Physiology and Practice of Induction and Control of Oestrus in Cattle

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Reproductive Targets

High reproductive performance of a dairy herd is an important component of overall productivity and hence, profitability. The optimum reproductive target to achieve will depend on overall herd milk yield and the relative importance of grazed forage in the diet. In herds with average milk yields (<1500 gallons/lactation), where seasonally produced forage is a major component of the diet, the targets to aim for are:

- a healthy calf per cow per annum,
- improved genetic merit of calf,
- a 305-day lactation period per cow,
- low (<20%) replacement rate.

These targets require effective uterine involution, early resumption of ovulation and oestrous expression, high efficiency of oestrous detection, with resultant high pregnancy rates to artificial insemination (AI). In high yielding herds (>2000 gallons per lactation) who are less dependent on seasonally produced grazed forage, the target of a 365-day calving interval could be extended to 400 days, because it may not make physiological or economic sense to dry off high yielding cows still in high production after a 305-day lactation. The two critical factors, therefore, that determine overall herd reproductive efficiency are:

- breeding of all eligible cows within 3 weeks of start of breeding season (high submission rate),
- insemination with high quality semen 12 hr before ovulation (high pregnancy rates to AI).

Factors that affect submission rate are:

i. the postpartum interval to resumption of normal oestrous cycles,
ii. the level of anoestrus in the herd, and
iii. the efficiency of oestrous detection.

In order to decrease anoestrus and increase submission rates of cows by use of exogenous hormones, it is desirable to understand how hypothalamic-pituitary interactions affect ovarian function. The rapid expansion of new knowledge makes it difficult for veterinary practitioners to keep abreast of the latest scientific information, potentially relevant to modern veterinary practice. The aim of this paper, therefore, is to review the current state of knowledge of cattle reproduction relevant to clinicians, and the appropriate scientific rationale for existing and new treatments.

Control of GnRH Secretion

Gonadotrophic releasing hormone (GnRH) is the key hormone that regulates the synthesis and release of LH and FSH from the anterior pituitary (AP) gland. It is produced in specialised neuronal cells within the hypothalamus, and is released in a pulsatile pattern into the portal blood supply to act on the AP gland. GnRH binds to specific receptors on the gonadotrophs, but this GnRH effect is transient because they become insensitive to GnRH if it is continually present (down regulation of GnRH receptors). Thus, the pulsatile nature of GnRH release is necessary to prevent receptor down regulation. The pattern of GnRH release is controlled by the activity of the complex neural network implinging on the GnRH neurons. The main forces that affect this network are either external such as suckling and nutrition, or internal such as concentrations of progesterone and/or oestradiol. The GnRH pattern, in turn, determines the specific pulsatile pattern of LH release; however, FSH is passively released following synthesis and GnRH only partially regulates FSH secretion. FSH synthesis is also regulated locally within the AP by the activin - inhibin axis in association with the activin binding protein (BP), follistatin. Thus, LH and FSH concentrations are divergent throughout the oestrous cycle and postpartum period of cows, despite the fact that they are produced in the same cell under the influence of a single releasing hormone. Clinically, GnRH can be given to cause LH and FSYH release, but it is important to re-

Presented at the XIX World Buiatrics Congress, Edinburgh, Scotland, July 8-12, 1996.

member that:

- sex steroids modulate the magnitude of pituitary release,
- it has a short half life and the resultant LH and FSH elevation lasts for only 2-4 hours,
- the pattern of administration determines the resultant LH and FSH release profile.

When GnRH is given as a single bolus injection, it causes a transient increase in LH and FSH, sufficient to ovulate a dominant follicle in anoestrus cows. If given in a pulsatile fashion (1 pulse every 1-2 hours) using a programmable pump, it will stimulate both follicular development, oestrogen production and eventually ovulation, mainly in mares or bitches where the duration of treatment can vary from 3-15 days. There are no clear cut indications for its use in the male, at this time.

Hormonal Regulation of the Oestrous Cycle

The length of the oestrous cycle is regulated by the secretion of progesterone from the corpus luteum (CL) (Fig 1).

