WHERE WE'VE BEEN AND WHERE WE ARE TODAY

HISTORY OF DEVELOPMENT OF PROTOCOLS FOR BREEDING MANAGEMENT OF CATTLE THROUGH SYNCHRONIZATION OF ESTRUS AND OVULATION

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Understanding the Estrous Cycle of Cattle

Chapman and Casida. 1935.

Efficient cow: first calf at an optimum age; calve at 12-13 month interval thereafter

- Requires regular: normal ova, fertilization, implantation, pregnancy, healthy calf
- Physiological studies needed to address these
- Until such physiology study data available, leads may be suggested from statistical analyses of breeding records
- Needs to conceive in 85-115 days PP

Estrous cycle duration

Group	Mode	Mean	17-27 d	28+ d	Exclude 32+ d
Copulation/infert.	21 d	37 d	56%	41%	22 d
Non-copulation	21 d	32 d	63%	31%	21 d

- Extreme variation of estrous cycle length due to ovarian abnormalities

Nellor and Cole. 1956.

- Beef heifer estrous cycle 20.1 d; range 14 to 26 d.

Understanding the Estrous Cycle of Cattle

Nalbandov and Casida. 1942 and Brewster and Cole. 1941.

- Ovulation occurred ~14 h after end of estrus
- 37% of variation in time of ovulation due to between-cow variability
- Marked similarity in means, variation and interrelationships for dairy cattle in WI and beef cattle in MI

Understanding the Estrous Cycle of Cattle

Postpartum Interval (PPI)

Guilbert and McDonald. 1934.
PPI for beef cows was 20-40 d (30%), 40-60 d (30%), 60-100 d (40%).

Chapman and Casida. 1935.
PPI was 69 d normal and 71 d abnormal cows

Chapman and Casida. 1936.
PPI was 150 d (70 d to 1st estrus, 50 d to 1st service, 30 d to conception)

Clapp. 1937.
PPI was 69.4±2.8 d for 92 Holstein heifers fed and milked 4X daily
PPI was 46.4±2.9 d for 67 Holstein cows fed and milked 2X daily

Olds and Seath. 1953.
PPI was 32.1±18.6 d (DHIA records for 210 cows with 472 calvings)

Warnick. 1955.
PPI was 62.7 d for Angus and Hereford cows

Understanding the Estrous Cycle of Cattle

Wiltbank, Warwick, Vernon and Priode. 1961.

Largest losses in potential calf crop

- Failure to conceive or early embryonic death
- Calf death at or shortly postpartum

Proportion of cows conceiving could be increased

- Shorten interval from calving to first estrus
- Increase proportion conceiving at first service
- Keep herds free from *Vibrio fetus*

Hormonal Factors Affecting the Estrous Cycle of Cattle

Pituitary Extracts and hCG Maintain CL

Casida, Meyer, McShan and Wisnicky. 1941.

- Intravenous injection resulted in consistent CL formation without negative effects on follicles

Wiltbank, Rothlisberger and Zimmerman. 1961.

Daily IM injection of 1,000 IU HCG into Hereford heifers

- Lengthened the estrous cycle of beef heifers
- PR did not differ between HCG=69% and C= 63%
- Accessory CL formed in 67% of pregnant, 42% for bred not-pregnant and 0% in estrous cycling heifers.

Hormonal Factors Affecting the Estrous Cycle of Cattle

Estrogens Regress CL

Wiltbank, Ingalls and Rowden. 1961.

- Estrogens caused luteal regression which could be blocked with gonadotrophins

Kaltenbach, Niswender, Zimmerman, and Wiltbank. 1964.

- Estrogen decreased CL weight, CL progesterone content, follicular fluid weight, and number of follicles <15mm

Hormonal Factors Affecting the Estrous Cycle of Cattle
Progesterone Blocks Estrus

Ulberg, Christian, Casida. 1951.

