Review

Deficiencies in luteal function during re-initiation of cyclic breeding activity in beef cows and in ewes

A.W. Lishman*
Department of Animal Science, University of Natal, P.O. Box 375, Pietermaritzburg 3200, Republic of South Africa
E.K. Inskeep
Division of Animal & Veterinary Sciences, West Virginia University, Morgantown, WV 26506-6108, United States of America

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Mechanisms that have been proposed to account for (i) premature regression or (ii) subnormal secretory activity of corpora lutea (CL) in cows or in ewes are reviewed. Processes which occur prior to, at the time of, or following, ovulation are considered. Infrequent pulsatile release of LH, particularly during early lactation, may result in ovulation of an immature follicle with the resulting CL exhibiting normal secretory activity. Such incompetent follicles possess reduced numbers of LH receptors and they secrete lower levels of oestradiol–17β. The evidence involving deficiencies, in (i) the preovulatory LH surge (ii) luteotropin support of the CL or (iii) LH receptors within the CL, is equivocal. A premature release of prostaglandin $F_2\alpha$ from the uterus apparently results in early demise of the first CL in cows and in ewes.

Keywords: Cattle, deficient luteal function, mechanisms, post-anoestrus, postpartum, progesterone, sheep.

* To whom correspondence should be addressed.

Introduction

It is generally recognized that calving rate and lambing percentage are major contributors to the profitability of beef herds and ewe-flocks. Often, the reproductive performance of beef breeding herds and sheep flocks is so low that culling rates have to be reduced severely in order to maintain herd/flock numbers. To produce a beef calf every 365 days, or to increase the frequency of lambing to more than once a year, requires that breeding females become pregnant during the early lactational period. This is particularly true when it is beneficial to advance the calving date of cows which calve late. Although much research effort has been expended in devising procedures, which favour early breeding in sheep and cows and out-of-season breeding in ewes, to date the success rate has been below expectations. Apparently, those mechanisms which favour conception need to be re-established in the early postpartum or anoestrous female.

The problem of poor luteal function, that occurs when breeding cycles are induced, is reviewed in this paper. The intention is also to describe how an understanding of the subject has evolved during the last decade. The main emphasis is on the beef cow but, since dairy cows and ewes appear to exhibit similar problems, information from these types of livestock is included in an attempt to clarify and understand the processes involved.

Artificial induction of breeding

In reviewing attempts at precipitating the onset of breeding activity, particularly those which have gained prominence during the last decade, it becomes apparent that whenever breeding was initiated, either naturally (Kiracofe *et al.*, 1969; Corah *et al.*, 1974; Yuthasatrakosol *et al.*, 1977; Humphrey *et al.*, 1976; Walton *et al.*, 1977; Bulman & Lamming, 1978; Lamming, 1978; Prybil & Butler, 1978; Schams *et al.*, 1979; LaVoie *et al.*, 1981; Peters & Riley, 1982; Manns *et al.*, 1983; Meisterling & Dailey, 1987) or artificially (Britt *et al.*, 1975; Crighton *et al.*, 1975; Haresign *et al.*, 1975; Fonesca *et al.*, 1977; Smith *et al.*, 1979; Carter *et al.*, 1980) the luteal function consequent to the first ovulation tended to be inferior in duration and/or quality. Even when pregnancy was allowed to continue for only 50 days the lifespan of the first luteal structure was reduced upon re-initiation of sexual cycles in a large proportion of heifers (Wright *et al.*, 1984; Copelin *et al.*, 1989a).

This phenomenon was highlighted when gonadotropin releasing hormone (GnRH) was first used to induce ovulation in lactating beef cows (Britt *et al.*, 1975; Webb *et al.*, 1977; Lishman *et al.*, 1979) and in lactating (Ainsworth *et al.*, 1982) or seasonally anoestrous ewes (Crighton *et al.*, 1975; Haresign *et al.*, 1975; Shareha *et al.*, 1976). However, luteal function which ceased prematurely has subsequently been demonstrated to occur even when ovulation was induced by injecting PMSG in lactating ewes (Fletcher *et al.*, 1980), by introduction of rams near the end of seasonal anoestrus (Oldham & Martin, 1979; Knight *et al.*, 1981), or when the suckling stimulus was manipulated to precipitate ovulation in beef cows (Flood *et al.*, 1979; Ward *et al.*, 1979; Odde *et al.*, 1980; Ramirez-Godinez *et al.*, 1980; Ramirez-Godinez *et al.*, 1981; Ramirez-Godinez *et al.*, 1982a). The foregoing discussion implies that, when exogenous hormones are utilized to precipitate the onset of breeding, the frequent occurrence of corpora lutea (CL) with a shortened lifespan, does not represent as great a failure of the technique as commonly believed. Apparently, exogenous hormones only mimic that which happens naturally in the cow or ewe when ovarian cycles commence spontaneously. Exposure of the reproductive system to progesterone (P4) for a short period of time could therefore be a vital prerequisite to the

restoration of full reproductive function. Although Peters & Lamming (1984) believed that P4 priming is not essential, evidence will be presented here to illustrate the beneficial consequences of prior exposure to this gonadal steroid.

The problem of luteal insufficiency may not end after the first short luteal cycle (Lishman *et al.*, 1979). Evidence continues to accumulate which suggests that the secretory activity of the CL improves over several cycles postpartum (Stevenson & Britt, 1979; Webb *et al.*, 1980; Duby *et al.*, 1985; Butterfield, 1986). This is supported by the finding that only 12% of first postpartum ovulations in beef cows were fertile (Holness *et al.*, 1980), particularly when they occurred before 50 days postpartum in *Bos indicus* cows (Wells *et al.*, 1985). There appeared to be an association between concentrations of P4 in the cycle preceding that in which mating occurred and the success of conception (Henricks *et al.*, 1971; Folman *et al.*, 1973; Corah *et al.*, 1974; Holness *et.al.*, 1977; Meisterling & Dailey, 1987). Further support for the belief that luteal incompetence may have been exerting an important influence on conception rates during the early postpartum period has been obtained for beef cows by Rutter & Randel (1984) and for sheep by Rhind *et al.* (1980).

Types of abnormal luteal function

Two distinct types of abnormal luteal function occurred in ewes (Fletcher *et al.*, 1980; Inskeep & Murdoch, 1980; diZerega & Hodgen, 1981; Lewis *et al.*, 1983) and in beef cows (Troxel & Kesler, 1984b). According to Murdoch *et al.* (1983) and Troxel & Kesler (1984b), one type incorporated a luteal lifespan of 6 to 12 days (the short luteal phase), while the other was characterized by a luteal phase of more than 14 days, but with depressed plasma P4 (the inadequate luteal phase).

Although short-lived CL occur almost exclusively when breeding is initiated for the first time or after a period of sexual rest, inadequate CL seem to occur at any stage during the reproductive life of cattle or sheep. Apparently, the short life-cycle CL functioned for a longer period in the ewe when large, single (Haresign, 1976; McNeilly *et al.*, 1981; O'Shea *et al.*, 1984) rather than multiple, low-dose treatment with GnRH was applied (Hunter *et al.*, 1988; Southee *et al.*, 1988). In the latter case only a transient rise in plasma concentrations of P4, which lasted for about four days, was seen (Hunter *et al.*, 1988; Southee *et al.*, 1988), resembling that which occurred prior to puberty in the ewe (Berardinelli *et al.*, 1979) and after ram introduction in anoestrous ewes (Knight *et al.*, 1981).

The possibility that inadequate and short-lived CL may be the result of different mechanisms will be examined in this review. In order to reduce the postpartum interval to conception, particularly in cows, the problem of luteal insufficiency in the early phases of reinitiation of sexual activity should be eliminated (Ramirez-Godinez *et al.*, 1981; 1982b). Elimination of short-lived luteal phases is also advantageous when reduction of the time interval between successive parturitions in cows that calve late is required. In demonstrating the relationship amongst factors contributing to infertility, Short *et al.* (1990) have illustrated the importance of short oestrous cycles in increasing postpartum infertility.

Cellular composition of the CL

Follicular origin

In attempting to account for deficiencies in luteal function, attention needs to be focused on the origin of the cells that differentiate to form the CL. Any changes in the final cellular composition of the CL also warrant consideration.

