Chapter 5

Regulation and Differential Secretion of Gonadotropins During Post Partum Recovery of Reproductive Function in Beef and Dairy Cows

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1. Introduction

Reproductive efficiency in dairy and beef cows is dependent on achieving high submission rates and high conception rates per service. However, to achieve good submission and conception rates cows must resume ovarian cyclicity, have normal uterine involution, be detected in estrus, and inseminated at an optimum time. In seasonally calving herds the aim is to achieve conception by 85 days following parturition so that calving to calving intervals are maintained at 365 days. Reproductive performance of cows affects the efficiency of milk production in the herd because of its influence on the calving to first service interval, calving pattern, length of lactation and culling rate.

The pattern of resumption of ovarian function in both dairy and beef cows was recently reviewed (Crowe 2008). Resumption of ovarian cyclicity is largely dependent on LH pulse frequency. Both dairy and beef cows have early resumption of follicular growth within 7 to 10 days post partum. The fate of the dominant follicle within the first follicular wave is dependent on LH pulsatility. This chapter will focus on the factors contributing to resumption of ovulation in postpartum dairy and beef cows.

2. Ovarian follicle growth in cattle

Ovarian follicle growth takes a period of 3-4 months and can be categorized into gonadotropin independent and gonadotropin dependent stages (Webb et al. 2004). Gonadotropin dependent follicle growth in cattle occurs in waves (Rajakoski 1960; Matton et al. 1981; Ireland and Roche 1987; Savio et al. 1988; Sirois and Fortune 1988). Each wave of growth involves emergence, selection and dominance followed by either atresia or ovulation. Emergence of a follicle wave is defined as growth of a cohort of follicles ≥ 5mm in diameter and coincides with a transient increase in FSH secretion (Adams et al. 1992; Sunderland et al. 1994). Selection is the process by which the growing cohort of follicles is reduced to the ovulatory quota for the species (in cattle it is generally one), selection occurs in the face of declining FSH concentrations (Sunderland et al. 1994). The selected follicle survives in an environment of reduced FSH due to the development of LH receptors in granulosa cells (Xu et al. 1995, Bao et al. 1997) and increased intrafollicular bioavailable insulin-like growth factor-I (IGF-I; Austin et al. 2001; Canty et al. 2006). The increased bioavailable IGF-I is achieved by reduced IGF-I binding proteins (IGFBP) due to increased IGFBP protease activity. Dominance is the phase during which the single selected follicle actively suppresses FSH concentrations and ensures suppression of all other follicle growth on the ovaries (Sunderland et al. 1994). The fate of the dominant follicle is then dependent on the prevailing LH pulse frequency during the dominance phase. In the presence of elevated progesterone (luteal phase of cyclic animals) LH pulse frequency is maintained at 1 pulse every 4 hours and the dominant follicle undergoes atresia, in the follicular phase (preovulatory period in cyclic animals) the LH pulse frequency increases to one pulse per hour and this stimulates final maturation, increased estradiol concentrations and positive feedback on gonadotropin-releasing hormone (GnRH), LH (and FSH) in a surge that induces ovulation (Sunderland et al. 1994). Normal follicle waves have an inherent lifespan of 7 to 10 days in duration from the time of emergence of a wave until emergence of the next wave (indicating either ovulation or physiological atresia of the dominant follicle). In cyclic heifers during the normal 21 day estrous cycle there are normally 3 waves (sometimes 2 waves and rarely 1 or 4 waves; Savio et al. 1988; Murphy et al. 1991).

2.1. Pattern of gonadotropin secretion and follicle growth during pregnancy

During pregnancy follicular growth continues during the first two trimesters (Ginther et al. 1989; Ginther et al. 1996) at regular 7 to 10 day intervals. In late pregnancy (last 22 days) the strong negative feedback of progestagens (mostly from the CL of pregnancy and partly of placental origin) and estrogens (mostly placental in origin) suppresses the recurrent transient FSH rises that stimulate follicle growth (Ginther et al. 1996; Crowe et al. 1998; Figure 1) so that the ovaries during the last 20 – 25 days are largely quiescent.

