

## Efficacy of repeatedly used CIDR device in cattle reproduction: a metaanalysis review of progesterone concentration and conception rate

Muhammad Furqan Asghar CHACHER<sup>1\*</sup>, Armağan ÇOLAK<sup>1</sup>, Armağan HAYIRLI<sup>2</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Faculty of Veterinary Medicine, Atatürk University, Erzurum, Turkey

<sup>2</sup>Department of Animal Nutrition and Nutritional Disorders, Faculty of Veterinary Medicine, Atatürk University, Erzurum, Turkey

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**Abstract:** In order to reduce estrus synchronization cost, utilization of residual progesterone ( $P_4$ ) in the used controlled internal drug release (CIDR) device upon sanitization can be possible. Two datasets were compiled from 8 and 7 research articles involving 3434 (2653 heifers + 771 lactating cows + 10 ovariectomized cows) and 7301 cattle (3879 heifers + 3422 lactating cows) to evaluate blood  $P_4$  concentration and conception rate, respectively, in response to repeatedly used CIDR devices after sanitization via autoclaving and disinfection. As the number of CIDR usages increased, blood  $P_4$  concentration decreased linearly ( $y = -0.484X + 3.135$ ,  $R^2 = 0.99$ ,  $P < 0.001$ ). Blood  $P_4$  concentration (1.52 vs. 2.20 ng/mL;  $P < 0.002$ ) and conception rate (40.76 vs. 32.96%,  $P < 0.05$ ) for lactating cows were lower than those for heifers. The sanitization method did not affect blood  $P_4$  concentration, but reused CIDR device subjected to disinfection was associated with reduced conception rate. In summary, depending upon the initial  $P_4$  load (1.38–1.90 g), the CIDR device could be used twice in lactating cows and four times in heifers after autoclaving to achieve target blood  $P_4$  concentrations.

**Key words:** Blood  $P_4$ , CIDR device, conception rate, sanitization

### 1. Introduction

Animal reproduction is an integration of a number of series of events and has vital importance in dairy and cow-calf operations. In order to maximize reproductive performance, different approaches are being applied in animal reproduction (1). One of these approaches covers the utilization of a variety of hormones such as prostaglandin  $F_{2\alpha}$  ( $PGF_{2\alpha}$ ), progesterone ( $P_4$ ), gonadotropin-releasing hormone (GnRH), and estradiol ( $E_2$ ) (2).  $P_4$  is a major steroidal hormone and is secreted by the corpus luteum (CL) and the placenta to maintain pregnancy (3). It is commonly employed in estrus synchronization in different forms such as oral feeding, ear implants, and intravaginal devices (4).

The intravaginal devices containing  $P_4$  have been used for more than 40 years in cattle and sheep reproduction for controlling estrous cycles. The controlled internal drug release (CIDR) device is an intravaginal insert that acts as a  $P_4$  source to maintain the blood  $P_4$  concentration (5,6). The CIDR device is a T-shaped device having a nylon spine molded by silicon rubber skin impregnated by either 1.90 or 1.38 g of  $P_4$  (7). Progesterone in the CIDR device acts at first via a negative feedback mechanism to block the surge release of luteinizing hormone (LH) and ovulation

(8). Later on, withdrawal of the CIDR device causes the release of LH to support follicular development and then to achieve ovulation (2). Moreover,  $P_4$  acts by a mechanism that promotes mRNA expression of galanin, which is a neuropeptide related to the preovulatory surge release of gonadotropins (9).

The CIDR device was first recommended to be used for 12 days in New Zealand in 1987 (7) but later on variable intervals were reported, e.g., 5 (10), 7 (8), 9 (11), 12 (12), and 14 (13) days. Although using  $P_4$  for longer durations produces excellent synchronization results, poor fertility linked to the maturation of stale follicles remains an obstacle. Employment of a CIDR device for a maximum of 7–8 days is recommended for effective synchronization and fertility (7). After being used for 7 days, the remaining  $P_4$  concentration in the CIDR device initially containing 1.9 and 1.38 g was reported to be 1.3 and 0.72 g, respectively (5,7). Moreover, CIDR devices achieved 2.3 and 1.9 ng/mL blood  $P_4$  in ovariectomized cows on days 14 and 15 relative to insertion (14). However,  $P_4$  concentration at a minimum of 1 ng/mL is needed to block LH surge release (5). Moreover, using a CIDR device up to 21 days still releases  $P_4$  at a sufficient level to suppress estrus and induce synchronization. Single use of CIDR devices is

