SYNCHRONIZING ESTRUS AND ABORTING BEEF HEIFERS WITH ALFAPROSTOL, A PROSTAGLANDIN $F_2\alpha$ ANALOG

by

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LITERATURE REVIEW

Properties of Prostaglandins

Prostaglandin $F_2\alpha$ ($PGF_2\alpha$) is a 20-carbon unsaturated fatty acid that contains a 5-carbon ring with two double bonds outside the ring (Stryer, 1975). The structure is shown in figure 1. $PGF_2\alpha$ is synthesized in the body from arachidonic acid.

Exogenous $PGF_2\alpha$ causes corpus luteum (CL) regression in several mammals including cattle (Lauderdale, 1972; Liehr et al., 1972; Louis et al., 1972; Rowson et al., 1972; Inskeep, 1973). Several synthetic analogs have been developed since the discovery of $PGF_2\alpha$ as a luteolytic agent. The structures (figure 1) and luteolytic properties of the analogs are quite similar (Schams and Karg, 1982). Some of the analogs which are luteolytic in cattle are ICI 79,939 (Tervit et al., 1973; Dobson et al., 1975), cloprostenol or ICI 80,996 (Cooper, 1974; Deletang, 1975), alfaprostol (Jóchle et al., 1982; Schams and Karg, 1982), fenprostalene (Diamond Laboratories, Inc., 1982), Prosolvin and HR 837V (Schams and Karg, 1982).

The luteolytic properties of $PGF_2\alpha$ and its analogs in cattle make them capable of controlling the estrous cycle and aborting unwanted pregnancies (Lauderdale, 1972).

Estrous Control Through Luteolytic Properties of $PGF_2\alpha$ and its Analogs

Estrous control day 1 through 4. Heifers treated with $PGF_2\alpha$ on d 1 to 4 of the estrous cycle do not respond by exhibiting estrus

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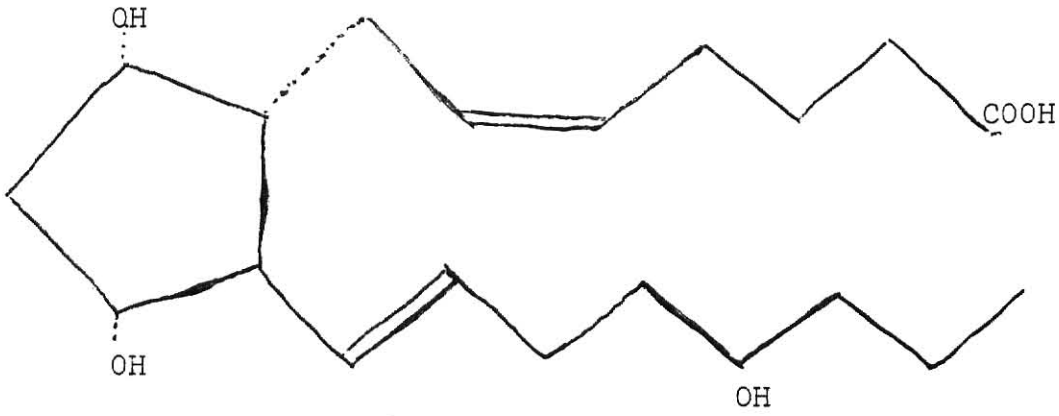

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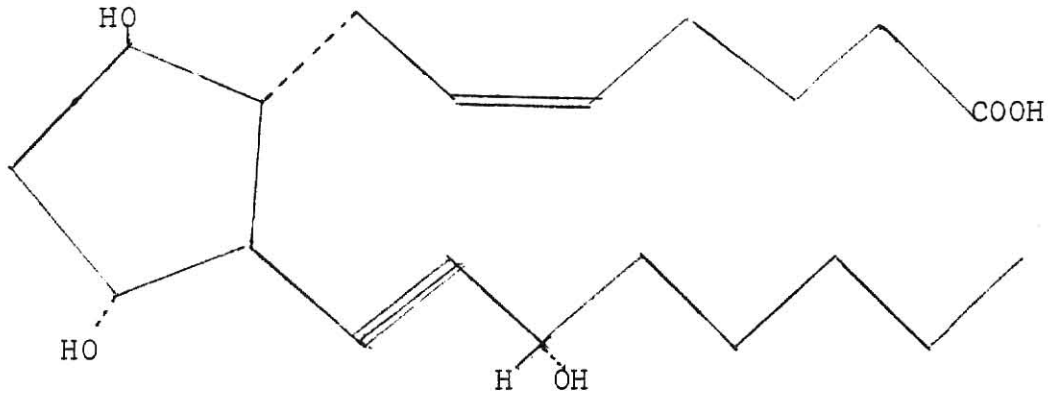

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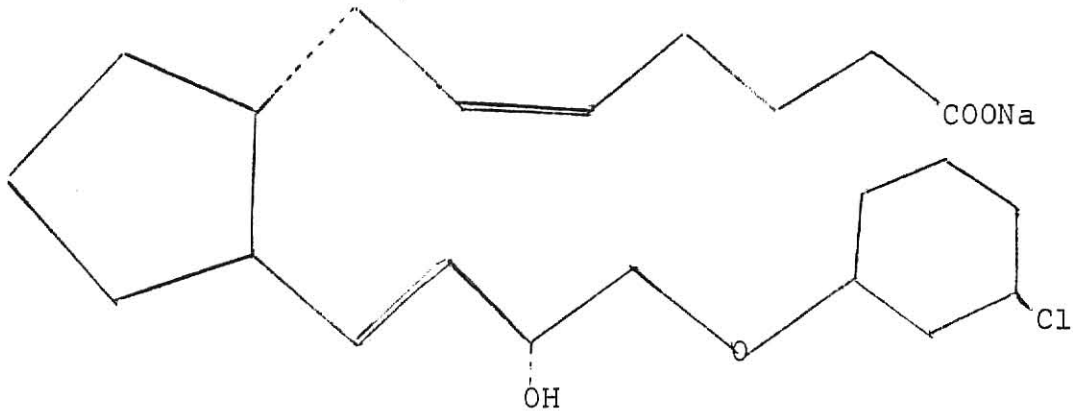

Cloprostenol

Figure 1. Chemical structures of prostaglandin $F_{2\alpha}$ and two analogs.

(Lauderdale, 1972; Rowson et al., 1972; Ellicott et al., 1974). Cloprostenol has also been ineffective for inducing estrus when injected early in the estrous cycle (Cooper, 1974). Uterine infusion of 500 ug or 2 mg $PGF_2\alpha$ d 3 to 5 caused a slight decrease in progesterone, however progesterone rebounded to normal levels with no reported change in cycle length (Liehr et al., 1972 and Henricks et al., 1974).

A single im injection or two im injections of 25 mg $PGF_2\alpha$ given on consecutive days within the first 3 d of the estrous cycle did not affect cycle length although progesterone secretion was reduced. In the same study, twice daily injections given on d 3 and 4 induced estrus but the same treatment given on d 2 and 3 gave no estrus response (Beal et al., 1980). One theory on the resistance of the newly formed CL to $PGF_2\alpha$ is that the preovulatory surge of LH saturates and bonds the regulatory units of the luteal cells, therefore acting to protect the new CL (Saumande and Chapin, 1981).

Estrous control day 5 through 16. $PGF_2\alpha$ and its analogs are effective in rapidly regressing the CL between d 5 and 16 in the normal bovine estrous cycle or in the case of a persistant CL (Rowson et al., 1972; Roche and Prendeville, 1979). Infusion of 5 mg $PGF_2\alpha$ into the uterine horn ipsilateral to the CL caused a 37 to 70% reduction in the size of the CL within 24 h (Louis et al., 1972). Edquist et al. (1975) reported similar results in that im injections of $PGF_2\alpha$ caused the CL to regress from 16 to 24 mm to 10 to 14 mm 24 h after injection.

