Québec/2004 Canada

23e Congrès mondial de buiatrie • Québec, Canada, 11-16 juillet 2004
23 Congreso Mundial de Buiatria • Québec, Canada, 11-16 de Julio 2004
23rd World Buiatrics Congress • Québec, Canada, July 11-16, 2004
23. Welt-Kongress für Buiatrik • Québec, Canada, 11.-16. Juli 2004

The Control of Ovarian Function for Embryo Transfer: Superstimulation of Cows with Normal or Abnormal Ovarian Function

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Introduction

Although embryo transfer techniques are widely used around the world, variability in response to the superstimulatory treatments remains an important limitation (6,17). With a better understanding of ovarian function has come a greater capability of controlling it. Recent protocols, designed to control both luteal and follicular function, permit the initiation of superstimulatory treatments at a self-appointed time and provide the possibilities for superstimulation of cows that have abnormal ovarian function. The intention of the following discourse is to discuss how these events impact the effectiveness of superstimulation regimens.

Manipulation of the follicular wave for superstimulation

The conventional protocol of initiating ovarian superstimulation during mid-cycle was originally based on anecdotal and experimental information in which a greater superovulatory response was reported when gonadotropin treatments were initiated 8-12 days after estrus (4,14). However, none of these early studies utilized ultrasonography to evaluate follicular status of the animals when superstimulation treatments were initiated. It is now known that 8-12 days after estrus (Days 7-11 after ovulation) would be the approximate time of emergence of the second follicular wave in cattle (11). However, the day of emergence of the second follicular wave differs among individuals and is 1 or 2 days later in 2-wave cycles, as compared to 3-wave cycles (11). In this regard, it has been clearly shown that superovulatory response was higher when gonadotropin treatments were initiated at the time of wave emergence; 1 day asynchrony reduced the superovulatory response compared to initiating treatments on the day of wave emergence (21).

Based on duration of the developmental phases of the dominant follicle in 2- and 3-wave interovulatory intervals, approximately 20% (4 or 5 days) of the estrous cycle is available for initiating treatment at the time of follicular wave emergence. Therefore, 80% of the estrous cycle is not conducive to an optimal superovulatory response. The necessity of waiting until mid-cycle to initiate superstimulatory treatment implies monitoring estrus and an obligatory delay. To obviate these problems, an alternative approach is to initiate superstimulation treatments subsequent to the synchronization of follicular wave emergence.

One approach to the synchronization of wave emergence involves transvaginal ultrasound-guided follicle ablation of all follicles ≥5 mm, followed by FSH treatments 1 day later (2,3). The timing of estrus was more synchronous when a progestin implant was inserted for the period of superstimulation and 2 injections of PGF were administered on the day of implant removal (3). Combined over 2 experiments, there was no difference in the superovulatory response between ablated and non-ablated groups (3). In a more recent study, ablation of the 2 largest follicles at random stages of the cycle was as efficacious in synchronizing follicular wave emergence for superstimulation as ablating all follicles ≥5 mm (1). Transvaginal ultrasound-guided follicle ablation of the dominant follicle during mid-diestrus (7,13), followed by superstimulation 2 days later has been reported to result in a higher superovulatory response than when the dominant follicle was not ablated. In a retrospective study of lactating dairy cows (23), follicle ablation resulted in a significantly higher number of ova/embryos collected, but a comparable number of transferable embryos as cows superstimulated 7-13 days after estrus.

It is possible to synchronize follicular wave emergence by an injection of GnRH or porcine LH. However, the reported asynchrony in follicular wave emergence (19) suggests that this approach may not be feasible for superstimulation. In 3 successive experiments (10), GnRH or pLH treatments resulted in fewer embryos than in Control animals; the use of GnRH or pLH to synchronize follicular wave emergence prior to superstimulation is not recommended.

The preferred approach for synchronization of follicular wave emergence prior to superstimulation in the field is an injection of 5 mg estradiol (E)-17β + 100 mg progesterone at CIDR insertion, with FSH beginning 4 days later (5). Experimental (4) and commercial (6,20) embryo transfer data have shown that the superovulatory response and embryo production following the administration of E-17β/progesterone at the time of progestin insertion at unknown stages of the estrous cycle was comparable to that of donors superstimulated 8-12 days after observed estrus.

Many practitioners are now utilizing E-17β + progesterone along with CIDR inserts in the superstimulation of donors. Commercial embryo transfer records have revealed that E-17β-treated beef (n=307) and dairy (n=187) donors produced a mean (±SEM) of 6.3 ± 0.9 and 6.0 ± 0.4 transferable embryos, respectively, while beef (n=1073) and dairy (n=254) donors treated between Days 8 and 12 of the cycle produced 6.6 ± 0.2 and 5.1 ± 0.3 transferable embryos, respectively (P>0.2). By synchronizing follicle wave emergence, the full extent of the estrous cycle was available for superstimulation and the need to detect estrus or ovulation, and waiting 8-12 days to initiate gonadotropin treatments was eliminated. At the same time, numbers of transferable embryos were not compromised.

