Control of the oestrous cycle in farm animals: A review

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ABSTRACT

Ultrasonography has permitted close visualisation of follicular development in cattle and has revealed that three waves of follicles normally develop during the oestrous cycle. Follicle stimulating hormone is important for the recruitment of follicles but it is not known how the recruited follicles are selected to become dominant over other follicles and eventually to ovulate. Hypothalamic, pituitary and ovarian hormones are secreted and released episodically. During the luteal phase of the oestrous cycle, the negative feedback of progesterone prevents any rise in luteinising hormone (LH). As progesterone levels fall, LH increases, prompting an increase in oestradiol which triggers the ovulatory LH surge and behavioural oestrus. LH causes ovulation and luteinisation of follicular cells. Luteal phase progesterone may be responsible for later increases in prostaglandin $F2\alpha$ (PG)$F2\alpha$, a luteolytic hormone in cattle and sheep which is transferred from the uterus, its site of synthesis, to the corpus luteum. Oestradiol and oxytocin, synthesised in the ovary, may be involved in regulation of uterine synthesis of $PGF2\alpha$, hastening luteolysis. At this time it is not known how essential these two hormones are to the process of luteolysis. The discovery and synthesis of new ovarian hormones should permit superovulation to become a more exact and a less expensive procedure and for embryonic mortality to be reduced.

Keywords Cattle ; sheep; oestrous cycle; progesterone; oestradiol; oxytocin; LH; FSH; follicles; CL

INTRODUCTION

The decade of the 1970s began with the ability to quantitate protein and steroid hormones in peripheral blood. Later it was recognised that hormones are secreted in a pulsatile fashion and therefore that pulse amplitude and pulse frequency were possibly of more importance in understanding endocrine regulation than mean hormone levels as ascertained by infrequent or daily sampling. Also in this decade the chemical composition of hypothalamic hormones was discovered which permitted the synthesis of these hormones and their analogues and antagonists. Hypothalamic hormones are now used therapeutically. It was also realised that, as the hypothalmic hormones (originally referred to as releasing factors) were secreted throughout the body, it could no longer be assumed that blood levels were representative of hypothalamic secretion. The role of prostaglandins in luteolysis was discovered in sheep and later applied to cattle.

The decade of the 1980s brought the ability to monitor ovarian action in terms of follicular growth through the use of ultrasonography which allowed visualisation of follicular activity without destruction of the follicles. Finally, this decade has led to the discovery of new hormones, secreted by the ovaries, which should help us understand the process of follicular development so that scientists can succeed in making superovulation a predictable event and in preventing reproductive losses caused by early embryonic mortality.

The object of this review is to gain a better understanding of the endocrine regulation of the oestrous cycle in cattle and sheep. Since the endocrine system in goats and deer are similar to sheep, this review will have application to these species as well. I will make no attempt to cover an exhaustive list of the literature that has accumulated in this area. Rather, I shall examine the most recent literature and attempt to collate this in a reasonable fashion so that we may be better able to deduce the mechanisms of oestrous cycle control so that we can manipulate it to our benefit.

FOLLICULOGENESIS

Rajakoski (1960) was the first to examine ovaries of the cow during the oestrous cycle and

originated the concept of waves of follicular growth. He concluded that there were two waves of follicular activity during the oestrous cycle. With the recent advent of ultrasonography, scientists could examine ovaries at frequent intervals without interfering with follicular development (Pierson and Ginther, 1984; Reeves *et al.*, 1984). Although Pierson and Ginther (1984) measured follicles as small as 2 mm, Fortune's group (Quirk *et al.*, 1986) did not measure follicles less than 5 mm but could track individual follicles from day to day. Pierson and Ginther (1987a) validated the method of ultrasonography and agreed with the data of Rajakoski that there were two waves of follicular activity (Pierson and Ginther, 1987b).

However, others (Sirois and Fortune, 1988; Fortune *et al.*, 1988; Savio *et al.*, 1988) have detected three waves of follicular growth during the oestrous cycle in cattle, a new wave beginning about every 7 days. This is likely correct since it agrees with the observation of three periods of increased levels of oestradiol (during oestrus, after ovulation up to day 5 to 6, and during days 10 to 16 before luteal regression) during the oestrous cycle (reviewed by Ireland and Roche, 1987; Britt *et al.*, 1981). Periods of follicular growth coincide with these peaks in oestradiol concentrations and, since a single follicle probably is synthesising all the oestradiol detected, these data agree very well. Not all heifers had three waves of follicular growth; some had two waves and some had four waves (Sirois and Fortune, 1988). Each wave was characterised by a dominant follicle and a variable number of smaller, non-dominant follicles. Although not examined, follicular waves likely occur in sheep as in cattle (Ireland, 1987).

Goodman and Hodgen (1983; reviewed by Ireland, 1987) divided folliculogenesis into three stages; recruitment, in which follicles gain the ability to respond to gonadotrophins; selection, in which only one or several of the recruited follicles are selected to avoid atresia; and dominance, the mechanism by which the dominant or ovulatory follicle(s) escape atresia.

It is not known how follicles are 'recruited' or 'selected' to become the dominant follicle. Ireland and Roche (1983) divided follicles into two categories; those whose follicular fluid contained higher concentrations of oestradiol than progesterone and androgens (oestrogen-active) and those whose follicular fluid contained higher concentrations of progesterone or androgens than oestradiol (oestrogen-inactive). Only oestrogen-active follicles were eligible to ovulate; the oestrogen-inactive follicles had a high incidence of atresia. Slight variations in the levels of follicle stimulating hormone (FSH) do occur during the oestrous cycle and 'selected' follicles may respond to this stimulation and become dominant (Ireland and Roche, 1987). A second FSH surge, independent of hypothalamic GnRH secretion, follows the preovulatory luteinising hormone (LH) and FSH surge and, in sheep, has been correlated with ovulation rate and the number of antral follicles 17 days later (Rajamahendran *et al.*, 1987; Goodman, 1988).

