Estrous Synchronization in Heifers

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Introduction: Heifers are excellent candidates for the use of artificial insemination for both practical and physiological reasons. Since they have not previously calved, the typical concerns of interval from parturition to onset of AI and its influence on success rate, the possibility of inappropriate uterine function due to a difficult birth or infection, and the challenges of separating calves to implement an AI program are non–existent. Furthermore, heifers often have been managed such that wide ranges or major deficiencies in body condition do not exist at the onset of the AI program, and they are often housed or pastured in, or can be more easily transported to, locations that are accessible to working facilities. From a physiological perspective, heifers are much more likely to have calving difficulty at their first parturition. Thus, the use of sires that will predictably transmit an acceptable birth weight in their progeny is critical. This predictability can be most easily obtained from proven AI sires with large databases and high accuracy for birth weights. Finally, from a genetic standpoint, heifers should represent the best and most genetically advanced females in the herd as a result of previous breeding decisions. The mating of AI sires that rank near the top of the breed in the categories of emphasis with the genetically superior females will accelerate the genetic progress achieved within the herd.

Given the advantages listed above, it would seem that achieving high pregnancy rates in a short period of time would be easily achievable using AI on heifers. However, a major factor that limits success rate of AI programs in heifers is the timing of puberty relative to the onset of the breeding season. It has been demonstrated that heifers are less likely to become pregnant on their first estrous cycle at puberty, and that fertility increases through the 3rd estrus (5). In some instances, producers are misled to think that all their heifers have reached puberty well before the start of the AI season due to the occurrence of estrus without ovulation (nonpubertal estrus; 38, 47). Precocious onset of estrous cycles does occur in a significant proportion of heifers (15, 54). However, in a recent paper that included 724 heifers across 5 locations in the US (31), 43% of heifers were prepubertal seven days before the onset of the AI season, with a range of 6 to 81% being prepubertal across the herds. The proportion of heifers that are prepubertal at the onset of their first breeding season can be reduced through proper nutrition management and selection of heifers that are more likely to reach puberty within the appropriate timeframe (25). However, it is a certainty that some heifers will be prepubertal as their first breeding season approaches, and synchronization programs should be structured to deal with both cyclic and prepubertal heifers.

Estrous Synchronization Programs in Heifers: A variety of programs for estrous synchronization have been developed and investigated (12, 13, 14). In this paper we will concentrate on those programs that are currently in use or which expanded use in the future may be anticipated. Many of the programs described include compounds, or combinations of treatments, that have not necessarily been approved by the FDA for use in this manner. A standard program for the synchronization of estrus in heifers that was used widely over the past 3 decades was the SYNCRO-MATE-B® program. This product is no longer available in the USA and will not be discussed in detail. Across 5 reports using this system in heifers (n=599; 4, 6, 10, 49, 56), mean conception rates were 51.6% (range 40.6-59.1) and in 4 reports that included timed AI (n=199;6, 30, 36, 57), pregnancy rates averaged 49.5% (range 35.4-70.3%).

Synchronization using Prostaglandin $F_2\alpha$: The most traditional approach to estrous synchronization in the USA has been through the use of prostaglandin $F_2\alpha$ (PGF). Prostaglandin $F_2\alpha$ regulates a female's estrous cycle by causing regression of the CL. An injection of a PGF will mimic natural PGF release from the uterus to cause CL regression. Coordinated regression of the CL will synchronize a decline in progesterone and result in a relatively synchronous display of estrus 2 to 5 days later. Thus, in order for PGF to be effective, females must be cyclic, and in a responsive phase of the estrous cycle. It has been established that PGF does not consistently cause luteal regression on days 1-5 of the estrous cycle (28) but is effective from days 6 to 17 (29). However, during this "effective period", a graded response has been noted as the estrous cycle progresses (J. Chenault, unpublished data). In this summary of data regarding the effects of day of the estrous cycle on responsiveness to PGF it was determined that the response was lowest in females treated between days 5 and 9 (67%), intermediate for those treated on days 9 to 12 (77%) and greatest in females treated after day 12 (91%). After day 17 of the estrous cycle, PGF does not appear to influence the timing of estrus, but since these females will spontaneously show estrus in the next 2 to 6 days, they are synchronized by default when using PGF.

