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Investigation of the effect of repeated use of PRIVD on serum progesterone, estrogen levels, and ovulatory follicle diameter in pubertal heifers

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Abstract: The purpose of this study was to evaluate the effect of reuse of progesterone-releasing intravaginal devices (PRIVDs) on serum progesterone, estrogen levels, and ovulatory follicle diameter in pubertal heifers. Three pubertal Holstein heifers were used in the study for three different periods with the usage of three PRIVDs up to three times from day 0 to 7 according to the Latin square model. Blood samples were collected on days 0, 3, 5, 7, and 9 for hormonal analysis. Ovulatory follicle diameter was measured by transrectal ultrasonography 60 h after removal of the PRIVD. Serum progesterone demonstrated a significant relationship with device use and day ($P < 0.01$) with the 1st use group showing the highest mean serum progesterone levels. Mean serum progesterone levels of the 2nd and 3rd use did not show any significant difference among them. The peak level of mean serum progesterone was recorded on day 3 of the study, whereas minimum levels were seen at days 0 and 9. Serum progesterone concentrations of days 5 and 7 had no significant differences among them. The interaction between use of PRIVDs and days interval was significant ($P < 0.01$). Serum estrogen concentration ($P > 0.05$) and ovulatory follicle diameter ($P > 0.05$) did not differ significantly with the use of the PRIVD at day 9. In the present study, even the 3rd use of the PRIVD produced similar results as the first use. In conclusion, PRIVDs can be reused or manufactured with low progesterone for heifers to reduce hormonal synchronization cost.

Key words: Heifer, progesterone-releasing intravaginal device, progesterone, estrogen, follicle diameter

1. Introduction

Continuous expansion in herd size of the dairy industry brings forth the need of development of systematic programs for reproductive management of dairy cattle. These programs have markedly evolved in the past 20 years with synchronization protocols, which allow the use of fixed-time artificial insemination (FTAI). Estrous synchronization with the use of FTAI programs has become an integral part of present-day reproductive management, which reduces the time and labor for estrus detection and increases the profitability of dairy farms (1,2). Progestins such as melengestrol acetate, controlled internal drug release (CIDR®), the progesterone-releasing intravaginal device (PRID Delta®), and norgestomet implants (Syncro-mate B®) are being used very often in FTAI-based synchronization protocols (3,4). Among progestins, intravaginal progesterone releasing devices (PRIVDs) have been used more than 40 years for estrous synchronization and artificial insemination protocols. The progesterone in a PRIVD suppresses the release of LH and ovulation at introduction and releases LH, supports follicle development, and causes ovulation on withdrawal (5). Moreover, progesterone promotes mRNA expression of galanin, which is a neuropeptide related to the preovulatory surge release of gonadotropins (6). The incorporation of PRIVDs in synchronization protocols requires an additional cost and to reduce this cost PRIVDs are being reused (7). Normally, a PRIVD is used once and single use is even recommended by producers; however, multiple uses of PRIVD in prepubertal (8), pubertal (9,10), postpubertal (11), dairy and beef (12,13) heifers, ovariectomized cows (5,14) nonlactating (15,16), lactating (7,17) primiparous (18,19), multiparous (19,20), and postpartum (12,21) beef and dairy cows and anestrous buffalo (22) have been reported. Among PRIVDs, the reutilization of PRID Delta is not common as that of CIDR in the literature (23). After the first use of CIDR for 7 days, the remaining progesterone in 1.9 g and 1.38 g CIDR was 1.3 g and 0.72 g, which indicated the possibility of its reuse (5,7). The residual progesterone after the first use of CIDR is well known; however, the remaining progesterone concentration in once used PRID DELTA has not been cited yet (23).

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Cows that received once used PRIVDs had greater estrus response than cows receiving new PRIVDs; however, the pregnancy rates per artificial insemination (AI) were the same for both treatments (23). Cows treated with either new or once used PRIVDs had similar pregnancy rates (24). Used PRIVDs successfully suppressed estrus for 7 days in dairy and beef cattle and in some studies showed similar pregnancy rates as compared to new PRIVDs after FTAI (5,25). In lactating beef cows once or twice used PRIVDs were as effective as new PRIVDs in terms of synchronization (17). Colazo et al. (15) found that cattle inserted with twice used PRIVDs had lower pregnancy rates as compared to cattle with once used PRIVDs; however, the results were nonsignificant. The conception and pregnancy rates were nonsignificant for used and new PRIVDs in primiparous cows; however, in multiparous cows, the new PRIVD group had greater conception and pregnancy rates as compared to the used PRIVD group (19).

