Control of estrus and ovulation in beef heifers and cows

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Abstract

Until recently, labor required to detect estrus for individual cows or heifers in a herd was the primary reason beef producers viewed artificial insemination as impractical. However, improvements in methods to control estrus and ovulation in beef heifers and cows are now expanding the use of artificial insemination by reducing the time required to detect estrus or eliminating estrus detection entirely. These methods evolved as a result of expanded understanding of the bovine estrous cycle and improved ability to effectively manipulate both follicular waves and luteal lifespan. Modern protocols are now capable of facilitating fixed time artificial insemination in beef cattle through orchestrated use of progestins, gonadotropin releasing hormone, and prostaglandin. These strategies offer effective control of estrus and ovulation in estrous cycling females and are also capable of inducing an ovulatory estrus in high percentages of peripubertal heifers and anestrous postpartum cows. Additionally, alternative breeding management strategies have been developed to achieve higher fertility while still reducing labor associated with estrus detection, such as combined estrus detection and fixed time artificial insemination approaches, or more recent approaches such as split time artificial insemination. Advancements in applied reproductive technologies now afford beef producers flexibility in matching specific breeding management protocols to defined management systems. This review focuses on systems currently recommended to facilitate fixed time artificial insemination among beef heifers and cows in the United States, where these technologies offer beef producers a clear opportunity to simultaneously improve genetic merit and reproductive management of their herds.

Keywords: Estrus synchronization, fixed time artificial insemination, beef heifer, beef cow

Introduction

Methods to control estrus and ovulation among beef heifers and cows have improved greatly over the past 25 years. Cow-calf producers can now successfully manage groups of females of mixed estrous cycling status and successfully perform fixed time artificial insemination (FTAI). These strategies offer more precise control of estrus and ovulation in estrous cycling females, while inducing an ovulatory estrus in high percentages of peripubertal heifers and anestrous postpartum cows. Collectively, improvements in methods to control estrus and ovulation in beef heifers and cows are expanding the use of artificial insemination (AI) by reducing the time required to detect estrus or eliminating estrus detection entirely. Breeding management strategies now offer the potential to effectively manage reproduction and expedite genetic progress, ultimately enhancing efficiencies of production and adding value to beef cattle produced and marketed in the US.[1-4] In total, these are important accomplishments considering the fact that estrus synchronization and artificial AI remain the most significant and widely applicable reproductive biotechnologies available for cattle.[5]

Development of the various systems currently in use by industry began with the initial discovery that progesterone inhibited ovulation[6] and preovulatory follicular maturation.[7-9] Subsequent research led to the finding that prostaglandin $F_{2\alpha}$ (PG) and its analogs were luteolytic in the bovine.[10-15] This led to the combined use of progestational agents and PG to control the luteal phase of the estrous cycle. With expanded understanding of changes that occur during a follicular wave,[16] it became clear that precise control of estrous cycles in cattle would require manipulation of both follicular waves and luteal lifespan. Assembling protocols that were ultimately capable of facilitating FTAI then hinged on orchestrated use of progestins, GnRH, and PG to enable beef producers to successfully breed cattle by appointment. Review articles published over the past nearly 60 years provide a sequential overview of research that subsequently led to development of these protocols and strategies that would enhance reproductive management of our nation's beef herds.[17-38]

The Beef Reproduction Task Force (BRTF) was formed during the recent period of evolving science in the US that resulted in systems to allow producer-acceptable results with a single FTAI.[39] The BRTF has provided scientific based recommendations for the application of reproductive technologies to the US beef industry since the turn of the century. In 2004, the BRTF was joined by leaders in the AI and pharmaceutical industries, along with bovine veterinary practitioners to form the US Beef Reproduction Leadership Team (BRLT). The group annually sponsors a 2 day workshop entitled "Applied Reproductive Strategies in Beef Cattle (ARSBC)", a program targeted at beef producers, AI industry personnel, veterinarians, allied industry representatives, and academicians. In addition, each year beginning in 2005, the BRTF publishes a list of recommended protocols for beef heifers and cows. This recommendation provides a detailed listing of protocols best suited to AI performed on the basis of: 1) detected estrus; 2) a combination of estrus detection followed by FTAI; and 3) FTAI.[39] One important consideration related to review of protocols recommended for use in the US is that no estrogen product is currently approved or legally available for use in estrus synchronization of cattle.[40] Estrogen products are available and in use with estrus synchronization protocols in other countries, such as Brazil and Canada; however, based on criteria used by the BRTF and BRLT and in compliance with FDA guidelines, no recommended estrus synchronization protocol uses an estrogen. This review will focus on systems currently recommended and used in the US to facilitate FTAT in beef heifers and cows; comprehensive reviews detailing development of these protocols was published in the most recent proceedings from ARSBC.[36-38]

Estrus synchronization and artificial insemination contribute to heifer development programs

Lifetime reproductive performance, longevity in the herd, and cumulative pounds of calf weaned over a heifer's productive lifespan are highly correlated with the date on which a heifer conceives during the first breeding season.[1,41-43] The investment in time and resources in heifers from weaning to breeding requires that management efforts be made to facilitate puberty onset and maximize the likelihood of early pregnancy. Estrus synchronization programs create an opportunity for heifers to conceive early in the breeding period, which is a significant opportunity given the relationship between early conception and long term reproductive success. In addition, estrus synchronization improves time management on farms and ranches by concentrating the breeding and resulting calving periods.[44-45] Beef producers are now able to utilize treatments that offer the potential to effectively synchronize estrus in pubertal heifers, while at the same time induce puberty among pre- or peripubertal heifers. This benefits groups of heifers with mixed cyclicity status, particularly breeds or biological types that are late-maturing, but of sufficient age and weight at the time of treatment to permit successful application.[46]

Progestins were first reported to induce estrus in peripubertal heifers[47] and were originally combined with estrogen to mimic changes that occur in concentrations of blood hormones around the time of puberty. Increased progesterone is thought to be a prerequisite for development of normal estrous cycles. Progesterone increases during the initiation of puberty in the heifer[48] and before resumption of normal ovarian cyclicity in postpartum suckled beef cows.[49-50] Progestins stimulate an increase in follicular growth that results in increased production of estrogen by ovarian follicles.[51-54] Progestin treatment results in increased LH pulse frequency during the treatment period[55-57] and initiation of estrous cyclicity in peripubertal beef heifers.[46-47,58] Studies suggest that stimulatory effects of progestins on LH secretion[59] are greatest after removal of the steroid[56-57,60] and increase with heifer age.[60]