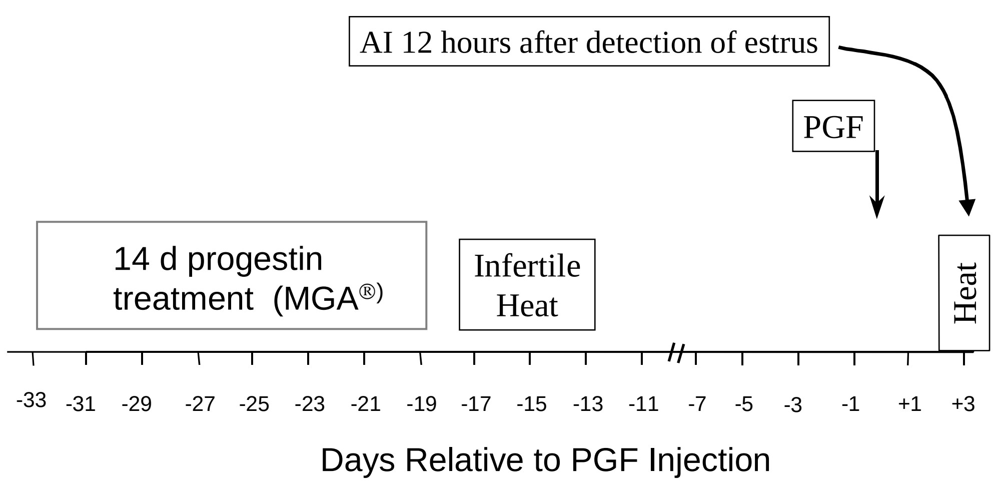
A variety of approaches have been developed in an effort to ensure that most cyclic females have a responsive CL at the time of PGF thereby increasing the proportion in which estrus is synchronized. Most common is a two-injection method, in which two treatments with PGF are spaced at intervals of 10 to 14 days. With this approach, the theoretical expectation would be that estrus would be synchronized in 60 to 70% of cyclic females following the first injection, and 90+% of females after the second injection, since no heifers would be in the first 5 days of their estrous cycle at the time of the second injection. Sometimes in practice, the females in estrus after the first injection are inseminated, and the second injection is given only to those that did not respond to the first PGF treatment. Alternatively, a period of heat detection and breeding for 5 to 7 days prior to administration of a single dose of PGF is another approach to eliminate heifers that will not respond to PGF.

In a majority of reports in which estrus has been synchronized with PGF, and AI has been performed based upon heat detection, fertility is approximately equal to that of females inseminated following detection of a spontaneous estrus. Across 12 experiments (3, 7, 10, 11, 16, 20, 24, 37, 50-53) which included over 1750 heifers receiving a PGF-based synchronization system, conception rates to the synchronized estrus ranged from 38.7 to 88%, with an average conception rate of 62.8% overall. The number of pregnancies that occur in a synchronization period is a function of both conception rate and submission rate (number of animals submitted for AI during the synchronization period). The pregnancy rates that will be achieved with a PGF -based system will obviously be determined in part by the system chosen (one injection, two injection, etc.). In practice, perhaps the largest determinant of pregnancy rate during a synchronization period would be the proportion of the females that are prepubertal. As an example, consider a group of heifers in which 40% are prepubertal and that are treated with a standard two-injection PGF program. It could be estimated that approximately 90% of the cyclic heifers would show estrus (90% x 60% = 54% submission rate) and using the average conception rate cited above (62.8%), the expected pregnancy rate during the synchronization period would be 34% (submission rate x conception rate).

