Published December 5, 2014

ASAS Centennial Paper: Contributions in the *Journal of Animal Science* to the development of protocols for breeding management of cattle through synchronization of estrus and ovulation

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ABSTRACT: American Society of Animal Science members, publishing in *Journal of Animal Science* (*JAS*), completed research that resulted in understanding the estrous cycle of cattle, which led to the ability to inseminate cattle on a given day with pregnancy rates similar to those achieved by 21-d breeding by a fertile and sound bull. Research published in *JAS* led to understanding estrus, ovulation, the estrous cycle, and postpartum interval for cattle (1930s through 1960s) and hormonal factors affecting corpus luteum lifespan of cattle (1950s through 1980s). Research during the 1940s to 1960s, using gonadotropins and progesterone to manage the estrous cycle of cattle, established the concepts for estrous synchronization and stimulated commercial research directed at developing cost-effective progestogen estrous synchronization products, leading to commercially available products from 1967 through today (Repromix, melengestrol acetate, Syncro-Mate-B, controlled internal drug release). Prostaglandin $F_{2\alpha}$ products were approved for estrous synchronization (1970s, 1980s), and GnRH products were approved for use in cattle to treat ovarian follicular cysts (1970s, 1980s). Research published in *JAS* was essential for understanding the biology of and potential value of both $PGF_{2\alpha}$ and GnRH and contributed both to new knowledge and scientific bases for future Food and Drug Administration Center for Veterinary Medicine approval of those products. Research during the1980s through 2000s led to understanding ovarian follicular waves and described the timing of follicular recruitment, selection, dominance, and atresia; this research was essential for the ability to effectively manage follicles to achieve success with timed AI. The knowledge gained through research published in *JAS* resulted in development of the numerous estrous synchronization and breeding management protocols that are cost-effective and meet the breeding management needs of most beef and dairy enterprises.

Key words: artificial insemination, cattle, estrous synchronization, history, timed artificial insemination

J. Anim. Sci. 2009. 87:801–812
doi:10.2527/jas.2008-1407

INTRODUCTION

Reproductive efficiency is one of the most important factors for successful cow-calf and dairy enterprises. Certainly, in the absence or reproduction, there is no cow-calf or dairy 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 estruos detection and AI over 60 to 90 d or more. Therefore, with the availability of AI, further control of estrus and breeding management was of greater interest and value, especially to the beef producer. This paper presents a review of the research, published primarily in the *Journal of Animal Science* (***JAS***), contributing to successful management of estrus and breeding of cattle. Additional publications, not addressed herein, provide reviews of the development of cattle estrus and breeding management (Wiltbank, 1970, 1974; Odde, 1990; Chenault et al., 2003; Kesler, 2003; Kojima, 2003; Lamb et al., 2003; Mapletoft et al., 2003; Patterson et al., 2003a,b; Stevenson et al., 2003).

DEVELOPMENT OF CATTLE ESTRUS AND BREEDING MANAGEMENT, 1920s TO 2000s

Early Research on the Estrous Cycle

Research to understand estrus and estrous cycles was initiated in the United States by F. F. McKenzie and his graduate students at the University of Missouri (Columbia) in the 1920s using sheep. McKenzie

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Received August 15, 2008.
Accepted October 14, 2008.

(1983) began leading an animal research laboratory at the University of Missouri in 1923. His first questions were related to estrus and ovulation, semen production, variability, and ways to control reproductive cycles of domestic animals because neither the local veterinarians nor scientific literature provided definitive responses. His first PhD student, in 1925, was L. E. Casida, who investigated estrus in the ewe, with emphasis on histology of the reproductive tract. Other students included R. Phillips (estrous cycle of the ewe, ram spermatogenesis, and semen evaluation), V. Berliner (ram fertility fluctuations), C. Terrill (ovulation in the ewe), and F. Andrews (stallion semen production and collection). McKenzie and Phillips (1931) published observations on the estrous cycle of the ewe. Before this paper, McKenzie and Phillips could find only 1 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 United States.

Understanding the Estrous Cycle and Postpartum Interval of Cattle

Chapman and Casida (1935) reported that an efficient cow produces its first calf at an optimal age and calves at 12- to 13-mo intervals thereafter. This required regular normal ova production, fertilization, implantation, pregnancy, and a healthy calf. Because data from physiological studies were not available, Chapman and Casida (1935) statistically analyzed 179 breeding records to obtain leads for subsequent studies. Mean postpartum interval was 69 d for cows calving normally and 71 d for cows calving abnormally. To calve yearly, cows needed to conceive between 85 and 115 d postpartum. The mode for estrous cycle duration was 21 d with a mean of 37 d for copulation nonfertile cycles and 32 d for noncopulation cycles. Excluding estrous cycles of 32 d or greater, the estrous cycle duration was 21 to 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 (n = 20, 210 estrous cycles) cattle mean estrous cycle duration to be 20.1 d with a range of 14 to 26 d.

Chapman and Casida (1936) examined statistically the breeding records of 1 commercial and 4 university herds and 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. Chapman and Casida (1936) cited Williams as suggesting calving at 2 yr with subsequent calving at 12-mo intervals to be the most productive.

A series of papers reported the postpartum interval for cattle. Guilbert and McDonald (1934) reported postpartum intervals for 43 beef cows to be 20 to 40 d for 30%, 40 to 60 d for 30%, and 60 to 100 d for 40%. Clapp (1937) reported the postpartum interval to be 69.4 ± 2.8 d for 92 Holstein heifers fed and milked 4 times daily but 46.4 ± 2.9 d for 67 Holstein cows fed and milked 2 times daily. Olds and Seath (1953), based on Dairy Herd Improvement Association records for 210 cows with 472 calvings, reported the postpartum interval to be 32.1 ± 16.6 d. Warnick (1955) reported the postpartum interval to be 62.7 d for 54 Angus cows and 97 Hereford cows.

