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Endometritis treatment with a $PGF_{2\alpha}$ analog does not improve reproductive performance in a large dairy herd in Argentina

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Abstract

In Argentina, most dairy cows with endometritis are treated with prostaglandin ($PGF_{2\alpha}$ or its analogs) and insemination is withheld until there are no signs of endometritis. The objective of the present study was to evaluate if this method of managing endometritis enhances reproductive performance. Three experiments were conducted over 4 years in a large farm in the west of Buenos Aires province. In Experiment 1, half of the cows diagnosed with endometritis (>1.5-fold difference in diameter of uterine horns, as determined by rectal palpation) received standard endometritis management (treatment with tiaprost, a $PGF_{2\alpha}$ analog, rectal palpation every 20 days, and withholding of AI until endometritis apparently resolved) and the other half was untreated, with AI at the first estrus after the voluntary waiting period. Untreated cows were inseminated and conceived 20 days earlier than treated cows, and the pregnancy rate by Day 90 postpartum was higher in the untreated group. In Experiment 2, cows with endometritis were divided into four groups according to the severity of symptoms; within each group, cows were allocated to treatment or control, as in Experiment 1. Although first service conception rate decreased as endometritis severity increased, reproductive performance in treated versus control cows was similar to that of Experiment 1 (with no interaction due to degree of endometritis). Re-evaluation of the treated cow (to confirm uterine ''normality'') may have been responsible for the delay in conception in both experiments. The objective of Experiment 3 was to determine the effects of tiaprost treatment on clinically normal postpartum cows (no evidence of endometritis). Tiaprost treatment reduced the interval from calving to conception in multiparous cows, but it delayed conception and reduced the conception rate in

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primiparous cows. In conclusion, treatment with tiaprost impaired reproductive performance in primiparous cows (in the absence of endometritis). Furthermore, the standard treatment for endometritis (treatment with a prostaglandin analog and withholding insemination until clinical signs abated) impaired reproductive performance and increased costs.

Keywords: Endometritis; Dairy cow; $PGF_{2\alpha}$; Tiaprost; Reproductive performance

1. Introduction

Postpartum endometritis in dairy cows reduces reproductive performance and potential profit [1,2]. Several periparturient factors, including dystocia, retained fetal membranes and twinning, affect the incidence of uterine infections [1]. Bacterial contamination of the uterus occurs during the first week after calving; subsequent inflammation of the endometrium occurs during the second through fourth postpartum weeks [3]. The severity of uterine inflammation varies from a mild superficial endometritis to an acute septic metritis, involving the entire thickness of the uterine wall. In most cases, the inflammatory response resolves over time. Uterine infections are usually detected by rectal palpation and vaginal speculum examination. There are many approaches for preventing and controlling postpartum endometritis, including intrauterine infusions of antibiotics and/or antiseptics, systemic administration of antibiotics, enzymes and hormonal therapy, including estrogens, prostaglandins and/or GnRH [3–7]. In particular, $PGF_{2\alpha}$ (or an analog) is commonly given, despite conflicting reports regarding the benefits of this treatment for uterine infection [6,8]. In the west of Buenos Aires (Argentina), dairy cows diagnosed with postpartum endometritis are usually treated with $PGF_{2\alpha}$ (or its analogs), and AI is withheld until the endometritis has apparently resolved. Therefore, the purpose of this study was to evaluate if this method of managing endometritis improves reproductive performance.

2. Materials and methods

This study was conducted in a large (2000 cows) dairy farm in Buenos Aires province, Argentina (latitude 35°S, longitude 63°W) over a 4-year interval. Cows were milked twice daily and were kept on mixed pastures (alfalfa, festuca, lolium) or winter annual grasses (ryegrass, oats) between milkings. Corn, corn silage, cottonseed and/or sunflower meal supplement were provided in accordance with nutritional requirements, individual milk yield and season. Mean (±S.E.) milk production was 16.4 ± 0.09 and 18.8 ± 0.15 L/day/cow for primiparous and multiparous cows, respectively. The herd was on a regular reproductive herd health program and all health and reproductive records were managed with Syscord-Tamb® software (Lincoln, Argentina).