Long term progestin-based protocols for heifers

Melengestrol acetate - prostaglandin $F_{2\alpha}$

Melengestrol acetate (MGA®) is an orally active progestin approved for use to synchronize estrus in replacement heifers when fed at a rate of 0.5/mg/head/day.[61] When consumed on a daily basis, MGA will suppress estrus and prevent ovulation.[57] It may be fed in a single daily feeding with a grain or protein carrier. Heifers that fail to consume the required amount of MGA on a daily basis may return to estrus prematurely during the feeding period, which will reduce estrous response during the synchronized period. Therefore, adequate bunk space (60 linear cm/head) must be available so that all animals consume feed simultaneously.[27-28] This practice ensures that all females receive adequate intake. Heifers should be observed for behavioral signs of estrus each day of the feeding period, which may be done as animals approach the feeding area and before feed distribution. Heifers will exhibit estrus beginning 48 hours after MGA withdrawal, and this will continue for 6 - 7 days. It is generally recommended that heifers that exhibit estrus during this period not be inseminated or exposed for natural service, due to reduced fertility at the first estrus after MGA withdrawal. Therefore, PG should be administered 19 days after the last feeding day of MGA, with FTAI performed 72 hours after PG (Figure 1).

It is important to note that use of MGA as part of any estrus synchronization protocol in beef cows constitutes an extra-label use of medicated feed that is prohibited by the Animal Medicinal Drug Use and Clarification Act and regulation 21 CFR 530.11(b). The feeding of MGA is specifically approved for estrus suppression in heifers only.[61] Although 35 years of feeding MGA to beef cows and beef heifers demonstrated that MGA is safe, effective and economical,[20,45,56,62-81] feeding MGA to adult cows is not an FDA approved label claim and therefore strictly prohibited by the FDA.

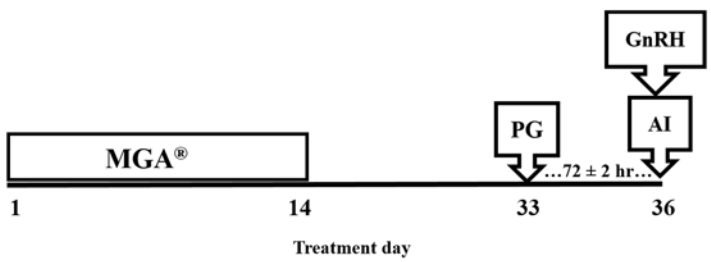

Figure 1. Melengestrol acetate (MGA®) - prostaglandin $F_{2\alpha}$ (PG) with FTAI. MGA-PG protocol consists of MGA feeding for 14 days at a rate of 0.5 mg/head/day, PG administration on day 19 and FTAI at 72 hours after PG, concurrent with administration of gonadotropin-releasing hormone (GnRH).[62-64]

14 day controlled internal drug release + prostaglandin $F_{2\alpha}$

A comprehensive series of studies in beef heifers led to development of the 14 day controlled internal drug release (CIDR®)-PG protocol (Figure 2), followed by comparisons of the protocol to the 7 day CoSynch + CIDR and MGA-PG protocols.[82-89] These studies carefully characterized estrus distribution patterns following removal or withdrawal of the progestins and subsequent distribution of estrus following the administration of PG. Results from these studies highlighted differences in variance for interval to estrus, which ultimately explain the degree of estrus synchrony that is achieved during the synchronized period. In every case, the degree of synchrony achieved was greatest for heifers assigned to the 14 day CIDR-PG protocol. In addition, results from these experiments noted similarities in FTAI pregnancy rates comparing heifers that were peripubertal or estrous cycling prior to treatment initiation. Mallory et al.[88] reported that conception to AI and AI pregnancy rates did not differ between 14 day CIDR-PG and MGA-PG treated heifers following inseminations performed on the basis of detected estrus. In addition, pregnancy rates after FTAI were later compared[90] among heifers assigned to the 2 protocols, with 62 and 61% of heifers conceiving to the MGA and CIDR treated groups, respectively.

Short term progestin-based protocols for heifers

7 day CoSynch + controlled internal drug release

Lucy et al.[58] summarized results from initial studies conducted in the US involving CIDR-based protocols for use in synchronizing estrus in beef heifers. These data were submitted to FDA in support of the original approval for the CIDR in beef heifers. Heifers with a CIDR inserted for 7 days with PG

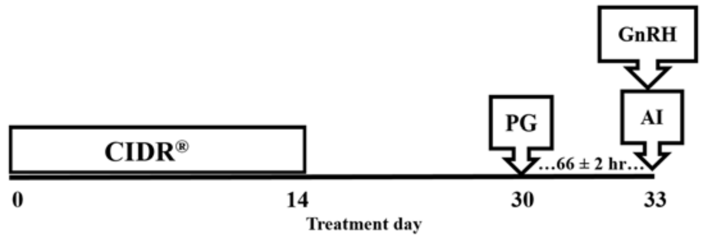

Figure 2. 14 day CIDR®-PG with FTAI. The 14 day CIDR-PG protocol involves CIDR insertion for 14 days, waiting 16 days to administer prostaglandin $F_{2\alpha}$ (PG) and FTAI at 66 hours after PG with gonadotropin-releasing hormone (GnRH) administered at AI.[89]

administered on day 6 of CIDR treatment had higher pregnancy rates compared to untreated control or PG treated heifers. Treatment with a CIDR increased synchronization rates within the first 3 days following PG, resulting in enhanced pregnancy rates. The improved pregnancy rate in prepubertal beef heifers treated with CIDR was noteworthy because control or PG treated heifers that were prepubertal prior to treatment never attained pregnancy rates that were comparable to those that received a CIDR.

Later, Lamb et al.[91] (Figure 3) lead a multi-state effort involving beef heifers assigned to a 7 day CoSynch + CIDR protocol to determine whether: 1) an injection of GnRH at CIDR insertion would enhance pregnancy rates in beef heifers; and 2) administration of an estrus synchronization protocol followed by FTAI could yield pregnancy rates similar to a protocol requiring detection of estrus. Lamb et al.[91] concluded that: 1) GnRH at CIDR insertion did not improve pregnancy rates after FTAI; 2) GnRH at CIDR insertion did not alter percentage of heifers detected in estrus or distribution of estrus after PG; and 3) a combination of detecting estrus and AI before clean-up AI enhanced pregnancy rates over FTAI.