Wiltbank et al. (1961c) investigated the breeding records for Angus, Hereford, and Shorthorn cattle at the Front Royal, Virginia, and Brahman, Brahman-Angus, and Africander-Angus cattle at the Iberia Livestock Station, Jeanerette, Louisiana, USDA facilities. The greatest losses in potential calf crop were identified to be failure to conceive or early embryonic death and calf death at or shortly postpartum. The proportion of cattle conceiving could be increased 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, published in *JAS* during 1934 to 1961, 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

Casida et al. (1943) reported that i.v. 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 after i.v. injection of unfractionated extracts of sheep pituitary glands. These data were the first to document that a pituitary hormone (eventually identified as LH) could ovulate ovarian follicles.

Ulberg et al. (1951) reported the dose response of progesterone (**P4**) in corn oil injected s.c. daily in cattle on estrous inhibition and block of CL formation. Daily P4 doses of 25 mg or greater prevented estrus and CL formation; follicular development was greatest at smaller doses (3.125 to 12.5 mg) but minimal at 50 mg. The authors interpreted the data to be consistent with the theory that P4 inhibits the gonadotrophic complex, mainly LH, acting on the ovary to cause ovulation.

Wiltbank and Casida (1956) reported that removal of the uterus in sheep and cattle resulted in maintenance of CL, whereas retention of about 13 to 20 cm of uterine horn resulted in CL regression, albeit sometimes at greater than the normal estrous cycle duration. These

data were the first to document that the uterus produced a luteolytic substance, which subsequently was identified to be $PGF_{2\alpha}$.

Wiltbank et al. (1961b) reported that daily (d 15 to 26 of the estrous cycle) i.m. injections of 1,000 IU of hCG lengthened the estrous cycle of 5 Hereford heifers from 17.7 to 32.4 d. Daily (d 15 to 35 post-hand mating to bulls) i.m. injections of 1,000 IU of hCG did not affect pregnancy rate (**PR**, 69% for hCG and 63% for control heifers); accessory CL formed in 67% of pregnant, 42% of bred but not pregnant, and 0% of estrous-cycling heifers. These data were interpreted that the conceptus was responsible for CL maintenance rather than vice versa. Subsequently, numerous papers have been published on stimulation of primary and accessory CL production of P4 on pregnancy in cattle, the data being variable relative to change in PR 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 to investigate various hormones at multiple doses for their luteotropic activity in cattle. Based on CL weight, P4 content, and cell type, bovine ST, equine LH, and ovine prolactin were not luteotropic, but hCG and bovine pituitary extracts were luteotropic.

Wiltbank et al. (1961a) reported that injection of estrogens could regress the CL of cattle and the regression could be blocked with gonadotropins. Kaltenbach et al. (1964) investigated the effect of daily i.m. injections of estrogen (estradiol-17α, estradiol-17β, estrone, and estradiol valerate) in estrous cycling, pregnant, hysterectomized, and control Hereford heifers (n = 99). Although estradiol-17β was more effective than the other estrogens, each estrogen resulted in decreased weight of CL, decreased CL P4 content, decreased follicular fluid weight, and decreased number of follicles less than 15 mm. Niswender et al. (1965) completed a dose response study with estradiol-17β (doses of 20 to 640 μg) in estrous-cycling beef heifers and reported, consistent with the data of Kaltenbach et al. (1964), decreased weight of CL, decreased CL P4 content and concentration, and decreased follicular fluid weight. The data did not support the hypothesis that low doses of estrogen have a differential effect on the pituitary of the heifer in that all doses of estradiol-17β tested decreased all measures of ovarian activity.

These studies, published in *JAS* 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 increase P4 production by CL. Oxytocin and estrogens were reported to regress CL. Progesterone was reported to block estrus, allow CL to regress and synchronize estrus upon withdrawal. Therefore, estrous synchronization research was directed at control of the lifespan of the CL. The CL could be regressed with oxytocin or estradiol-17β or allowed to regress at the end of the estrous cycle but block estrus with progestogens.

Managing the Estrous Cycle of Cattle: Early Studies with P4

Trimberger and Hansel (1955) injected P4 in corn oil s.c. daily to dairy cows (n = 30, each cow functioning as its control). For cows receiving P4, the interval from last P4 injection to estrus was 4.6 d and PR was 12.5%; 50% had abnormal follicles and 53% had abnormal estrus. However, the estrous cycle subsequent to the synchronized estrus for the nonpregnant cows was normal for estrous cycle length, estrus, and ovarian structures; PR was 65.2%, indicating no carry-over effect of P4 on reproduction.

Nellor and Cole (1956) ground crystalline P4 in a starch emulsion and injected beef heifers once s.c. with 540 to 1,120 mg of P4 on various days of the estrous cycle. Estrus and CL formation were prevented. Estrus was detected in 89% of heifers 15 to 19 d after 540 to 560 mg of P4 but 15 to 23 d after 700 to 1,120 mg of P4 (fat heifers receiving these doses did not express estrus d 15 to 23). In a second study, the P4 emulsion was injected once s.c. in 19 beef heifers at 540 mg followed by 2,140 IU of equine gonadotropin 15 d after P4; estrus was detected in 84% one to 4 d post-equine gonadotropin and 14% were pregnant to AI at detected estrus. Pregnancy rate was 67% for 6 controls. In a third study, the P4 emulsion was injected once s.c. in 35 beef heifers at 540 mg followed by 750 IU of equine gonadotropin 15 d after P4; 89% were detected in estrus during 4 h one day post-equine gonadotropin and all heifers were AI 48 h post-equine gonadotropin. 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 of P4 emulsion followed by 750 IU of equine gonadotropin 15 d after P4; 100% of estrous cycling and 50% of non-estrous cycling heifers were detected in estrus during 3 d, suggesting that P4 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 estrogens, P4 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 estrous synchronization research for potential commercialization. Additionally, John Babcock (Duncan et al., 1966) asked if PG, 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 $PGF_{2\alpha}$ being luteolytic in cattle and to $PGF_{2\alpha}$ products becoming available for commercial use in cattle.

