Muttukrishna et al., 1996, 2000, 2002). Concentrations of follistatin, the specific activin binding protein, do not appear to change throughout the menstrual cycle in women, and there is no evidence for an endocrine role during the cycle (Muttukrishna et al., 2004).

As described above, ovarian function and FSH are functionally coupled. The fall in inhibin A, oestradiol and progesterone concentrations, concomitant with the rise in activin A from the mid-luteal phase may induce the transient rise of FSH during the luteal–follicular transition, and the initial FSH decline is coincident with a rise in inhibin B when cohort follicles emerge. The DF and its increasing secretion of mainly oestradiol, but also inhibin A, causes the continuous decline in FSH in the follicular phase (Ginther et al., 2005; Zeleznik, 2001), and luteal secretion of both inhibitors maintains low FSH following ovulation (Muttukrishna et al., 2002). Based on these feedback systems, it appears that subtle increases in activin A during the luteal phase, reduced progesterone and oestradiol secretion from the corpus luteum, smaller preovulatory follicle size and reduced inhibin A and inhibin B, which has been related to a decline in growing antral follicle numbers, lead to the raised FSH seen in reproductively older women (Mersereau et al., 2008; Muttukrishna et al., 2000; Santoro et al., 2003). In addition, systemic levels of anti-müllerian hormone (AMH), a product of preantral and small antral follicles, correlate positively with inhibin B concentrations on Day 3 of the cycle (Fanchin et al., 2005), and thus decline slowly with follicle depletion until they become undetectable at menopause (van Rooij et al., 2005).

8. Molecular regulation of dominant follicle selection, ovulation and follicle atresia

Multiple studies have addressed the endocrine, intra-ovarian and intracellular mechanisms regulating follicle growth, differentiation, atresia, ovulation and luteinization in the different monovulatory species including the woman. Key mechanisms involved in dominant follicle selection in the woman, cow and mare appear to be (1) the regulation of the gonadotrophin response, by upregulating LH-receptor and downregulating FSH-receptor expression, (2) ensuring maximum intra-follicular levels of free IGF by reducing the lower molecular weight IGF binding proteins and increasing the specific protease PAPP-A, and 3) stimulating angiogenesis and blood flow by inducing endothelial growth factor (VEGF) expression and function (Fraser and Duncan, 2005; Jokubkiene et al., 2006a; Mihm and Evans, 2008). While genomic or molecular studies using human granulosa cells have focused on alterations occurring during gonadotrophin stimulation, atresia, or ovarian pathology, specific transcriptomic studies of important stages of follicle development such as DF selection have only been carried out in the bovine model (Mihm and Evans, 2008).

9. Molecular aspects of luteal function, regression and rescue by the trophoblast

In contrast to our large animal species luteal progesterone production is dependent on LH throughout the luteal phase, and the result of interactions between steroids, prostaglandins, growth factors and cytokines synthesized by the small and large luteal cells (del Canto et al., 2007; Niswender et al., 2000; Patton and Stouffer, 1991). Corpus luteum regression is independent of the uterus, and is probably due to reduced luteal LH sensitivity rather than systemic reductions in LH pulsatility (Messinis et al., 2009). Functional and structural luteolysis involves cytokines and prostaglandin F2α, and results in cellular apoptosis and autophagocytosis (Niswender et al., 2000).

Luteal rescue in maternal recognition of pregnancy is achieved by maintenance of the LH stimulus due to secretion of human chorionic gonadotrophin (hCG) into circulation by the invasive trophoblast from Day 8 after the mid-cycle LH surge (Fig. 3). Human CG can prevent luteolysis by binding to the luteal LH-receptor and stimulating progesterone, oestradiol and inhibin A production, protecting against prostaglandin F2α and inducing neovascularisation (del Canto et al., 2007; Messinis et al., 2009; Niswender et al., 2000).

10. The dynamic endometrium

The endometrium undergoes a steroid-induced monthly cycle of proliferation (regeneration during the follicular phase), differentiation (in the luteal phase) and shedding (menstruation). The upper functional layer is where the activities of proliferation, secretion and degeneration take place, and where the blastocyst implants following conception 7–10 days after ovulation (Strassmann, 1996); regeneration takes place in the lower basal layer (Jabbour et al., 2006). Oestradiol is responsible for the proliferative changes during the follicular phase, while progesterone inhibits endometrial growth, and differentiates the glandular and stromal cells of the endometrium during the secretory phase. Menstruation in the late secretory stage is the response of the endometrium to progesterone (and oestradiol) withdrawal at regression of the corpus luteum due to the absence of the trophoblast and hCG secretion (Jabbour et al., 2006).

