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Hormonal treatment and estrus synchronization in cows: A mini-review

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ABSTRACT

Perfect detection of estrus is crucial for good husbandry practice of cow. Estrus synchronization is the alternative strategy to bypass the critical problem of estrus detection. Synchronization program allows fixed timed artificial inseminations (FTAI) to evade the estrus detection. The most recently developed programs include protocols for re-synchronization following first or subsequent inseminations. These re-synchronization protocols may involve selected forms of hormonal intervention during the diestrus and pro-estrus periods following FTAI, or following pregnancy diagnosis by ultrasound from 28 days after FTAI. Almost all programs involve strategically timed treatment of prostaglandin F2α (PGF) and gonadotropin releasing hormone (GnRH). Treatment of an estradiol ester and progesterone supplementation per vaginum may be included in some programs. The basic program is the "Ovsynch" regimen. This mini-review discusses a number of key points related to external hormonal stimulation on ovarian follicular wave to improve pregnancy rate following timed AI.

Keywords

Dairy cows, Estrus, Synchronization, Timed AI

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INTRODUCTION

The reproductive performance of high yielding cows with high genetic merit declines in many dairy industries. One of the major constrains of profitable dairy farming is low pregnancy rate in cows (Alam et al., 1994, Shamsuddin et al., 2001). The productivity of cattle could be low because of poor nutrition (Alam et al., 2006), and incorrect detection of estrus (Roelofs et al., 2010; Macmillan, 2010; Paul et al., 2011). However, the specific reasons for the decline have not been documented. These might be directly related to or exacerbated by environmental and management conditions. The same management advantages are less relevant to reproductive management where each animal must be considered as an individual within its own estrus cycle so that estrus, ovulation, insemination, fertilization and conception occur within a sequence that is within restricted behavioral and biological limits. Similar situations can arise during the management of parturition, although they are usually less complex and more predictable.

Estrus detection and animal identification have become increasingly difficult in large dairying operations to the extent that decisions related to the breeding management of individual cows are usually made by "barn" staff working with cows that may only have limited periods to interact in an unrestricted manner (Macmillan, 2010). This situation can limit the likely expression of the classic symptoms of behavioral estrus; namely, standing when mounted by a herd mate.

Estrus detection rates of over 90% have been reported with cows that have recommenced cycling in herds with seasonally concentrated calving systems that can express estrus under ideal conditions when grazing pasture. However, an increasing incidence of early lactation anovulatory anestrus combined with a greater likelihood of early embryonic death without a return to estrus (Macmillan, 2007). Potential benefits from estrus synchronization in dairy cattle include reduced time devoted to estrus detection and reduced variability in days from parturition to first service, leading to reduced variability and length of calving intervals within a herd (Waldmann et al., 2006).

Under these circumstances, it is not surprising that synchronization programs have become increasingly common, especially those that allow every animal within a selected group of cows within a herd to receive a programmed series of preparatory injections or treatments culminating in either a short intensive period of inseminating associated with detected estrus, or insemination at a pre-determined time without regard to estrus (timed AI; TAI).This review discussed about the different hormones that are used controlled breeding or synchronization programs and their application in dairy herds.

ADVANCEMENT OF SYNCHRONIZATION AND CONTROLLED BREEDING PROGRAMS

***Progestogens*:** Initial treatments focused on synchronizing behavioral estrus as a prelude to insemination. Potent synthetic progestogens were administered orally or by subcutaneous implants to heifers or beef cows but were unable to be used with lactating dairy cows because of hormonal residues in the milk likely to be orally active. The principle involved in these forms of treatment was to extend the normal estrus cycle by extending the period of diestrus. Induced luteolysis was attempted by injecting high doses of long acting estradiol esters (Macmillan, 2010).

