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WHERE WE HAVE BEEN AND WHERE WE ARE TODAY: HISTORY OF THE DEVELOPMENT OF PROTOCOLS FOR BREEDING MANAGEMENT OF CATTLE THROUGH SYNCHRONIZATION OF ESTRUS AND OVULATION

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Introduction

Reproductive efficiency is one of the most important factors for successful cow-calf enterprises. Certainly, in the absence or reproduction, there is no cow-calf enterprise. During the 1950s frozen bovine semen was developed and AI with progeny tested bulls became recognized as effective to make more rapid genetic progress for milk yield and beef production. During the interval 1950s through 1960s, a major detriment to AI in beef cattle was the requirement for daily estrus detection and AI over 60 to 90 days or more. Therefore, with the availability of artificial insemination, further control of estrus and breeding management was of greater interest and value, especially to the beef producer. Additional publications, not addressed herein, provide reviews of the development of cattle estrus and breeding management (Wiltbank, 1970; Wiltbank, 1974; Odde, 1990; Mapletoft et al., 2003; Patterson et al., 2003a; Kojima, 2003; Kesler, 2003; Patterson et al., 2003b; Chenault et al., 2003; Stevenson et al., 2003; Lamb et al., 2003).

Early research on the estrous cycle

Research to understand estrus and estrous cycles was initiated in the United States by Dr. Fred F. McKenzie and his graduate students at the University of Missouri in the 1920s utilizing sheep. McKenzie (1983) began leading an animal research laboratory at the University of Missouri in 1923. His first Ph.D. student, 1925, was L. E. Casida who investigated estrus in the ewe, with emphasis on histology of the reproductive tract. Other students included Ralph Phillips (estrous cycle of the ewe, ram spermatogenesis and semen evaluation), Victor Berliner (ram fertility fluctuations), Clair Terrill (ovulation in the ewe), and Fred Andrews (stallion semen production and collection). McKenzie and Phillips (1931) published observations on the estrous cycle of the ewe. Prior to this paper, McKenzie and Phillips could find only one paper to cite regarding duration of estrus and estrous cycle length in sheep. McKenzie et al., (1934) published a preliminary report on reproduction in the ewe.

McKenzie trained graduate students (1930s) and their graduate students (1940s to present) have been and continue to be significant contributors to research in animal reproduction in the US.

Understanding the estrous cycle and postpartum interval of cattle

Estrous cycle

Data from physiological studies were not available so Chapman and Casida (1935) statistically analyzed 179 breeding records and reported the mode for estrous cycle

duration was 21 d with a mean of 37 d for copulation non-fertile cycles and 32 d for non-copulation cycles. Excluding estrous cycles of 32 d or greater, the estrous cycle duration was 21-22 d. The authors reported extreme variation of estrous cycle length due to ovarian abnormalities. Nalbandov and Casida (1942), participating in a collaborative cattle study with Brewster and Cole (1941), reported that ovulation occurred approximately 14 h after end of estrus, 37% of the variation in time of ovulation was due to between-cow variability, and there was a marked similarity in means and variances for dairy cattle in Wisconsin and beef cattle in Michigan. Nellor and Cole (1956) reported cattle mean estrous cycle duration to be 20.1 d with a range of 14-26 d.

Postpartum interval

A series of papers reported the postpartum interval for cattle. Guilbert and McDonald (1934) reported postpartum intervals for beef cows to be 20-40 d for 30%, 40-60 d for 30%, and 60-100 d for 40%. Chapman and Casida (1935) reported the mean postpartum interval was 69 d for cows calving normally and 71 d for cows calving abnormally. Chapman and Casida (1936) reported postpartum intervals averaged 150 d **(**70 d to first estrus plus 50 d to first service plus 30 d to conception**)** and 1.66 services per conception. They cited Williams (Cornell Vet. IX 4:204, 1919) as suggesting calving at 2 yr with subsequent calving at 12 mo intervals to be the most productive. Clapp (1937) reported the postpartum interval to be 69.4±2.8 d for Holstein heifers fed and milked 4x daily but 46.4±2.9 d for Holstein cows fed and milked 2x daily. Olds and Seath (1953), based on DHIA records, reported the postpartum interval to be 32.1±16.6 d. Warnick (1955) reported the postpartum interval to be 62.7 d for Angus cows and Hereford cows.

Influences on calf crop

Wiltbank et al**.,** (1961c) investigated the breeding records for Angus, Hereford, Shorthorn, Brahman, Brahman-Angus and Africander-Angus cattle. The largest losses in potential calf crop were identified to be failure to conceive or early embryonic death and calf death at or shortly postpartum. Increasing the proportion of cattle conceiving could be achieved by shortening the interval from calving to first estrus, by increasing the proportion of cattle conceiving to first service, and by keeping herds free from *Vibrio fetus*.

These studies established the metrics of the estrous cycle and postpartum interval of cattle and identified questions needing future physiological and endocrinological investigation.

Hormonal factors affecting the estrous cycle of cattle

Luteotropic

Casida et al**.,** (1943) reported that intravenous injection of sheep pituitary extract gonadotropins resulted in consistent corpus luteum (CL) formation without negative effects on follicles. Casida et al (1944) reported successful induction of CL in cattle with cystic ovaries following i.v. injection of unfractionated extracts of sheep pituitary glands. These data were the first to document a pituitary hormone (eventually identified as LH) could ovulate ovarian follicles.