- 25 mg and 50 mg progesterone i.m. but not lower doses
- prevented estrus and CL if started before estrus
- Follicular development greatest at lower progesterone doses; minimal at 50 mg if started d-15

Trimberger and Hansel. 1955.

- Progesterone in corn oil injected daily SC for 13 d delayed estrus, achieved estrus synchronization in about 5 d but PR was 12.5% (65% for Controls)

Nellor and Cole. 1956.

Crystalline P4 ground in starch emulsion injected once SC on various days of estrous cycle followed by eGonado. 15 d later

- heifers detected in estrus 1-4 d post eGonado
- AI 20-24 h after estrus first detected: PR was 14% for synchronized heifers but 67% for controls
- 24 heifers TAI. No PR data
- estrous cycling and 50% non-estrous cycling in heat over 3 d; 20% CR

REPROMIX®, commercial progestogen for estrus synchronization of cattle

Zimbelman. 1965.

- Repromix (product name for medroxyprogesterone acetate,MAP).
- Cattle fed at 180 mg/animal for 18 d.
- University (9) and commercial (63) facilities used for studies

Year	Group	N	1-6 d ALF ES % (Range)	Pregnancy %	
				1st AI	1+2 AI (26 d)
1962-1963 52 studies	Repromix	2401	74 (25-100)	36	64
	Control	1068	37	37	53
1964 18 studies	Repromix	1925	78 (56-100)	36	62 (57)
	Control	831		51	65 (37)

- The 45 page booklet provided information on the reproductive cycle, synchronization of the reproductive cycle effectiveness and safety for Repromix, field trial data, and good management needed for successful cattle estrus synchronization and AI.
- Repromix was sold in the USA for cattle estrus synchronization during about 1965-1966, was too expensive for commercial cattle producers, and sales were ceased voluntarily by TUCO.

Syncro-Mate-B®, commercial progestogen for estrus synchronization of cattle

Wiltbank, Zimmerman, Ingalls and Rowden. 1965.

Wiltbank, Shumway, Parker and Zimmerman. 1967.

Wiltbank and Kasson. 1968.

Wiltbank, Sturges, Wideman, LeFever, and Faulkner. 1971.

Spitzer, Miksch and Wiltbank. 1976.

Miksch, LeFever, Mukembo, Spitzer and Wiltbank. 1978.

Spitzer, Jones, Miksch, and Wiltbank. 1978.

Syncro-Mate-B®, commercial progestogen for estrus synchronization of cattle (cont)

Spitzer, Mares and Peterson.1981.

- Syncro-Mate-B® (SMB) consists of a 6 mg implant of norgestomet for 9-d plus an injection of 3 mg norgestomet and 5 mg estradiol valerate (EV) at time of implantation.
- SMB and TAI at "54 h" resulted in PR not different from Controls or SMB AI at detected estrus and all PR were in the "acceptable range" for beef heifers in these studies

Group	N		% AI		% Pregnant	
	Trials	Heifers	5 d	21 d	5 d	21 d
Control	4	276	--	94	--	62
SMB AI @ estrus	5	307	93	98	50	61
SMB TAI 2X @ 48+60 h	1	47	100	100	45	57
SMB TAI 1X @ 45/48/50 h	3	176	100	100	62	70
SMB TAI 1X @ 54/55 h	3	152	100	100	58	67

Anonymous. 1982. Syncro-Mate-B® 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." Federal Register 47 FR 55477, December 10, 1982.

MGA, commercial progestogen for estrus synchronization of cattle

Zimbelman and Smith. 1966.

Zimbelman and Smith. 1966.

- 0.25 and 0.50 mg or greater doses inhibited estrus and CL formation but allowed follicular development
- Estrus was detected 1.5 to 4.5 d ALF
- ES CR was 50% for 0.5 mg MGA dose

Bloss, Northam, Smith and Zimbelman. 1966.

