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Fertility in dairy cows treated in the early luteal phase with a reused progesterone-releasing intravaginal device

Abstract

In this study, we tested whether early luteal phase treatment with a previously used progesterone-releasing intravaginal device (DIV) increased conception rate (CR) in dairy cows. Two experiments were performed; in the first, progesterone concentrations were determined in cows treated with a reused DIV. Seven cows received PGF2 α and a reused DIV was inserted for seven days. Blood samples were collected daily for progesterone determination. Progesterone increased from 0.42 ± 0.17 ng/mL (mean $\pm$ standard deviation) at DIV insertion to 1.99 ± 0.52 ng/mL at 24 h and 2.11 ± 0.40 ng/mL at 48 h after; during the treatment period, progesterone showed an average concentration of 1.4 ± 0.55 ng/mL. In the second experiment, 383 cows were randomly divided on day 4 post-insemination, into two treatment groups: DIV ($n = 188$), received a reused DIV, which was removed on day 14; Control ($n = 195$), did not receive DIV. Progesterone concentrations were determined in seven cows from each group. The CR was not affected by treatment [DIV (33.5 %) vs. Control (37.4 %); $P > 0.05$]. No interaction was observed between treatment and service number, parity, the type of postpartum (normal or pathological), body condition, or days in milk ($P > 0.05$). Progesterone concentrations were similar between treatments ($P > 0.05$). We conclude that the insertion of a reused DIV at early diestrus did not increase serum progesterone concentrations or conception rate in dairy cows.

Keywords: progesterone; intravaginal progesterone-releasing device; dairy cows; fertility.

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Study contribution

High-production dairy cows require a high intake of dry matter, which increases the hepatic catabolism of progesterone, a condition associated with low fertility. Various strategies to increase fertility by administering progesterone have been evaluated with varying results. In one study, discrete increases in progesterone concentrations during the early luteal phase with reused progesterone-releasing intravaginal device-increased fertility. However, no other work has corroborated these results. In this study, we tested whether the insertion of a reused progesterone-releasing intravaginal device in the early luteal phase increased fertility. Three hundred eighty-three cows were used; on day four post-insemination, 188 cows received a reused device, while 195 cows received no device. The results did not show an increase in fertility in cows receiving a reused device.

Introduction

Abnormalities of embryonic development and subsequent embryo death are the leading cause of reproductive failure in dairy cows.⁽¹⁾ Such abnormalities may be a consequence of the low serum concentrations of progesterone suffered by dairy cows in intensive production systems, which is because the corpus luteum produces less progesterone and steroid hormones are catabolized more rapidly.⁽²⁻⁵⁾

A common approach to the clinical management of infertility in dairy cows has consisted of the administration of progesterone using an intravaginal progesterone-releasing device (DIV); however, the results have been variable. While in some studies, the administration of progesterone increases the ratio of pregnant cows to total inseminated cows (conception rate or P/AI), in others, no effect has been observed.⁽⁶⁻⁹⁾

The physiological window in which progesterone is administered has influenced the response. Mann et al. observed that progesterone supplementation between days five and nine post-insemination favors embryo development, whereas the same treatment between days 12 and 16 has no effect.⁽¹⁰⁾ Progesterone concentrations are also critical for embryo survival between days four and nine after estrus.^(11,12) Stronge et al. also found a positive association between progesterone concentrations between days five and seven of the estrus cycle and embryo survival.⁽¹³⁾

Larson et al. proposed that a discrete increase in serum progesterone levels during the early luteal phase could improve the conception rate.⁽¹⁴⁾ In their study, the insertion of a previously used controlled internal drug-release device (CIDR) from day 3.5 to day 10 post-insemination increased progesterone concentrations and conception rates. The increase in serum progesterone concentrations in this experiment was only 0.7 ng/mL on the day after CIDR placement.

The authors suggest that the increase in the conception rate is due to this modest increase in the concentration of progesterone, since a greater increase such as that caused by the usage of a new DIV could have a negative effect on corpus luteum lifespan. These results could justify the use of recycled DIV to increase fertility in dairy cows; however, there is no other work in which the same treatment has been evaluated. Therefore, this study tested whether the insertion of a reused DIV in the early luteal phase increased the conception rate in dairy cows.