2.2. Resumption of gonadotropin secretion and follicle growth post partum

At the time of parturition progesterone and estradiol concentrations cascade to basal concentrations. This allows for the almost immediate resumption of recurrent transient increases in FSH concentrations (within 3 to 5 days of parturition) that occur at 7 to 10 day intervals (Crowe et al. 1998). The first of these increases stimulates the first postpartum wave of follicle growth that generally produces a dominant follicle by 7-10 days post partum (Savio et al. 1990a; Murphy et al. 1990; Crowe et al. 1993). The fate of this first follicular wave dominant follicle is dependent on its ability to secrete sufficient estradiol to induce a gonadotropin surge. The capacity for estradiol secretion is in turn dependent on the prevailing LH pulse frequency during the dominance phase of the follicle wave, the size of the dominant follicle and IGF-I bioavailability (Austin et al. 2001; Canty et al. 2006). So the major driver for ovulation of a dominant follicle during the postpartum period is the LH pulse frequency. This has been tested and validated by the LH pulsatile infusion studies of Duffy et al. (2000) in early postpartum anestrous beef cows. The LH pulse frequency required to stimulate a dominant follicle towards ovulation is one LH pulse per hour. Figure 2 is a schematic indicating the likely fate of the early postpartum dominant follicles in beef and dairy cows. In beef cows the first dominant follicle generally does not ovulate (Murphy et al. 1990, Stagg et al. 1995), but rather it undergoes atresia. With beef cows in good body condition the first postpartum dominant follicle to ovulate is generally from wave 3.2 ± 0.2 (~ 30 days; Murphy et al. 1990); whereas for beef cows in poor body condition there are typically 10.6 ± 1.2 waves of follicular growth before ovulation occurs (~ 70-100 days; Stagg et al. 1995; Figure 3). In the case of dairy cows ovulation of the first postpartum dominant follicle typically occurs in 50 to 80% of cows, it undergoes atresia in 15 to 60% of cows or becomes cystic in 1-5% of cows (Savio et al. 1990b; Beam and Butler 1997; Sartori et al. 2004; Sakaguchi et al. 2004).

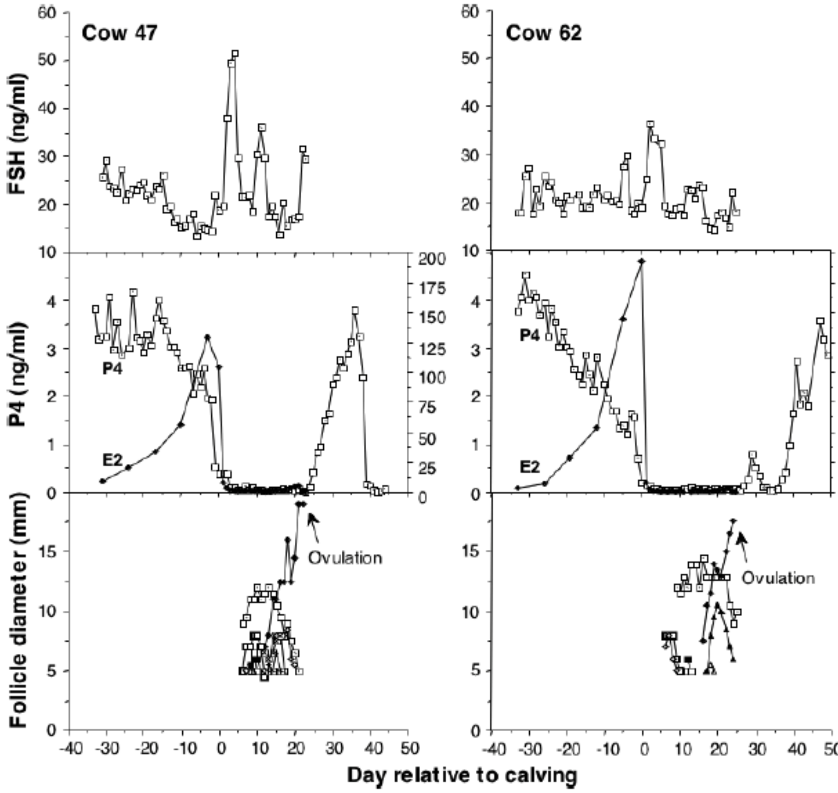

Figure 1. Follicle-stimulating hormone (FSH), progesterone (P4), estradiol (E2) and follicular diameter profiles in two representative beef cows from ~30 days prepartum until 50 days postpartum (Crowe et al. 1998).

