Clinical Uses of Gonadotropin-Releasing Hormone and Prostaglandin in Cattle

Gonadotropin-releasing hormone (Cystorelin: CEVA) is commercially available in the US for treatment of cystic conditions of the bovine ovary. Prostaglandin F alpha (Lutalyse: Upjohn) and a synthetic prostaglandin analog (Estrumate: Haver-Lockhart) are available for estrus synchronization and termination of pregnancy in beef cattle and nonlactating dairy heifers. The purpose of this paper is to review the therapeutic application of these drugs for clinical use in cattle.

Gonadotropin-Releasing Hormone

Tropic releasing factors (hormones) originate from the hypothalamic region at the base of the brain of mammals. Gonadotropin-releasing hormone (GnRH) is a synthetic decapeptide believed to stimulate or cause the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary (pars distalis). In cattle, these gonadotropins are intimately involved in follicle maturation, ovulation of ovarian follicles, and formation and maintenance of luteal tissues.

The most common clinical use of GnRH is treatment of follicular and luteal cysts in cattle. Follicular cysts are enlarged, anovulatory follicles that persist on the ovary, resulting in irregularities of the estrous cycle or a state of anestrus. If these follicular cysts partially luteinize, often a luteal cyst forms, which may contribute to an anestral state. Both types of cyst appear to be the result of insufficient or altered LH release, caused by hormonal imbalance or stressful stimuli.

An IM injection of 100-250 mcg GnRH stimulates luteal tissue formation in bovine follicular cysts.
About 75-85% of treated cows respond positively to GnRH, with normal estrus in 67% of the females within 10-30 days after treatment. However, for the GnRH treatment to be effective in cattle, the natural luteolytic mechanism must be functional. A luteolytic dose of prostaglandins (PGF2α) can be given 9-14 days after GnRH to ensure luteolysis and hasten the onset of estrual behavior. Estrus usually occurs within 2-5 days of PGF2α injection; if desired, these treated females can be mated at this time.

Exogenous GnRH treatment induces ovulation in follicles ≥15 mm in diameter in postpartum dairy cows. However, the pituitary gland of these females generally is not responsive to GnRH-induced LH release before postpartum day 10. Prophylactic treatment of dairy cows with GnRH at 8-23 days postpartum reduces the incidence of follicular cysts and the number of reproductive culs in the herd. However, treatments for the entire herd such as this may not be economically feasible, especially if a good reproductive health program is in effect.

GnRH has also been used to treat uterine infections in postpartum dairy cows. A 100-mcg dose of GnRH is given for LH release to elicit a luteotrophic effect on the ovary. An injection of PGF2α could be given 10-14 days later to induce luteolysis, which is generally followed by final follicular maturation and estrus. Circulating estrogen released from the developing follicle before the onset of estrus appears to stimulate the natural defense mechanisms of the uterus to cope with the infection. This treatment has not been critically evaluated.

Cows with a history of delayed ovulation have been successfully treated with 100 mcg GnRH either 6 hours before or at the time of breeding to hasten ovulation.

### Prostaglandins and Control of the Estrous Cycle

Prostaglandins in mammalian cells are derived primarily from arachidonic acid, which is a long-chain fatty acid believed to be essential for animal health. Prostaglandin is available in commercial formulations (Lutalyse: Upjohn; Estrumate: Haver-Lockhart), with the major use indicated for cattle based on its potent lytic action of functional luteal tissue. An IM injection of 25-35 mg dinoprost (Lutalyse) or 500 μg cloprostenol (Estrumate) given to cattle with an active corpus luteum (between days 5 and 18 of the estrous cycle) results in functional luteolysis, a decline in circulating progesterone levels and return to estrus in 2-5 days. Since this agent is not effective during the remainder of the estrous cycle, synchronization schemes have been devised for effective use of this drug in breeding herds (Figs 1-3).

Inseminating females 80 hours after PGF2α injection often is recommended; however, highest pregnancy rates often result when prostaglandin-treated females are inseminated at estrus.

Ovulation times apparently vary among cattle, which may result in lowered fertility after synchronization and timed insemination. Inseminating females twice, at 72 and 96 hours postinjection, may slightly improve first-service pregnancy rates at synchronized estrus. In attempts to synchronize ovulation, GnRH has been incorporated into various estrus synchronization schemes; however, improved first-service pregnancy rates after synchronization have not been reported.

Following synchronized estrus, cows not settling are expected to form a functional corpus luteum, have natural luteolysis and return to estrus in 18-24 days. Females can be inseminated a second time 8-10 hours after onset of this estrus or be exposed to cleanup bulls if estrus detection procedures are marginally efficient.

Breeding management with prostaglandins offers the advantage of concentrating breeding and calving intervals as well as maximizing the use of artificial insemination to improve the genetic potential of breeding stock. Estrus synchronization can also increase reproductive efficiency in herds bred by artificial insemination, where estrus detection is a problem.