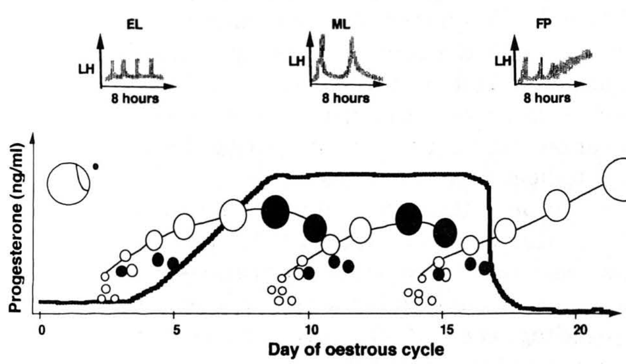

Figure 1. Concentrations of progesterone (thick dark line) during the oestrous cycle of heifers in association with the pattern of turnover of follicle waves (clear circle healthy dominant follicle; cloudy circles atretic dominant follicle) and LH pulse frequencies (15 min blood samples for 8 hours) in early luteal (EL), Midluteal (ML) and follicular phases (FP) of the oestrous cycle.

Progesterone is the key hormone regulating the secretion of GnRH from the hypothalamus. Mean concentrations of LH are low during the luteal phase of the oestrous cycle due to the strong negative feedback effect of progesterone on GnRH, resulting in decreased GnRH and hence LH pulse frequency. Following luteolysis, caused by oxytocin induced release of prostaglandin F2α (PGF) on days 16-18 of the oestrous cycle, progesterone concentrations decline to their lowest level during the follicular phase, and the pulse frequency and the mean concentrations of LH both increase (Rahe *et al.*, 1980). The maturing dominant follicle (DF) develops increased numbers of LH receptors on granulosa cells, resulting in increased oestradiol concentrations and onset of proestrus. This elevation in estradiol stimulates a further increase in GnRH pulse frequency, and a prolonged surge in GnRH (Moenter *et al.*, 1991) which induces the gonadotrophin surge and ovulation. Following ovulation, the CL is formed and progesterone concentrations increase gradually to maximum luteal phase concentrations by days 9-12 of the oestrous cycle. In contrast to the basal concentrations of LH during the luteal phase, there are sequential periods of elevation and decline in FSH concentrations every 7-10 days throughout the cycle (Fig 2). These recurrent changes in FSH are associated with emergence of new waves of follicular growth in cattle (Adams *et al.*, 1992; Sunderland *et al.*, 1994). Thus, it appears that progesterone is the major regulator of LH pulse frequency, while oestradiol and the balance between activin and inhibins regulate FSH during the oestrous cycle of cattle.

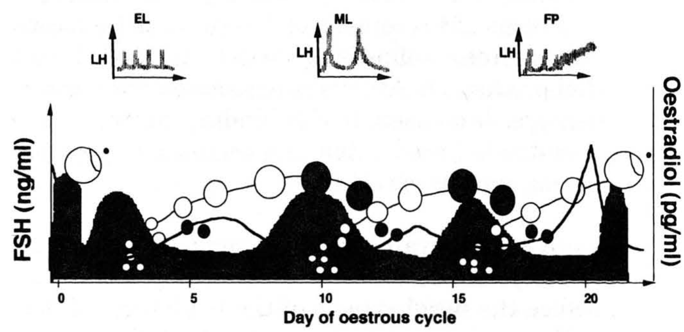

Figure 2. Recurrent 2-3 day quantitative elevations in FSH (shaded area) concentrations associated with new follicle wave emergence and concentrations of oestradiol (dark line) in peripheral blood during the oestrous cycle. LH concentrations and follicle wave turnover are those described in Figure 1.

Occurrence and Regulation of Follicle Waves

The recurrent transient elevations of FSH in cattle during the oestrous cycle and anoestrus initiate the development of sequential waves of follicular development (Fig 3).