Wiltbank et al**.,** (1961b) reported that daily i.m. injections in heifers of 1,000 IU hCG lengthened the estrous cycle but did not affect pregnancy rate, although accessory CL formed in 67% of pregnant, 42% of bred but not-pregnant, and 0% in estrus cycling heifers. Subsequently, numerous papers have been published on stimulation of primary and accessory CL production of progesterone on pregnancy in cattle, the data being variable relative to change in pregnancy rate due to treatment.

Armstrong and Hansel (1959) reported that oxytocin would regress the CL in cattle. Simmons and Hansel (1964) used the oxytocin-induced regression of the CL in cattle model and reported bovine somatotropin, equine LH, and ovine prolactin were not luteotropic but hCG and bovine pituitary extracts were luteotropic.

Progesterone

Ulberg et al**.,** (1951) reported the dose response of progesterone in corn oil injected subcutaneously daily in cattle on estrus inhibition and block of CL formation. Daily progesterone doses of 25 mg or greater prevented estrus and CL formation; follicular development was greatest at lower doses (3.125 mg to 12.5 mg) but minimal at 50 mg. The authors interpreted the data to be consistent with the theory that progesterone inhibits the gonadotrophic complex, mainly LH, acting on the ovary to cause ovulation.

Luteolytic

Wiltbank and Casida (1956) reported that removal of the uterus in sheep and cattle resulted in maintenance of CL. These data were the first to document the uterus produced a luteolytic substance, which, subsequently was identified to be prostaglandin $F_2\alpha$ ($PGF_2\alpha$).

Wiltbank et al**.,** (1961a) reported injection of estrogens could regress the CL of cattle and the regression could be blocked with gonadotropins. Kaltenbach et al**.,** (1964) and Niswender et al**.,** (1965) reported daily i.m. injections of estrogen, especially estradiol-17β, were luteolytic in cattle.

These studies, published during 1943 to 1965, provided the initial data that hormones might be used to "manage" the estrous cycle of cattle. Gonadotropins were reported to stimulate release of LH that ovulated ovarian follicles and to increased progesterone production by CL. Estrogens were reported to regress CL. Progesterone was reported to block estrus, allow CL to regress, and "synchronize" estrus upon withdrawal. Therefore, estrus synchronization research was directed at control of the lifespan of the CL. The CL could be regressed with estradiol-17β or allowed to regress at the end of the estrous cycle by blocking estrus with progestogens.

Managing the estrous cycle of cattle: Early studies with progesterone

Following the paper published by Ulberg et al**.,** (1951), Trimberger and Hansel (1955) injected dairy cows with progesterone in corn oil subcutaneously daily. Interval from last progesterone injection to estrus was 4.6 d, pregnancy rate was 12.5%, 50% had abnormal follicles, and 53% had abnormal estrus. However, the estrous cycle subsequent to the "synchronized estrus" for the non-pregnant cows was normal for estrus cycle length,

estrus, ovarian structures, and pregnancy rate, indicating no carry-over effect of progesterone on reproduction.

Nellor and Cole (1956) injected beef heifers once subcutaneously with 540 mg crystalline progesterone in a starch emulsion on various days of the estrous cycle. Estrus and CL formation were prevented. Estrus was detected in 89% of heifers 15-19 d after injection (fat heifers were not synchronized, most likely due to progesterone being retained and released from the fat at the site of injection). In a second study, the 540 mg progesterone emulsion was injected once subcutaneously in beef heifers followed by 2140 IU equine gonadotropin (eGonado) 15 d after progesterone; estrus was detected in 84% 1 to 4 d post-eGonado and 14% were pregnant to AI at detected estrus**;** pregnancy rate was 67% for 6 Controls. In a third study, the 540 mg progesterone emulsion was injected once subcutaneously in beef heifers followed by 750 IU eGonado 15 d after progesterone; 89% were detected in estrus during 4 h one d post-eGonado and all heifers were AI 48 h post-eGonado; unfortunately, pregnancy rates were not reported for the timed AI (TAI). This is the first report of using TAI as a component of managing estrus and breeding of cattle. An additional 20 beef heifers, 10 estrous cycling and 10 non-estrous cycling were treated with the 540 mg progesterone emulsion followed by 750 IU eGonado 15 d after progesterone; 100% of estrous cycling and 50% of non-estrous cycling heifers were detected in estrus during 3 d, suggesting that progesterone could initiate estrus in some non-estrus cycling heifers. Pregnancy rate was 20% to AI at detected estrus.

The Second Brook Lodge Workshop on problems of reproductive biology, held May 1965, facilitated discussion by research leaders in reproductive biology of domestic animals to address use of estrogen**s**, progesterone and progestogens, and gonadotropins to manage estrus and breeding in cattle, the luteotrophic and luteolytic mechanisms controlling CL lifespan, and mode of action of LH on steroidogenesis of CL (Duncan et al., 1966). Meeting participants were reinforced to pursue existing fledgling cattle estrus synchronization research for potential commercialization. Additionally, John Babcock (Duncan et al., 1966**,** pp. 47) asked if prostaglandins, a new class of compounds with vasoconstructive properties released from the uterus might be the luteolytic factor controlling regression of the CL. Babcock's question stimulated research that led to identification of PG $F_2\alpha$ being luteolytic in cattle and to $PGF_2\alpha$ products becoming available for commercial use in cattle.