Materials and methods

Statement of ethics

This work did not require the approval of the Institutional Committee for the Care and Use of Experimental Animals (SICUAE) of the National Autonomous University of Mexico School of Veterinary Medicine and Animal Husbandry. The practices to which the cows were subjected during the study such as intravaginal insertion of a device, an injection of PGF2 α , blood sampling, and transrectal pregnancy diagnosis are routine in commercial herds.

Animals

The study was performed in a commercial dairy herd located in Tizayuca, Hgo. The climate of the region is temperate subhumid, with an average annual temperature of 15.5°C and an average annual rainfall of 861 mm. The cows were housed in free-stall pens and fed a total mixed ration. Milk production fluctuated between 7 000 and 8 000 kg per lactation (305 days). Cows were identified in estrus by observing standing behavior and were inseminated by two technicians under the am-pm/pm-am program. In all cases, the presence of uterine tone and cervical mucus was determined, as well as the external signs of estrus. The pregnancy diagnosis was made by transrectal palpation between days 45 and 50 post-insemination.

Experiment 1

This experiment determined serum progesterone concentrations obtained with a reused DIV (PRID Delta; Ceva Animal Health) in dairy cows. To this end, seven cycling cows 50 to 80-day postpartum were used. The devices, which had already been used for six days in other cows, were washed with running water and sterilized with gamma irradiation. Before the insertion of the DIV, the cows received two injections of PGF2 α (Celosil; MSD Animal Health) intramuscularly with a 14 day interval; 24 h after the second injection of PGF2 α , the cows received another injection of PGF2 α and the DIV was inserted, remaining *in situ* seven days.

Starting from the day of insertion, blood samples were collected daily for seven days. Samples were obtained by venipuncture in vacuum tubes without anticoagulant and centrifuged at 1 500 g for ten minutes for separating the serum, which was stored at -20°C. Addition, from the time the device was inserted, an estrus detection patch (EstroTECT[®]) was placed on all cows. Following the removal of the device, estruses were detected twice a day in two-hour periods (morning and afternoon).

Experiment 2

Based on the results of Experiment 1, Experiment 2 determined the effect of insertion of the reused DIV in the early luteal phase on the conception rate in dairy cows. Three hundred eighty-three Holstein cows of one to three services 120 $\pm$ 3.2-day postpartum was used, with 3.1 $\pm$ 0.09 births and a body condition score of $\geq$ 2. On day four post-insemination, the cows were randomly divided into two treatment groups: DIV (n = 188), which received a reused DIV removed on day 14 post-insemination, and Control (n = 195), in which cows did not receive DIV treatment. Blood samples were collected daily during the treatment days in seven cows from