There are generally two, but sometimes only one non-ovulatory follicle wave in the luteal phase of the cycle, before the development of the ovulatory DF following CL regression (Savio *et al.*, 1988; Sirois and Fortune 1988; Ginther *et al.*, 1989). Following emergence of a follicle wave, 2-5 medium size follicles develop, from which only one follicle is selected (days 2-3 of the cycle) to form the DF by days 4-5. The subordinate follicles undergo atresia during the dominance phase while serum FSH is low (Ireland and Roche, 1983; Adams *et al.*, 1992; Sunderland *et al.*, 1994). Coincidentally, the dominant non-ovulatory follicle continues to grow, gains LH

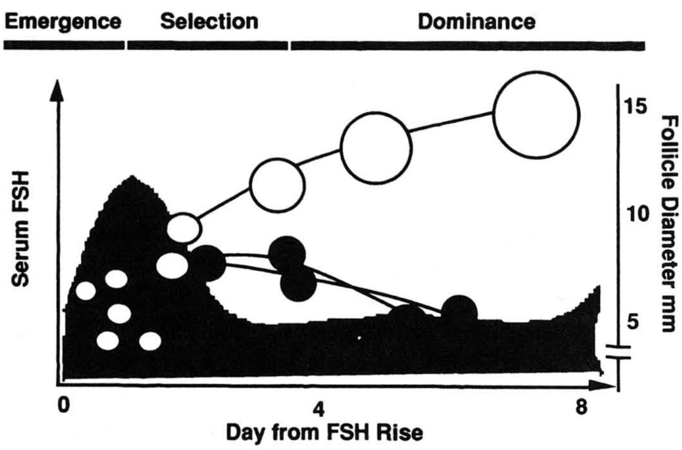

Figure 3. Elevation of FSH (shaded area) concentrations in association with follicle wave emergence; selection of a dominant follicle (clear follicle) occurs in association with declining FSH which induces atresia of subordinal follicles (cloudy follicles). The dominant follicle develops LH receptors and maintains high concentrations of free insulin-like growth factor (IGF-1) and oestradiol production. Atresia is associated with loss of LH receptors, increased IGF-1 binding proteins, decreased oestradiol production and increased apoptosis of granulosa and theca cells.

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The Postpartum Period

Endocrine changes associated with parturition remove steroid negative feedback on gonadotrophins, which allows the AP - ovarian axis to resume normal cyclical activity. In the early postpartum period, there is a 2 -3 day elevation of FSH concentrations within 1-2 weeks of calving which initiates emergence of the first postpartum follicular wave and selection of the first DF (Figure 3). The mean interval to detection of the first postpartum DF was 12 ± 8.9 days in dairy cows (Savio *et al.*, 1990). The fate of this first DF is determined by LH pulse frequency, and the interval to attainment of an LH pulse frequency of 1 per hour is variable and under direct GnRH control. In postpartum dairy cows, in reasonable body condition, the first DF ovulated in 70-80% of dairy cows. In contrast, beef suckler cows have a longer postpartum anoestrous period than dairy cows; a new follicle wave emerges early after calving, with the formation of the first dominant follicle, within 10 to 14 days (Murphy *et al.*, 1990; Stagg *et al.*, 1995). Even in cows with prolonged postpartum anoestrus (up to 100 days), resumption of follicular growth occurs soon after calving (Stagg *et al.*, 1995). However, the incidence (11%) of ovulation of the first DF postpartum in suckler beef cows is low (Murphy *et al.*, 1990; Stagg *et al.*, 1995). Thus, the prolonged anoestrus period of beef cows is due to failure of ovulation of dominant follicles rather than a delay in their development (Table 1); it appears that infrequent LH pulses in the early postpartum period lead to atresia rather than ovulation of the DF. Factors that determine the postpartum interval to first ovulation are:

i. declining negative energy balance post calving,
ii. poor body condition score (BCS) at calving,
iii. suckling,
iv. maternal bond.

LH pulse frequency of dairy cows increases post calving after the nadir point of negative energy balance has been reached; this then leads to first ovulation (Canfield and Butler, 1990). Cows in poor BCS or beef cows suckling their calves generally have a longer interval to first ovulation (Table 1).

Table 1. Comparative reproductive parameters of dairy and beef cows suckling their calves in the early postpartum period.

Parameter	Dairy Cow	Beef Cow
1st postpartum FSH rise	7-17 Days	7-17 Days
Emergence of 1st follicle wave post partum	10-20	10-20
% cows that ovulate 1st DF[1]	78-80	10-35
% cystic follicles that develop	0-15	0-2%
Days to 1st oestrus	25-45	30-130
% short cycles after 1st ovulation	>70	>70
Regulation of LH pulse frequency	• Nadir E[2] balance • BCS[3] at calving	• Nadir E balance • BSC at calving • Suckling • Maternal bond

[1]DF - Dominant follicle
[2]E - Energy
[3]BCS - Body condition score

Thus, days to nadir energy balance and low BCS are two common factors determining postpartum interval to 1st ovulation, while suckling frequency and maternal bond additionally affect beef cows (Stagg *et al.*, 1995; Williams and Griffith, 1995).