The ovulatory follicle is nominated between day 16 and day 17 in cattle (Pierson and Ginther, 1988). Once nominated, the growing follicle responds to circulating LH by secreting more oestradiol (Richards, 1979) until the LH surge (Goodman *et al.*, 1981). The increased levels of oestradiol secretion help secure its selection as the dominant follicle by suppressing FSH. Other factors to ensure dominance include the negative feedback of follistatin and inhibin on FSH secretion, which prevents other follicles from developing (Baird, 1987; Fortune *et al.*, 1988; Ying, 1988); paracrine secretion of follicle regulatory protein (FRP) which can block non-dominant follicles (Ono *et al.*, 1986; Ireland and Roche, 1987; Fortune *et al.*, 1988); and secretion of follicle growth inhibitor, which inhibits growth of other follicles (Driancourt, 1987). The dominant follicle is able to continue development in the face of decreased levels of FSH whereas smaller antral follicles are unable to. The length of proestrus was negatively correlated with the size of the pre-ovulatory follicle at the beginning of proestrus (Sirois and Fortune, 1988).

The decrease in circulating progesterone (as the result of luteolysis of the corpus luteum (CL)) permits increased levels of LH secretion which stimulates increased oestradiol synthesis. The increased levels of oestradiol cause behavioural

oestrus and the LH surge. Follicles developing during periods of progesterone dominance don't mature and ovulate but rather become atretic because LH levels cannot increase and therefore follicles cannot increase their synthesis of oestradiol.

ENDOCRINE CONTROL

Originally the hypothalamus was thought of as having two centres for control of the gonadotrophin hormones (LH and FSH), a tonic centre and a surge centre. Now that we know that most hormones, including gonadotrophins, are secreted episodically, it is not so obvious that two centres exist. Gonadotrophin releasing hormone (GnRH), also known as luteinising hormone releasing hormone, is secreted by a loose aggregation of GnRH-producing neurons which depolarise rhythymically and in synchrony, resulting in coordinated episodes of GnRH release; this has been referred to as the hypothalamic pulse generator (Karsch, 1987). Specific, high affinity GnRH receptors have been located in the anterior pituitaries of cattle and sheep (Brown and Reeves, 1983).

The frequency and amplitude of the pulses of gonadotrophins vary during the oestrous cycle and, in sheep, deer, and goats, during the breeding season. In cattle, the pulses of LH and FSH occur at a higher frequency during the early luteal phase as compared to the mid-luteal phase of the oestrous cycle, although the amplitude and mean hormone levels don't change (Walters *et al.*, 1984; Rahe *et al.*, 1980). Almost all LH pulses are accompanied by an FSH pulse; although it's probable that the two hormones are controlled by the same releasing hormone (GnRH), FSH also appears to be under the control of inhibiting hormones such as inhibin, follistatin and FRP (Ying, 1988). Episodic release of LH continues during the ovulatory surge; in fact, the LH surge is a result of greatly increased amplitude (25-fold) and, to a lesser degree, frequency (2-fold) of LH pulses (Karsch, 1987; Walters and Schallenberger, 1984; Goodman, 1988).

Secretion and release of the gonadotrophin hormones is controlled by the ovarian hormones, oestradiol and progesterone. Progesterone always has a negative feedback at the level of the hypothalamus, controlling the frequency of GnRH pulses(Karsch *et al.*, 1984; Karsch, 1987). Oestradiol, on the other hand, can have either a negative or positive feedback at the hypothalamus or anterior pituitary. Feedback at the hypothalamus regulates GnRH frequency while feedback at the pituitary affects the amplitude of the LH pulses (Karsch, 1987).

During the luteal phase of the cycle, progesterone prevents any increase in LH, thus preventing oestrus. During the latter stages of the oestrous cycle, after blood levels of progesterone have declined to <0.5 ng/ml (Nanda *et al.*, 1988), progesterone has a permissive effect, allowing GnRH pulse frequency to increase, causing increased LH pulse frequency and stimulating oestradiol synthesis which, through its positive feedback effect, causes the LH surge. During proestrus the increased oestradiol levels have a positive feedback, resulting in the ovulatory LH surge. During the anoestrous season in sheep, oestradiol has a negative feedback on the hypothalamus, maintaining GnRH at a very low frequency (Karsch, 1987). Negative feedback by the ovarian hormones was illustrated by castration, when the frequency and amplitude of the gonadotrophic hormones increased; exogenous progesterone decreased the frequency of LH pulses while exogenous oestradiol decreased amplitude of the LH pulses (Rahe *et al.*, 1980).

Steroid synthesis in follicles can be referred to as the 2-cell, 2-hormone process (Richards, 1979). Androstenedione is synthesised via the delta-5 pathway in the outer cell layer, the thecal cells; androstenedione synthesis is enhanced by the availability of pregnenolone precursor which diffuses from the granulosa cells (Fortune, 1986). Androstenedione then diffuses across to the avascular granulosa cells where it is aromatised to oestradiol. The first stage is under the control of LH; LH receptors on the thecal cells are induced by oestradiol. LH stimulates the conversion of cholesterol to androstenedione through the cyclic adenosine monophosphate (cAMP) system. The rate-limiting step is the conversion of cholesterol to pregnenolone (Hsueh *et al.*, 1984).

