Synchronization of the bovine estrous cycle: Current and emerging opportunities

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Abstract

Controlling the bovine estrous cycle is a necessity if performing fixed-time artificial insemination or embryo transfer. Additionally, irrespective of the genetic objectives driving the decision to use reproductive technologies, the use of synchronization protocols often has beneficial effects on the overall reproductive performance and commercial production output of a beef cattle operation. This proceedings paper provides a general review of the conceptual goals and challenges associated with synchronization of estrus, and directs readers to resources on current protocols and emerging opportunities in the field.

Key words: estrous cycle, bovine, beef cattle

Introduction

Protocols for control of the bovine estrous cycle have evolved rapidly in the last 2 decades, and pregnancy outcomes now achievable with fixed-time artificial insemination (AI) far exceed previously held preconceptions of what was once possible. Scientific progress in this field stemmed largely from research efforts to understand the wave-like pattern of bovine ovarian follicular development. This was largely enabled by the use of ultrasound for non-lethal and minimally invasive visualization of the ovaries throughout the course of an estrous cycle. We now more fully understand the biological variance that exists within a group of females prior to synchronization treatments. As a result of this understanding, translational research efforts led to the development of synchronization systems that more effectively control stage of cycle than ever before.

Protocols that facilitate fixed-time artificial insemination (FTAI) have essentially become standard practice among beef cattle operations using AI – though, to be fair, use of AI in general remains uncommon. Likewise, fixed-time embryo transfer (FTET) is increasingly a realistic opportunity depending on the goals and limitations of the specific operation. This is remarkable progress considering these ideas were hypothetical just a few short decades ago.

Current opportunities for control of the estrous cycle

Each year, the Beef Reproduction Task Force reviews and updates a publication outlining recommended protocols for control of the estrous cycle for beef cows and heifers. Additionally, the Beef Reproduction Task Force provides guidance as to protocols to consider when using sex-sorted semen or when synchronizing estrus prior to natural service. The commercial beef industry is indebted to the task force and its founders for their service and contribution to advancing the use of reproductive technologies. Rather than provide an extensive review here of the protocols currently available and promoted for use among beef cattle, the author refers readers to the Beef Reproduction Task Force materials, available at **https://beefrepro.org**.