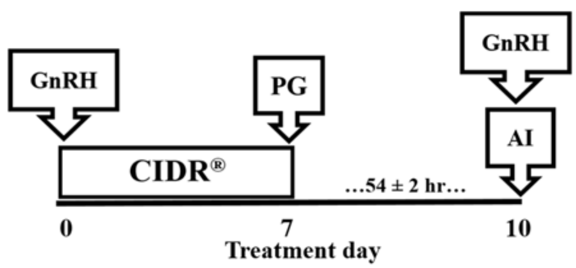

Figure 3. 7 day CoSynch + CIDR® with FTAI. The 7 day CoSynch + CIDR protocol consists of a 7 day controlled internal drug release intravaginal insert (CIDR; 1.38 g progesterone), gonadotropin-releasing hormone (GnRH) administration at CIDR insertion and prostaglandin $F_{2\alpha}$ (PG) administered at CIDR removal on day 7. FTAI is performed 54 hours following PG, concurrent with GnRH administration.[91]

5 day CoSynch + controlled internal drug release

The 5 day CoSynch + CIDR protocol (Figure 4) was added most recently by the BRTF to the list of recommended protocols for FTAI in beef heifers. Development of this protocol was based on the hypothesis[92-93] that reducing the length of CIDR treatment from 7 to 5 days in the CoSynch + CIDR protocol would increase secretion of estradiol by the ovulatory follicle, decrease the incidence of induced ovulation of follicles with reduced estrogenic activity and potentially result in improvements in FTAI pregnancy rates. The hypothesis was based on the premise that day 4 dominant follicles have higher intrafollicular concentrations of estradiol-17β (E_2) and a greater ability to produce E_2 compared to older follicles.[94] Bridges et al.[95] reported that maximum preovulatory concentrations of E_2 tended to be greater in 5 day compared to 7 day CIDR treated cows that failed to respond to GnRH at CIDR insertion and that postovulatory circulating concentrations of progesterone were greater among 5 day compared to 7 day treated cows. Increased follicular concentrations of E_2 and elevated postovulatory concentrations of progesterone are believed to reflect greater physiological maturity of the dominant follicle and to result in higher pregnancy rates resulting from AI.[96-97] Therefore, Bridges et al.[92] proposed that if CIDR removal and AI are more optimally timed with the 5 day protocol to coincide with follicular development, higher AI pregnancy rates may be achieved. Regrettably there are no published studies illustrating estrus distribution patterns for the 5 day CoSynch + CIDR protocol in beef heifers on the basis of estrous cyclicity status of heifers at the time treatments are imposed.[98] Recently, however, pregnancy rates after FTAI were compared in heifers assigned to the 5 day and 7 day CoSynch + CIDR protocols[99,100] and the 5 day CoSynch + CIDR and 14 day CIDR-PG protocols.[101-103] The only reported difference between protocols from any of these studies was an increase in pregnancy rate that resulted after FTAI among 5 day compared to 7 day CoSynch + CIDR treated heifers.[99]

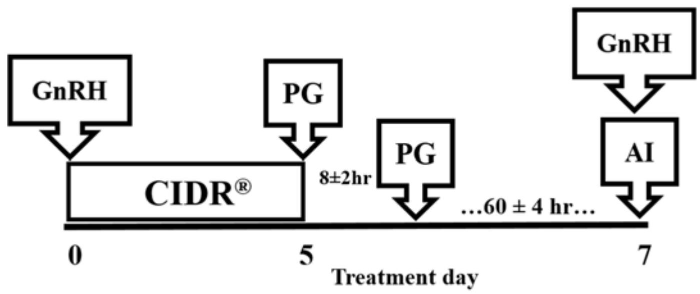

Figure 4. 5 day CoSynch + CIDR® with FTAI. The 5 day CoSynch + CIDR protocol consists of a 5 day CIDR insert (1.38 g progesterone), gonadotropin-releasing hormone (GnRH) administration at CIDR insertion and prostaglandin $F_{2\alpha}$ (PG) administered at CIDR removal and again 8 ± 2 hours later. FTAI is performed 60 hours following the first injection of PG, concurrent with GnRH administration.[93,98]

Comparing pregnancy rates resulting from fixed time artificial insemination on the basis of reproductive tract score and protocol

An on-farm beef heifer development and marketing program was initiated in Missouri in 1996 (Show-Me-Select™ Replacement Heifer Program)[104] to enable beef producers to improve breeding performance of heifers during their first breeding season and during subsequent calving and rebreeding periods as 2 year olds. The intent of the program was to ensure that heifers that enter the herd as raised or purchased replacements contribute to the sustained increase in performance and productivity of cowherds for the long term.[105] The program has improved reproductive management of beef herds in Missouri through increased use of reproductive technologies.[106-107] Field data collected in support of this program include an array of reproductive evaluations unique to the beef industry. Producers that enroll heifers in the program are required to follow detailed management guidelines and adhere to approved animal health protocols. Prebreeding evaluations are performed on all heifers 4 - 6 weeks prior to breeding by licensed veterinarians. As part of the evaluation, each heifer is assigned a reproductive tract score (RTS), which is used to characterize pubertal status and resulting fertility.[108-110] The scores range from 1 to 5 (1 = infantile; 2 and 3 = noncycling/prepubertal; 4 and 5 = cycling/pubertal) and are determined using transrectal ultrasonography or palpation. In recent years, participants in the program have relied heavily on FTAT to breed heifers. Heifers enrolled in the program that receive AI may not be exposed for natural service for a minimum of 14 days after AI and pregnancy diagnoses must be performed within 90 days after the start of the breeding period. These requirements, when considered in total, provide a unique opportunity to evaluate reproductive data on large numbers of beef heifers from the perspective of: 1) pretreatment estrous cyclicity status; 2) the various protocols used to synchronize estrus; and 3) pregnancy rates resulting from FTAI. Field data collected from 2010 to 2018 were used to evaluate relationships between RTS and pregnancy outcome after FTAI. A summary of RTS and FTAI pregnancy rate is provided in Table 1 for 39,938 heifers that were evaluated from 2010-2018.[111]

These data support establishing prebreeding criteria that may be used to identify heifers that are good candidates for a FTAI program. Pregnancy rates resulting from FTAI are compared in Table 2 on the basis of RTS prior to the time the various protocols to synchronize estrus were initiated. Data for heifers assigned RTS score of 1 were excluded from this summary, as the majority of these heifers are culled by producers prior to breeding. These data indicate that evaluation of reproductive status of heifers prior to the first breeding season is useful in determining success of the development period and in determining which protocol to use to synchronize estrus prior to FTAI.[111-112] The 14 day CIDR-PG protocol has gained widespread use in heifer programs across Missouri, as seen from numbers presented in Table 2. Pregnancy rates resulting from FTAI suggest more favorable field results are obtained on-farm using the 14 day CIDR-PG compared to the 7 day CoSynch + CIDR and MGA-PG protocols. Additionally, the 14 day CIDR-PG protocol has gained widespread acceptance among veterinarians involved in the program, as prebreeding booster vaccinations and reproductive exams are performed coincident with CIDR insertion.[111]

Table 1. Pregnancy rates resulting from FTAI among heifers in the Missouri Show-Me-Select™ Replacement Heifer Program, based on pretreatment RTS (n = 39,938).