Progesterone levels fall rapidly with a decrease in size and activity of the CL. Inskeep (1973) showed serum progesterone decreased by 50% within 4 h after injection and numerous researchers (Chenault et al., 1976; Edquist et al., 1975; Sequin, 1979; Bosu et al., 1981) have shown

levels below .5 ng/ml 24 h after injection. Many $PGF_2\alpha$ analogs exhibited similar characteristics in work reported by Schams and Karg (1982).

Day of treatment during diestrus may influence the rate of serum progesterone decline. An earlier decline was noted in cattle treated on either d 11 or 14 than in those treated on d 5 or 7 (King et al., 1982 and Louis et al., 1974).

Other reproductive hormones are usually affected by a decline in progesterone levels. Estradiol increased linearly after $PGF_2\alpha$ treatment to greater than 4 pg/ml at 52 h (Chenault et al., 1976) and LH increased concurrently with decreases in progesterone 4 to 5 h after injection of .5 mg cloprostenol (Schams and Karg, 1982). Cattle treated with 30 mg $PGF_2\alpha$ exhibited peak LH levels 2.3 $\pm$ .6 h after the onset of the induced estrus (Ellicott et al., 1974). Schams and Karg (1982) reported neither cloprostenol nor alfaprostol affected FSH secretions.

Several factors can affect the interval to estrus after administering $PGF_2\alpha$ on d 5 to 16 of the estrous cycle. Uterine infusion of .5 mg $PGF_2\alpha$/d on two consecutive days caused estrus within 3 d in most cases (Rowson et al., 1972). Infusion of 5 mg $PGF_2\alpha$ into the uterine horn ipsilateral to the CL on d 11 or 15 resulted in estrus on an avg of 68 $\pm$ 1.5 h or 73 $\pm$ .7 h after injection, respectively (Louis et al., 1972). However in repeating the experiment Louis et al. (1974) reported that uterine infusions on d 7, 11, or 15 caused no significant differences in interval to estrus although progesterone decreased more rapidly in animals treated on d 11. Dosage was not a factor in response time in cows infused intrauterine with 1.5 or 2 mg $PGF_2\alpha$ on d 6 to 17 since all were in estrus 60 to 80 h later (Inskeep, 1973). Intramuscular injections of $PGF_2\alpha$ resulted in a similar interval to estrus. A single injection of 30 mg of $PGF_2\alpha$ on d 6 to 9

resulted in estrus within 2 to 4 d while treatment on d 13 to 16 resulted in estrus within 3 to 4 d (Lauderdale, 1972). Cattle injected with 30 mg of $PGF_2\alpha$ on d 6 or 7, d 8 or 9, or d 10 to 15 were in estrus an avg of 47 $\pm$ 1.9, 79.9 $\pm$ 12.5 or 74 $\pm$ 3.4 h later, respectively (Ellicott et al., 1974). Cows and heifers injected on d 4 to 9 had significantly shorter intervals to estrus than those injected on d 10 to 15 (King et al., 1982). Intervals to estrus after injection of $PGF_2\alpha$ analogs have been similar to those after injection of $PGF_2\alpha$. Heifers injected with ICI 79,939 on d 9 to 13 were in estrus 48 to 96 h after injection (Dobson et al., 1975). Johnson reported heifers injected im with 500 ug cloprostenol had an avg interval to estrus of 57 $\pm$ 12.5 h. The avg interval to estrus was 53.1 $\pm$ 4.3 h and 60.8 $\pm$ 3.4 h for heifers treated with 500 ug cloprostenol im on d 5 to 8 or d 9 to 17, respectively (Refsal et al., 1980). Others have also reported a shorter interval to estrus using the same dosage in heifers treated on d 7 and 8 vs d 12 to 14 (Jackson et al., 1979).

The difference in interval to estrus and the degree of variability between those treated d 5 to 10 and those treated d 11 to 15 may be due to follicular growth waves. A large ovulatory follicle is present and developing between d 1 to 12, but due to high progesterone concentrations it becomes atretic. A second ovulatory follicle begins developing d 12 or 13 which will eventually ovulate (Ireland et al., 1979). However, with $PGF_2\alpha$ treatment on d 7 or 8 the CL is regressed and the first follicle ovulates rapidly possibly causing the shorter interval to estrus with less variation among individuals (Johnson, 1978 and Jackson et al., 1979).

Estrus control day 17 through 20. Cattle treated with $PGF_2\alpha$ after d 16 will exhibit estrus within 4 d after injection. However, estrus will likely be due to the spontaneous regression of the CL by prostaglandins

released from the nonpregnant uterus after d 16. Progesterone falls rapidly from d 17 to 20 (Schams et al., 1977) and reaches its lowest point about 1 d before estrus (Adeyemo and Heath, 1980). At this point, the large ovulatory follicle which started development on d 12 will ovulate (Ireland et al., 1979).

Fertility after treatment. Treatment with $PGF_2\alpha$ or its analogs does not affect the process of ovulation or fertility. Infusion of 5 mg $PGF_2\alpha$ into the uterine horn ipsilateral to the CL resulted in ovulation approximately 26 h after the onset of estrus which is comparable to ovulation time after a non-induced estrus (Louis et al., 1972). Intrauterine infusion of 1.5 or 3 mg $PGF_2\alpha$ did not affect fertility regardless of whether infused once or twice (Rowson et al., 1972; Motlik et al., 1976). Inskeep (1973) reported conception rates of 59% in cows infused with 1 mg $PGF_2\alpha$. Cattle injected im with $PGF_2\alpha$ exhibited no difference in fertility rates as compared to nontreated cattle (Roche, 1974). Lauderdale et al., (1974) reported no significant difference in pregnancy rates among heifers and cows treated with 30 mg $PGF_2\alpha$ and non-treated controls (52.2% and 53.3%, respectively). Similar conception rates between heifers treated with $PGF_2\alpha$ (57.5%) and nontreated heifers (55%) have been recorded by Ellicott et al. (1974). Drastic improvements in fertility rates have been reported in Holstein and Zebu cattle treated with two injections of $PGF_2\alpha$ vs nontreated (61% vs 45%) (Adeyemo et al., 1979). However, this increase in conception rates may have been due to improved estrus detection in treated cattle.

Conception rates between cattle treated with one or two 500 ug im injections of cloprostenol and controls were not different (Cooper, 1974; Deletang, 1975; Roche and Prendeville, 1979). Jóchle et al. (1982) reported

conception rates between dairy heifers treated with alfaprostol and non-treated controls to be 78.3% and 73.5%, respectively indicating no adverse effects. The only case of reduced fertility after treatment with cloprostenol was reported in Brahman cattle, apparently due to ovary supression or alteration of the temporal relationship between estrus and ovulation (Hardin and Randel, 1982).

Failures in estrus control. Cattle that do not have a functional CL will not respond to treatment with $PGF_2\alpha$ or its analogs. $PGF_2\alpha$ had no effect on non-cycling heifers 3.5 to 5.4 mo postpartum (Adeyemo et al., 1979). On occasion, normal cycling cattle within diestrus will not respond to treatment with $PGF_2\alpha$. After two injections of 25 mg $PGF_2\alpha$ 11 d apart, only 72% of the treated cows returned to estrus (Peters et al., 1977). Similar results were reported by Burfening et al., (1978). King et al. (1982) reported synchronization failures ranging from 10 to 27.5%. After treatment on d 7 to 11 with either 20 or 30 mg $PGF_2\alpha$ injected im only 5 of 6 and 4 of 6 heifers exhibited estrus (Roche, 1974). Refsal and Sequin (1980) reported 2 of 14 heifers in early diestrus failed to respond after injection with 500 ug cloprostenol. Although apparent synchronization failure may be due to poor heat detection or animals not showing overt signs of estrus, Thatcher and Chenault (1976) reported that in animals not responding to $PGF_2\alpha$ treatment a decline in progesterone still occurred. However, progesterone concentrations never fell below 1 ng/ml therefore inhibiting estrus. The CL apparently recovered since progesterone levels increased and a normal 21 d cycle occurred. This may be true of animals which fail to respond during early diestrus.