***Prostaglandin F2a (PGF2a)*:** Luteolysis consists of functional and structural regression of the corpus luteum (CL) (McCracken et al., 1999; Stocco et al., 2007). Functional luteolysis is characterized by a decrease in secretion of progesterone (P_4) in sheep (McCracken et al., 1999) and cattle (Ginther et al., 2007). In heifers, the length of the luteolytic period is 24 h, based on hourly sampling (Ginther et al., 2010a). During spontaneous and induced luteolysis, luteal size and blood flow decrease during functional luteolysis in cattle (Araujo et al., 2009). In cattle, the prominence of PGFM pulses increases after the transition between preluteolysis and luteolysis (Ginther et al., 2010a; Ginther et al., 2010b). Luteolysis is temporally associated with an increase in E_2 concentration (Ginther et al., 2010c; Ginther et al. 2011).

The identification of PGF as the uterine luteolysis was quickly followed by the commercialization of a natural synthetic form (Lutalyse) (Hafs et al, 1975) and potent analogues (Estrumate) (Cooper, 1974). Their use was based on shortening the luteal phase by injecting PGF to induce luteolysis. This meant that a treatment was only effective in the presence of a functional CL from Day 7 to Day 17 of a normal estrus cycle (Estrus=Day 0). Although luteolysis could be successfully synchronized when a PGF was administered during this period, the interval to the onset of behavioral estrus could vary from 2 to 5 days. This variation was due to differences in the size of the dominant ovarian follicle at the time of injection and was demonstrated to be closely related to the wave-like pattern of normal follicle development. For example, when dairy cows were injected with PGF on Day 6 of their cycles, the average interval to estrus and insemination was 3.7 days, increasing to 4.9 days for injections at Day 10 and then declining to 3.4 days at Day 16 (Macmillan and Henderson, 1984). The percentage detected in estrus from 3 to 10 days after injection increased from 81 to 98% with advancing stage of diestrus at the time of PGF injection. These results clearly showed that synchronizing luteolysis did not result in the synchronized onset of estrus and ovulation. Detecting behavioral estrus had to be a necessary component of synchronizing estrus within a prostaglandin system. However, when cows were inseminated following the estrus associated with a single PGF injection, their pregnancy rates were significantly higher than in untreated contemporaries (70.5 vs. 58.5%; n=1151 & 1450) (Macmillan and Day, 1982).

Although the degree of synchronization of luteolysis was enhanced by the administration of a second injection of PGF from 9 to 14 days after the first, the response to the second injection in terms of cows detected in estrus was frequently less than predicted. For example, Xu et al. (1997) reported that whereas 78.5% of cows were detected in estrus within 7 days of the first injection of PGF, it only increased to 82.5% after the second injection given 13 days later. The poorest response to the second injection of 77% was from cows that were at Days 5 to 9 of their cycles when given the second injection. In contrast to original reports using 2 × PGF protocols, the treated cows that were inseminated following a detected estrus had lower conception rates to first insemination than untreated contemporaries (61.1 vs. 70.5%; Xu et al., 1997). As with the estrus response, the greatest difference in conception rate involved those cows inseminated when injected at early stages of their cycles (Days 5 to 9=45.9%; Days 10 to 13=67.7%; Days 14 to19=67.5%). These reduced responses involving cows at Days 5 to 9 of their cycles at the time of the second injection would be associated with an extended interval of low progesterone between the two injections. If progesterone was supplemented per vaginum for a period of 5 days before the second injection of PGF, the estrus response rate was increased from 82.9 to 89.6% and the conception rate from 59.7 to 65.1% so that the pregnancy rate over the first 6 days of inseminating was increased from 49 to 59.3% (Xu et al., 1997). Most of the beneficial treatment responses involved the cows that were at Days 5 to 9 of their cycles.

It is likely that results obtained from routinely using 2 × PGF protocols with lactating cycling dairy cows could be enhanced by the strategic use of supplemental progesterone. Pugliesi et al. (2012) was reported that repeated E_2 exposure stimulates increasing prominence of PGFM pulses was not supported. Instead, repeated exposure reduced the prominence of PGFM pulses, in contrast to the stimulation from the first E_2 treatment. Reduced prominence of a PGF2α pulse during luteolysis can lead to a transient resurgence in P_4 concentration.