Development of Follicular Cysts

Cystic follicles develop due to failure of DF either to ovulate or undergo atresia (Savio *et al.,* 1990). They continue to grow to sizes of 25-45 mm and suppress new follicle wave emergence due to production of oestradiol from the cyst. The cyst becomes oestrogen inactive after a variable time period; this presumably allows a transient 2 to 3 day rise in FSH to occur, emergence of the next follicle wave, and ovulation. A possible endocrine cause of cysts may be an increase in LH pulse frequency, insufficient to cause ovulation but sufficient to cause continued growth of the DF and high oestrogen production. Savio *et al.* (1990) reported that the first DF in 4 of 19 autumn calving dairy cows, detected between days 5 and 8 after calving, became cystic. Either single or multiple cysts were detected. Single cysts were large, spherical and grew to 40-45 mm in diameter; cysts were oestrogen active for variable periods. They decrease reproductive efficiency by prolonging the postpartum interval to first ovulation (Nanda *et al.*, 1989). Two approaches to treat follicular cysts are:

i. luteinization with LH, hCG or GnRH induced LH release to suppress oestradiol production; cows will not show oestrus until the luteal structure/CL regresses, generally 14-18 days after formation;
ii. induce atresia by suppression of LH and FSH support through steroid negative feedback i.e. use a progesterone intra-vaginal device with an injection of 5 mg oestradiol.

Luteinization of the cyst results in a variable interval to oestrus; this interval can be shortened by use of PGF 7-10 days later. The progesterone treatment should be 9-10 days duration, to allow physiological termination of cysts, and new follicle wave emergence about 4 days after start of treatment; this results in the presence of an oestrogen active DF 5 to 6 days later when the progesterone treatment is terminated. Oestrus generally occurs 2-4 days later.

Induction of Oestrus in Anoestrous Cows

The cause of true anoestrus in cattle is the failure of dominant follicles to ovulate rather than the absence of their development (Murphy *et al.*, 1990; Stagg *et al.*, 1995). FSH is secreted on a recurrent basis in anoestrus, resulting in emergence of follicle waves and atresia of the DF, due presumably to insufficient LH pulse frequency. First ovulation in cattle is often associated with a short subsequent luteal phase (Inskeep, 1995) and the absence of oestrous behaviour (Morrow *et al.*, 1966). The main role of progesterone therapy in anoestrus is to prime the brain and uterus to overcome the above deficiencies associated with first ovulation, so that coincident oestrus occurs at first ovulation, and the subsequent luteal phase is normal. Currently, the main hormonal approaches to induce ovulation in anovulatory cows are presented in table 2, of which the following will be discussed:

i. use of LH, hCG or GnRH to cause LH release,
ii. use of progestagen and oestradiol at the start of treatment with or without further hormone stimulation at the end of treatment.

Table 2. Pharmacological approaches to induction of ovulation in anoestrous cattle.

Approach	Hormone used	Effects	Potential Problems
Cause release of GnRH from hypothalamus	Oestradiol	GnRH release Induce oestrus	• Oestrus without ovulation? • Lower fertility?
Cause release of LH/FSH from putuitary	GnRH or one of its synthetic analogues	Stimulate follicular growth and ovulation	• Stage of follicle wave affects response. • Short luteal phases. • Low or no oestrus.
Direct action on ovary	(a) LH/FSH	Follicular growth and ovulation	• Expensive and compounds scarse. • May require multiple injection. • Ovulation without oestrus.
	(b) eCG	Follicular growth and ovulation	• Multiple ovulations? • No response? • Require progesterone priming
Mimick ovarian cycle e.g. progesterone + gonadotrophins	Progesterone / progestagen + eCG or progestagen + GnRH	Primes uterus / brain Stimulates follicular growth, oestrus and ovulation	• Need adequate nutrition. • Sufficiently long postpartum interval

i. Use of hCG or GnRH:

Knowledge of the dynamics of follicle waves has to be taken into account when using this approach. Appropriate doses of either hormone will induce ovulation, if a DF is present. The response depends, therefore, on the stage of the follicle wave when the animal is treated. Oestrus will rarely be expressed and the first cycle may be of short duration. This approach could be useful to initiate reproductive events, although the response may be dictated more by the time of resumption of increased LH pulse frequency, rather than the exogenous use of GnRH. Studies have been carried out on the blanket use of GnRH at specific times postpartum with generally inconclusive results (Thatcher *et al.*, 1993). The logic of such an approach, in the light of follicle dynamics, is now questionable. Risco *et al.* (1995) used sequential treatments with GnRH (days 14 and 15) and PGF (days 21, 35 and 57 postpartum) to stimulate early cyclicity in dairy cows. Treatment shortened days to first ovulation and decreased number of days with palpable cystic disease; but overall herd reproductive efficiency between treated and controls was not different, due mainly to low heat detection efficiency (42%) in the herd.

ii. Progesterone:

Progesterone or synthetic progestagen (norgestomet) in conjunction with oestradiol at the start of treatment will induce oestrus in anoestrous cows that have adequate LH pulse frequency after treatment to cause final maturation and ovulation and a DF. However, where the LH pulse frequency is likely to be suppressed, e.g.:

- high yielding dairy cows in a poor body condition score (BCS),
- beef suckler cows in poor BCS,
- beef suckler cows calved <50 days,

progesterone therapy needs supplementation with a gonadotrophin such as equine chorionic gonadotrophin (eCG) to increase oestrogen production from the follicle. An injection of 400-700 iu eCG, given at the end of a 7 to 12 day progestagen treatment, increases the number of anoestrous cows responding. The dose of eCG, however, must be carefully selected to minimise twin pregnancies. An alternative to the use of eCG has been developed recently in New Zealand (Macmillan *et al.*, 1994); it involves exogenous supplementation of oestradiol after the end of a 7 day progesterone treatment, to cause oestrous behaviour and a pre-ovulatory gonadotrophin surge. Any cow not in oestrus 48 hours after progesterone device removal is given an injection of 600μg oestradiol. Oestradiol will not induce twins, but further research is required to clarify fertility following oestradiol supplementation close to the follicular phase.

Nutrition and suckling can be manipulated to shorten the postpartum anoestrous period in beef cows. Anoestrus is more common in beef cows in poor BCS (scale of 1 to 5). In general, beef cows with a BCS at calving of:

- <2.0 have prolonged anoestrus
- > 2.5 show oestrus within 40-60 days of calving.

Thus, pre-partum nutrition is an important determinant of the postpartum anoestrus interval. This interval can also be shortened by:

- 10 to 15 days with once daily suckling,
- 10 to 15 days by breaking the maternal bond.

Thus, once daily suckling in association with calf isolation initiated at 30 days postpartum will shorten the interval to first ovulation by 20 to 40 days, and where it is practically feasible, is a useful method to shorten anoestrus in beef cows.

Synchronisation of Oestrus in Cattle

Synchronisation of oestrus in cattle facilitates increased use of AI, super-ovulation, and embryo-transfer techniques at farm level. This technology is less widely used in cows because of variable responses obtained often associated with postpartum reproductive problems. The main limitation to increased use of AI and high reproductive efficiency where AI is currently used is low efficiency of oestrous detection (40-60%). Effective synchronisation techniques must therefore synchronise oestrus in cyclic animals and, also, induce fertile oestrus and ovulation in anoestrous animals. The control of oestrus and ovulation requires firstly that the life span of the CL is reduced, and secondly that follicle wave emergence is synchronised so that a healthy, oestrogen active DF is present at the end of treatment. The basic methods available are:

i. induction of CL regression using PGF,
ii. regulation of time of ovulation using progestagen/oestrogen treatments,
iii. synchronisation of follicle waves with GnRH before PGF use.

i. The use of PGF

An injection of PGF from day 6 of the cycle until the time of natural luteolysis will cause immediate CL regression. It does not, however, affect follicle wave dynamics. Therefore, the time of onset of oestrus is dependent on the stage of follicular wave when CL regression was induced (Fig 4):

- onset of oestrus 2-3 days later if a mature dominant follicle is present, e.g. Days 6 and 7 (1st DF) and 13-15 (2nd DF) of the cycle,
- delayed onset of oestrus if the follicle wave is emerging or undergoing the selection process, e.g. Days 9-11 of the cycle.