The aromatisation of androstenedione to oestradiol occurs in the granulosa cells under the stimulus and control of FSH and LH, whose receptors are located on the cell membrane although LH receptors are found only in large preovulatory follicles (Richards, 1980). Although many antral follicles are capable of synthesising androstenedione, only a few follicles have granulosa cells able to aromatise it to oestradiol (McNatty *et al.*, 1984). FSH is important for the induction of the aromatase enzyme system and its effects are enhanced by androgens from the theca cells (Leung and Armstrong, 1980). FSH, through occupation of its receptor, acts through the cAMP system to increase aromatase activity and oestradiol synthesis (Richards and Hedin, 1988).

Of course the theca and granulosa cells can also synthesise progesterone but the presence of high levels of oestradiol in the follicular fluid inhibits 3 beta-hydroxysteroid dehydrogenase, the enzyme which converts pregnenolone to progesterone, and thereby exerts positive feedback on its own synthesis by increasing the delta-5 pathway which generates androstenedione (Fortune, 1986). The aromatase enzymes are inhibited by FRP which is thought to permit the dominant follicle to maintain its control over surrounding follicles (Ono *et al.*, 1986). Furthermore, if conditions do not permit the dominant follicle to ovulate (ie., high progesterone levels), FRP increases, oestradiol and progesterone decrease, androgens increase (ie., oestrogen-inactive follicle) and the follicle becomes atretic (Ireland and Roche, 1987). FSH is thought to be important for the recruitment of follicles but to have a more permissive role as the dominant follicle develops (Goodman *et al.*, 1981).

Oestradiol also has a positive feedback upon its own synthesis by enhancing the ability of FSH to stimulate cAMP, enhancing the proliferation of granulosa cells and stimulating the further production of LH receptors on the theca and granulosa cells (Richards, 1979; Richards, 1980). Of course, oestradiol can increase at this time because, with the fall in progesterone, LH levels increase and stimulate the synthesis of oestradiol.

Increased levels of LH and FSH during this periovulatory period are a result of increased frequency of pulses, stimulated by decreased levels of progesterone and oestradiol (Schallenberger *et al.*, 1984). Shortly before the LH surge, oestradiol has been observed to have a positive feedback on the anterior pituitary and a negative feedback on the hypothalamus (Walters and Schallenberger, 1984). At least a part of the positive feedback involves the synthesis of GnRH receptors in the anterior pituitary (Nett *et al.*, 1987; Clarke *et al.*, 1988). GnRH can up-regulate its own receptors in the anterior pituitary of the sheep (Clarke *et al.*, 1988); GnRH can also decrease its anterior pituitary receptors (Karsch, 1987). Then, immediately prior to the LH surge, oestradiol levels decrease, removing the negative feedback on the hypothalamus and allowing the ovulatory LH surge to occur (Walters and Schallenberger, 1984; Goodman, 1988). In fact, the lowered levels of oestradiol exert a positive feedback at the hypothalamus by increasing GnRH levels through increased frequency of GnRH pulses (Karsch, 1987). No LH pulses have been observed for 6-12 h after the LH surge (Walters and Schallenberger, 1984).

Oestradiol and progesterone are also synthesised in a pulsatile pattern; most pulses of LH are followed within 60 min by a pulse of oestradiol (Walters and Schallenberger, 1984). Progesterone is synthesised in a pulsatile manner (8.0 ± 0.63 pulses/24 h) and is independent of LH pulses (Alecozay *et al.*, 1988) but appears to be associated with FSH pulses (Walters *et al.*, 1984).

OVULATION

Few of the details concerning ovulation are known. We do know that plasminogen activator increases in the preovulatory follicle at this time which participates in follicular rupture (Richards and Hedin, 1988) and increased number of mast cells appear which affect cell permeability (Nakamura *et al.*, 1987). The granulosa cells are the source of many of these products, including inhibin, plasminogen activator, proteoglycans, and oocyte maturation inhibitor (Richards, 1980; Hsueh *et al.*, 1984; Tsafriri *et al.*, 1987). Further discussion of this topic is beyond the scope of this review.

FORMATION OF CL

After ovulation, the follicular fluid containing oestradiol disappears, permitting the shift from androgen synthesis to synthesis of progesterone (Richards, 1980; Fortune, 1986). Aromatase activity rapidly declines as the theca and granulosa cell luteinise (Keyes and Wiltbank, 1988). Receptors for LH, FSH and oestradiol disappear (Richards, 1980) and the early corpus luteum seems capable of developing without any direct enhancement by the gonadotrophins (Keyes and Wiltbank, 1988).

The thecal cells of the cow, sheep, and pig luteinise to form small luteal cells (<22 μm) and the granulosa cells form large luteal cells (>22 μm)(Niswender *et al.*, 1985). However, with time during the luteal phase the number of cells decreases as the small luteal cells gradually differentiate into large cells (Hansel and Dowd, 1986). The small cells have most of the LH receptors and are therefore more responsive (6-fold) to stimulation by LH but the large cells synthesise most (20-fold more) of the progesterone (Schwall *et al.*, 1986; Alila *et al.*, 1988; Stormshak *et al.*, 1987). Occupied LH receptors increase from day 2 to a maximum at day 10 at which level they remain until day 14. However, even at this level only 0.6% of the luteal LH receptors are occupied (Niswender *et al.*, 1985). As in the follicles, LH stimulates progesterone synthesis through the cAMP system (Schwall *et al.*, 1986; Hansel and Dowd, 1986).