Heifers fed MGA at 0.35 to 0.53 had

- Mean increase in ADG of 6.2% over controls
- Mean increase in FE of 6.4% over controls

Subsequent extensive studies in commercial feedlots led to the approval of MGA for use as a heifer growth promotion product.

Anonymous. 1968. MGA approved by the FDA/CVM: "For increased rate of weight gain, improved feed efficiency, and suppression of estrus in heifers fed in confinement for slaughter". Federal Register Vol. 33, No.25, pp.2602, February 6, 1968.

MGA, commercial progestogen for estrus synchronization of cattle (cont)

Research, 1960 through 1969, at The Upjohn Company was directed to achieve FDA approval for estrus synchronization of beef cattle

- Label claim was delayed until 1997 due to business, political and regulatory decisions.
- MGA was used for beef cattle estrus synchronization during the 1970s through today since MGA was available commercially through the feedlot approval and extensive data were available on programs of effective use.

Zimbelman, Lauderdale, Sokolowski and Schalk. 1970.

MGA group-fed at 0.5 or 1.0 mg per head daily for 10-d or 14-d or 18-d (1965-1969)

Anonymous. MGA approved by the FDA/CVM for feeding 0.5 mg MGA daily for up to 24 d to suppress estrus in heifers intended for breeding. FDA/CVM, NADA 034-254 & 039-402 FOI, February 1997.

Group (15 Trials)	% estrus (range)	
	3-8 d ALF	1-20 d ALF
MGA, N= 556	70 (39-95)	86 (50-100)
Control, N=829		71 (28-90)

Group (24 Trials)	CR % (range)		FSCR	28-day PR
	First (3-8 d ALF)	Second (21-28 d ALF)		
MGA, N=1853	36 (11-75) %	61 (8-100) %		56%
Control, N=537			50 (24-91) %	48%

Prostaglandin $F_2\alpha$
Regresses CL and synchronizes estrus

Lauderdale. 1972.
Liehr, Marion and Olson. 1972.
Rowson, Tervit and Brand. 1972.
Louis, Hafs and Seguin. 1973.
Inskeep. 1973
Lauderdale, Seguin, Stellflug, Chenault, Thatcher, Vincent and Loyancano. 1974.

- Heifers returned to estrus in 2-4 d if injected between d 6-9 and d 13-16 but not d 2-4 of the estrous cycle
- $PGF_2\alpha$ analog luteolytic in cattle with return to estrus in about 3 d
- serum P4 decreased by 12 h and CL diameter reduced by 24 h
- intervals to estrus 72±5 h, peak LH 71±4 h, ovulation 95±5 h
- subsequent estrous cycle 21.0±3 d
- CR to AI at estrus normal

Prostaglandin $F_2\alpha$ for estrus synchronization (cont)

Lauderdale, Moody and Kasson. 1977.
Lauderdale, McAllister, Kratzer and Moody. 1981.

Anonymous. Food & Drug, Center for Veterinary Medicine for NADA 108-901, http://www.fda.gov/cvm, Freedom of Information (FOI).

Double injection of $PGF_2\alpha$ at 10-12 d interval followed by AI at either detected estrus during the 5-d post-second $PGF_2\alpha$ or at 80 h post-second $PGF_2\alpha$. Controls AI at detected estrus during 24 d.

- Dose response study (9 herds, 1215 beef cattle) resulted in selection of 25 mg $PGF_2\alpha$ as the "optimal dose".
- Efficacy study (24 herds, 1844 beef cattle). Controls were AI at detected estrus during 24 days. $PGF_2\alpha$ AI estrus were AI at detected estrus during the 5-d post-second $PGF_2\alpha$. $PGF_2\alpha$ AI @ 80 h were AI at 80 h post-second $PGF_2\alpha$.