Another cause of synchronization failure is slow response after treatment with $PGF_2\alpha$ or its analogs. The delayed estrus may not occur

until 5 to 10 d after injection. Of 29 animals failing to synchronize after two injections of $PGF_2\alpha$, five were in estrus 7 to 10 d after injection (King et al., 1982).

Management Considerations for Estrus Synchronization with $PGF_2\alpha$ and its Analogs

Use of $PGF_2\alpha$ or its analogs to synchronize estrus in a cowherd requires some additional management considerations. One injection can only be expected to synchronize those animals within 5 to 16 d after estrus, therefore a randomly cycling herd cannot be expected to be completely synchronized. To get more animals closely synchronized, a system involving two injections given 10 to 12 d apart was developed. This system not only causes a larger number of cattle to be in estrus, but because most animals are at approximately the same stage of early diestrus the interval to estrus is shorter and less variable as described earlier in the text. The increased number in estrus was demonstrated in work by Adeyemo et al. (1979) with cycling dairy heifers. Two injections of PGF_2 , 11 d apart, resulted in estrus in only 42% of the heifers after the first injection and 100% after the second injection. Heifers injected im twice with 25 mg mg PGF_2 , 11 d apart, resulted in an avg interval to estrus of 53 h after the first injection and 51 h after the second. Cows receiving the same treatment were in estrus an avg of 72.5 h and 67.9 h after the first and second injections, respectively (Burfening et al., 1978). The decrease in variability in interval to estrus after injection was shown in work by Dobson et al. (1975) with cloprostenol. Two 750 ug im injections given 10 d apart reduced the range in response time from 48 to 95 h to estrus after the first injection to 48 to 55 h to estrus after the second injection. Two 500 ug injections of cloprostenol 11 d apart caused

a significantly shorter interval to estrus with less variability after two injections (59.9 $\pm$ 5.8 h) than after the first injection (68.6 $\pm$ 20.8 h) (Johnson, 1978). Similar results were reported by Cooper (1974).

Another management option to be considered is ovarian palpation of cows to be treated, thereby eliminating the second injection if a CL is present. Peters et al. (1977) reported no advantages in estrus response or fertility between one or two injections in those cows with palpable corpora lutea. Success in this management option is dependent on the ability of the palpator to accurately detect a CL that will regress in response to a $PGF_2\alpha$ injection.

Timed inseminations became a reality with the development of the two injection system. Although good estrus detection is still important for maximum conception rates, good fertility can be accomplished with one or two inseminations at appointed times. After treatment with two injections of $PGF_2\alpha$, cows inseminated either once at 80 h or twice at 72 and 96 h had the best conception rates compared to those inseminated once at 72 h (Bosu et al., 1981). Hafs (1975) reported that heifers inseminated at 70 and 88 h after the second injection of $PGF_2\alpha$ had fertility rates equal to those of the controls inseminated by estrus. Breeding both cows and heifers at either 74 h or 72 and 96 h after two injections of $PGF_2\alpha$ resulted in conception rates of 36% and 37%. However, a high percentage of the animals were in standing estrus at 72 h (Peters et al., 1977). One important aspect of breeding by appointment is the chances of those cattle conceiving which didn't exhibit estrus and which may not have been inseminated if estrus detection had been used. Burfening et al. (1978) reported cows which didn't exhibit estrus after the second injection of $PGF_2\alpha$ were inseminated at 84 h after injection resulting in a 44% conception rate.

Timed insemination may also be used with $PGF_2\alpha$ analogs. Roche (1979) reported normal fertility in heifers with timed inseminations at 72 and 96 h after the second injection of cloprostenol. After two im injections of alfaprostol, heifers inseminated at 48 and 72 h had conception rates comparable to nontreated contemporaries (Jóchle et al., 1982).

One consideration with timed inseminations is the difference in interval to estrus between cows and heifers which can cause lower conception rates if insemination is not properly timed with estrus and ovulation. Several researchers have reported differences in the interval to estrus between heifers and cows. Heifers were in estrus an avg of 7 to 14 h earlier than cows (King et al., 1982; Burfening et al., 1978). King et al. (1982) reported after two injections of $PGF_2\alpha$ heifers injected 5 to 9 d after estrus and inseminated at 80 h had conception rates significantly lower than those bred by estrus, but the difference in conception was not significant in cows. It appears that in using a single timed insemination the best results may be obtained by inseminating at approximately 80 h after the second injection in cows and 72 h in heifers.

Doses of 25 mg $PGF_2\alpha$ given to heifers on d 10 of the estrous cycle for 6 consecutive cycles caused no cystic follicles and continued to induce estrus (Blaschke et al., 1982). Therefore, there appears to be no potential problems in repeated use of $PGF_2\alpha$ and its analogs in contemporary practices such as synchronizing estrus in recipient cows in embryo transfer programs.

Luteolytic Properties of $PGF_2\alpha$ and its Analogs in Inducing Abortions

Maintenance of pregnancy in cattle is dependent on progesterone secretion from luteal tissue during early gestation. During this time the use of $PGF_2\alpha$ or its analogs will regress the CL and abortions will occur. The use of $PGF_2\alpha$ and its analogs are popular in the feedlot industry for aborting pregnant feeder heifers entering the feedlots.

Cows between 40 to 120 d of gestation were injected im with doses ranging from 15 to 150 mg. Injections of 45 or 150 mg caused abortions in 100% of the treated animals while 15 or 30 mg injections caused abortions in 50% (Lauderdale, 1972). When a single injection of 15 or 30 mg of $PGF_2\alpha$ was injected into the fetal fluid of 9 cows in the second and third trimester of pregnancy six aborted with no differences found between stages of pregnancy and dosage (Sloan, 1977). Six heifers in the 1st trimester of pregnancy, carrying 10 fetuses were injected im with 25 mg $PGF_2\alpha$ with 100% effectiveness (Kosugiryama et al., 1978). Copeland et al. (1978) reported doses of 375 and 500 ug cloprostenol appeared to be most effective for inducing abortions as 100% of the heifers treated within the first 100 d of pregnancy aborted. Heifers from 100 to 120 d and greater than 120 d gestation length responded with 93% aborting in each group. Diamond Laboratories, Inc. (1982) reported abortion rates of 97.7% in animals less than 100 d of gestation and 85.2% in animals from 101 to 140 d when injected im with 1 mg of fenprostalene.

The interval from treatment to abortion is highly variable. In general, most $PGF_2\alpha$ analogs have a shorter response time possibly due to longer half-lives than $PGF_2\alpha$. Diamond Laboratories, Inc. (1982) reported the half-life of fenprostalene to be 18 to 23 h compared to 3 to 4 h for

cloprostenol and only 2 to 3 min for $PGF_2\alpha$. The effect of different half-lives has been demonstrated in several trials. Lauderdale (1972) reported abortions up to 14 d after injection of $PGF_2\alpha$ in cattle between 0-120 d of gestation. Treatment of 209 heifers at various gestation lengths with cloprostenol resulted in 15 abortions within 48 h, 72 by d 5, and none reported later than d 9 (Copeland et al., 1978).

The progesterone decline resulting in an abortion is similar to the progesterone decline when synchronizing estrus. Sloan (1977) reported progesterone fell to 2 ng/ml within one d after treatment. However, Kosugiryama et al. (1978) reported progesterone levels did not decline to basal levels until 48 to 54 h after injection.