2.1. Basic reproductive management

Cows calved in small pens (calving = Day 0) and received a transition diet. Every 20 days, cows from Days 30–50 were subjected to rectal palpation to assess the

uterus and detect endometritis. Cows with endometritis were those with moderate asymmetry between the two uterine horns (1.5–2-fold, with or without intrauterine fluid, and with or without modifications of the thickness and consistency of the uterine wall) or total enlargement of the uterus (metritis). Before the beginning of the trials, all cows diagnosed with endometritis were given 0.75 mg i.m. of the $PGF_{2\alpha}$ analog, tiaprost (Iliren; Intervet Argentina SA, Buenos Aires), when endometritis was diagnosed, and they were subsequently rechecked by rectal palpation 20 days later. If the reproductive tract was still abnormal at re-examination, a second tiaprost treatment was given, and the cow re-examined. If the tract was still abnormal at the third examination, systemic antibiotics (amoxicillin, 15 mg/kg) were given in addition to tiaprost. Up to five doses of tiaprost could be applied. Cows diagnosed with metritis (systemically ill and febrile) were given systemic antibiotics at the time of diagnosis. Cows without diagnosed endometritis in the first postpartum control were inseminated at the first estrus after 45 ppd (voluntary waiting period), whereas cows with an abnormal uterus were not inseminated until the uterus was deemed normal. Manual pregnancy examinations were conducted no sooner than 35-day post-insemination.

2.2. Experiment 1 (years 1 and 2)

Cows ($n = 678$) diagnosed with endometritis at the first postpartum examination were assigned alternatively to one of two groups. Cows in group 1 ($N = 378$) received the standard endometritis management with $PGF_{2\alpha}$ treatment and rechecking until cured, as described above (without the use of antibiotics; cows that required antibiotic treatment were excluded from the experiment). Cows in group 2 ($N = 300$) received no treatment; they were managed as healthy cows and inseminated at the first estrus after the voluntary waiting period.

2.3. Experiment 2 (years 2–4)

At the first postpartum examination, 1308 cows with endometritis were classified according to the severity (Table 1); the scale used was developed by the authors, based on previous classifications [3,9]. During each examination, for each classification of degree of endometritis, cows were alternatively assigned to treated or untreated groups until a maximum number was reached (determined by the dairy manager). Thereafter, all remaining cows in that classification were left untreated group (resulting in more untreated than treated cows in each classification). Treated cows received the $PGF_{2\alpha}$ analog and were rechecked (as described above), whereas the others were managed as healthy cows.

2.4. Experiment 3 (years 2 and 3)

Cows were examined between 30 and 60 days postpartum (mean: 44.1 ± 0.2 ppd); only those with a normal uterus and palpable CL were used ($n = 952$). Of these, 410 were chosen at random and treated with tiaprost (mean day of treatment: 43.9 ± 0.4 ppd), and 542 remained as untreated controls.

Table 1
Classification (based on rectal palpation) of endometritis in dairy cows (Experiment 2)

Classification	Uterine status	Number of cows (u = untreated; t = treated)
1	Moderate asymmetry between horns (1.5–2-fold)	686 (607 u + 79 t)
2	Marked asymmetry (2–4-fold), intrauterine fluid, mild edema	488 (323 u +165 t)
3	Enlarged uterus, increased thickness of uterine wall, marked edema	95 (49 u + 46 t)
4	Metritis (marked compromise of all the layers of uterine wall)	39 (9 u + 30 t)

Treated cows received a $PGF_{2\alpha}$ analog and were rechecked at 20-day intervals, whereas untreated cows were controls.

