



# Maintenance of Pregnancy in Beef Cattle after a Luteolytic Dose of Prostaglandin F<sub>2α</sub>

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## Abstract

The increased use of assisted reproductive technologies (ARTs), increase the risks of erroneous prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) administration. The objective of this study was to determine if pregnancies could be maintained if P<sub>4</sub> was administered after PGF<sub>2α</sub> administration. A total of seven pregnant heifers between 30-40 days of gestation and 19 pregnant cows between 30 to 40 (n=12) or 80 to 90 (n=7) days of gestation were used. All females were administered a maintenance dose of P<sub>4</sub> or progesterin at either 2, 6, 8, 10, 12 or 18 hours post-PGF<sub>2α</sub> for 7 days. A total of 18 of 25 (72%) pregnancies were maintained for a minimum of 7 days. The success rate for cows and heifers receiving P<sub>4</sub> or progesterin 2, 6, 10, 12 or 18 hours after PGF<sub>2α</sub> was 4/6 (75%), 6/6 (100%), 2/3 (67%), 2/4 (50%), 1/2 (50%) and 3/4 (75%), respectively. Maintenance P<sub>4</sub> or progesterin was continued on selected females (12 of the 18) and they were examined via ultrasonography 2 to 3 times weekly until a follicle ≥10 mm developed on the ovary ipsilateral to the gravid uterine horn, at which time hCG (2,500 IU) was administered. Luteal tissue was successfully induced in 10 of the 12 (83%) and 8 of these calved (80%). These results indicate that it is possible to maintain a bovine pregnancy by administering maintenance dose of P<sub>4</sub> from 2 to 18 hours post-PGF<sub>2α</sub>.

**Keywords:** Cattle, abortion, induced luteal tissue, pregnancy, progesterone

## Introduction

Administration of prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) can induce luteolysis in cycling cattle and abortion at various times during pregnancy [1,2,3] and the most effective time for PGF<sub>2α</sub> to induce abortion is from day 10 to 150 of gestation [4]. Although, pregnancy may be maintained on progesterone (P<sub>4</sub>) following PGF<sub>2α</sub> induced luteolysis, there have been no reports of reviving or rescuing the original corpus luteum (CL) of pregnancy.

In early studies exploring the effect of CL ablation on bovine pregnancy, maintenance P<sub>4</sub> was administered prior to CL ablation [5,6,7] or simultaneously with CL ablation [8,9,10,11,12]. In the previous cases, pregnancy was maintained until near the end of gestation; however, it is unknown if pregnancy can be maintained when maintenance P<sub>4</sub> is administered after PGF<sub>2α</sub> administration. As this will be the often be the situation when PGF<sub>2α</sub> is erroneously administered to pregnant cows as a result of on farm estrous cycle synchronization for use in artificial insemination (AI) or embryo transfer (ET).

In addition to rescuing and maintaining a pregnancy in PGF<sub>2α</sub>-treated gestating cows an additional obstacle would involve maintaining the pregnancy to term and it resulting in normal parturition. Cows that undergo parturition without a CL have a higher incidence of premature calving, dystocia, increased incidence of retained placental tissues, increased cow and calf mortality, and insufficient milk production post-

calving [8,10,11,13,14]. Additionally, there are reported cases of a lack of maternal instinct and increased incidence of calf abandonment [11]. An increase in dystocia occurring in the absence of a CL has also been described in swine [15,16].

There have been reports of induction of luteal tissue during early pregnancy in beef cattle, however the induced luteal tissue needed to be ipsilateral to the gravid uterine horn or it was only transient [12,17,18]. Later, it was reported that induced luteal tissue was capable of continuing a pregnancy to term regardless to which ovary produced the luteal tissue [19].

These reports provide insight into a possible mechanism to prevent problems that commonly occur in CL ablated pregnant cows. Therefore, the objectives of these studies were to: (1) determine if pregnancies could be maintained in the absence of a CL with P<sub>4</sub> or altrenogest administration post-PGF<sub>2α</sub> treatment and (2) determine if induced luteal tissue could successfully support the maintained pregnancy to term and result in normal parturition, producing a viable offspring.

