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HISTORY, EFFICACY AND UTILIZATION OF PROSTAGLANDIN F2 ALPHA FOR ESTROUS SYNCHRONIZATION

James W. Lauderdale, Lauderdale Enterprises, Inc
Augusta, MI 49012

General History of Prostaglandins

In 1930 Kurzroc and Lieb reported the human uterus would either contract or relax upon instillation of fresh human semen. M.W. Goldblatt (1933) and von Euler (1934) reported strong smooth-muscle stimulating activity of human seminal plasma. Von Euler (1935) reported strong smooth-muscle stimulating activity of seminal fluid from the monkey, sheep, and goat and in extracts of the vesicular glands of male sheep but not in a number of other species. Von Euler prepared lipid extracts of sheep vesicular glands and found the strong smooth-muscle stimulating activity to be associated with a fraction containing lipid-soluble acids. The active factor was named prostaglandin. The new names prostaglandin and progesterone were published on the same page.

Research on the prostaglandins did not proceed until 1963, in contrast to the extensive research between 1935 and 1963 with progesterone and progestogens, especially for control/management of reproductive cycles of numerous mammals, especially the human. An important contributor to renewed interest in and collaborative support for research with prostaglandins resulted from the friendship developed as graduate students at The Ohio State University between Dr. David Weisblatt, Vice-President of Research at The Upjohn Company and Professor Sune Bergstrom of the Karolinska Institute in Stockholm, Sweden. The collaboration between Karolinska scientists primarily addressing chemical structure identification, metabolism and pharmacology of the prostaglandins and Upjohn scientists addressing production of usable quantities, biology and pharmacology of the prostaglandins allowed research to proceed rapidly. For example, the number of papers published in scientific literature was five by 1963, but about 63 by 1965; the publication rate thereafter approached two per day.

During the 1960s and 1970s the prostaglandin families were identified, characterized, and hundreds of analogs were synthesized. Early production of prostaglandins at The Upjohn Company depended on extracting harvested *Plexaura homamalla* (Caribbean sea whip) for substrate for further chemical modification to the desired specific prostaglandins. Subsequently, Corey (Harvard) chemical synthesis was established for prostaglandin production. Prostaglandins were termed ubiquitous since they were detected in or released from lung, thymus, brain, spinal cord, kidney, iris, umbilical cord, deciduas, fat, adrenals, stomach, intestines, nerves, menstrual fluid, amniotic fluid, seminal plasma, blood skeletal muscle, cardiac muscle, salivary glands, thyroid, pancreas, and uterus. Biological activity was described for cardiovascular, kidney and ureter, reproductive, gastrointestinal, respiratory, central nervous, and peripheral nervous systems.

History of Prostaglandin $F_2\alpha$ for Luteolysis and Relationship to the History of Progestogens for Cattle Estrus Synchronization

Perceived need for beef cattle estrous synchronization

Cattle estrous synchronization was perceived (1960) to meet an unmet need of beef cattle producers who desired to utilize artificial insemination (AI). During the 1950s frozen bovine semen was developed and AI to progeny tested bulls became recognized as effective to make more rapid genetic progress for milk yield and beef production. In the 1960s, for beef cattle, a major detriment to AI was the requirement for daily estrus detection and AI over 60 to 90 days or more. Thus, numerous companies, cited below, believed an orally active progestogen that could be delivered under farm and ranch conditions at an economically attractive price would both meet an unmet need in the beef industry and would generate income for the successful company. Based on both the paper by Ulberg, Christian and Casida (1951) that injected progesterone would block estrus and the understanding of reproductive biology of the bovine estrous cycle in 1960, progestogens, to block estrus for 18 days and then release the block, were the only potentially practical hormones available.

Brook Lodge 1965 conference-impact on development of progestogens for cattle estrous synchronization

Numerous university and pharmaceutical company researchers were seeking use of progesterone and progestogens to synchronize estrus in cattle and other species during the 1960s. *Ovarian Regulatory Mechamisms* was a conference hosted by The Upjohn Company's Robert Zimbelman (animal health) and Gordon Duncan (human fertility research). Zimbelman received his PhD at the University of Wisconsin Madison in the laboratories of L. E. Casida and Duncan received his PhD at Iowa State University in the laboratories of R. M. Melampy. This conference was held at The Upjohn Company Conference Center, Brook Lodge, Augusta, MI in 1965 and the proceedings were published in the Journal of Reproduction and Fertility, Supplement No.1, 1966. This conference was one of a series of conferences held at Brook Lodge beginning in 1956 and continuing into the 1980s, several of which addressed reproductive biology. The topics of the 1965 Brook Lodge Conference and the presenters were:

- Introductory Note, A.S. Parkes
- Modification of ovarian activity in the bovine following injection of oestrogen and gonadotropin, J.N. Wiltbank
- Effect of progestogens on ovarian and pituitary activity in the bovine, R.G. Zimbelman
- Pituitary-ovarian-uterine relationships in pigs, L.L. Anderson
- Luteotrophic and luteolytic mechanisms in bovine corpora lutea, W. Hansel
- The nature of the luteolytic process, I. Rothchild
- Luteal maintenance in hypophysectomized and hysterectomized sheep, C. Thibault
- Localization and sexual differentiation of the nervous structures which regulate ovulation, R.A. Gorski
- Steroidogenesis in the perfused bovine ovary, E.B. Romanoff