In many domestic animals the CL contain two distinct steroidogenic cell-types (Niswender *et al.*, 1985a). These cell-types, which have different morphological and biochemical properties (O'Shea *et al.*, 1979; 1980; Fitz *et al.*, 1982; Glass *et al.*, 1984; Hoyer & Niswender, 1985) have been termed small or large luteal cells. The follicular origin of the small luteal cells appears to be the theca interna of the preovulatory follicle in cattle (Donaldson & Hansel, 1965; Priedkalns *et al.*, 1968) and in the ewe (Deane *et al.*, 1966; McClellan *et al.*, 1975), whereas the large luteal cells originate from the granulosal cells (Donaldson & Hansel, 1965; McClellan *et al.*, 1977; O'Shea *et al.*, 1980). The question as to whether large and small luteal cells persist as discrete and closed populations throughout the lifespan of the CL is more controversial (O'Shea, 1987). Several lines of evidence (Donaldson & Hansel, 1965; Alila & Hansel, 1984; Farin *et al.*, 1985; Niswender *et al.*, 1986; Farin *et al.*, 1988) support the suggestion that small luteal cells may be able to differentiate into large luteal cells as the cycle progresses (Hansel & Dowd, 1986). However, Farin *et al.* (1988) postulated that such conversion to large luteal cells occurs only during the early part of the oestrous cycle. There may even be stem cells in the CL which differentiate into small steroidogenic cells. These, in turn, may become large luteal cells (Niswender *et al.*, 1985).

Contribution of different cell types to circulating P4 concentrations

LH is the major luteotropin in domestic ruminants (Niswender *et al.*, 1985) and in both sheep (Fitz *et al.*, 1982; Rodgers & O'Shea, 1982; Rodgers *et al.*, 1983) and cattle (Ursely & Leymarie, 1979; Koos & Hansel, 1981) a marked difference in the response to LH by large and small luteal cells is exhibited *in vitro* (Koos & Hansel, 1981; Harrison *et al.*, 1897; O'Shea, 1987). Because of much higher numbers of LH receptors on small than on large luteal cells (Fitz *et al.*, 1982; Harrison *et al.*, 1987), the P4 secretory response to LH is probably confined almost entirely to these cells (O'Shea, 1987). Furthermore, Niswender *et al.* (1985) have calculated that during mid-cycle approximately 20% of the P4 in the ovarian vein is secreted by the small luteal cells, while nearly 80% appears to be secreted by large cells, which have only a few functional receptors for LH (Harrison *et al.*, 1987). On a per cell basis the large luteal cells produce substantially more P4 than small luteal cells (O'Shea, 1987).

Mechanisms contributing to reduced luteal function

The foregoing brief description of the cellular components

of the normally functioning CL, their reputed follicular origins and the contribution each type of cell could be making to circulating P4, facilitates an evaluation of the mechanisms which may be resulting in impaired function of induced CL (Figure 1). The mechanisms can be classified into three main categories: (A) deficiencies in the maturational process within the preovulatory follicle and/or inadequacies of the ovulatory stimulus; (B) shortcomings in the support of the CL once they have formed; or (C) a premature activation of the luteolytic process.

Theoretically, the CL could be influenced by at least two different types of tropic stimuli, the one increasing its secretory activity and the other prolonging its lifespan (Schomberg *et al.*, 1967). Such considerations are important when evaluating possible imperfections in the normal process of CL formation and continued function. The proposal (Troxel & Kesler, 1984a) that inadequate luteal function could be composed of two distinct aspects, namely, luteal lifespan and secretory activity, agrees with the foregoing.

The possibility that deficiencies of the follicle may be reflected in subnormal concentrations of P4 during the course of a cycle of approximately normal duration, whereas short-lived CL could more probably be the consequence of premature activation of luteolysis, is examined in this article. An attempt will thus be made to answer the question posed by Short *et al.* (1990), namely, 'Why is the first oestrous cycle short — is it because the CL are not capable of functioning normally, or is it because signals are being given prematurely for regression to occur?' The former would imply that although the luteotropic signal (Figure 1, Component 12) is normal, either the CL do not recognize the luteotropin because of a lack of LH receptors (Component 13) or the cellular make-up may be altered in some way. Premature regression could involve release of $PGF_2\alpha$ at an inappropriate stage of the development of the CL (Component 20) and this could in turn be the consequence of lack of P4 priming of the uterus (Component 22). The reader should refer also to the papers by Lauderdale (1986) and by Garverick & Smith (1986).

The short-lived CL formed following spontaneous ovulation after parturition appears to be due to mechanisms similar to those resulting in short-lived CL after an artificially induced ovulation. This is supported by the results obtained when (1) the first CL formed spontaneously after parturition was compared with the CL of normally cycling cows (Smith *et al.*, 1986; Braden *et al.*, 1989a) or ewes (Braden *et al.*, 1989b) and (2) CL induced following a period of pretreatment with P4 or without P4 were compared (Rutter *et al.*, 1985) However, care should be exercised in assuming that the deficiencies of the former are necessarily the same as those of the latter. Kesler *et al.* (1981) have made a similar conclusion.

Deficiencies prior to ovulation

The need for proper maturation of the preovulatory follicle

In 1975, it was suggested by one of us (EKI) that to induce ovulation in lactating beef cows, using GnRH, at least one ovarian follicle should have matured sufficiently to be palpable on the ovarian surface prior to administration of releasing hormone. This contention was subsequently substantiated (Lishman *et al.*, 1979) and has found support elsewhere (Kesler *et al.*, 1978; Garverick *et al.*, 1980; Smith *et al.*, 1983; Peters & Lamming, 1984). Furthermore, Haresign & Lamming (1978) have demonstrated that in anoestrous ewes, stimulation of the pre-ovulatory follicle with PMSG, prior to administration of GnRH, significantly increased the incidence of ovulation. The foregoing discussion relates to the success with which ovulation can be induced. This event usually precedes formation of the CL, and as pointed out by Garverick *et al.* (1988), formation of the CL is a continuation of follicular maturation. It has been suggested (Odde *et al.*, 1980) that inadequate preparation of the follicle (Component 9) might also be responsible for poor luteal function in the cow. In fact, gonadotropin treatment prior to the induction of ovulation in sheep (Haresign & Lamming, 1978; Grobbelaar *et al.*, 1989) and cows (Lishman *et al.*, 1979; Sheffel *et al.*, 1982) has resulted in improved function of the resulting CL.

Changes within the maturing follicle that may influence the function of the resulting CL

In the rat as follicles mature during the pre-ovulatory stage, under the influence of a sustained increase (Figure 1, Components 6 and 8) in LH or FSH (Richards, 1980), the number of LH receptors in the thecal and granulosal cells increases (Uilenbroek & Richards, 1979). The appearance of LH receptors in the granulosal cells denotes the follicle destined to ovulate (Webb & England, 1982). These granulosal cells also possess receptors to FSH (see Richards, 1980 for review).

With this information as background, it is possible to consider what deficiencies of the follicle destined to ovulate could result in an inadequate CL in a cow or ewe. The cellular composition and source of the large and of the small luteal cells should be borne in mind here. One possibility is a deficiency in cell numbers, cell sizes, or proportions of large to small luteal cells (O'Shea *et al.*, 1984) while another is a deficiency of receptors (Component 13) to luteotropin could result in the CL failing to recognize or respond to luteotropin (Kesler *et al.*, 1981; Rutter & Randel, 1984). The latter assumes that quantities of luteotropin are adequate at such times.

O'Shea *et al.* (1984) believed that the defect of the follicle which ovulates following treatment with releasing hormone may in fact encompass sub-optimal numbers of granulosal and/or thecal cells (Component 9). A deficiency of granulosal cells is likely to be more significant, as their capacity for mitosis, after ovulation, is probably non-existent (McClellan *et al*, 1975; O'Shea *et al.*, 1980); and stimulation of the follicle before ovulation possibly improves P4 production (by the CL) by favouring development (numbers, sizes, or receptors) of granulosal cells from which the large luteal cells develop. On the other hand, the LH-sensitive thecal cells continued to divide for at least 5 days after ovulation during the normal oestrous cycle (O'Shea *et al.*, 1980) while the GnRH-induced CL did not persist beyond this time (Kesler *et al.*, 1981). This agrees with the findings of Lishman *et al.* (1979).