Traditionally, donor cows have been subjected to embryo collection at approximately 60 day intervals. However, the elective synchronization of wave emergence permits successful superstimulation every 25 to 35 days, without regard to expression of estrus (17). Once multiple CL regress and cows re-ovulate, normal follicular wave patterns are re-established and superstimulation can be rescheduled. Briefly, cows receive a progestin insert at random stages of the estrous cycle and an injection of estradiol/progesterone; 4 days later FSH treatments are initiated. Progestin inserts are removed 12 hours after administration of PGF and cows are

inseminated at estrus; 7 days later ova/embryos are collected and cows receive PGF (often repeated in 4 to 5 days). The protocol is repeated 10-15 days later without regard to the stage of the estrous cycle.

The estradiol/progesterone/CIDR protocol is fairly robust and practitioners are utilizing different variations e.g., it is possible to use 2.5 mg E-17β and 50 mg progesterone with no apparent effect on results. Furthermore, FSH is often administered for 3 days before PGF is administered and the progestin insert can be removed 24 h after PGF treatment to avoid early expression of estrus. In addition, FSH is often not administered on the last day of the protocol i.e., Day 7 above.

Unfortunately, E-17β is not commercially available in many countries. Therefore, other estrogen esters (i.e. estradiol benzoate or valerate) have been investigated. Treatment with 2.5 mg estradiol benzoate and 50 mg progesterone at the time of progestin insertion, resulted in synchronous emergence of a new follicular wave in 3-4 days (8). Superstimulatory treatments initiated 4 days after treatment resulted in superovulatory responses comparable to those initiated 4 days after treatment with 5 mg or 2.5 mg E-17β + 50 mg progesterone (9) or those initiated 8-12 d after estrus (20). On the other hand, 5 mg estradiol valerate and 3 mg norgestomet resulted in less synchronous emergence of a follicular wave and a lower superovulatory response (16). However, a dose of 1.0 or 2.0 mg estradiol valerate has been recently been shown to result in follicular wave emergence in 3-4 days, with little variability (18), suggesting that the lower dose may be useful in the synchronization of follicular wave emergence for superstimulation.

Collectively, results demonstrate that exogenous control of follicle wave emergence offers the advantage of initiating superstimulatory treatments at a time that is optimal for follicle recruitment, regardless of the stage of the estrous cycle. Treatments are practical, easy to follow and, more importantly, eliminate the need for detecting estrus or ovulation and waiting 8-12 days to initiate FSH treatments. Synchronization of follicular wave emergence by follicle ablation or estradiol/progesterone treatments has resulted in comparable superovulatory responses (1,4).

Superstimulation of donor cattle with abnormal ovarian function

Cows with abnormal ovarian function are difficult to superstimulate because they usually do not have a function CL, or they come into estrus at unpredictable times. In addition, it is almost impossible to predict the stage of follicle development in these cows. Progestin inserts and elective synchronization of follicle wave emergence have been used in superstimulation protocols for donor cattle with abnormal ovarian function. It was the need to superstimulate cows with abnormal ovarian function that led to the use of estradiol prior to the administration of FSH (12). Embryo production did not differ between 190 problem cows superstimulated 7 days after the receiving a norgestomet implant and an injection of norgestomet and estradiol valerate and 260 Control cows superstimulated between Days 8 and 12 of the cycle (15). Although this protocol was developed to provide an artificial CL with the norgestomet implant, it was subsequently shown that estradiol valerate played a role by synchronizing emergence of a new follicle wave (4). Benefits probably accrued from both the implant (artificial CL) and the

EV (induction of a follicle wave); recent data indicate that FSH treatments should begin on Day 4.

The progestin/estradiol treatment has been followed with the administration of pLH at the time of first AI to induce ovulation in cows with history of poor superovulatory response due to anovulation (22). Administration of 25 mg (Armour) pLH in problem cows increased the number of transferable embryos (4.1 ± 1.2) as compared to the previous superstimulation without pLH (1.0 ± 0.4; $P<0.03$). However, pLH did not improve embryo production in normal cows (22).

Résumé
Des protocoles de synchronisation des vagues folliculaires ont été développés permettant d'induire la surovulation selon les besoins, sans nécessité de détecter l'œstrus et cela, sans compromettre les résultats. De plus, ces mêmes protocoles peuvent être utilisés pour surovuler des vaches ayant une fonction ovarienne anormale.

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