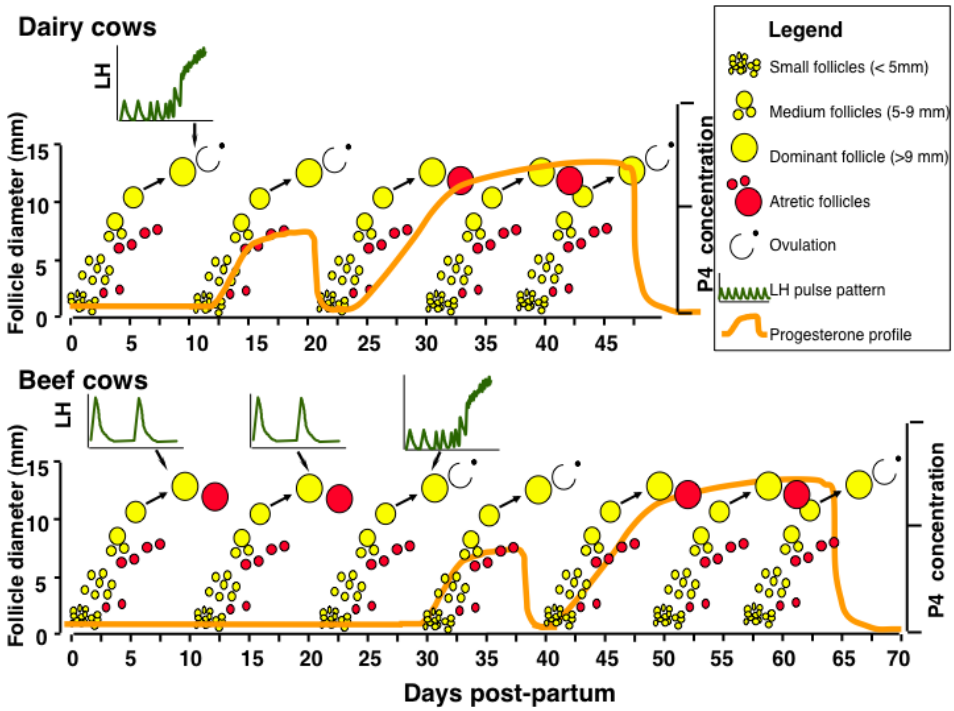

Figure 2. Diagrammatic scheme of resumption of dominant follicles and ovarian cycles during the postpartum period in dairy and beef suckler cows not nutritionally stressed. LH pulse frequency is that occurring during an 8 h window where cows are blood sampled every 15 min. Short cycles occur in most (70%), but not all cows after first ovulation (Reprinted with permission Crowe, 2008).

First ovulation in both dairy and beef cows is generally silent (i.e., no behavioural estrus; Kyle et al. 1992) and is generally (>70%) followed by a short cycle, usually containing just one follicle wave. This first luteal phase is reduced in length due to the premature release of prostaglandin F2α (PGF2α; Peter et al. 1989) presumably arising from the increased estradiol produced from the formation of the post-ovulatory dominant follicle on days 5-8 of the cycle inducing premature estradiol and oxytocin (Zollers et al., 1993) receptors. Thus the corpus luteum regresses prematurely around days 8-10 of the cycle, with the second ovulation (of this post-ovulatory dominant follicle) occurring around days 9-11 after the first ovulation. This second ovulation is generally associated with the expression of estrus and a normal length luteal phase.