Although $PGF_2\alpha$ and its analogs aren't 100% effective, they are one of the best methods currently available for aborting cattle when compared to treatment with estradiol cypionate, manually aborting or ovariectomizing heifers (Horstman et al., 1982). Abortions with $PGF_2\alpha$ and its analogs during early and mid-gestation are usually accomplished with a minimum of complications. No distress or retained placentas were reported in 209 heifers aborted with cloprostenol and most uteri had completely involuted by 21 d (Copeland et al., 1978). Horstman et al. (1982) reported fewer side effects with $PGF_2\alpha$ compared to estradiol cypionate.

To increase the effectiveness of $PGF_2\alpha$ and its analogs as abortifacients in late gestation it is sometimes combined with dexamethasome. Barth et al. (1981) reported treatment of 80 heifers between 4 to 8 mo pregnant with 500 ug cloprostenol and 25 mg dexamethasome resulted in 74 abortions.

SYNCHRONIZING ESTRUS AND ABORTING BEEF HEIFERS WITH ALFAPROSTOL, A PROSTAGLANDIN $F_2\alpha$ ANALOG

SUMMARY

The efficacy of alfaprostol, a prostaglandin $F_2\alpha$ analog, in synchronizing estrus and aborting feeder heifers was tested in three trials. In the first trial, two 6 mg injections, 12 d apart, were used to synchronize estrus. The first injection was given according to the day of the estrous cycle. Approximately four heifers received their first injection on each representative day of the estrous cycle (d 1 through 20). After 78 heifers received the first im injection, 77 exhibited a decline in serum progesterone concentration, 75 demonstrated some signs of estrus, and 50 stood for mounting within 120 h after injection. Ninety percent of the injected heifers were in standing estrus by 120 h after the second injection and 80.8% of those conceived to the first insemination. First service conception rates were not different from the 39 nontreated controls (80.8% vs 81.6%). Pregnancy rates for the 55 d breeding period were similar for treated (89.7%) and control (87.2%) heifers. Due to a high estrous response in heifers injected between d 1 through 4 of the cycle, the second trial was conducted to examine the ability of alfaprostol to induce estrus and ovulation in heifers injected on d 1, 2, 3, or 4 of the cycle. Either a single 6 mg im injection or two 5 mg im injections given 12 h apart induced only 3 of 20 treated heifers to show estrus. None conceived after insemination and all inseminated heifers had normal length estrous cycles indicating ovulation did not occur although serum progesterone concentrations were low in most heifers after injection.

The third trial tested the effectiveness of alfaprostol as an abortifacient. Alfaprostol was injected im at the rate of 1.5 mg/100 kg body weight. Abortions occurred in 19 of 24 heifers injected during early gestation ($\bar{x}$ = 82 d) and in 22 of 23 heifers injected during mid-gestation ($\bar{x}$ = 142 d).

INTRODUCTION

Artificial insemination in cattle has allowed dairy and beef cattlemen to make greater use of genetically superior sires. However, the time and effort required for heat checking has limited the use of artificial insemination particularly in the beef industry. Hormonal control of the estrous cycle allows large numbers of cattle to be inseminated in a short period of time, but the methods commercially available have had limited success.

Lauderdale (1972) first described the luteolytic properties of prostaglandin $F_2\alpha$ ($PGF_2\alpha$) in cattle and since then extensive research efforts have led to its development as a bovine estrus synchronization agent. $PGF_2\alpha$ has been relatively effective in lysing the corpus luteum and promoting estrus when cattle are treated between days 5 and 16 of the estrous cycle (Rowson et al., 1972). Two injections of $PGF_2\alpha$ given 10 to 12 days apart have become the standard method of synchronizing cycling cattle (Lauderdale et al., 1974) and inseminating by appointment approximately 80 hours after the second injection eliminates checking for heat. This procedure has met with limited success. Approval has been obtained for cloprostenol, a $PGF_2\alpha$ analog, to be used as a bovine estrus synchronization agent. Cloprostenol has had the same limited success as $PGF_2\alpha$. Both compounds have also been approved for use as abortifacients along with a second analog, fenprostalene. Other $PGF_2\alpha$ analogs are being manufactured, but remain virtually untested in cattle. Alfaprostol is one such analog. Differences in luteolytic capabilities of a $PGF_2\alpha$ analog

during the cycle or during pregnancy could make it superior as an estrus synchronizing agent or an abortifacient in cattle.

The purpose of this experiment was to determine the efficacy of alfaprostol, a $PGF_2\alpha$ analog, for synchronizing estrus at all stages of the cycle and as an abortifacient during two stages of gestation.

MATERIALS AND METHODS

The efficacy of alfaprostol[1] as a synchronization agent and the effect of stage of estrous cycle at treatment on the subsequent reproductive events in beef heifers were studied in two trials. Alfaprostol was injected in propylene glycol at a concentration of 1 mg/ml. Estrus (day 0) was defined as the time when an animal would stand to be mounted by another animal, however all signs of estrus were recorded. In the third trial the efficacy of alfaprostol as an abortifacient was studied.

Trial 1

One hundred seventeen Hereford x Angus heifers confined to dry lots at Kansas State University were divided according to previous nutritional treatments into a treated group (78 heifers) which received two 6 mg injections of alfaprostol and a non-injected control group (39 heifers). All heifers had been observed for estrus behavior twice daily for 5 mo prior to the start of the trial. Heifers averaged 305.4 kg and were 13 to 15 mo old in May 1982. All heifers were observed in estrus at least once before the start of the trial.

The first injection was given according to the day of the estrous cycle. Three or four heifers received the first injection for each representative day of a 20 d estrous cycle. No heifers received the first injection while in estrus.

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[1]Alfaprostol -- 18, 19, 20-trinor-19-cyclohexyl-13, 14 didehydro-$PGF_2\alpha$-methylester supplied by Hoffmann-LaRoche, Inc., Nutley, New Jersey 07110.

Blood samples were taken by jugular venipuncture from all treated heifers. Samples were taken at 12 h intervals from 12 h before the first injection through 48 h postinjection. A final sample was taken 72 h after injection. Blood samples were allowed to clot for 24 h at 2 C, centrifuged for 15 min at 2400 rpm and serum collected. Serum was stored at -20 C until samples were analyzed for progesterone by radioimmunoassay (Stevenson et al., 1981). Serum collected at 48 h after injection from some heifers injected the first 4 d of the cycle and which exhibited estrus 52 to 72 after injection was also assayed for FSH (Bolt and Rollins, 1983) and LH (Niswender et al., 1969) in 1983.

KaMar[2] heatmount detectors were applied to each treated heifer at the time of the first injection to aid in detection of estrus. After the first injection all heifers were observed for estrus behavior and activated KaMars at 6 h intervals (0600, 1200, 1800, and 2400) for 5 d. Observations were made at 12 h intervals (0600, 1800) for the next 7 d. Intervals to estrus, activated KaMars, and other signs of estrus were recorded.

Each treated heifer received a second injection 12 d after the first injection and new KaMars were applied. All heifers (treated and controls) were observed for estrus behavior at 6 h intervals (0600, 1200, 1800, 2400) for 5 d. Heifers were observed for estrus at 12 h intervals (0600, 1800) for the next 50 d.

Any heifer observed in standing estrus during the 55 day breeding period was artificially inseminated 12 to 18 h later. Heifers in estrus

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[2]KaMar, Inc., Box 773838, Steamboat Springs, CO 86477.

the first 21 d of the breeding period were inseminated by one inseminator. A different inseminator was used for the rest of the breeding period. All heifers were inseminated with semen from a single ejaculate and all were rectally palpated 50 d after the end of the breeding period to confirm conception date.

Data on interval to estrus and serum progesterone were analyzed by SAS General Linear Model procedure (SAS Institute, Inc., 1982). Conception data was analyzed by Chi-square tests (Snedecor and Cochran, 1980).