2.5. Reproductive performance measures and statistical analyses

Herd reproductive parameters are described in Table 2. For Experiments 1 and 3, days to first estrus and days to first service were compared between groups by *t*-test for independent measures, and days open were compared by a Mann–Whitney test. Conception rates and pregnancy rates were compared using a Chi-square. Effect of parity was analyzed by Friedman's two-way analysis for each parameter. For Experiment 2, Friedman's two-way analysis was used to compare days to first estrus, days to first service and days open, and a Cochran *Q* test was used for conception and pregnancy rates.

3. Results

3.1. Experiment 1

Reproductive and experimental parameters for Experiment 1 are shown in Table 3. Cows were diagnosed with endometritis at similar postpartum day (40.3 ± 0.5 and 39.5 ± 0.4 for untreated and treated cows, respectively). The endometritis prevalence during this experiment was 18.9%. Although there was no difference between groups for days to first estrus, untreated cows were inseminated and became pregnant earlier than treated cows

Table 2
Definitions of reproductive parameters for postpartum reproductive performance in dairy cows

Parameter	Definition
Days to first estrus	Interval from calving to first estrus
Days to first service	Interval from calving to first service
Days open	Interval from calving to conception
First service conception rate	Cows pregnant after first service × 100/all cows receiving first service
Total conception rate	Cows pregnant × 100/total number of inseminations
Pregnant by Day 90 (%)	Cows pregnant by Day 90 × 100/cows inseminated
Pregnant by Day 150 (%)	Cows pregnant by Day 150 × 100/cows inseminated
Services per conception	Number of services/cows pregnant

Day 0 = day of calving.

Table 3
Reproductive parameters (mean ± S.E.) in dairy cows (Experiment 1) with endometritis (based on rectal palpation) that were either untreated (with AI at the first estrus after the voluntary waiting period) or treated with a $PGF_{2\alpha}$ analog (with re-examination at 20-day intervals and AI only after disappearance of clinical signs of endometritis)

	Untreated	Treated
Number of cows	300	378
Number of PGF treatments/cow	0	1.6 ± 0.04
Days to first estrus	56.0 ± 1.99	57.0 ± 1.88
Days to first service	72.0 ± 1.68	92.6 ± 1.51***
Days open[a]	100.2 ± 3.37	121.9 ± 3.19**
Services per conception[a]	2.03 ± 0.11	1.98 ± 0.08
Estrus without services[a]	0.58 ± 0.05	1.50 ± 0.07***
First service conception rate (%)[b]	48.0	49.2

Difference between untreated and treated cows (**$P < 0.01$, ***$P < 0.001$).
[a] Excluding cows that did not conceive (45 untreated and 56 treated).
[b] All cows received a first service.

(Table 3). Parity did not influence the differences encountered in days to first service and days open (Table 4). The percentage of pregnant cows by Day 90 postpartum was higher in the untreated group regardless of parity, but by Day 150 postpartum, the difference was not significant (Table 4).

3.2. Experiment 2

The endometritis prevalence was 21.8% in Experiment 2. Reproductive performance of cows in Experiment 2 was similar to cows in Experiment 1, with no interaction of severity of endometritis. Since parity did not influence any of the parameters measured, data were pooled. Days to first service and days open were higher in treated than in untreated cows, regardless of endometritis severity (Table 5). The first service conception rate was negatively affected by endometritis severity in both treatment groups (Fig. 1). There was no significant effect of endometritis severity on percentage pregnant by Days 90 and 150 postpartum (Table 5).

3.3. Experiment 3

Treatment of healthy cows with the $PGF_{2\alpha}$ analog resulted in different reproductive performance in primiparous compared to multiparous cows (Table 6). Days to first service and days open were shorter in primiparous untreated compared to primiparous treated heifers. On the other hand, days to first service was shorter in multiparous treated cows compared to untreated cows. Furthermore, first service conception rate was higher in untreated than in treated primiparous cows. In treated and untreated multiparous cows, there were no differences in first service conception rate or days open. The percentage of pregnant cows by Days 90 and 150 was higher in untreated than treated primiparous cows, but did not differ between treated and untreated multiparous cows.