\* Correspondence: [vetchachar@gmail.com](mailto:vetchachar@gmail.com)

recommended by the manufacturer due to the risk of spreading venereal diseases. However, the considerable residual  $P_4$  concentration in used CIDR (U-CIDR) devices and the achieved blood  $P_4$  concentration on days 14–15 after insertion suggest that CIDR devices can be reused upon disinfection in order to minimize the cost (8,15,16). A number of disinfecting and autoclaving methods before reutilizing U-CIDR are available (17). The objective of this metaanalysis study was to withdraw conclusions from the available literature regarding  $P_4$  concentrations in devices and animals as well as conception rate (CR) responses in cases of multiple U-CIDR devices subjected to various disinfection methods in cattle.

## 2. Materials and methods

Research articles published in different peer-reviewed journals were collected through Scopus, PubMed, and Web of Science. The selection criteria were data from experiments 1) dealing with repeated use of CIDR devices, 2) involving cattle, and 3) having a control group (single use of the CIDR device). The response variables were limited to blood  $P_4$  concentration and CR (Table 1). On the basis

of use, CIDR devices were divided into four categories: 1st use (new), 2nd use, 3rd use, and 4th use. Data (blood  $P_4$  concentration and CR) were subjected to ANOVA to determine effects of times CIDR devices were used, animal type, and sanitization methods and regression analysis to determine changes in response variables depending on times CIDR devices were used (or total days CIDR devices were inserted). Due to insufficient replications, two-way interactions were not determined. Differences among factors were attained by the LSD option. Statistical significance was declared at  $P < 0.10$ .

## 3. Results

The blood  $P_4$  concentration data were gathered from 8 experiments involving 3434 cattle (2653 heifers + 771 lactating cows + 10 ovariectomized cows). Initial  $P_4$  concentration in brand new CIDR devices was  $1.71 \pm 0.23$  (1.38–1.90) g. The mean days CIDR devices were inserted were  $8.58 \pm 0.24$ ,  $15.27 \pm 0.31$ ,  $27.00 \pm 0.42$ , and  $39.00 \pm 0.73$  days for the 1st, 2nd, 3rd, and 4th use, respectively. As the CIDR devices continued to be used, blood  $P_4$  concentration decreased linearly (Table 2). This relationship was fit to

**Table 1.** Data compiled from the literature for the current metaanalysis study.

Blood progesterone data						
Reference	N	Animal type	Times used	Days fresh used	Total days used*	Sanitization method
Abdallah and Rahim (18)	700	Lactating cows	2	7	14	Disinfection
Cerri et al. (8)	62	Lactating cows	2	7	14	Autoclaving
Dias et al. (25)	525	Heifers	2	9	18	Not reported
Júnior et al. (21)	935	Heifers	4	12	39	Not reported
Long et al. (14)	4	Ovariectomized beef cows	2	7	14	Disinfection
Mantovani et al. (26)	40	Heifers	2	8	16	Not reported
Peres et al. (11)	1153	Heifers	3	9	27	Not reported
van Cleeff et al. (27)	9	Lactating cows	2	9	18	Disinfection
Zuluaga and Williams (5)	6	Ovariectomized cows	2	7	14	Disinfection
Conception rate data						
Reference	N	Animal type	Times used	Days fresh used	Total days used**	Sanitization method
Abdallah and Rahim (18)	700	Lactating cows	2	7	14	Disinfection
Cerri et al. (8)	515	Lactating cows	2	7	14	Autoclaving
Colazo et al. (17)	616	Heifers	2	9	16	Autoclaving
Dias et al. (25)	1175	Heifers	2	9	18	Not reported
El-Tarabany (16)	2207	Lactating cows	2	7	14	Disinfection
Júnior et al. (21)	935	Heifers	4	12	39	Not reported
Peres et al. (11)	1153	Heifers	3	9	27	Not reported

\*CIDR device was inserted for  $8.58 \pm 0.24$ ,  $15.27 \pm 0.31$ ,  $27.00 \pm 0.42$ , and  $39.00 \pm 0.73$  days for 1st, 2nd, 3rd, and 4th uses, respectively.