	Group	% estrus	FSCR (%)	PR (%)
Beef Cows	Control, AI @ estrus 24 d	66	61	48
	$PGF_2\alpha$ AI estrus	47	61	34
	$PGF_2\alpha$ AI @ 80 h	---	---	35
Beef Heifers	Control, AI @ estrus 24 d	81	58	53
	$PGF_2\alpha$ AI estrus	66	55	38
	$PGF_2\alpha$ AI @ 80 h	----	---	36

Anonymous. $PGF_2\alpha$ (Lutalyse® sterile solution) approved by the FDA/CVM for double injection @ 11-14 d (1979) and single injection (1981) programs for synchronization of estrus for breeding. FDA/CVM, NADA 108-901. Subsequently, generics and analogs of Lutalyse have been approved (ProstaMate®, Estrumate®, In Synch®, estroPlan®). Dose of $PGF_2\alpha$ analogs 0.5 mg.

Gonadotropin Releasing Hormone (GnRH)
Releases LH
Treat Cystic Ovarian Follicles

Mauer and Rippel. 1972.

Kittok, Britt and Convey. 1972.

Zolman, Convey, Britt and Hafs. 1973.

Anonymous. 1986. Cystorelin approved by the FDA/CVM for treatment of ovarian follicular cysts in cattle. FDA/CVM, NADA 098-379. Subsequently, generics of Cystorelin have been approved (Factryl®, Fertagyl®, OvaCyst®).

Ultrasonic Imaging and Ovarian Follicular Waves

Pierson and Ginther. 1984.

Savio, Keenan, Boland and Roche. 1988.

Sirois and Fortune. 1988.

Ginther, Knopf, and Kastelic. 1989.

Transrectal ultrasonic imaging allowed noninvasive monitoring of ovarian follicular recruitment, selection, dominance, ovulation, regression and identified ovarian follicular waves in cattle.

Gonadotropin Releasing Hormone (GnRH)

Releases LH and Induces Ovulation and/or Follicle Turnover

Thatcher, Macmillan, Hansen and Drost. 1989.

Twagiramungu, Guilbault, Proulx and Dufour. 1992.

Twagiramungu, Guilbault, Proulx and Dufour. 1992.

Twagiramungu, Guilbault, Proulx, Villeneuve and Dufour. 1992.

Schmitt, Diaz, Drost and Thatcher. 1994.

- Large and/or dominant ovarian follicles in cattle either ovulate of continue to regress by atresia in response to exogenous GnRH.
- Timing of GnRH important is successful ovulation management protocols to achieve acceptable pregnancy rates.

Progestogens and Prostaglandin $F_2\alpha$ for estrus synchronization

Roche. 1976.

Silastic coils impregnated with P4 around a stainless steel core inserted for 12-d intravaginal plus 5 mg EB and 50 mg P4 IM at insert (PRID) resulted in estrus synchrony, CR and PR at estrus AI, and TAI similar to control 21 d CR and PR.

Smith, Pomerantz, Beal, McCann, Philbean and Hansel. 1984.

Silastic coils impregnated with P4 around a stainless steel core inserted intravaginal plus 25 mg $PGF_2\alpha$ IM (Holstein heifers) resulted in estrus synchrony, CR and PR at estrus AI, and TAI similar to control 21 d CR and PR.

Progestogens and Prostaglandin $F_2\alpha$ for estrus synchronization (cont)

Lucy, Billings, Butler, Ehnis, Fields, Kesler, Kinder, Mattos, Short, Thatcher, Wettemann, Yelich and Hafs. 2001. The CIDR (Eazi-Breed^{TM}CIDR^{R}) contains 1.38g progesterone, was inserted intravaginally for 7-d, and 25 mg $PGF_2\alpha$ injected IM on d-6.