- Competitive studies of the action of luteinizing hormone upon ovarian steroidogenesis, D.T. Armstrong
- Studies on the mode of action of luteinizing hormone on steroidogenesis in the corpus luteum *in vitro*, J. Marsh and K. Savard
- Summation, R.O. Greep, A.V. Nalbandov, R.M. Melampy

Additional participants from academia who did not present papers were C.A. Barraclough, E.M. Bogdanove, L.E. Casida, B.N. Day, H.D. Hafs, Carl Hartman, K.A. Laurence, and M.B. Nikitovich-Winer. This 1965 Brook Lodge Conference featured the thought and research leaders in reproductive biology of domestic animals.

I interpret the 1965 Brook Lodge Conference as the scientific discussion that launched and/or reinforced existing fledgling cattle estrous synchronization progestogen development programs. During the 1960s, progestogens were THE orally active and potentially economically feasible hormones with promise to be developed for estrous synchronization of cattle. Companies actively seeking progestogens during the 1960s for use in estrous synchronization of cattle were The Upjohn Company, Elanco, Squibb, American Cyanamid, Searle and Syntex. The only progestogen to survive as an orally active progestogen available today for cattle estrous synchronization is MGA (melengestrol acetate). The Squibb product, norgestomet, eventually became available as SyncroMate-B.

Brook Lodge 1965 Conference; Impact on development of prostaglandins for cattle estrous synchronization

I interpret the 1965 Brook Lodge Conference as the scientific discussion that launched research and development of prostaglandins for both human and domestic animal use. Specifically, during the general discussion of Hansel's paper (listed above), John Babcock, The Upjohn Biochemical Research Division, is cited: "I wonder if anyone here has thought of the possible role of a family of agents known as prostaglandins, which have been studied extensively by Bergstrom. They have found a pronounced effect on smooth muscle, for one thing, and have found they may play a role in fertility because they are found in very high concentrations in the semen of some species. Whether or not release of prostaglandins from the uterus could have a luteolytic effect, I have no idea" (J. Reprod. Fertil. Suppl. No.1:47, 1965). Immediately following the 1965 Brook Lodge Conference, Bruce Pharriss, The Upjohn Company Fertility Research (Duncan's group) initiated research, in collaboration with scientists of Babcock's group, to investigate prostaglandins for luteolytic activity. Babcock and Pharriss chose $PGF_2\alpha$ as the prostaglandin to investigate and chose the pseudopregnant rat as the animal model to investigate luteolysis. Their report that $PGF_2\alpha$ was luteolytic in the pseudopregnant rat was not published until 1969 (19). An attendee at the 1965 Brook Lodge Conference shared Babcock's comment with a colleague in the United Kingdom who secured PGE_2, tested it for luteolytic activity, and, finding none, concluded prostaglandins were not luteolytic.

Development of prostaglandins for cattle estrous synchronization

From 1963 onward The Upjohn Company leadership invested extensively in prostaglandins for human potential products, and, until more effective synthesis strategies were developed, supply of prostaglandins was limited. Following the discovery by Pharriss and Wyngarden (1969) that $PGF_2\alpha$ was luteolytic, research for human

fertility/parturition/abortion was underway and senior leadership chose not to allow research in cattle until 1971. At the same time, ICI of the United Kingdom had hired Mike Cooper to research and develop $PGF_2\alpha$ analogs for use in cattle. We initiated our $PGF_2\alpha$ research in cattle at The Upjohn Company using the 35-40 day confirmed pregnant (rectal palpation being the only method available in 1971) beef heifer as the model to investigate luteolysis. $PGF_2\alpha$ was reported to be luteolytic in the bovine in 1972 (Rowson et al., 1972; Lauderdale, 1972; Liehr et al., 1972). $PGF_2\alpha$ was reported to be luteolytic in equine (Douglas and Ginther, 1972) and ovine (Thorburn and Nicol, 1971, Goding et al., 1972) and potential uses to control reproductive cycles in domestic animals were described (Inskeep, 1973). Thus, in ten years, between 1963 and 1973, prostaglandin research was reinitiated and data were published stating $PGF_2\alpha$ and $PGF_2\alpha$ analogs were luteolytic in cattle and the potential existed for them to have practical value for estrous synchronization.

Research at The Upjohn Company was directed towards achieving approval for $PGF_2\alpha$ in the mare, a non-food animal, which would allow for more rapid approval through the Food and Drug Administration Center for Veterinary Medicine (FDACVM), followed by approvals in cattle and other species. $PGF_2\alpha$ was approved for 1) equine (Prostin F2 Alpha®;1 mL ampoule,1976), 2) 10 mL vial, (1977), 3) beef cattle and dairy heifer double injection program for estrous synchronization (Lutalyse, 1979), 4) 30 mL vial (1980), 5) beef cattle and dairy heifer single injection program for estrous synchronization (1981), 6) feedlot cattle abortion (1981), 7) lactating dairy cattle no-visible estrus (1983), 8) non-lactating cattle abortifacient (1983), 9) lactating dairy cattle pyometra treatment (1983), and 10) swine parturition (1983).