	Reproductive Tract Score				
	1	2	3	4	5
Number of heifers	237	1,155	11,104	14,340	13,102
Number pregnant	11	313	5,260	7,269	6,698
FTAI pregnancy rate (%)	5[a]	27[b]	47[c]	51[d]	51[d]

*Pregnancy rates resulting from FTAI based on RTS. These data include pregnancy rates for 39,938 heifers that were inseminated beginning during the fall of 2010 through fall of 2018.
[a-d]Percentages without a common superscript differ ($p < 0.05$).

The Missouri Show-Me-Select™ Replacement Heifer Program continues to see an increase in the overall percentage of heifers exposed for AI, with the majority of these heifers are being inseminated using a FTAI approach rather than detection of estrus. An important consideration related to the success of these AI programs and the expanded use of AI in Missouri is that all heifers are required to undergo a prebreeding examination to determine estrous cyclicity status. This practice allows for better determination of the appropriate estrus synchronization protocol and also provides critical information in situations where troubleshooting may be required.[111-112] These conclusions are supported by studies reported by Hall[113] and Gutierrez et al.[114] which involved comparison of heifers that were inseminated on the basis of FTAI followed by a natural service clean-up period versus natural service only. Gutierrez et al.[114] reported that RTS influenced both the number of beef heifers that became pregnant during the breeding season and the time at which heifers became pregnant.

Table 2. Pregnancy rates resulting from FTAI among heifers in the Missouri Show-Me-Select™ Replacement Heifer Program, based on pretreatment estrous cyclicity status based on RTS and protocol used to synchronize estrus (n = 39,695).

FTAI protocol	Non-cycling[+]		Cycling[++]		Combined total	
	No.	%	No.	%	No.	%
7 day CoSynch + CIDR	205/616	33[a,x]	526/1,193	44[b,x]	731/1,809	40[x]
MGA – PG	81/230	35[a,x]	274/576	48[b,x]	355/806	44[x]
14 day CIDR – PG	5,287/11,413	46[a,y]	13,163/25,667	51[b,y]	18,450/37,080	50[y]

[+,++]Non-cycling heifers were assigned a RTS of 2 or 3; Cycling heifers were assigned RTS of 4 or 5 (Anderson et al. 1991).
[a,b]Percentages within rows with different superscripts differ $p < 0.01$.
[x,y]Percentages within columns with different superscripts differ $p < 0.01$.

Short term progestin-based protocols for postpartum beef cows

7 day CoSynch + controlled internal drug release

Lucy et al.[58] smmarized results from initial studies conducted in the US involving CIDR based protocols for use in synchronizing estrus in postpartum beef cows. These data were submitted to FDA in support of the original approval for the CIDR. Three treatments were involved in the study and included:

1) untreated control; 2) PG only; and 3) 7 day CIDR-PG with PG administered on day 6 of CIDR treatment. The 7 day CIDR-PG protocol yielded greater pregnancy rates compared to control or PG treatments. Treatment with CIDR increased synchronization rates within the first 3 days following PG, resulting in enhanced pregnancy rates. The improved pregnancy rate in anestrous cows treated with the CIDR was noteworthy, because anestrous cows in the control or PG treatments never attained pregnancy rates that were similar to those of the 7 day CIDR-PG treated group. The drawback of the protocol was that PG was administered on day 6 after CIDR insertion, which required an additional day of animal handling.

A series of studies were then designed to determine whether inclusion of a CIDR to a GnRH-PG (CoSynch)[115-116] based protocol would increase pregnancy rates resulting from AI.[117-118] Larson et al.[118] reported an improvement in FTAI pregnancy rates in postpartum beef cows with addition of a CIDR to the CoSynch protocol, noting that differences resulted from the potential added benefit of induced cyclicity among anestrous cows that occurred following CIDR removal. Furthermore, addition of a CIDR to the CoSynch protocol prevented premature expression of estrus that occurs between GnRH and PG among cows that do not receive a CIDR; in the absence of a CIDR, it is estimated that 5 - 20% of the total number of cows treated will exhibit estrus prior to or immediately after PG injection[82,119-121] Therefore, addition of the CIDR to the CoSynch protocol successfully prevented the premature expression of estrus prior to or following PG (Figure 5).

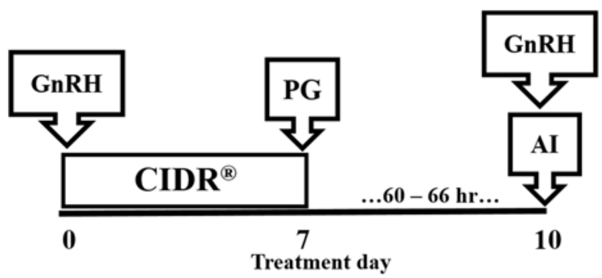

Figure 5. Cows in the 7 day CoSynch + CIDR® treatment received GnRH and CIDR inserts on day 0. PG was administered and CIDR inserts were removed on day 7. All 7 day treated cows were inseminated (FTAT) 66 hours following treatment, with GnRH administered at AI.[80,118,122]

Does timing of insemination affect pregnancy rates resulting from FTAI following administration of the CoSynch + controlled internal drug release protocol?

Several studies involving the CoSynch + CIDR protocol evaluated effect of timing of FTAI on subsequent pregnancy rates. Timing of insemination following the CoSynch + CIDR protocol was based on recommendations from pharmaceutical and AI industries (54 - 66 hours) and other reports where the timing of AI included 48, 54, 56, 60, 64, 66, and 72 hours post PG[80, 117-118,122-124] Therefore, Busch et al.[122] compared FTAI pregnancy rates among lactating beef cows synchronized with the CoSynch + CIDR protocol that were inseminated at 54 or 66 hours after PG and characterized estrous response of cows in each treatment prior to FTAI (Figure 6). Busch et al.[122] reported a significant effect of time of insemination on pregnancy rates resulting from FTAI; cows inseminated at 66 hours after PG were 1.32 times more likely to conceive to FTAI than cows inseminated at 54 hours following PG. Busch et al.[122] reported that estrous response following PG and prior to FTAI was greater among cows inseminated at 66 hours (50%) than cows inseminated at 54 hours (26%). Cows that exhibited estrus prior to FTAI had significantly higher pregnancy rates (76%) than cows that failed to exhibit estrus before AI (56%). Perhaps the most interesting observation from the study, however, was the fact that pregnancy rates among cows that exhibited estrus prior to insemination were higher for cows inseminated at 66 hours (81%) compared to those inseminated at 54 hours (65%), highlighting importance of properly timed inseminations when appointment breeding is performed.