These initial studies using P4, 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 d to block estrus, were of greatest interest for practical estrous 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 estrous synchronization. Hereford cattle (n = 32) were fed 968/500 mg of MAP for 20 d, with 16 being injected with 0.5 mg of estradiol-17β at time of AI. Estrus or CL formation, or both, was detected in 91% during 3 to 5 d after last feeding of MAP and 25% conceived to that AI. Injection of 0.5 mg of estradiol-17β at time of AI had no effect on conception rate.

Zimbelman (1963), based on dose response studies, identified the effective oral dose of MAP for cattle to be 180 mg fed daily for 18 d, with feeding beginning at random stages of the estrous cycle. In 5 studies with 170 beef heifers and cows, 86% of the cattle were detected in estrus during 1 to 6 d after last MAP feeding, 93% of those detected in estrus were detected on d 2 to 4, conception rate to AI at the synchronized estrus was 51% but highly variable among the 5 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 BW were not different between cattle of the MAP and control groups. During MAP feeding, no new CL were formed, old CL regressed, but follicular development was not altered. These data were interpreted that MAP inhibited the ovulatory surge of LH. Feeding MAP to cattle postpartum before resumption of estrous cycles resulted in a significant reduction in the variability but not average interval from calving to first posttreatment 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 estrous synchronization in beef cattle. These orally active progestogens were fed at 240 mg of MAP daily and 10 mg of CAP daily, each for 18 d. Pooling the data for 1963 and 1964, estrous detection rate for d 1 to 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 to 9 and was 46% for control 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 was 74, 68, and 66%, respectively.

The research by Hansel's group at Cornell (Ithaca, NY) and Zimbelman's group at The Upjohn Company (Kalamazoo, MI) stimulated the commercial development by The Upjohn Company of MAP, which was sold as Repromix. Repromix was the first product for estrous 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 estrous synchronization product, field trial data, and good management needed for successful cattle estrous synchronization and AI (Upjohn, 1965). Cattle were fed MAP at 180 mg daily for 18 d beginning at unknown days of the estrous cycle. University (n = 9) and commercial (n = 63) facilities participated in the research, with 4,326 cattle fed MAP and 1,899 cattle being untreated controls. Pooling the data for 1962 to 1963 (52 studies) with 1964 (18 studies), 76% of the MAP cattle were detected in estrus d 1 to 6 after last feeding of MAP with a PR of 36%. Control cattle had a PR of 42% for AI at estrus detected during 20 d. Pregnancy rate for AI at detected estrus during 26 d was 60% for MAP and 45% for controls.

Repromix was sold in the United States for cattle estrous synchronization during about 1965 to 1967, but 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) investigated progestogens alone and in combination with estrogens for cattle estrous synchronization. In the initial study, beef heifers (n = 324 in 2 trials) were injected s.c. with various doses of P4 in corn oil and estradiol for various durations staring on various days of the estrous cycle. Estrous synchrony during 4 d was 68 to 100% (control 100% over 21 d) and conception rates were 12 to 53% (control 50% over 21 d).

Wiltbank et al. (1967) fed dihydroxyprogesterone acetophenonide (**DHPA**) to beef heifers either alone or in combination with estradiol valerate (**EV**) to synchronize estrus. Beef heifers were assigned either to be fed 500 mg of DHPA daily for 20 d (n = 50) beginning at unknown days of the estrous cycle or untreated controls (n = 54). Estrous detection over 48 h was 96% and conception rate was 54% for DHPA heifers. Artificial insemination at detected synchronized estrus and conception rate was 26% for controls. Ova were collected from a subset of the heifers at 48 h after AI and fertilization rate was 54% for DHPA and 86% for controls. In a second study, 100 beef heifers were assigned to a treatment-control switchback design. Treated heifers

were fed 400 mg of DHPA daily for 9 d and injected i.m. with 5 mg of EV on d 2 of DHPA feeding. Estrous detection was 84% in 96 h; conception rates were 32% for DHPA-EV and 50% for control heifers. Wiltbank and Kasson (1968) further investigated the combination of DHPA fed for 9 d and EV injected i.m. on d 2 of DHPA feeding. Beef heifers were fed 400 mg of DHPA for 9 d and were injected with 5 mg of EV on d 2 of DHPA feeding (n = 66) or served as untreated controls (n = 33).The DHPA feeding was started without regard to day of the estrous cycle. Percentage of treated heifers detected in estrus were 82% in 48 h, 86% in 72 h, and 95% in 96 h. Conception rates were 54% for estrous-synchronized heifers and 52% for control AI during 21 d.