During the 1970s and 1980s, data were not available regarding follicular waves. Researchers investigating $PGF_2\alpha$ and its analogs recognized something other than the regression of the CL, was contributing to the variance in consistency both of return to estrus in a predictable 48 hours and of effective pregnancy rates in response to timed AI post-$PGF_2\alpha$ injection. Research of follicular waves in cattle now allows for more consistent pregnancy rates resulting from timed-AI protocols utilizing $PGF_2\alpha$ products, with or without progestogens, and gonadotropin releasing hormone.

Prostaglandin products

Because the market for $PGF_2\alpha$ products was perceived, and then documented, to be lucrative for companies, numerous $PGF_2\alpha$ products were approved and sold in various countries. Some of the products were Lutalyse/Dinolytic Pronalgon F (Upjohn), Estrumate/Planate and Equimate (ICI, with subsequent sale to numerous companies), Prosolvin (Intervet), Bovilene (Fort Dodge), Iliren (Hoechst), Alfabedyl (Hoechst-Roussel), and numerous generics throughout the world.

Product indications

Control CL lifespan for cattle and equine; pregnancy termination for bovine, equine and porcine; parturition induction for bovine, porcine and equine; and treatment for mummified foetus, pyometra/endometritis/metritis, and luteal cysts in bovine.

Lauderdale's interpretation of the scientific literature for effectiveness of $PGF_2\alpha$ products used in cattle

Estrus synchronization → Effective

Early postpartum, in the absence of a CL (hasten involution) → Minimal to ineffective
Single injection 14 or more days postpartum (return to estrus, increased pregnancy) → Minimal to ineffective
Treatment of retained placenta → Minimal to ineffective
Treatment of metritis → Effective
Treatment of cystic ovarian follicles → Effective when the follicles are luteinized
Do $PGF_2\alpha$ products cause ovarian cysts → No

Original Programmed Breeding Programs Using $PGF_2\alpha$ (Lauderdale et al., 1977; Moody, 1977; Lauderdale, 1979)

Older and current technology allows for programmed breeding at the first synchronized estrus. Breeding management protocols under development should result in continuous programmed breeding management until 100% of the cattle are pregnant in the designated time interval.

Today we recognize effective programmed breeding requires synchronization of follicle waves, management of the CL lifespan, and induction of ovulation. Thus, selection of an effective programmed breeding program is dependant upon matching the components of follicle wave management, CL lifespan management, ovulation induction, labor management, and economic management consistent with the farm/ranch/dairy objectives. However, when $PGF_2\alpha$ and its analog products were developed, the component of follicular wave management was not recognized. Thus, all programs reported herein are the ones originally developed for $PGF_2\alpha$ and its analogs. Cattle must be in cycling estrous in order to achieve estrous synchronization and pregnancy. Additionally, with understanding of follicle waves, research documented the interval between Lutalyse injections should be increased from 11 (10-12) days (the original recommendation) to 14 days to achieve more precise estrus control and higher pregnancy rates. The original selection of 10 to 12 days between Lutalyse injections was based on an attempt to minimize the days between injections but achieve a sufficient interval to assure CL regression of both those CL not responsive to the first injection and those CL formed subsequent to regression of the CL after the first injection.

Definitions

$$\text{Estrus Detection Rate} = \frac{\text{No. Detected in estrus x 100}}{\text{No. Assigned}}$$

Estrus % was calculated for each interval of interest.

$$\text{Conception Rate} = \frac{\text{No. Pregnant x l00}}{\text{No. Detected in Estrus and AI}}$$

Conception Rate was calculated for first service only.

$$\text{Pregnancy Rate} = \frac{\text{No. Pregnant x 100}}{\text{No. Assigned}}$$

Pregnancy Rate was calculated for each interval of interest.

The pregnancy rate is the measure that provides the number of pregnant heifers/cows resulting from the breeding program and is the cumulative result of estrus detection rate and conception rate.

Figure 1 identifies the schedule for using either Double or Single Lutalyse injection programs.

Program Designation			Breeding Method					
LLAIE	L↓	L↓	AIE			AIE or Bull	AIE or Bull	
LLAI80	L↓	L↓		TAI		AIE or Bull	AIE or Bull	
LAIE		L↓	AIE			AIE or Bull	AIE or Bull	
AILAI			AIE		L↓	AIE	AIE or Bull	AIE or Bull
-14 to –12		-1	0	3	5	9	22	27
Days before Breeding Season			Days of Breeding Season					

Figure 1. Cattle Breeding Management with 5 mL Lutalyse sterile solution (**L↓**; 25 mg $PGF_2\alpha$/33.5 mg dinoprost tromethamine; IM). **AIE**: inseminated 6 to 13 hours after detected estrus. **TAI**: inseminated at about 77 to 80 h after the second injection of Lutalyse.