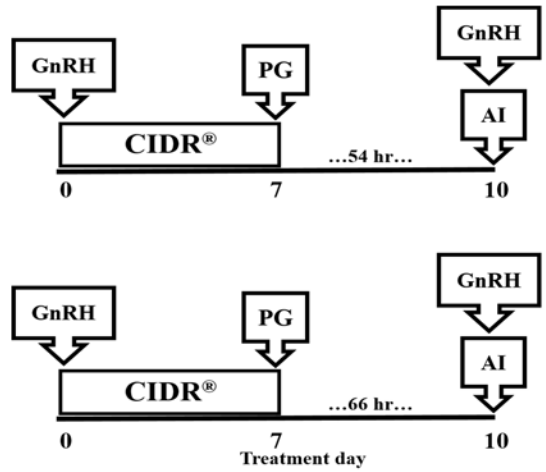

Figure 6. Busch et al.[122] compared FTAI pregnancy rates among lactating beef cows synchronized with the CoSynch + CIDR® protocol in which case cows were inseminated at 54 or 66 hours after CIDR removal and PG.

The onset of estrus prior to FTAI in beef cows improved pregnancy rates when compared to cows that fail to exhibit estrus.[125] Busch et al.[122] reported that cows that exhibited estrus following administration of the CoSynch protocol had greater serum E_2 concentrations during the 2 days prior to insemination compared to cows that were induced to ovulate. Busch et al.[122] concluded that cows that exhibited estrus may have attained concentrations of E_2 necessary to effectively prepare follicular cells for luteinization and (or) induced an adequate number of uterine progesterone receptors,[126] thereby providing an adequate uterine environment for pregnancy establishment and maintenance. Based on these data, higher estrous response rates prior to FTAI in beef cows should result in greater pregnancy rates resulting from FTAI, provided that AI is performed within an acceptable interval after the peak estrous period.

Mirando et al.[127] reviewed efforts in Missouri to integrate fundamental aspects of control of the estrous cycle in beef cattle, with wide-scale application of the technology in the field, both of which are required to enhance competitiveness of the US livestock industry. Justification for this approach centered on the concern that continued low adoption rates of these technologies in the US will ultimately erode the competitive position of the US beef cattle industry. On-farm field demonstrations were conducted in Missouri (Figure 7) involving 73 herds and 7,028 cows. FTAI was performed on postpartum beef cows using the 7 day CoSynch + CIDR protocol, with FTAI performed 66 hours after CIDR removal and PG administration. Pregnancy rates resulting from FTAI averaged 62% for the 73 herds. Pregnancy rates resulting from FTAI ranged from 38 to 86%, and only 7 of the 73 herds had pregnancy rates that were below 50%. Field demonstrations in Missouri[127] and Florida[4] illustrate that increased profits can be achieved through changes in calving distribution patterns of herds by increasing percentage of cows that calve over a more concentrated interval and earlier in the calving period.

5 day CoSynch + controlled internal drug release

The rationale for and development of the 5 day CoSynch + CIDR protocol developed by Bridges et al.[92,95] (Figure 8) was presented in the heifer portion of this review. Bridges et al. [92,95] concluded that reducing the interval from GnRH and CIDR insertion from 7 to 5 days, administering 2 injections of PG at CIDR removal and again 12 hours later and extending the interval to 72 hours from CIDR removal to FTAI was an effective estrus synchronization protocol for use in facilitating FTAI in postpartum beef cows.

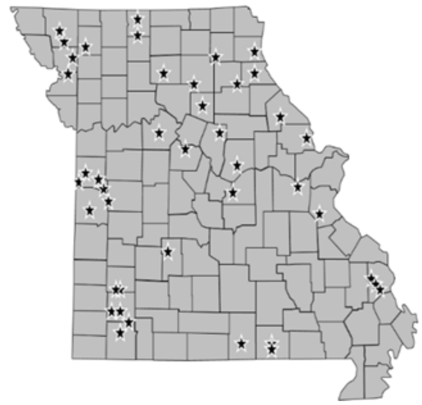

Figure 7. Locations of on-farm field demonstrations in Missouri involving 7,028 cows in 73 herds. Cows at these various locations were synchronized using the 7 day CoSynch + CIDR protocol and were inseminated 66 hours after CIDR removal and PG. Pregnancy rates resulting from FTAI averaged 62%.[127]

It is important to note that 2 injections of PG are required with the 5 day protocol to effectively regress accessory corpora lutea that form as a result of GnRH-induced ovulations at the initiation of treatment. Therefore, the current recommendation for use of this protocol to facilitate FTAI in beef cows is to administer 2 doses of PG 8 hour apart, the first coincident with the time of CIDR removal and the second 8 hours later[95,97,128-129]

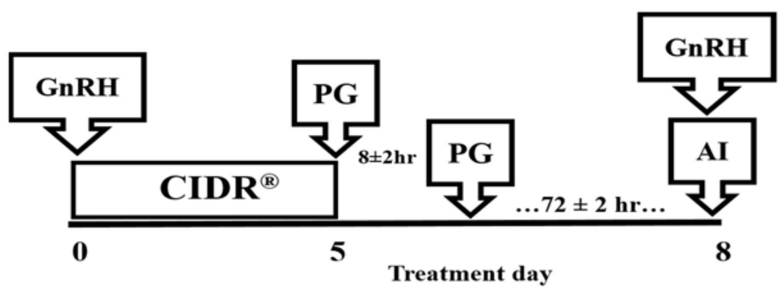

Figure 8. The 5 day CoSynch + CIDR® protocol for cows consists of a 5 day CIDR insert (1.38 g progesterone), gonadotropin-releasing hormone (GnRH) administration at CIDR insertion, and PG administered at CIDR removal and again 8 ± 2 hours later. FTAI is performed 72 hours after the first injection of PG, concurrent with GnRH administration.[92, 95]

How do the 7 day and 5 day CoSynch + controlled internal drug release protocols compare in postpartum beef cows?

