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Concentrations of Progesterone Alter the Odds of Retention of Transferred Bovine Embryos

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Abstract

Two studies were conducted to examine the role of progesterone on the odds of survival of embryos transferred into lactating and non-lactating recipient cows. In each study, recipients were synchronized for estrus following the Select Synch + CIDR® protocol. On d 7, after exhibiting estrus, embryos were inserted in all cows bearing a viable corpus luteum; embryos were placed in the uterine horn of the ovulating side. Randomly, animals were divided into two groups. Contrary with the control group, cows in the CIDR-group had a CIDR inserted on that same day the embryo was inserted and removed 14 days later. Blood samples for analysis of progesterone were taken at insertion (d 7) and continued at 7-day intervals for three more weeks. All animals were weighed and body condition scored at the beginning of the studies. Pregnancy diagnosis was performed around d 90. No significant differences were observed in body weights between treatments. Progesterone between treatments within days and between days within treatments are reported. Progesterone between pregnant and non-pregnant cattle was also reported between treatments and within treatments. Progesterone seems to increase the odds of retention of transferred bovine embryos during early gestation. Results also seem to point out that patterns of progesterone secretion during the first two weeks after the transfer have a decisive effect on the survival of bovine embryos. Nevertheless, authors of this document suggest that more research is needed to closely examine these findings.

Keywords: Cattle; Embryo; Reproductive Physiology; Survival

Introduction

The technology of embryo transfer has recently gained considerable popularity within cattle producers as a means to make genetic improvement. Consequently, each year thousands of bovine embryo transfers are performed

in the US to improve reproduction efficiency and genetics. Data reported in the fall of 2015 by the American Society of Embryo Transfer indicates that more than half a million embryos were collected and about 50% of them were transferred in 2014. Despite the current progress, embryonic retention still remains as one of the main factors limiting application of embryo transfer.

Studies have revealed embryonic losses of up to 40% in embryo transfer programs during the first 18 days of gestation in sheep and cattle [1]. In retrospect, authors of this study believe that improving retention rate of the transferred embryos would make cattle farmers more receptive to the use of the technique. In support of that, Ribeiro et al. [2] concluded that as embryo technologies become more efficient and cheaper, then their use as a tool to improve reproductive efficiency in dairy herds would become more attractive and economically justifiable.

There is no doubt that progesterone plays an essential role during pregnancy and, therefore, is widely viewed as critical for embryo survival and for establishment of pregnancy [3-6]. Hence, at present, controlled internal drug release (CIDR; Pharmacia Animal Health, Kalamazoo, MI) devices are commonly used in research studies and in routine reproductive practices to supplement exogenous progesterone; results from these studies have not always concurred [7-14].

The process of embryonic retention is without any doubt highly regulated by progesterone [15,16]. The literature also reveals other management and environmental factors associated with retention of the embryo that may be partially responsible for the disagreement in the outcomes of those studies. Thus, a study conducted by Jousan et al. [17] concluded that heifers are less likely to suffer early fetal losses when compared to lactating cows. Additionally Santos et al. [18] observed that fertilization rates are higher for nulliparous dairy and beef heifers and non-lactating beef cows than for lactating beef and dairy cows. On the other hand, timing of onset of the progesterone influence is important for successful pregnancy outcome; particularly in first and second lactation cows [19]. Furthermore, other researchers [20] have clearly demonstrated the negative impact environmental conditions have on pregnancy rates in cattle. In line with this, Putney et al. [21] and Geisert et al. [22] have also observed detrimental effects of environmental factors on pregnancy in cattle. Therefore, these studies were designed to examine the role of progesterone on the odds of embryo survival on lactating and non-lactating recipient cows.

Materials and Methods

Studies and Animals

Two studies (June 2003, April 2004) were conducted to examine the effects of supplementation of progesterone on the survival of embryos transferred to lactating and non-lactating Angus - crossed recipients. The research site for these studies was the Brown Loam Experiment Station of Mississippi State University in Raymond, Mississippi. Animals participating in these studies were grazing on annual ryegrass and on Bermuda and Bahia grass previous and during completion of the 2003 and 2004 studies, respectively.

Experimental Design and Hormonal Protocol

In both studies, recipients were synchronized for estrus following the Select Synch + CIDR® protocol. Animals were checked for estrus (d 0) behavior daily and determined by visual observation at 6:00 AM, 2:00 PM, and 6:00 PM. On d 7, after exhibiting estrus, embryos were inserted in all cows bearing a viable corpus luteum; embryos were placed in the uterine horn of the ovulating side. Randomly, animals were divided into two groups. Contrary with the control group, cows in the CIDR-group had a CIDR inserted on the same day the embryo was inserted and removed 14 days later. In both studies (June 2003 and April 2004), collection of blood samples started at the insertion of the CIDR's and continued at 7-day intervals for three more weeks. Pregnancy diagnosis by rectal palpation was performed by 90 days after insertion of the embryos. Body weights of animals were recorded at the beginning of both studies.