If it is accepted that large luteal cells can develop from

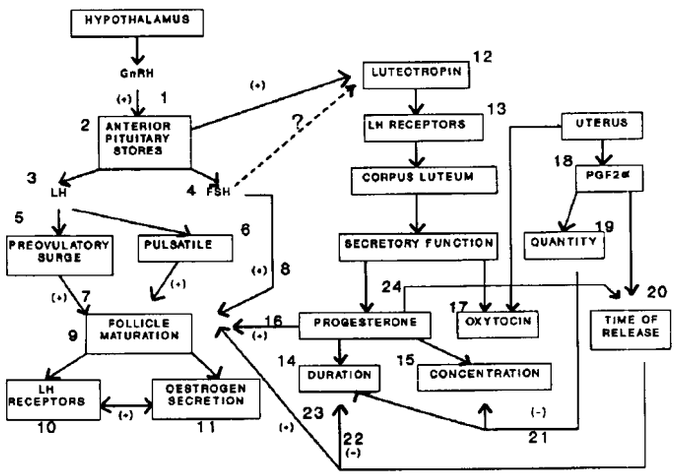

Figure 1 Possible deficiencies of the hypothalamo-pituitary-ovarian complex which could lead to a short-lived or subnormal corpus luteum and the role of the uterus in reducing luteal competence.

small luteal cells, then the statement by Gamboni *et al.* (1984) that large luteal cells increase in abundance about the middle of the normal oestrous cycle implies that the number of thecal cells within the developing follicle is of cardinal importance.

Based on morphometric examination, O'Shea *et al.* (1984) demonstrated that the reduced luteal volume of the GnRH-induced CL, in anoestrous ewes, was associated with reduced numbers of luteal cells per CL. However, no evidence was found of a fall in the proportion of large to small luteal cells which could explain the lowered basal P4 production observed in induced CL.

These findings have been confirmed in spontaneously ovulating, lactating ewes (Braden *et al.*, 1989b) and cows (Duby *et al.*, 1985), and also in cows induced to ovulate with GnRH (Rutter *et al.*, 1985). The former authors concluded that although the number of granulosal cells was almost doubled in preovulatory follicles expected to form short-lived CL in cows (Braden *et al.*, 1989a) this does not result in CL containing a greater proportion of large luteal cells.

Even though thecal cells appear to give rise to the luteal cells which respond to luteotropin, the granulosal layer of the preovulaytory follicle may play a role in the response to post ovulatory LH. This is supported by the suggestion (Kesler *et al.*, 1981) that non-proliferating granulosal cells could acquire the ability to respond to LH and thereby increase concentrations of P4 between days 5 and 7 in cycling ewes. Fritz *et al.* (1982) and Gamboni *et al.* (1984) maintained, however, that the sources of the small and large luteal cells are unclear; they supported the conclusion that the large cells lack receptors for LH.

It thus appears possible that increased concentrations of postovulatory LH could promote secretion of P4 via cells of granulosal or thecal origin (Kesler *et al.*, 1981; Fitz *et al.* 1982), with the evidence favouring an effect of LH on the small luteal cells (Fitz *et al.*, 1982).

Why are mature follicles scarce during times of sexual rest?

Research into the reasons why mature follicles are rare in the ovaries during periods of anoestrus has been based upon the observed low concentrations of LH in plasma at such times (see Peters & Lamming, 1984 and Nett, 1987 for review). This situation was at least partly the result of low pituitary reserves of LH (Component 2) during the early postpartum period (Jenkin *et al.*, 1977; Crowder *et al.*, 1982; Clarke *et al.*, 1984; Moss *et al.*, 1985). Consequently, in attempting to account for the poor response to releasing hormone in the postpartum cow, the deficiencies were considered to possibly include inadequate release of LH, either for several days prior to ovulation (Component 6), or in shortcomings (duration and/or peak concentrations; Component 5) of the preovulatory surge of LH (Kesler *et al.*, 1978; Lishman *et al.*, 1979; Troxel *et al.*, 1980).

In order to determine the deficiencies of the follicle which ovulates in response to GnRH and which cellular components are being affected, a close study of follicle maturation in spontaneously ovulating ewes or cows and an evaluation of the hormonal mechanisms which support this maturation are necessary.

Hormonal mechanisms which drive the follicle to maturation

Since the work of Haresign & Lamming (1978), suggesting that exogenous gonadotropin priming of the ovary can promote induction of normal luteal function when GnRH is used to induce ovulation, considerable research has focused on this aspect.

The final stages of follicular development (Component 9), in both the spontaneously cycling ewe and cow, were associated with a marked increase in the frequency of LH episodes (Yuthasastraskosol *et al.*, 1977; Baird, 1978; Rahe *et al.*, 1980; Karsch *et al.*, 1983). Following regression of the CL, the frequency of the LH episodes increased from one per 3 to 12 h interval to one every 1 to 2 h immediately before the LH peak (see McLeod *et al.*, 1982a, for review). A similar mechanism has been proposed for the prepubertal ewe (Foster & Olster, 1985). In contrast, periods of ovarian acyclicity were associated with a low frequency of LH episodes (Lamming *et al.*, 1981; Peters *et al.*, 1981; McLeod *et al.*, 1982a; 1982b; Wright *et al.*, 1983; Clarke, 1988; Savio *et al.*, 1990). Thus, during seasonal anoestrus in the ewe (Hunter & Southee, 1987) and during the early postpartum period in dairy cows (Savio *et al.*, 1990), the pulsatile release of LH was insufficient to promote the final maturation of follicles (Hunter & Southee, 1987).

LH (McNeilly *et al.*, 1982) or GnRH (McLeod *et al.*, 1982a; 1982b; McNatty *et al.*, 1982; Guajardo *et al.*, 1988) was administered repeatedly in anoestrous ewes and postpartum cows (Riley *et al.*, 1981), so as to increase the LH pulse frequency to that seen during the follicular phase of the normal oestrous cycle. This induced ovulation, as it did in prepubertal ewes (Keisler *et al.*, 1985; Pirl & Adams, 1987). However, CL function was still subnormal (McNeilly *et al.*, 1981; McLeod *et al.*, 1982a; 1982b; Hunter *et al.*, 1986).

These findings agree with the observation that although weaning induced short-lived CL after the first oestrus in beef cows, the pattern of gonadotropins did not differ for

three days prior to to the first or second oestrus (Garverick *et al.*, 1988). The second oestrus was followed by normal luteal phases in that study.

The formation of properly functional CL apparently requires a duration (at least 20 h), and possibly a pattern, of LH stimulation of the ovary similar to that occurring in cyclic females from the time of luteolysis to the start of the preovulatory surge (Wright *et al.*, 1984). While it may be obligatory for the pituitary to release LH in a pulsatile fashion (Wang *et al.*, 1976; Jewelewicz *et al.*, 1977), it is not clear whether the pattern of episodic delivery of LH to the ovary is critical for promoting the final stages of follicular maturation (McNatty *et al.*, 1982). To support follicular maturation a pulsatile delivery of LH to the ovary may be preferable to constant exposure (McNatty *et al.*, 1981). However, widely differing patterns of LH stimulation during the pre-ovulatory period have resulted in normal follicular maturation and some CL function (Keisler *et al.*, 1985). Such considerations have important practical implications should it become necessary to supply exogenous gonadotropin. Obviously, it would be much simpler to achieve a relatively continuous delivery, whereas pulsatile patterns are difficult to duplicate on any reasonable scale.

Recently, it has been suggested that $PGF_2\alpha$ may also be involved in follicular development (Component 23) in early postpartum cows (Guilbault *et al.*, 1987); and evidence to support this hypothesis has been obtained in cows (Villeneuve *et al.*, 1988) and in ewes (Villeneuve *et al.*, 1989). Accordingly, either the quantity or pattern of $PGF_2\alpha$ release may be inappropriate prior to ovulation resulting in subnormal CL function.

Why are LH pulses infrequent in early postpartum?

Pituitary reserves of LH and patterns of GNRH secretion

Nett (1987) has reviewed possible deficiencies of the hypothalamic-hypophysial axis that could result in a reduced secretion of LH during the early part of the postpartum period, while Clarke (1988) has discussed the seasonally anoestrous ewe. Moss *et al.*, (1985) suggested that lowered pituitary concentrations of LH (Component 2) was more likely to be one of the initial limitations to the re-establishment of oestrous cycles rather than alterations in the sensitivity of this organ to GnRH.