LH is the major luteotrophin although other luteotrophins have been identified. Prostacyclin I2 and PGE_2 are luteotrophic in the cow and sheep, respectively (Hansel and Dowd, 1986; Niswender *et al.*, 1985). The large luteal cells contain most of the receptors for PGE_2 and $PGF_{2\alpha}$ (Braden *et al.*, 1988). $PGF_{2\alpha}$ may also have a paracrine luteotrophic effect, stimulating the synthesis of progesterone (Alila *et al.*, 1988).

LUTEOLYSIS

McCracken was first to establish $PGF_{2\alpha}$ as the luteolytic agent in sheep (McCracken *et al.*, 1971). He correctly ascertained that $PGF_{2\alpha}$ was synthesised in the uterus and transferred from the utero-ovarian vein to the ovarian artery by a countercurrent mechanism. However, the mechanism by which $PGF_{2\alpha}$ accomplishes luteolysis is still unsure. Mechanisms may include decreased blood flow; a direct, toxic affect on luteal cells; uncoupling of the LH receptor from adenyl cyclase; and acting as a Ca^{2+} ionophore by elevating Ca^{2+} and inactivating cAMP to decrease progesterone synthesis (Niswender *et al.*, 1985; Hansel and Dowd, 1986; Auletta and Flint, 1988).

Most receptors for $PGF_{2\alpha}$ are located on the large luteal cells and are the target for the luteolytic action of $PGF_{2\alpha}$ yet luteolysis includes the small luteal cells as well although, as discussed above, many of the small cells have by this time differentiated into large cells (Schwall *et al.*, 1986; Alila *et al.*, 1988; Auletta and Flint, 1988). However, the decrease in cell numbers occurs after the decrease in progesterone (Braden *et al.*, 1988). Likewise, decreased blood flow doesn't seem to be the primary agent since low doses of exogenous $PGF_{2\alpha}$ cause luteal regression without affecting blood flow (Auletta and Flint, 1988).

Another factor in luteolysis is the hormone oxytocin (OT). This was first brought to our attention by Armstrong and Hansel (1959) who found that exogenous OT, given early in the oestrous cycle of the cow, shortened the oestrous cycle. The CL failed to attain normal size and the effect was prevented by hysterectomy. Later, the same situation was found in the ewe (Flint and Sheldrick, 1986) and goat (Schams *et al.*, 1987). In retrospect it was realised that OT either stimulated $PGF_{2\alpha}$ synthesis from the uterus (Wathes, 1984) or inhibited synthesis of the luteotrophin, PGI2 (Dowd and Hansel, 1986).

Further confirmation of the role of OT was provided by the observation that immunisation with OT prolonged the oestrous cycle in sheep and goats (Hansel and Dowd, 1986). The problem with this scenario is that exogenous OT doesn't cause luteolysis when given during the mid-luteal phase of the oestrous cycle and OT doesn't decrease progesterone synthesis *in vitro* (Hansel and Dowd, 1986). However, the uterus must be exposed to oestradiol for a OT-induced $PGF_{2\alpha}$

release; progesterone alone has no effect, but the greatest response occurs after exposure to both oestradiol and progesterone (Goodman, 1988). Thus, OT is most effective during the follicular phase of the oestrous cycle rather than the luteal phase. Furthermore, increased $PGF_{2\alpha}$ synthesis by the endometrium has been observed *in vitro* in response to OT (Roberts *et al.*, 1976) and, during mid-cycle, high levels of progesterone may prevent the induction of uterine OT receptors (Hansel and Dowd, 1986).

Oxytocin is synthesised in the large luteal cells of the CL and OT receptors are located on the uterine endometrium (Niswender *et al.*, 1985; Auletta and Flint, 1988; Braden *et al.*, 1988). Uterine synthesis of $PGF_{2\alpha}$ is stimulated by binding of OT to its receptor; after progesterone has declined, oestradiol stimulates the synthesis of OT receptors in the endometrium (McCracken *et al.*, 1984) and the number of OT receptors increases at the end of the oestrous cycle (Roberts *et al.*, 1976; Flint and Sheldrick, 1986). Uterine sensitivity to OT also peaks at oestrus (Flint and Sheldrick, 1986) and the maximal $PGF_{2\alpha}$ response to OT occurs at this time (Schams *et al.*, 1987). Oxytocin and $PGF_{2\alpha}$ have a positive feedback effect on each other; exogenous $PGF_{2\alpha}$ causes the release of luteal OT and exogenous OT causes uterine release of $PGF_{2\alpha}$; furthermore, both occur in simultaneous pulses at luteal regression (Flint and Sheldrick, 1986).

In summary, an initial uterine release of $PGF_{2\alpha}$ causes a decline in progesterone synthesis toward the end of the oestrous cycle and a release of OT (Stormshak *et al.*, 1987). Following progesterone priming during the luteal phase, oestradiol, in response to increased LH levels, increases and stimulates the formation of OT receptors in the uterus; however, this is not the triggering event for luteal regression (Wathes, 1984). As further OT is synthesised in the CL, transported to the uterus, and bound to its endometrial receptor, it stimulates the synthesis of $PGF_{2\alpha}$ from the uterus. $PGF_{2\alpha}$ is carried to the CL where it causes luteolysis and stimulates the further synthesis of OT (McCracken *et al.*, 1984; Auletta and Flint, 1988; Flint and Sheldrick, 1986).