Based on data from the above-cited studies, Wiltbank et al. (1971) investigated use of poly-hydroxy polmer subcutaneous implants to deliver an estrous inhibition agent (norethandrolone, **Nor**) in combination with EV injected i.m. at implantation to regress the CL. Beef heifers were implanted with the Nor implant for 9 d and injected with 5 mg of EV at implantation (n = 42) or assigned as untreated controls (n = 62). Percentage in estrus in 96 h was 93% for Nor. Conception rates were 56% for Nor treated and AI at synchronized estrus and 67% for control AI at estrus during 22 d. Intramuscular injection of 2 mg of estradiol-17β 24 h after implant removal resulted in 98 to 100% estrous detection in a 48-h interval and 100% ovulation in a 36-h interval.

Three studies were published on synchronization of estrus in beef cattle using 9-d poly-hydroxy polmer subcutaneous implants containing norgestomet instead of Nor and either an i.m. injection of EV or a combination injection or EV and norgestomet (Spitzer et al., 1976, 1978; Miksch et al., 1978). These studies provided data that led to the final product investigated as the commercial product, Syncro-Mate-B (**SMB**).

Syncro-Mate-B is a 6-mg norgestomet poly-hydroxy polmer implant inserted subcutaneous for 9 d plus an i.m. injection of 3 mg of norgestomet and 5 mg of EV at time of implantation. Spitzer et al. (1981) investigated use of SMB with AI either at detected estrus or at specific times (TAI) after implant removal. Beef heifers were assigned to control 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, 48, or 50 h (n = 176); and SMB TAI at 54 or 55 h (n = 152). Percentage pregnant was 62% in 21 d for controls; 50% for SMB AI at estrus in 5 d; 45% for SMB TAI at 48 and 60 h; 62% for SMB TAI 45, 48, or 50 h; and 58% for SMB TAI 54 or 55 h. Pregnancy rate after 21 d of AI was 62, 61, 57, 70, and 67% for the 5 groups, respectively.

Based on data such as presented above, SMB was approved by the Food and Drug Administration Center for Veterinary Medicine (**FDA CVM**): "For synchronization of estrus/ovulation in cycling beef cattle and non-lactating dairy heifers" (Food and Drug Administration, 1982).

At least 196 papers-abstracts have been published on norgestomet (SMB) in *JAS*, not including abstracts published in separate supplements. These publications addressed development of numerous use programs with both British-based and Brahman-based cattle and mode of action.

Melengestrol Acetate

Zimbelman and Smith (1966a,b) reported a series of studies designed to investigate the effective oral dose of melengestrol acetate (**MGA**) to inhibit estrus and effect changes in ovarian follicles and CL in cattle. The effective oral daily dose for estrous inhibition and prevention of CL formation but continued follicular development was determined to be 0.25 to 0.50 mg. Feeding MGA for 14 to 18 d was equally effective to synchronize estrus after last feeding. During these studies, Bloss et al. (1966) and Zimbelman and Smith (1966b) observed that heifers fed MGA appeared to increase BW gain compared with control heifers, especially at MGA doses of 0.25 to 0.75 mg. As a result of the observation of increased BW gain in heifers fed MGA, Bloss et al. (1966) investigated MGA as a growth promotant for beef heifers. Beef heifers (n = 255) were fed MGA in a typical feedlot ration at various doses between 0.35 and 0.53 mg and physiological conditions (pubertal, immature, ovariectomized) daily for 106 to 119 d. Heifers ovariectomized or immature did not increase BW gain or feed efficiency greater than or less than controls. However, pubertal heifers fed MGA had a mean increase in ADG of 6.2% and feed efficiency of 6.4% over controls. 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" (Food and Drug Administration, 1968).

Research at The Upjohn Company during 1960 through 1969 was directed to achieve FDA CVM approval of MGA for estrous synchronization of beef cattle. However, the estrous synchronization label claim was delayed until 1997 due to business, political, and regulatory decisions. Because MGA was commercially available through the feedlot approval and extensive data were available on effective beef cattle estrous synchronization programs, MGA was used for beef cattle estrous synchronization from about 1970. Estrous synchronization was investigated (Zimbelman et al., 1970) in 15 trials with 556 MGA-fed and 829 untreated control cattle. Estrus was detected in 70% MGA heifers 3 to 8 d after last feeding and 86% were detected during 20 d; 71% of controls were detected in estrus during 20 d. The range in estrous detection among the 15 trials was 39 to 95% for MGA 3 to 8 d and 28 to 90% for controls 20 d. First service conception rates (range) were based on 24 trials with 1,853 MGA and 537 control cattle and were 36% (11 to 75%) for MGA 3 to 8 d and 50% (24 to 91%) for controls 20 d. Second service conception rate for MGA heifers was 61% (8 to 100%).

The observed 0.72 conception rate of MGA-fed heifers AI at estrus 3 to 8 d compared with control conception rate over 20 d has been observed consistently for the past 40 yr and the apparent increase in conception rate of MGA-fed heifers at the second estrus post-MGA has been a consistent observation.

Although never pursued to FDA CVM approval, MGA was investigated for use in managing estrus in dairy cows. Studies published by Johnson et al. (1964), Britt and Ulberg (1970), Britt et al. (1972), and Ulberg et al. (1974) led to the first computerized system for evaluation of dairy cow reproduction and MGA was used to systematically manage estrus and breeding throughout the year. Sequential 10 d of MGA then 11 d of no MGA with estrous detection and AI during no MGA allowed, with the computerized system for evaluation of dairy cow reproduction, for an organization to furnish services and consultation for maximum reproductive efficiency. For example, beginning the MGA program either early (n = 134) or late (n = 159) postpartum compared with conventional dairy herd estrous and breeding management (n = 102), percentage dairy cows culled did not differ among the 3 groups (18, 15, and 18%, respectively), but the percentage of dairy cows pregnant was greatest in the MGA early group (71, 30, and 22%, respectively), thus allowing culling for factors other than reproduction (Ulberg et al., 1974).