Cyclic postpartum cows may have 2, 3 or occasionally 4 follicle waves during the estrous cycles that occur in the postpartum period (Savio et al. 1990a; Sartori et al. 2004). Unlike non-lactating heifers, lactating Holstein postpartum dairy cows tend to have two follicle waves per 18-23 day cycle (Sartori et al. 2004). Progesterone concentration is the major factor that affects LH pulse frequency in cyclic animals. Generally lactating Holstein dairy cows tend to have lower progesterone concentrations during the cycle than cyclic heifers (Sartori et al. 2004; Wolfenson et al. 2004). These lower progesterone concentrations tend to allow a subtle increase in LH pulse frequency and allows for prolonged growth of each dominant follicle rather than the faster atresia that occurs in cyclic heifers. Cows with prolonged luteal phases tend to have a fourth follicle wave (Savio et al. 1990a). The number of follicle waves or rate of turnover of dominant follicles are directly related to the duration of dominance of each dominant follicle, and cattle with shorter durations of dominance for the ovulatory dominant follicles tend to have higher conception rates (Austin et al. 1999). Therefore nutrition, by altering metabolic clearance of progesterone can affect the duration of dominance of a dominant follicle, the number of follicle waves per cycle and have an indirect effect on conception rates.

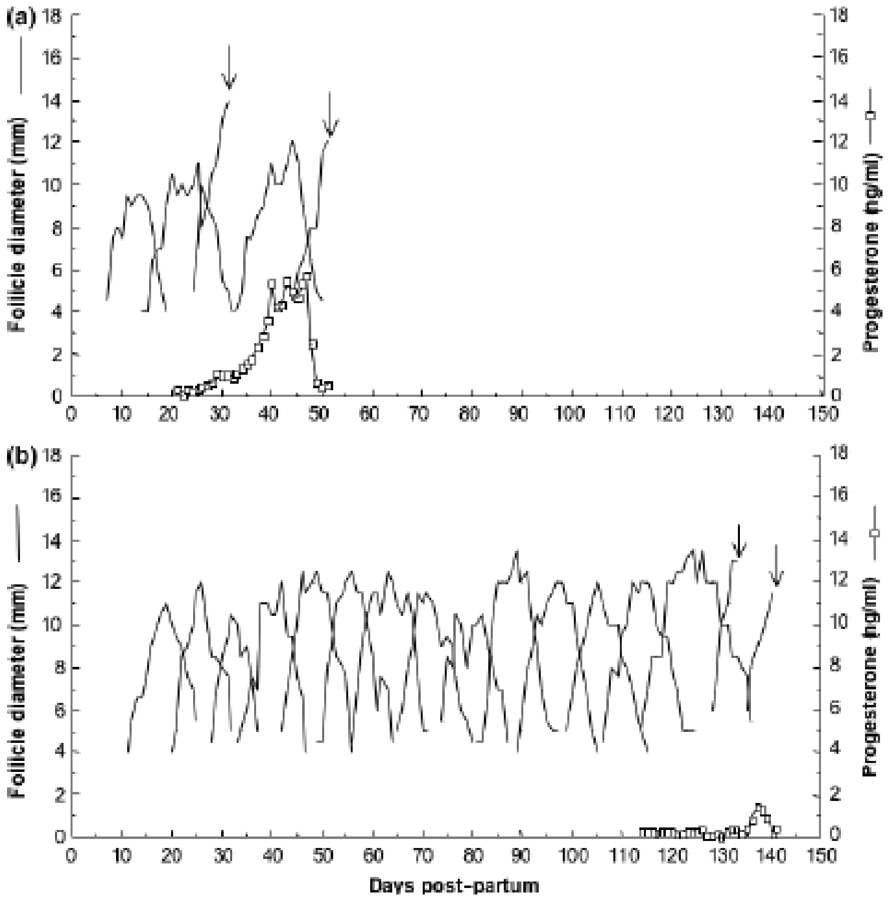

Figure 3. Pattern of growth and regression of dominant follicles from calving to second ovulation in (a) a beef suckler cow with two non-ovulatory follicle waves prior to first ovulation, and (b) a beef suckler cow with 14 non-ovulatory waves prior to first ovulation. Arrows indicate ovulation. Reproduced with permission Stagg et al. (1995); Crowe 2008.