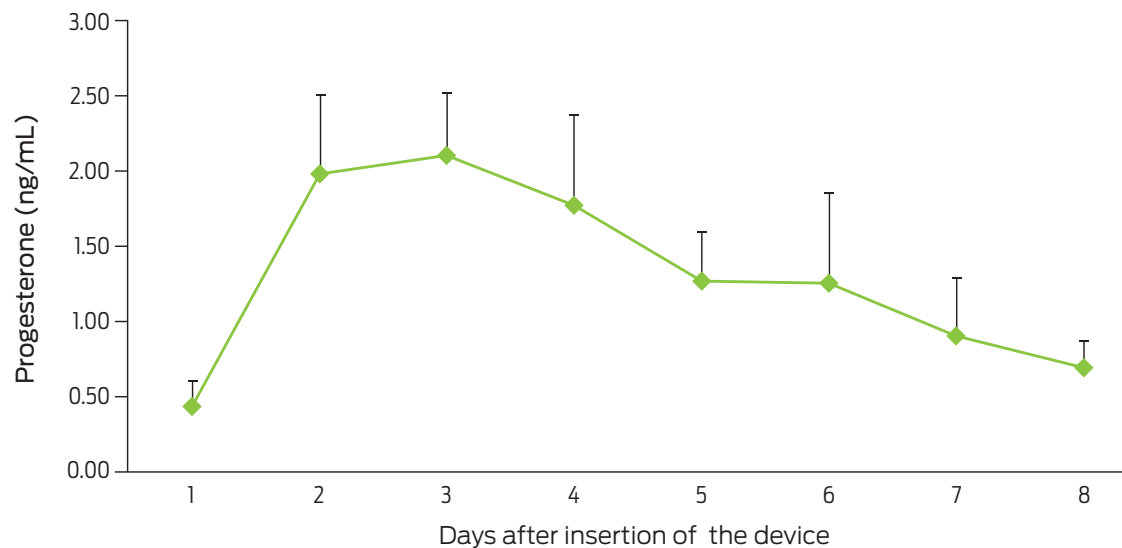


Figure 1. Progesterone concentrations (mean + standard deviation) in cows treated with a reused DIV (PRID Delta). Day 1 corresponds to the day of insertion of the DIV.

the reused DIV group and six from the control group. Samples were obtained by venipuncture in vacuum tubes without anticoagulant and centrifuged at 1 500 g for ten minutes for separating the serum, which was stored at -20°C.

Determination of progesterone concentrations

Progesterone concentrations were determined by solid-phase radioimmunoassay (*Coat-A-Count Progesterone Diagnostic Product Corporation, USA*), with a sensitivity of 0.1 ng/mL and an intra-assay coefficient of variation of 6.4 percent.

Statistical analysis

A logistic regression analysis was performed for binary variables to determine the significance of the categorical explanatory effects of the treatment, the number of services, parity (primiparous vs multiparous), type of postpartum [normal vs pathological (cows that suffered placental retention and/or purulent vaginal discharge)], body condition score, and days in milk on the conception rate. Progesterone data were analyzed with a mixed linear statistical model using days, days², treatment, interaction effects days x treatment and days² x treatment as fixed effects. The random cow effect was included to model the repeated structure of the measurements; a residual effect was also included.⁽¹⁵⁾

Results and discussion

The serum progesterone concentrations of Experiment 1 are shown in [Figure 1](#). Progesterone concentrations increased from 0.42 ± 0.17 at the time of insertion of the DIV, to 1.99 ± 0.52 ng/mL at 24 h and 2.11 ± 0.40 ng/mL at 48 h later. During the treatment period, serum progesterone showed an average concentration of 1.4 ± 0.55 ng/mL.

Table 1. Odds ratio of gestation according to variables in the logistic regression model

Variables	Classes	Number of cows	Conception rate	Odds ratio	CI 95 %	P
Group	DIV	188	33	Reference		
	Control	195	37	1.05	0.6-1.6	0.08
Days in milk*	≤100	187	35	Reference		
	101-200	145	36	1.37	0.4-1.3	0.29
	>200	45	35	1.15	0.3-2.1	0.77
Parity	Primiparous	101	35	Reference		
	Multiparous	282	36	1.2	0.4-1.4	0.52
Body condition score	<2.5	15	27	Reference		
	2.5-3	274	37	1.91	0.9-4.0	0.07
	>3	94	31	1.41	0.5-3.5	0.45
Number of services	First	203	31	Reference		
	Second	120	42	2.06	1.1-3.7	0.01
	Third	60	37	2.24	1.0-5.0	0.04
Postpartum	Pathological	196	32	Reference		
	Normal	187	39	1.68	1.0-2.7	0.03

*For days in milk, the total number of cows is lower because some cows did not have this information in the records.

During the treatment period with the reused DIV, no cows showed estrus. All cows presented estrus following removal of the DIV. The insertion of the reused DIV increased serum progesterone concentrations sufficiently to suppress the presentation of estrus and to cause, following its removal, the presentation of a fertile estrus.

The best model for this type of study is that of the ovariectomized cow.⁽¹⁶⁾ However, in other studies designed to determine the progesterone released by an DIV, an animal model without ovariectomy was used, in which after inducing luteolysis with two injections of PGF2 α within a 24-hour period, a norgestomet ear implant was placed for two days to prevent ovulation before inserting the DIV.^(17,18) In this study, the fact that the cows that received the reused DIV did not show estrus during the treatment period and presented synchronized estrus after removing the DIV, allows us to propose that the source of serum progesterone was only from the reused DIV.