These initial studies using progesterone, with and without gonadotropins, along with the data derived from studies addressing hormonal factors affecting the estrous cycle of cattle, stimulated research to find commercially viable products to manage the estrous cycle and breeding of cattle. During these years, orally active cost-effective progestogens**,** fed for about 18 days to block estrus**,** were of greatest interest for practical estrus synchronization.

Managing the estrous cycle of cattle: Development of progestogens for commercial use

Repromix®

Hansel et al**.,** (1961) investigated use of medroxyprogesterone acetate (MAP), an orally active synthetic progestogen, for cattle estrus synchronization. Hereford cattle were fed MAP for 20 d, with 50% being injected with 0.5 mg estradiol-17β at time of AI. Estrus and/or CL formation was detected in 91% during 3-5 d after last feeding of MAP, 25% conceived to that AI, and. 0.5 mg estradiol-17β at time of AI had no effect on conception rate.

Zimbelman (1963) reported the effective oral dose of MAP for cattle to be 180 mg fed daily for 18 d. In five studies with 170 beef heifers and cows, 86% of the cattle were detected in estrus during 1-6 d after last MAP feeding, 93% of those detected in estrus were detected on d 2-4, conception rate to AI at the synchronized estrus was 51% but highly variable among the five studies, and conception rate to AI at estrus subsequent to the synchronized estrus was 76% for previously fed MAP cattle and 74% for Control cattle. Gestation length and calf birth weights were not different between cattle of the MAP and Control groups. During MAP feeding, no new CL formed and old CL regressed, but follicular development was not altered. Feeding MAP to cattle postpartum prior to resumption of estrous cycles resulted in a significant reduction in the variability but not average interval from calving to first post-treatment ovulation, data suggesting a progestogen could stimulate resumption of estrous cycles in postpartum cattle.

Hansel et al**.,** (1966) investigated MAP and chlormadinone acetate (CAP) for estrus synchronization in beef cattle. The**se** orally active progestogens were fed for 18 d. Estrus detection rate for d 1-9 after last feeding was 84% for MAP (n=232) and 87% for CAP (n=236); 93% of Controls (N=229) were detected in estrus in 20 d. Pregnancy rate to AI was 49% for MAP and 31% for CAP at synchronized estrus d 1-9 and was 46% for Controls AI during 20 d. Pregnancy rate from AI at synchronized estrus plus subsequent estrus for MAP and CAP and AI for 40 d for Controls were 74%, 68% and 66% respectively.

The research by Hansel's group at Cornell and Zimbelman's group at The Upjohn Company stimulated the commercial development by The Upjohn Company of MAP which was sold as Repromix®. Repromix® was the first product for estrus synchronization of cattle. The Repromix® Story was a 45 page booklet that provided information on the reproductive cycle of cattle, synchronization of the reproductive cycle, effectiveness and safety of Repromix® as a cattle estrus synchronization product, field trial data, and good management needed for successful cattle estrus synchronization and AI (Anonymous, (1965). Cattle were fed MAP at 180 mg daily for 18 d starting at unknown days of the estrous cycle. University (n=9) and commercial (n=63) facilities participated in the research, with 4326 cattle fed MAP and 1899 cattle being untreated Controls. Estrus detection and pregnancy rates are presented in Table 1.

Table 1. Estrus detection rate (ED) was 6 d for MAP & 20 d for Control; pregnancy rate (PR) was 6 d for MAP & 26 d for Control.

Group	ED (%)	PR (%)
MAP 6 d	76	36
Control 21 d	42	45

Repromix® was sold in the US for cattle estrus synchronization during about 1965-1967, was too expensive for commercial cattle producers, and sales were ceased voluntarily by The Upjohn Company in 1967.

Syncro-Mate-B®

Wiltbank et al**.,** 1965, Wiltbank et al**.,** 1967, Wiltbank and Kasson, 1968, and Wiltbank et al**.,** 1971 investigated synchronization of estrus in beef cattle using injections of progesterone in corn oil with estradiol, feeding dihydroxyprogesterone acetophenonide (DHPA) daily for 9 d in combination with estradiol valerate injected i.m. d 2 of DHAP feeding, and poly-hydroxy polmer subcutaneous implant**s** to deliver an estrus inhibition agent (norethandrolone, Nor) in combination with EV injected i.m. at implantation to regress the CL. Based on biological success but not practical or potential economic success of the research cited above, research shifted to investigating 9 d poly-hydroxy polmer subcutaneous implant**s** containing norgestomet instead of norethandrolone and either an i.m. injection of EV or a combination injection or EV and Norgestomet (Spitzer et al**.**, 1976; Miksch et al**.,** 1978; Spitzer et al**.**, 1978). These studies provided data that led to the final product investigated as the commercial product, Syncro-Mate-B®.