3. Post-partum anestrus

3.1. Factors contributing to LH pulse frequency in early post-partum beef cows

The major factors that control LH pulse frequency (and therefore the fate of early postpartum dominant follicles) in postpartum beef cows include maternal bond / calf presence (presumably due to effects on opioid release), suckling inhibition (Myers et al. 1989), and poor body condition (Canfield and Butler 1990). Calf presence has a very clear negative effect on resumption of ovulation in beef suckler cows nursing calves. Restricted suckling of beef cows (once per day) from day 30, where calves were in an isolated pen away from sight of the cows, significantly advanced the interval from calving to first ovulation (51 days) compared with *ad libitum* suckled control cows (79 days). The effect of calf presence can be further compartmentalized into suckling stimuli (mammary sensory pathways) and maternal behaviour / bonding effects (Silveira et al. 1993; Williams et al. 1993) but requires positive calf identification by either sight or olfaction (Griffith and Williams 1996). Beef cows that calve down in poor BCS (<2.5; scale 1-5 as described by Lowman et al. 1976) are more likely to have a prolonged anestrous period (Stagg et al. 1995) due presumably to lower LH pulse frequency (Stagg et al. 1998). Similarly anestrus can be induced by chronic nutrition restriction in post-partum beef cows, and occurs when cows lose 22-24% of their initial body weight (Richards et al, 1989).

As beef suckler cows (with prolonged anovulatory anestrus) approach their first postpartum ovulation LH pulse frequency increases (observed during each sequential follicle wave from 6 waves before ovulation until the ovulatory wave; Stagg et al. 1998). Concentrations of IGF-I increased linearly from 75 days before first ovulation until ovulation which was associated with a linear decrease in growth hormone concentrations during the same period (Stagg et al. 1998). Thus postpartum beef cows require increased LH pulse frequency that is mediated largely by suckling inhibition and plane of nutrition, in addition to increased IGF-I concentrations to help stimulate dominant follicle maturation and growth so that there is sufficient secretion of estradiol to induce an LH surge and ovulation. Management may be used to encourage earlier ovulation by restricting suckling / access of the cows to the calves from approximately day 30 post partum (Stagg et al. 1988) or by increased plane of nutrition and body condition.

3.2. Factors contributing to LH pulse frequency in early postpartum dairy cows

In dairy cows the major factors affecting resumption of ovulation include BCS and energy balance (yield and dry matter intake), parity, season and disease (Bulman and Lamming 1978; Beam and Butler 1997; Beam and Butler 1999; Opsomer et al. 2000; Wathes et al. 2007). Energy intake, BCS and milk yield interact to affect energy balance in dairy cows. There is evidence to link many of these factors to reduced LH pulse frequency; indeed a negative association between energy balance and prolonged post-partum anestrous interval is well established for dairy cows (Butler et al. 1981; Canfield and Butler 1990; Staples et al. 1990) and is mediated by reduced LH pulse frequency (Canfield and Butler, 1990). A number of studies have been conducted in dairy cows of various yield potential that have categorised the pattern of resumption of ovarian function with the use of milk progesterone. These range from a study by Fagan and Roche (1986) using what would now be classified as traditional moderate yielding Friesian cows (4,000 – 5,000 kg milk per lactation) to that of Opsomer et al. (1998) using modern high yielding Holstein type cows (6,900 – 9,800 kg milk per lactation). The data from these two studies are summarised in Table 1. Furthermore, this pattern of resumption of ovarian function has been validated in a series of equivalent papers and the two key problem categories (prolonged interval to first ovulation and prolonged luteal phase) are summarized in Figure 4. Risk factors for these two ovarian abnormalities have been determined in a large epidemiological study by Opsomer et al. (2000). The major risk factors for a prolonged interval to first ovulation included (odds ratio in parentheses): acute body condition score loss up to 60 days post calving (18.7 within 30 days, 10.9 within 60 days), clinical ketosis (11.3), clinical diseases (5.4), abnormal vaginal discharge (4.5), and difficult calving (3.6).