Table 4
Reproductive performance in dairy cows (Experiment 1) according to parity

	Parity							
	1		2		3		4 or more	
	Untreated[a]	Treated[a]	Untreated[a]	Treated[a]	Untreated[a]	Treated[a]	Untreated[a]	Treated[a]
Number of cows	166	178	86	116	34	77	14	7
Days to first service	76.2 ± 2.4	95.2 ± 2.6*	67.4 ± 2.9	87.7 ± 2.1*	67.4 ± 3.8	93.7 ± 2.6*	61.1 ± 4.8	95.6 ± 9.9*
Days open[b]	102.2 ± 4.4	122.0 ± 4.8*	94.6 ± 6.5	116.2 ± 5.1*	107.8 ± 10.8	129.9 ± 7.5*	91.8 ± 3.3	129.0 ± 3.2*
Pregnant by Day 90 (%)	47.0	31.9*	50.6	30.3*	40.0	22.5*	40.0	12.5*
Pregnant by Day 150 (%)	76.2	65.9	72.4	69.7	57.1	61.3	58.3	50.0

All cows had endometritis (based on rectal palpation) that was either untreated (with AI at the first estrus after the voluntary waiting period) or treated with a $PGF_{2\alpha}$ analog (with re-examination at 20-day intervals and AI only after disappearance of clinical signs of endometritis). Day 0 = day of calving. Difference between untreated and treated cows ($*P < 0.05$).

[a] Group.

[b] Excluding cows that did not conceive.

Table 5
Reproductive performance in dairy cows (Experiment 2) according to severity of endometritis (scored on a scale of 1–4)

	Endometritis (score)							
	1		2		3		4	
	607[a]	79[a]	323[a]	165[a]	49[a]	46[a]	9[a]	30[a]
No. $PGF_{2\alpha}$ treatments	0	1.83 ± 0.09	0	1.81 ± 0.07	0	1.84 ± 0.01	0	2.21 ± 0.19
Days to first estrus	55.8 ± 1.4	59.9 ± 4.1	53.1 ± 1.7	50.4 ± 2.3	54.3 ± 4.7	58.5 ± 4.4	62.7 ± 9.6	52.9 ± 5.9
Days to first service	67.8 ± 1.9	93.9 ± 2.8*	65.9 ± 1.6	91.6 ± 1.9*	63.9 ± 4.0	93.6 ± 3.8*	71.2 ± 7.3	100.6 ± 5*
Days open[b]	99.9 ± 2.6	120.0 ± 6.1*	95.3 ± 2.9	115.6 ± 3.9*	91.6 ± 7.1	134.7 ± 13.1*	96.9 ± 13.6	132.1 ± 9.9*
Services per conception[b]	2.12 ± 0.07	1.77 ± 0.15	2.12 ± 0.10	1.94 ± 0.11	1.88 ± 0.20	2.37 ± 0.32	2.00 ± 0.41	2.13 ± 0.28
Estrus without services[b]	0.47 ± 0.03	1.45 ± 0.15*	0.47 ± 0.04	1.61 ± 0.11*	0.39 ± 0.09	1.57 ± 0.24*	0.44 ± 0.24	1.48 ± 0.31*
Pregnant by Day 90 (%)	52.2	24.7	52.7	27.5	46.0	18.4	18.8	24.4
Pregnant by Day 150 (%)	75.6	74.1	77.4	71.3	76.0	55.1	88.9	46.9

All cows had endometritis (based on rectal palpation) that was either untreated (with AI at the first estrus after the voluntary waiting period) or treated with a $PGF_{2\alpha}$ analog (with re-examination at 20-day intervals and AI only after disappearance of clinical signs of endometritis). Difference ($*P < 0.05$) between untreated and treated cows (within an endometritis score).

[a] Number of cows.

[b] Excluding 122 cows that did not get pregnant (49, 4, 31, 17, 8, 6, 0, 7 in data columns 1–8, respectively).