Trial 2

The ability of alfaprostol to regress the corpus luteum and synchronize estrus in heifers during the first 4 d of the estrous cycle (estrus = d 0) was tested in purebred Angus, Hereford, and Simmental heifers 12 to 15 mo old. A total of 45 heifers were housed in drylots at Kansas State University and checked for signs of estrus twice daily. Heifers found in estrus were assigned by breed to receive either one 6 mg im injection of alfaprostol or two 5 mg im injections of alfaprostol given 12 h apart. Treatments were given according to the day of the cycle and heifers received their treatment on either d 1, 2, 3 or 4. Breed and day of cycle were kept as equal as possible within groups.

Blood samples were taken by jugular venipuncture from all treated heifers immediately before the first injection and at 12 h intervals from 48 h through 96 h after the first injection. Blood sampling was discontinued on heifers found in estrus before 96 h after injection. Blood samples were handled and assayed for progesterone as described in Trial 1. Observations for estrus were continued for approximately 6 d after injection at 0700 and 1900 daily. All heifers found in estrus

were artificially inseminated 12 h after detection by the same inseminator. Semen from two different bulls was used. A single blood sample was taken 72 h after insemination from all heifers returning to estrus within 6 d after injection. Pregnancy was determined by rectal palpation approximately 55 d after insemination.

Trial 3

The efficacy of alfaprostol as an abortifacient for feedlot heifers at early (avg 82.9 d) or mid (avg 134 d) gestation was tested. Ninety-three pregnant Hereford x Angus heifers housed at the Kansas State University Beef Research Unit were divided into four treatment groups according to weight and conception date. Two groups were injected with alfaprostol at a rate of 1.5 mg/100 kg body weight and two control groups were injected with propylene glycol, the alfaprostol carrier, at a dosage of 1 ml/100 kg body weight.

Immediately after dividing heifers into four groups, one group (avg wt. 359.1 kg; avg gestation length 82.9 d, range 64 to 86 d) was injected with alfaprostol and another group (avg wt. 358.6 kg; avg gestation length 81.4 d, range 70-87 d) was injected with propylene glycol. After injection both groups were observed twice daily for abortions, abortion-related complications, and estrous behavior for 21 d. Heifers from both groups were rectally palpated 14 and 28 d after injection to determine if fetuses were present. Size and condition of the uterus was recorded if heifers had aborted.

Forty-seven days after injection of the first two groups, the other two groups were injected. One group (avg wt. 390 kg; avg gestation length 134 d, range 119 to 143 d) was injected with alfaprostol and the other

(avg wt. 442.7 kg; avg gestation length 137.9 d, range 130 to 141 d) with propylene glycol. All heifers were weighed and determined pregnant by rectal palpation before injection. Procedure after injection was the same as for the first two groups.

RESULTS AND DISCUSSION

Trial 1. The number of heifers that exhibited signs of estrus or had low progesterone levels after the first injection of alfaprostol is shown in table 1. Ninety-six percent of the treated heifers exhibited some type of estrous response after the first injection. Of 16 heifers injected on either d 1, 2, 3 or 4, 13 showed some signs of estrus and six of those were in standing estrus 56 to 156 h after injection. The estrual response after injection on d 1 through 4 differs from responses observed after $PGF_2\alpha$ injections (Lauderdale, 1972; Beal et al., 1980). The estrual response after alfaprostol in the present study was accompanied by low progesterone concentrations (table 1 and figure 2). It is not possible to determine from this data if complete luteal regression and subsequent ovulation occurred since heifers were not inseminated after the first injection and all received a second injection of alfaprostol 12 d after the first. The possibility exists that a temporary luteal supression occurred followed by a rebound as reported by Beal et al. (1980) and Thatcher and Chenault (1976) after $PGF_2\alpha$ was injected early in the cycle. Completion of the LH and FSH assays indicated no rise in serum FSH or LH occurred before estrus in some heifers injected during the first 4 d of the cycle (table 2).

The interval to standing estrus after the first injection is shown in figure 2. Between 54 to 84 h after injection, 47% of the heifers were in standing estrus. Day of the cycle at injection significantly affected the interval to estrus. Heifers injected on d 3 and 4 had longer ($p < .05$)

Table 1. HEIFERS EXHIBITING SIGNS OF ESTRUS AND/OR HAVING LOW SERUM PROGESTERONE AFTER THE FIRST INJECTION OF ALFAPROSTOL

Day of cycle at injection[a]	No. standing for mounting	No. exhibiting signs of estrus other than standing for mounting	No. with serum progesterone < .5 ng/ml after injection
1	3	1	4
2	0	3	4
3	2	1	3
4	1	2	2
5	1	2	3
6	3	1	4
7	3	1	4
8	4	0	4
9	4	0	4
10	2	2	4
11	2	2	4
12	3	1	4
13	4	0	4
14	3	1	4
15	3	1	4
16	4	0	4
17	4	0	4
18	4	0	4
19	3	1	4
20	2	1	3
Total	55	20	75

[a]Four heifers treated/d of cycle except cycle d 5 and 20 when 3 were treated. Estrus = d 0.

intervals to estrus. Although not significantly different, there was a trend for heifers injected d 6 to 8 of the cycle to be in estrus earlier

