Application of the CIDR-B® to Estrous Synchronization in Beef Cattle

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Introduction

Progesterone, or progesterone - like compounds, (progestins) have been investigated and used for estrous synchronization for several decades. However, the success rates of programs that use progestins have varied considerably. A primary challenge to the use of this hormone for synchronization was the repeated observation in the past of reduced fertility at the synchronized estrus. Perhaps of even greater impediment to the development and adoption of this technology was that we did not understand why these negative responses were occurring or what modifications were necessary to make corrections. Research findings over the past decade have, however, helped to describe why fertility is impaired in some situations when progestins are used. More importantly, this knowledge has been applied toward developing systems that permit the use of progestins while avoiding some of the previously observed detrimental responses. Thus, we are now in a position to capture the benefits of the advantages of using progesterone without sacrificing fertility.

Advantages of Using Progestins in Estrous Synchronization

Physiological diversity in females to be synchronized: When the decision is made to synchronize estrus in a group of postpartum beef cows or yearling heifers, these groups of females are typically very dissimilar from a physiological standpoint at the time that synchronization program is started. Some of the females will have started to cycle and will be showing estrus, ovulating and developing a CL in the ovary every ~21 days. These cyclic females will be at random stages of the estrous cycle on the first day of synchronization, and this variation represents one of the sources of diversity of physiological status. Another portion of the females will <u>not</u> be cycling at the start of the synchronization program. In these anestrous females, many of the functions of the reproductive system are absent, most noticeable being the lack of estrus, ovulation and CL formation. When anestrous females ovulate spontaneously for the first time, the first cycle is abnormal in length in most females. Instead of an interval of ~21 days between the first and second ovulation, this interval is shortened to ~10 days. This short cycle is a normal occurrence in greater than 80% of anestrous cows. Some cows (20-30%) will show heat at the beginning of the short cycle, however, cows that are inseminated or mate with a bull at this heat will not become pregnant. The purpose of the short cycle is to provide a period of progesterone exposure before the first normal ovulation. The short period of progesterone pre - exposure is necessary for the <u>next</u> ovulation to be followed by a normal, 21-day estrous cycle. These anestrous females represent a second major source of physiological diversity in the group of females to be synchronized. The use of progestins in a synchronization system provides a means to deal with much of the variation that is introduced by both cyclic females and anestrous females, increasing the probability that a majority of them will have a potentially fertile ovulation during the synchronization period.

Benefits of Using Progestins in Cyclic Females: In essentially all estrous synchronization systems, an injection of prostaglandin $F_2\alpha$ (PGF) is used to induce regression of the CL to aid in synchronizing estrus. The primary limitation to the use of PGF to synchronize estrus in cattle is that it is less effective in causing CL regression in females that are in the early stages of the estrous cycle. In a group of randomly cycling females, some will undoubtedly be in this unresponsive stage of the cycle on the day that PGF is given, unless this variation is dealt with. In this regard, a key influence of progestins is that they block the occurrence of estrus and ovulation during the time that they are administered. Consider a group of cyclic cows that is given a progestin for 7 days. During this time, no females will show heat or ovulate, and on the last day of progestin treatment, there will be no females in the less responsive (day 0- 7) stages of the estrous cycle. Injection of PGF on the last day of progestin treatment will result in regression of the CL in essentially all of the females. Thus the large degree of diversity in stage of the cycle, that would normally limit the effectiveness of PGF to induce luteal regression, is corrected for by the progestin. This capacity of progestins to prevent females from showing heat at an inappropriate time relative to the synchronization protocol or AI period is the primary advantage of their use in cyclic females.

Benefits of Using Progestins in Anestrous Females: Anestrous females usually represent a major proportion of the females to be synchronized. This proportion varies among herd and within a herd from year to year. Since it is not unusual for 50% (or more) of cows to be anestrus when a synchronization program is initiated, it is critical to the success of the program that the appropriate stimuli are provided to induce onset of estrous cycles. It has been established that pre exposure of anestrous females to a short period of progesterone is necessary for 2 reasons. First, as mentioned earlier, anestrous females typically provide this short period of pre-exposure through the short cycle that follows the first spontaneous ovulation. In synchronized females, it is essential that we provide for this short cycle within the synchronization treatment, to ensure that the synchronized ovulation at which AI occurs is a fertile estrous cycle of normal length. Second, it has been shown that after treatment with progesterone for at least 5 days, a substantial proportion of cows will be induced to start to cycle within a few days after withdrawal of the progesterone. There are currently two methods used to provide this period of progestin exposure to anestrous females. In one approach, giving an injection of the hormone GnRH to induce ovulation and formation of a CL provides the progestin. Since this is the first ovulation in the anestrous female, the resulting CL is short- lived, however this is irrelevant since the entire purpose is to provide a short period of progestin exposure. The limitation of this approach is that within groups of anestrous cows, the response in terms of ovulation can vary from <10 to >80+ %. An alternative to using GnRH to induce progesterone pre-exposure is to administer progesterone to the animal for a short period of time (5-7 days). This is a more predictable method, as all animals receive progesterone directly, instead of only those that ovulate; as is the case when GnRH is used. The number of cows that ovulate following the short period of progesterone exposure can be increased substantially by providing a stimulus to induce ovulation during the period 1 to 3 days <u>after</u> progesterone withdrawal. This is most commonly achieved in US systems with an injection of GnRH 1 to 3 days after withdrawal of progesterone. The ability of short-term progesterone exposure to induce anestrous cows to begin to cycle, and to have an ovulation associated with an estrous cycle of normal length are the primary advantages of this approach in anestrous females.