In summary, PGF can be used to synchronize an estrus of normal fertility in a majority of the cyclic heifers treated. The precision of the synchronized estrus is acceptable for an AI program in which heat detection is used to determine the appropriate time to AI but does not yield predictable outcomes if timed AI is used. If a significant proportion of heifers are prepubertal, pregnancy rates will be lower than anticipated.

MGA and PGF Synchronization System: Currently, this system is widely used for synchronization of estrus in heifers. This approach involves feeding the orally active progestin, MGA (melengestrol acetate), for 14 days and injecting PGF 17 – 19 days after the last feeding of MGA (MGA - PGF; 4; Figure 1).

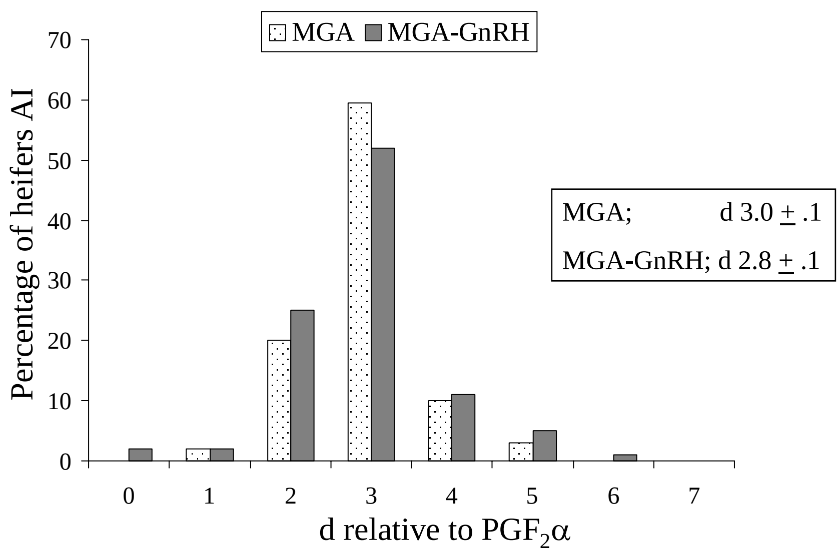
Figure 1. MGA- PGF for Heifer Synchronization



Feeding of the orally active progestin, MGA, for 14 days serves two purposes. First, this treatment will synchronize estrus in cyclic heifers such that all these females will be in estrus during the 7 day period following the MGA feeding period. Secondly, this treatment will induce some prepubertal heifers to ovulate during this same time period as it has been demonstrated that similar progestin treatments induce puberty in heifers (2, 19, 22, 45). The synchronized estrus/ovulation that occurs during the 7 days following the last day of MGA feeding (26, 39, 42) is of low fertility as a result of the extended progestin treatment. Females are not bred at this initial estrus, but an injection of PGF is given 17 - 19 days after the last feeding of MGA (approximately 10 to 16 days after the infertile estrus) when a majority of females are in the last half of their estrous cycle. As a result, the efficacy of PGF for luteal regression is high and the PGF - induced estrus is of optimal fertility. Also, since a majority of females are in the second half of their estrous cycle at the time of PGF administration, the precision of estrus is generally higher than that achieved with PGF alone. With this combination, the capacity of progestins to induce onset of and synchronize estrus is used in order to group females in a stage of the estrous cycle at which PGF is of greatest efficacy.

In a recent experiment involving 709 heifers at 4 locations, we reported (23) submission rates of 83.4% in heifers receiving the MGA – PGF protocol during the 7 days following PGF with the peak timing of AI occurring the 3rd day after PGF (Figure 2; d 3.0 ± .1, MGA). Conception rate in this experiment was 75.8%, resulting in a pregnancy rate of 63.2% in this group of heifers.