Chacher et al. (26) metaanalyzed the reutilization of PRIVDs in lactating cows and heifers and found that conception rates decreased in lactating cows with the use of PRIVD; however, in heifers, conception rates increased with frequency of usage. Surprisingly, heifers tend to show higher conception rates as the use of PRIVDs increases. In prepubertal *Bos indicus* heifers used PRIVDs produced greater conception rates as compared to new PRIVDs (10). The pregnancy rates of heifers treated with used intravaginal devices were greater (59.7% vs. 49.5%) than that of heifers treated with new intravaginal devices. In heifers once used PRIVDs are more successful as compared to new PRIVDs; however, the exact mechanism behind this is not well understood (27).

The same PRIVDs are being used for both heifers and lactating cows since their development with just a reduction in days in its use, whereas the requirement and metabolism of progesterone are different for these animals. The purpose of this research is to find the reason behind improved pregnancy rates in heifers with reuse of PRIVDs by evaluating the blood serum progesterone, estrogen levels, and ovulatory follicle diameter after creating a low progesterone environment through reutilization of PRIVDs.

2. Materials and methods

All procedures were approved by the Animal Experiments Local Ethics Committee of Ataturk University (75296309-050.01.04-E.1700196076; Decision No. 71).

The present study was conducted on the research and development farm of the Faculty of Veterinary Medicine, Atatürk University, Erzurum, Turkey. A total of three (A, B, and C) pubertal Holstein heifers with an average age of 13 months, 350 kg body weight, and 3.5 BCS were included in the study. Heifers were kept under standard management and nutritional conditions. Total mixed ration and concentrates were fed to the all the heifers on the farm. Ad libitum feed and water supply were available to the heifers. A PRIVD (PRID Delta®) was applied sequentially for each heifer for 7 days according to the Latin square plan. In the first period, a new PRIVD was inserted into the vagina of heifer A. After 7 days the PRIVD was removed from heifer A and introduced into heifer B and then C, respectively. Through this rotation, one PRIVD was used for the 1st, 2nd, and 3rd time in heifers A, B, and C, respectively. The same rotation was used for the 2nd and 3rd new devices, maintaining the Latin square plan as shown in Figure 1. At the end of each period, a resting interval of 21 days was given to the heifer to prevent remaining effects of the previous device. Each device was disinfected before each use in the heifers.

The day of insertion of the device was labeled as day 0 and on day 7 the PRIVD was removed from the heifers. These protocols were initiated regardless of the stage of the estrous cycle. Prostaglandin F2α injection was given two days before insertion of the device and at the day of removal, whereas gonadotropin-releasing hormone was injected on day 0 and day 9 of the treatment. Blood samples were taken from the coccygeal vein of the heifers on days 0, 3, 5, and 7 for progesterone analysis and on day 9 (60 h after withdrawal) for measurement of both progesterone and estrogen concentrations. Blood samples on days 0 and 7 were taken before the insertion and removal of the device, respectively. Serum was extracted from the blood samples by performing centrifugation at 4000 rpm for 10 min. Serum samples were stored at –20 °C until analysis of serum progesterone and estrogen. Hormonal concentrations were measured by enzyme-linked immunosorbent assay (ELIZA) method according to the manufacturer's instructions (Cusabio Biotech Co., Ltd., Wuhan, China). At day 9, ovulatory follicle diameter was measured by using transrectal ultrasonography (AgroscanAL®, Noveko International Inc., Angoulême, France; mode B, depth 8 cm, 7.5 MHz). The general linear model of the Latin square was used for analyzing serum progesterone, estrogen levels, and ovulatory follicle diameters. The three different periods of the study were also considered in the statistical model. Statistical analysis was performed with SAS software (Version 9.1; SAS Institute Inc., Cary, NC, USA).