ANOESTRUS

Sheep and deer are short-day breeders, that is, the breeding season is initiated as daylength becomes shorter (Tamarkin *et al.*, 1985). The anoestrous season in sheep is characterised by a 50% decrease in pulse frequency of LH and extremely low serum levels of LH as a result of negative feedback of oestradiol on GnRH pulse frequency at the hypothalamus and anterior pituitary (I'Anson and Legan, 1988a; Goodman, 1988). At the onset of the breeding season the negative feedback of oestradiol changes to a positive feedback (Legan *et al.*, 1977), LH levels increase, stimulating an increase in oestradiol which causes the LH surge and ovulation. If a mature follicle is present at this time a full length luteal phase occurs; if not, a transient increase in progesterone results with a short luteal phase (I'Anson and Legan, 1988b). These seasonal effects can be mimicked by placing the sheep in an artificial environment where daylength is regulated.

Recently the pineal gland was found to be involved in the regulation of seasonal breeding in sheep. The pineal gland synthesises melatonin in a circadian rhythym; serum levels are 10-fold higher at night (Stellflug *et al.*, 1988). Exogenous melatonin simulates the effect of short days. It is believed that melatonin acts at the hypothalamus to control the LH pulse generator but the mechanism is unknown (Karsch *et al.*, 1984). Several experiments using exogenous melatonin (injected or oral) have successfully advanced the breeding season and increased the prolificacy in anoestrous sheep (Nett and Niswender, 1982; Stellflug *et al.*, 1988; Luhman and Slyter, 1986; Stellflug and Nett, 1988).

Another successful approach involves the use of vaginal devices containing progesterone. For example, Asher and Macmillan (1986) induced oestrus and ovulation in anoestrous deer through the use of progesterone-containing vaginal devices and GnRH. Similar experiments have been successful in sheep.

PREGNANCY

Recognition of pregnancy occurs on day 12-13 in

the ewe and day 16-17 in the cow. Antiluteolytic trophoblast-derived proteins have been identified after this time period in the conceptus of the ewe (oTP-1) and the cow (bTP-1); they are believed to inhibit the ability of oestradiol and OT to induce $PGF_{2\alpha}$ synthesis from the uterus (Bazer *et al.*, 1986), although Thatcher *et al.* (1989) recently reported that bTP-1 may directly decrease $PGF_{2\alpha}$ secretion by inducing the synthesis of an endometrial prostaglandin synthetase inhibitor. Additional protection of the conceptus during pregnancy is assured by decreases in endometrial OT receptor and in luteal OT synthesis (Flint and Sheldrick, 1986). Unfortunately, these trophoblast proteins are not present in any body secretions and therefore are not practical for pregnancy tests (Kazemi *et al.*, 1988).

SUPEROVULATION

Success has been attained in controlling luteolysis, but not in controlling proestrus. Therefore, superovulation has been subject to a high degree of variation in terms of the number of ovulations and number of embryos recovered, making the procedure quite expensive. Recently, some scientists (Rajamahendran *et al.*, 1987; Ware *et al.*, 1988) have improved the efficiency (more good embryos recovered) of superovulation in cattle and sheep by administration of a priming dose of FSH early in the oestrous cycle (days 3 to 4 in cattle; day 1 in sheep), prior to the usual FSH regimen. However, other experiments using a FSH priming dose have not enjoyed a similar success (Lussier and Carruthers, 1987; Guilbault *et al.*, 1988; Rieger *et al.*, 1988). It appears that ovarian responsiveness is related to ovarian status at the time of FSH treatment for superovulation (Monniaux *et al.*, 1983).

Certain species of sheep naturally have a higher number of ovulations. Obviously it would be to our advantage to understand why this occurs. While no definite answers are available at this time, some possibilities include less follicular atresia, greater sensitivity to FSH, a deficiency in follicle growth inhibitor and less ovarian inhibin. Some success has been noted, taking advantage of such differences. Henderson *et al.* (1986), for example, increased the ovulation rate in ewes following the administration of bovine follicular fluid. Apparently, differences in gonadotrophin levels are not responsible (Driancourt, 1987; Ireland, 1987), although this is questionable.

SUMMARY

Karsch *et al.* (1978) have referred to progesterone as the organiser of the oestrous cycle because its presence dictates when oestrus and ovulation can occur. Progesterone, not oestradiol, is the primary negative feedback hormone during the oestrous cycle (Goodman, 1988). The discovery of $PGF_{2\alpha}$ has allowed a precise control of luteolysis but, because proestrus cannot be precisely controlled, procedures such as oestrous synchronisation and superovulation have not become commercially acceptable. Therefore, only a minor percentage of the beef cattle population are artificially inseminated and superovulation is very expensive. As additional ovarian hormones are discovered and synthesised, their use should permit oestrus to be controlled with enough precision to permit timed inseminations and for superovulation to become a more exact procedure and therefore to decrease its cost. Judicious use of these hormones and other factors, such as recombinant interferon (Thatcher *et al.*, 1989), may also allow a decrease in embryonic mortality.

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REFERENCES

Alecozay A.A.; Selcer K.W.; Clark J.R.; Burns J.M., Norman R.L.; Niswender G.D.; Leavitt W.W. 1988. Pattern of ovarian progesterone secretion during the luteal phase of the ovine estrous cycle. *Biology of reproduction* **39**:287-294.

Alila H.W.; Dowd J.P.; Corradino R.A.; Harris W.V.; Hansel W. 1988. Control of progesterone production in small and large bovine luteal cells separated by flow cytometry. *Journal of reproduction and fertility* **82**:645-655.