Dose Titration for Lutalyse® sterile solution for cattle

Beef cows (9 herds, 767 cows), beef heifers (9 herds, 448 heifers) and dairy heifers (3 herds, 243 heifers) were investigated to estimate the optimal dose for Lutalyse. Doses investigated were 0, 5, 15, 25 and 35 mg dinoprost intramuscularly at an 11 (10 to 12) day interval. Response variables were percent in estrus and pregnancy rate for days 2-5 post-second injection. Walker-Carmer statistical estimates for the optimal dose, based on estrus and pregnancy rates, were 25.7 mg and 22.8 mg for beef cows, 25.1 and 21.5 for beef heifers, and 26.4 and 30.2 for dairy heifers. Based on these data, FDA CVM approved a dose of 25 mg dinoprost as the dose for use in cattle. This dose was used in all subsequent studies to investigate the various breeding management programs with Lutalyse. Papers can be found in the scientific literature reporting the dose should be something less than the FDA CVM approved dose of 25 mg dinoprost (5 mL Lutalyse). Additionally, rumors abound the dose is too little for big framed cattle or breed X. However, those papers consistently report data based on a single or minimal locations and minimal numbers of cattle. The dose of 25 mg dinoprost (5 mL Lutalyse) is the dose derived by a statistically valid process to consistently be effective across farms and ranches with various management styles and cattle types and sizes.

Double injection of Lutalyse® sterile solution breeding programs

Cattle were injected intramuscularly (IM) with 5 mL Lutalyse twice at an 11 (10-12) day interval. Cattle were artificially inseminated (Al) either at detected estrus (LLAIE) or at about 80 h (LLAI80) after the second injection (Fig. 1). For the studies represented by the data in the presentation, cattle of the control and LLAIE groups were observed for estrus twice daily and Al about 6 to 13 h after first observation of estrus. Cattle of the LLAI80 were Al at about 77 to 80 h after the second injection of Lutalyse and were rebred at any estrus detected 5 days or more after the 80 h AI. Dates of injections of Lutalyse

were established such that the second injection would be administered the day prior to initiation of the normal breeding season within herd.

Beef cows. Beef cows from 24 herds with 1844 cows were investigated.

Estrus detection. Significantly ($P < 0.05$) greater percentages of cows were detected in estrus during the first 5 days of the AI season for the LLAIE cattle (47%) compared to Controls (11%). Fewer percents of LLAIE cattle (47%) were detected in estrus at least once during the first 5 days compared to Controls (66%) during the first 24 days (one estrous cycle) of the AI season, indicating the cows were just beginning to estrus cycle at the beginning of the breeding season.

Conception rate. First service conception rates were similar between Control and LLAIE cattle for both the first 5 days (68%, 61%) and days 1-24 (61%, 66%) of AI. These data reinforce previously reported data that conception rate was not altered significantly following use of $PGF_2\alpha$ (2, 3, 7).

Pregnancy rate. Pregnancy rates were greater for both LLAIE (34%) and LLAI80 (35%) cattle compared to Controls for 5 days (11%) and were slightly lower than Controls for 24 days (48%). These investigations did not identify a significant difference in pregnancy rate between cattle of LLAIE (5 days of AI at estrus, 34%) and LLAI80 (single timed AI, 35%). Pregnancy rates generally were similar between Control, and either LLAIE or LLAI80 cattle for days 1-24 (48% Control and 55%/49%) and 1-28 (52% Control and 61%/57%).

Beef heifers. Beef heifers from 22 herds with 1614 heifers were investigated.

Estrus detection. Significantly ($P < 0.05$) greater percentages of heifers were detected in estrus during the first 5 days of the AI season for the LLAIE cattle (66%) compared to Controls (13%). Fewer percents of LLAIE cattle (66%) were detected in estrus at least once during the first 5 days compared to Controls (81%) during the first 24 days (one estrous cycle) of the AI season, indicating that not all heifers were estrous cycling at the beginning of the breeding season.

Conception rate. First service conception rates were similar between Control and LLAIE cattle for both the first 5 days (50%, 55%) and days 1-24 (58%, 54%) of AI. These data reinforce previously reported data that conception rate was not altered significantly following use of $PGF_2\alpha$ (2, 3, 7).

Pregnancy rate. Pregnancy rates were greater for both LLAIE (38%) and LLAI80 (36%) cattle compared to Controls for 5 days (9%) and were slightly lower than Controls for 24 days (53%). These investigations did not identify a significant difference in pregnancy rate between cattle of LLAIE (5 days of AI at estrus, 38%) and LLAI80 (single timed AI, 36%). Pregnancy rates generally were similar between Control, and either LLAIE or LLAI80 cattle for days 1-24 (53% Control and 56%/51%) and 1-28 (56% Control and 58%/50%).

For both beef cows and heifers, the 80 hr timed AI reported herein had a similar pregnancy rate to the cows bred at estrus for 5 days. However, the success of timed AI was

highly variable among herds and within herds over time. The bases for this variation in response are the variation both in control of follicular waves and in the percent of cattle anestrus at the beginning and 14-days prior to the breeding season. In those groups of cattle where timed AI worked well, the incidence of anestrus or pre-puberty was very low and the cattle were in the stage of the estrus cycle where follicular waves were "similar" among the cohort of cattle treated. We now know, based on an understanding of follicle waves, that, to achieve consistently high pregnancy rates using timed AI, follicular waves must be synchronized/managed and the lifespan of the corpus luteum (CL) must be managed. Follicle waves can be managed through the use of GnRH and the CL lifespan can be managed by use of $PGF_2\alpha$. The results of these studies have been confirmed both by repeated research studies by numerous academicians and by use on-farm and on-ranch over the past 25 years.