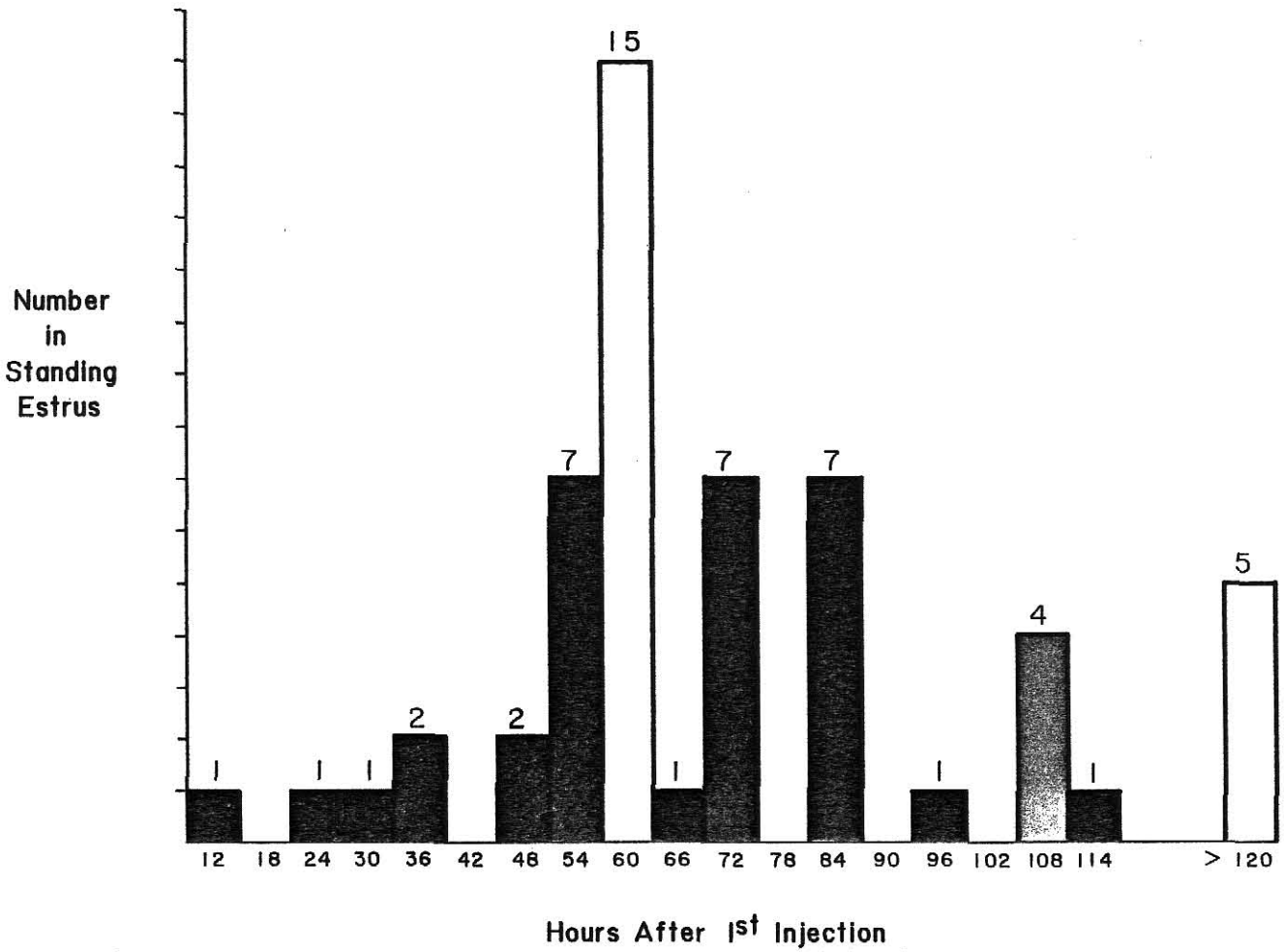

Figure 3. Intervals to standing estrus after first injection of alfaprostol. Numbers above bars represent the number of heifers observed in estrus at the time indicated.

Table 2. SERUM FSH AND LH CONCENTRATIONS[a] IN SOME HEIFERS INJECTED ON DAY 1, 2, 3 or 4 WITH ALFAPROSTOL AND SHOWING SOME SIGNS OF ESTRUS

Day of cycle at injection	No. of heifers	Avg FSH concentration (ng/ml)	Avg LH concentration (ng/ml)
1	3	23	.16
2	3	17	.16
3	1	15	.77
4	1	ND	ND

[a]Serum samples taken 48 h after alfaprostol injection which was 4 to 24 hours before any signs of estrus.

than those injected d 10 to 16. This agrees with work by Schams et al. (1977), Jackson et al. (1979) and King et al. (1982). Some expression of estrus was reported in 88.5% of the heifers within 120 h after injection. The number of heifers showing signs of estrus was larger, however the variation in interval to estrus was also greater than that reported by Cooper (1974) and Johnson (1978) with cloprostenol.

Serum progesterone declined after injection in all heifers except one injected on d 3 of the cycle. Serum progesterone concentrations in all heifers were not different at 24 and 48 h after injection. Decline in progesterone concentrations in heifers injected d 1 to 5 (figure 3) was irratic although levels decreased in all groups at 12 h after injection. Heifers injected on d 2 had the smallest decrease in progesterone and none were found in standing estrus. Serum progesterone concentrations of heifers injected on d 6 through 20, with the exception of d 11, are shown in figure 4. Data from heifers injected on d 11 were significantly

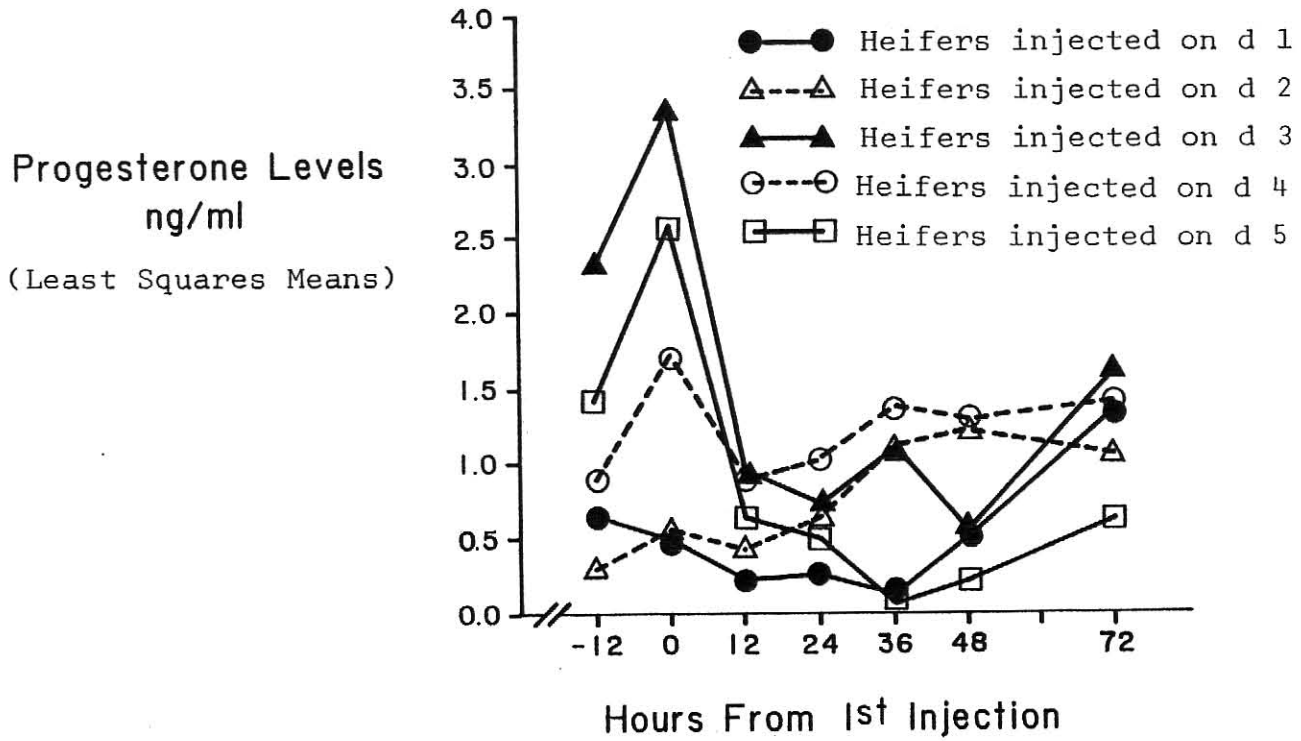

Figure 3. Serum progesterone levels of heifers at the first injection of alfaprostol administered on d 1, 2, 3, 4, or 5 of the estrous cycle. Each point represents the mean of 4 heifers except for three on d 5.