Melengestrol acetate was approved in 1997 by FDA CVM for feeding 0.5 mg daily for up to 24 d to suppress estrus in heifers intended for breeding (Food and Drug Administration, 1997).

At least 220 papers and abstracts have been published on MGA in *JAS*, not including abstracts published in separate supplements. These publications addressed mode of action and development of use programs for MGA.

Managing the Estrous Cycle of Cattle: Development of $PGF_{2\alpha}$

Publications by Kurzroc and Lieb (1930), Goldblatt (1933), and von Euler (1935) identified 1) that the human uterus would either contract or relax upon instillation of fresh semen, 2) the strong smooth muscle-stimulating activity of seminal fluid from human, monkey, sheep and goat, and extracts of vesicular glands of male sheep, and 3) lipid extracts of sheep vesicular glands, the fraction containing lipid-soluble acids, elicited strong smooth muscle stimulation. The active factor was named PG. Research with PG was quiet until the 1960s when scientists at the Karolinska Institute (Stockholm, Sweden) and The Upjohn Company collaborated to produce sufficient quantities for research. The question by J. Babcock during the Brook Lodge meeting initiated research on PG for their luteolytic action (Duncan et al., 1966).

Prostaglandin $F_{2\alpha}$ was reported to be luteolytic in cattle by Lauderdale (1972), Liehr et al. (1972), and Rowson et al. (1972). Lauderdale (1972) reported heifers injected s.c. with 30 mg of $PGF_{2\alpha}$ tromethamine salt returned to estrus in 2 to 4 d if injected between 6 and 9 d and 13 to 16 d but not 2 to 4 d of the estrous cycle. Liehr et al. (1972) reported 6 mg of $PGF_{2\alpha}$ 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.

Louis et al. (1973) reported, following intrauterine delivery of 5 mg of $PGF_{2\alpha}$ tromethamine salt into the ipsilateral horn, that serum P4 decreased by 12 h, CL diameter decreased by 24 h, and the intervals to estrus, peak LH, and ovulation were 72 ± 5, 71 ± 4, and 95 ± 5 h, respectively. Subsequent estrous cycle was 21 ± 3 d.

Inskeep (1973) reported that introducing 1.5 or 2.0 mg of $PGF_{2\alpha}$ into the ipsilateral uterine horn of 34 beef cows once between 6 and 15 d of the estrous cycle resulted in 74% in estrus 60 to 80 h post-$PGF_{2\alpha}$ and 52% conceived to AI at detected estrus. If 400 μg of estradiol-17β was injected i.m. 48 h post-$PGF_{2\alpha}$, 69% were in estrus 60 to 80 h post-$PGF_{2\alpha}$ with a 69% conception rate to AI at detected estrus.

Lauderdale et al. (1974) investigated fertility of cattle at 4 locations in 3 states after i.m. injection of 30 mg of $PGF_{2\alpha}$ tromethamine salt. Cattle were palpated and those with a CL were assigned randomly in replicates to control, AI at detected estrus during 18 to 25 d (n = 153), $PGF_{2\alpha}$ with AI at estrus detected within 7 d after injection (n = 119), and $PGF_{2\alpha}$ with AI at 72 and 90 h after injection (n = 120). Estrous detection was 80, 58, and 72% and PR was 42, 30, and 40% for the 3 groups, respectively.

Peters et al. (1977) synchronized estrus in beef cattle with 25 mg of $PGF_{2\alpha}$ injected i.m. either once or twice at a 12-d interval and either with or without 400 μg of estradiol benzoate (**EB**) injected i.m. 48 h after $PGF_{2\alpha}$. Cattle were AI at detected estrus. The percentage of cattle detected in estrus 56 to 86 h after $PGF_{2\alpha}$ was 72% for no EB (n = 333) and 90% for EB (n = 272); the calving rate to that AI was 34 and 42% for the 2 groups.

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, 1,215-beef cattle and dairy heifer dose response study; the dose identified was 25 mg of $PGF_{2\alpha}$ 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- to 12-d interval in an attempt to synchronize all cattle because cattle will not respond to a luteolytic dose of $PGF_{2\alpha}$ injected during 0 to 5 d of the estrous cycle. The efficacy study was completed with 24 herds and 1,844 cattle. Controls were AI at estrus detected during 24 d (control); cattle assigned to $PGF_{2\alpha}$ were injected i.m. with 25 mg of $PGF_{2\alpha}$ at

an interval of 10 to 12 d and were AI either at estrus during 5 d after second $PGF_{2\alpha}$ ($PGF_{2\alpha}$ AI estrus) or at 80 h after second $PGF_{2\alpha}$ ($PGF_{2\alpha}$ TAI). Percentage of cattle in estrus was 66% for controls and 47% for $PGF_{2\alpha}$ AI estrus for cows and 81% for controls and 66% for $PGF_{2\alpha}$ AI estrus for heifers. Conception rate was 61% for controls and 61% for $PGF_{2\alpha}$ AI estrus for cows and 58% for controls and 55% for $PGF_{2\alpha}$ AI estrus for heifers. Pregnancy rate was 48, 34, and 35% for the respective groups for cows and 53, 38, and 36% for the respective groups for heifers.

Prostaglandin $F_{2\alpha}$ (Lutalyse sterile solution) was approved by the FDA CVM for synchronization of estrus of cattle for double injection at 11 to 14 d (1979) and single injection (1981) programs (Food and Drug Administration, 1979, 1981). Subsequently, generics and analogs of Lutalyse (Pfizer, New York, NY) have been approved (ProstaMate, Teva, St. Joseph, MO; Estrumate, Intervet/Schering-Plough, Millsboro, DE; In Synch, Pro Labs, St. Joseph, MO; and estroPlan, Pfizer).

