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Estrus synchronization in dairy animals: A review

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Abstract
Estrus synchronization is a manipulation of the reproductive process that can increase the reproductive efficiency of dairy animals and helps in achieving one calf per year. It can be a labour-saving management technique to eliminate the need of detecting estrus. Synchronization of dairy animals can be accomplished with prostaglandins, progesterone-based treatments and various combinations of prostaglandins, progesterone and gonadotrophin-releasing hormone.

Keywords: Estrous cycle, prostaglandins, progesterone and gonadotrophin-releasing hormone

Introduction

Managing estrous in appropriate and desirable ways to increase the efficiency of reproductive life is always in demand. Estrous synchronization creates the opportunity to capture the economic benefits of artificial insemination (AI). Variation in duration of the estrous cycle, i.e.17 to 26 days, with a mean of approximately 21 days (Thakur *et al.*, 2013) [30] and variable duration of estrus from 4 to 64 hours (Baruselli *et al.*, 2001) [1] and the difficulty encountered in predicting the time of ovulation limits the success rate of artificial insemination (AI) in bovines. Treatments aimed at synchronizing estrous or inducing ovulation to allow effective management of timed AI in lactating dairy animals without detecting estrus, so imparting knowledge about the implication of different possible estrus induction protocols will be beneficial to improve reproductive efficiency. The manipulation of the estrous cycle and induction of estrus to bring a large percentage of a group of females into estrus at a short, pre-determined time is known as estrous synchronization (Odde, 1990) [19]. Estrus synchronization provides more economic returns by improving the production efficiency of animals. Most estrus synchronization protocols are mainly based on luteolytic agents, prostaglandins, or synthetic analogues. Several protocols have been published in which prostaglandins are combined with other hormones for therapeutic estrus synchronization in dairy animals with an ovarian disorder (Lopez-Gatius and Lopez-Bejar, 2002) [16].

Estrous Synchronization Using Prostaglandins ($PGF_{2\alpha}$)

The hormone prostaglandin (PG) was the first agent available for estrous synchronization. Prostaglandin systems work equally well for cows or heifers. Cows must be cycling for PG to have any effect. For PGF2α treatment to achieve its luteolytic effects, the cows must be in the diestrus stage of the estrus cycle (day 7 to 17). Prostaglandin treatment in the early stage of the estrous cycle (first five days) was ineffective in causing a luteolytic response in cattle (Cooper and Rowson, 1975) [6].

Consequently, a double protocol in which PGF2α was given at 7, 11, or 14 days intervals was developed so that cows at a stage in the estrous cycle other than diestrus would have a functional corpus luteum when they received the second PGF2α dose (Kristula *et al.*, 1992) [13]. Furthermore, an enhanced estrous response and normal fertility were reported when PGF2α was given late, rather than early to the middle stage of the luteal phase in dairy cows and heifers (Xu *et al.*, 1996) [36]. Thus, the 14-day interval double prostaglandin regimen seems to show an improved response over the 11-day protocol because two injections given 14 days apart ensures that most animals are in the late luteal stage (cycle day 11 to 14) when they receive the second PGF2α dose (Rosenberg *et al.*, 1990) [26]. The mean interval to estrus was 48 to 72 h when PGF2α was administered on Estrous cycle Day 5 or Day 8 in dairy cows (Watts and Fuquay, 1985) [33]. Prostaglandin administration in mid-cycle (day 8 to day 11) or later in the luteal phase (day 12 to 15) resulted in a mean time to estrus of 70 and 62 hours, respectively (Stevenson *et al.*, 1984) [28]. There are also reports of higher progesterone concentrations at the time of prostaglandin administration being associated with a delayed onset of estrus (Larson and Ball, 1992) [15].

The stage of follicular wave development at the time of PGF2α treatment appears to be the factor determining the time of estrus onset (Twagiramungu *et al.*, 1995) [31]. Kastelic and Ginther (1991) [11] reported that the time from PGF2α administration to ovulation depended on the maturity and size of the most emergent dominant follicle because a small dominant follicle takes longer to grow into an anovulatory follicle. When the dominant follicle had reached the static phase, the time from treatment to ovulation was three days, and if a new dominant follicle had emerged at the time of luteolysis, this period increased to 4.5 days.