\*\*CIDR device was inserted for  $7.85 \pm 0.56$ ,  $15.00 \pm 0.66$ ,  $26.40 \pm 1.11$ , and  $39.00 \pm 2.48$  days for 1st, 2nd, 3rd, and 4th uses, respectively.

**Table 2.** Blood P<sub>4</sub> concentration and conception rate responses to insertion of new and repeatedly used CIDR devices.\*

Factor	P <sub>4</sub>	CR
Times used		
1st	2.68 ± 0.26	36.92 ± 2.22
2nd	2.11 ± 0.38	33.20 ± 1.66
3rd	1.71 ± 0.28	ND
4th	1.20 ± ND	ND
Animal type		
Heifers	2.20 ± 0.23 <sup>b</sup>	40.76 ± 2.19
Cows	1.52 ± 0.23 <sup>c</sup>	32.96 ± 0.95
Ovariectomized cows	3.03 ± 0.37 <sup>a</sup>	---
Sanitization method		
New	2.68 ± 0.26	36.92 ± 2.22 <sup>ab</sup>
Autoclaving	3.36 ± 1.54	41.33 ± 2.95 <sup>a</sup>
Disinfection	1.65 ± 0.24	30.58 ± 1.10 <sup>b</sup>
Not Reported	1.84 ± 0.22	42.91 ± 2.98 <sup>a</sup>
ANOVA		
Times used	0.04	0.06
Animal type	0.002	0.05
Sanitization method	0.10	0.38

\*The CIDR device was inserted for 8.58 ± 0.24, 15.27 ± 0.31, 27.00 ± 0.42, and 39.00 ± 0.73 days in 8 experiments dealing with blood P<sub>4</sub> concentrations and involving 3434 cattle (2653 heifers + 771 lactating cows + 10 ovariectomized cows) and 7.85 ± 0.56, 15.00 ± 0.66, 26.40 ± 1.11, and 39.00 ± 2.48 days in 7 experiments dealing with conception rate and involving 7301 cattle (3879 heifers + 3422 lactating cows) for 1st, 2nd, 3rd, and 4th use, respectively. Values in a given category with different superscripts are significantly different.

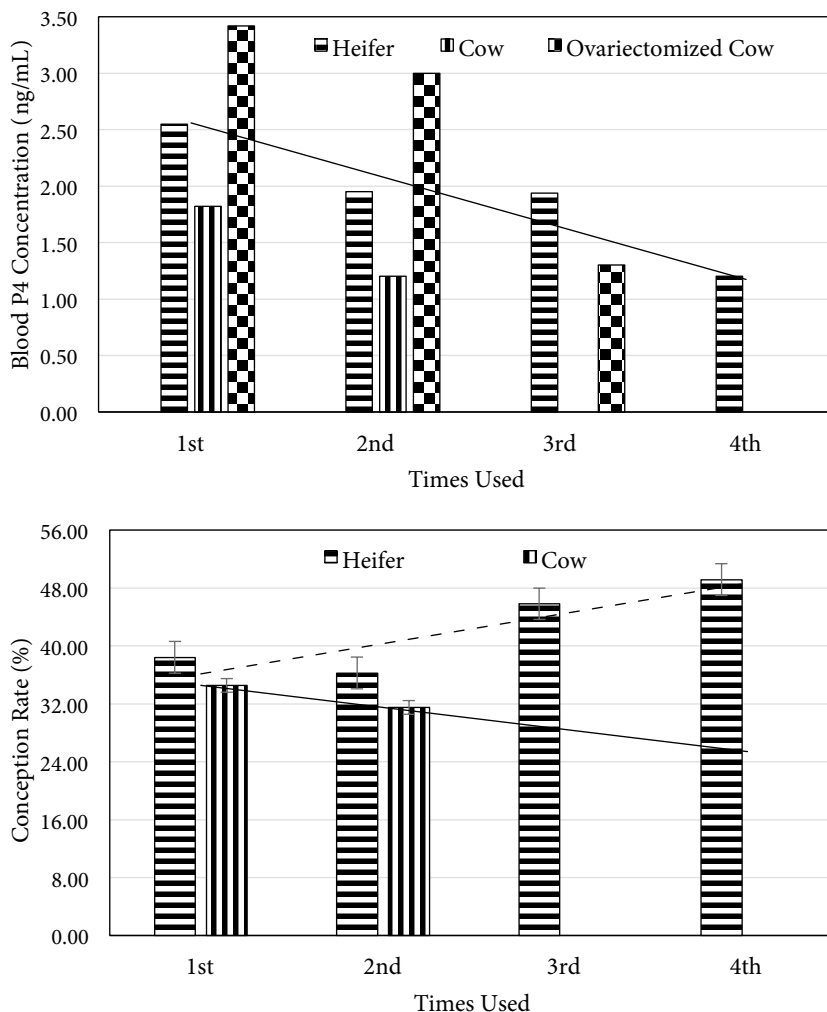
blood P<sub>4</sub> concentration =  $-0.484 \times \text{times CIDR was used} + 3.135$  ( $R^2 = 0.99$ ,  $P < 0.001$ ). The decrease in blood P<sub>4</sub> concentration for lactating cows was sharper than that for heifers (Figure, upper panel). Ovariectomized cows had the highest blood P<sub>4</sub> concentration, followed by heifers and then lactating cows ( $P < 0.002$ ; Table 2). The sanitization method did not affect blood P<sub>4</sub> concentration.