Armstrong D.T.; Hansel W. 1959. Alteration of the bovine estrous cycle with oxytocin. *Journal of dairy science* **42**:533-542.

Asher G.W.; Macmillan K.L. 1986. Induction of oestrus and ovulation in anoestrous fallow deer (*Dama dama*) by using progestrone and GnRH treatment. *Journal of reproduction and fertility* **78**:693-697.

Auletta F.J.; Flint A.P.F. 1988. Mechanisms controling corpus lutem function in sheep, cows, nonhuman primates, and women especially in relation to the time of luteolysis. *Endocrine r reviewss* **9**:88-105.

Baird D.T. 1987. A model for follicular selection and ovulation: Lessons from superovulation. *Journal of steroid biochemistry* **27**:15-23

Bazer F.W.; Vallet J.L.; Roberts R.M.; Sharp D.C.;Thatchr W.W. 1986. Role of conceptus secretory products in establishment of pregnancy. *Journal of reproduction and fertility* 76:841-850

Braden T.D.; Gamboni F. Niswender G.D. 1988. Effects of prostaglandin $F_{2\alpha}$ -induced luteolysis on the populations of cells in the ovine corpus luteum. *Biology of reproduction* **39**:245-253

Britt J.H.; Cox N.M.; Stevenson J.S. 1981. Advances in reproduction in dairy cattle. *Journal of dairy science* **64**:1378-1402.

Brown J.L.; Reeves J.J. 1983. Absence of specific LHRH receptors in ovine, bovine and porcine ovaries. *Biology of reproduction* **29**:1179-1182.

Clarke I.J.; Cummins J.T.; Crowder M.E.; Nett T.M. 1988. Pituitary receptors for gonadotropin-releasing hormone in relation to changes in pituitary and plasma gonadotropins in ovariectomized hypothalamo/pituitary-disconnected ewes. II. A marked rise in receptor number during the acute feedback effects of estradiol. *Biology of reproduction* **39**:349-354.

Driancourt M.A. 1987. Follicular dynamics and intraovarian control of follicular development in the ewe. *In* Follicular Growth and Ovulation Rate in Farm Animals. *Eds*. J.F. Roche; D. O'Callaghan. Martinus Nijhoff Publishers, Lancaster. p.87-105.

Flint A.P.F.; Sheldrick E.L. 1986. Ovarian oxytocin and the maternal recognition of pregnancy. *Journal of reproduction and fertility* **76**:831-839.

Fortune J.E. 1986. Bovine theca and granulosa cells interact to promote androgen production. *Biology of reproduction* **35**:292-299.

Fortune J.E.; Sirois J.; Quirk S.M. 1988. The growth and differentiation of ovarian follicles during the bovine estrous cycle. *Theriogenology* **29**:95-109.

Goodman A.L.; Hodgen G.D. 1983. The ovarian triad of the primate menstrual cycle. *Recent progress in hormone research* **39**:1-73.

Goodman R.L. 1988. Neuroendocrine control of the ovine estrous cycle. *In* The Physiology of Reproduction, Vol. 2. *Eds*. E. Knobil; J.D. Neill. Raven Press, New York. p. 1929-1969 (Chap. 46).

Goodman R.L.; Reichert L.E. Jr.; Legan S.J.; Ryan K.D.; Foster D.L.; Karsch F.J. 1981. Role of gonadotropins and progesterone in determining the pre–ovulatory estradiol rise in the ewe. *Biology of reproduction* **25**:134-142.

Guilbault L.A.; Roy G.L.; Grasso F.; Menard D.P.; Bousquet D. 1988. Ovarian follicular dynamics in superovulated heifers pretreated with FSH-P at the beginning of the estrous cycle. An ultrasonographic approach. *Theriogenology* **29**:257. Abstr.

Hansel W.; Dowd J.P. 1986. New concepts of the control of corpus luteum function. *Journal of reproduction and fertility* **78**:755-768.

Henderson K.M.; Prisk M.D.; Hudson N.; Ball K.; McNatty K.P.; Lun S.; Heath D.; Kieboom L.E.; McDiarmid J. 1986. Use of bovine follicular fluid to increase ovulation rate or prevent ovulation in sheep. *Journal of reproduction and fertility* **76**:623-635.

Hsueh A.J.W.; Adashi E.Y.; Jones P.B.C.; Welsh T.H. Jr. 1984. Hormonal regulation of the differentiation of cultured ovarian granulosa cells. *Endocrine reviews* **5**:76-127.

I'Anson H.; Legan S.J. 1988a. Changes in LH pulse frequency and serum progesterone concentrations during the transition to breeding season in ewes. *Journal of reproduction and fertility* **82**:341-351.

I'Anson H.; Legan S.J. 1988b. Does the first LH surge of the breeding season initiate the first full-length cycle in the ewe? *Journal of reproduction and fertility* **82**:761-767.

Ireland J.J. 1987. Control of follicular growth and development. *Journal of reproduction and fertility, Suppl.* **34**:39-54.

Ireland J.J.; Roche J.F. 1983. Development of nonovulatory antral follicles in heifers: Changes in steroids in follicular fluid and receptors for gonadotropins. *Endocrinology* **112**:150-156.

Ireland J.J.; Roche J.F. 1987. Hypotheses regarding development of dominant follicles during a bovine estrous cycle. *In* Follicular Growth and Ovulation Rate in Farm Animals. *Eds*. J.F. Roche; D. O'Callaghan. Martinus Nijhoff Publishers, Lancaster. p. 1-18.

