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REPRODUCTIVE PERFORMANCE OF DAIRY COWS FOLLOWING TREATMENT WITH FENPROSTALENE, DINOPROST, OR CLOPROSTENOL BETWEEN 24 and 31 DAYS POST PARTUM: A FIELD TRIAL

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ABSTRACT

Three hundred and one Holstein cows (n=301), calving at a commercial free-stall dairy farm, were randomly assigned to 1 of 3 prostaglandin treatment groups or a placebo group. The placebos were packaged 3 ways to mimic the 3 commercial prostaglandin preparations. Group 1 received 1 mg fenprostalene and 1.6 mg oxytetracycline; Group 2 received the fenprostalene placebo (2 ml polyethylene glycol and 1.6 mg oxytetracycline); while Group 3 was given 25 mg dinoprost. Group 4, the dinoprost placebo received 5 ml saline; Group 5 received 500 ug cloprostenol; and Group 6 the cloprostenol placebo received 2 ml saline. The treatments were administered between Days 24 and 31 post partum. Double blind techniques were used in administering treatments and in assessing the response to treatment. There were no significant differences among treatment groups with respect to incidence of retained fetal membranes, endometritis, pyometra, anestrus, number of services per pregnancy, calving-to-first estrus interval, services per conception, number of prostaglandin treatments other than those administered between Days 24 and 31 post partum, the percentage culled for reproductive reasons and all factors combined. Cows receiving fenprostalene, dinoprost or cloprostenol had a decreased calving-to-conception interval compared with that of the controls ($P = 0.05$). It is concluded that, in the herd studied, treatment with any of the 3 commercially available prostaglandin products between Days 24 and 31 post partum was beneficial for reproductive performance.

Key words: dairy, fenprostalene, dinoprost, cloprostenol, reproduction

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INTRODUCTION

Prostaglandin $F_{2\alpha}$ and its analogues (PG) can be valuable aids in dairy herd reproductive health management programs during a given postpartum period before breeding (19, 28, 36). Research has indicated that as the number of estrous cycles which dairy cows experience prior to the first service increases, the conception rate at that service also increases (33). It has been suggested that PG administered to postpartum dairy cows may induce an additional estrus prior to the first service, resulting in a higher first service conception rate (38). The results of previous studies suggest that the administration of dinoprost[a] at 30 d post partum (30) or its analogue cloprostenol[b] to dairy cows 20 to 30 d and/or 40 d post partum (7, 8) can lead to improved reproductive performance. These effects were shown to be independent of the progesterone concentration (stage of the estrous cycle) at the time of treatment (8, 9, 30). Subsequently, the results of histological and bacteriological assessment of endometrial biopsies and clinical findings at Day 40 post partum were compared between the cows that received PG at Day 26 post partum and those that did not (4). In that study, the PG-treated cows had less vaginal discharge, smaller diameter uterine horns, less inflammation and fibrosis in the endometrium, and were less likely to have *Actinomyces pyogenes* isolated from a biopsy at Day 40 than untreated cows. These effects were also independent of progesterone level at the time of treatment.

The present study was designed to further compare the effects of 3 commercially available PGs (dinoprost tromethamine,[a] cloprostenol,[b] or fenprostalene[c]) administered to dairy cows between Days 24 and 31 post partum, on subsequent reproductive performance.

MATERIALS AND METHODS

Holstein cows (n=301) that calved at a commercial dairy herd[d] between May 1989 and July 1990 were randomly assigned to receive 1 of 3 PG treatments or a placebo. The placebos were packaged 3 ways to mimic the 3 commercial PG preparations in volume, color and consistency. Oxytetracycline[e] (1.6 mg) was added to the fenprostalene treatment and to the placebo. Cows were assigned to the treatment groups using a computer-generated list of random numbers. The treatments were randomized and allocated to animals in groups of 40 such that each contained an equal number of animals treated with fenprostalene, dinoprost, cloprostenol or placebo. This was done in order to minimize seasonal disparity in the allocation of treatments within the herd.