The following formula illustrates the advantage of improved estrus detection during a 24-day breeding interval: No. cows to breed = estrus detection rate x conception rate = total no. cows pregnant. If there were 100 cows to breed and the estrus detection and conception rates were both 50%, then 100 x 50% x 50% = 25 pregnant cows. If estrus synchronization reduced the conception rate to 40% but increased estrus detection accuracy to 100%, then 100 x 100% x 40% = 40 pregnant cows.
Fig 1. In this first method, a single im injection of PGF2α is given to
cycling cows and heifers with a
palpable corpus luteum (day 1) and
the same dose is given to the
remaining unmated females 8 days
later. Females are artificially insemi-
nated by appointment or at estrus
between days 1 and 12.

![Diagram of synchronized AI process with injection schedules and stages]

Fig 2. A second method is to treat
all cycling females in the herd with 2
separate im injections of PGF2α
10-12 days apart. Females are
inseminated at estrus or by appoint-
ment after the second injection. This
approach was designed to eliminate
the need for pretreatment palpation
for luteal tissue. Since about 66% of
the animals should exhibit estrus
after the first injection, one could
inseminate those in estrus at that
time.

![Diagram of synchronized AI process with treatment days and estrus detection]

Fig 3. This third method uses estrus
detection and insemination during
the first 5 days of the breeding
season. The remaining unmated
cows receive an im injection of
PGF2α on the morning of day 6. After
PGF2α treatment, estrus detection is
continued and females are insemi-
nated at estrus or by appointment in
the synchronized group.

![Diagram of synchronized AI process with estrus detection and synchronized AI]

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In evaluating a client's herd for potential use of estrus synchronization, the condition of cattle-handling facilities, labor expenditures, veterinary fees and cost of materials associated with synchronization must be critically evaluated against the potential for success. Proper planning and good herd management are essential to any breeding program, and synchronized insemination is no exception. Veterinary input in evaluating herd status is of critical importance to a successful estrus synchronization program. Cattlemen too often blame failures on "bad" semen, the AI technician, the veterinarian or the synchronizing agent, when in fact, poor nutrition and herd mismanagement are at fault. Dispensing the synchronization drug without herd evaluation may lead to mishandling of the drug and poor synchronization results.

The following points must be seriously evaluated in each herd before the initiation of an estrus synchronization program:

- The breeding herd must be on a good plane of nutrition for at least 30 days before the onset of treatment. Heifers should be about 65% of their estimated mature body weight at the time of breeding. Cows should be in good body condition at calving and on a weight-gaining plan at the time of treatment. A conveniently placed weighing scale is essential for body weight assessment.

- Rectal palpation of the reproductive tract or estrus detection for at least 25 days before treatment is necessary to determine if the breeding herd is ready to be synchronized with PGF$_2$alpha. Because PGF$_2$alpha elicits its response by inducing regression of functional luteal tissues, only cycling animals in diestrous respond to prostaglandin treatment, resulting in the desired estrus synchrony. Many cattlemen decide their cattle are cycling normally if they have seen a few animals exhibiting estrual activity in the herd.

- If the third method of estrus synchronization (Fig 3) is recommended to the producer, a clue to breeding herd cyclicity can be obtained by evaluating the number of females exhibiting estrus during the first 5 days of the procedure. In a group of randomly cycling cattle, 4-5% of the animals should exhibit estrus each day. This would indicate that 20-25% of the herd should have been in estrus before PGF$_2$alpha is given on the morning of day 6. Professional judgement is required on whether the luteolytic agent should be given on day 6 if less than 20% of the animals were detected in estrus during this 5-day interval.

- Use of teaser animals, wearing chin-ball marking harnesses, can be recommended to the producer to aid in estrus detection.

- Cattle assigned to any estrus synchronization scheme must have anatomically normal reproductive tracts and not be pregnant. This should never be assumed. Often cows mysteriously become pregnant even though the owner insists the females have never been near a bull. PGF$_2$alpha induces luteolysis in early-pregnant cattle; these females will likely abort during the first 10 days after treatment. Although electronic pregnancy testers are commercially available, the surest way to determine the presence of reproductive abnormalities and pregnancy is by rectal examination. The veterinarian must develop palpation skills to evaluate herd reproductive status for estrus synchronization.

- Cattle-handling facilities must be adequate to corral cattle for palpation and artificial insemination of synchronized cows. If timed insemination is used in a synchronization program, females should be inseminated within 2 hours of the appointed time. Mating by appointment is often difficult to manage with a large number of synchronized females to inseminate.

- Avoid using the same squeeze chute used for such things as separating calves, branding or dehorning to inject or inseminate cattle in an estrus synchronization program. Animals may remember these painful experiences and respond accordingly. Females exposed to stressful stimuli at estrus may have reduced conception rates.

- Adequate help in artificial insemination is vital to the success of an estrus synchronization program.
Technicians must be proficient and available when needed. Technician fatigue becomes a factor with a large number of females to inseminate. Use of 3 inseminators if about 100 cows are bred in a day and rotation of inseminators every 5 cows are recommended. Only high-quality semen from reputable distributors should be used.

- Good herd health measures, with an adequate record system, must already be in effect before treatment. This includes vaccination for diseases affecting reproduction. The reproductive history of the breeding herd should reveal good management. Estrus synchronization does not usually eliminate, but rather concentrates and exposes existing reproductive and herd management problems.