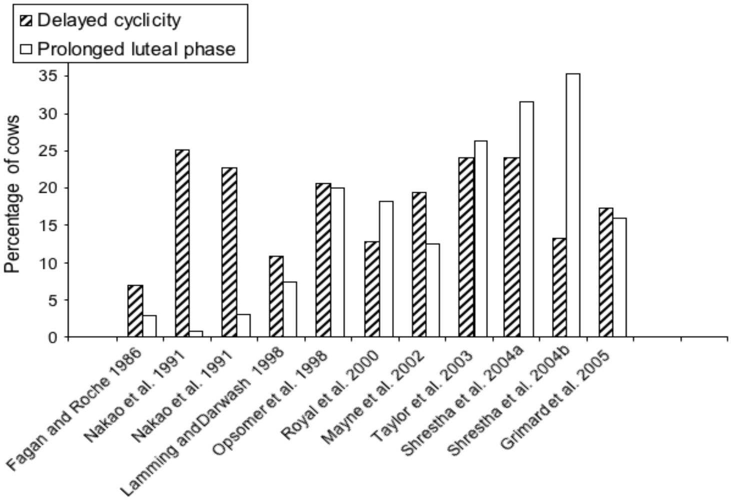

Figure 4. Percentage of cows defined as having either i) delayed resumption of ovulation or ii) prolonged luteal phases based on evaluation of milk progesterone profiles across a number of studies in dairy cows (compiled by Benedicte Grimard, France, personal communication; Reproduced with permission, Crowe 2008).

The greatest of these risk factors is acute body condition score loss. Current evidence suggests that dairy cows should calve down in a BCS of 2.75 – 3.0 (Scale 1-5; as described by Edmonson et al. 1989) and not lose more than 0.5 of a BCS unit between calving and first service (Overton and Waldron 2004; Mulligan et al. 2006) rather than earlier recommendations of 3.0 – 3.5 (Buckley et al. 2003). Cows that lose excessive body condition (≥ 1.0 BCS unit) have a longer postpartum interval to first ovulation. Thus monitoring BCS from before calving to first service is essential to good reproductive management. Body condition score changes are good indicators of energy balance and reflect milk yield and dry matter intake. It is necessary to prevent a steep decline in energy balance and shorten the duration of postpartum negative energy balance. This is best achieved by ensuring that dry matter intake in the early postpartum period is maximized and by having cows in appropriate BCS (2.73 – 3.0) at calving. Cows that are mobilizing tissue at a high rate have increased blood non-esterified fatty acids, and β-hydroxy butyrate, but reduced concentrations of insulin, glucose and IGF-I (Grummer et al. 2004). The metabolic status associated with high rates of tissue mobilization increases the risk of hypocalcaemia, acidosis, fatty liver, ketosis and displaced abomasa (Gröhn and Rajala-Schultz 2001; Overton and Waldron 2004, Maizon et al. 2004). Cows affected by these metabolic disorders are more prone to anestrus, mastitis, lameness and reduced conception rate to AI (Fourichon et al. 1999; Gröhn and Rajala-Schultz 2001; Lucy 2001; Lopez-Gatius et al. 2002; Maizon et al. 2004). It is hypothesized that serum IGF-I concentrations could be useful as a predictor of nutritional status and hence reproductive efficiency in dairy cows (Zulu et al. 2002a). Plasma IGF-I concentrations before calving and in the first few weeks of lactation have been linked to subsequent cyclicity and conception rate (Taylor et al. 2006). This emphasizes the critical role of correct nutritional management to ensure that the deficit in energy balance post calving is mild rather than severe. Current approaches to minimize the energy balance deficit post calving includes: the optimization of body condition score at calving (2.75 - 3.0), shorter dry periods and maintenance of normal rumen function (Mulligan et al. 2006).

Item	Fagan and Roche 1986 Moderate yielding Friesian cows	Opsomer et al. 1998 High yielding Holstein cows
No. of cows / postpartum periods	463	448
Normal cyclic patterns (%)	78	53.5*
Prolonged interval to 1st ovulation (%)	7	20.5*
Prolonged luteal phase (%)	3	20*
Temporary cessation of ovulation (%)	3	3
Short cycles (%)	4	0.5
Other irregular patterns (%)	4	2.5

Table 1. Pattern of resumption of ovarian cyclicity in postpartum dairy cows (traditional moderate yielding Friesians vs modern high yielding Holsteins), using milk progesterone profiling (samples collected twice weekly). *Categories with a major disparity between the two studies.