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[a] Lutalyse, Tuco, Orangeville, Ontario, Canada.
[b] Estrumate, Coopers Agropharm, Ajax, Ontario, Canada.
[c] Synchrocept-B, Syntex, Mississauga, Ontario, Canada.
[d] Frisia Farms, RR#1 Ariss, Ontario, Canada.
[e] Liquamycin LP - Rogar/STB, London, Ontario, Canada.

All treatments were stored in a refrigerator on the study farm. Every tuesday morning the herd manager generated a computer printout of cows that were between 24 and 31 d post partum, using the database applications function of the dairy herd management software employed by the farm.[f] The cows included on the list were administered 1 of the treatments. Double-blind techniques were used so that neither the farmer nor the investigators were aware of the treatment status of the cows at any time during the trial (22).

Cows were bred by artificial insemination (AI) using frozen semen, commencing at the first estrus observed after 50 d post partum. Postpartum, prebreeding and pregnancy examinations were performed at reproductive herd health visits every 4 wk. Pregnancy was diagnosed by palpation per rectum at ≥ 42 d and again at ≥ 120 d post insemination.

Cows were housed in a free-stall barn and were milked twice daily. The herd was not part of the Ontario Dairy Herd Improvement production recording program during the period of the trial. Average production per cow per day ranged between 22 and 24 l per cow per day as calculated based on bulk tank shipments. During the period from 1983 to 1989, the rolling herd average 305 d production ranged between 5,500 and 6,000 l of milk.

There were 2 different feeding groups for lactating cows as well as a dry cow group. Ration 1 consisted of corn silage, alfalfa haylage, soybean meal, high moisture grain corn, cobalt-iodized salt and a commercially prepared mineral.[g] This ration was fed ad libitum to all cows producing more than 20 l per day. Ration 2, consisting of the same feeds mixed in different relative amounts, was fed to all cows milking less than 20 l per day. Ration 3, dry cow ration, consisted of corn silage, haylage and mineral, and salt.

Samples of the 2 total mixed rations fed to lactating cows and the dry cow mix were analyzed for dry matter, crude protein, energy and essential vitamins and minerals. Computer analysis was performed to determine if requirements were being met at various milk production levels,[h] however, herd managers did not always implement recommended feeding practices.

Health and reproductive records were stored using the on-farm micro-computer based dairy herd management software. The dairy herd manager performed all data entry at the farm. Relevant data was later transferred to a dBase IV[i] dataset on a microcomputer in the research lab. This dataset combined reproductive health and

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f DairyTRAC, Control Data, Minneapolis, MN, USA.

g Dairy Premix, Grand Valley Fortifiers, Cambridge, Ontario, Canada.

h Grand Valley Fortifiers Dairy Nutritional Advisory Service, Cambridge, Ontario, Canada.

i dBase IV, Borland Canada, Toronto, Ontario, Canada.

performance information with treatment information. Statistical analysis was performed using SAS (Statistical Analysis System).

Postpartum reproductive tract examinations were conducted on all cows between 14 and 50 d postpartum during herd health visits. Reproductive abnormalities detected during these examinations were defined and entered into the database as follows. Cystic ovarian degeneration was characterized by anestrus, continuous exhibition of estrus or irregular estrous cycles and one large fluid-filled structure or many smaller fluid filled structures on one or both ovaries diagnosed subsequent to 31 d post partum. Pyometra was characterized by a fluid-filled uterus with palpable luteal tissue present on at least one ovary subsequent to 31 d post partum. Retained fetal membranes were recorded by the herd manager. A cow was considered to have retained her placenta if fetal membranes were still present 24 or more hours after parturition. Endometritis was diagnosed either by the herd manager or the veterinarian and was defined by cows which exhibited a purulent discharge from the vulva at any time greater than 31 d post partum.

Postpartum metritis cases occurred prior to 14 days post partum and were attended to by veterinarians from a neighbouring veterinary practice. Postpartum metritis cases were not entered into the computer herd record system, hence the incidence of this abnormality is unknown for the population under study. Since cows were assigned to treatment groups in a random manner it is likely that the incidence of postpartum metritis did not differ significantly amongst treatment groups.