***Gonadotropin Releasing Hormone (GnRH)*:** Treatments with GnRH increased conception in primiparous cows, during summer, and in cows with lower body condition (Kaim et al., 2003). As with PGF, the identification of GnRH as the "LH releasing agent" was quickly followed by the natural form and potent analogues of GnRH being synthesized. They were initially used to treat cystic follicles (Cystorelin) and delayed ovulation in dairy cows. However, trials that were initiated to study its use to improve the precision of the synchronized estrus with 2 × PGF treatments showed that injecting a GnRH analogue (buserelin) from as little as 15 min and as much as 3 days before injecting PGF, extended the interval from the PGF injection to estrus from 4.6 days to 7.9 days as well as reducing the estrus response rate. The later interval was the approximate duration of an ovarian follicle wave. The mechanisms for these effects was shown to be associated with the luteinization of ovarian follicles so that they could no longer pro-duce estradiol with the consequential effect of preventing complete luteolysis by the injected PGF (Macmillan et al., 1984; Macmillan and Thatcher, 1991; Thatcher et al., 1991). These effects were incorporated into the design of two field trials which showed that injecting 10µg of the GnRH analogue buserelin from 8 to 10 days after insemination could significantly improve conception rates (Macmillan et al., 1986); subsequent studies could not confirm this benefit (Macmillan et al., 2003). The counter parts that GnRH injection at the FTAI was not improve the pregnancy rate regardless of whether estrus occurred following FTAI (SaFilho et al., 2011).

Role of Estrogen 17β (E_2): The $\mathbf{E_2}$ plays an important role for showing estrus signs of cows and also help to initiate the LH surge which is momentous for estrus detection of cows (Macmillan, 2010). Pugliesi et al. (2012) was reported that the sequential treatment with 0.05 or 0.1mg E2 initially induced a stimulatory followed by a reduced or inhibitory effect on prominence of PGFM pulses in heifers. This indicated that the chronic exposure of the uterus to elevated E_2 is involved in the reduction of PGF2α secretion and may account for the reported decrease in PGFM prominence during post luteolysis. The prominence of PGFM pulses after sequential E_2 treatment was greater for heifers in luteolysis than for heifers in preluteolysis. Sequential E_2 treatment was associated with functional and structural luteolysis. A transient resurgence in P_4 concentrations in heifers treated with sequential doses of 0.05 mg $E_2$was related to a less prominent PGFM pulse and a longer interval to completion of luteolysis. The LH concentration increased within 2 h after a peak of an E_2-induced PGFM pulse during preluteolysis and luteolysis and was temporally related during these periods to a complete and incomplete rebound in P_4, respectively.

***Combinations of PGF and GnRH*:** Once it was shown that delaying the interval between an injections of PGF until 7 days after an initial injection of GnRH would not compromise the PGF-induced luteolysis, it became possible to produce a synchronized estrus. This was because the injected GnRH had synchronously terminated most stages of ovarian follicle development to be followed by a synchronized emergence of a new follicle wave leading to the presence of a maturing dominant follicle 7 days after injection (Twagiramunga et al. 1992; Twagiramunga et al., 1995). These initial studies utilized lactating beef cows that were cycling as well as anestrus and beef heifers. It was reported that the basic GnRH-PGF-GnRH protocol was equally effective with each classification of female.

Although the original studies using combinations of GnRH and PGF were conducted and reviewed by Thatcher et al. (1991), it was the comprehensive studies by Pursely et al. (1997a, 1997b) that demonstrated the suitability of the basic "Ovsynch" protocol (**Figure 1**). This involved a series of injections using a synthetic natural form of both GnRH (Gonadorelin at 100 µg i.m.) and PGF (Dinoprost at 25 mg i.m.), with a 7 day interval from the first GnRH injection to PGF followed