Karsch F.J. 1987. Central actions of ovarian steroids in the feedback regulation of pulsatile secretion of luteinizing hormone. *Annual review of physiology* **49**:365-382.

Karsch F.J.; Bittman E.L.; Foster D.L.; Goodman R.L.; Legan S.J.; Robinson J.E. 1984. Neuroendocrine basis of seasonal reproduction. *Recent progress in hormone research* **40**:185-232.

Karsch F.J.; Legan S.J.; Ryan K.D.; Foster D.L. 1978. The feedback effects of ovarian steroids on gonadotrophin secretion. *In* Control of Ovulation. *Eds*. D.B. Crighton; N.B. Haynes; G.R. Foxcroft; G.E. Lamming. Butterworth & Co., London. p. 29-48.

Kazemi M.; Malathy P.V.; Keisler D.H.; Roberts R.M. 1988. Ovine trophoblast protein-1 and bovine trophoblast protein-1 are present as specific components of uterine flushings of pregnant ewes and cows. *Biology of reproduction* **39**:457-

Keyes P.L.; Wiltbank M.C. 1988. Endocrine regulation of the corpus luteum. *Annual review of physiology* **50**:465-482.

Legan S.J.; Karsch F.J.; Foster D.L. 1977. The endocrine control of seasonal reproductive function in the ewe: A marked change in response to the negative feedback action of estradiol on luteinizing hormone secretion. *Endocrinology* **101**:818-

824.

Leung P.C.K.; Armstrong D.T. 1980. Interactions of steroids and gonadotropins in the control of steroidogenesis in the ovarian follicle. *Annual review of physiology* 42:71-82.

Luhman C.M.; Slyter A.L. 1986. The effect of photoperiod and melatonin feeding on reproduction in the ewe. *Theriogenology* 26:721-732.

Lussier J.G.; Carruthers T.D. 1987. Endocrine and superovulatory responses in heifers pretreated with FSH or follicular fluid. *Theriogenology* 27:253. Abstr.

McCracken J.A.; Baird D.T.; Goding J.R. 1971. Factors affecting the secretion of steroids from the transplanted ovary in the sheep. *Recent progress in hormone research* 27:537-582.

McCracken J.A.; Schramm W.; Okulicz W.C. 1984. Hormone receptor control of pulsatile secretion of $PGF_{2\alpha}$ from the ovine uterus during luteolysis and its abrogation in early pregnancy. *Animal reproduction science* 7:31-55.

McNatty K.P.; Heath D.A.; Henderson K.M.; Lun S.; Hurst P.R.; Ellis L.M.; Montgomery G.W.; Morrison L.; Thurley D.C. 1984. Some aspects of thecal and granulosa cell function during follicular development in the bovine ovary. *Journal of reproduction and fertility* 72:39-53.

Monniaux D.; Chupin D.; Saumande J. 1983. Superovulatory responses in cattle. *Theriogenology* 19:55-81.

Nakamura Y.; Smith M.; Krishna A.; Terranova P.F. 1987. Increased number of mast cells in the dominant follicle of the cow: Relationships among luteal, stromal, and hilar regions. *Biology of reproduction* 37:546-549.

Nanda A.S.; Ward W.R.; Dobson H. 1988. Effect of endogenous and exogenous progesterone on the oestradiol-induced LH surge in dairy cows. *Journal of reproduction and fertility* 84:367-371.

Nett T.M.; Cermak D.; Braden T.; Manns J.; Niswender G. 1987. Pituitary receptors for GnRH and estradiol, and pituitary content of gonadotropins in beef cows. I. Changes during the estrous cycle. *Domestic animal endocrinology* 4:123-132.

Nett T.M.; Niswender G.D. 1982. Influence of exogenous melatonin on seasonality of reproduction in sheep. *Theriogenology* 17:645-653.

Niswender G.D.; Schwall R.H.; Fitz T.A.; Fann C.E.; Sawyer H.R. 1985. Regulation of luteal function in domestic ruminants: New concepts. *Recent progress in hormone research* 41:101-151.

Ono T.; Campeau J.D.; Holmberg E.A.; Nakamura R.M.; Ujita E.L.; Deuereaux D.L.; Tonetta S.A.; DeVinna R.; Ugalde M.; diZerega G.S. 1986. Biochemical and physiologic characterization of follicle regulatory protein: A paracrine regulator of folliculogenesis. *American journal of obstetrics and gynecology* 154:709-716.

Pierson R.A.; Ginther O.J. 1984. Ultrasonagraphy of the bovine ovary. *Theriogenology* 21:495-504.

Pierson R.A.; Ginther O.J. 1987a. Reliability of diagnostic ultrasonography for identification and measurement of follicles and detecting the corpus luteum in heifers. *Theriogenology* 28:929-936.

Pierson R.A.; Ginther O.J. 1987b. Follicular populations during the estrous cycle in heifers. I. Influence of day. *Animal reproduction science* 14:165-176.

Pierson R.A.; Ginther O.J. 1988. Follicular populations during the estrous cycle in heifers. III. Time of selection of the ovulatory follicle. *Animal reproduction science* 16:81-95.

Quirk S.M.; Hickey G.J.; Fortune J.E. 1986. Growth and regression of ovarian follicles during the follicular phase of the oestrus cycle in heifers undergoing spontaneous and PGF-2-a-induced luteolysis. *Journal of reproduction and fertility* 77:211-219.

Rahe R.E.; Fleeger J.L.; Newton H.J.; Harms P.G. 1980. Pattern of plasma luteinizing hormone in the cyclic cow: Dependence upon the period of the cycle. *Endocrinology* 107:498-503.