Single injection of Lutalyse® sterile solution breeding programs

The AILAI cattle management system requires the observation of cattle for estrus and AI for 4 days, followed by injection of cattle not detected in estrus during those four days with 5 mL Lutalyse, IM, on the morning of day 5, followed by continued observation of cattle for estrus and AI accordingly on days 5 through 9, i.e. a 9-day AI season (Fig. 1). Breeding for the remainder of the breeding season can be by AI, bulls or some combination of AI and bulls. The LAIE cattle management system is IM injection of cattle with 5 mL Lutalyse on the day before initiation of the breeding season followed by observation of cattle for estrus and AI for 5 days (Fig. 1). Breeding for the remainder of the breeding season can be by AI, bulls or some combination of AI and bulls. For the data presented in support of the results derived from these breeding programs, within herd comparisons were made between Control and LAIE cattle and between Control and AILAI cattle. In three additional herds, within herd comparisons were made among Control, LLAIE and LAIE cattle.

AILAI Beef Heifers. Beef heifers from ?? herds with ?? heifers were investigated.

Estrus detection. The percent cattle detected in estrus the first time for days 1 through 5 was similar between AILAI (25%) and Control (24%) beef heifers. The percent heifers detected in estrus the first time during days 1 through 9 was greater ($P < 0.01$) for AILAI than for Controls (64% vs 38%). First estrus detection rates for the first 24 days of breeding were similar between AILAI and Control cattle (77% vs 78%).

First service conception. Conception rates were not different between cattle assigned to AILAI and Control groups respectively for days 1 through 5 (62%, 62%), 1 through 9 (56%, 53%), and 1 through 24 (59%, 57%).

Pregnancy rate. Pregnancy rate for days 1 through 5 was similar between AILAI and Control heifers (16% vs 15%). Pregnancy rates were greater ($P < 0.01$) for AILAI than for Control heifers for days 1 through 9 (45% vs 24%). Pregnancy rates were not different significantly between Control (55%) and AILAI (56%) heifers for days 1 through 24. Pregnancy rates for days 1 through 28 were 63% and 59% for AILAI and Control ($P < 0.16$) heifers.

The percentages of cattle detected in estrus the first time, first service conception rates and pregnancy rates should be similar between Controls and cattle assigned to the AILAI group for days 1 through 5 since the AILAI cattle would not have been injected with Lutalyse. That was the case for beef heifers.

AILAI Beef Cows

Pregnancy rate. Pregnancy rates for Control (N=638) and AILAI (N=637) cows respectively were 17% and 32% at 9 days and 57% and 70% at 32 days.

The data on enhanced pregnancy rates after 9 days of AI with the AILAI management system are consistent with data published previously (1, 4, 5). The greater pregnancy rate in the AILAI group for days 1 through 9 demonstrated the effectiveness of use of Lutalyse in that system of breeding management. The trend for more pregnancies in the AILAI group after 28 days of AI reinforces the conclusion that the AILAI management system was effective. The results of these studies have been confirmed both by repeated research studies by numerous academicians and by use on-farm and on-ranch over the past 25 years.

LAIE Beef Heifers. Beef heifers from ?? herds with ?? heifers were investigated.

Estrus detection. The percent of heifers detected in estrus the first time during days 1 through 5 was greater for LAIE than for Controls (52% vs 28%, $P < 0.05$). The percent of heifers detected in estrus the first time during days 1 through 24 was similar between LAIE and Controls (83% vs 82%). The percentage of Control heifers detected in estrus during the first 24 days of AI was 82. This value should be an over estimate of the percent of the herd having estrous cycles on the day of Lutalyse injection, since the Control heifers had 24 more days to initiate estrous cycles. Since $PGF_2\alpha$ has been shown to be ineffective in regressing the CL during days 1 through 4 or 5 after estrus and cattle have an 18 to 24 ($x = 21$) day estrus cycle, a single injection of $PGF_2\alpha$ would be expected to regress the CL and synchronize about 75% to 80% of a group of estrous cycling cattle. Calculation of the predicted estrus detection rates for cattle of this study would be as follows for the Lutalyse single injection program: 75% with responsive CL of 82% of estrous cycling heifers equals 62% expected (actual was 52% for LAIE heifers). Thus, the predicted and observed estrus detection rates of 62% and 52% for heifers appeared to be similar, which reinforces the conclusion that a single injection of Lutalyse yielded the predicted response.

First service conception rate. These were similar for heifers of the Control and LAIE groups, as would be expected (47%, 52%).

Pregnancy rate. Pregnancy rates for days 1 through 5 for LAIE and Control heifers were 28% and 12% ($P < 0.04$). Pregnancy rates for days 1 through 24 for LAIE and Control heifers were 55% and 49%. Pregnancy rates for days 1 through 28 for LAIE and Control heifers were 57% and 52%.