Cognisance should be taken of the fact that in the majority of studies on pituitary LH content and release patterns, LH was measured by radio-immunoassy. Moss *et al.*, (1988) have pointed out that only a fraction of the immunoactive LH in the bovine pituitary is biologically active. Furthermore, Weesner *et al.*, (1987) concluded that low biological activity of LH may contribute to postpartum infertility in cows.

Evaluation of the GnRH content of hypothalamic neurons (Leshin *et al.*, 1988) suggested a reduced synthesis of GnRH during early postpartum (up to about day 40 postpartum). With reduced synthesis of GnRH, there could be a lack of stimulus (Component 1) for secretion of LH and for its release in an appropriate manner. This conclusion is not supported by the findings in anoestrous ewes (Clarke, 1988). GnRH pulses were seen to be half as frequent as during the luteal phase, suggesting reduced hypothalamic secretion of GnRH. However, injecting oestradiol benzoate did not cause a surge in GnRH secretion within 12 h. Consequently, deficiencies in secretion of LH (frequency and/or pulse amplitude) are possibly not due to a lack of hypothalamic GnRH. Nett (1987) concluded that during the postpartum period the hypothalamus in fact contained sufficient stores of GnRH to stimulate the anterior pituitary. He maintained that the critical question which needed to be answered was whether GnRH is secreted in a manner which will stimulate ovarian cyclicity. Once the pituitary stores of LH had been replenished, then pulses in the secretion of LH could increase in frequency to culminate in the first postpartum oestrus (Humphrey *et al.*, 1983) with the LH pulse amplitude reflecting the releasable pituitary reserves (Clarke & Cummins, 1985). Ovarian acyclicity thus appeared to be the result of a failure of follicle development, possibly due to an inadequate frequency of LH pulses (Component 6). This, in turn, reflected inadequate pulsatile release of GnRH (Wright *et al.*, 1981; 1983; Wise *et al.*, 1989).

Feedback response to E2

Infrequent pulses of LH may not be the only deficiency during early postpartum. Peters (1984) has proposed that although the positive feedback mechanism of E2 in triggering the pre-ovulatory LH release may be functional, recovery of maximal activity may continue over an extended period. Therefore, the hypothalamo-pituitary axis would need to recover responsiveness to increasing plasma concentrations of E2 before the first ovulation can occur. The results of Nancarrow *et al.* (1977), Wright & Findlay (1977), Zaied *et al.* (1980) and Irvin *et al.* (1981) support the conclusion that pituitary responsiveness to GnRH was restored before that of the hypothalamus to E2. Wise *et al.* (1986) concluded that the resumption of reproductive cycles in postpartum ewes occurred about the time that the concentration of receptors for E2 in the anterior pituitary and hypothalamus increased.

Parfet *et al.* (1986) stated that the absence of oestrous cycles in suckled beef cows near 30 days postpartum was not due to deficiencies in (1) ovarian follicular development, (2) anterior pituitary concentrations of LH and FSH or *in vitro* releasability of LH or (3) pituitary receptors for GnRH.

Apparently, in the properly fed cow, at about one month after calving, the hypothalamo-pituitary axis is fully able to support resumption of ovarian cycles, but the suckling stimulus inhibits pulsatile release of LH (see Williams, 1989 for review).

Is FSH deficient during early postpartum period?

FSH is considered to play only a permissive role in the onset of ovarian cycles postpartum. Nevertheless, the existence of a threshold which needs to be exceeded, so as to enable LH to stimulate ovarian activity, has not been excluded (Peters & Lamming, 1984; Garcia-Winder *et al.*, 1986).

Fortune & Quirke (1988) proposed that FSH is critical to support growth and development of bovine preovulatory follicles during and after luteolysis. Consequently, a deficiency of FSH during the late luteal to early follicular

phase could perhaps inhibit the development and function of the preovulatory follicle (Fortune & Quirke, 1988). If FSH is deficient during the early lactational period then maturation of the pre-ovulatory follicle (Component 9) might be impeded. This contention is supported by the observation that P4 priming increased the lifespan of induced CL only in beef cows in which the plasma concentrations of FSH were relatively high at the time of P4 implantation (Garcia-Winder *et al.*, 1986). This agrees with the observation that suppression of FSH release by administration of follicular fluid, while Norgestomet was implanted, reduced the incidence of ovulation in cycling ewes (Larson *et al.*, 1987) and tended to shorten luteal lifespan in postpartum cows (Larson, 1987). Furthermore, FSH concentrations were lower over the last four days before the first preovulatory LH surge induced by weaning in beef cows. FSH concentrations were also lower compared to the same period prior to the second preovulatory LH surge (Ramirez-Godinez *et al.*, 1985b). The former preceded short-lived CL, while the latter preceded normal luteal function. However, Garverick *et al.* (1988) reported no difference in FSH concentrations prior to the first induced (weaning) oestrus as compared to the subsequent oestrus. This is supported by Lewis & Bolt (1987) who found that suckling did not reduce GnRH-induced release of FSH in postpartum ewes.

The proposal (Driancourt & Fry, 1988) that follicles must first be primed (i.e. sensitized) by FSH before they are able to respond to LH is in accordance with the foregoing suggested role for FSH. The magnitude of the FSH changes that are required is, however, unknown (Driancourt & Fry, 1988).

Lack of follicular maturation in the postpartum cow

A model to explain inadequate maturation of follicles in the postpartum, anoestrous cow has been derived by Nett (1987). To account for low concentrations of LH during early lactation, he suggested that during pregnancy the high concentrations of P4 and E2 resulted in a prolonged negative feedback on the hypothalamic-hypophysial axis. Accordingly, the synthesis of LH was inhibited and pituitary stores became depleted so that basal release of LH was reduced. Weesner *et al.* (1987) have produced results which supported this conclusion. After parturition, a two-phase recovery of the hypothalamic-pituitary-gonadal axis occurred with the first phase (lasting 2 – 5 weeks) perhaps characterized by infrequent releases of GnRH (one pulse / 4 – 8h). Once pituitary stores of LH had been replenished then the amplitude of the LH pulses was sufficient to stimulate follicular growth. This denoted the start of the second phase of the recovery process, during which the increased circulating concentrations stimulated growth of ovarian follicles, which in turn produced E2. At this point in time, the frequency of release of GnRH also increased with a consequent increase in the frequency of LH pulses. The final stages of follicular development ensued and culminated in the first ovulation.

Intrafollicular receptors for LH and the role of E2

Development of LH receptors

Even if luteotropin secretion is sufficient to support normal CL function (discussed later), then short-lived or inadequate CL may not recognize LH. This raises the question (of sufficient LH receptors, possibly within the maturing follicle and subsequently in the CL (Component 10 and 13).

According to Fortune & Quirke (1988), E2, in addition to its role as the major steroid messenger produced by mature follicles, also acted within the follicle to regulate its development and function. They proposed that as the preovulatory follicle matured, the initial action of E2 was that of positive feedback on its own production, via increased androgen synthesis.

During pre-ovulatory growth, follicles become more responsive to LH and acquire an increased ability to synthesize E2 (see Webb & England, 1982, for review). Improved responsiveness to basal levels of LH was related to an increase in LH receptors in the granulosal cells (Webb & England, 1982); the induction of these vitally important receptors, in turn, may have been influenced by E2 (Richards, 1980; Webb & England, 1982). This suggested that increased follicular concentrations of E2 may have played a leading role in the induction of increased numbers of granulosal LH receptors (Component 10) during the pre-ovulatory period (Uilenbroek *et al.*, 1979). The E2 may have been derived via small changes in basal LH not detected by the usual assays (Richards, 1980) and may be important in the function of the resulting CL. Both E2 and FSH are necessary for production of LH receptors before luteinization of granulosal cells (McNatty, 1979; Richards, 1980). Also, numbers of thecal and granulosal receptors for LH within the maturing follicle were related to subsequent luteal function in rats (Richards & Midgley, 1976) and in humans (McNatty, 1979). However, Spicer *et al.* (1986) observed that despite increased E2 in the fluid of large follicles between days 14 and 28 postpartum, neither the receptors for LH nor FSH increased in number. The results obtained by Braden *et al.* (1989a) support these findings with regard to E2 and LH receptors in the first preovulatory follicle formed (by weaning) during the postpartum period as compared to preovulatory follicles in cycling cows.