Wilson et al.[130] (Figure 9) and Whittier et al.[131] compared the 5 day and 7 day CoSynch + CIDR protocols on the basis of pregnancy outcome and practical application in the field. Wilson et al.[130] reported comparable pregnancy rates resulting from FTAI among cows assigned to the 2 protocols, although the study reported by Whittier et al.[131] showed a 3% improvement in pregnancy rate resulting from FTAI among cows assigned to the 5 day protocol. The 5 day protocol provides an effective alternative to the 7 day protocol for use in facilitating FTAI; however, beef producers must consider the increased labor and treatment costs associated with its use. Although Bridges et al.[95] reported higher pregnancy rates among cows assigned to the 5 day versus 7 day CoSynch + CIDR protocol, it is important to contrast those results with the study by Wilson et al.[130] Cows assigned to the 7 day protocol

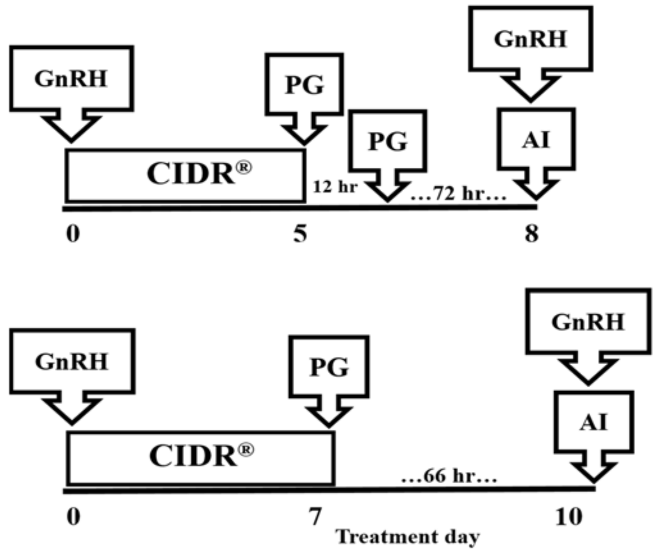

Figure 9. Cows in the 5 day CoSynch + CIDR® treatment received GnRH and a CIDR insert on day 0. PG was administered and CIDR inserts were removed on day 5. A second injection of PG was administered 12 hours after the first PG injection. All 5 day treated cows were inseminated (FTAT) 72 hours following treatment with GnRH administered at AI. Cows in the 7 day CO-Synch + CIDR treatment received GnRH and CIDR inserts on day 0. PG was administered and CIDR inserts were removed on day 7. All 7 day treated cows were inseminated (FTAT) 66 hours following treatment with GnRH administered at AI.[128]

in Wilson's experiment received a single injection of PG and were inseminated 66 hours after PG; whereas, 7 day treated cows in Bridges' study received 2 injections of PG, with AI performed 60 hours after the first PG injection. A possible explanation for differences in results between the 2 studies[130] related to differences in timing of AI for the 7 day treated cows in each study.

Timing of insemination for the respective protocols paralleled the timing of peak estrus for each protocol based on the results from Wilson et al.[130] For cows assigned to the 5 day protocol, the mean time of AI (72.6 hours), paralleled the mean interval to estrus (71.2 hours) reported by Wilson et al.[130] from a separate experiment. Likewise, for the 7 day treated cows, the mean time of AI (66.5 hours) paralleled the mean interval to estrus (64.8 hours). Bridges et al.[95] hypothesized that shortening the duration of CIDR treatment from 7 to 5 days would better time CIDR removal coincident with optimal follicular development, and that lengthening the time interval between PG and AI would result in higher pregnancy rates following FTAI. Arguably, lengthening this time period between PG and AI to 66 hours for cows assigned to the 7 day protocol may explain the similarity in FTAI pregnancy rates between treatment groups, versus those reported by Bridges et al.[95] Collectively, the results from Busch et al.[122] and Wilson et al.[130] suggest that pregnancy rates resulting from FTAI are perhaps more a function of properly timed AI, rather than timing CIDR removal and follicular development.

How do the 14 day controlled internal drug release - prostaglandin $F_{2\alpha}$ and 7 day CoSynch + controlled internal drug release protocols compare in primiparous 2 year old beef cows?

Reproductive management of primiparous 2 year old cows presents a unique challenge in managing beef herds, since this age group of females typically experiences the highest incidence of reproductive failure.[132] Abel et al.[133] designed a study to compare short and long term CIDR-based protocols to synchronize estrus and ovulation in primiparous 2 year old beef cows (Figure 10). Abel et al.[133] proposed that extended progesterone exposure using the 14 day CIDR-PG protocol would successfully overcome problems related to protracted postpartum intervals in younger age females, improve pregnancy rates to FTAI and increase final pregnancy rates at the end of the breeding season.

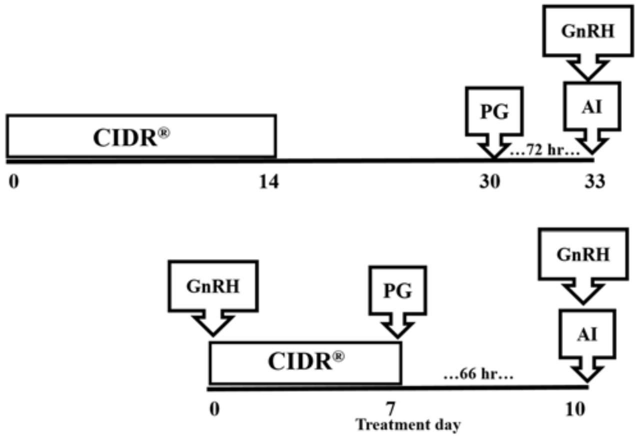

Figure 10. Abel et al.[131] compared short and long term CIDR® based protocols to synchronize estrus and ovulation in primiparous 2 year old beef cows. The 14 day CIDR-PG and 7 day CoSynch + CIDR protocols were compared on the basis of estrous response following PG up to the point of FTAI, pregnancy rates after FTAI, and final pregnancy rate.

The study[133] compared the 14 day CIDR-PG and 7 day CoSynch + CIDR protocols on the basis of estrous response following PG up to the point of FTAI, pregnancy rates after FTAI and final pregnancy rate. Estrous response prior to FTAI was higher for 7 day compared to 14 day treated cows (74 versus 43%, respectively); however, pregnancy rates resulting from FTAI were similar (7 day, 64%; 14 day, 63%). Despite the significant difference in estrous response between cows assigned to each protocol, there was no difference in pregnancy rate between groups after FTAI. Low estrous response rates were observed in previous studies that evaluated long term CIDR-based protocols in mixed-age groups of beef cows; however, despite lower numbers of cows that exhibited estrus, pregnancy rates resulting from FTAI were acceptable.[134-136]

It is worth noting that, among a subset of cows in Abel's study, circulating concentrations of E_2 at FTAI were nearly 2 fold higher among 14 day CIDR-PG treated cows, irrespective of estrous status, compared to 7 day treated cows. Higher concentrations of E_2 among 14 day treated cows, despite smaller dominant follicle diameter, suggest that dominant follicles were in an active growth stage among cows within this treatment group, compared to 7 day treated cows for which growth of the dominant follicle already plateaued.[133] This may be a logical conclusion, as aromatase activity decreases in granulosa cells when growth of the dominant follicle plateaus.[94] Abel's results support the concept that preovulatory follicles among cows assigned to the 14 day protocol were physiologically mature at the time GnRH was administered and FTAI performed. This may help to explain the similarity in pregnancy rate in the face of reduced estrous response among cows assigned to the 14 day CIDR-PG protocol.