Emerging opportunities for control of the estrous cycle

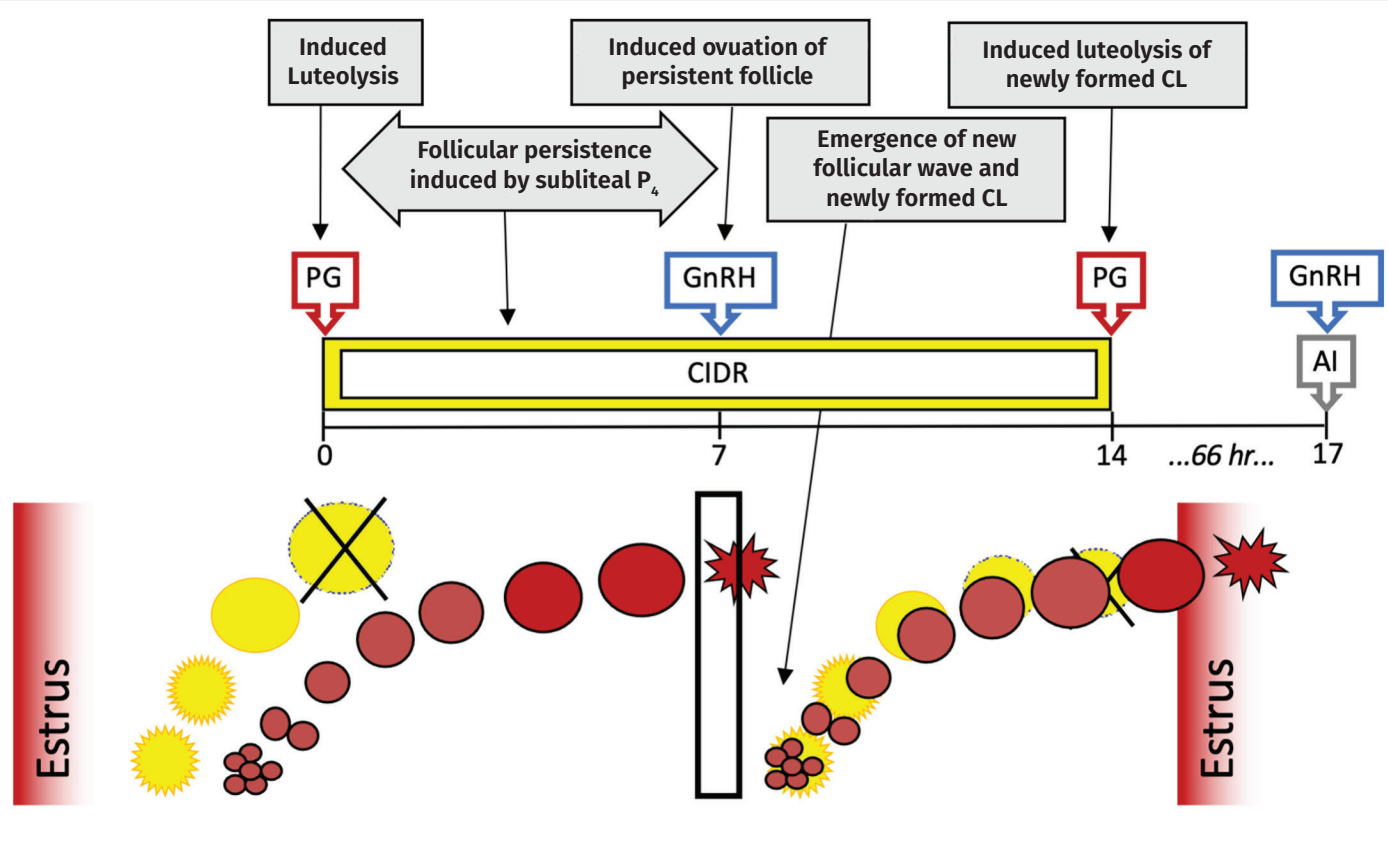
This portion of the proceedings paper will provide context for the research efforts discussed by the author during his presentation at the AABP Recent Graduate Conference. These research efforts related to 7 & 7 Synch protocol (Figure 1) are of course described more fully in other publications (Bonacker et al., 2020a; Bonacker et al., 2020b; Andersen et al., 2021), and the rationale has likewise been discussed in other previously published proceedings by our lab. Efforts by the author's research and extension program at the University of Missouri are built around systems theory. In short, we approach reproductive management as the study of how system quality can be continuously improved. System quality management is in opposition to common industry practices such as "management by metric," in which key metrics (i.e., pregnancy rate) are monitored in order to assess productivity. Detailed discussion of the differences between whole system management and metric-focused management is beyond the scope of this paper. However, the author is increasingly of the opinion that metric-focused management has done harm to beef cattle operations as well as agriculture, industry, education, and science as a whole. More holistic, integrative management is badly needed to address a number of agricultural challenges (Liu et al., 2015).

In systems management, the components of the system are recognized to be complex and often incompletely understood. It can be helpful visually to diagram the system and the relationships of components within the system. Complex interactions need to be considered relative to the overall aim of the system. A key feature of systems management is a strive for continual improvement of the quality of the system rather than simply monitoring the output of the system overall (Deming, 1982; Senge, 1993). System quality often improves not by improving the average output of the system but the variability, or variance, of the output (Shewhart, 1931; Shewhart, 1939). Variance stemming from one component and variance stemming from another component generally compound, resulting in even greater variance in overall output. Reducing variance within the system is therefore a major priority.

Variance in response of cows to estrus synchronization

When addressing control of the estrous cycle as a system, the focus shifts away from monitoring the output of the system with metrics like pregnancy rate and toward evaluating variance resulting from individual components within the system. In taking a system quality management approach to estrus synchronization, the management focus is on minimizing variance in response of cows to key treatments in a synchronization protocol. Designing synchronization systems that minimize variance in stage of cycle effectively, economically, and efficiently

Figure 1: Underlying physiology of the 7 & 7 Synch protocol.



among a widely varied group of females is not a trivial task – especially considering that, in typical production settings, some females are not having normal estrous cycles prior to the protocol due to various management and/or environmental factors.

Protocols commonly used for estrus synchronization elicit a much less uniform response than end users of these protocols often realize. Consider, for example, the 7-day CO-Synch + CIDR protocol widely used across the industry. Although this protocol has facilitated increased use of reproductive technologies in North America, the pregnancy results often attained are almost surprising considering the variation among females treated with the protocol. For a detailed discussion of variance in response to this protocol, see discussion by Bonacker et al., 2020a.