The CR data were gathered from 7 experiments involving 7301 cattle (3879 heifers + 3422 lactating cows). Initial P<sub>4</sub> concentration in brand new CIDR devices was 1.66 ± 0.27 (1.38–1.90) g. The mean days CIDR devices were inserted were 7.85 ± 0.56, 15.00 ± 0.66, 26.40 ± 1.11, and 39.00 ± 2.48 days for the 1st, 2nd, 3rd, and 4th use, respectively. The CR tended to decrease in lactating cows, whereas it tended to increase in heifers as the CIDR

devices continued to be used ( $P < 0.06$ ; Table 2; Figure, lower panel). Overall, heifers had higher CR than lactating cows (40.76 vs. 32.96%,  $P < 0.05$ ; Table 1). It appeared that disinfection of the CIDR device was associated with reduced CR (Table 2).

#### 4. Discussion

The dataset provided an overall view of the nature of the response of blood P<sub>4</sub> concentration and CR in response to the times CIDR devices were used, animal type, and sanitization method of the U-CIDR device. However, a number of factors were not taken into account, spanning from nutritional status, metabolic profile, experimentation season, and breed to technician skill.



**Figure.** Blood P<sub>4</sub> concentration (upper panel) and conception rate (lower panel) responses to insertion of new and repeatedly used CIDR devices according to the animal type. The CIDR device was inserted for  $8.58 \pm 0.24$ ,  $15.27 \pm 0.31$ ,  $27.00 \pm 0.42$ , and  $39.00 \pm 0.73$  days in 8 experiments dealing with blood P<sub>4</sub> concentrations and involving 3434 cattle (2653 heifers + 771 lactating cows + 10 ovariectomized cows) and  $7.85 \pm 0.56$ ,  $15.00 \pm 0.66$ ,  $26.40 \pm 1.11$ , and  $39.00 \pm 2.48$  days in 7 experiments dealing with conception rate and involving 7301 cattle (3879 heifers + 3422 lactating cows) for the 1st, 2nd, 3rd, and 4th uses, respectively.

#### 4.1. Blood progesterone concentration

The standard approach to evaluate blood P<sub>4</sub> concentration is to include ovariectomized cows and/or intact cows in estrus as the basis (18). As the number of usages of the CIDR devices increased, delivered blood P<sub>4</sub> concentrations linearly decreased, especially after the 2nd use (Table 2). The inhibitory mechanism of CIDR on LH surge release and estrus requires more than 1 ng/mL of P<sub>4</sub> circulation in the blood, which is considered the threshold level for CIDR device administration (17,19). In the current study, even at the 4th usage of the CIDR device it exceeded the threshold level as long as the device was sanitized. However, this

postulation might not be valid because there were no data involving lactating cows with CIDR devices inserted after the 2nd usage (Figure, upper panel). Moreover, repeated usage up to four times could be related to initial P<sub>4</sub> load in the CIDR device, which ranged from 1.38 to 1.90 g. Because the sample size was small, the current data were not adjusted to initial P<sub>4</sub> load in new CIDR devices. The mean initial P<sub>4</sub> concentration in new CIDR devices was calculated to be  $1.71 \pm 0.23$  g.