The CIDR® Insert

The three primary techniques available worldwide for administering progestins to cattle are through the feed, via subcutaneous implants in the ear, or through intravaginal, progesterone - releasing devices. In the USA we currently have the ability to provide progestins in the feed (MGA®) and had access to ear implants (SYNCRO-MATE-B®) until this product was recently discontinued. We have, however, not had the opportunity to utilize the intravaginal delivery technology. Approval of one of these products, that has been used in some countries for several years, is currently pending with the FDA. This controlled, internal drug - releasing insert for cattle (B for bovine), or CIDR-B®, may be available for use by producers in the USA in the coming year. The CIDR is made by molding a thin layer of silicon and progesterone mixture (10% w/w) around a nylon spine under high temperature. The CIDR contains 1.38 g progesterone and was designed to maintain elevated blood concentrations of progesterone to at least 2 ng/ml for up to 10 days. Being relatively thin, the CIDR is easily inserted into the vagina and has good retention (2.5% loss rate is normal). A flexible nylon tail is attached to the device to allow for easy removal. The pending availability of the CIDR for producers in the USA will provide a predictable method to deliver progesterone to cattle for the purposes of estrous synchronization.

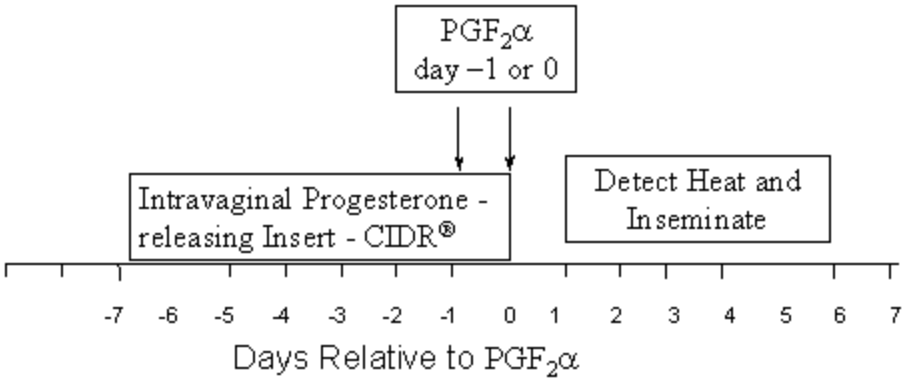
Application of the CIDR to Estrous Control Programs

The CIDR has been incorporated into a wide variety of estrous control programs in other countries and many research trials with this insert have been performed in the US. The CIDR-based systems of estrous synchronization outlined below are not currently approved by the FDA. Various combinations of the CIDR with PGF and other hormones to regulate follicular development and induce estrus/ovulation (estradiol and GnRH) have been developed. The descriptions below will only include systems that use hormones available in the USA.

CIDR and Prostaglandin $F_2\alpha$:

The CIDR will be marketed in the USA to be used in combination with an injection of PGF as described in Figure 1. The CIDR is inserted into the vagina of the female for 7 days. The label will indicate that an injection of PGF is to be given on day 1, or 1 day before the CIDR is withdrawn. Females are inseminated based upon detection of estrus during the 3 to 6 day period beginning on day 1. This system should effectively synchronize estrus in a large proportion of cyclic females since treatment for 7 days with the CIDR prevents animals from being in the early stage of the cycle and not responsive to $PGF_2\alpha$ - induced regression of the CL. Some anestrous females will be induced to ovulate and show heat during the synchronization period. A large experiment involving 851 postpartum beef cows at 6 locations and 724 yearling heifers at 5 locations across the US was performed to compare the effectiveness of this approach (CIDR + PGF) to a single PGF injection (PGF) and to non-synchronized (Control) females (Lucy et al., 2001). In this study, approximately 53% of the postpartum cows, and 43% of the heifers were anestrus at the start of the CIDR + PGF treatment. Comparing the two synchronization treatments, the CIDR + PGF treatment increased synchronization rate by approximately 30%, and pregnancy rate by approximately 20%, during the 3 day synchronization period (day 1- 3); relative to the PGF treatment. These gains were similar in both the anestrous and cyclic females.