E2 and luteal lifespan

A positive role of E2 is supported by the finding (Larson, 1987) that in postpartum beef cows, administration of hCG (to induce ovulation) more often led to CL with a normal lifespan in cows with high plasma E2 than in cows with low E2. Similarly, the largest preovulatory follicle possessed decreased numbers of receptors for LH in the granulosa and theca in cows which were predicted to have short luteal phases than in Norgestomet pretreated cows which were expected to show normal luteal lifespans (Inskeep *et al.*, 1988). Garcia-Winder *et al.* (1987) and Inskeep *et al.* (1988) found a higher concentration of E2 in the fluid of the largest follicle of cows which had been implanted with synthetic progestogen (Norgestomet). Such implanted cows commonly had CL with a normal lifespan. Similarly, implanting E2 in addition to the intermittent injection of GnRH (Wright

et al., 1982), implanting E2 shortly after calving (Dyer *et al.*, 1988; Day *et al.*, 1990) or the infusion of catechol estradiol (a metabolite of oestradiol) into the uterine horn (Nephew *et al.*, 1989) promoted normal luteal lifespan in lactating beef cows.

Intrafollicular E2

The improved responsiveness of the follicle may reflect an improved number of granulosal cells per follicle or even an effect of intrafollicular E2 (Richards, 1980). If the latter is important then it could explain why raising the systemic levels of this steroid, through exogenous sources, has not necessarily been beneficial to CL function (Lishman *et al.*, 1979; Grobbelaar *et al.*, 1989), i.e. concentration of E2 may not have been increased within the follicle. Accordingly, Garverick & Smith (1986) have concluded that high concentrations of E2 and adequate thecal vascularization may be important determinants of subsequent luteal function. Hunter *et al.* (1988) supported this, stating that inadequate vascularization of the CL may lead to premature regression of this structure in anoestrous ewes because the CL were then more vulnerable to the vasconstrictive effects of $PGF_2\alpha$. The ability of vasodilatory drugs to negate the cycle shortening effect of oxytocin administered early in the cycle in cows, provides additional supportive evidence (Kotiwica, 1988).

The conclusion that E2 may be required, within the mature follicle, at a level which is not achieved by the usual im. dose of E2 administered, seems justified, particularly since microgram quantities of E2 are known to occur in the follicular fluid (England *et al.*, 1973). Further support is provided by the demonstration that, in the cow, concentrations of E2 were higher and more pulsatile in the vena cava than in the jugular (Walters *et al.*, 1984). In addition, the stimulation of normal luteal activity in anoestrous ewes, by repeated low doses of GnRH, was probably dependent on ovulation being induced via E2 from the developing follicle and not due to a fairly immediate release of LH in response to the exogenous GnRH (McLeod & Haresign, 1984a; 1984b). A similar situation may hold with regard to the ram-induced ovulation at the onset of the breeding season. This ovulation reputedly is not preceded by a preovulatory rise in circulating concentrations of E2 (Pearce *et al.*, 1985; Knight *et al.*, 1978).

Exposure of the granulosal cells to LH may promote luteinization within the follicle (Channing, 1970) and this could occur during the preovulatory surge (Moor *et al.*, 1973) when E2 production by the thecal cells is terminated (Moor, 1974). It has been demonstrated (Moor, 1973) that the preovulatory follicle produced significant amounts of P4. This was supported by the finding of an increased blood level of P4, particularly in the vena cava, before ovulation in the cow (Walters & Schallenberger, 1984). It is perhaps at this critical stage that inadequacies of the follicle that will be ovulated by GnRH first become evident and this is supported by the association between a small elevation in plasma P4 on the day of GnRH injection or calf removal and subsequent function of the induced CL (Williams, 1989).

Evidence from a number of sources supports the conclusion that E2 within the preovulatory follicle is associated with the function of the resulting CL. Whether follicular concentrations of E2 are directly involved in fully maturing the follicle destined to ovulate or whether they simply reflect the degree of maturation, remains to be clarified.

Deficiencies at the time of ovulation or post ovulation

Could abnormalities of the preovulatory LH surge result in a short-lived or defective CL?

The preovulatory LH surge induced by GnRH was smaller in anoestrous ewes (Foster & Crighton, 1974) and of shorter duration in postpartum cows (Lishman *et al.*, 1979) than that observed at spontaneous oestrus. Nevertheless, it was concluded (Crighton *et al.*, 1975; Haresign *et al.*, 1975) that deficiencies of the preovulatory LH release (Component 7) could not be implicated in the ability of GnRH-induced CL to function normally. A similar conclusion has been made concerning the preovulatory release induced by weaning in beef cows (Ramirez-Godinez *et al.*, 1982b). In contrast, McNatty *et al.* (1981) maintained that an inappropriate preovulatory LH surge was involved. They proposed that to realise ovulation and normal CL in anoestrous ewes, the LH surge should persist for about four hours and the peak concentration should rise above 30 ng/ml. Troxel & Kesler (1984b) were in agreement, stating that the magnitude and duration of the GnRH-induced LH surge appeared to be associated with enhanced CL function and lifespan. Similarly, Cruz & Kesler (1988) reported that cows with normal luteal function had a greater GnRH-induced LH release than cows with short luteal phases. Shirar *et al.* (1989) supported this viewpoint, but emphasized the importance of duration of the preovulatory LH release. They observed that progestogen treatment, prior to GnRH, changed the pattern of LH release and possibly thereby improved luteal function. Lewis *et al.* (1983) confirmed the effect on LH release, but not on luteal function, in postpartum, anoestrous ewes.

Can the reduced lifespan or lowered secretory activity of the first CL be attributed to sub-optimal luteotropic support?

Prolongation of luteal lifespan and stimulation of P4 secretion

In discussing the problem of luteal insufficiency during the postpartum period, little distinction has been made between luteal secretion and lifespan of the CL, although it has been suggested that different mechanisms might be involved. Schomberg *et al.* (1967) believed that from a biological viewpoint, prolongation of the functional life of the CL may be more important than increasing its secretory activity. Until recently, both the luteotropic stimulus responsible for increased secretory activity and that prolonging lifespan have been assumed to be vested in one hormone (Schomberg *et al.*, 1967). There is an extensive body of evidence that the bovine CL is dependent primarily on LH to maintain secretion of P4 (Hansel & Echternkamp, 1972). Whether CL showing weak secretory activity are more likely to be overcome by marginal levels of luteolytic agents or fail to recognise LH, as could occur during lactation, has not been elucidated.

Niswender *et al.* (1986) have reviewed the roles of LH

and prolactin in regulating luteal function in ewes; their research led them to conclude that LH is the primary luteotropic hormone with no role for prolactin being detectable. FSH receptors have been detected in luteal cells of cows Manns *et al.* (1984); and Walters *et al.* (1984) suggested that since 97% of separate FSH pulses during the mid-luteal phase in the cow were associated with P4 pulses, it is possible that FSH could be the principal hormone that stimulates P4 secretion. They maintained that this did not exclude a luteotropic action of LH (Hoffmann *et al.*, 1974) in addition to a stimulatory action of FSH on release of P4 in the cow. Baird *et al.* (1976) believed that a certain minimal basal level of LH is necessary for P4 secretion.

There was even the possibility of an interaction of oxytocin (from the CL) and LH in regulating P4 synthesis, with oxytocin increasing the reponse to LH (Pekala *et al.*, 1983). In ewes it appeared that disruption of luteotropic support from the pituitary during formation of the CL (± day 1 of the cycle) resulted in premature luteal regression (Kaltenbach *et al.*, 1968; Mallory *et al.*, 1986) or reduced CL function (Mallory *et al.*, 1986). However, once the CL had formed, alterations to the luteotropic signal appeared to have had little effect on P4 secretion, providing LH was not removed completely (Niswender *et al.*, 1986). The foregoing was supported by the demonstration of large numbers of LH receptors on steroidogenically active luteal cells, which fell precipitously at the time of luteolysis (Diekman *et al.*, 1978; Rao *et al.*, 1979; Spicer *et al.*, 1981).