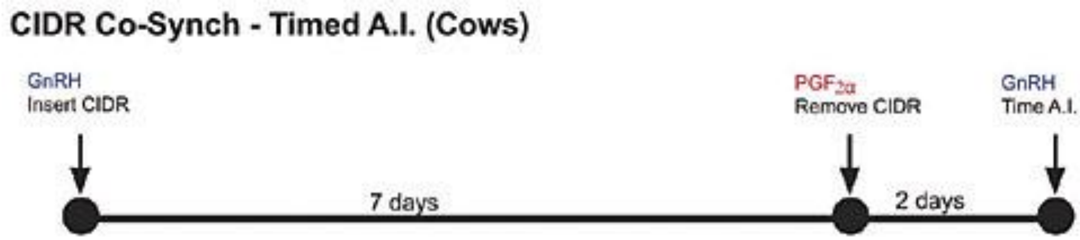

Figure 1: CIDR Co-Synh and timed AI protocol in cows

30 to 36 h later by the second GnRH and timed AI (TAI) 16 to 20 h later (Pursely et al., 1997a). The pregnancy rates per AI were 38.9% in PGF-treated control cows inseminated following detected estrus com-pared to 37.8% in the Ovsynch treated cows. In contrast, the later protocol was not successful in non-lactating Holstein heifers (74.4 vs. 35.1%) due to lack of synchronization. The use of the Ovsynch protocol with cows that had a standardized voluntary waiting period of 50 days increased herd pregnancy rates at 60 days post-partum from 5 to 37%, and at 100 days from 35 to 53% (Pursely et al., 1997b). A subsequent study showed that the interval from the second GnRH injection to insemination could be varied from 0 to 32 h, although highest pregnancy rates (45%) were with an interval of 16 h (Pursely et al. 1998). This study was also one of the first to report that the calving rate of 29% in the synchronized Holstein cows was 10% lower than the original pregnancy rate of 39% because 22% of embryos present at pregnancy diagnosis were lost (Pursely et al., 1998).

RECENT VARIATIONS TO THE OVSYNCH PROGRAM

The basic component of the Ovsynch program and its variations that remains unchanged has been the interval of 7 days between the first GnRH injection and the following PGF one. Those that have included estrus detection following the PGF injection and before the ovulating injection of GnRH have been referred to as "Heatsynch". Attempting to synchronize the patterns of follicle development before the first GnRH injection either with a GnRH or PGF injection or two PGF injections have been referred to as "Presynch". Others have been described as "Selectsynch" and "Cosynch". A meta-analysis of 71 trials that had "treated and control groups" around the basic Ovsynch program that were reported in 53 manuscripts concluded that: "There was little or no significant improvement in pregnancy rates using Ovsynch over other programs" (Rabiee et al., 1998). It is likely that underlying differences between the cows enrolled in these comparative studies may have contributed to the variation in the results obtained in many of these trials. For example, results from 9 studies recently summarized by Bamber et al. (2009) reported an average of 14.4% pregnancy loss among 3,775 cows between about 30 and 60 days post-TAI, varying from 7.6% to 21.6%. They also reported that the heritability of the condition (on a sire-son regression basis) was 0.49. The same study showed that the incidence of anestrus at about 56 days post-partum (based on plasma progesterone concentrations) ranged from 7.3 to 41.7% around an average of 23.3% and a calculated heritability of 0.19.

Anestrus is now recognized as being associated with a reduced ability by GnRH to terminate an ovarian follicle wave and/or to initiate the emergence of a new wave. It is reported that 51% of the 49 cows that were treated with Ovsynch, but failed to conceive to the TAI were detected in estrus either within 13 days (22%) or from 14 to 17 days (29%) following TAI (Cordoba and Fricke, 2002). Most of the cows with abnormal progesterone profiles had been or were anestrus. These anestrus cows with irregular return patterns to TAI were the main reason why the conception rate to TAI was only 27.3%, whereas it was 47.3% in cows not synchronized but accurately detected in estrus before being inseminated. Shephard (2005) made similar observations relating to a high incidence of return-to-service intervals of less than 18 days in a study in which 3559 cows in New Zealand and Australian herds was synchronized using Ovsynch combined with TAI. Clearly, conception rates will not be maximized if the synchronization protocol that has been used does not achieve precise control of ovarian follicle development (Macmillan et al., 2003). Attempts to enhance the control of ovarian follicle development have included the addition of an extra GnRH injection or administering two PGF injections 14 days apart before initiating the Ovsynch protocol (Andringa et al., 2012), as mentioned in **Figure 2**. The later alternative is now widely used in American herds preceding a first TAI at about 60 days post-partum. While the Presynch