Syncro-Mate-B® (SMB) is a 6 mg Norgestomet poly-hydroxy polmer implant inserted subcutaneous for 9 d plus an i.m. injection of 3 mg Norgestomet and 5 mg EV at time of implantation. Spitzer et al**.,** (1981) investigated use of SMB with AI either at detected estrus or at specific times (TAI) following implant removal. Beef heifers were assigned to Controls AI at detected estrus during 21 d (n=276), SMB and AI at synchronized estrus (n=307), SMB and TAI twice at 48 and 60 h (n=47), SMB and TAI at 45 or 48 or 50 h (n=176), and SMB TAI at 54 or 55 h (n=152). Estrus detection and pregnancy rate data are presented in Table 2.

Table 2. Estrus detection rate (ED) and pregnancy rate (PR) for Syncro-Mate-B® (SMB). Data adapted from Spitzer et al**.,** (1981).

Group	ED (d)	ED (%)	PR (%)	45 d PR (%)
Control	21	94	62	78
SMB AI E	5	93	50	78
SMB AI @ 48 + 60 h	2	---	45	85
SMB AI @ 45 or 48 or 50 h	1	---	62	83
SMB AI @ 54 or 55 h	1	---	58	82

Based on data such as presented above, SMB was approved by Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM): “For synchronization of estrus/ovulation in cycling beef cattle and non-lactating dairy heifers” (Anonymous, 1982). However, the Syncro-Mate-B® product is no longer available for use in the USA.

Melengestrol acetate or MGA

Zimbelman and Smith (1966a, b) reported the effective MGA oral daily dose for estrus inhibition and prevention of CL formation but continued follicular development was 0.25-0.50 mg. Feeding MGA for 14-18 d was equally effective to synchronize estrus after last feeding. During these studies, Zimbelman and Smith (1966b) and Bloss et al., (1966) observed heifers fed MGA appeared to increase body weight gain compared to control heifers, especially at MGA doses of 0.25-0.75 mg. Subsequent studies in commercial feedlots led to the approval of MGA: "For increased rate of weight gain, improved feed efficiency, and suppression of estrus in heifers fed in confinement for slaughter" (Anonymous, 1968). However, the estrus synchronization label claim was delayed until 1997 due to business, political and regulatory decisions.

Estrus synchronization was investigated by Zimbelman et al.(1970). Table 3 presents estrus synchronization data from 15 trials with 556 MGA fed and 829 untreated Control cattle and first service conception rates (range) from 24 trials with 1853 MGA and 537 Control cattle. The observed about 0.72 conception rate of MGA fed heifers AI at estrus 3-8 d compared to Control conception rate over 20 d has been observed consistently for the past 40 years and the apparent increased in conception rate of MGA fed heifers at the second estrus post-MGA has been a consistent observation. Pregnancy rates for 28 d of AI were 56% and 48% for MGA and Control cattle.

Table 3. Percentage of cattle in estrus days 3-8 after MGA, conception and pregnancy rates. MGA studies 1965-1969[c].

Experimental Group	Estrus detection (%)		Conception rate (%)	
	d 3-8	d 1 to 20	d 3-8	2 nd AI MGA; 1st AI Control
MGA[a,d]	70 (39-95) %	86 (50-100) %	36 (11-75)	61 (8-100)
Control[b,d]		71 (28-90) %	---	50 (24-91)

[a]MGA group-fed at 0.5 or 1.0 mg per head daily for 10-d or 14-d or 18-d.
[b]Control cattle were not fed MGA but were fed the carrier.
[c] Adapted from Zimbelman et al (1970).
[d] Numbers in parentheses represent the lowest and highest % among the 15 herds.

Since MGA was commercially available through the feedlot approval and extensive data were available on effective beef cattle estrus synchronization programs, MGA was used for beef cattle estrus synchronization from about 1970. FDA CVM approved MGA in 1997 for feeding 0.5 mg daily for up to 24 d to suppress estrus in heifers intended for breeding (Anonymous, 1997).

Managing the estrous cycle of cattle: Development of Prostaglandin $F_2\alpha$ ($PGF_2\alpha$)

$PGF_2\alpha$ was reported to be luteolytic in cattle by Lauderdale (1972), Liehr et al**.,** (1972) and Rowson et al**.,** (1972). Lauderdale (1972) reported heifers injected subcutaneously with 30 mg $PGF_2\alpha$ tromethamine salt returned to estrus in 2-4 d if injected between 6-9 d

and 13-16 d but not 2-4 d of the estrous cycle. Liehr et al**.,** (1972) reported 6 mg $PGF_2\alpha$ tromethamine salt introduced into the ipsilateral uterine horn during the responsive days of the estrous cycle resulted in return to estrus in 2.4±0.5 d. Rowson et al**.,** (1972) reported an analog of $PGF_2\alpha$, cloprostenol, was luteolytic in the bovine and cattle returned to estrus in about 3 d.

Lauderdale et al**.,** (1977) described the dose response for $PGF_2\alpha$ to synchronize estrus in cattle. The effective dose to regress the CL leading to return to estrus was identified in a 9 herd, 1215 beef cattle and dairy heifer dose response study; the dose identified was 25 mg $PGF_2\alpha$ injected i.m. Lauderdale et al**.,** (1981) described several practical use programs for $PGF_2\alpha$ to synchronize estrus in cattle. The earliest programs injected cattle twice at a 10-12 d interval in an attempt to synchronize all cattle, since cattle will not respond to a luteolytic dose of $PGF_2\alpha$ injected during 0-5 d of the estrous cycle (Figure 1). Cattle that are not estrous cycling do not respond to $PGF_2\alpha$ since they do not have a CL.