Parity, in relation to milk yield, dry matter intake, dietary nutrient profile and composition, and energy balance, also affects steroid catabolism, resulting in differences in blood

$P_4$  concentrations. More specifically, the absorbability of  $P_4$  may also vary by the estrus cycle stage due to alterations in the vaginal membrane (18). Interrelationships among body weight, feed intake, and milk yield, leading to alterations in hepatic blood flow and steroidal hormone metabolism, are well established (3,18). Lower blood  $P_4$  concentration in lactating cows compared to heifers (Table 2) could be linked to faster hepatic blood flow accompanied by higher milk production (20) and heavier body weight (8), which affect the clearance of steroidal hormones and circulatory concentration, respectively.

It is very critical to sanitize CIDR devices when they are reused in order to avoid sexually transmitted diseases. With respect to elevation in blood  $P_4$  concentration, used CIDR devices subjected to autoclaving were superior to those subjected to disinfection as compared to new CIDR devices (Table 2). Autoclaving produces a flare action by increasing  $P_4$  concentration in the 2nd use. This effect could happen because high-pressure steam sterilization leads to the formation of crystalline  $P_4$  on the surface of the intravaginal device or alteration in the structural integrity of silicon molding impregnated by  $P_4$  (19). In spite of the fact that disinfectants are excellent at reducing the risk of disease transmission, they may also cause a decrease in  $P_4$  concentration (17).

#### 4.2. Conception rate

The CR data in response to the 3rd and 4th use in lactating cows were not available. Overall, repeated use of CIDR devices tended to be associated with a linear decrease in CR ( $P < 0.06$ ; Table 2). The CR increased in heifers, whereas it decreased in lactating cows with the frequency of repeated usages of CIDR devices (Figure, lower panel). The amount of  $P_4$  delivery prior to artificial insemination (AI) is critical to improve CR through enhancing the ovulation rate (3). It seems that a slower decrease in blood  $P_4$  concentration benefits heifers in terms of increasing CR, but not lactating cows, as the CIDR devices were repeatedly reused (Figure). Some authors recommend U-CIDR devices

over new CIDR devices in prepubertal heifers (21). This could be explained by the subluteal-phase  $P_4$  hypothesis that providing a low  $P_4$  environment during follicular development increases preovulatory follicle size. The diameter of the preovulatory follicle is directly related to the number of granulosa cells, which reflects the ability of the CL to produce  $P_4$ . In other words, the larger the follicle, the larger the CL will be, which could produce higher  $P_4$  concentrations leading to improved fertility. However, this hypothesis has one drawback. In a low  $P_4$  environment, a growing follicle tends to become a persistent follicle. During low  $P_4$  concentrations, LH pulsatility is enhanced, resulting in prematuration of oocytes. These oocytes can be fertilized but do not have development competence (22–24).

Overall, the CR was lower for lactating cows than for heifers (32.96 vs. 40.76%;  $P < 0.05$ ; Table 2). This could be mainly related to being heifers in anabolic status, whereas lactating cows are in a catabolic state at the time of AI. In agreement with blood  $P_4$  concentration data, cattle inserted with U-CIDR devices subjected to disinfection tended to be inferior in achieving CR as compared to those with autoclaved devices (Table 2).

#### 4.3. Conclusions

Despite many constraints associated with sample size within nested subgroups, the following inferences were made: 1) depending upon the initial  $P_4$  load, the CIDR devices could be used up to four times in heifers and twice in lactating cows after preferably autoclaving to exceed a blood  $P_4$  concentration of 1 ng/mL; 2) overall, lactating cows had lower blood  $P_4$  concentration than heifers; 3) autoclaving was superior to disinfection to elevate blood  $P_4$  concentration and improve CR when CIDR devices were reused; 4) probably in association with the residual  $P_4$  amount and blood  $P_4$  concentration, the CR rate decreased in lactating cows, but not in heifers, when CIDR devices were reused.

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