## Materials and methods

### Animals

In this experiment, seven pregnant heifers from 30 to 40 days of gestation and 20 pregnant cows between 30 to 40 days (n=13) or 80 to 90 days (n=7) of gestation were randomly assigned to a treatment time. All females (cross-bred Angus and Simmental

were pastured at the Center for Reproductive Biology at Louisiana State University, St. Gabriel, LA. All animals in these experiments were treated in accordance with guidelines set forth by the Institute of Animal Care and Use Committee of the Louisiana State University Agricultural Center.

### Maintenance of pregnancy

Females were determined pregnant via transrectal ultrasonography (Aloka 500-V, Corometrics, Wallingford, CT) using a 5 MHz rectal probe. All pregnancies were defined by the presence of uterine fluid and a fetus with a viable heartbeat. All females received a luteolytic dose of PGF<sub>2α</sub> (i.m., 25 mg Lutalyse, Pfizer Animal Health, New York, NY) at time designated 0 hour. Following PGF<sub>2α</sub> treatment, females received either 100 mg of P<sub>4</sub> (s.c., Progesterone, Sigma Chemical Co., St. Louis, MO) dissolved in 3 ml of 100% ethanol (Aaper Alcohol, Shelbyville, KY) at either 2 hours (n=3), 6 hours (n=3), 10 hours (n=3), 14 hours (n=2) or 18 hours (n=2). The females continued to receive 100 mg of P<sub>4</sub> daily for 7 days. The other females received 100 mg of altrenogest (orally, Regumate, Intervet, Millsboro, DE) at either 2 hours (n=3), 6 hours (n=4) or 12 hours (n=4) 18 hours (n=3) post-PGF<sub>2α</sub> and at 24 hours post-PGF<sub>2α</sub> all of these females received two 15 mg norgestomet implants (s.c.) [11] that were exchanged at 14 day intervals.

### Induction of luteal tissue

From females that successfully maintained pregnancy following PGF<sub>2α</sub>-treatment; three cows from 30 to 40 days of gestation group, two cows from 80 to 90 days of gestation group and seven heifers from the 30 to 40 days of gestation group were selected for testing of the second experimental objective. These females were ultrasound three times per week to determine the development of a follicle ≥10 mm on the ovary ipsilateral to the gravid uterine horn. Once a follicle of this size and position occurred, the female received 2,500 IU of hCG (i.m., Chorulon, Intervet Inc., Millsboro, DE) and was continually monitored for luteal development via ultrasonography and plasma P<sub>4</sub> concentration. Once induced luteal tissue was detected via ultrasonography in cows receiving maintenance P<sub>4</sub> the dose of P<sub>4</sub> was decreased to 50 mg per day for 7 days then to 25 mg per day for 3 days and finally P<sub>4</sub> treatment was terminated. At this time blood samples were collected to verify induction of luteal tissue. Both norgestomet implants were removed from females once induced luteal tissue persisted for 10 days.

### Sample collection and progesterone assay

Blood samples were collected at 0, 2, 6, 12, 24 and 30 hours post-PGF<sub>2α</sub> for cows and 0, 6, 12, 18 and 30 hours for heifers following PGF<sub>2α</sub> and again following hCG administration. The rationale for the change from P<sub>4</sub> to altrenogest to maintain pregnancy the first 24 hour time period was to allow for more accurate plasma P<sub>4</sub> assays as altrenogest does not and did not cross-react in radioimmunoassay (RIA), nor did the norgestomet.

Blood samples were collected via jugular venipuncture using sodium heparin tubes, and plasma samples were stored at -4°C until the assay was performed. Plasma P<sub>4</sub> concentrations were determined using a commercial P<sub>4</sub> assay kit (Diagnostics Systems Laboratory, Webster, TX) and the intra- and interassay CV and assay sensitivity were 5%, 10% and 0.05 ng/ml for progesterone.