These data are similar to those reported previously relative to use of the LAIE management system (Inskeep, 1973; Lauderdale et al., 1974; Moody, 1979; Turman et al., 1975). The pregnancy rates for 5 days of breeding in the LAIE management system demonstrated that system to be effective. The results of these studies have been confirmed both by repeated research studies by numerous academicians and by use on-farm and on-ranch over the past 25 years.

Comparison of LAIE and LLAIE

Cattle of the LLAIE system compared to cattle of the LAIE system should have about a 20% to 25% greater estrus detection rate and pregnancy rate for breeding during the first 5 days after $PGF_{2\alpha}$ since $PGF_{2\alpha}$ is ineffective or less effective as a luteolytic agent when injected during the first five days after ovulation (Lauderdale, 1972). The observed percentage differences between LAIE and LLAIE heifers for first estrus were 23% and for pregnancy rate were 23%. Thus, the expected percentage differences of about 20% to 25% and the observed percentage differences of 23% and 23% were similar in this limited study.

MGA and Lutalyse

Ed Moody, Montana State University, collaborating with The Upjohn Company scientists, investigated MGA and Lutalyse to synchronize estrus in beef cattle in about 1977-1978 (9). For example, beef heifers were fed MGA at 1.0 mg/heifer daily (the estrus synchronization dose we were pursuing at that time) for either 4-days or 5-days immediately prior to start of 19 days of AI followed by 26 days of bull breeding. Heifers fed MGA were fed for 4-days (T1, N=31, last day of feeding was 2-days before breeding start) or fed 5-days (T2, N=32, last day of feeding was 1-day before breeding start) and all MGA fed heifers were injected with Lutalyse 1-day before breeding started. Non-treated Control heifers (T3, N=33) were included in this study. Heifers were observed for estrus twice daily for the 19 days of AI.

First service AI conception rate. This was 61%, 44% and 58% for T1, T2 and T3, respectively.

Pregnancy rate. Pregnancy rates for T1, T2, T3 were 42%, 25%, 18% for five days of AI, were 65%, 47%, 61% for 19 days of AI, and were 90%, 88%, 85% for the 44 days (19 days of AI followed by 25 days with bulls).

Prostaglandin $F_{2\alpha}$ Product Comparisons

Rumors abound regarding relative effectiveness of various $PGF_{2\alpha}$ products. The $PGF_{2\alpha}$ products either contain the natural $PGF_{2\alpha}$ or various analogs of $PGF_{2\alpha}$. Analogs of $PGF_{2\alpha}$ were developed to obviate patents existing at the time of initial marketing or to increase "potency" and/or decrease side effects. Although active ingredients and their properties differ among the various $PGF_{2\alpha}$ products, each $PGF_{2\alpha}$ product induces luteolysis by triggering a cascade of endogenous events that ultimately lead to the regression of the corpus luteum. Each U.S. $PGF_{2\alpha}$ product has been approved by the Food and Drug Administration/Center for Veterinary Medicine (FDA/CVM); to be approved by FDA/CVM each product had to have sufficient data documenting efficacy for the label indication. Efficacy is based on dose, route of administration, species, and endpoints for label indication(s). Some U.S. $PGF_{2\alpha}$ products have more label claims than others simply due to the decisions of the various companies developing the $PGF_{2\alpha}$ products that the market did or did not justify the additional expense of securing said label claims.

One example (Figure 2) of a $PGF_{2\alpha}$ analog compared to $PGF_{2\alpha}$ is Estrumate, containing cloprostenol sodium, and Lutalyse, containing the natural $PGF_{2\alpha}$. The label

intramuscular doses, based on extensive field studies with cattle, are 2 mL (0.5 mg) for Estrumate and 5 mL (25 mg) for Lutalyse.

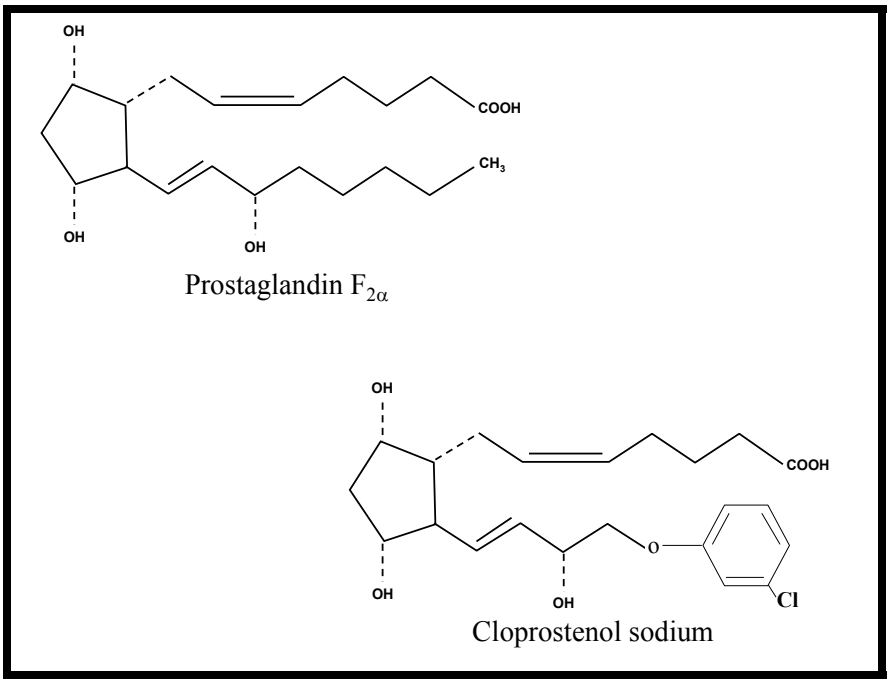

Figure 2. Chemical structures of $PGF_{2\alpha}$ (dinoprost) and a $PGF_{2\alpha}$ analog (cloprostenol).