	Group	% estrus in 3-d anestrus/cyclic	3-d CR anestrus/cyclic	3-d PR anestrus/cyclic
Cows	Control (31-d)	(67/82)	(58/64)	(42/58)
	CIDR + $PGF_2\alpha$	45/72	57/63	26/46
Heifers	Control (31-d)	(54/87)	(56/61)	(31/64)
	CIDR + $PGF_2\alpha$	48/80	58/61	28/49

Anonymous. 1997. FDA/CVM approved Eazi-Breed^{TM}CIDR^{R} (CIDR) to be used with $PGF_2\alpha$ for estrus synchronization of beef cattle and dairy heifers, FDA/CVM, NADA 141-200 FOI, July 1997.

BEEF REPRODUCTION TASK FORCE (BRTF)

Formation of BRTF

University Beef Cattle Extension personnel: Beef cattle estrus synchronization and breeding management protocols (2000):

- Were too numerous
- Had confusing acronyms
- Needed clear protocol recommendations
- Needed standardized protocol acronyms

Objectives of BRTF

- Promote: Adoption of cost effective reproduction technology
- Educate: Management to increase successful AI
- Educate: Marketing options to capture benefits of cost effective reproduction technology and successful AI

Approach to reach objectives-Applied Reproductive Strategies for Beef Cattle (ARSBC) Meetings and Proceedings in key beef cattle cow/calf states

- 2002 Manhatten, KS. Meeting and Proceedings
- 2004 North Platte, NE. Meeting and Proceedings. Formation of the Beef Reproduction Leadership Team (BRFT plus veterinarians and both AI and pharmaceutical company personnel)
- 2005-2008. Meetings and Proceedings in Reno, NV; Lexington, KY; College Station, TX; Rapid City, SD; St. Joseph, MO; Billings, MT; Fort Collins, CO

Progestogens, Prostaglandin $F_2\alpha$ and GnRH for estrus synchronization

Pregnancy Rate (PR) = Estrus detection rate (EDR) X Conception Rate (CR)

- If, EDR = 70% and CR = 55%, PR = 38%
- What is an acceptable PR?
- Zebu based cattle do not respond as well as British based cattle (Mikeska and Williams. 1988)

Comparisons

- Bull breeding for 21-d: PR ~65%
- Single $PGF_2\alpha$, 5-d ED + AI: PR 28%
- Double $PGF_2\alpha$, 5-d AI: PR 36%, 80 h TAI PR 35%

Hassle Factors

- Times through the chute
- Feeding MGA
- Vaginal insertion & removal of CIDR
- Scheduling

Out of pocket costs

Protocol Compliance Essential for best PR

Progestogens, Prostaglandin $F_2\alpha$ and GnRH for estrus synchronization

Summary: Estrus Detection (ED) and AI Programs

ARSBC 2006, 2007, herein 2008

Duration of ED & AI: 10 d
Cow Protocol
Times through the chute: 2 + AI
Hormones: GnRH & $PGF_2\alpha$
Estimated cost of hormones: $4.85
Expected PR: 46% (38%-70%)

Duration of ED & AI: 7 d
Times through the chute: 2 + AI
Hormones for cow: GnRH, $PGF_2\alpha$ & CIDR
Estimated cost of hormones: $14.85
Hormones for heifer: $PGF_2\alpha$ & CIDR
Estimated cost of hormones: $12.25
Expected PR: Cows, 51% (42%-85%); Heifers, 51% (41%-59%)

Duration of ED & AI: 7 d
Heifer Protocol
Times through the chute: 1 + AI
Hormones: MGA fed 14 d & $PGF_2\alpha$
Estimated cost of hormones: $2.50
Expected PR: 60% (40%-71%)

Protocol Compliance Essential for best PR

Progestogens, Prostaglandin $F_2\alpha$ and GnRH for estrus synchronization
Summary: Estrus Detection (ED) and AI plus TAI Programs

ARSBC 2006, 2007, herein 2008

Duration of ED & AI: 7 d
Cow Protocol
Times through the chute: 2 + ED AI cows but 3 + AI for cows not AI at ED
Hormones: GnRH & $PGF_2\alpha$ (GnRH to heifers TAI)
Estimated cost of hormones: $6.15
Expected PR: 50% (31%-89%)