Rajakoski E. 1960. The ovarian follicular system in sexually mature heifers with special reference to seasonal, cyclical, and left-right variations. *Acta endocrinologica, Suppl.* 52:1-68.

Rajamahendran R.; Canseco R.S.; Denbow C.J.; Gwazdauskas F.C.; Vinson W.E. 1987. Effect of low dose of FSH given at the beginning of the estrous cycle and subsequent response in Holstein cows. *Theriogenology* 28:59-65.

Reeves J.J.; Rantanen N.W.; Hauser M. 1984. Transrectal real-time ultrasound scanning of the cow reproductive tract. *Theriogenology* 21:485-494.

Richards J.S. 1979. Hormonal control of ovarian follicular development: A 1978 perspective. *Recent progress in hormone research* 35:343-373.

Richards J.S. 1980. Maturation of ovarian follicles: Actions and interactions of pituitary and ovarian hormones on follicular cell differentiation. *Physiological reviews* 60:51-89.

Richards J.S.; Hedin L. 1988. Molecular aspects of hormone action in ovarian follicular development, ovulation, and luteinization. *Annual review of physiology* 50:441-463.

Rieger D.; Desaulnier D.; Goff A.K. 1988. Ovulatory response and embryo yield in superovulated Holstein heifers given a priming dose of FSH-P at day 2 of the estrous cycle. *Theriogenology* 30:695-699.

Roberts J.S.; McCracken J.A.; Gavagan J.E.; Soloff M.S. 1976. Oxytocin-stimulated release of prostaglandin $F_{2\alpha}$ from ovine endometrium *in vitro*: Correlation with estrous cycle and oxytocin-receptor binding. *Endocrinology* 99:1107-1114.

Savio J.D.; Keenan L.; Boland M.P.; Roche J.F. 1988. Pattern of growth of dominant follicles during the oestrous cycle of heifers. *Journal of reproduction and fertility* 83:663-671.

Schallenberger E.; Schams D.; Bullermann B.; Walters D.L. 1984. Pulsatile secretion of gonadotrophins, ovarian steroids and ovarian oxytocin during prostaglandin-induced regression of the corpus luteum in the cow. *Journal of reproduction and fertility* 71:493-501.

Schams D.; Koll R.; Ivell R.; Mittermeier Th.; Kruip Th.A.M. 1987. The role of oxytocin in follicular growth and luteal function. *In* Follicular Growth

and Ovulation Rate in Farm Animals. *Eds.* J.F. Roche; D. O'Callaghan. Martinus Nijhoff Publishers, Lancaster. p. 221-235.

Schwall R.H.; Sawyer H.R.; Niswender G.D. 1986. Differential regulation by LH and prostaglandins of steroidogenesis in small and large luteal cells of the ewe. *Journal of reproduction and fertility* **76**:821-829.

Sirois J.; Fortune J.E. 1988. Ovarian follicular dynamics during the estrous cycle in heifers monitored by real-time ultrasonography. *Biology of reproduction* **39**:308-317.

Stellflug J.N.; Fitzgerald J.A.; Parker C.F.; Bolt D. 1988. Influence of concentration, duration and route of administration of melatonin on reproductive performance of spring-mated Polypay and Polypay-cross ewes. *Journal of animal science* **66**:1855-1863.

Stellflug J.N.; Nett T.M. 1988. Influence of exogenous melatonin and altered day length on reproductive performance of Polypay ewes. *Theriogenology* **29**:535-543.

Stormshak F.; Zelinski-Wooten M.B.; Abdelgadir S.E. 1987. Comparative aspects of the regulation of corpus luteum function in various species. *In* Regulation of Ovarian and Testicular Function. *Eds.* V.B. Mahesh; D.S. Dhindsa; E. Anderson; S.P. Kalra. Plenum Press, New York. p.327-360.

Tamarkin L.; Baird C.J.; Almeida O.F.X. 1985. Melatonin: A coordinating signal for mammalian reproduction. *Science* **227**:714-720.

Thatcher W.W.; Macmillan K.L.; Hansen P.J.; Drost M. 1989. Concepts for regulation of corpus luteum function by the conceptus and ovarian follicles to improve fertility. *Theriogenology* **31**:149-164.

Tsafriri A.; Abisogun A.O.; Reich R. 1987. Steroids and follicular rupture at ovulation. *Journal of steroid biochemistry* **27**:359-363.

Walters D.L.; Schallenberger E. 1984. Pulsatile secretion of gonadotrophins, ovarian steroids and ovarian oxytocin during the periovulatory phase of the oestrous cycle in the cow. *Journal of reproduction and fertility* **71**:503-512.

Walters D.L.; Schams D.; Schallenberger E. 1984. Pulsatile secretion of gonadotrophins, ovarian steroids and ovarian oxytocin during the luteal phase of the oestrous cycle in the cow. *Journal of reproduction and fertility* **71**:479-491.

Ware C.B.; Northey D.L.; Boland M.P.; First N.L. 1988. Early cycle FSH-p priming as a prelude to superovulatory gonadotropin administration in ewes and heifers. *Animal reproduction science* **16**:97-105.

Wathes D.C. 1984. Review. Possible action of gonadal oxytocin and vasopressin. *Journal of reproduction and fertility* **71**:315-345.

Ying S.-Y. 1988. Inhibins, activins, and follistatins: Gonadal proteins modulating the secretion of follicle-stimulating hormone. *Endocrine reviews* **9**:267-293.