Figure 1. Concept for use of $PGF_2\alpha$ to synchronize estrus in beef cattle (11-day injection interval).

Day of estrous cycle at first $PGF_2\alpha$	Days to estrus post-first $PGF_2\alpha$	Day of estrous cycle at second $PGF_2\alpha$	Days to estrus post-second $PGF_2\alpha$
0-5	No response	11-16	2-5
6-16	2-5	6-9	2-5
17-21	0-5	6-11	2-5

The efficacy study was completed with 24 herds and 1844 cattle. Controls were AI at estrus detected during 24 d (C)**;** cattle assigned to $PGF_2\alpha$ were injected i.m. with 25 mg $PGF_2\alpha$ at an interval of 10-12 d and were AI either at estrus during 5 d after second $PGF_2\alpha$ ($PGF_2\alpha$ AI estrus) or at 80h after second $PGF_2\alpha$ ($PGF_2\alpha$ TAI). Estrus detection, conception and pregnancy rates are presented in Table 4.

Table 4. Estrus detection, conception and pregnancy rates for double injection program.

	Treatment	Estrus Detection Rate (%)		Conception Rate (%)		Pregnancy Rate (%)	
		5-day	24-day	5-day	24-day	5-day	24-day
Cows	Control	11	66	68	61	11	48
	LLAIE	47	70	61	66	34	55
	LLAI80	na	na	na	na	35	49
Heifers	Control	13	81	50	58	9	53
	LLAIE	66	84	55	54	38	56
	LLAI80	na	na	na	na	36	51

Use of $PGF_2\alpha$ with either double or single injection programs is depicted in Figure 2. Data for each program are presented in Tables 5, 6 and 7. Details of the use of each of those estrus synchronization programs can be found in Lauderdale (2007).

Figure 2**.** Double and single Lutalyse® injection estrus synchronization programs. Cattle injected 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.

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					

Table 5. Estrus detection, conception and pregnancy rates for single injection (AILAI) program.

	Treatment	Estrus Detection (%) days			Conception Rate (%) days			Pregnancy Rate (%) days		
		1-5	1-9	1-24	1-5	1-9	1-24	1-5	1-9	1-24
Cows	Control	21	38	73	59	64	63	14	26	54
	AILAI	17	54	70	64	58	59	12	39	56
Heifers	Control	24	38	78	62	56	59	15	24	55
	AILAI	25	64	77	62	53	57	16	45	56

Table 6. Estrus detection, conception and pregnancy rates for single injection (LAIE) program.

	Treatment	Estrus Detection (%) days		Conception Rate (%) days		Pregnancy Rate (%) days	
		1-5	1-24	1-5	1-24	1-5	1-24
Cows	Control	31	68	49	53	14	56
	LAIE	57	76	54	63	30	60
Heifers	Control	28	82	47	53	12	49
	LAIE	52	83	52	57	28	55

Table 7. Estrus detection and pregnancy rates for LAIE vs LLAIE.

	Treatment	Estrus Detection (%) days (% difference between LLAIE – LAIE)		Pregnancy Rate (%) days (% difference between LLAIE – LAIE)	
		1-5	1-24	1-5	1-24
Cows	Control	32	64	16	48
	LAIE	67 (9%)	76	36 (22%)	58
	LLAIE	74	67	46	59
Heifers	Control	27	68	7	37
	LAIE	40 (23%)	68	17 (23%)	40
	LLAIE	52	70	22	38

$PGF_2\alpha$ (Lutalyse® sterile solution) was approved by the FDA/CVM for synchronization of estrus of cattle for double injection at 11-14 d (1979) and single injection (1981) programs (Anonymous, 1979, 1981). Subsequently, generics and analogs of Lutalyse have been approved (ProstaMate®, Estrumate®, In Synch®, estroPlan®).

Managing the estrous cycle of cattle: Development of Gonadotropin releasing hormone (GnRH)

Publications by Mauer and Rippel (1972), Kittock et al**.,** (1972) and Zolman et al**.,** (1973) documented that GnRH released LH in cattle. Kaltenbach et al**.,** (1974) reported that both intracarotid and i.m. injections of GnRH released both LH and follicle stimulating hormone (FSH) in cattle. Additionally, these authors reported that SMB treated heifers responded with an LH surge, estrus**,** and ovulation to 250 μg GnRH injected i.m. 24 or 36 h after implant removal.

In a series of papers, Thatcher et al**.,** (1989), Twagiramungu et al**.,** (1992a**),** Twagiramungu et al**.,** (1992b), Twagiramungu et al**.,** (1992c) and Schmitt et al**.,** (1994) documented that large and/or dominant ovarian follicles in cattle either ovulate or continue to regress by atresia in response to exogenous GnRH. When GnRH is a component of estrus synchronization and breeding management protocols, timing (day of the estrous cycle relative to stage of follicle dominance) of GnRH injection is important for follicle turnover and ovulation management to be successful as measured by acceptable pregnancy rates, especially when TAI is the method of breeding.