Figure 1. CIDR® and PGF Synchronization System



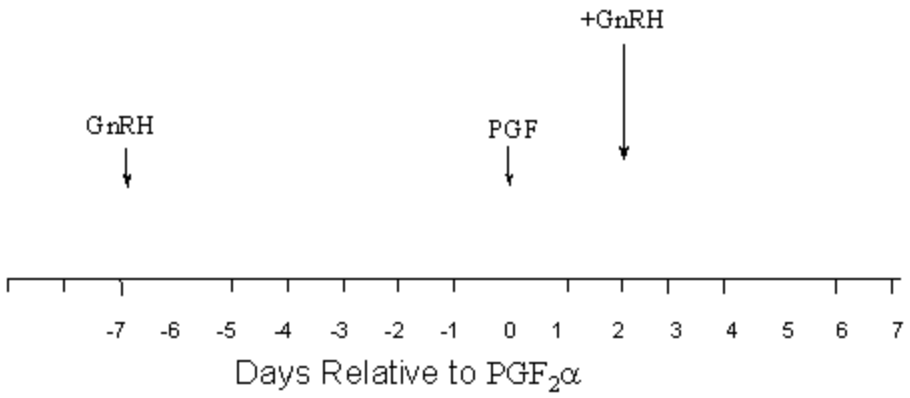
Conception rates during the synchronization period were not different among the treatments, suggesting that addition of the CIDR did not impair fertility at the synchronized estrus. Pregnancy rates during the 3-day synchronization period were 39% for postpartum cows, and 36% for yearling heifers in the CIDR + PGF treatment. This approach secures some of the benefits of the incorporation of the CIDR into an estrous control program.

A common question regarding this approach is whether the PGF can be given on the day of CIDR withdrawal, rather than 1 day in advance, to avoid handling of cattle on two consecutive days. These two approaches have not been directly compared in a large - scale experiment. However, some data exists comparing treatments in which PGF was given either the day of progestin withdrawal, or 1- 2 days before (Smith et al., 1984; Macmillan and Peterson, 1993; Xu and Burton, 2000). Collectively, these data suggest that the primary benefit of injecting PGF before CIDR withdrawal is that the precision of estrus is increased, but neither synchronization nor pregnancy rate during the synchrony period was altered. It does not appear in these reports, or that of Lucy et al., (2001) that this precision is sufficient to consistently support the use of a timed AI protocol.

GnRH Based Systems:

A wide variety of synchronization systems that include GnRH are used to synchronize beef cattle in the USA. The general framework of this approach is outlined in Figure 2. The 3 main components of GnRH based systems are the GnRH, $PGF_2\alpha$ and +GnRH treatments as diagrammed below. The initial GnRH injection (day 7; GnRH) is used to program follicle growth in cyclic females and to induce ovulation (to provide progestin pre-exposure) in anestrous females. The $PGF_2\alpha$ (PGF; day 0) induces regression of CL that are present to cause a decline in progesterone. The second GnRH given on day 2 to 3 (+ GnRH) will induce ovulation

Figure 2. GnRH - Based Systems in Postpartum Cows



of dominant follicles that have been pre programmed by the first GnRH treatment. The major GnRH programs that do not involve use of the CIDR are described first in the following section.

GnRH PGF System: This combination represents the simplest GnRH based system and involves the GnRH treatment followed 7 days later by the PGF treatment. A common name for the GnRH PGF system is Select Synch. Some cows (~8 %) will exhibit estrus up to 48 hours before PGF (d-2). The early heats are fertile and cows can be inseminated 12 hours after detection. The peak estrous response will occur 2-3 days after PGF with a range of days 1 - 5. With this system, a minimum of 5 days of estrus detection after PGF and 2 days preceding PGF is required to detect most heats.

GnRH PGF + GnRH System: This system is a GnRH PGF system that includes a second GnRH injection (+ GnRH) given to all, or some cows between 48 and 72 hours after PGF (day 2 to 3), with timed AI on all or a portion of the herd. Several variations of this system are being used. The *GnRH PGF +GnRH with timed AI of <u>all</u> cows* involves giving the GnRH treatment on day 7, PGF on day 0, +GnRH on day 2 (48 - 60 hours after PGF), and inseminating all cows at the time of the +GnRH injection. No heat detection is performed. A common name for this system is CO Synch. If cows are inseminated 12 - 16 hours after +GnRH, this system is commonly referred to as Ovsynch. The *GnRH PGF +GnRH with AI of cows in estrus before timed AI* includes estrus detection and AI from approximately day 2 until the timed AI in conjunction with the +GnRH treatment. Approximately 8% of cyclic females (on average) will exhibit early heats with a range of 0- 15 % of treated females across several research studies. The

cows inseminated early would not receive the +GnRH treatment and would not be included in the timed AI group. This approach can be used with the CO-Synch or Ovsynch systems. One can also extend the period of heat detection to 72 hours, with timed AI of cows not detected in estrus by 72 hours after PGF in conjunction with the +GnRH treatment. Common names for this system are Hybrid Synch or MSU Synch.