Figure 2. Day of AI During the Synchrony Period

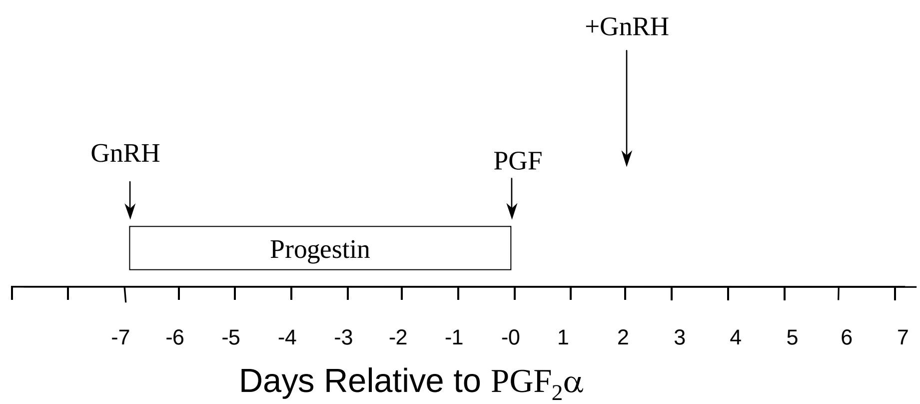


A review of 8 reports (4, 17, 21, 27, 41, 48, 51, 55) which included over 2800 heifers receiving an MGA – PGF system indicated that the average submission rate across these experiments was 84.8%. Average conception rate across these studies was 67.2% (range 44 to 82%) and pregnancy rates averaged 57% (range 41 – 80%). Generally, it is reported that conception rates of heifers inseminated after detection of estrus in the MGA-PGF system are equal to, or greater, than those achieved with insemination at a spontaneous estrus or following administration of PGF alone (3) and this agrees with the data we have derived from review of the literature (65.7 vs. 62.8 %, respectively).

Results of experiments in which timed insemination has been used with the MGA-PGF system have been variable. However, there have been attempts to improve the precision of estrus with this program to support timed AI by addition of a GnRH treatment. It was demonstrated (58) that treatment of heifers with 100 µg of GnRH seven days before PGF (see Figure 1) would coordinate follicular development and potentially increase the precision of the estrus following PGF. However, in the study represented by Figure 2 (23), this additional treatment failed to increase the precision of estrus (MGA – GnRH, d 2.8 ± .1) and had no detrimental effect on conception rate (61.5%).

GnRH – PGF Programs: Several programs of estrous control in cattle have been developed in the last decade that use a combination of GnRH and PGF. All GnRH - based systems of estrous control include administration of GnRH (or an analogue) followed 6 or 7 days later with PGF (GnRH-PGF). Administration of GnRH is aimed at inducing a synchronous emergence of a new wave of follicular growth 1 to 2 days later, and regression of corpora lutea on day 6 or 7 permits initiation of the follicular phase. If this initial GnRH injection is effective, follicles are in a standard and mature stage of development at the time of luteal regression and the precision of the synchronized estrus is increased.

Figure 3. GnRH - Based Systems of Estrous Synchronization



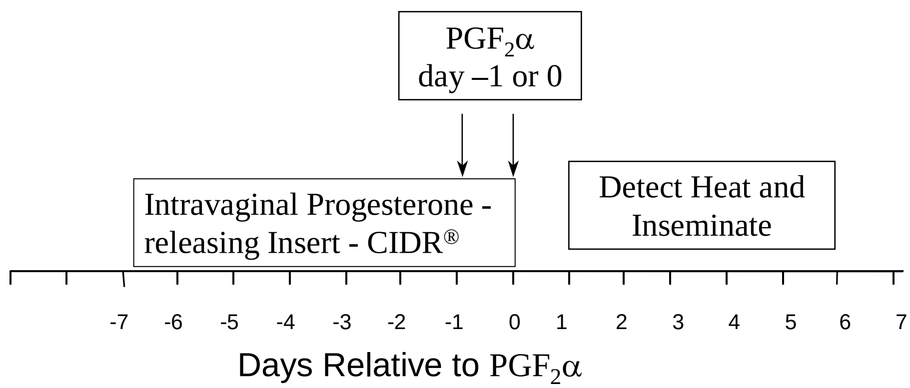
If only GnRH and PGF are given, and females are inseminated based upon detection of estrus, this program is commonly referred to as “Select Synch”. If the +GnRH (Figure 3) is administered on day 2 to 2.5, and females are timed AI coincident with the +GnRH treatment, this is referred to as a “CO-Synch” protocol. If AI is delayed for 8-16 hours after +GnRH, the terminology used in the field is “Ovsynch”. When a combination of heat detection and timed AI are used after PGF, with timed AI usually occurring on day 3 in females that are not detected in estrus, this program is referred to as “Hybrid-Synch” or “MSU-Synch”. The addition of a progestin usually involves treatment with a CIDR or MGA, thus programs are usually referred to as “MGA – Select”, “CO-Synch + CIDR”, or similar terminology.