Products containing $PGF_{2\alpha}$ analogs consistently require lower doses to regress the corpus luteum in cattle than products containing natural $PGF_{2\alpha}$. One rumor is $PGF_{2\alpha}$ products with $PGF_{2\alpha}$ analogs are more potent (lower dose) therefore more efficacious. There are hundreds of papers reporting use of $PGF_{2\alpha}$ products in cattle with response measured as return to estrus, conception rate and pregnancy rate. I interpret the scientific literature to support an interpretation of "no difference" among the FDA/CVM approved $PGF_{2\alpha}$ products used in cattle. I interpret anyone skilled in the art can select papers to show what we want; such as one $PGF_{2\alpha}$ product is better or worse than another. This can be accomplished since, either by chance or due to insufficient numbers of cattle on a study, a paper will report one $PGF_{2\alpha}$ product is numerically superior or inferior to another $PGF_{2\alpha}$ product, usually the differences are numerical but not statistically different, but the difference is interpreted to be real.

The $PGF_{2\alpha}$ and $PGF_{2\alpha}$ analogue products achieve efficacy through regression (luteolytic) of the corpus luteum (CL). Following CL regression, progesterone concentrations decrease to baseline in about 24 hours, which allows maturation of the dominant pre-ovulatory follicle that results in an increase in serum concentrations of estradiol-17β. Increased serum estradiol-17β concentration leads to the LH surge that induces ovulation. Increased serum estradiol-17β concentration stimulates the immune system in the uterus. These biological relationships are the bases for the label indications of the various $PGF_{2\alpha}$ products, synchronization of estrus, treatment of uterine infections such as pyometra, and induction of abortion in pregnant cattle.

The following published papers address effectiveness of various $PGF_{2\alpha}$ products. I did not place the references for this section in "References" but retained the references within this section.

1. Comparison among dinoprost, cloprostenol and fenprostalene (Theriogenology 29:1193,1988, Guay, Rieger, Roberge). No difference in serum progesterone (P4) rate of decrease (all P4 at baseline by 24 hr after injection). No difference in ova/embryos collected between Days 6 and 8 of gestation.
2. Comparison among cloprostenol, alfaprostenol, prosolvin, and iliren (Theriogeno. 17:499, 1982, Schams and Karg). P4 decreased to baseline in 24 hr for each. Visual inspection of the P4 patterns suggested support of the author's conclusion of "no difference" among the $PGF_{2\alpha}$ products.
3. Comparison between dinoprost and fenprostalene (Theriogen. 28:523, 1987. Stotts et al). No difference in P4 profile following injection on either day 6 or day 11 of the estrous cycle.
4. Comparison among dinoprost, cloprostenol and fenprostalene (Theriogen. 34:667, 1990. Desaulniers, Guay, Vaillancourt) . Similar pattern of return to estrus. However, 5/10 fenprostalene cattle, but zero cattle for dinoprost and cloprostenol groups, had P4 greater than 1 ng/mL at 48 hr, suggesting slower P4 decline with fenprostalene. However, note the data of "1)" and "3)" above did not show such a difference.
5. Comparison between dinoprost and cloprostenol. The series of papers by Macmillan et al using either dinoprost of cloprostenol and measuring return to estrus/estrus synchrony, conception rate and pregnancy rate indicate to me "no difference" (An. Repro. Sci, 6:245, 1983/1984; NZ Vet. J. 31:110, 1983 and 43:53, 1983; Theriogen.18:245, 1982).
6. Comparison between dinoprost and cloprostenol (Theriogen. 21:1019, 1984. Donaldson). Estrus control similar, although the dose of dinoprost was 65mg in three doses. I grant Donaldson has published other papers criticising dinoprost vs cloprostenol for embryo transfer use.
7. Tiaprost. P4 decreased to baseline in about 24 hours, a pattern reported above for various $PGF_{2\alpha}$ products.
8. Alfaprostol. (Theriogen.24:737, 1985. Kiracofe, Keay, Odde). Pattern of return to estrus, day of estrous cycle response rate, conception rate and pregnancy rate patterns similar to those reported for various $PGF_{2\alpha}$ products.
9. Fenprostalene (Theriogen. 25:463, 1986. Herschler, Peltier, Duffy, Kushinsky). Patterns of P4 decrease and return to estrus similar to those reported for various $PGF_{2\alpha}$ products.
10. Comparison among dinoprost, cloprostenol and luprostiol (Theriogen. 33:943,1990. Plata et al). Estrus response (5-d synchrony) and pregnancy rates did not differ among the $PGF_{2\alpha}$ products.
11. Comparison between luprostiol and cloprostenol (J. Animal Sci. 67:2067, 1989. Godfrey et al). Brahman cattle. P4 declined but needed a dose of about 30mg luprostiol vs 0.5 mg cloprostenol and fertility apperaed depressed by that dose of luprostiol.