3. Results

Mean serum progesterone concentration decreased with each use of the PRIVD as expected and maximum progesterone was seen in the 1st use. There was no significant difference between mean serum progesterone levels of the 2nd and 3rd uses. The heifers showed

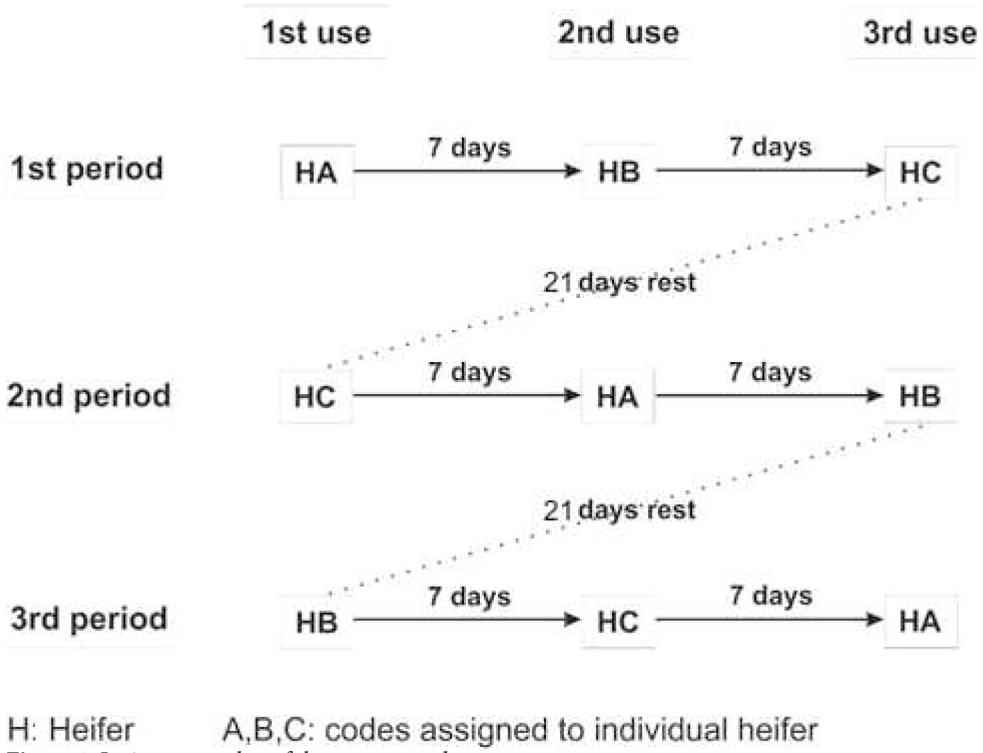

Figure 1. Latin square plan of the present study.

Table 1. Mean serum progesterone concentration (ng/mL) of 1st, 2nd, and 3rd use of PRIVDs at days 0, 3, 5, 7, and 9 of the trial.

	Serum progesterone (ng/mL)
Use	
1st	5.08 ± 0.73[a]
2nd	3.26 ± 0.71[b]
3rd	2.80 ± 0.40[b]
Day	
0	0.91 ± 0.15[c]
3	5.32 ± 0.76[a]
5	3.34 ± 0.59[b]
7	2.81 ± 0.41[b]
9	0.68 ± 0.12[c]

[a,b,c] Values with different superscripts differ significantly ($P < 0.01$).

minimum serum progesterone level at day 0 (1st use 0.94 ± 0.02; 2nd use 0.71 ± 0.11; 3rd use 1.07 ± 0.46) and at day 9 (1st use 0.71 ± 0.33; 2nd use 0.68 ± 0.16; 3rd use 0.68 ± 0.17) of the treatment. On the other hand, maximum serum progesterone concentrations were observed on day 3, which decreased at day 5 and remained constant at day 7. There was no significant difference between serum progesterone levels of day 5 and 7, as shown in Table 1. The interaction between use of PRIVD and days interval was significant ($P < 0.01$), as shown in Figure 2. There was no significant relationship found between use of PRIVD, serum estrogen concentration, and ovulatory follicle diameter at day 9, as shown in Table 2. Moreover, on the same day, no correlation was found between serum progesterone, serum estrogen, and ovulatory follicle diameter. However, serum estrogen concentration and ovulatory follicle diameter increased numerically with the use of the PRIVD as shown in Table 2.