Prebreeding examinations were conducted on all cows greater than 50 d post partum which had not received a service at the time of herd health visits. Anestrus cows fell into 2 categories, those which had not been observed in estrus by 60 d post partum and those which had been seen in estrus and had received a service but were open at the time of pregnancy diagnosis. Both categories were combined under one category (anestrus) for purposes of statistical analysis. All cows diagnosed as anestrus were administration PG and serviced at observed estrus.

Chi-square and odds ratio analyses were used to compare the effects of treatments on the occurrence of reproductive abnormalities subsequent to treatment (7, 12). Analysis of variance was used to compare the effect of treatment combinations on continuous variables such as days from calving to the first estrus, first service and conception (7, 29).

RESULTS

Initial descriptive analysis indicated that some records did not contain essential data, hence these records were excluded from further analysis. Of the original 301 records, 256 were deemed

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suitable for use in the analyses which yielded the following results.

Nutrient analysis of the ration indicated that total digestible nutrient (energy) requirements were deficient for the lactating cows producing more than 40 kg of milk per day. The amount of crude protein in the ration was less than adequate for cows producing more than 30 kg per day. The analysis indicated that the study cows were receiving an adequate amount of salt, vitamins and minerals.

The frequencies of periparturient clinical events following 256 calvings are listed in Table 1. The 2 most common periparturient problems were anestrus and cystic ovarian disease.

Table 1. Incidence rates and absolute frequencies of reproductive abnormalities in 256 dairy cows calving between May 1, 1989, and July 30, 1990

Reproductive abnormality	Incidence rate (%)	Absolute frequency
Retained fetal membranes	4.3	11
Endometritis	3.9	9
Pyometra	2.7	7
Cystic ovarian disease	9.8	25
Anestrus	33.0	83

Pregnancy rates were not significantly different in the PG treated (69.4%) and control (71%) groups. There were no significant differences among treatment groups with respect to incidence of retained fetal membranes, endometritis, pyometra, anestrus, number of services per pregnancy, calving-to-first estrus interval, services per conception, and number of PG treatments subsequent to 31 d post partum. Culling rates for all criteria and specifically for reproductive reasons did not differ among the treatment groups (Table 2).

Table 2. Reproductive performance parameters of the entire study population (256 Holstein cows) compared to parameters for 4 treatment groups

Reproductive Outcome Parameter	Entire population n = 256	1 Fenprostalene (n)	2 Dinoprost (n)	3 Cloprostenol (n)	4 Placebo (n)
Days calving to first observed estrus ±SEM	67.6 ±2.6	62.6 (52)	68.3 (60)	70.0 (63)	69.0 (51)
Days calving to first service ±SEM	83.5 ±2.5	75.5 (47)	87.9 (57)	83.6 (62)	86.0 (49)
Days calving to conception ±SEM	116.6 ±4.2	114.2[a] (41)	104.9[a] (45)	112.2[a] (51)	137.3[b] (43)
First service conception rate (No. with at least 1 service)	42.5 (219)	46.0 (50)	44.8 (58)	45.2 (62)	32.7 (49)
Services per pregnancy (Total services for pregnant cows=327)	1.8	1.8	1.6	1.7	2.2
(No. pregnant)	(180)	(41)	(45)	(51)	(43)
Services per pregnancy (Total services for all cows=430)	2.4	2.6	2.2	2.3	2.5
(No. pregnant)	(180)	(41)	(45)	(51)	(43)
% Overall culling rate (No. culled)	32.5 (83)	28.1 (16)	32.9 (22)	36.2 (25)	32.3 (20)
% Culled for reproductive reasons	13.7	15.8	13.4	13.0	12.9
(No. culled for reproductive factors)	(35)	(9)	(9)	(9)	(8)

a,b . Significantly different (P=0.050).

Potential confounders in the treatment and calving-to-conception interval relationship were determined to be the age at calving, occurrence of cystic ovarian disease, and number of days from calving to first service. These factors were identified as potential confounders because they were non-uniformly distributed among treatment groups (the univariate analysis of each factor with treatment group was significant in the case of age at calving and days from calving to first service, and approached significance in the case of cystic ovarian disease). These were included in the analysis of variance model. The calving-to-conception interval means were compared using ANOVA for treatment versus the control while controlling for potential confounders. Significant effects of treatment on the calving-to-conception interval remained but the residuals were skewed. Since this violates ANOVA assumptions, another analytic technique was employed. The response was transformed by taking the log of the calving-to-conception interval, which resulted in more normally distributed data. The ANOVA was run again, and significant effects of treatment on the calving-to-conception interval remained (P=0.050 ; Table 3).