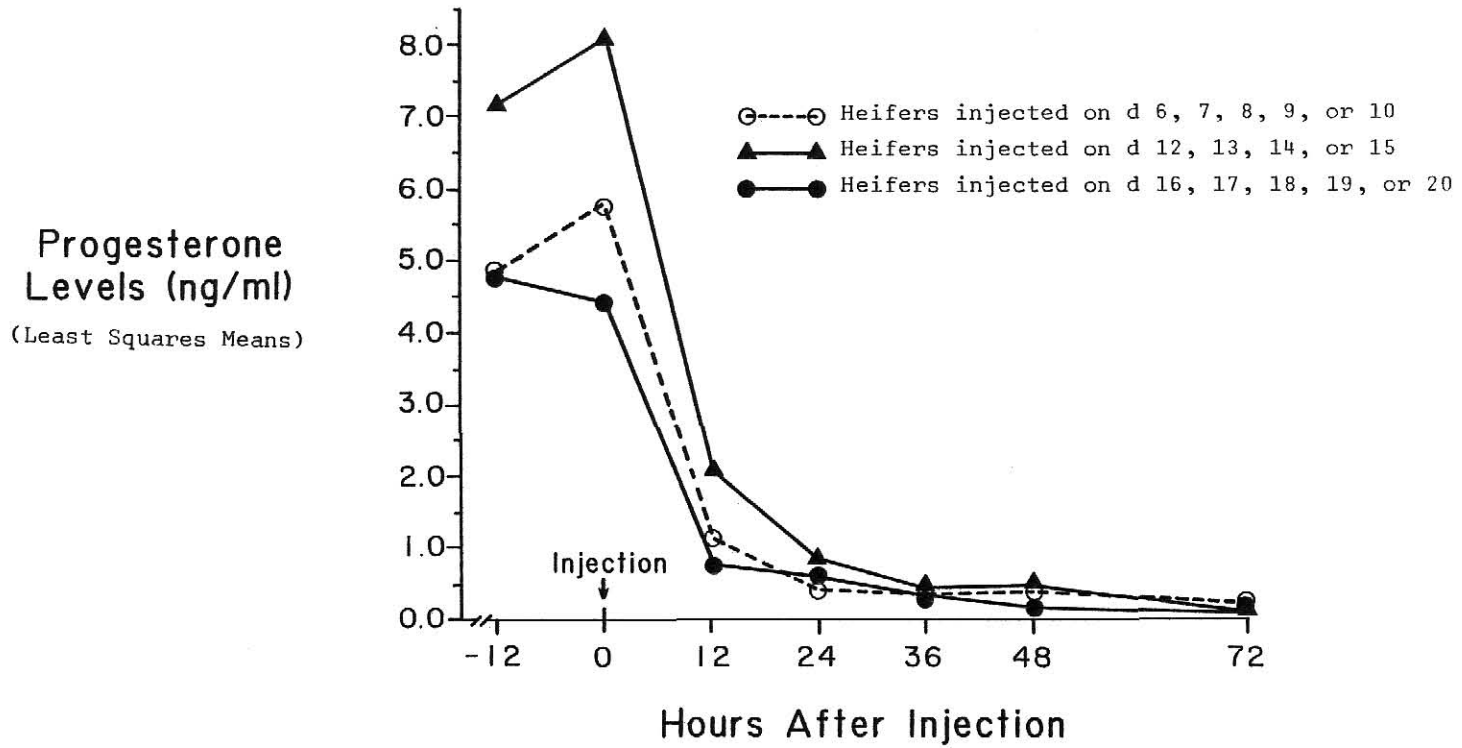

Figure 4. Serum progesterone levels according to physiological period of the estrous cycle at the first injection of alfaprostol.

more variable than heifers treated on any other day of the cycle. After d 5 all heifers had progesterone levels greater than 4.0 ng/ml before injection. Twenty-four h after injection serum progesterone was below 1 ng/ml in 43 of 59 (72.9%) heifers injected d 6 to 20. This appeared to be a slower decline than reported by Chenault et al. (1976) and Bosu et al. (1981) after $PGF_2\alpha$ injection. Progesterone concentrations at injection had no effect on interval to estrus which is in agreement with King et al. (1982). Heifers injected d 16 to 20 exhibited a drop in progesterone levels from -12 to 0 h which could be associated with the spontaneous regression of the CL. However, after alfaprostol was injected the deline was more pronounced.

Seventy (89.7%) of the heifers were in standing estrus within 120 h after the second injection of alfaprostol. However, within 179 h, 73 (93.5%) had been detected in standing estrus. The distribution of heifers in standing estrus (figure 5) does not appear to be satisfactory for a single timed insemination. If a single, timed insemination were used, data indicates that insemination at 80 h after injection would give the best conception rate. The avg interval to estrus after the second injection was 69.6 h.

Conception rates were not affected by interval from treatment to estrus or day of cycle at first injection. Fifty-seven of the 70 heifers (81.4%) in estrus within 120 h after the second injection conceived to the first insemination. There was no affect of treatment on first service conception or conception during the 55 d breeding period (table 3).

A single 6 mg injection of alfaprostol was effective in reducing serum progesterone in heifers at all stages of the estrous cycle. Two

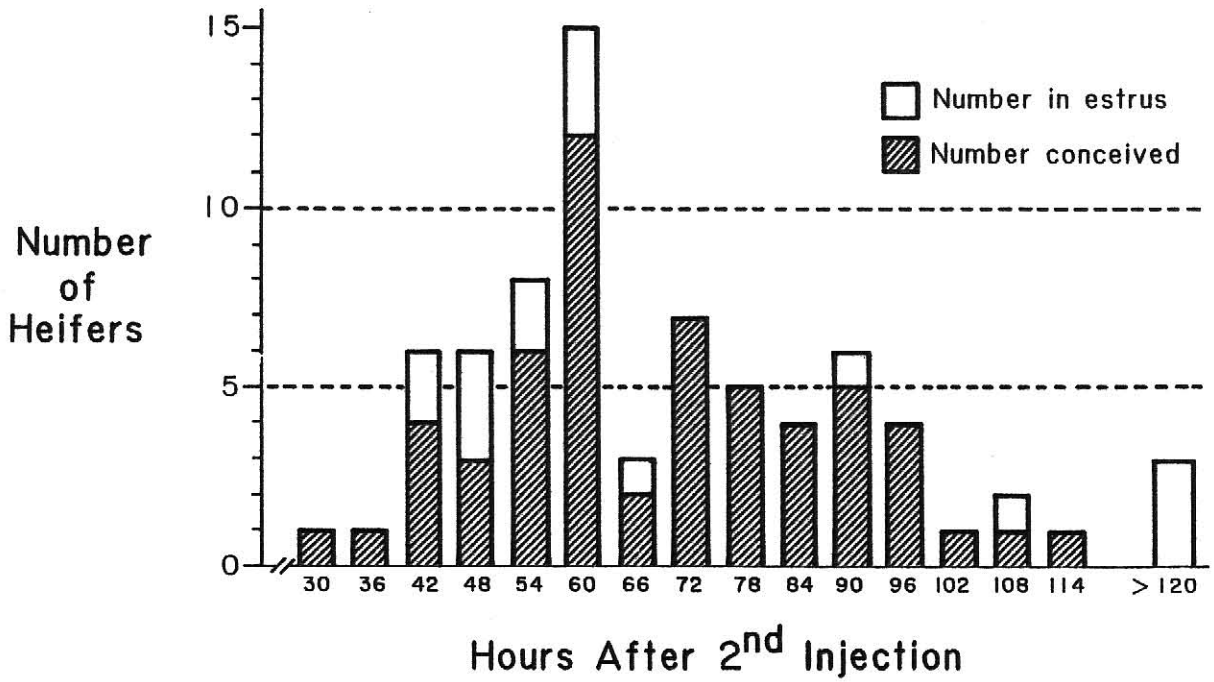

Figure 5. Time to standing estrus and conception rates in heifers after two injections of alfaprostol, 12 d apart.

Table 3. EFFECT OF ALFAPROSTOL SYNCHRONIZATION OF ESTRUS ON CONCEPTION RATES

	1st Service			2nd Service[b]			Total Pregnancy Rate[c]		
	No. Inseminated	No. Conceived	% Conceived[a]	No. Inseminated	No. Conceived	% Conceived	Total No. of Heifers	No. Conceived	% Conceived
Treated	73	59	80.8[d]	19	11	57.4	78	70	89.7[d]
Control	38	31	81.6[d]	6	3	50.0	39	34	87.2[d]

[a]Percent conceived = number conceiving divided by number in estrus within first 21 d of breeding period.

[b]22 to 55 d of breeding period, no heifers inseminated three times.

[c]Total for 55 d breeding period. Pregnancy rate = number pregnant regardless of number of inseminations divided by total number of heifers in trial.

[d]$P > .05$.

6 mg injections, 12 d apart, resulted in 93.6% of the heifers in standing estrus within 179 h. Conception rates were not affected after two injections of alfaprostol.

Trial 2. Results of trial 2 are given in table 3. Only 3 of 20 heifers injected exhibited estrus and all did so between 60 and 96 h after injection. Those three were inseminated and none conceived. Two heifers that were inseminated returned to estrus 11 and 14 d after insemination. Calculated from the preinjection estrus, both heifers had normal length estrous cycles (18 and 19 d) indicating that the corpus luteum was not regressed and a false estrus occurred after injection. Heifers exhibiting signs of estrus without standing also returned to estrus 18 d after their preinjection estrus.