Deficiencies in luteotropic support

The short-lived CL

The possibility that the luteotropic stimulus (Component 12) may be insufficient during early postpartum to maintain the CL for its normal lifespan has been the subject of several studies. Peters & Lamming (1984) and Rutter & Randel (1984) supported the conclusion that concentrations of LH were in fact adequate during the short P4 rise that often preceded the first oestrus, and Copelin *et al.* (1987) and Garverick *et al.* (1988) obtained results to confirm this. In contrast, O'Shea *et al.* (1984) have suggested that besides defects of the follicle which ovulated in response to GnRH, sub-optimal luteotropic support in the post-ovulatory period could have accounted for subnormal luteal-cell numbers and sizes which were characteristic of the CL induced by GnRH. Atkinson & Williamson (1985) have concluded that lack of luteotropic support may be implicated in the short-lived CL induced by ram introduction. Kesler *et al.* (1981) do not agree that luteotropin could be lacking at such times, and Duby *et al.* (1985) favour Kesler's viewpoint. Similarly, in cattle, mean concentrations, as well as frequency and amplitude of pulses of LH were similar for short-lived and normal CL (Ramirez-Godinez *et al.*, 1982b; Rutter *et al.*, 1985; Garcia-Winder *et al.*, 1986; Garverick *et al.*, 1988), while a chronic increase in secretion of LH via continuous infusion of GnRH did not sustain the activity of GnRH-induced CL (D'Occhio *et al.*, 1989). However, elevation of LH concentrations by injection of microencapsulated GnRH did promote normal luteal function (Roberts *et al.*, 1989). When Carruthers *et al.* (1986) injected hCG after treatment with GnRH, the incidence of short cycles was in fact increased.

The inadequate CL

From the foregoing presentation, it appears reasonable to conclude that short-lived CL are not the result of a deficiency in luteotropic support. The question then arises as to whether a similar conclusion would be valid for the inadequate CL (Component 15). Grobbelaar *et al.*, (1989) attempted to determine whether additional luteotropic support would improve the secretory activity of GnRH-induced CL. They administered PMSG for up to 17 days, commencing at the time of GnRH infusion, and this appeared to elicit a supraphysiological response with plasma concentrations of P4 rising to almost twice the peak concentrations seen in normally cycling ewes. These results are somewhat similar to those obtained when GnRH was administered in small doses over eight days (McLeod *et al.*, 1982a); and O'Shea *et al.* (1984) concluded that this could be taken as demonstration of a lack of luteotropic support at such times.

If it is accepted that luteotropin may not be sufficient to realise normal luteal function (Component 12), then the problem becomes one of just when endogenous supplies need to be augmented. In cyclic cows, Walters & Schallenberger (1984) could detect no pulsatile LH for 6 to 12 h after the LH surge with basal levels falling even below those recorded before the preovulatory LH release. In contrast, FSH showed a distinct increase in basal concentrations 4 to 12 h after the LH surge. By limiting the administration of PMSG to only three days, Pearson & Lishman (1989) demonstrated that a luteotropic stimulus provided early in the induced cycle (days 3–5) improved luteal function to a greater extent than when PMSG was provided after day 5.

Improving pregnancy rates through stimulation of CL function

When the possibility of inadequate luteal function, shortly after mating, has been related to pregnancy rates, the results have at times been encouraging, but often inconsistent. Thus, injection of hCG after ovulation improved luteal function in ewes (Gamboni *et al.*, 1984) and cows (Breuel *et al.*, 1989), but the pregnancy rate was not always improved (Breuel *et al.*, 1990).

The possibility remains that inadequate luteal function, particularly, soon after resumption of cyclic ovarian activity, could reduce pregnancy rates.

Provision of additional luteotropin to inhibit luteolysis?

The possibility that luteal lifespan may be extended by negating the luteolytic action of $PGF_2\alpha$ (to be reviewed later) via provision of extra luteotropin also has been investigated.

It was proposed that the short-lived CL might also be particularly sensitive to $PGF_2\alpha$. This hypothesis was based partly on the observation that in the normal cycling ewe large luteal cells possessed a higher number of receptors for this luteolysin than small luteal cells did (Fitz *et al.*, 1982). Similarly, in cows it has been shown that the large luteal

cells are the target of the luteolytic effect of $PGF_2\alpha$ (Alila *et al.*, 1988). An increased sensitivity to $PGF_2\alpha$ would presuppose a greater proportion of large luteal cells in the short-lived CL. This was supported by the demonstration that in ewes expected to exhibit short cycles, the CL had a higher number of large luteal cells having greater numbers of receptors for $PGF_2\alpha$ than CL anticipated to have a normal lifespan (Braden & Niswender, 1985). However, the proportion of large luteal cells was apparently not increased when the CL were short-lived in other studies in ewes (O'Shea *et al.*, 1984; Braden *et al.*, 1989b) and in cows (Rutter *et al.*, 1985). From their research, Garcia-Winder *et al.* (1986), Garverick *et al.* (1988), and Copelin *et al.* (1986; 1988) concluded that hypersensitivity to uterine luteolysin was not a cause of short-lived CL in cows. In contrast, Hunter *et al.* (1988) maintained that the short life-cycle CL in prepuberal and in anoestrous ewes was due to an increased sensitivity to tonic release of $PGF_2\alpha$. Hunter *et al.* (1988) based their opinion on the finding that although GnRH-induced CL were maintained after removal of the uterus, the secretory activity appeared limited. They suggested that inadequate vascularization of the CL could increase the vulnerability to the vasoconstrictive effects of $PGF_2\alpha$ released on about day 4 after ovulation (Hunter *et al.*, 1988).

Schirar *et al.* (1989) concluded that the first luteal tissue formed in postpartum ewes possessed reduced functional capacity (Component 15), and Lewis & Bolt (1987) showed that the uterus suppressed function of GnRH-induced CL in postpartum ewes. In attempting to overcome the luteolytic action of $PGF_2\alpha$, Bolt (1979) demonstrated that multiple injections of hCG could inhibit the luteolytic effect of $PGF_2\alpha$ and thereby postpone luteal regression in the cycling ewe. Similar effects of hCG (Donaldson & Hansel, 1960; Wiltbank *et al.*, 1961; Seguin *et al.*, 1977) and of LH (Karsch *et al.*, 1971) in counteracting natural luteolysis have been shown in the cow. Although administration of hCG on days 9 and 10 of the cycle did increase plasma concentrations of P4, this did not overcome the regressive action of a subminimal dose (10 mg) of $PGF_2\alpha$ (Copelin *et al.*, 1986). These results agree with those of Sasser *et al.* (1977) for the ewe and of Gonzalez-Mencio *et al.* (1977) for the cow, where constant infusion of LH did not inhibit the luteolytic effect of $PGF_2\alpha$. The possibility that the CL was desensitized by the hCG treatment was excluded (Litch & Condon, 1988).

LH receptors within the CL and luteal function

It is possible that the induced CL may be unable to respond to the luteotropin (Component 13) even though concentrations of LH may be adequate to support normal luteal function. Copelin *et al.* (1987) have evaluated the evidence that has been obtained in favour of this proposal. This hypothesis is in accordance with the suggestion (McNeilly *et al.*, 1981) that the increased numbers of receptors for LH, on the granulosal cells of the bovine CL, could be a major factor in regulation of secretion of P4 by the ensuing CL (Diekman *et al.*, 1978).

Kesler *et al.* (1981) have shown that the GnRH-induced ovulations which did not develop beyond day five post-ovulation also did not respond to LH *in vitro*. McNeilly *et al.* (1981) have confirmed this by demonstrating that in ewes the GnRH-induced, subnormal CL were less responsive to LH *in vitro*. McNeilly *et al.* (1981) and O'Shea *et al.* (1984) concluded that such CL were not less responsive to LH than normal CL. The latter implies that LH receptors are not deficient in the inadequate CL, and Rutter *et al.* (1985), Smith *et al.* (1986) and Braden *et al.* (1989b) have provided evidence to support this contention.