Peer-reviewed studies comparing the efficacy of Lutalyse and Estrumate to synchronize estrus in cattle are summarized in the following Table, courtesy of Fred Moreira.

Reference	Type[4]	N[5]	Estrus detection rate[1] (%)			Conception rate[2] (%)			Pregnancy rate[3] (%)		
			Lutalyse	Estrumate	*P*	Lutalyse	Estrumate	*P*	Lutalyse	Estrumate	*P*
Johnson, 1984	LDC	52	61.5	42.3	NS[6]	45.8	20.8	NS	54.2	29.2	NS
Seguin et al., 1985	NLDC	124	88.7	96.8	NS	60.0	64.3	NS	56.3	62.5	NS
	LDC	245	66.1	65.3	NS	51.2	50.6	NS	33.9	33.1	NS
Turner et al., 1987[7]	BC-BH	63	66.6	76.8	NS	50.2	44.1	NS	35.3	34.5	NS
Salverson et al., 2002	BH	1002	85.9	88.7	NS	66.5	67.5	NS	57.5	60.6	NS
Martineau, 2003	LDC-DH[8]	203	85.9	82.8	NS	33.7	41.8	NS	29.3	34.9	NS
	LDC-DH[9]	404	82.6	83.0	NS	38.6	46.6	NS	31.4	39.2	NS

[1] Percentage of animals detected in estrus relative to the total number of animals within each group.
[2] Percentage of animals that conceived relative to the number of animals inseminated.
[3] Percentage of animals that conceived relative to the total number of animals within each group.
[4] Type of cattle used in the study (LDC = lactating dairy cows; NLDC = non-lactating dairy cows; BC = beef cows; BH = beef heifers; DH = dairy heifers).
[5] Number of animals included in the experiment.
[6] NS = differences were not statistically significant.
[7] Pregnancy rates were calculated based on reported Least Square Means for estrus detection and conception rates.
[8] Includes only cows injected with LUTALYSE and ESTRUMATE intramuscularly.
[9] Includes both intramuscular and intravenous route of administration for LUTALYSE and ESTRUMATE.

Of the 217 prostaglandin papers published in the Journal of Animal Science, Journal of Dairy Science and Theriogenology, citations per $PGF_{2\alpha}$ product were 86% (186/217) for Lutalyse, 3% (7/217) for Estrumate, 4% (9/217) for all others, and 7% (15/217) no $PGF_{2\alpha}$ product identified (courtesy of Dr. Fred Moreira).

The scientific literature does not support a defendable interpretation that, when each $PGF_{2\alpha}$ product is used at the label dose, there are real differences among the $PGF_{2\alpha}$ products in efficacy. I propose technical service available per $PGF_{2\alpha}$ product makes the greatest significant difference among the $PGF_{2\alpha}$ products, assuming price to be competitive among the $PGF_{2\alpha}$ products.

Summary

This presentation provides data from studies conducted in commercial herds with various breeding management programs. The variety of breeding management programs available today gives the producer wide flexibility is selecting the program that best fits the breeding objectives for that herd. However, the large variety of breeding management programs also brings the potential for high confusion as to “what to do”. I encourage us to remember the biology of the heifer/cow and attempt to match that biology with the

breeding objectives for the herd. Thus, selection of the breeding management program for a herd might take into consideration some of the following:

- If puberty is of concern, progestogens, such as MGA and CIDR, where approved for use by Regulatory Authorities, are justified to increase the percent of heifers estrus cycling at the time of desired breeding initiation.
- If timed AI is of interest, control of both follicle waves and lifespan of the CL is required. Thus, $PGF_2\alpha$ or $PGF_2\alpha$ analog products and GnRH, with or without a progestogen, are required.
- If limited input is desired, one might consider
  - Single $PGF_2\alpha$ or $PGF_2\alpha$ analog products followed by AI at estrus for 5 days
  - Single GnRH followed by $PGF_2\alpha$ or $PGF_2\alpha$ analog products 7 days later followed by AI at estrus for 5 days
  -Double $PGF_2\alpha$ or $PGF_2\alpha$ analog products at 14 days followed by either AI at estrus for 5 days or AI at about 80 hours after $PGF_2\alpha$ or $PGF_2\alpha$ analog products, or a combination of estrus detection and breeding to "80 hours" with timed AI of those not bred.

Although not presented, data exist that, with breeding management programs that result in estrus detected over several days, such as is achieved with Double or Single $PGF_2\alpha$ or $PGF_2\alpha$ analog product breeding programs, cattle can be bred with bulls rather than by AI. However, bull management, rotation of bulls into breeding for a few days followed by rest, is essential for the full success of this breeding program.

The scientific literature does not support a defendable interpretation that, when each $PGF_{2\alpha}$ product is used at the label dose, there are real differences among the $PGF_{2\alpha}$ products in efficacy. I propose that technical service available per $PGF_{2\alpha}$ product makes the greatest significant difference among the $PGF_{2\alpha}$ products, assuming price to be competitive among the $PGF_{2\alpha}$ products.

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