Progesterone analysis revealed serum concentrations below .8 ng/ml in all heifers and 16 with less than .5 ng/ml at injection. These levels were extremely low when compared to levels reported in trial 1, although they are consistent with findings by Schams et al. (1977). Progesterone decreased in 5 nonresponsive heifers 48 h after injection and increased slightly in the rest. Although heifers ranged from d 3 to 6 of the estrous cycle, progesterone levels were all less than 1.7 ng/ml. The low progesterone concentrations after injection correspond with work by Beal et al. (1980).

Alfaprostol was not capable of inducing a significant estrus response when injected in the first 4 d of the estrous cycle as was observed in trial 1. Heifers in trial 2 were early puberal while most heifers in trial 1 had several cycles before treatment. This and the fact that heifers in trial 2 had low serum progesterone concentrations when compared to trial 1 may have contributed to the difference in response, but no direct evidence is available. Alfaprostol appears to induce some heifers to show signs of estrus after injection early in the cycle although

results from this trial and the assays for LH and FSH in trial 1 indicate that ovulation didn't occur.

Table 4. RESPONSE TO ALFAPROSTOL ADMINISTERED TO HEIFERS DURING THE FIRST FOUR DAYS OF THE CYCLE[a]

No. heifers injected	No. of injections[b]	Day of cycle at injection	No. in estrus	No. exhibiting signs of estrus[c]
2	1	1	-	-
1	2	1	-	-
4	1	2	1	1
1	2	2	-	-
3	1	3	-	1
3	2	3	1	-
3	1	4	-	1
3	2	4	1	-
Total 20			3	3

[a] Estrus = d 0; all injections given im in propylene glycol.

[b] Either one injection given on day indicated or two injections given 12 h apart.

[c] Nervousness, riding other heifers, being mounted but not standing.

Trial 3. Results from using alfaprostol as an abortifacient are given in table 5. The number of heifers that had aborted by 14 d after injection was the same at 28 d. However, two heifers in the early alfaprostol treated group aborted approximately 60 d after injection increasing the abortion rate to 87.5%. Both fetuses were in utero at the 28 d palpation. Two control heifers aborted. Although the reason for the abortions is unknown, a possible cause could be disease and stress as reported by Horstman et al. (1982).

Alfaprostol given during early gestation did not appear to be as effective in inducing abortions as it was at mid-gestation (79% vs 96% aborting). This may be due to the smaller dosage (5.4 mg) given the lighter weight heifers in early gestation as compared to the larger dosage (5.9 mg) administered to the heavier heifers in mid-gestation. It should be noted that the avg dosage of alfaprostol given to induce abortion was less than that given to synchronize estrus. However, at an avg dosage of 5.9 mg/head, mid-gestation heifers were successfully aborted.

Within 42 h after injection 10 heifers in early gestation exhibited signs (mucus, blood, or fetal membranes emitting from the vulva) of impending abortions. By 6 d after injection 11 expelled fetuses had been found, 19 heifers had exhibited some signs of abortion, and 16 heifers had been found in estrus. Fetal membranes were retained up to 10 d and some thick mucus and bloody discharge from the vulva was observed up to 14 d after injection. The uterus was involuted in all but one heifer 28 d after injection.

In the mid-gestation group 11 heifers showed signs of abortion within 42 h after injection. Twenty-two fetuses were expelled and 13

Table 5. ABORTION RATES IN HEIFERS AFTER TREATMENT WITH ALFAPROSTOL

Treatment	Mg alfaprostol injected (avg)	Avg wt. kg	Avg day of gestation	No. treated	No. aborted 14d[a]	No. aborted %
Alfaprostol	5.4	359.1	82.9	24	19	79
Propylene Glycol	0[b]	358.6	81.4	23	2	9
Alfaprostol	5.9	390	134	23	22	96
Propylene Glycol	0[c]	442.7	137.9	23	0	0

[a]Determined by rectal palpation.

[b]Control heifers injected with an avg 5.4 ml propylene glycol carrier.

[c]Control heifers injected with an avg 6.6 ml propylene glycol carrier.

heifers had exhibited estrus within 6 d after injection. The interval from injection to fetus expulsion was shorter than that reported with 30 mg of $PGF_2\alpha$ (Lauderdale, 1972). The shorter interval may be due to a longer half-life of alfaprostol. Four heifers were in standing estrus before the fetus was expelled. Fetal membranes were retained up to 10 d although a thick uterine discharge was noted up to 20 d after injection in one heifer. Significant mammary development was observed in 11 heifers. A similar observation was made by Copeland et al. (1978). Appetites appeared normal and only two heifers showed signs of depression or distress. Three heifers had partially distended uteri 28 d after injection.

In this trial alfaprostol was an effective abortifacient in heifers up to 140 d of gestation when given at a dosage of at least 5.9 mg/head. As an abortifacient it can be expected to abort heifers in a minimal amount of time with few side effects or complications.

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SYNCHRONIZING ESTRUS AND ABORTING BEEF HEIFERS WITH ALFAPROSTOL, A PROSTAGLANDIN $F_2\alpha$ ANALOG

by

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ABSTRACT

The efficacy of alfaprostol, a prostaglandin $F_2\alpha$ analog, in synchronizing estrus was studied in two trials involving 162 beef heifers. Its effectiveness as an abortifacient was determined in a single trial with 93 feedlot heifers.

Two 6 mg im injections of alfaprostol were given 12 d apart in the first synchronization trial. The first injection was given according to the day of the estrous cycle. Four heifers were given the first injection for each d (1 through 20, estrus = 0). Blood samples were taken from treated heifers at 12 h intervals from 12 h before the first injection through 48 h after injection. A final sample was taken at 72 h postinjection. All samples were analyzed for serum progesterone. Thirty-nine nontreated heifers served as controls. All heifers were observed for estrus four times daily for 5 d after both the first and second injections and twice daily the remainder of the trial. Any treated or control heifer detected in estrus after the second injection was artificially inseminated 12 to 18 h after detection during the 55 d breeding period.

After 78 heifers received their first injection, 77 had a decline in serum progesterone concentration, 75 exhibited some signs of estrus, and 50 were standing estrus within 120 h after injection. After the second injection 70 of the 78 heifers were in standing estrus within 120 h. Alfaprostol did not affect fertility as 80.8% of the treated heifers and 81.6% of the controls conceived to the first insemination.

In trial 2, one 6 mg im injection or two 5 mg im injections 12 h apart were administered to heifers on d 1, 2, 3 or 4 of their estrous cycle to determine the effectiveness of alfaprostol to regress the CL in early cycle. Blood samples were taken immediately before injection and at 12 h intervals from 48 h through 96 h after the first injection. Samples were analyzed for progesterone. Observations for estrus were made twice daily for 6 d after injection. Heifers found in estrus were inseminated 12 h after detection and a final blood sample taken 72 h after insemination.

Contrary to the results of the first trial, only three heifers expressed estrus after injection although progesterone levels were below 1 ng/ml in 15 of the 20 treated heifers 48 h after injection. Post-injection cycle lengths indicated the CL was not regressed and a new ovulation had not occurred with the estrus activity shown after injection.

In the abortion trial, 93 pregnant heifers were allotted to receive an im injection of either 1.5 mg alfaprostol/100 kg body weight or 1.5 ml propylene glycol carrier/100 kg body weight at either early gestation ($\bar{x}$ = 82.1 d) or mid-gestation ($\bar{x}$ = 136 d). Heifers in early gestation received a total dose of 5.4 mg of alfaprostol and those in mid-gestation received 5.9 mg. Heifers were observed two times daily for 21 d and rectally palpated 14 and 28 d after injection. Alfaprostol aborted 19 of 24 heifers treated in early gestation and 22 of 23 heifers treated in mid-gestation. Two of 23 heifers treated with propylene glycol in early gestation aborted. All abortions occurred before 14 d after injections. Alfaprostol was effective in inducing abortion particularly at the 5.9 mg dosage with a minimum of side effects.