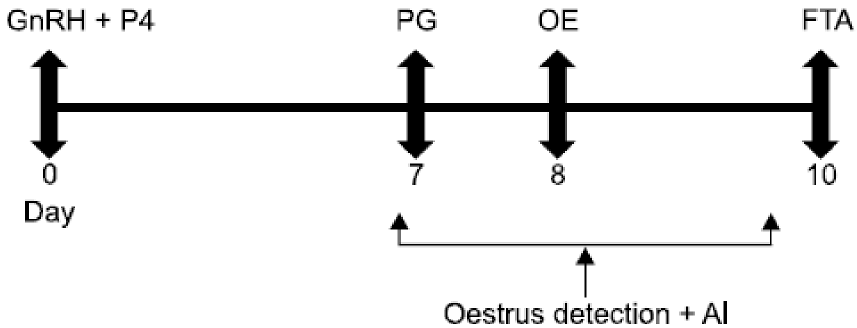

Figure 2: Schemes of the estrus synchronization protocol. PG: Prostagrandin, OE: Oestradiol, FTAI: fixed time artificial insemination (Andringa et al., 2012)

protocol can improve the results obtained with cows that have ovulated before the first PGF injection, it is less effective with anestrus cow (Chebal et al., 2006).

The general consequences of anestrus in lactating Holstein cows in American herds were highlighted by Chebal et al. (2006). They showed that cows that had ovulated a follicle to the first GnRH injection had a 31 day pregnancy rate of 37% compared to 21% in cows that failed to have a induced ovulation. However the pregnancy loss rates at Day 60 were higher in the ovulated group (25 vs 15%) The presence or absence of CL at the time of PGF injection proceeding the second GnRH injection had an even more dramatic effect on the 31 day pregnancy rate (+CL=40-%; -CL=8%).

TREATING ANESTRUS DAIRY COWS

Extended period of post-partum ovarian inactivity as reflected by failure of ovulation will extend the interval from calving to first insemination as well as days open with significance effects on inter calving interval and lifetime productivity. There is an obvious case for intervention, but the likely treatment outcomes rarely produce reproductive results as good as those obtained with cows that recommence cycling within 30 day of calving(Chebal et al., 2006; Rhodes et al., 2003).

The most successful treatments for anestrus have usually involved as a period of progesterone supplementation almost invariably using an intravaginal insert. Chebal et al. (2006) showed that a 7-day treatment with an intravaginal progesterone insert increase the incidence of ovulation in anestrus cows by day 62 of the study protocol from 30% to 46%. Rhodes et al. (2003) reported that combining a 7 day or 8 day treatment with an invag P_4 insert with injection with estradiol benzoite (1 or 2 mg i.m) coincidentally with treatment initiation and 24 h after insert removal (1 mg i.m) could achieve estrus in over 90% and ovulation in over 80% of anestrus cows. More resent study in New Zealand and Australia have demonstrated that GnRH can be submitted for estradiol benzoite but must also involve TAI. However, conception rates involving the treatment of anestrus Holstein cows in Australian herds have not been a successful as those with the smaller anestrus Friesian cows that make up New Zealand herds (Shephard, 2005). In spite of this difference, the treatment of anestrus has not produced conception rates to first inseminations following TAI or detected estrus in Holstein or Friesians that are as high as those obtained with cycling contemporaries (Day et al., 2000; Cordoba and Fricke, 2002; Chebal et al., 2006; McDougall and Compton, 2006; Rhodes et al., 2003).