The GnRH, Cystorelin®, was approved by the FDA CVM for treatment of ovarian follicular cysts in cattle in 1986 (Anonymous, 1986). Subsequently, generics of Cystorelin have been approved (Factryl®, Fertagyl®, OvaCyst®).

Managing the estrous cycle of cattle: Development of transrectal ultrasonography to identify ovarian follicular waves

In a series of papers, transrectal ultrasonic imaging was reported to allow non-invasive monitoring of ovarian follicle recruitment, selection, dominance and atresia, ovulation, and regression of CL (Pierson and Ginther, 1984; Savio et al**.**, 1988; Sirois and Fortune,

1988; Ginther et al**.**, 1989). The authors identified cattle exhibit two or three ovarian follicle waves each estrous cycle. Ultrasonography was essential to understanding stage of ovarian follicle development by day of the estrous cycle and follicle responsiveness to GnRH**.** This information and ultrasonography contributed significantly to understanding that time of administration of GnRH is critical, relative to the day of the estrous cycle and stage of follicle dominance at the time of GnRH injection, for follicle turnover and ovulation management in order to achieve acceptable pregnancy rates, especially when TAI is the method of breeding.

Understanding ovarian follicle recruitment, selection, dominance and atresia provided understanding as to why progestogen and $PGF_2\alpha$ based estrus synchronization protocols resulted in estrus detected over 4-6 d and the variance in TAI pregnancy rates. Progestogen and $PGF_2\alpha$ based estrus synchronization protocols control CL lifespan but do not control ovarian follicles. Control of each is essential to minimize variance in return to estrus and achieve acceptable TAI pregnancy rates.

Managing the estrous cycle of cattle: Use of progestogens and prostaglandins

Lucy et al**.,** (2001) published results of an extensive field trial investigating estrus synchronization using the an intravaginal progesterone-releasing insert containing 1.38 gm progesterone (CIDR) inserted for 7 d plus 25 mg $PGF_2\alpha$ on d 6. Cattle were AI at estrus during 31 d for Control and 3 d for CIDR. Estrus detection, conception rate and pregnancy rate data are presented in Tables 8, 9 and 10.

Table 8. Estrus synchronization rates, with numbers of cattle in parentheses, for beef cattle treated with 7-day CIDR and $PGF_2\alpha$. Estrus detected during the 3-days and 31-days post- $PGF_2\alpha$

	Treatments	Anestrous 3-d	Cyclic 3-d	Anestrous 31-d	Cyclic 31-d
Cows	Control	11 (151)	19 (134)	67 (151)	82 (134)
	CIDR+ $PGF_2\alpha$	45 (142)	72 (141)	66 (142)	91 (141)
Heifers	Control	7 (107)	17 (144)	54 (107)	87 (144)
	CIDR+ $PGF_2\alpha$	48 (105)	80 (116)	71 (105)	92 (116)

Table 9. Conception rates, with numbers of cattle in parentheses, for beef cattle treated with 7-day CIDR and $PGF_2\alpha$ and AI at estrus detected during the 3-days and 31-days post-$PGF_2\alpha$.

	Treatments	Anestrous 3-d	Cyclic 3-d	Anestrous 31-d	Cyclic 31-d
Cows	Control	38 (16)	58 (26)	58 (99)	64 (108)
	CIDR+ $PGF_2\alpha$	57 (63)	63 (101)	61 (92)	65 (127)
Heifers	Control	75 (8)	52 (25)	56 (55)	61 (124)
	CIDR+ $PGF_2\alpha$	58 (50)	61 (93)	57 (74)	61 (107)

Table 10. Pregnancy rates, with numbers of cattle in parentheses, for beef cattle treated with 7-day CIDR and $PGF_2\alpha$ and AI at estrus detected during the 3-days and 31-days post-$PGF_2\alpha$.

	Treatments	Anestrous 3-d	Cyclic 3-d	Anestrous 31-d	Cyclic 31-d
Cows	Control	4 (151)	11 (134)	42 (149)	58 (132)
	CIDR+ $PGF_2\alpha$	26 (141)	46 (140)	46 (140)	71 (139)
Heifers	Control	6 (107)	9 (144)	31 (104)	64 (143)
	CIDR+ $PGF_2\alpha$	28 (105)	49 (116)	50 (104)	69 (116)

The Eazi-Breed^{TM}CIDR^{R} (CIDR), to be used with $PGF_2\alpha$, for estrus synchronization of beef cattle and dairy heifers was approved by FDA CVM in 1997 (Anonymous, 1997).