$PGF_{2\alpha}$ in Progesterone-Based Treatments

One of the major limitations of the use of prostaglandins to synchronize estrus in dairy animals is the failure of the drug in anestrus or non-cyclic cows. Progestagens have the advantage that, besides improving estrus synchronization, they also induce estrus and ovulation in an acceptable percentage of anestrus cows (Imwalle *et al.*, 1998) [9]. Several workers have shown that the estrous cycle in buffaloes and cows can be controlled by prolonging the luteal phase or establishing an artificial luteal phase by the administration of exogenous progesterone or synthetic progestogens because progesterone suppresses estrus and ovulation by inhibiting the release of luteinizing hormone, impeding the final maturation of follicles (Peters, 1986) [20]. Long-term progesterone treatment (14 to 16 days) leads to reduced fertility (Pierson and Ginther, 1988) [21], probably due to the development of persistent follicles and reduced oocyte competence (Revah, 1996) [25].

Lane *et al.* (2001) [14] recommended prostaglandin administration when short-duration (7-9 days) progesterone treatments were started early or mid-cycle because the proportion of animals requiring exogenous luteolysis induction increases during this period. Indeed, short-term progesterone treatment using progesterone releasing intravaginal devices or subcutaneous ear implants combined with treatment with a luteolytic agent has proved successful in cattle (Macmillan and Peterson, 1993) [17]. Pregnancy rates equal to or greater than control rates for cows in natural estrus were achieved when progesterone releasing devices were used in conjunction with PGF2α or one of its analogues (Johnson and Spitzer, 2001) [10].

7-day exposure: Progestins mimic the progesterone produced by the CL and inhibit ovulation. When ovulation is inhibited for seven days, all animals will have a CL that is at least seven days old at the time of PG injection. Therefore, all animals with a CL will respond to the PG. Animals in which a CL had regressed during the seven days will show standing estrus following removal of the progestin. Recently, 5-day exposure of the progesterone has also been tried with good conception rates in bovines. In a study undertaken during the AI breeding period in lactating dairy cows, pregnancy rates were higher among cows synchronized with GnRH and a progesterone CIDR followed seven days later by PGF2α treatment, and device removal one day after or at the time of prostaglandin treatment, compared with control unsynchronized cows (Xu and Burton, 2000) [35].

Combination protocols

When PG, Gonadotrophin-releasing hormone (GnRH), or progesterone is used alone, they will only synchronize the luteal or follicular phases of the estrous cycle. Therefore, most estrous synchronization protocols combine the PG, GnRH, or progestins to control both phases of the estrous cycle.

GnRH is a naturally occurring hormone that, when injected, induces an LH surge and causes ovulation of a dominant follicle even in the presence of progesterone. The random administration of GnRH during the estrous cycle results in LH release (Chenault *et al.*, 1990) [4], causes ovulation or luteinization of large follicles present in the ovary, synchronizes the recruitment of a new follicular wave and equalizes follicle development waves (Schmitt *et al.,* 1996) [27]. Subsequent administration of PGF2α induces the regression of an original or GnRH-induced CL and allows the final maturation of the synchronized dominant follicle. Furthermore, there is no apparent detrimental effect of GnRH on the responsiveness of GnRH-induced CL or spontaneous CL to prostaglandin. Several reports have described a higher rate of estrus synchronization when GnRH is administered 6 or 7 days before PGF2α (80%) compared with prostaglandin alone (50% to 60%). Depending on the estrous cycle stage, these animals can exhibit standing estrus before the time of the PG injection. In the past ten years, several estrus and ovulation synchronization protocols for cattle and buffalo have been developed that allow a timed artificial insemination program without estrus detection.

Ovsynch

In 1995, the Ovsynch protocol, a milestone protocol for estrus synchronization having a sequence of a combination of GnRH-PGF2α-GnRH injections, was developed to synchronize follicular development, luteal regression and ovulation such that artificial insemination can be done at a fixed time without the need for estrus detection (Pursley *et al.*, 1995) [22]. Ovsynch requires an injection of GnRH on day 0and and injection of PGF2α 7 days later. A second injection of GnRH is administered 48 hours later, and the cow/buffalo is inseminated 8 to 24 hours after the final injection of GnRH. The success of the Ovsynch program has been proven to be influenced by the number of follicular waves or length of the follicular wave (Pursley *et al.*, 1997) [23] and the stage of the estrous cycle when the first GnRH dose is administered. The success rate of the Ovsynch protocol is dependent on the stage of the estrous cycle at the time of onset of the protocol. When the Ovsynch protocol was applied between days 13 and 17 or early in the estrous cycle (days 2-4) led to a reduced pregnancy rate (Moreira *et al.*, 2000; Vasconcelos *et al.*, 1999) [18. 32].