Both McNeilly *et al.* (1981) and Hunter *et al.* (1988) concluded that lack of gonadotropin receptors was probably not a fundamental cause of premature regression of the short-lived CL. In contrast, there is evidence for a lack of LH receptors. This may be deduced from the finding that where postpartum cows were primed with Norgestomet, the concentrations of LH receptors were increased in both the granulosa and thecal cells of the largest follicle compared to the largest follicle of non-primed cows (Inskeep *et al.*, 1988). Such acquisition of increased numbers of LH receptors and greater secretion of E2 were critical to preovulatory dominance of a single follicle (Spicer *et al.*, 1986b). However, McNeilly *et al.* (1981) believed that there may not be a simple relationship between the binding of LH to luteal cells and the secretion of P4. Consequently, the failure of the short-lived CL to recognise LH was not a factor that caused early luteal regression (Rutter *et al.*, 1985). Whether such a mechanism could account for subnormal CL function is not clear.

The role of the uterus and of $PGF_2\alpha$ in subnormal luteal function

Presence of $PGF_2\alpha$ during early lactation

The possibility that premature regression of CL, which appeared to function normally for approximately 7 days after induced ovulation, was due to the luteolytic effect of $PGF_2\alpha$, (Components 19 and 20; Odde *et al.*, 1980; 1981) needs consideration. Lewis *et al.* (1981) investigated this aspect but measured $PGF_2\alpha$ only on day 7 after administration, and also excluded those ewes which exhibited short cycles. Nevertheless, they recorded lower concentrations of $PGF_2\alpha$ in ewes treated with P4, and such ewes commonly show normal luteal function. Subsequently, increased jugular plasma concentrations of prostaglandin metabolite (PGFM) during the early postpartum interval have been demonstrated in milked dairy cows (Thatcher *et al.*, 1980) and suckled beef cows (Troxel *et al.*, 1984).

Oxytocin and the release of $PGF_2\alpha$

Oxytocin administration during the early part of the cycle has reduced luteal lifespan in cycling cows (Armstrong & Hansel, 1959; Hansel & Wagner, 1960; Milvae & Hansel, 1980) and it was suggested that oxytocin functioned via elevated levels of uterine $PGF_2\alpha$ (Schomberg *et al.*, 1967; Newcomb *et al.*, 1977; Milvae & Hansel, 1980) in a manner similar to that of an IUD inserted early in the cycle in ewes (Pexton *et al.*, 1975). This would account for the effect of suckling via the pituitary release of oxytocin (Troxel & Kesler, 1984a). Suckling has not been clearly shown to affect luteal lifespan, although increasing the number of lambs suckled did reduce plasma concentrations of P4

(Lewis *et al.*, 1981) and also the proportion of ewes that formed CL in response to GnRH (Lewis & Bolt, 1987).

When the CL releases oxytocin (Component 17), it may cause $PGF_2\alpha$ release (Component 18) which in turn, regresses the CL (McCracken *et al.*, 1984; Schams *et al.*, 1985). An imbalance in luteal levels of oxytocin or a change in the response of the uterus to basal levels of oxytocin was proposed (Hunter *et al.*, 1988) as a cause of the eventual demise of the CL. Schirar *et al.* (1989) did not agree with such a simple explanation and proposed that early release of $PGF_2\alpha$ may have been only one of several possible factors which may control the lifespan of the first CL after lambing. This is supported by the finding that in anoestrous ewes, when the uterine horn adjacent to the induced CL was removed 3 days before ovulation, this induced more normal synthesis of P4 than removal of an adjacent horn 2 days after the bolus injection of GnRH (Day *et al.*, 1989).

Cooper & Inskeep (1989), using blood from the posterior vena cava, could not demonstrate a close association between pulses of oxytocin and $PGF_2\alpha$ in lactating beef cows induced to ovulate with hCG, but concentrations of PGFM were highly correlated with oxytocin concentrations, both at the same hour ($r = 0,69$) and one hour earlier ($r = 0,83$). Peter *et al.* (1989) were able to detect parallelism between concentrations of PGFM and oxytocin in early postpartum dairy cows.

Negating the effect of $PGF_2\alpha$

The possibility of involvement of $PGF_2\alpha$ in premature regression of the CL (Components 19 and 20) is supported by the observation that treatment with substances which block the action of $PGF_2\alpha$ increased the functional lifespan of CL destined to be short-lived in beef cows (Troxel & Kesler, 1984a), in goats (Battye *et al.*, 1988) and in dairy cows (Dobson *et al.*, 1987). Further evidence for the involvement of $PGF_2\alpha$ comes from the demonstration that active immunization of early-weaned, anoestrous beef cows against $PGF_2\alpha$ extended the lifespan of the first CL (Copelin *et al.*, 1989b).

Removing the source of $PGF_2\alpha$

Strong evidence that a premature release of $PGF_2\alpha$ from the uterus (Component 20) could be reponsible for the early demise of the first induced CL in beef cows has been provided by Copelin *et al.* (1988). They demonstrated that CL formed after early weaning of calves did not possess an inherently short lifespan because removal of the uterus did not result in premature luteolysis. Furthermore, Wright *et al.* (1988) showed that the previously gravid uterus had to be present to induce premature regression of the first CL, subsequent to induced abortion in heifers. Similar results had been reported following formation of the first luteal tissue in prepuberal lambs (Keisler, 1983) and following GnRH-induced ovulation in anoestrous (Southee *et al.*, 1985; Hunter *et al.*, 1988) and lactating ewes (Lewis & Bolt, 1987).

Demonstrating the release of $PGF_2\alpha$

Neither Troxel & Kesler (1984b) nor Garcia-Winder *et al.* (1986) could show that the metabolite of $PGF_2\alpha$ (15keto–13,14 dihydro $PGF_2\alpha$) increased in cows having short-lived CL, but this has been demonstrated in super-ovulated goats (Battye *et al.*, 1988) and in dairy cows (Peter *et al.*, 1989).

An important piece of new evidence is the finding that in postpartum beef cows induced to ovulate with hCG and in which the CL were short-lived, an early release of $PGF_2\alpha$ could be demonstrated in plasma from the inferior vena cava (Cooper & Inskeep, 1989). In the same cows, PGFM and oxytocin did not show early rises. Similarly, in dairy cows which ovulated spontaneously, increased concentrations of PGFM were detected early in the cycle when the CL were short-lived (Peter *et al.*, 1989).

How does progesterone priming result in CL with a normal lifespan?

In seeking an explanation for the frequent failure of corpora lutea, when ovulation is induced through the use of exogenous hormones, it may be helpful to study the changes that occur when cycles commenced naturally. Both at puberty in cattle (Berardinelli *et al.*, 1979) and sheep (Berardinelli *et al.*, 1980) and following parturition in both dairy (Morrow *et al.*, 1966) and beef cows (Short *et al.*, 1972; Ward *et al.*, 1979), the first full-length oestrous cycle that occurred spontaneously was often preceded by a period of several days during which plasma P4 levels were increased (see Lauderdale, 1986 for a more extensive review). Furthermore, when exogenous P4 was administered for a number of days, this promoted the restoration of full luteal activity in postpartum cows induced to ovulate with GnRH or hCG (Pratt *et al.*, 1982; Sheffel *et al.*, 1982).

Such results support the generally accepted hypothesis that the short-lived CL provides a minimum critical concentration of P4 to ensure normal function of the subsequent CL in ewes (Pearce, 1985) and cows (Lamming *et al.*, 1981).

Lishman *et al.* (1979) proposed that future work should consider the mechanisms by which P4, prior to the first oestrus, affected follicular development. McLeod & Haresign (1984b) have discussed how P4 priming achieved normal luteal function in the seasonally anoestrous ewe given GnRH, and Smith *et al.* (1983) have considered the postpartum cow.

Delaying the LH surge

Although P4 priming has been observed to delay the LH surge (Martin *et al.*, 1980; McLeod *et al.*, 1982b; Pearce *et al.*, 1985; Pearce *et al.*, 1987; Southee *et al.*, 1988) the prolongation of exposure of follicles to gonadotropin is probably not the reason why P4 priming promotes subsequent luteal function (McLeod & Haresign, 1984). Wright *et al.* (1984) agreed with this conclusion, suggesting that P4 has effects on the hypothalamo-pituitary axis not mediated simply by delaying the LH surge. In the opinion of McLeod & Haresign (1984) the most likely explanation is that P4 had a direct effect on the ovulatory follicle (Component 16), perhaps having altered its ability to respond to changes in tonic gonadotropins or in some way changed the pattern of growth, thereby ensuring that all antral follicles were at the appropriate stage of development

to respond to the increase in LH episodes (McLeod *et al.*, 1982b; Hunter & Southee, 1987).