History of the Beef Reproduction Task Force

By 2000, more precise methods of estrous cycle control and breeding management of beef cattle were identified, including use of progestogens to block estrus, management of ovarian follicular waves with GnRH, and control of the lifespan of the corpus luteum with $PGF_2\alpha$ and estrogens. The rapid development of numerous protocols to synchronize estrus and their associated acronyms created confusion in both the beef industry and the research community. The Beef Reproduction Task Force was formed by extension personnel in 2000 in response to the need for extension personnel to communicate effectively to beef producers the latest information related to reproductive technologies, which was made more difficult due to the extensiveness of estrus synchronization protocols and the confusion associated with their acronyms. The first objective of The Beef Reproduction Task Force was to embark on a coordinated effort to provide clear recommendations for beef cattle estrus synchronization protocols and to standardize protocol acronyms. The Beef Reproduction Task Force organized the first "Applied Reproductive Strategies in Beef Cattle" Symposium (ARSBC) in 2002, held in Manhattan, KS. Representatives from the veterinary, AI and pharmaceutical industries were invited to meet with members of the Beef Reproduction Task Force at the 2004 symposium in North Platte, NE. Together they formed the Beef Reproduction Leadership Team and established a common mission: "To optimize the productivity and improve the profitability of cow-calf operations by facilitating the adoption of cost-effective, applied reproductive technologies." The Beef Reproduction Leadership Team is dedicated to educate beef cattle producers on sustainable reproductive management systems to maintain U.S. leadership and competitiveness in the world beef market. Between 2004 and 2008, symposia have been held at seven high concentration cow-calf locations across the U.S. to achieve this goal.

A major outcome stemming from the Beef Reproduction Leadership Team was the development of standardized nomenclature for the various estrus synchronization protocols and establishment of a short list of recommended protocols for beef heifers and cows. These protocols and their acronyms are published in catalogs of the major AI companies. The lists of recommended protocols are updated annually based on current research. The Beef Reproduction Leadership Team along with the Beef Reproduction

Task Force work together in hosting the ARSBC symposia, planning future symposia based on program content and location, and in identifying future research needs. The Beef Reproduction Task Force and Leadership Team partnered with the Iowa Beef Center to incorporate the lists of recommended protocols into the Estrus Synchronization Planner, a spreadsheet tool that provides scheduling and cost estimates for a variety of estrous synchronization protocols.

The goals of the Beef Reproduction Leadership Team provide insight to objectives of the ARSBC symposia and a road map to educational programming stemming from the Beef Reproduction Task Force and are:

- Promote wider adoption of reproductive technologies among cow-calf producers that are cost effective and contribute to the economic viability of the beef enterprise.
- Educate cow-calf producers in management considerations that will increase the likelihood of successful AI breeding.
- Educate producers in marketing options to capture benefits that result from use of improved reproductive technologies.

Managing the estrous cycle of cattle using progestogens, prostaglandin $F_2\alpha$ and GnRH

To summarize:

Progestogens

- Block estrus
- Estrus is synchronized following removal of the progestogen block
- Conception rate consistently is reduced at synchronized estrus AI
- Two progestogen products are available

Prostaglandin $F_2\alpha$

- Regress the CL (effective on or after d 6 but not d 1-5 of the estrus cycle)
- Estrus synchronization programs have been developed
- Not effective if cattle are not estrous cycling at time of treatment
- Conception rate is normal
- Several $PGF_2\alpha$ products are available

GnRH

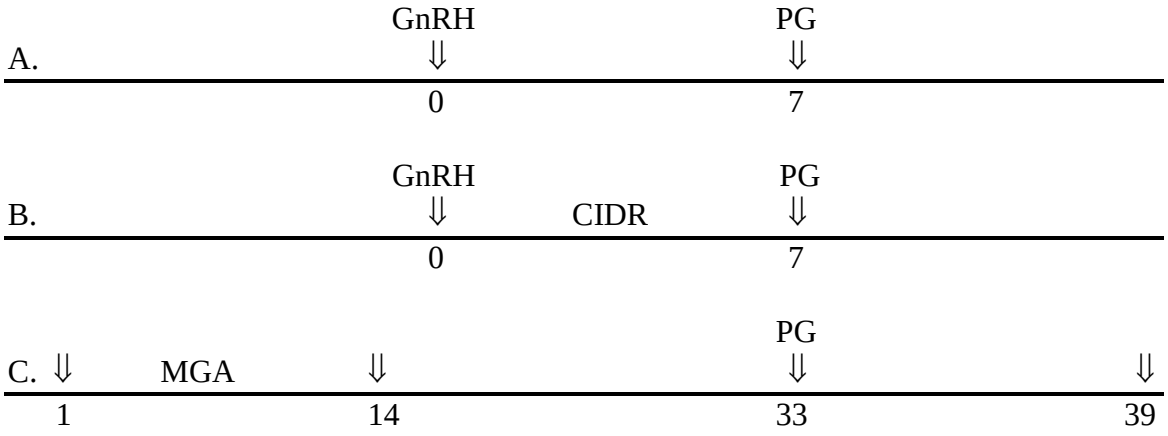
- Turn-over follicles
- Induce ovulation and CL formation
- Several GnRH products are available

Since these hormone products are available and have known biologic actions useful for breeding management, numerous estrus and breeding management protocols have been developed for beef cattle that incorporate progestogens, prostaglandin $F_2\alpha$ and GnRH. Examples of the numerous protocols are presented below. Since pregnancy rate (PR) is the mathematical product of estrus detection rate and conception rate, PR is an effective measure of success of an estrus and breeding management protocol, and will be used in the following examples as an estimate of protocol success across studies. The data presented below are from cattle studies with *Bos tarus* breeding; cattle with *Bos indicus*

breeding are not expected to respond as well (Mikeska and Williams, 1988; Lemaster et al**.**, 2001).