- When incorporating estrus synchronization into a breeding program, plans should be made to have additional labor and adequate facilities to handle grouped calvings.

Estrual behavior after prostaglandin treatment usually is similar among dairy and European beef breeds. Handling of Brahman females during an estrus synchronization program may affect their estrual behavior. Brahman females are very temperamental, especially if mishandled or exposed to strange surroundings.

Expectations for a successful estrus synchronization program vary from herd to herd. If all of the heifers were cycling and managed properly before synchronized breeding, the first-service pregnancy rate should range from 45% to 75% for mature dairy heifers. The pregnancy rate in beef heifers would likely be lower, ranging between 40% and 65% from first service. If the cows had no calving problems, were treated at least 45 days after calving and had a corpus luteum at the time of treatment, first-service pregnancy rates should be 40-70% for dairy cows. If beef cows were treated at least 50 days after calving, were nursing healthy calves and had a corpus luteum at the time of treatment, the first-service pregnancy rate would likely be 30-60%. Estrus in Brahman and Brahman-based cattle can be successfully synchronized with PGF$_{alpha}$; however, first-service pregnancy rates have been disappointing.

Estrus synchronization with prostaglandins does not improve the conception rate in a breeding herd. Pregnancy rates in treated cattle are similar to those of herdmates similarly handled and not given prostaglandins.

Therapeutic Use of Prostaglandins

Subestrus or silent estrus results when cycling cows fail to exhibit external signs of estrus. This physiologic state often is difficult to distinguish from inadequate estrus detection by the herdsman. Cows in this category should be evaluated via rectal palpation to detect pregnancy, ovarian structures and evidence of uterine pathologic changes. Depending on uterine tone, ovarian size, presence or absence of luteal structures and the degree of follicular development, often an estrus date can be predicted. If a corpus luteum is detected at palpation, PGF$_{alpha}$ can be given and the cow bred at estrus. Often subestrual dairy cattle are mated by appointment at 72 and 96 hours or 80 hours after PGF$_{alpha}$ injection since the lack of estrual behavior remains a complaint.

As mentioned previously, prostaglandins can be used in conjunction with GnRH to treat luteal as well as follicular cysts. When cows with luteal cysts are treated with PGF$_{alpha}$, luteolysis occurs in over 90%, with estrual behavior expected within 5 days postinjection. However, bovine luteal cysts often are difficult to differentiate clinically from follicular cysts, for which prostaglandin therapy is presumably ineffective.

True pyometra in cattle is characterized by a persistent corpus luteum, a uterus containing purulent material and a state of anestrus. Prostaglandin injection results in luteolysis, induction of estrus and uterine evacuation. Intrauterine infusions after prostaglandin therapy are not indicated since follow-up treatment may adversely affect the subsequent pregnancy rate.

Cows with endometritis and that are still cycling may also benefit from prostaglandin treatment. By shortening diestrus with PGF$_{alpha}$, more estrous periods can be induced over a shorter interval, resulting in more frequent exposure of endometrial tissues to natural defense mechanisms. In a recent study, prostaglandin injection of beef animals on day 10 of the estrous cycle for 6 consecutive estrous cycles
resulted in normal estrous responses without any evidence of post-treatment cystic follicle formation. Prostaglandins and Pregnancy

Prostaglandins have also been shown to have luteolytic properties during pregnancy. PGFα, given to gestating cattle before 120-150 days of pregnancy, induces abortion within 10 days post-injection. Prostaglandins are less effective in inducing abortion when given between 150 and 270 days of gestation. A combination treatment of PGFα and 25 mg dexamethasone is a safe and effective method of inducing abortion in cattle during all stages of gestation.

Prostaglandins, as with potent synthetic glucocorticoids, can be used to successfully induce calving during the last 14 days of pregnancy. Although parturition induced by PGFα occurs in 1-4 days and is uneventful, treated cows often have retained placental tissues as with glucocorticoid-induced calvings. Estrogen priming before PGFα use for calving induction has been proposed as a method to reduce retained placentae in beef cattle. Induction of calving earlier than 14 days before the expected due date often results in decreased calf viability. Therapeutic indications for induction of parturition include vagus indigestion and hydropic conditions of the fetal membranes. Assistance at calving and supportive therapy also may be required for these conditions. Antibiotics may be necessary to combat the metritis that often follows hydrops.

A mummified fetus can be expelled 3-5 days after prostaglandin treatment. In such cases, the cow should be re-examined 3-5 days after injection since the fetus may be lodged in the cervix or vagina. Cows with macerated fetuses usually do not respond satisfactorily to prostaglandin treatment, possibly due to the damaged uterus being unable to expel the fetus.

Embryo transfer programs use prostaglandins to synchronize the estrous cycles of donor and recipient females. For the embryo donor, PGFα usually is given 48-72 hours after the onset of gonadotropin treatment to induce functional regression of the corpus luteum. Injection of PGFα stimulates uterine contractions during nonsurgical embryo collection and induces regression of multiple corpora lutea in the donor.

References