Table 6
Reproductive performance in primiparous and multiparous dairy cows (without clinical signs of endometritis) untreated or treated with tiaprost (Experiment 3)

	Primiparous		Multiparous	
	Untreated	Treated	Untreated	Treated
N	312	266	230	144
Days to first estrus	47.5 ± 1.6	52.9 ± 2.1	46.2 ± 1.8	42.5 ± 2.0
Days to first service	67.1 ± 1.3	72.0 ± 1.9*	64.5 ± 1.6	61.0 ± 1.8*
Days open[a]	97.9 ± 3.3	111.1 ± 4.0*	91.6 ± 3.3	89.6 ± 4.2
Services per conception[a]	2.05 ± 0.10	2.26 ± 0.11	1.90 ± 0.10	2.00 ± 0.12
Estrus without services[a]	0.79 ± 0.05	0.72 ± 0.05	0.77 ± 0.06	0.81 ± 0.06
First service conception rate (%)[b]	50.3	41.7*	47.8	45.1
Pregnant by Day 90 (%)[b]	60	47**	60	61
Pregnant by Day 150 (%)[b]	85	79*	84	89

Difference (*$P < 0.05$; **$P < 0.01$) between untreated and treated (cows) within a parity group.
[a] Excluding 75 cows that did not get pregnant (20, 14, 26, and 15 in data columns 1–4, respectively).
[b] Excluding cows that were not inseminated (5, 2, 5, and 5 in data columns 1–4, respectively).

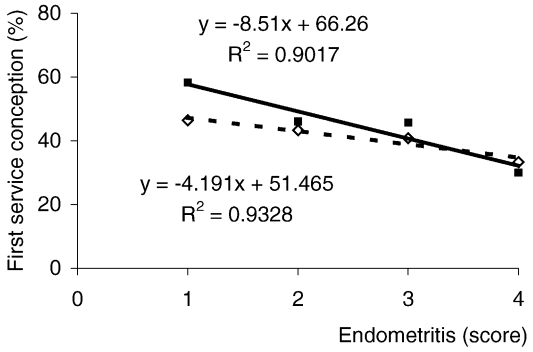

Fig. 1. Linear regression of first service conception rate and degree of endometritis (scored on a scale of 1–4) in both treated and untreated cows (both slopes $P < 0.05$). All cows had endometritis (based on rectal palpation) that was either untreated (with AI at the first estrus after the voluntary waiting period) or treated with a $PGF_{2\alpha}$ analog (with re-examination at 20-day intervals and AI only after disappearance of clinical signs of endometritis).

4. Discussion

The prevalance of endometritis varied from 18 to 22%. This was typical for grazing herds in Argentina, where cows do not receive individual attention at parturition, and supplement is offered in large common feeders. In this situation, individual feed intake, and therefore mineral and energy balance, depends on each cow. However, the prevalance of endometritis seemed lower than the expected 25% observed by Klingborg [10] in large ''California-Style'' dairies in well-managed herds. In the UK, the prevalance was 10–15% [9].

Transrectal palpation is the most common method for diagnosing endometritis, but it is subjective and dependent on training and skill [1]. Furthermore, this diagnostic method

tends to include healthy cows in the diseased group as it only evaluates size and morphology of the horns. In one review, a study was cited that only 20% of the cows classified as having moderate endometritis had bacteria cultured [3]. However, it is the only suitable diagnostic procedure for field use in large herds available at the time, and our practitioners are skillful and experienced.

Whereas the reported effects of endometritis on reproductive performance are variable [2], most farmers and practitioners in Argentina assume that endometritis is a cause of economic loss due to decreased reproductive capacity. In addition, treatment costs are substantial, and usually increase herd health costs.