Across 4 reports (18, 46, 50, 51) in which heifers received the Select Synch treatment and were inseminated based upon estrus detection (n=547 heifers), conception rates averaged 63.9%, ranging from 59.3 to 69.2%. In general the GnRH–PGF system results in conception rates similar to those achieved with PGF or MGA-PGF programs. The submission rates with the GnRH–PGF system in heifers is highly dependent upon the defined period of estrus detection. For example, in two large studies 20 and 12 % of heifers receiving this treatment were in estrus before, or at the time, of PGF treatment. If these animals are inseminated, and included in the calculated pregnancy rates, similar, or slightly lower pregnancy rates relative to the MGA-PGF system are typically evident. The occurrence of estrus outside the planned synchronization period is greater in heifers than cows, probably due to a reduced ability of the initial GnRH treatment to induce ovulation and reset follicular development in heifers (35, 44). While the early occurrence of estrus (and in some cases delayed estrus) can be managed with liberal heat detection in a Select Synch approach, they present a greater problem when a timed AI program is used. For example, pregnancy rates to timed AI were substantially lower (average of 38.9% across 3 studies with 213 heifers; 33, 43, 50) when a CO-Synch approach was used. In work from our lab, we implemented a CO-Synch program following MGA pretreatment (23) to implement timed AI in heifers. Pregnancy rate to the timed AI with CO-Synch was 19% lower than when Select Synch with estrus detection, or the standard MGA–PGF program was implemented. Inclusion of all heifers that were in estrus and AI either before or shortly following the timed AI in this study restored the pregnancy rate to that of the Select Synch or MGA-PGF approach. Thus use of a CO-Synch approach in heifers typically will be less effective than when systems that involve detection of estrus are employed.

Some experiments have been performed to determine if the addition of a progestin to a CO-Synch type of program in heifers would improve pregnancy rates (Figure 3). In two studies (32, 33) in which a CIDR was added to a CO-Synch protocol in heifers, pregnancy rates were 65 and 68%. Addition of the progestin, MGA, resulted in an average pregnancy rate of 45.3% (range 36 to 52.5%) across 3 studies (32, 34, 40). In a study directly comparing a CO-Synch to a CO-Synch + CIDR treatment (33), addition of the CIDR increased pregnancy rates to timed AI from 39 to 68.0%, however, numbers are limiting in this study. These findings provide encouragement that this may be an effective approach for timed AI in heifers, but further research is needed.