Disease state may also regulate follicle fate via LH and other mechanisms. Uterine conditions such as retained foetal membranes, endometritis and metritis contribute to reproductive efficiency via various mechanisms. Local infection of the uterus in postpartum cows delays uterine involution, causes inflammation of the endometrium, reduce conception rate to first insemination (Sheldon 2004), but may also affect follicle growth, decrease estradiol secretion from dominant follicles, and delay the interval to first ovulation (LeBlanc et al. 2002; Sheldon et al. 2002; Sheldon and Dobson 2004; Williams et al. 2007;

Sheldon et al. 2008). These effects on follicle growth and ovulation implicate potential roles mediated by either direct effects within follicles and reduced LH secretion / failure of the gonadotropin surge. Indeed the evidence supports both possible mechanisms: uterine disease associated with *E. Coli* or infusion of endotoxins reduces estradiol secretion from dominant follicles (Sheldon et al. 2002; Herath et al. 2007) and delays the LH surge and ovulation (Suzuki et al. 2001). Other diseases such as mastitis (Huzenicza et al. 2005) and lameness (Petersson et al. 2006) delay resumption of luteal activity by 7 to 17 days, respectively. For these there is considerable evidence that this is mediated due to acute stressors reducing GnRH and hence LH pulse frequency, leading to decreased estradiol production by dominant follicles and preventing or reducing the gonadotropin surge, thus delaying ovulation.

4. Abnormal ovarian function during the post-partum period

4.1. Prolonged luteal phases

Irregular estrous cycles in cows once they have resumed ovulation tend to be predominantly prolonged luteal phases. The incidence of prolonged luteal phases has increased from 3% (Fagan and Roche 1986) to 11-22% (Lamming and Darwash 1998; Opsomer et al. 1998; Shrestra et al. 2004; Figure 4). It is generally considered that prolonged luteal phases are associated with an abnormal uterine environment that disrupts prostaglandin production. Interestingly in the study of Opsomer et al. (1998), where the incidence of cows with prolonged luteal phases was 20% (89/448 cows), only 43/89 cows had abnormal uterine content, 2/89 had ovarian cysts and 44/89 had no detectable abnormalities. However in this study abnormalities were identified only by rectal palpation. The major risk factors for a prolonged luteal phase in cows having resumed ovulation included (odds ratio in parentheses; Opsomer et al. 2000): metritis (11.0), abnormal vaginal discharge (4.4), retained placenta (3.5), parity (2.5 for parity 4+ vs primiparous), earlier resumption of ovulation (2.8 for resumption < 19 days post partum, 2.4 for resumption 19-24 days post partum). These data support the concept that prolonged luteal phases are related to uterine problems rather than ovarian problems.

4.2. Follicular cysts

These occur where dominant follicles in the early postpartum period (often the first dominant follicle postpartum) fail to ovulate. Cysts typically continue to grow to diameters >20-25 mm over a 10 to 40 day period in the absence of a CL (Savio et al. 1990a; Gümen et al. 2002, Hatler et al. 2003). This continued growth appears to be due to lack of positive feedback induced by estradiol and thus failure of the LH/FSH pre-ovulatory surge, despite increased LH pulse frequency (to an intermediate level). At this time progesterone concentrations are low, while estradiol concentrations are elevated above normal pro-estrus concentrations (Savio et al. 1990b; Hatler et al. 2003), resulting in many cases in strong exhibition of estrous behaviour by cows in the early phases of a follicular cyst. This is followed by a period of time when there is an absence of estrous behaviour in the second half of the cysts lifespan. The elevated estradiol in conjunction with elevated inhibin suppresses FSH concentrations, so that no new follicle waves emerge during the early active phase of a follicular cyst. The cyst then becomes estrogen inactive (despite being morphologically still present) and a new follicle wave emerges. The dominant follicle of this new wave may either ovulate, undergo atresia or become cystic. Many cows with follicular cysts correct themselves, but some develop sequential follicular cysts. The metabolic risk factors associated with cows that develop cysts in the early postpartum period are over conditioned cows, a reduction in insulin (Vanholder et al. 2005) and IGF-I, and increased non-esterified fatty acids (Zulu et al. 2002b).