4. Discussion

4.1. Serum progesterone

The 1st use of the PRIVD demonstrated the highest serum mean progesterone concentrations in this trial, which decreased at the 2nd use. No significant difference was observed between the 2nd and 3rd uses of the device. These findings were similar to the results found by Abdallah and Rahim (7) in lactating cows. Similarly, Cerri et al. (18) also found that new PRIVDs elevated blood progesterone concentrations as compared to once used PRIVDs in nulliparous and multiparous cows. Overall, blood progesterone concentration decreased with repeated use in nulliparous and multiparous beef cows, which is in agreement with Muth-Spurlock et al. (10).

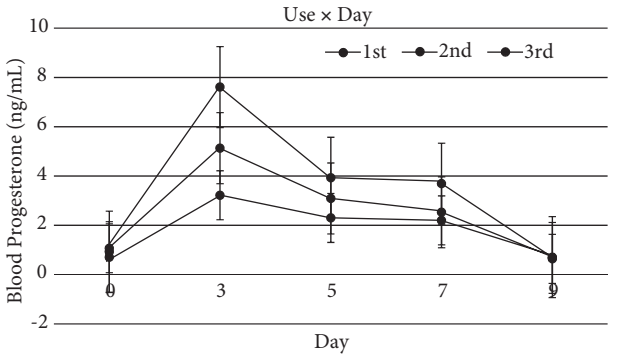

Figure 2. Mean serum progesterone concentrations (ng/mL) with 1st, 2nd, and 3rd uses of PRIVD at different day intervals ($P < 0.01$).

PRIVDs previously used three times resulted in lower serum progesterone concentrations than new PRIVDs in prepubertal heifers (8). The inhibitory mechanism of progesterone on LH surge release and estrus requires more than 1 ng/mL of progesterone circulation in the blood, which is considered to be the threshold level for PRIVDs to work (10,28). In the present study, even the 3rd use of PRIVD crossed this threshold level.

In this study, the serum progesterone concentration showed a steady increase, reaching the peak at day 3. According to these results, the repeatedly used PRIVD also elevated serum progesterone level above the critical threshold level (1 ng/mL) in a few days and could provide sufficient suppression of luteinizing hormone. This result was in agreement with Abdallah and Rahim (7) and Van Cleff et al. (29), who also measured peak serum progesterone level at days 3 and 2 of PRIVD insertion. After day 3, serum progesterone had a drop in its level at day 5 and became constant after that at day 7. The similar drop in progesterone concentration after a peak was also reported by Martinez et al. (30); however, that drop was seen at days 2 to 3 of PRIVD placement. Kesler (31) also demonstrated a fall in blood progesterone concentration after 2 days of insertion of both 1.9 and 1.38 g PRIVDs. This drop in progesterone might occur because of metabolism of progesterone or variation in its absorption from the vaginal membrane, as already discussed. Higher progesterone concentration during follicle growth is beneficial for the proper development of follicles (32). Denicol et al. (33) compared the fertility of cows in whom ovulatory follicles were grown under different progesterone concentrations. Cows in whom follicles grew under progesterone concentration of 3.7 ng/mL had greater fertility rates as compared to the ones under 1.4 ng/mL progesterone. The authors remarked that during synchronization protocols the progesterone concentration must be greater than 2 ng/mL to ensure proper follicle development. Bisinotto et al. (34) also reported that cows in whom follicles grew under greater progesterone concentrations had greater fertility rates as compared to the others with lower progesterone concentrations. However, the exact mechanism behind this scenario is still not clear (32). In the current study, even the 3rd use of the PRIVD in heifers produced serum progesterone greater than 2 ng/mL during follicle growth so this reused PRIVD could provide pregnancy rates similar to the first use.

Serum progesterone concentrations were minimum at day 0 (before insertion of the PRIVD) and day 9 (2 days after removal of the PRIVD). Progesterone level at day 9 was lower in the third use, which could beneficially affect the ovulatory follicle growth and estrogen concentration. Mauer et al. (35) recorded minimum progesterone concentration 24 h after PRIVD removal in cows. Higher blood progesterone near insemination decreased the frequency of GnRH pulses and GnRH receptors in the anterior pituitary, and increased levels of progesterone suppressed the release of LH and reduced the ovulatory response following administration of GnRH in both heifers and cows. Even increasing the dose of GnRH and the use of estradiol benzoate before GnRH did not increase ovulation rates in heifers with elevated blood progesterone. In that research, 94% of heifers in the low progesterone group ovulated, whereas 34% of heifers ovulated in high progesterone group (11). The blood progesterone measurement near the last GnRH of the Ovsynch protocol showed that greater blood progesterone concentrations

Table 2. Mean serum progesterone (ng/mL), serum estrogen (pg/mL) concentrations, and ovulatory follicle diameter (mm) of 1st, 2nd, and 3rd uses of PRIVDs at day 9.