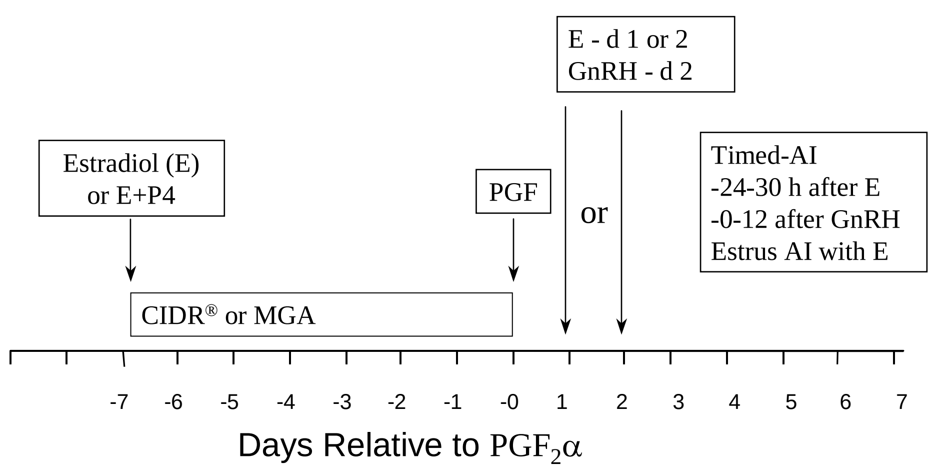
CIDR–PGF Program: The CIDR is marketed in the USA to be used in combination with an injection of PGF. The CIDR is inserted into the vagina of the female for 7 days (Figure 4). An injection of PGF is given on day –1 (or day 0) and females are inseminated based upon detection of estrus during the 3 to 6 day period beginning on day 1. The progesterone from the CIDR suppresses heat from days –7 to 0, thus no heat detection is necessary during this time. A large experiment that included 724 yearling heifers at 5 locations across the US was performed to compare the effectiveness of this approach (CIDR+PGF) to a single PGF injection (PGF) and to non-synchronized (Control) females (31). In this study, approximately 43% of the heifers were prepubertal at the start of the CIDR+PGF treatment. Comparing the two synchronization treatments, the CIDR+PGF treatment increased synchronization rate by approximately 35%, and pregnancy rate by approximately 25%, during a 3 day synchronization period (day 1 – 3); relative to the PGF treatment. These gains occurred in both prepubertal and cyclic heifers. Pregnancy rates during the 3-day synchronization period were 39% for yearling heifers in the CIDR+PGF treatment (49% in cyclic and 28% in prepubertal heifers). Use of the CIDR in this manner concentrated breeding, induced anestrus females to cycle, increased pregnancy rates and did not negatively affect conception rate.

Figure 4. CIDR® and PGF Synchronization System



Estradiol–Progestin Programs: Systems of estrous control that include estradiol (or estradiol and progesterone) administered by injection, a progestin delivered with either a CIDR or MGA for 6-8 days, PGF for luteal regression and either estradiol or GnRH to synchronize ovulation have been developed and are used as a primary means of estrous control in many countries. In the US, the only form of injectable estradiol that is approved for use in cattle is estradiol cypionate (ECP). Research findings using estradiol benzoate and estradiol 17β will be discussed below but the fact that these are not approved compounds in the USA should be reiterated.

Figure 5. Progestin and Estradiol Systems in Cattle



Only a few reports have been published regarding the use of estradiol and progestins in beef heifers. In a study (32) using estradiol benzoate in conjunction with a CIDR or MGA, timed AI pregnancy rates were 61.5 and 60.4% respectively in beef heifers. In unpublished work from our laboratory, treatment with 1 mg of estradiol benzoate (EB) at CIDR insertion and .5 mg of EB 2 days after CIDR withdrawal resulted in a 64% pregnancy rate in heifers bred by AI 12 h after detection of estrus. Comparisons between the use of estradiol and GnRH to synchronize ovulation have been inconclusive. In unpublished data from our laboratory, similar pregnancy rates (57%) were obtained when estradiol or GnRH were used to synchronize ovulation following a Select Synch protocol in postpartum cows.

Since ECP is available for use in cattle in the US, interest in using this estrogen, rather than estradiol benzoate or 17β, in conjunction with the CIDR to reset follicular development and to synchronize ovulation has increased. Comparisons of the use of ECP to estradiol 17β in heifers to synchronize ovulation at the end of an estradiol 17β+CIDR program resulted in a similar pregnancy rate (64%) to timed AI (8, 9). A recent comparison of an “ECP CIDR ECP” program to a CO-Synch+CIDR program (9) with over 900 heifers indicated that similar pregnancy rates (~56.5%) could be achieved with using either GnRH or ECP at the initiation of these programs. This report further indicated that use of ECP 24 hours after CIDR withdrawal to synchronize ovulation resulted in greater pregnancy rates than when GnRH was used 52 hours after CIDR withdrawal to synchronize ovulation. Additional work is needed to determine the best use for ECP in synchronization programs in heifers.