Managing anestrus with progestin-based protocols

Herd owners are faced with uncertainty in knowing the number of cows that have returned to estrus following calving and the number that remain anestrus prior to each breeding period. One of the overlooked advantages in administering a CIDR based protocol in postpartum beef cows lies in the fact that these protocols can effectively induce estrous cyclicity among a high proportion of cows that were anestrus prior to treatment initiation. Figure 11 illustrates results from 6 published studies conducted by our laboratory at the University of Missouri comparing pregnancy rates after FTAI. Blood samples were collected from cows in each of these studies at 2 time points before assignment to an estrus synchronization protocol to determine pretreatment estrous cyclicity status, based on concentrations of progesterone. Pregnancy rates following FTAI were then compared between cows that were anestrus prior to treatment and cows that were estrous cycling. The combined results from these 6 studies clearly demonstrate the significant benefit that results from using progestins in protocols designed to facilitate FTAI programs. By advancing the date during the breeding season on which anestrous cows have a first opportunity to conceive, these protocols support improved reproductive management of the entire cow herd, regardless of cyclicity status.

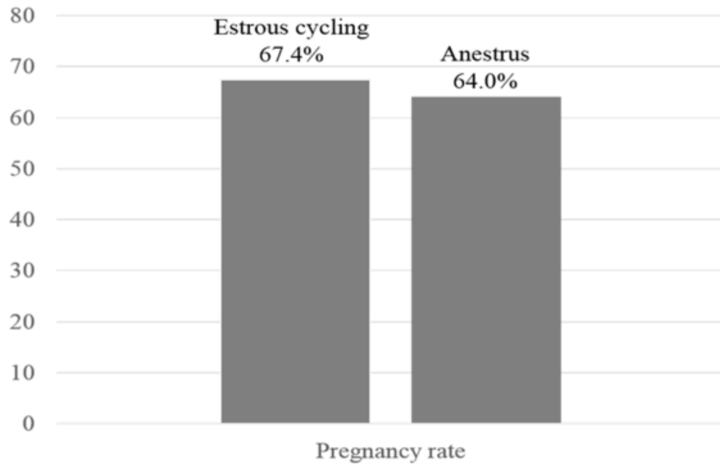

Figure 11. Pregnancy rates among postpartum beef cows resulting from FTAT and based on pretreatment estrous cyclicity status. Estrous cyclicity status was determined based on 2 blood samples for progesterone 8 - 10 days before and on the day treatments to synchronize estrus were initiated. The graph illustrates results from 6 published studies involving 3,074 cows, of which 54 and 46% of the cows were estrous cycling or anestrus, respectively, prior to initiation of treatment.[79,80,122,130,134,136]

Protocols for *Bos indicus* influenced females

Efforts to improve the reproductive and genetic management of beef cattle operations in the US should encompass the full complement of breeds and biological types of cattle that comprise our nation's cowherd. In total, a plethora of research has been designed and conducted specifically for *Bos indicus* influenced females; however, as indicated in the Introduction to this review, many of these protocols involve estrogen products that cannot be used legally in the US There are however, limited numbers of published reports specifically focused on development and evaluation of protocols to synchronize estrus and ovulation prior to FTAT for *Bos indicus* influenced females in the US This point is unfortunate, given the fact that breeds or breed crosses in Gulf Coast states that comprise this biological type represent nearly 25% of the entire US cowherd.[137] *Bos indicus* influenced cattle are known to exhibit increased susceptibility to stress and are unique from *Bos taurus* females based on their distinct reproductive physiology.[138-144] These differences have influenced development of systems to effectively control estrous cycles of *Bos indicus* influenced cattle and limited the use of AI in regions of the US where these breeds or biological types are ideally better adapted to tropical and subtropical environments.

Thomas and Locke[38] recently reviewed current strategies designed to synchronize estrus in *Bos indicus* influenced females and noted that there are currently no protocols recommended by the BRTF for use in synchronizing estrus in heifers of these breeds or biological types. Inherent genetic differences in age at puberty between *Bos indicus* and *Bos taurus* breeds are apparent and affect the outcome of treatments designed to synchronize estrus and ovulation. Management as it relates to development of these heifers during the postweaning to prebreeding period is critical[143,145-147], and implementation of an AI program among a group of mixed-cyclicity *Bos indicus* influenced heifers is a challenge. Recent studies[148-149] suggest that long term progestin-based (MGA-PG and 14 day CIDR-PG) protocols may be used effectively in synchronizing estrus in *Bos indicus*-influenced heifers prior to natural service or FTAI. These protocols appear to perform similarly among *Bos indicus*-influenced heifers compared to *Bos taurus* heifers, when results are considered on the basis of pubertal status of heifers at the time treatments are initiated. There is evidence to suggest that short term progestin-based protocols (5 and 7 day CoSynch + CIDR) currently used in *Bos taurus* heifers perform poorly when used to synchronize estrus in *Bos* *indicus*-influenced heifers.[150-151] However, results with short term protocols also seem to be highly influenced by pubertal status of heifers prior to treatment initiation.[144, 152] Although short term protocols may effectively induce estrous cyclicity in pre or peripubertal heifers,[46-47] an advantage of long term protocols may be that heifers are not exposed for breeding or inseminated on the first pubertal estrus.[153-154]

Currently, only 1 protocol is recommended by the BRTF for *Bos indicus*-influenced cows: the PG 5 day CoSynch + CIDR or "Bee-Synch" protocol[151] (Figure 12). This protocol requires that PG and GnRH be administered concurrent with CIDR insertion to induce luteolysis among cyclic cows, reduce circulating concentrations of progesterone during treatment and enhance follicular development. Administering PG at CIDR insertion alters the timing of estrous response compared to the standard 5 day CoSynch + CIDR protocol, so FTAI is performed at 66 hours following CIDR removal.

Split time artificial insemination

Thomas et al.[155-156] tested the hypothesis that pregnancy rates in beef heifers and cows to timed AI may be improved by delaying insemination of females that fail to express estrus prior to the time FTAI is scheduled to be performed. This approach, termed split time artificial insemination (STAI), improved pregnancy rates compared to FTAI following administration of the 14 day CIDR-PG protocol for heifers and the 7 day CoSynch + CIDR protocol for cows. When STAI is performed, activation status of an estrus detection aid at the time of FTAI determines whether AI is performed at the standard time or delayed until 20 - 24 hours later. Heifers and cows were administered GnRH at 66 hours, irrespective of estrous status in the original field trials that compared STAI and FTAI. The working hypothesis in those studies[155-156] was that delayed insemination of nonestrous females would better align the timing of insemination with the timing of GnRH-induced ovulations. This approach to breeding management increased overall pregnancy rates.