CO-Synch

The CO-Synch program is comprised of an injection of GnRH on day 1, an injection of prostaglandin on day eight, and then a second injection of GnRH with breeding on day 10. The advantages are tight synchronization of estrus, most females respond to the program, and it encourages estrus in non-cycling cows that are at least thirty days postpartum (Harrison, 1990) [8].

Hybrid-Synch

The Hybrid-Synch program is implemented with GnRH injection on day 1, prostaglandin on day eight, and then estrous detection and breeding from day 7 to 10. Females not observed in estrus from day 7 to 10 are bred on day ten and given a second injection of GnRH. This program has a lower cost and less handling compared with Ovsynch and CO-Synch but more than Select-Synch. The primary advantage is that

Hybrid-Synch appears to have the highest conception rates among all GnRH-PGF2α programs (Ravikumar and Asokan, 2008) [24].

Doublesynch

The doublesynch that includes the administration of an additional PGF2α injection 48 h before beginning the Ovsynch protocol has an advantage over the ovsynch protocol that can be used irrespective of stages of the estrous cycle. Cattle showed 88.9% and 94.5% ovulation rates after the first and second GnRH treatments in Doublesynch protocol, respectively and increased pregnancy rates compared to the ovsynch protocol (Cirit*et al.*, 2007) [5].

Different studies by various workers have shown that maximum fertility response can be obtained by initiating Ovsynch on days 5 to 9 of the cycle (Moreira *et al.*, 2000; Keith *et al.*, 2005; Wiltbank and Pursley, 2014) [18, 12, 34]. These observations provided the physiological basis for subsequent pre-synchronization methods that attempted to maximize the number of treated animals at a more optimal stage of the estrous cycle at Ovsynch initiation.

Pre-synchronization using PGF2α

Two injections of PGF2α are used with variable duration (10-14 days) interval before the start of Ovsynch to synchronize stage of estrus cycle best suited for the start of Ovsynch (Fricke, 2018) [7]. The first such pre-synchronization protocol was used in 2000 by Moreira *et al.*[18] using two PGF2α with a 14-day interval, followed by Ovsynch 12 days after the second PGF2α and termed it Presynch-Ovsynch or Presynch-12 and found an increased conception rate of 49% as compared to 37% with presynchronization in heifers.

Pre-synchronization using GnRH plus PGF2α

The combination of GnRH and PGF2α for pre-synchronization can overcome the limitations posed by PGF2α alone because the addition of GnRH into a presynchronization strategy increases conception rate by resolving the anovulatory condition before initiation of the Ovsynch protocol and follicular development and luteal regression will be more tightly controlled (Carvalho *et al.*, 2018) [3]. Newer pre-synchronization protocols have been developed, which uses a combination of PGF2α & GnRH with two days intervals 6 or 7 days before starting of Ovsynch and terms as G6G (Bello *et al.*, 2006) [2] and G7G (Stevenson and Pulley, 2012) [29]. Bello *et al.* (2006) [2] initiated ovsynch 6, 5, 4 days after giving the combination of PGF2α & GnRH with two days interval and found that percentage of cows ovulating to the first GnRH of Ovsynch was highest (85%) when ovsynch is started after six days than 67% at five days and 56% at four days.

Conclusion

Estrous synchronization manipulates the bovine estrous cycle, resulting in most animals exhibiting standing estrus in a short period. Prostaglandin alone or combined with different hormones has proved efficient at synchronizing estrus in postpartum dairy animals, improving reproductive efficiency in dairy farms. Future investigations should be directed toward developing cost-effective estrous synchronization-based timed-insemination protocols that lead to high synchrony of ovulation and thus improve pregnancy rates, especially in early postpartum non-cyclic or anovulatory dairy animals.

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