At least 2,252 papers and abstracts have been published on $PGF_{2\alpha}$ in *JAS,* not including abstracts published in separate supplements. These publications addressed mode of action and development of numerous estrus-ovulation synchronization use programs.

Managing the Estrous Cycle of Cattle: Development of GnRH

Publications by Kittock et al. (1972), Mauer and Rippel (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 FSH in cattle. Additionally, these authors reported that SMB-treated heifers responded with an LH surge, estrus, and ovulation to 250 μg of GnRH injected i.m. 24 or 36 h after implant removal.

In a series of papers, Thatcher et al. (1989), Twagiramungu et al. (1992a,b,c), and Schmitt et al. (1994) documented that large or dominant, or both, ovarian follicles in cattle either ovulate or continue to regress by atresia in response to exogenous GnRH. When GnRH is a component of estrous 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 (Food and Drug Administration, 1986). Subsequently, generics of Cystorelin (Merial, Athens, GA) have been approved (Factryl, Fort Dodge, Fort Dodge, IA; Fertagyl, Intervet/Schering-Plough; and OvaCyst, Teva).

At least 687 papers and abstracts have been published on GnRH in *JAS*, not including abstracts published in separate supplements. These publications addressed mode of action and development of numerous estrous and ovulation synchronization use programs.

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 noninvasive 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 that cattle exhibit 2 or 3 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 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 estrous synchronization protocols resulted in estrus detected over 4 to 6 d and the variance in TAI pregnancy rates. Progestogen and $PGF_{2\alpha}$-based estrous 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.

At least 828 papers and abstracts have been published on ultrasonography in *JAS*, not including abstracts published in separate supplements.

Managing the Estrous Cycle of Cattle: Use of Progestogens and PG

Roche (1976) investigated estrous synchronization and breeding in dairy and beef cattle using silastic coils impregnated with P4 wrapped around a stainless steel core and inserted into the vagina (P4-releasing intravaginal device, **PRID**) for 12 d plus an i.m. injection of 5 mg of EB and 50 mg of P4 in corn oil at time of PRID insertion. Control cattle were AI at estrus and PRID cattle were AI at estrus detected during 2 to 6 d after PRID removal. Estrous synchrony was 86% for dairy cows (n = 159) and 81% for dairy heifers (n = 253). Calving rate to first AI for controls and synchronized estrous AI for PRID was 49 and 45% for dairy cows and was 45 and 53% for dairy heifers. In a second study, beef cows were assigned to control with AI at estrus (n

= 14), PRID with AI at synchronized detected estrus (n = 16), PRID with AI at 48 h after PRID removal (n = 14), and PRID plus 100 μg of GnRH at 30 h with AI at 48 h after PRID removal (n = 23). Pregnancy rate was 71, 69, 21, and 52%, respectively. In a third study, beef heifers were assigned to control with AI at estrus (n = 24), PRID with AI at 56 h after PRID removal (n = 26), PRID with AI at 74 h after PRID removal (n = 25), and PRID with AI at 56 and 74 h after PRID removal (n = 25). Pregnancy rate was 58, 65, 46, and 68%, respectively.

Smith et al. (1984) investigated estrous synchronization and breeding of Holstein heifers using the PRID plus $PGF_{2\alpha}$. In this study, unlike that reported by Roche (1976), PRID were in place for either 6 or 7 d and 25 mg of $PGF_{2\alpha}$ was injected i.m. on d 6. Cattle were assigned to control with AI at estrus during 25 d (n = 79), PRID in place for 6 d with AI 1 to 5 d after PRID removal (n = 80), and PRID in place for 7 d with AI 1 to 5 d after PRID removal (n = 83). Estrous detection rate was 97, 99, and 99%, respectively. Pregnancy rate was 72, 82, and 73%, respectively. In a second study, estrous synchronization was investigated using the double injection of 25 mg of $PGF_{2\alpha}$ at an 11-d interval. Cattle were assigned to control AI at estrus during 25 d (n = 91), 25 mg of $PGF_{2\alpha}$ injected twice at 11 d and TAI at 80 h (n = 90), and PRID in place for 7 d and TAI at 84 h (n = 93). Estrous detection rate was 93, 84, and 94%, respectively. Pregnancy rate was 73, 52, and 66%, respectively. These data documented effective estrous synchronization with either PRID plus $PGF_{2\alpha}$ or $PGF_{2\alpha}$ alone but enhanced PR with PRID plus $PGF_{2\alpha}$ compared with $PGF_{2\alpha}$ alone.

Moody et al. (1978) synchronized estrus by feeding 0.5 mg of MGA daily to beef heifers for 6 d (MGA6, n = 32) or 7 d (MGA7, n = 31) and injected 25 mg of $PGF_{2\alpha}$ on d 6 to cattle of each group; controls (n = 33) and MGA-fed cattle were AI at detected estrus. First service conception rate was 58% (controls), 44% (MGA6), and 61% (MGA7). Pregnancy rate was 18, 25, and 42% for the respective groups for 5 d of AI and was 61, 47, and 65% for the respective groups for 19 d of AI.