A direct effect of P4 on the follicle

The possibility that P4 priming may have been acting via a direct effect on the follicle, as proposed by McLeod & Haresign (1984) and Hunter *et al.* (1986), was supported by the finding that as little as two days of exposure to P4 facilitated full luteal function. In contrast, the final stages of follicular growth were said to require 4 – 5 days (Wodzicka-Tomaszewska *et al.*, 1974; Legan & Karsch, 1979). Similarly, Pearce *et al.* (1987) suggested that pretreatment with P4 may have induced changes within the developing follicle to convert short-lived CL induced by ram introduction to CL having a normal lifespan. The beneficial effects of P4 were produced by a minimum of 30 h priming and were found to persist for at least 5 days after termination of the P4 administration (Pearce *et al.*, 1985; 1987).

Where multiple low doses of GnRH (250 ng every 2 h for 48 h) were used to induce ovulation in anoestrous ewes, only a transient rise in plasma P4 (levels rose to a peak of ± 0,5 ng/ml over about 4 days) was recorded where P4 priming had not been applied. In contrast, P4 priming resulted in a normal luteal lifespan (Southee *et al.*, 1988). A similar positive effect of pretreatment with P4 on lifespan of CL, induced by weaning of the calf (Ramirez-Godinez *et al.*, 1981) or by exogenous gonadotropin (Pratt *et al.*, 1982; Sheffel *et al.*, 1982) on level of function of the CL in anoestrous postpartum cows, has been reported.

The hypothesis incorporating a direct effect of P4 on the follicle was supported by Hunter & Southee (1987). They noted a significant increase in the concentration of P4 in follicles < 4 mm in diameter; during *in vitro* incubation the largest follicle from P4-primed anoestrous ewes secreted less E2, but bound more hCG to the thecal cells. Their results supported the hypothesis that P4 retarded the rate of follicle development and thereby secretion rate of E2. This is in accordance with the finding that the LH surge is delayed in P4-primed anoestrous ewes treated with GnRH (McLeod *et al.*, 1982; Hunter *et al.*, 1986). It appeared that P4 priming synchronized the random anoestrous pattern of follicular development (Legan *et al.*, 1985), so that the persistence of a single follicle was encouraged (Garcia-Winder *et al.*, 1987). Interestingly, both the size and position of the largest follicle were altered, so that fewer F1 follicles were imbedded within the ovary in Norgestomet-pretreated cows (Garcia-Winder *et al.*, 1987).

Increased LH receptors

Garcia-Winder *et al.* (1987) speculated that P4 may increase receptors for LH in the largest follicle (Component 10), and Inskeep *et al.* (1988) have confirmed this; whereas Jones *et al.* (1989) proposed that P4 may be involved in the regulation of LH receptors during development of the CL. Support for an effect on the responsiveness of the follicle (Martin *et al.*, 1984; McLeod & Haresign, 1984; Hunter *et al.*, 1986) can be obtained from Walters & Schallenberger (1984). They accounted for the increased E2 pulse amplitude before the LH surge in cows (Chenault *et al.*, 1975; Schams *et al.*, 1977) as having been due to an increase in the number of LH receptors in the pre-ovulatory follicle at that time (Walters *et al.*, 1982; Staigmiller *et al.*, 1982).

Increased blood flow

Brown & Mattner (1984) have proposed a further mechanism by which P4 priming, prior to introduction of rams or treatment with GnRH, might have led to normal luteal function. They argued that P4 could have promoted the response of ovarian vasculature to endogenous E2. The marked increase in blood flow to the ovary could then have augmented the supply of nutrients to the developing CL. Continuation of this work has shown that administration of P4 before onset of two–hourly GnRH pulse injections, while inducing normal oestrous cycles in anoestrous ewes, also significantly increased the mean capillary blood flow in the ovaries (Brown *et al.*, 1988). They proposed that rate of capillary blood flow in the ovaries, near the time of ovulation, may have been a critical factor in normal development and maturation of ovulatory follicles which then became fully functional CL.

Preventing premature release of $PGF_2\alpha$

Recently, a further mechanism by which P4 pretreatment ensures a normal lifespan of the CL, induced in an anoestrous ewe, has been proposed. This suggestion incorporated a direct action on the uterus to lower concentration of oxytocin and to prevent premature release of $PGF_2\alpha$ (Hunter *et al.*, 1989). In postpartum cows induced to ovulate via injection of hCG, Cooper & Inskeep (1989) demonstrated that pretreatment with Norgestomet implants reduced the concentrations of $PGF_2\alpha$ from days 4 through 10 postovulation (Component 24). The latter appeared to prematurely regress the CL in those cows not primed with P4.

Although Cooper & Inskeep (1989) found no effect of Norgestomet on concentrations of oxytocin or of PGFM, their results for $PGF_2\alpha$ are supported by the demonstration of higher *in vitro* production of $PGF_2\alpha$ by day 5 endometria obtained from cows expected to have short-lived CL compared to cows pretreated with Norgestomet (Zollers *et al.*, 1989). Using this experimental model, Hu *et al.* (1989) found that the CL destined to be short-lived secreted higher levels of $PGF_2\alpha$ than CL expected to function normally. Furthermore, the first postpartum CL in ewes was found to have 2,4 times as many receptors for $PGF_2\alpha$ as normal CL (Braden & Niswender, 1986).

A question which still needs to be answered is what role, if any, increased concentrations of E2 play, within the preovulatory follicle, in preventing premature release of $PGF_2\alpha$.

General comments

The research which has been conducted to investigate the possible mechanisms by which luteal lifespan or function could be reduced has yielded results which point to only a few deficiencies. These are summarized in Figure 2.

Based on available findings it would seem that premature demise of the first CL (formed at puberty, after parturition

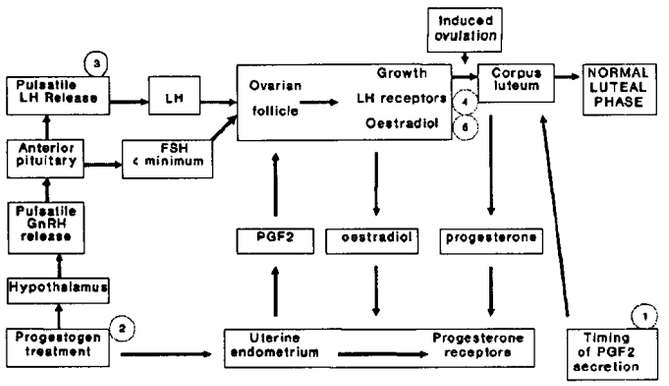

Figure 2 Mechanisms which have been demonstrated to contribute to deficient luteal function in lactating ewes and cows.

or at the onset of the new breeding season) is the result of early release of $PGF_2\alpha$ by the uterus (Figure 2, Component 1). Although pretreatment with P4 is an effective countermeasure (Component 2), the processes involved remain obscure.

In contrast, the explanation for subnormal luteal function of approximately normal duration appears more complex. Improper or incomplete maturation of the preovulatory follicle remains implicated in both the formation of the CL and the preparation of the uterus for its normal role. Although an increased frequency of LH pulses (Component 3) appears to be vital in promoting follicular maturation, the interrelationship between the interval between parturition and first oestrus in beef cows maintained under ranching conditions, varies considerably. There is also much individual variation in response to stimuli aimed at reducing this open period. Consequently, it would be advantageous if some objective indication of just when a cow is ready to respond to stimuli could be obtained. From the published research it would appear the the pulsatile release of LH (Nett *et al.*, 1987) is the indicator sought after. However, this is completely impractical to measure on the farm, and because of the interdependence of the pituitary and the follicles within the ovary (Kesler *et al.*, 1977; Lishman *et al.*, 1979; Troxel *et al.*, 1980; Irvin *et al.*, 1981; Smith *et al.*, 1983), ovarian examination per rectum appears to be the only practical tool presently available. However, more widespread application of ovarian examination by ultrasonography holds considerable promise for the future.

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