Special causes vs. common causes of variance

A common complaint among users of estrus synchronization is the variability in results with FTAI or ET from year-to-year. In commercial agricultural production systems, cashflow is often just as important as profitability. Thus, the variability in results from year-to-year can be economically devastating for producers, even if the average output may be acceptable and profitable longterm. Scientists and practitioners need to take this into account and strive for continual improvement in system quality, so as to not only improve the average result but decrease the variability in results.

In a systems management approach, variability in outcome can be conceptualized as stemming from one of two broad categories of variance: special cause variance versus common cause variance (Shewhart, 1931; Shewhart, 1939; Deming, 1993). When pregnancy rates are reduced compared to the average, producers often seek to identify a special cause of variance: a specific issue or set of issues beyond the control of the manager that explains the poor results. From a systems perspective; however, it is far more likely that the poor results stem from one or more common causes of variance: issues that are inherent sources of variance within the system and ultimately are (or could be) under the control of management. The realization that poor results stem primarily from common causes – issues management could control – should be empowering rather than discouraging. Identification of the underlying causes of variance allow these components of the system to become leverage points to improve the overall quality of the system and, ultimately, the results the system produces.

Presynchronization

A major priority of our research program is to improve the quality of estrous cycle control systems used for postpartum beef cows, with the understanding that this is in turn an opportunity to improve the overall quality of the reproductive management system. An underlying belief in our program is that results with current industry standard protocols, while certainly acceptable, are not consistently approaching the biological maximum possible simply due to the variance in animal response tolerated within the protocol. Efforts by other research programs and by our own program have demonstrated opportunities to reduce variability in response of females to synchronization through efforts to manage stage of cycle prior to the start of a synchronization protocol. Such treatments

are often referred to as presynchronization. Presynchronization treatments have become an important component of protocols for lactating dairy cows (Bello et al., 2006; Navanukraw et al., 2004; Souza et al., 2008; Wiltbank and Pursley, 2014), and research efforts by our program at the University of Missouri are by no means the first attempts to use presynchronization treatments for beef cows. Indeed, the approach used in the 7 & 7 Synch protocol stems largely from informative studies conducted by other programs using either PG alone prior to GnRH administration (Perry et al., 2012) or, even more similarly, PG followed by CIDR treatment prior to GnRH administration (Small et al., 2009; French et al., 2013).

Results with 7 & 7 Synch

Prior to any large field trials, the effect of varying treatments in advance of GnRH administered at the start of estrus synchronization were investigated (Bonacker et al., 2020a). Administration of PG followed by treatment with an intravaginal progesterone-releasing insert (CIDR) was hypothesized to result in increased follicle size at GnRH, thereby enhancing response to GnRH and overall response to estrus synchronization. With the 7-d CO-Synch + CIDR protocol as a reference, 4 additional treatments were tested to evaluate the effect of a CIDR insert in place 7 days prior to GnRH with or without administration of PG at the start of the CIDR treatment, as well as to evaluate the effect of the CIDR remaining in place following GnRH administration. Blood samples were collected for hormone concentration analysis, ovarian ultrasound was performed to assess ovarian follicle size and presence of corpora lutea, and cows were monitored for onset of estrus using transmitters. In comparison to a standard 7-d CO-Synch + CIDR protocol, administering PG and placing a CIDR insert for 1 week in advance of GnRH significantly enhanced factors associated with follicular maturity and likelihood of GnRH response, such as follicle size (13.4 ± 0.8 versus 8.3 ± 0.7 mm; $P < 0.05$) and serum estradiol concentrations determined by radioimmunoassay (4.7 ± 0.4 versus 2.7 ± 0.2 pg/ml; $P < 0.05$). Based on further observations of CL status at CIDR removal and PG administration, the presynchronization treatment also tended to reduce variation in CL status among cows at PG, with a greater proportion of cows having a single CL (75% [15/20] versus 45% [9/20]; $P = 0.08$) rather than no CL or multiple CL. In addition, this approach tended to increase the proportion of cows expressing estrus prior to FTAI in this pilot study (82% [31/38] versus 68% [25/37]; $P = 0.08$).

A large-scale field trial was designed and conducted in collaboration with Cross Country Genetics (Westmoreland, KS) to evaluate the effectiveness of the 7 & 7 Synch protocol on producer operations (Bonacker et al., 2020b). 7 & 7 Synch was compared to the 7-Day CO-Synch + CIDR protocol to synchronize estrus and ovulation among recipients prior to ET. The trial took place across 13 locations in Missouri and Kansas and included over 1,300 postpartum beef cows of varying age, postpartum interval, and body condition scores. The proportion of cows expressing estrus and presenting with palpable CL at ET was significantly greater ($P < 0.001$) among cows following treatment with the 7 & 7 Synch protocol (Table 1).