Classical histological features, particularly of the secretory stage, such as glandular structure and secretions, coiling of spiral blood vessels, predecidual reaction (cuff-like stromal cell accumulation surrounding spiral arterioles), oedema, and transformation of stromal cells into decidual cells have been used to define the stage of the cycle or endometrial receptivity (Jabbour et al., 2006; Speroff et al., 1999). Ultrasound determination of endometrial thickness and volume show that both are correlated and increase throughout the follicular phase with a peak before ovulation and a decline before menstruation (Alcazar, 2006; Baerwald and Pierson, 2004). Because of earlier oestradiol rises and the oestradiol-dependence of endometrial proliferation, an earlier increase in endometrial area, perimeter, thickness and echotextural pattern scores is detected in the follicular phase in 2-wave compared with 3-wave women (Baerwald et al., 2003b; Baerwald and Pierson, 2004). The same endometrial parameters are constant during the early to mid-luteal phase, with a decline about 10 days after ovulation, with no differences between 2- and 3-wave women in the luteal phase, or in 3-wave women with different wave patterns (Baerwald and Pierson, 2004).

Remodelling of the endometrial vasculature is important during the differentiative luteal phase and menstruation, and this is mediated by the angiogenic VEGF, which influences new blood vessel formation and vascular permeability important for leukocyte entry and vasoconstriction (Jabbour et al., 2006). Ultrasound studies show an oestradiol-related increase in endometrial and subendometrial vascularisation to a peak 2–3 days before ovulation, decreasing thereafter to a nadir 2–5 days after ovulation, then rising again during the mid- to late luteal phase (Alcazar, 2006; Jokubkiene et al., 2006b).

11. Process of menstruation

Cyclical growth and decline of the endometrium is universal in non-pregnant mammals, but external loss of blood is only seen in old world primates and very few other species (Martin, 2007). The luteal phase places metabolic demands on the woman, and it appears more economical to regenerate and shed than to continuously sustain a fully secretory endometrium (Strassmann, 1996). The cost of menstrual bleeding is considered low, and thus bleeding may only be a side-effect of a blood volume which cannot be re-absorbed during endometrial regression (Strassmann, 1996).

Decidualisation of stromal cells, critical for both implantation and the onset of menstruation, occurs in the mid-secretory phase of the endometrium. The initial processes causing menstruation when progesterone

declines are mediated via progesterone receptor expressing stromal cells, and involve prostaglandin E2 and F2α synthesis, influx of leukocytes, spiral vessel vasoconstriction, and VEGF expression. Processes then become progesterone-independent and irreversible, and are mediated by leukocytes which secrete matrix metalloproteases for breakdown of cellular membranes and dissolution of the extracellular matrix (Irwin et al., 1996). Increased prostaglandins cause myometrial contractions and vasoconstriction of endometrial spiral arteries, intercellular blood enters the endometrial cavity, and an area of cleavage appears between the basal and the functional layer which is then almost completely lost (Jabbour et al., 2006; Salamonsen, 1994; Speroff et al., 1999). Menstrual bleeding is aided by fibrinolytic activity, however, thrombin production in the basal layer achieves haemostasis, and, synchronous with shedding, regeneration takes place from this layer under the influence of oestradiol (Jabbour et al., 2006). The new surface epithelium develops from the glandular stumps in the basal layer left after menstrual desquamation, and by Days 5–6 the entire cavity is covered (Jabbour et al., 2006; Speroff et al., 1999).

12. Conclusions

Reproduction in the woman contrasts markedly with economically important domestic animal species. High variability in cycle length and ovulation time within the cycle, low fertility per cycle, no overt sign of impending ovulation and the accelerated decline in fertility in our late thirties limit reproductive success. Similarities to the oestrous cycles of cows and mares proposed as model species for women exist and can potentially be exploited to address important questions, such as whether in women follicle wave dynamics vary from cycle to cycle, with age, and, crucially, influence pregnancy rates. On the other hand, research into AMH as a marker of the ovarian reserve, the reproductive consequences of gonadotrophin receptor mutations, or characterisation of reproductive aging of women surpasses studies in monovulatory animal species. Clearly, there is sufficient overlap to justify concerted research efforts into comparative aspects of menstrual and oestrous cycles of monovulatory species.

Conflict of interest

The authors have no conflict of interest in publishing this review.

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