The beneficial effect of prostaglandins on resolution of uterine infections has been widely demonstrated [6,9]. In addition to the uterotonic effect, the decrease in progesterone and the increase in estrogen (associated with luteolysis and follicular growth) result in maximal resistance of the uterus to bacterial infection, as progesterone down-regulates and estrogens up-regulate immune function [1]. The subsequent occurrence of estrus often results in elimination of endometritis [3]. However, in Experiments 1 and 2, cows with endometritis given prostaglandin had delayed conception due to delayed day of first service. In both experiments, the delay between groups was about 20 days, which is exactly the time interval between two controls of the cows by rectal palpation. As no differences were observed on parturition to first estrus, services per conception and first service conception rate, we conclude that only the protocol for management of treated cows (that involves rechecking the treated cow to confirm uterine ''normality'') is responsible for the delay. This was also confirmed by the observation that estrus without service differed between groups in nearly one estrus. This delay in releasing the cow to service is reflected in the lower pregnancy rate observed in treated cows by 90 days. Although visits to the farm for rectal examinations were performed every 20 days throughout the study, it is more typical in commercial dairies for the veterinarian to come once monthly and for farmers to delay insemination until confirmation that the cow is ready and suitable for breeding. In this case, cows diagnosed with endometritis and treated would inevitably experience a longer delay than those in the present study.

When cows were classified according to their endometritis severity (Experiment 2), results in reproductive performance due to treatment did not change, not even in the group with profound infection. Once again we found that reproductive parameters were better in untreated than in treated cows. In both treatment groups, first service conception rate decreased as the severity of endometritis increased, but the decrease was not enough to produce statistically significant diminution of pregnancy by 90 days postpartum.

Using the results in Experiment 1, we can estimate the additional costs of treating endometritis. Including the costs of tiaprost (mean of 1.6 doses @US $1.6), an additional 21 days open (total cost US $42) and an additional examination (@US $1.25); the total cost was US $45.87 per treated cow.

The effect of treatment with tiaprost on reproductive performance in cows with a normal uterus was also evaluated to determine the deleterious effects of the prostaglandin analog per se in this herd. In healthy cows, treatment with $PGF_{2\alpha}$ can decrease the interval from calving to first AI, as it causes luteolysis and thus initiates a new cycle [11,12]. Surprisingly, we found that primiparous and multiparous cows responded differently. In multiparous cows, tiaprost advanced first service by 4 days, but at Day 90 postpartum, the

percentage of pregnancy was not significantly different between treated and untreated cows, probably due to a lower first-service conception rate in the treated group. Therefore, we can assume that there was no beneficial goal in using the drug in multiparous cows. In primiparous cows, tiaprost delayed first service by 5 days, and also impaired first service conception rate. Consequently, pregnancy rates at Days 90 and 150 postpartum were lower in the treated group.

In an early study attempting to accelerate estrus onset in postpartum beef cows, cows were given estradiol-17beta and conception rates were reduced [13]. Since then, a variety of hormonal protocols have been developed to regulate the bovine estrous cycle without impairing fertility [12]. Most of them include PGFα or its analogs as they induce a rapid luteolysis, decreasing endogenous progesterone by 24 h and then promoting a new cycle. Fertility of heifers after prostaglandin-based estrus synchronization protocols was normal [14,15]. However, deleterious effects of $PGF_{2\alpha}$ on conception rates were reported in lactating cows [16]. In that study, there were two prostaglandin treatments; reduced conception rates occurred when the second treatment was given in the early luteal phase. In the present study, there was only one treatment; although a palpable CL was a prerequisite, no distinction was made for early, middle or late luteal phase. Recently, deleterious effects of a treatment with progesterone and estradiol on conception rates were also reported [17]. In most of those studies in which $PGF_{2\alpha}$ or its analogs were used for estrus synchronization, parity was not considered in the analysis of the pregnancy rates. Perhaps primiparous cows, which are often in poor body condition, respond differently to exogenous hormonal treatment, as negative energy balance impairs reproduction [18].

In conclusion, the benefits of treating endometritis with a prostaglandin analog must be carefully evaluated as the drug per se may have deleterious effects on reproductive performance. Furthermore, the common practice (in Argentina) of giving dairy cows with endometritis a prostaglandin analog and then delaying insemination until recovery is verified is certainly impairing reproductive performance and unnecessarily increasing costs.

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