EFFECTS OF PROGESTERONE SUPPLEMENTATION

The actual research to measure changes in plasma progesterone concentrations in animal treated with the CIDR invag P_4 insert used non lactation g 19 moth old beef heifers that weighed about 400 kg (Macmillan et al., 1991). The insert has been designed originally to be able to use with jersey heifers at 15 months of age and weighed only 300 kg in New Zealand herds. In the case of beef heifers that were treated during diestrus, plasma P_4 concentration were increased by 66.7% or 5.8 ng/mL by 24 h and remind elevated to be 48.2% or 4.5 ng/mL higher after 4 days. Mann et al. (2006) used non lactating Holstein cows to show that the application of an invag P_4 insert during early diestrus increased plasma P_4 concentration by a similar average of 67.5% average or 2.7 ng/mL, whereas treatment initiated after mid estrus increased concentration by 41.2% or 3.3 ng/mL. However, only the early diestrus treatment

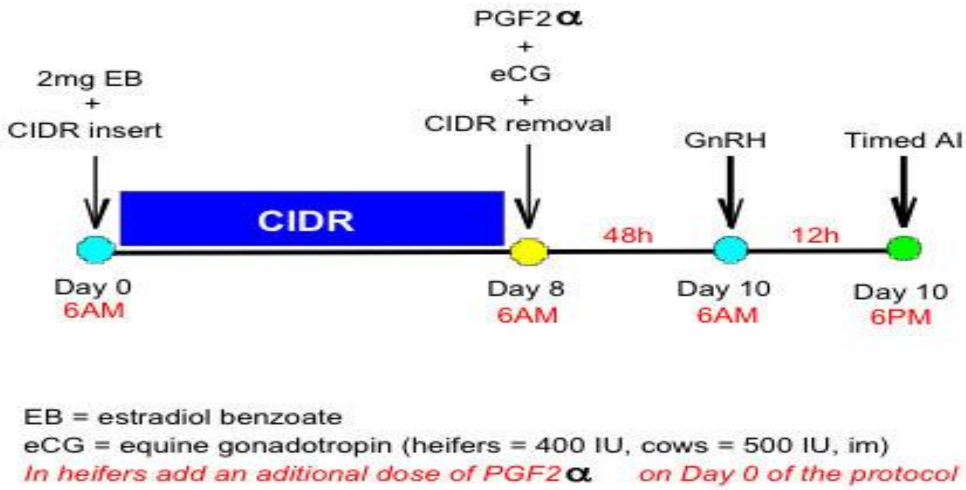

Figure 3: Ovsynch combined with TAI

significantly increased the production of interferon tau as well as accelerating embryo development.

The positive effect was considered to be the reason why a meta-analysis of studies where P_4 supplementation initiated during early diestrus concluded that this form of use of invag P_4 inserts with lactating cows could reliably be expected to increase conception rates (Mann and Lamming, 1999). The largest studies had been conducted in New Zealand using lactation cows that weighed about 450 kg. The multiple herd studies involving over 3,000 cows showed that if a CIDR invag P4 insert was applied from 4 to 9 days after first insemination for from 6 to 12 days (**Figure 3**), conception rates could be increased from 66.1% in untreated cows to 74.6% in the treated contemporaries (Macmillan and Peterson, 1993). Subsequent field trails have not been able to demonstrate a consistently positive effect because of significant herd-treatment interactions (Macmillan et al., 2003). The situation may be quite different in lactating Holstein cows receiving an average invag P4 insert during peak lactation when daily yields may exceed 40 liters (Macmillan, 2010).

CONCLUSION

Synchronization programs have been successful in reducing the intervals from calving to pregnancy in different management systems. The increasing use of Ovsynch programs and its numerous variations have coincidentally been associated with high incidence of anestrus and early embryonic death. A permanent solution might be required in genetic intervention. Although anestrus is estimated to be only moderately inherited (0.17-0.19), whereas early embryonic heath is highly inherited (0.49), as found in sir-maternal gland sire model. Above all progesterone supplementation has been demonstrated to have seceral advantages; its rapid metabolism in high producing dairy breed may mean that a novel variation in combination with variations to Ovsynch protocols deserve to be evaluated.

CONFLICT OF INTEREST

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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