Collection and Laboratory Analysis of Blood Samples

Plasma samples were analyzed for concentration of progesterone via radioimmunoassay to evaluate luteal cell function. Progesterone assays were performed using a commercial enzyme immunoassay kit provided by Oxford Biomedical Research (Oxford, Michigan).This is an enzyme-linked immune assay that operates on the basis of competition of solid-phase RIA system relying upon competitive binding between a radioactive and non-radioactive antigen for a fixed number of antibody sites coated to the assay tubes. The specificity of this assay as reported by the manufacturer was 100% cross-reactivity

with progesterone, 2.5% with deoxycorticosterone, 2.0% with corticosterone, 2.0% with pregnenolone, 1.0% with androstenedione and less than 1.0% with other steroid hormones tested.

	Treatment	Breed	Lactating	Non-lactating	Survival %
***Study 1**	CIDR	Angus	14		64.3%; 9/14
(June 2003)	CONTROL	Angus	14		28.6%; 4/14
***Study 2**	CIDR	Angus		13	76.9%; 10/13
(April 2004)	CONTROL	Angus		13	61.5%; 8/13

*Brown Loam Experiment Station, Raymond, Mississippi.

Table 2: Percent Survival Rate of Transferred Embryos in Both Studies.

Statistical Analysis

Body weights of experimental animals were analyzed using the GLM procedure (SAS, Inst. Inc., Cary, NC). Data on conception rates (%) was also analyzed using the GLM procedure with a significance level of 5%; treatment means were compared using the Duncan multiple range test. Concentrations of progesterone in blood were analyzed using the MIXED procedure SAS (SAS Inst., Inc., 9.3) with repeated measures. The repeated measures model for the response plasma hormone concentrations on each day of the studies contained the fixed effect of the treatments and the repeated factors of day and their corresponding interactions. Least squares means by the Bonferroni adjustment were analyzed and separated when a protected F test of $P \leq 0.05$ was detected. All comparisons in the statistical analysis were established at a 5% level of significance. Logistic regression was used to determine the association of embryo retention with concentrations of progesterone during the different days of the studies. Throughout results, LSMeans ± standard errors are presented.

Results

No significant differences were observed between treatments in body weights and body condition scores of recipients participating in studies 2003 and 2004 ($P \leq 0.05$; Table 1). Additionally, postpartum days (mean ± std. error) did not differ between the CIDR (104.57±2.2) and the control (104.71 ± 2.3; $P \geq 0.05$) groups in the study conducted in June of 2003. The percent of embryo survival in both treatments and for the two studies are shown in Table 2.

Treatment	2003 Study	2004 Study
Control	486.5 ± 11[a]	567.66 ± 18[a]
CIDR	513.0 ± 12 [a]	530.24 ± 14[a]

[a] Means within the same column and under the same year lacking a common superscript differ ($P \leq .05$).

Table 1: Means ± Standard Errors for Body weights (Kg) at Transfer of Embryos.

In the study 2003, concentrations of progesterone (ng/ml; mean ± std. error; Table 3) in recipients allocated in the control group did not differ between d 7 and 14 and neither between d 14 and 21 ($P \geq 0.05$). However, concentration of progesterone significantly declined from d 14 to 28 in this experimental group. This was not the case between days in the cows allotted in the CIDR group ($P \geq 0.05$). Furthermore, no significant differences were observed between treatments in progesterone at any day of the study.

Similarly, concentrations of progesterone did not differ ($P \geq 0.05$) between pregnant and non- pregnant cows at any day of this study as well (Table 4). Also, progesterone did not significantly change within each of these two groups at any day of the study. Nevertheless, the study revealed that the odds of recipients being pregnant by bearing a CIDR were 1.14 greater compared to control cows (OR = 3.139; P= 0.0008); additionally, odds of being pregnant increase by a factor of 1.008 for every unit of progesterone increased (OR = 1.008) and 3.139 by cows bearing a CIDR (OR = 3.139).

	TREATMENT	Day 7*	DAY 14	DAY 21	DAY 28
Study 2003	Control	4.71 ± 1.91[ab]	8.16 ± 1.91[a]	5.00 ± 1.91[ab]	2.72 ± 1.91[b]
	CIDR	6.44 ± 2.16[a]	5.06 ± 2.16[a]	7.77± 2.16[a]	6.97 ± 2.16[ab]
Study 2004	Control	7.24 ± 0.98[a]	7.19 ± 0.92 [a]	6.15 ± 1.4[a]	8.47 ± 1.00[a]
	CIDR	5.99 ± 1.69[a]	8.07 ± 1.37[a]	8.14 ± 1.25[a]	6.16 ± 1.27[a]

*Day of the transfer (d 7 of the estrous cycle).
[ab]Means within the same row and column and in the same study lacking a common superscript differ ($P \leq .05$).

Table 3: Concentrations of progesterone (means ± standard errors; ng/ml) in treatment groups at different days after the transfer in both studies.