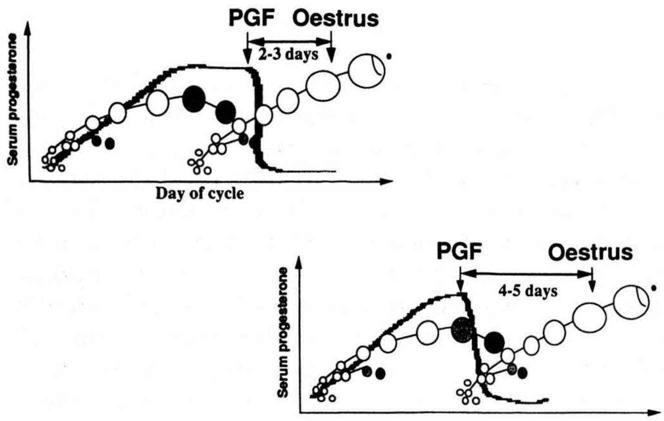

Figure 4. Effect of stage of follicle wave on subsequent onset of oestrus following induced luteolysis during the mid-luteal phase of the oestrous cycle of heifers with prostaglandin F2α (PGF).

Because animals will be at different stages of follicle wave growth during the luteal phase when given PGF, there will be a spread in onset of oestrus post PGF injection (2-5 days). Different PGF regimes are used; (i) two injections 11 days apart which works well in heifers, but not in dairy cows; (ii) inject cyclic heifers or dairy cows calved > 45 days preferably with the use of tail paint to aid oestrous detection; (iii) diagnose a CL (rectal palpation, ultrasound scanning or progesterone assay) and only inject those animals with a CL. Fertility is normal following AI at the optimum time prior to ovulation. In general, PGF should not be used in beef suckler cows due to a variable percent of anoestrous cows. In the absence of either knowledge of exact stage of cycle or use of other hormones to control follicular waves, a spread in onset of oestrus will occur following a single injection of PGF in cyclic cattle.

ii. The use of Progesterone / Progestagen

In contrast to PGF therapy, progestagens in conjunction with oestradiol at the start of treatment not only partially regulate the life span of the CL in most animals, but also have a role to play in the management of follicular waves. When deciding which progesterone regimen to use, the following points need to be considered:

1. Method of administration

a) the intravaginal route: a silastic device impregnated with progesterone is used. There are two products available:

- PRID - progesterone releasing intravaginal device (Sanofi Ltd, France),
- CIDR - controlled internal drug release device (InterAg, New Zealand).

Both devices seem to deliver similar concentrations of progesterone to the animal with an initial fast release elevating concentrations to those of the luteal phase for 3-5 days; this is followed by a decline to about half luteal phase concentrations for the remainder of the 9-12 days treatment period (MacMillan & Peterson, 1993).

b) the subcutaneous route: the progestagen norgestomet (Crestar, Intervet Ltd, Netherlands) is administered by insertion of a small ear implant to the animal. The pattern of release has not been published.

The relative merit of each system for specific conditions of use is a matter of choice for each veterinarian.

2. Duration of treatment

With current methods, the maximum duration of treatment *should not exceed 12 days* in order to maintain normal fertility in synchonised cattle. Persistent dominant follicles form in those cows without a CL or those undergoing luteolysis at the start of treatment because subluteal concentrations of progesterone from the intravaginal devices 3-4 days after insertion result in an increase in LH pulse frequency, sufficient to block follicular wave turnover, but stimulates continued growth of the DF. Dominant follicles of > 8 days of age result in ovulation of incompetent or aged oocytes, and hence decrease fertility despite the good synchrony of oestrus obtained (Mihm *et al.*, 1994). The minimum length of treatment is dependent on the hormone(s) used to control CL life span and synchronise follicular wave emergence. Currently, there is a general trend to shorten the duration of treatment to 8-10 days; however, it should be at least 7 days (Ryan *et al.*, 1995).