Van Cleef et al. used new and reused DIV for nine days (CIDR, 1.9-g progesterone) in ovariectomized dairy cows.⁽¹⁹⁾ As expected, the new CIDRs obtained higher plasma progesterone concentrations than the reused CIDRs; in addition, the progesterone concentrations with the reused CIDRs were greater than 1 ng/mL (mean of 1.5 ± 0.14 ng/mL), which is consistent with the concentrations obtained in this study. Moreover, the progesterone profile obtained is similar to the profiles observed with the use of recycled CIDRs.^(17,19)

To our knowledge, no study has been published showing the progesterone profile generated with the use of a reused PRID Delta in dairy cows, a situation that determined the performance of the first experiment. The reuse of DIVs is not recommended by manufacturers; however, reused DIVs are used in synchronization programs with satisfactory results. Additionally, thermal treatment for sterilization of reused DIVs (CIDRs) facilitates the release of progesterone, which is reflected in plasma progesterone concentrations similar to those observed when new DIVs are used.⁽¹⁷⁾

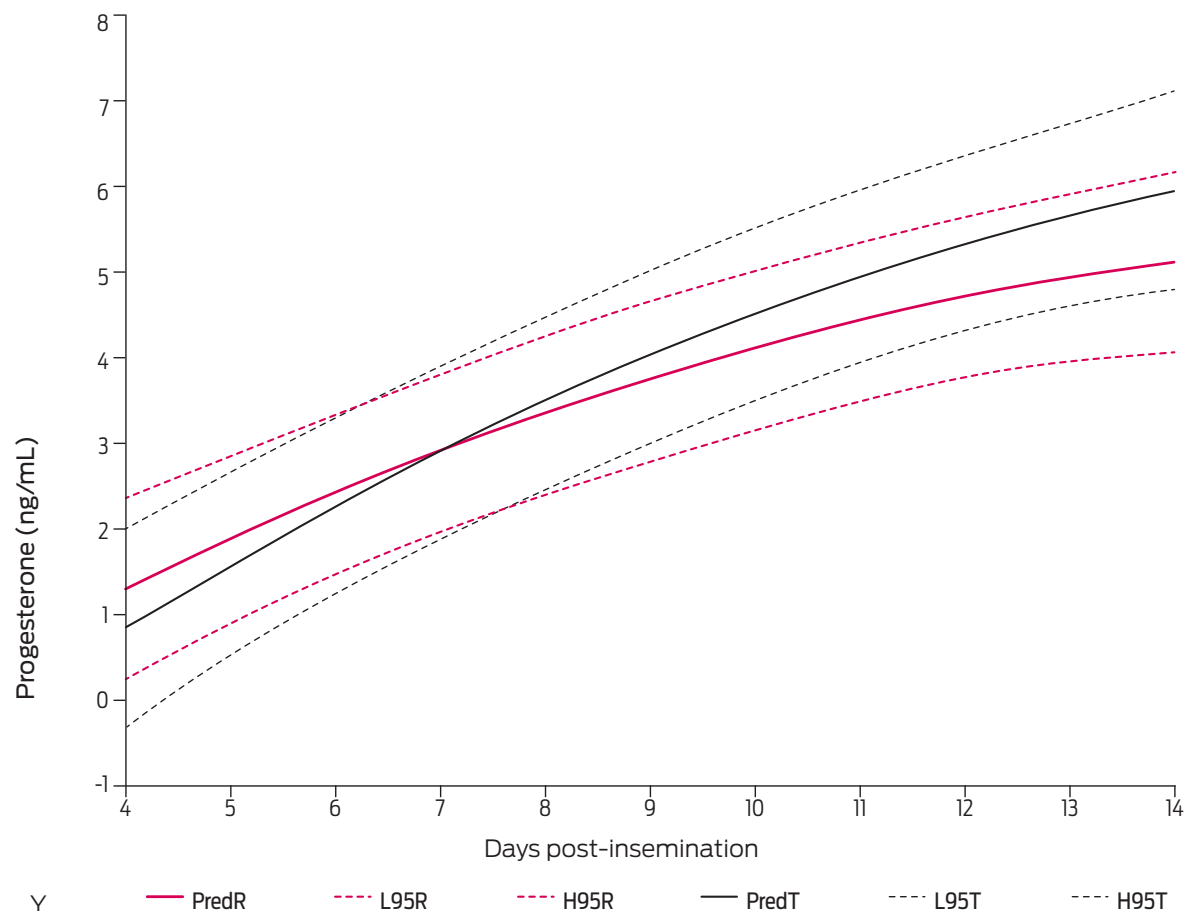


Figure 2. The evolution of predicted (Pred) values of mean serum progesterone concentration in cows treated with a reused DIV (R; red lines) and control (T; black lines) and lower (L95) and upper (H95) 95% confidence limits, by second-degree polynomial regression, between days 4 and 14 after insemination. Mean progesterone concentrations were similar between treatments ($P > 0.05$); however, the treatment x day interaction indicates a lack of parallelism between curves ($P < 0.05$).

The favorable effect of high progesterone concentrations on embryonic development has been demonstrated in different scenarios;^(9,20) however, the effect of administering an external source of progesterone in fertility is contradictory.^(6–9) The results of the logistic regression analysis (Table 1) show that treatment with a reused DIV did not increase the odds ratio of pregnancy; nor was any treatment interaction observed with the variables included in the analysis. Based on the hypothesis raised in this study, it was expected that the insertion of a reused DIV would cause a discrete increase in progesterone concentrations during the early luteal phase (day four post-insemination), which would increase the conception rate; however, progesterone was not increased or fertility affected.

Figure 2 shows the serum progesterone concentrations of Experiment 2, which were similar between those of cows that had a reused DIV and the control group ($P > 0.05$). The results of this study contrast with those obtained by Larson et al., who observed that the insertion of a reused DIV (CIDR) at day 3.5 post-insemination increased ($P < 0.05$) the serum concentration of progesterone by 0.7 ng/mL, which is associated with a favorable effect on fertility.⁽¹⁴⁾