Addition of a CIDR to GnRH -Based Systems:

Upon approval, the CIDR will not be labeled for use in conjunction with GnRH. However, some research studies have been performed in this regard. The GnRH-based systems listed are, and have been, successfully used to synchronize large groups or herds of postpartum beef cattle. However, in some cases, these systems have yielded less than optimal results. Depending upon the system used, failures can often be traced to low synchronization rates (in programs that depend upon estrus detection) or low conception rates (when timed AI is used on all animals). Failure to appropriately synchronize cyclic animals or to induce a potentially fertile ovulation in anestrous females can have major influences on the success of a synchronization program. The addition of a CIDR to GnRH-based programs has the potential to reduce losses in each of these areas. The most common use of the CIDR with GnRH based systems involves insertion of the CIDR on day 7, and withdrawal of the CIDR on day 0 (see Figure 2). The primary benefit that is provided by inclusion of the CIDR in GnRH-based programs is that it guarantees that females will be exposed to progesterone during the period between day 7 and day 10.

One reason the progesterone exposure is beneficial is that it ensures that most ovulations occurring in previously anestrous cows, either spontaneously or in response to the +GnRH treatment during the synchrony period, will result in normal (~21 day) rather than short (~10 day) cycles. Furthermore, since the withdrawal of a progestin has been demonstrated to induce onset of cycles in some anestrous females, the likelihood of an ovulation (either spontaneous or in response to +GnRH) is enhanced. Since the initial response to GnRH can be variable, the inclusion of a CIDR removes the requirement that ovulation be induced by GnRH on day 7.

A second benefit to inclusion of the CIDR in GnRH -based programs is that the early heats (days 2 to day 1) that are inherent to these systems are prevented. The progesterone released by the CIDR, will prevent estrus and ovulation between days 7 and 1. This increased control of the time of ovulation is particularly important in timed AI systems in which no heat detection is performed. The females that show early heats in GnRH-based programs would have conception rates of near 0% if timed AI is performed on day 2 or 3.

The CIDR can be strategically used to provide insurance in cattle that are most likely to be anestrus. One approach would be to use a CIDR in all 2 year-old cows and in mature cows that calved less than 45 days before the start of the synchronization program. It has been well established that these types of females are the most likely to be anestrus and in need of the additional stimuli that are provided by the CIDR. With this approach, the high-risk animals are provided with insurance and the additional investment in the CIDR is not made in the low risk,

cyclic females. In herds in which a majority of animals are high risk (e.g. cows in lower body condition), use of the CIDR could be expanded to more cows to protect against potential failure.

The use of short-term calf removal, as a tool to enhance induction of ovulation in anestrous cows, can be augmented by use of the CIDR. It has been demonstrated that calf removal will induce ovulation is some anestrous females. However, in the absence of progesterone pre-exposure, the first spontaneous heat after short-term weaning (during the synchrony period), or short-term weaning and an ovulation induced by +GnRH would be expected to be followed by a short estrous cycle (~10 days) that is infertile. For example, if a GnRH PGF system is followed by calf removal on days 0 to 2, anestrous cows that did not ovulate to the GnRH (no progesterone pre-exposure), but show heat in response to calf removal are likely to have a short cycle and very low fertility. However, if short-term calf removal is preceded by progesterone from either a GnRH - induced CL or a CIDR, the ensuing cycle is likely to be of normal length and the potential for establishing a pregnancy exists. This combination would also be expected to induce more cows to cycle than either CIDR withdrawal or calf removal alone. Since each of these tools have been shown to stimulate reinitiation of estrous cycles in postpartum cows, together these treatments could provide dual stimuli towards inducing estrus and ovulation. Therefore, in this type of system, the CIDR again provides insurance through enhancing the probability that high risk cows will be induced to ovulate and that the ovulation has the potential to result in a pregnancy.

Summary

Approval for use of the CIDR in the USA will provide another valuable tool for use in estrous synchronization programs. The strategic use of this technology should permit more precise control of the estrous cycle in cyclic females and enhance our ability to induce estrus and ovulation in anestrous cows and prepubertal heifers. As these inserts become readily available to producers and scientists alike, the expectation is that multiple additional uses and approaches will be investigated and developed.

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