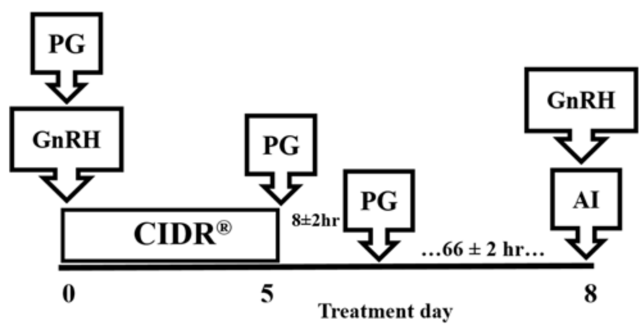

Figure 12. The PG 5 day CoSynch + CIDR® (Bee Synch) protocol for *Bos indicus* influenced beef cows consists of: 5 day CIDR insert (1.38 g progesterone); prostaglandin $F_{2\alpha}$ (PG) and gonadotropin releasing hormone (GnRH) administration at CIDR insertion; and PG administered at CIDR removal and again 8±2 hours later. FTAI is performed 66 hours following the first injection of PG, concurrent with GnRH administration.[151]

Later experiments[157-161] (Figure 13) evaluated the optimal timing of GnRH administration when using STAI. Results from these studies clearly demonstrated that administration of GnRH was not required for heifers or cows that exhibit estrus prior to AI and that administration of GnRH to females that fail to exhibit estrus could occur concurrent with insemination at the delayed time point. This work confirmed that higher pregnancy rates resulting from STAI compared to FTAI are due primarily to higher total rates of estrous response prior to insemination, in contrast to the theory that timing of insemination is more optimally aligned relative to GnRH-induced ovulations. Despite the high overall estrous response that is observed in heifers and cows when split time AI is practiced following administration of 14 day CIDR-PG and 7 day CoSynch + CIDR protocols, a percentage of females still fail to exhibit estrus by the delayed time point.[157-159] Pregnancy rates resulting from AI are generally reduced among females that fail to exhibit estrus,[125] despite the fact GnRH is routinely administered concurrent with AI.

Knickmeyer et al.[162] designed experiments to evaluate pregnancy rates resulting from FTAI or STAI among beef heifers following administration of the MGA-PG and 7 day CoSynch + CIDR protocols in heifers. Total estrous response increased among beef heifers assigned to STAI versus FTAI treatments for MGA-PG (STAI 88%; FTAI 72%) and 7-day CoSynch + CIDR (STAI 74%; FTAI 47%) protocols, respectively. The increased estrous response resulting from STAI was associated with a corresponding increase in pregnancy rates to AI following the MGA-PG protocol; however, similar improvements in pregnancy rate were not observed following the 7 day CoSynch + CIDR protocol. Differences in results between protocols may have occurred as a result of differences following treatment with long versus short term progestin-based protocols (Figure 13). Although short term treatment with a progestin was reported to effectively induce estrous cyclicity in pre or peripubertal heifers[46-47,60] there may be an advantage to long term treatments when considering resulting pregnancy outcomes.[153-154] This point is worth considering based on the observation that fertility associated with the first pubertal ovulation is typically reduced compared to subsequent ovulations.[153-154] Long term progestin-based protocols may offer an advantage over short term protocols in that inseminations are not performed on the pubertal estrus and improvements obtained using a split time AI approach have been observed among heifers only following long term protocols.

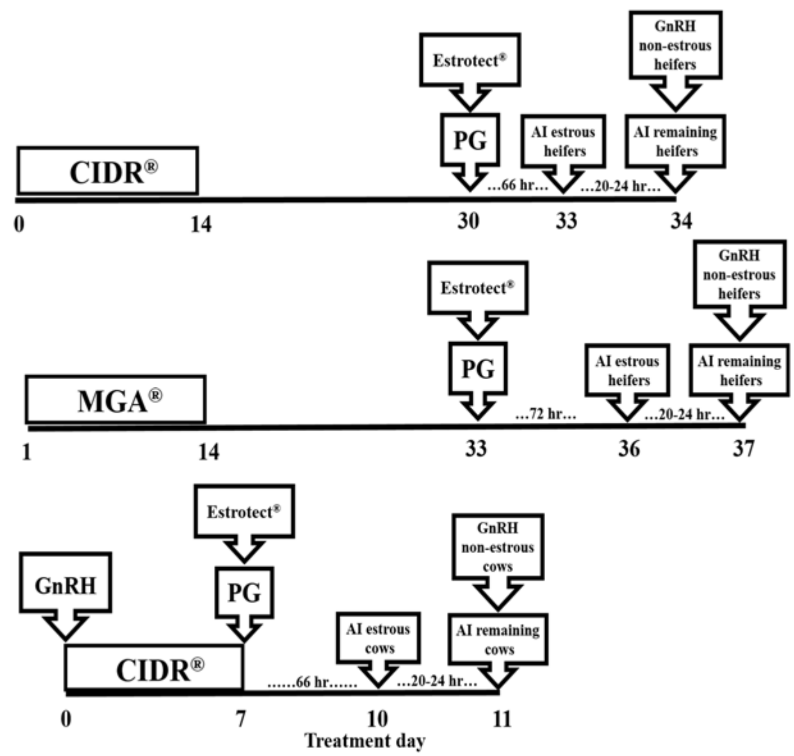

Figure 13. The 14 day CIDR®-PG and MGA-PG protocols with split time AI for heifers and 7-day CoSynch + CIDR protocol with STAI for cows.[157-159;162-163] Estrotect patches are applied at PG treatment. Females with activated patches at 66 hours are inseminated without administering GnRH at AI. Nonestrous females at 66 hours are inseminated 20 - 24 hours later and GnRH is only administered to females at this point that failed to exhibit estrus.

Conclusion

Ensuring long term sustainability of US beef cattle operations will require continued research of new technologies in reproduction and effective integration of these technologies with other disciplines, including genomics, health, and economics. Given the anticipated growth in global population and declining availability of natural resources, application of effective technologies will be critical as agriculture seeks ways to improve efficiencies of production. Outcomes stemming from use of the various protocols and breeding strategies outlined in this review are remarkable and exemplify high-impact transfer of fundamental research to industry end-users. As innovations in reproductive technologies continue to evolve, the need for additional applied research efforts is without question. Moving forward, research efforts should focus on developing: 1) improved methods of estrous cycle control for *Bos indicus* influenced females; 2) improved strategies to expand use of sexed semen; 3) ways in which to distinguish sires based on fertility differences when used in conjunction with FTAI; and 4) ways in which to more effectively translate improvements in technology to industry partners.

Conflict of interest

There are no conflicts of interest to declare.

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