Parameter	Use			P-value
	1st	2nd	3rd	
Serum progesterone (ng/mL)	0.71 ± 0.33	0.68 ± 0.16	0.64 ± 0.17	
Serum estrogen (pg/mL)	102.49 ± 8.64	115.54 ± 13.12	124.54 ± 11.47	0.28
Ovulatory follicle diameter (mm)	14.87 ± 0.18	15.50 ± 1.41	15.87 ± 0.13	0.70

near AI decrease fertility. The pregnancy rates decreased sharply as progesterone increased from 0.4 to 0.5 ng/mL near the time of the second GnRH of Ovsynch (32). In the present study, the serum progesterone level was lowest in the 3rd use (0.64 ng/mL) at 60 h after PRIVD removal and no measurements were performed after that time. The finding showed that the first 60 h after removal could be earlier for the reduction in progesterone level to induce ovulation in heifers because after complete luteolysis the blood progesterone concentration must be <0.5 ng/mL for successful insemination and pregnancy (31).

4.2. Serum estrogen

There was no significant difference observed for serum estrogen concentrations and ovulatory follicle diameter with the usage of the PRIVD at day 9. However, numerically, serum estrogen concentration and ovulatory follicle diameter increased with reutilization of the device. Estrogen has a positive effect on luteinizing hormone and was related with gonadotropin-dependent follicle development (36). Estrogen is inversely related to the progesterone concentration as cows in control, 2PRIVD (two PRID Delta®), and 0.5PRIVD (half PRID Delta®) groups with blood progesterone of 6.3, 4.6, and 1.3 ng/mL had 1.6, 3.5, and 12.7 pg/mL of 17 beta-estradiol in a study (37). The present findings in heifers are in agreement with the findings of Cerri et al. (18), in which the low plasma progesterone group had higher estrogen concentrations and ovulatory follicle diameters in cows. The diameter of the ovulatory follicles under once used PRIVD treatment also showed numerically greater diameters than the new PRIVD group but overall it was nonsignificant. Follicle growth is negatively related to the progesterone concentration as it blocks LH releases and development of dominant follicles. Cows with lower levels of circulating progesterone developed follicles with greater diameters than those with higher levels of circulating progesterone (38,39). The used PRIVD, which was previously used three times, led to the production of follicles with greater diameters than those produced by a new PRIVD in prepubertal heifers (8). Lower progesterone produced by twice used PRIVDs induced greater follicle sizes than the new device (39). Dias et al. (11) also found larger diameters of the largest ovarian follicle in low progesterone groups than in the high progesterone one at GnRH treatment in postpubertal heifers. The inverse relationship between progesterone concentration and follicle diameters under physiological conditions has been proposed by the following arguments: 1) the diameter of the dominant ovulatory follicle was greater for the first wave after ovulation in a three-wave estrous cycle because the 1st wave was under minimal luteal dominance compared to the second wave; 2) in the second wave, the highest progesterone concentration produced dominant follicles with smaller maximum diameters (40). Large follicles produced by used PRIVDs are an indicator of elevated fertility in heifers. Dadarwal et al. (12) gave subluteal progesterone concentrations to elevate LH pulsatility, which produced follicles with greater diameters. These follicles resulted in larger corpus luteum after ovulation (27).

4.3. Conclusions

Serum progesterone levels decreased with the usage of PRIVDs in heifers. The serum estrogen level and ovulatory follicle diameter remained unaffected with the 1st, 2nd, and 3rd uses of PRIVDs; however, serum estrogen concentration and ovulatory follicle diameter increased numerically with the usage of the device. PRIVDs can be reused for estrous synchronization in heifers or producers can prepare a separate intravaginal device with lower doses of progesterone for heifers to reduce the cost. However, extensive research is needed for evaluation of low dosage PRIVDs with respect to follicle and oocyte quality, ovulation, and optimal insemination time.

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