Summary: Some of the major programs used to synchronize estrus are discussed in the preceding sections of this paper. We surveyed the literature from the last 15 to 20 years to develop estimates for pregnancy and/or conception rates that can be achieved with the primary systems discussed. This is far from a complete compilation of all that has been published, but for some of the programs there are enough animals represented to give some assurance that the true level of efficacy is not too far removed from those derived. For other programs, the numbers of observations are low, and more information is necessary to establish a more predictable estimate. To cover the entire milieu of minor variations within each program that have been investigated is beyond the scope of this manuscript. Table 1 below presents some of these estimates for comparison.

Some general observations can be gained from review of Table 1. First, it appears that in systems that use AI based upon estrus detection, conception rates are very similar and exceed 60%. In timed AI programs that use GnRH, the CIDR appears to provide a substantial level of control of early heats and permits acceptable pregnancy rates using this approach. The CIDR+ PGF result is based on a single experiment, and further replication is necessary to determine how this system will compare to some of the others listed. The estradiol+CIDR results are very positive, although number of observations is limiting. The lack of an estradiol product approved for use by the FDA other than ECP is of some concern. However, initial results using of ECP in this type of program in heifers suggest that it might be at least as efficacious as GnRH and the other estrogens that are traditionally used. Further investigations are necessary to establish the effectiveness of the estradiol+CIDR programs in heifers.

Table 1. Estimates of conception and pregnancy rates for heifers synchronization programs.

Synchronization System	Conception Rate % (Range)	Pregnancy Rate % (Range)
PGF–Based Systems	62.8 (39–88)	na[a]
MGA–PGF System	67.2 (44-82)	57 (41-80)
Select Synch System	63.9 (59-69)	na[b]
CO–Synch System	38.9[c]	38.9[c]
CO–Synch+CIDR	66.5 (65-68)	66.5 (65-68)[d]
CIDR+PGF System	60[e]	39[e]
Estradiol+CIDR[f]	60.6 (57-64)[f]	60.6 (57-64)[f]

[a]Pregnancy rate varies widely, depending upon the proportion of prepubertal heifers and the system used (e.g. 2 injections of PGF, estrus detection for 5 days followed by PGF, etc.)

[b] Pregnancy rates depend highly upon duration of the heat detection period. If heifers in estrus before or at the time of PGF treatment are AI and included, pregnancy rates tended to be slightly lower than for the MGA – PGF treatment.

[c] Pregnancy rates include only those pregnancies established at timed AI. If pregnancies in heifers in estrus and AI before or shortly after timed AI are included, pregnancy rates appear to be similar to Select Synch or MGA – PGF.

[d] Limited numbers of animals in this estimate.

[e] Data from a single report

[f] Includes use of estradiol benzoate, 17β, and/or cypionate. Limited numbers of animals in some studies.

In conclusion, a variety of systems exist, or are in development, for synchronization of estrus in heifers. Further research will help define the expected outcomes that can be achieved with the different approaches that are and will be available in the future. The relative outcomes are critical when comparing costs of various systems of estrous control, however, as should be evident from Table 1, variation in response between differing approaches is not as great as might be predicted. Costs of pharmaceutical compounds and labor for each program can be estimated. Choosing the system that is optimal for a given situation will include careful consideration of the product costs. However, at least as important as these "cash costs" is how an individual program meshes with the expertise of the cattle manager, the manner in which the cattle are managed, the facilities available, the value of the semen to be used, the value of a synchronized AI pregnancy relative to one that is established later in the breeding season and other factors. The most cost effective program for an individual situation will be the system that can be effectively implemented in that situation and matches the needs and expertise of the production system.

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