Table 3. ANOVA with log of calving to conception interval as the dependent variable, comparing the 4 treatment groups

Source	df	F value	P value
Age at calving	1	5.41	0.021
Ovarian cyst	1	0.28	0.598
Days to the first service	1	53.16	0.001
Treatment group	3	2.66	0.050

The same analysis was run to compare the 3 prostaglandin treatments, and there was no difference in the 3 treatments with respect to their effect on the calving-to-conception interval (P=0.263) or any of the measures of reproductive performance examined in this study (Table 4).

DISCUSSION

The average interval from calving to the first estrus and calving to the first service interval (67.6 and 83.5 d respectively) are similar to those reported in another study (66 and 88 d) of Southern Ontario herds (6). One might anticipate that his interval would be shorter for cows receiving PG compared with that of the controls. The fact that PG therapy between Days 24 and

Table 4. ANOVA with log of calving to conception interval as the dependent variable, comparing the 3 prostaglandin treatments

Source	df	F value	P value
Age at calving	1	2.45	0.120
Ovarian cyst	1	0.08	0.781
Days to first service	1	52.88	0.001
Treatment group	2	1.35	0.263

31 post partum did not have a significant effect on this parameter is consistent with the results of previous studies (3, 7, 31).

The calving-to-conception interval is a useful measure of reproductive performance in herds where calving is spread over the year and there is no defined breeding season (21, 25). The calving to conception interval for the study herd (116.6 d) was comparable to the 118.0 d average reported in a previous study of Ontario dairy herds (6) and similar to that reported in earlier studies of the same herd (7, 9). The calving-to-conception interval for cows receiving PG (fenprostalene, dinoprost or cloprostenol) between Days 24 and 31 (110.4 d) was approximately 27 d shorter than the average number of days open (137.4 d) for cows receiving a placebo. Many previous studies have provided evidence that PG administered to cows during the postpartum period may increase the first service conception rate or reduce the calving-to-conception interval (7, 8, 9, 30, 38, 39). A recent Australian study determined that PG administered between 14 and 28 d post partum did not have a beneficial effect on reproductive performance in 3 seasonally calving pasture based dairy herds (26). The authors stated that a low proportion of cows more than 2 wk post partum were detected with abnormal vaginal discharges, and postulated that delayed uterine involution and postpartum uterine inflammation may not have been limiting reproductive performance significantly in the trial herds. They also stated that the period of treatment ranged from 14 to 28 days post partum, therefore many of the trial cows would have been treated earlier than in studies where a positive association between treatment and improved fertility were seen.

The administration of PG during the immediate postpartum period (first 15 d) has resulted in variable but predominantly disappointing and inconclusive results (1, 2, 13, 16, 32). However, one well designed study conducted in the southern United States did show evidence of improved reproductive performance in dairy cows administered PG at 14 to 16 d post partum (24). Another study conducted in Switzerland demonstrated a positive association between treatment with dinoprost and expulsion of fetal membranes in cows which had undergone Caesarian surgery (35). While the current study does not deal with the administration of PG prior to Day 20 post partum, this work is discussed here as evidence that there may be a distinction between the immediate postpartum period and the period beyond Day 20 post partum with respect to response to PG treatment.

The improved fertility following postpartum PG therapy between 20 and 30 d post partum may have been due to a number of factors. Prostaglandin treatment may have caused premature regression of the corpus luteum that developed after the first postpartum ovulation. Previous studies have suggested that the postpartum factors most important to improved subsequent fertility were ovulation and the occurrence of estrus before the first service (3, 31, 33). Research by Benmrad and Stevenson (3) pertaining to progesterone profiles in cows treated with PG during the postpartum period would indicate that cows which experience precocious ovulations, and hence an increased number of estrous cycles prior to first service, are not necessarily observed in estrus earlier than control cows. This may explain why cows receiving PG between Days 24 and 31 post partum in the current study exhibited improved fertility, even though they had a similar interval to the first observed estrus and service compared with that of the controls.