Lucy et al. (2001) published results of an extensive field trial investigating estrous synchronization using the an intravaginal P4-releasing insert containing 1.38 g of P4 (controlled internal drug-releasing device, **CIDR**) inserted for 7 d plus 25 mg of $PGF_{2\alpha}$ on d 6. Cattle were AI at estrus during 31 d for control and 3 d for CIDR. For control and CIDR cows estrous cycling at the beginning of the study, estrous detection rate was 82 and 72%, conception rate was 64 and 63%, and PR was 58 and 46%. For control and CIDR cows not estrous cycling at the beginning of the study, estrous detection rate was 67 and 45%, conception rate was 58 and 57%, and PR was 42 and 26%. For control and CIDR heifers estrous cycling at the beginning of the study, estrous detection rate was 87 and 80%, conception rate was 61 and 61%, and PR was 64 and 49%. For control and CIDR heifers not estrous cycling at the beginning of the study, estrous detection rate was 54 and 48%, conception rate was 56 and 58%, and PR was 31 and 28%.

The Eazi-Breed CIDR (CIDR, Pfizer), to be used with $PGF_{2\alpha}$, for estrous synchronization of beef cattle and dairy heifers was approved by FDA CVM in 1997 (Food and Drug Administration, 1997).

At least 76 papers and abstracts have been published on CIDR and 33 on PRID in *JAS*, not including abstracts published in separate supplements. These publications addressed development of numerous estrous and ovulation synchronization use programs.

Managing the Estrous Cycle of Cattle Using Progestogens, $PGF_{2\alpha}$, and GnRH

Estrus can be blocked with progestogens and estrus is synchronized after removal of the P4 block; fertility generally was decreased when cattle were AI at the synchronized estrus. Commercial progestogen products are available. Prostaglandin $F_{2\alpha}$ will regress the CL of cattle, estrous synchronization programs have been developed, $PGF_{2\alpha}$ is not effective if cattle are not estrous cycling at time of treatment, and several $PGF_{2\alpha}$ products are available. Gonadotropin-releasing hormone can be used in estrous synchronization and breeding management protocols to turn over follicles and induce ovulation and CL formation. Numerous estrous and breeding management protocols are available for beef and dairy cattle that incorporate progestogens, $PGF_{2\alpha}$, and GnRH. Examples of the numerous protocols are presented below. Because PR is the mathematical product of estrous detection rate and conception rate, PR is an effective measure of success of an estrous 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).

The data for beef cattle estrous synchronization and breeding management protocols presented below were adapted from papers, many published in *JAS*, too numerous to cite herein. Estrous synchronization and breeding management protocols are found in papers by Kesler (2007), Lamb et al. (2007), and Patterson et al. (2007); specific protocols and summary data are found in the paper by Johnson (2007). The basic estrous and breeding management protocols are presented in Figure 1. Specific differences from the basic protocols are described in the following sections for AI at detected estrus, AI at detected estrus plus TAI, and TAI. The days identified in Figure 1 and in the text describing the estrous synchronization and breeding management protocols are protocol treatment days. The estrous synchronization and breeding management protocols are initiated on a day of the week identified to best meet the goals of the beef or dairy enterprise, independent

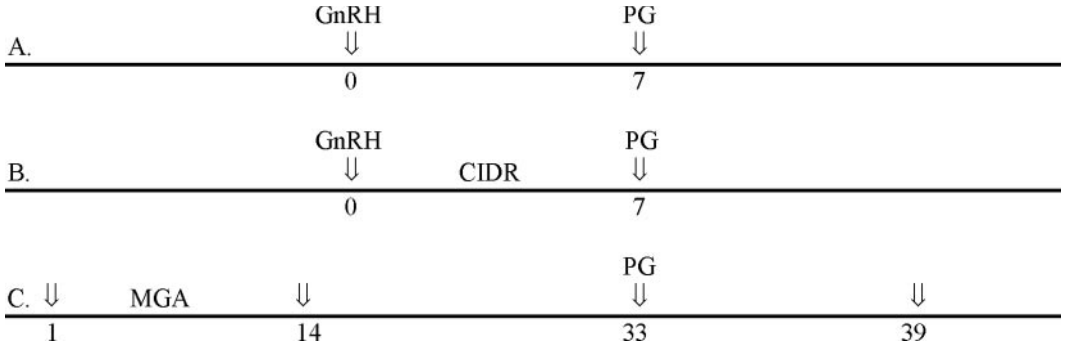

Figure 1. Basic estrous and breeding management protocols. MGA = melengestrol acetate; CIDR = controlled internal drug-releasing device; PG = prostaglandin $F_{2\alpha}$. Arrows with either GnRH or PG above each arrow identify that hormone is to be administered to the animal on that day. Arrows, without any hormone identified above, identify the hormone (MGA or CIDR) to be administered to the animal during the days between arrows. Numbers (0, 1, 7, 14, 33, 39) below each line designate the day of the protocol.

of the day of the estrous cycle. The historically accepted and currently used designations for the first day of treatment for a protocol are used herein. Protocols with MGA identify the first day of treatment as d 1 (Figure 1C). Protocols without MGA identify the first day of treatment as d 0 (Figure 1A and B).

AI at Detected Estrus–Beef

Cow. Gonadotropin-releasing hormone is injected i.m. on d 0 and $PGF_{2\alpha}$ is injected i.m. on d 7 (Figure 1A). Cows are observed for estrus and AI on d 6 to 13. Mean (range) PR has been 46% (38 to 70%). Approximate drug cost is $4.85. Note that estrous observations begin before $PGF_{2\alpha}$ because some cows return to estrus early.

Cow. Gonadotropin-releasing hormone is injected i.m. on d 0, $PGF_{2\alpha}$ is injected i.m. on 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 to 7; Figure 1B). Cows are observed for estrus and AI on d 7 to 13. Mean (range) PR has been 51% (42 to 85%). Approximate drug cost is $14.85. Because CIDR blocks estrus, estrous detection begins after CIDR removal.