5. Induction of estrus and ovulation in anovulatory anestrous cows

From the previous sections it is clear that in many cases (especially with dairy cows) anovulatory anestrus is associated with management risk factors and other diseases (excessive loss of BCS, severe lameness, uterine disease, displaced abomasum, etc). Therefore before embarking on a specific treatment for anestrus, the underlying factors and diseases should be first addressed before commencement of specific treatments for the ovarian problems.

5.1. GnRH

The major cause of delayed ovulation in postpartum cows is an infrequent LH pulse frequency (and by inference GnRH pulse frequency). GnRH treatment was used with variable effectiveness in numerous studies of postpartum cows when the follicle status of the animals was unknown. A single injection, two injections 10 days apart, or frequent low dose injections at 1- to 4-h intervals of GnRH or GnRH analogues failed consistently to induce ovulation in over 90% of treated anestrous cows (Mawhinney et al. 1979; Riley et al. 1981; Walters et al. 1982; Edwards et al. 1983). However, when a GnRH analogue (20 μg Buserelin) was used at known stages of follicle growth (determined by daily ultrasound scanning) of the first postpartum DF, all cows ovulated when administered during the growing phase of the DF (12/12) and the majority (7/10) ovulated when the first postpartum DF was in its plateau / early declining phase of growth (Crowe et al. 1993). In a further study conducted by Ryan et al. (1998), 250 μg GnRH resulted in ovulation in 20 of 20 cows when given at dominance of a follicular wave, this was followed by emergence of a new wave of ovarian follicular growth 1.6 ± 0.3 days later and dominance of the subsequent wave was attained in 5 ± 0.3 days. However, there was no effect of GnRH on follicular dynamics when given at emergence of a follicular wave. The existing cohort of follicles continued to develop unaffected in 17 of 17 cows, and dominance occurred 3.6 ± 0.5 days later. Thus, GnRH may cause ovulation or no effect on follicle development depending on the animal's stage of follicle development at treatment. Thus when GnRH is used as part of an ovsynch protocol (GnRH-PGF2α-GnRH treatment) in postpartum anestrous cows the effectiveness of the treatment is wholly dependent on the presence or absence of a DF at the time the first GnRH injection is administered.

5.2. Progesterone

Treatment of anestrous cows with progesterone (and estradiol) will induce estrus and shorten the postpartum interval to conception (Rhodes et al. 2003). Anestrous cows require progesterone treatment to ensure that the first ovulation is associated with expression of estrus and a normally functioning luteal phase. The use of eCG may accompany progesterone treatment in cows that are in deep anovulatory anestrus to ensure ovulation (Mulvehill and Sreenan 1977), but care must be taken not to induce too high an ovulation rate.

5.3. Restricted suckling (beef cows)

Earlier onset of ovulation in beef cows may be induced by restricting suckling by calves from 30 days post partum (Stagg et al. 1998). Restricted suckling involves once or twice daily access of calves to cows for suckling and at other times of the day the calves are isolated and out of sight of the cows (Stagg et al. 1998).

6. Conclusions

Follicular growth generally resumes within 7-10 days post partum in the majority of cows associated with a transient FSH rise that occurs within 3 to 5 days of parturition. A summary of reproductive parameters for beef and dairy cows is presented in Table 2. Delayed resumption of ovulation is invariably due to a lack of LH pulse frequency whether it is due to suckling inhibition in beef cows or metabolic related stressors in high yielding dairy cows. First ovulation in both dairy and beef cows is generally silent and followed by a short cycle. The key to optimizing resumption of ovulation in both beef and dairy cows is appropriate pre-calving nutrition and management so that cows calve down in optimal body condition (body condition score 2.75-3.0) with postpartum body condition loss restricted to <0.5 body condition score units.

	Dairy cows	Beef cows
Emergence of the 1st follicle wave (days post partum)	5-10	5-10
% cows that ovulate the 1st dominant follicle	50-80	20-35
Postpartum interval to first estrus (days)	25-45	30-130
Nature of 1st ovulation	silent	silent
% short cycles after 1st ovulation	>70	>70
Regulation of LH pulse frequency	• declining energy balance • BCS at calving • dry matter intake	• suckling • maternal bond • declining energy balance • BCS at calving

Table 2. Reproductive parameters in the early postpartum period of dairy and beef suckler cows

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