There is also evidence that PG treatment may have benefits unrelated to its ability to cause luteolysis. In one study a single postpartum injection of dinoprost between Days 16 and 28 in all cows calving in the herd improved subsequent fertility, even in the cows with nonluteal phase plasma progesterone concentrations (< 1 ng/ml) at the time of therapy (39). In another study where cloprostenol was administered to all cows at Day 26 post partum without regard for ovarian status, cows with milk progesterone concentrations lower than 1 ng/ml at the time of treatment had a mean calving-to-conception interval 24 d shorter than cows with luteal-phase milk progesterone concentrations (9).

It has been suggested that PG administration may provide therapeutic benefits in the face of uterine infection (17). Losses associated with the occurrence of infectious reproductive abnormalities include those of reduced reproductive efficiency in the form of increased number of services per conception and days open (10). The incidence of pyometra was decreased in cloprostenol-treated cows compared with that of controls in 2 previous studies (7, 9). It has been postulated that this may have been due to the therapeutic effect of estrus subsequent to PG induced luteolysis (30, 35). A subsequent study determined that PG treated cows had less vaginal discharge, smaller diameter uterine horns, less inflammation and fibrosis in the endometrium, and were less likely to have Actinomyces pyogenes isolated from a biopsy taken 14 days subsequent to PG therapy than the untreated cows (4). These effects were independent of progesterone level at the time of treatment. It is possible that PG therapy may have oxytocic effects which cause uterine smooth muscle stimulation, resulting in enhanced uterine involution and voidance of uterine debris (14, 20). It has been suggested that $PGF_{2\alpha}$ may stimulate bovine polymorphonuclear leucocyte activity; however, the results of a recent study to investigate this hypothesis were equivocal (18).

One study was designed to investigate the efficacy of intrauterine treatment with chloramphenicol and framycetin (a kanamycin-like compound) or intramuscular treatment with PG (30). The authors indicated that cows diagnosed with endometritis approximately 30 d post partum and treated with either regimen had a significantly decreased calving-to-conception interval as compared with the controls. However, a more recent study indicated that cows diagnosed with endometritis approximately 30 d post partum and treated with a uterine infusion of either penicillin or oxytetracycline at approximately 30 d post partum did not have a decreased calving-to-conception interval as compared with that of the control cows (34). Another study designed to investigate the effect of PG treatment of cows with normal reproductive tracts and palpable corpora lutea between 20 and 40 d post partum (median 25 d) determined that treatment reduced median days to first service but did not have a significant effect on median days to conception (15). The number of cows pregnant by 110 d post partum did not differ among treatment and control groups (64.7 vs 69.6%).

The improved reproductive performance in PG-treated cows in this study supports previous results, indicating that postpartum PG therapy can be of economic benefit in some dairy herds (8, 30). Estimates of the cost of days open beyond the optimum are variable, ranging between $2.00 and $5.00 (5, 21, 23) and are probably herd-specific. A value of $3.00 per day was used in the following example. A decrease of 27 d in the calving-to-conception interval would result in a gross savings of $81 per cow. Since an injection of PG costs approximately $7.00 per cow (in Canada), the net savings would be $74 per cow, per year.

The variability of results pertaining to the effect of postpartum PG therapy on subsequent reproductive performance in dairy herds, indicates a need to consider factors such as the number of days post partum at PG treatment, herd reproductive performance, herd nutritional status, ability of the herd manager, frequency of herd visits by a veterinarian, and other management factors that could affect the outcome of a therapeutic intervention (37). Assessment of reproductive performance in dairy herds requires comprehensive information pertaining to breeding practices, health, production and other management factors. The development and implementation of better computerized dairy herd information management programs has resulted in the availability of multiple herd health and production databases which enable researchers to evaluate the effect of postpartum PG therapy on subsequent reproductive performance in numerous herds while controlling for factors which could potentially confound this association. Eventually, a multifactorial decision model may be developed which would assist veterinarians and producers in determining if postpartum PG therapy would be profitable in a particular dairy or individual animal.

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