Studies that support recommendations for various estrus synchronization and breeding management protocols are reported in these proceedings and are found in papers by Pursley et al. (1997), Kesler (2007), Patterson et al**.,** (2007), Lamb et al**.,** (2007) and Johnson (2007). A summary of the basic estrus and breeding management protocols are presented in Figure 3. Specific differences from the basic protocols are summarized in the following sections for AI at detected estrus, AI at detected estrus plus TAI, and TAI.

Figure3. Basic estrus and breeding management protocols.



AI at detected estrus

Cow. GnRH is injected i.m. d 0 and $PGF_2\alpha$ is injected i.m. d 7 (Figure 3 A). Cows are observed for estrus and AI d 4-13. Mean (range) PR has been 46% (38-70%). Approximate drug cost is $4.85. Note that estrus observations begin before $PGF_2\alpha$ since some cows return to estrus early.

Cow. GnRH is injected i.m. d 0, $PGF_2\alpha$ is injected i.m. d 7, and a CIDR is inserted intravaginally at the time of GnRH injection and is removed at the time of $PGF_2\alpha$ injection (d 0-7; Figure 3.B). Cows are observed for estrus and AI d 7-13. Mean (range) PR has been 51% (42-85%). Approximate drug cost is $14.85. Since CIDR blocks estrus, estrus detection starts after CIDR removal.

Heifer. CIDR is inserted intravaginally d 0 and removed d7 at the time of $PGF_2\alpha$ i.m. injection (Figure 3.B.). Heifers are observed for estrus and AI d 7-13. Mean (range) PR has been 51% (41-59%). Approximate drug cost is $12.25. Note that GnRH is not used in this heifer protocol.

Heifer. MGA is fed d 1-14 and $PGF_2\alpha$ is injected i.m. d 33 (Figure 3.C.). Heifers are observed for estrus and AI d 33-39. Mean (range) PR has been 60% (40-71%). Approximate drug cost is $2.47.

AI at detected estrus plus TAI

Cow. GnRH is injected i.m. d 0 and $PGF_2\alpha$ is injected i.m. d 7 (Figure 3. A). Cows are observed for estrus and AI d 4-10 followed by GnRH and TAI d 10 for all cows not AI by d 10. Mean (range) PR has been 50% (31-89%). Approximate drug cost is $6.15.

Cow and Heifer. GnRH is injected i.m. d 0, $PGF_2\alpha$ is injected i.m. d 7, and a CIDR is inserted intravaginally at the time of GnRH injection and is removed at the time of $PGF_2\alpha$ injection (d 0-7; Figure 3.B). Cows and heifers are observed for estrus and AI d 7-10 followed by GnRH and TAI d 10 for all cows and heifers not AI by d 10. Mean (range) PR has been 59% (36-77%) for cows and 56% (31-67%) for heifers. Approximate drug cost is $16.15.

Heifer. MGA is fed d 1-14 and $PGF_2\alpha$ is injected i.m. d 33 (Figure 3.C.). Heifers are observed for estrus and AI on d 33-39 followed by GnRH and TAI on d 39 of all heifers not AI by d 39. Mean (range) PR has been 56% (48-64%). Approximate drug cost is $3.77.

TAI

Cow and heifer. GnRH is injected i.m. d 0, $PGF_2\alpha$ is injected i.m. d 7, and CIDR is inserted intravaginally d 0-7 (Figure 3.B.). Cows are TAI plus GnRH 60±6 h after $PGF_2\alpha$. Mean (range) PR has been 56% (43-74%). Heifers are TAI plus GnRH 54±2 h after $PGF_2\alpha$. Mean (range) PR has been 49% (24-68%). Approximate drug cost is $17.45.

Heifer. MGA is fed d 1-14 and $PGF_2\alpha$ is injected i.m. d 33 (Figure 3.C.). Heifers are TAI plus GnRH 72-84 h after $PGF_2\alpha$. Mean (range) PR has been 46% (36-62%). Approximate drug cost is $5.07.

Pregnancy rate from bull breeding during 21 days is on the order of 65%. Several of the estrus synchronization and breeding management protocols cited resulted in TAI pregnancy rates “not much different” from a fertile and sound bull breeding cattle for 21 days. To achieve such pregnancy rates with a single insemination on a given predetermined day is impressive.

Research is underway to identify effective re-synchronization protocol**s** for both beef and dairy cattle. To date, no effective protocol has been reported.

Conclusions

Discovery research led to applied research, which led to products for estrus synchronization and breeding management of cattle being available today. Such research contributed significantly and positively to animal agriculture and society. The estrus synchronization and breeding management cattle protocols enhance use of AI for increased genetic capability to produce meat and milk and are essential for viable commercial embryo transfer. Use of the protocols can increase efficiency for beef production, contributing both to enterprise economic viability and positive environmental impact. The cost/benefit of the protocols is positive for most beef enterprises and protocols exist to meet the breeding management “needs” of most beef enterprises. The

protocols are based on biology of the cow, the hormones used in the protocols are FDA CVM approved and have been documented to be safe to the animal and environment, to be effective, and the animal products safe for human consumption.

On the consumer side, producers who use these protocols are meeting consumer "wants" by providing high quality beef and beef products at acceptable price, are decreasing production effects on the environmental through increased efficiency of production, and the hormones in use have no negative animal welfare issues.

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