Duration of ED & AI: 7 d
Cow & Heifer Protocol
Times through the chute: 2 (3 for cows/heifers not AI at ED)
Hormones: GnRH, $PGF_2\alpha$, CIDR (GnRH to cows/heifers TAI)
Estimated cost of hormones: $16.15
Expected PR: Cow 59% (36%-77%); Heifer PR 56% (31%-67%)

Duration of ED & AI: 7 d
Cow Protocol
Times through the chute: 1 (2 for cows not AI at ED)
Hormones: MGA fed 14 d & $PGF_2\alpha$ (GnRH to heifers TAI)
Estimated cost of hormones: $3.75
Expected PR: 56% (48%-64%)

Protocol Compliance Essential for best PR

Progestogens, Prostaglandin $F_2\alpha$ and GnRH for estrus synchronization
Summary: TAI Programs

ARSBC 2006, 2007, herein 2008

Duration of ED & AI: NO ED
Cow & Heifer Protocol
Times through the chute: 3
Hormones: GnRH, $PGF_2\alpha$, CIDR, & GnRH at TAI
Cows TAI @ 60±6 h after $PGF_2\alpha$
Heifers TAI @ 54±2 h after $PGF_2\alpha$
Estimated cost of hormones: $17.45
Expected PR: Cow 56% (43%-74%); Heifer PR 49% (24%-68%)

Duration of ED & AI: NO ED
Heifer Protocol
Times through the chute: 2
Hormones: MGA fed 14 d, $PGF_2\alpha$ & GnRH at TAI
Estimated cost of hormones: $5.05
Expected PR: 46% (36%-62%)

Protocol Compliance Essential for best PR

SUMMARY

Estrus and ovulation, the estrous cycle and PPI of cattle were established during the 1930s, 1940s. 1950s, 1960s.

Hormonal factors affecting the estrous cycle and, corpus luteum lifespan of Cattle were established during the 1950s, 1960s, 1970s, and 1980s.

Managing the Estrous Cycle of Cattle using gonadotropins and progesterone were developed during the 1940s, 1950s, and 1960s:

- Established the concept for estrus synchronization
- Stimulated commercial research directed at developing cost-effective progestogen estrus synchronization products

Progestogen products were approved for estrus synchronization of cattle during the 1960s, 1970s, and 1980s:

- Repromix (orally active, not cost effective, medroxyprogesterone acetate) 1965
- MGA (orally active, cost effective, melengestrol acetate) "1968"/1997
- Syncro-Mate-B (cost effective, ROI too small and lost to the market, norgestomet implant + Norgestomet & estradiol valerate injection) 1982

SUMMARY (cont)

Prostaglandin $F_2\alpha$ products were approved for estrus synchronization during the 1970s and 1980s

Gonadotropin releasing hormone (GnRH) products were approved for use in cattle to treat ovarian follicular cysts during the 1970s and 1980s.

Understanding ovarian follicular waves, describing the timing of follicular waves, and identifying the essentialness of managing follicles to achieve success with TAI were established during the 1980s, 1990s, and 2000s.

Progestogens and Prostaglandin $F_2\alpha$ for estrus synchronization protocols were established during the 1970s, 1980s, and 1990s, with CIDR + $PGF_2\alpha$ being approved in 1997.

Progestogens, Prostaglandin $F_2\alpha$ and GnRH protocols were developed during the 1970s, 1980s, 1990s, and 2000s.

- For research
- For commercial applicability for cost effective estrus synchronization protocols to meet the breeding management "needs" of most beef and dairy enterprises
- Average across herd PR:
  50% to 60% with 7 d ED + AI
  50% to 59% with 7 d AI + TAI
  46% to 56% with no ED and TAI

Protocol compliance required for consistent best PR