The reason a significant increase was not observed in serum progesterone concentrations in cows receiving an additional source of this hormone is unknown. One factor that may have influenced this finding is the amount of progesterone contained in the different devices. The new device used in the Larson et al. study had 1.9 g progesterone while the new PRID Delta contains 1.55 g;⁽¹⁴⁾ thus, it is possible that after one use, the progesterone content was lower in the PRID Delta than in the CIDR.

However, in this study, the progesterone released by the reused PRID Delta was similar to that observed in studies performed with reused CIDRs.^(17,19) Alternatively, milk production, and in particular dry matter intake, determine the hepatic clearance rate of steroid hormones. Thus, high-producing cows have lower serum progesterone concentrations than cows that produce less milk or are not in lactation.^(3,4) The cows used in this study have moderate production (7 000 to 8 000 kg of milk/305 days; therefore, it was expected that the administration of exogenous progesterone would be reflected in higher serum levels of this hormone, which did not occur.

It is likely that the variability of fertility outcomes reported in the different published studies when progesterone is administered is highly dependent on differences in management, dry matter intake, changes in body condition score, milk production, nutrition, uterine health, and climate, among other factors.^(9,21) Additionally, the source of progesterone used has been DIVs, which are effective for estrus synchronization, i.e., they work efficiently for the purposes for which they were developed. It is necessary to have an exogenous source of progesterone that generates blood concentrations replacing the progesterone eliminated by hepatic metabolism, a condition that tends to worsen due to the sustained increase in milk production observed in modern dairy cows.

It is worth noting that a strategy in which more consistent results to increase progesterone blood concentrations have been observed involves inducing a second corpus luteum with the injection of hCG on day five post-insemination; in several studies, this treatment has increased conception rate in dairy cows.⁽²²⁻²⁴⁾

Conclusions

The insertion of a reused progesterone-releasing intravaginal device in the early luteal phase did not increase serum progesterone concentrations or improve the conception rate in dairy cows.

Data availability

The data generated and analyzed in this work will be made available upon request to the corresponding author.

Acknowledgments

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Conflicts of interest

We declare that we have no conflicts of interest.

Author contributions

Conceptualization: G Meneses, J Hernández, F Rivera.

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Data analysis: HH Montaldo, J Hernandez.

Research: G Meneses, M Ramírez.

Writing of the original draft: J Hernandez, H. H. Montaldo, F. Rivera.

Revision, editing and approval of the final version of the manuscript: J Hernandez, G Meneses, F Rivera, H Montaldo, M Ramirez.

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