An additional large-scale field trial was conducted to compare the 7 & 7 Synch and the 7-day CO-Synch + CIDR protocols for synchronization of estrus among postpartum beef cows prior to FTAI. To assess field fertility of both sex-sorted and conventional semen, half of the cows assigned to each protocol received sex-sorted semen (SexedULTRA 4M®) and half received conventional semen. The trial took place in eleven locations across Missouri and South Dakota and included over 1,500 postpartum beef cows of varying ages, postpartum intervals, and body condition scores. 7 & 7 Synch increased ($P = 0.01$) the proportion of cows expressing estrus prior to fixed-time AI (Table 2). Additionally, 7 & 7 Synch resulted in increased ($P = 0.001$) pregnancy rates to FTAI when using conventional or sex-sorted semen (Table 3).

As a resource for producers and practitioners, University of Missouri Extension publication G2023 has been developed, entitled "7 & 7 Synch: An Estrus Synchronization Protocol for Postpartum Beef Cows". Similar treatment schedules have been evaluated among heifers and cows by other research programs around the country, and the 7 & 7 Synch protocol is now included on the list of protocols promoted annually by the Beef Reproduction Task Force.

Not a silver bullet – taking a multi-year perspective to synchronization

Of course, not every group of cows will routinely achieve a pregnancy rate of > 70% to FTAI following 7 & 7 Synch or any other currently existing protocol, nor will transfer rates and pregnancy results following ET always be exceptional among recipients. Results will vary from location-to-location based on other special causes or common causes of variance. In general,

Table 1: Results with embryo transfer recipients.

Protocol	Expressed estrus	Pregnant/synchronized
7 & 7 Synch	86% (529/615) [a]	40% (263/653) [x]
7-day CO-Synch + CIDR	76% (488/640) [b]	34% (228/664) [y]

Source: Bonacker et al., 2020b.

Table 2: Estrus expression prior to fixed-time artificial insemination.

Protocol	Expressed estrus
7 & 7 Synch	82% (630/769) [a]
7-day CO-Synch + CIDR	64% (492/769) [b]

Source: Andersen et al., 2020.

Table 3: Pregnancy rates to fixed-time artificial insemination.

Protocol	Conventional semen	Sexed semen
7 & 7 Synch	72% (280/389) [a]	52% (199/380) [c]
7-day CO-Synch + CIDR	61% (233/383) [b]	44% (170/386) [d]

Source: Andersen et al., 2021.

producers and practitioners should focus on common causes of variance in the overall system: cow age, body condition score, postpartum interval, plane of nutrition, etc. Some products used in a synchronization protocol (e.g., a CIDR) can mitigate the impact of these factors, but it must be emphasized that synchronization is only one component of the overall reproductive management system.

The synchronization protocol used is an important component of the system, however, and it is one of few components of the system over which a veterinarian can exert a great deal of influence. Thus, the variance stemming from the synchronization protocol itself is an important consideration. Results from our research program demonstrate that the presynchronization approach used in the 7 & 7 Synch protocol reduced variation among cows in luteal status and increased follicular maturity prior to the first GnRH administration of the protocol, thereby reducing variance among cows in ovarian presentation at the end of the protocol. This results in reduced variance among cows in estrous status thereafter, as a greater proportion of cows go on to express estrus within a narrow period of time. As a result, extensive on-farm field trials using this synchronization system have yielded exceptional pregnancy rates when used to facilitate an ET program or a FTAI program using either conventional or sex-sorted semen.

Reproductive management of beef cattle is too often viewed with a single year focus. One year simply represents far too narrow of a window of time within the overall beef cattle production cycle, as most common causes of variance in pregnancy rate are carryover effects from previous years' management. Multi-year perspectives are needed to understand and address causes of suboptimal reproductive performance. Much the same way, a multi-year perspective is needed to understand and capture the value stemming from estrus synchronization protocols. Results from our research program using the 7 & 7 Synch protocol clearly demonstrate the efficacy of this protocol when used across the herd. However, results are optimized among cows that are likely to be cyclic at the start of the synchronization protocol. Ultimately, if a multi-year perspective is taken, the proportion of cows that are cyclic prior to treatment is largely under the control of the manager. With a multi-year commitment to ever-improving the quality of the overall system – which includes not only the synchronization protocol but a host of other components under the influence of management – reproductive outcomes will improve steadily and approach the biological maximum for the population.