Heifer. A CIDR is inserted intravaginally on d 0 and removed on d 7 at the time of $PGF_{2\alpha}$ i.m. injection (Figure 1B). Heifers are observed for estrus and AI on d 7 to 13. Mean (range) PR has been 51% (41 to 59%). Approximate drug cost is $12.25. Note that GnRH is not used in this heifer protocol.

Heifer. Melengestrol acetate is fed on d 1 to 14 and $PGF_{2\alpha}$ is injected i.m. on d 33 (Figure 1C). Heifers are observed for estrus and AI on d 33 to 39. Mean (range) PR has been 60% (40 to 71%). Approximate drug cost is $2.47.

AI at Detected Estrus Plus TAI–Beef

Cow. Gonadotropin-releasing hormone is injected i.m. on d 0 and $PGF_{2\alpha}$ is injected i.m. on d 7 (Figure 1A). Cows are observed for estrus and AI on d 6 to 10 followed by GnRH and TAI on d 10 for all cows not AI by d 10. Mean (range) PR has been 50% (31 to 89%). Approximate drug cost is $6.15.

Cow and Heifer. Gonadotropin-releasing hormone is injected i.m. on d 0, $PGF_{2\alpha}$ is injected i.m. on 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 to 7; Figure 1B). Cows and heifers are observed for estrus and AI on d 7 to 10 followed by GnRH and TAI on d 10 for all cows and heifers not AI by d 10. Mean (range) PR has been 59% (36 to 77%) for cows and 56% (31 to 67%) for heifers. Approximate drug cost is $16.15.

Heifer. Melengestrol acetate is fed on d 1 to 14 and $PGF_{2\alpha}$ is injected i.m. on d 33 (Figure 1C). Heifers are observed for estrus and AI on d 33 to 39 followed by GnRH and TAI on d 39 of all heifers not AI by d 39. Mean (range) PR has been 56% (48 to 64%). Approximate drug cost is $3.77.

TAI–Beef

Cow and Heifer. Gonadotropin-releasing hormone is injected i.m. on d 0, $PGF_{2\alpha}$ is injected i.m. on d 7, and a CIDR is inserted intravaginally on d 0 to 7 (Figure 1B). Cows are TAI plus GnRH 60 to 66 h after $PGF_{2\alpha}$. Mean (range) PR has been 56% (43 to 74%). Heifers are TAI plus GnRH 54 ± 2 h after $PGF_{2\alpha}$. Mean (range) PR has been 49% (24 to 68%). Approximate drug cost is $17.45.

Heifer. Melengestrol acetate is fed on d 1 to 14 and $PGF_{2\alpha}$ is injected i.m. on d 33 (Figure 1C). Heifers are TAI plus GnRH 72 ± 2 h after $PGF_{2\alpha}$. Mean (range) PR has been 46% (36 to 62%). Approximate drug cost is $5.07.

TAI–Dairy Cow

Cows are injected i.m. with GnRH on d 0 and $PGF_{2\alpha}$ on d 7 (Figure 1A). Pursley et al. (1997) reported cows injected i.m. with GnRH 48 h after $PGF_{2\alpha}$ and TAI 20 to 24 h after GnRH had PR of 37%. Sterry et al. (2005) reported cows injected i.m. with GnRH plus TAI at 48

h after $PGF_{2\alpha}$ had PR of 54%. Approximate drug cost is $7.45.

Cows are injected i.m. with $PGF_{2\alpha}$ twice at a 14-d interval; 12 d after the second $PGF_{2\alpha}$, the GnRH-$PGF_{2\alpha}$ protocol of Figure 1A is implemented. Gonadotropin-releasing hormone is injected i.m. 48 h after $PGF_{2\alpha}$ followed with TAI 16 h after GnRH. Mean PR has been 36% (28 to 41%; adapted from Moreira et al., 2000, 2001; Pancarci et al., 2002; Santos et al., 2004). Approximate drug cost is $11.95.

TAI–Dairy Heifer

Heifers are injected with GnRH on d 0 and $PGF_{2\alpha}$ on d 7 (Figure 1A). Gonadotropin-releasing hormone is injected i.m. either 24 or 48 h after $PGF_{2\alpha}$, with TAI 15 h after GnRH. Pregnancy rate was 26% for the 24-h interval and 46% for the 48-h interval, PR for estrous detection and AI was 48%, and 25% of heifers assigned to 48 h of TAI were detected in estrus and AI and not TAI (Schmitt et al., 1996). Approximate drug cost is $7.45.

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

Research is underway to identify effective resynchronization protocols for both beef and dairy cattle. To date, no effective protocol has been reported.

Conclusions

At least 3,513 papers and abstracts have been published on cattle estrous synchronization in *JAS,* which does not include abstracts published in separate journal supplements. Before about 1980, *JAS* was the journal of choice to publish research in this field. However, beginning in the 1980s, basic research began to be published in journals specializing in reproductive research, such as *Journal of Reproduction*, *Biology of Reproduction*, and *Theriogenology.*

Discovery research led to applied research, which led to products for estrous synchronization and breeding management of cattle being available today. Such research contributed significantly and positively to animal agriculture and society. The estrous 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 and dairy production, contributing both to enterprise economic viability and positive environmental effect. The cost-benefit of the protocols is positive for most beef and dairy enterprises and protocols exist to meet the breeding management needs of most beef and dairy enterprises. The protocols are based on biology of the cow, and 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 dairy products at an acceptable price, are decreasing production effects on the environment through increased efficiency of production, and the hormones in use have no negative animal welfare issues.

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