	Pregnant/Non-Pregnant	DAY 7*	DAY 14	DAY 21	DAY 28
Study 2003	Pregnant	5.83 ± 1.26 [a]	7.33 ± 1.58 [a]	6.23 ± 1.30 [a]	5.85 ± 1.29 [a]
	Non-Pregnant	5.31 ± 1.26[a]	6.04 ± 1.47 [a]	5.85 ± 1.30 [a]	3.24 ± 1.29 [a]
Study 2004	Pregnant	6.64 ± 1.20 [a]	7.95 ± 1.07 [a]	8.10 ± 1.07 [a]	7.93 ± 1.02 [a]
	Non-Pregnant	6.57 ± 1.72 [a]	6.90 ± 1.06 [a]	4.99 ± 1.73 [a]	5.64 ± 1.45 [a]

*Day of the transfer (d 7 of the estrous cycle).
[ab]Means within the same row and column and in the same study lacking a common superscript differ ($P \leq .05$)

Table 4: Concentrations of progesterone (means ± standard errors; ng/ml) between pregnant and non-pregnant cows at different days after the transfer in both studies.

In the 2004 study, the difference in percent retention rates between the two experimental groups (CIDR: 76.90 %; Control: 61.50 %) at 90 days after the transfer was not as wide as it was in the previous study (CIDR: 64.3%; Control: 28.6%). Systemic concentrations of progesterone (ng/ml; mean ± std. error) did not differ at any day of the study between the control and the CIDR group ($P \leq 0.05$; Table 3). Similarly, no differences in concentrations of progesterone were observed between pregnant and non-pregnant cows at any day of the study (Table 4). Moreover, there was no difference in embryo retention between cows bearing a CIDR and the control recipients at 90 days after the transfer (P=0.0803). This was not due to difference in concentration of progesterone (P=0.0838), but to increasing progesterone in one unit or by bearing a CIDR, the odds of being pregnant can be increased by a factor of 1.101 and 2.177, respectively.

In an attempt to strengthen the results observed in these two studies, we used logistic regression on the data obtained from a control and CIDR groups in two other studies previously published by our laboratory [23,24]. Results in the study conducted in 2008 revealed that retention of transferred embryos in cattle is highly associated with the concentration of progesterone ($P = 0.0028$); thus, odds of being pregnant increase by 1.118 for an increase of progesterone in one unit (OR = 1.118). On the other hand, the study conducted in 2011 did not show a difference in embryo retention (P=0.3356) between cows bearing a CIDR and the control recipients; however, odds of cows getting pregnant increased by 1.533 by having a CIDR inserted (OR = 1.533). Additionally, there was a trend toward better embryo retention rates by increasing concentration of progesterone in the blood ($P \leq 0.10$). These findings from these two previous studies were not reported when published; however, differences in concentrations of progesterone between and within treatments are detailed in those two publications.

Discussion

The 2003 study for this project was conducted at the Brown Loam Experiment Station of Mississippi State University in Raymond, Mississippi in the summer months. Retention rates observed in the control group (28.6%; Table 2) of this study are in agreement with data previously reported from studies conducted under similar conditions [25]. High temperatures and the lactating stage of these animals were partly responsible for the low retention rate in this group [1,26]. Even though percent retention rates for recipient cows bearing a CIDR were higher (64.3%) than those observed in the control group, this difference was not significant due to the small number of animals in each group.

Despite the fact animals in the 2003 study did not show any significant differences in concentration of

progesterone between treatments and neither between continuous blood samples collected within treatments, concentrations of progesterone were steadier in the CIDR group through the days of the study. This may have played a role in the retention rate observed in this group [27]. Additionally, the likelihood of recipients being pregnant was higher (OR=3.139; P=0.0008) by bearing a CIDR and also by a factor of 1.008 for every unit of progesterone increased (OR=1.008).

The study conducted in 2004 took place at the same location as in the study implemented in 2003; however, this study was carried out during the spring of 2004 and with non-lactating cows as recipients (Table 2). Disparately, the gap in retention rates between the two experimental groups was not as wide as that observed in the previous study. Furthermore, concentrations of progesterone in both groups were very steady throughout the study; this may have contributed to the slight difference in retention rates observed in this study.

Authors of these studies suggest that the non-lactating stage of the recipients in the 2004 study and the environmental and grazing conditions may have played a crucial role in establishing the differences in retentions rates when compared to the difference in retention rates observed in the study conducted in 2003. Likewise, patterns of concentrations of progesterone were very steady through days of the study in both treatment cows. In addition, this study also demonstrated that the likelihood of a cow's pregnancy is increased with progesterone and by bearing a CIDR.

Conclusion

Findings from these studies clearly demonstrate that progesterone increases the odds of retention of transferred bovine embryos during early gestation. These results also seem to point out that patterns of progesterone secretion during the first two weeks after the transfer have a decisive effect on the survival of bovine embryos. Presumably, steady concentrations of progesterone appeared to be favorable to retention of the transferred embryo. Furthermore, lactation apparently played a role in these studies in regulating patterns of secretion of progesterone in the recipients. Nevertheless, authors of this document suggest that more research is needed to closely examine these findings.

Conflict of Interest Statement

None of the authors of this article has a financial or personal relationship with other people or organizations that could inappropriately influence the content of the article.

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