References

Andersen CM, Bonacker RC, Smith EG, Spinka CM, Poock SE, Thomas JM. Evaluation of the 7 & 7 Synch and 7-day CO-Synch + CIDR treatment regimens for control of the estrous cycle among beef cows prior to fixed-time artificial insemination with conventional or sex-sorted semen. *Anim Reprod Sci* 2021;235:106892. **https://doi.org/10.1016/j.anireprosci.2021.106892**

Bello NM, Steibel JP, Pursley JR. 2006. Optimizing Ovulation to First GnRH Improved Outcomes to Each Hormonal Injection of Ovsynch in Lactating Dairy Cows. *J Dairy Sci*. 89:3413-3424. **https://doi.org/10.3168/jds.S0022-0302(06)72378-5**

Bonacker RC, Stoecklein KS, Locke JWC, Ketchum JN, Knickmeyer ER, Spinka CM, Poock SE, Thomas JM., 2020a. Treatment with prostaglandin F2α and an intravaginal progesterone insert promotes follicular maturity in advance of gonadotropin-releasing hormone among postpartum beef cows. *Theriogenology* 157:350-359. **https://doi.org/10.1016/j.theriogenology.2020.08.018**

Bonacker RC, Gray KR, Breiner CA, Anderson JM, Patterson DJ, Spinka CM, Thomas JM., 2020b. Comparison of the 7 & 7 Synch protocol and the 7-day CO-Synch + CIDR protocol among recipient beef cows in an embryo transfer program. *Theriogenology* 158:490–496. **https://doi.org/10.1016/j.theriogenology.2020.09.033**

Deming WE. 1982. *Out of the Crisis*. The MIT Press.

Deming WE. 1993. *The New Economics for Industry, Government, and Education*. The MIT Press.

French JT, Ahola JK, Whittier JC, Giles RL, Repenning PE, Seidel GE, Peel RK. 2013. Ovarian response and pregnancy rates to timed artificial insemination in beef heifers after synchronization of follicular waves and ovulation via a 14-day controlled internal drug-release insert estrus synchronization protocol. *Prof Anim Sci*. 29:64-74. **https://doi.org/10.15232/S1080-7446(15)30197-2**

Liu J, Mooney H, Hull V, Davis SJ, Gaskell J, Hertel T, Lubchenco J, Seto KC, Gleick P, Kremen C, Li S. 2015. Systems integration for global sustainability. *Science*. 347:1258832. **doi:10.1126/science.1258832**.

Navanukraw C, Redmer DA, Reynolds LP, Kirsch JD, Grazul-Bilska AT, Fricke PM, 2004. A Modified Presynchronization Protocol Improves Fertility to Timed Artificial Insemination in Lactating Dairy Cows. *J Dairy Sci* 87:1551-1557. **https://doi.org/10.3168/jds.S0022-0302(04)73307-X**

Perry GA, Perry BL, Krantz JH, Rodgers J, 2012. Influence of inducing luteal regression before a modified fixed-time artificial insemination protocol in postpartum beef cows on pregnancy success. *J Anim Sci*. 90:489–494. **https://doi.org/10.2527/jas.2011-4319**

Senge P. 1993. *The Fifth Discipline: The Art & Practice of the Learning Organization*. Currency.

Shewhart WA. 1931. *Economic Control of Quality of Manufactured Product*. D. Van Nostrand Company.

Shewhart WA. 1939. Statistical Method from the Viewpoint of Quality Control. U.S. Department of Agriculture.

Small JA, Colazo MG, Kastelic JP, Mapletoft RJ. 2009. Effects of progesterone presynchronization and eCG on pregnancy rates to GnRH-based, timed-AI in beef cattle. *Theriogenology*. 71:698-706. **https://doi.org/10.1016/j.theriogenology.2008.09.045**

Souza AH, Ayres H, Ferreira RM, Wiltbank MC, 2008. A new presynchronization system (Double-Ovsynch) increases fertility at first postpartum timed AI in lactating dairy cows. *Theriogenology*. 70:208-215. **https://doi.org/10.1016/j.theriogenology.2008.03.014**

Thomas JM, Bonacker RC, Andersen CM. 2020. 7 & 7 Synch: An Estrus Synchronization Protocol for Postpartum Beef Cows. University of Missouri Extension. Available at: **https://extension.missouri.edu/g2023/**

Wiltbank MC, Pursley JR, 2014. The cow as an induced ovulator: Timed AI after synchronization of ovulation. *Theriogenology* 81, 170–185. **https://doi.org/10.1016/j.theriogenology.2013.09.017**