3. Luteolytic agent used

There are two choices;

a) use of oestradiol: a 10mg oestradiol capsule is used with PRID or CIDR. When using norgestomet, an injection of 5 mg oestradiol valerate and 3mg norgestomet is given at the time of ear implant insertion. Oestradiol is only partially and slowly luteolytic, and maximum duration of treatments are:

i. *12 days* with progesterone intravaginal devices and the oestradiol capsule, and
ii. *10 days* with the norgestomet ear implant regime.

b) use of PGF: allows the length of treatment to be shortened to 7-10 days by giving an injection of PGF at or 1-2 days before the end of the progesterone/progestagen treatment (Ryan *et al.,* 1995). It is necessary to wait 6-7 days after initiation of progesterone treatment before giving PGF, so that all CL are responsive to PGF. The optimum time to inject PGF relative to the end of the progressive treatment is still under discussion.

4. Synchronisation of follicle waves

In order to have a DF with a competent oocyte in all animals, it is necessary to synchronise follicle waves. There are two ways to achieve this aim:

a) use of oestradiol and progesterone: high concentrations of progesterone and oestradiol at the start of treatment suppress LH and FSH respectively (Twagiramungu *et al.,* 1995); the decreased LH and FSH concentrations starve the unselected cohort or DF, resulting in termination of the ongoing follicle wave and the emergence of a wave 3-5 days later. Therefore, the oestradiol given at the start of the treatment has both a luteolytic role as well as a key role in synchronising follicle waves. The dose and route of administration of oestradiol to use, and interactions with progesterone concentration at the start of treatment, require further work. If PGF is used at or near the end of an oestradiol-progesterone treatment regimen, it allows the treatment period to be shortened to 8-10 days.

b) use of GnRH: administration of the potent GnRH agonist buserelin (Hoechst Ltd) causes LH release and induces the unselected cohort follicles to luteinize or DF to ovulate. This treatment results in the emergence of a new follicle wave 1-2 days later. If GnRH agonist is used, it is mandatory to use PGF 6-7 days later, to regress any new GnRH induced CLs. The progesterone/progestagen treatment can be of shorter duration because of the faster new follicle wave emergence; it still must be long enough (7 days) to allow PGF to cause regression of the induced CLs (Ryan *et al.*, 1995).

iii. Use of GnRH and PGF

The current limitation of variable onset of oestrus following use of PGF has been partially overcome (Thatcher *et al.*, 1993; Pursley *et al.*, 1995) by use of a new synchronisation regime depicted in Fig 5. This treatment involves synchronisation of follicle waves with GnRH at the start and control of time of ovulation by using GnRH two days after PGF. Current data indicate it works better in cows than in heifers but further large scale field testing of this or variants of this regime are required, before definitive recommendations can be given.

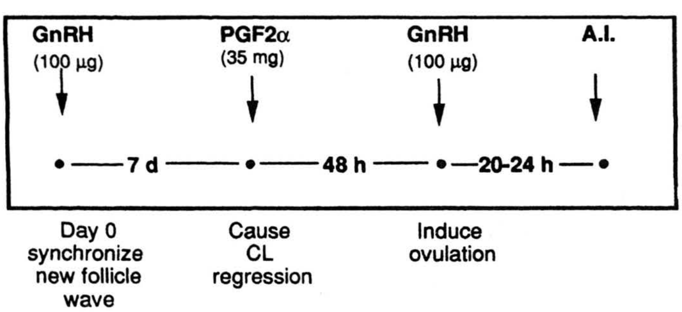

Figure 5. Proposed treatment schedule for combination of GnRH and PGF treatment of heifers and cows currently being developed.

Conclusion

It is clear that we are only beginning to understand the control of follicle wave dynamics and how this knowledge needs to be applied to hormone treatments which include, regulate or synchronise oestrus in cattle. The interactions of energy status, suckling, postpartum interval, individual clinical problems, variation in response to specific treatments all need to be considered. This will likely result in the development of specific treatments for different categories of cattle. In conclusion, hormonal regimes to obtain effective synchronisation of follicle waves need to be integrated with current methods used to obtain precise control of luteolysis, in order to obtain tight synchrony of oestrus (necessary for fixed timed AI) and optimum fertility (healthy DF with a competent oocyte).

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