## Results

### P<sub>4</sub> Concentrations Following PGF<sub>2α</sub>

Among the 20 pregnant females treated with PGF<sub>2α</sub>, ultrasonography showed that two cows did not experience luteolysis and plasma P<sub>4</sub> levels in both of these cows were > 2 ng/ml plasma P<sub>4</sub> by 30 hours post-PGF<sub>2α</sub> (one from 30 to 40 days of gestation 18 hour treatment group and one from 80 to 90 days of gestation 6 hour treatment group). Failing to undergo luteolysis, both were removed from the remainder of this experiment. The mean±SE plasma P<sub>4</sub> concentrations for cows (80 to 90 days gestation, n=7) receiving altrenogest and subsequently norgestomet at 0, 2, 6, 12, 24 and 30 hours were: 8.5±1.6 ng/ml, 9.5±2.1 ng/ml, 4.6±1.0 ng/ml, 2.7±0.3 ng/ml, 2.1±0.6 ng/ml and 0.7±0.2 ng/ml respectively. The mean±SE plasma P<sub>4</sub> concentrations for heifers (30 to 40 days gestation, n=7) receiving altrenogest and subsequently norgestomet at 0, 6, 12, 18, 30 and 72 hours were: 12.4±1.5 ng/ml, 4.2±0.5 ng/ml, 2.6±0.5 ng/ml, 1.3±0.1 ng/ml, 1.3±0.1 ng/ml and 0.7±0.2 ng/ml respectively. The mean P<sub>4</sub> concentrations did not decline below 2 ng/ml until 12 to 18 hours among heifers at 30 to 40 days of gestation and until 24 to 30 hours among cows at 80 to 90 days of gestation.

### Maintenance of pregnancy by administering P<sub>4</sub> hours after PGF<sub>2α</sub>

Excluding the two cows not responding to PGF<sub>2α</sub>, pregnancy was maintained for 7 days in 9/11 (82%) of cows at 30 to 40 days of gestation and 3/6 (50%) of cows at 80 to 90 days of gestation and 7/7 (100%) among the 30 to 40 day heifer group (Table 1). Among cows treated with P<sub>4</sub> or altrenogest at 2, 6, 10, 12 or 18 hours post-PGF<sub>2α</sub>, 4/6 (67%), 4/4 (100%), 2/3 (67%), 1/4 (25%) and 0/1 (0%), respectively, maintained their pregnancies for 7 days. In the heifer group, 2/2 (100%), 2/2 (100%), and 3/3 (100%) remained pregnant for 7 days, respectively, with altrenogest treatment 6, 12 or 18 hours after PGF<sub>2α</sub>.

### Induction of luteal tissue and continuance of pregnancy

Induction of luteal tissue was successful in 2 of 3 (67%) cows from the 30 to 40 days group; however, only one of the two cows continued gestation to parturition with induced luteal tissue. The cow that successfully maintained pregnancy to parturition on induced luteal tissue received hCG at day 10 and 15 post-PGF<sub>2α</sub>. The other cow received one administration at day 15 and aborted 37 days following hCG, which was 27 days following removal from P<sub>4</sub>. The third cow aborted 3 days

**Table 1. The number of cows in which pregnancy was rescued and the number of cows in which induced luteal tissue was successful in resulting in calving.**

Days of gestation at time of PGF <sub>2α</sub> treatment	No. of maintained pregnancies (%) <sup>1,2</sup>	No. of cows with induced luteal tissue (%) <sup>3,4</sup>	No. of cows calving (%) <sup>5</sup>
30 to 40 days (mature cows)	8/12 (67%)	2/3 (67%)	1/2 (50%)
Time from PGF <sub>2α</sub> to P <sub>4</sub> (2 hours)	2/3	1/2	1/1
Time from PGF <sub>2α</sub> to P <sub>4</sub> (6 hours)	3/3	1/1	0/1
Time from PGF <sub>2α</sub> to P <sub>4</sub> (10 hours)	2/3	--	--
Time from PGF <sub>2α</sub> to P <sub>4</sub> (12 hours)	1/2	--	--
Time from PGF <sub>2α</sub> to P <sub>4</sub> (18 hours)	0/1	--	--
<b>80 to 90 days (mature cows)</b>	<b>3/6 (50%)</b>	<b>2/2 (100%)</b>	<b>2/2 (100%)</b>
Time from PGF <sub>2α</sub> to P <sub>4</sub> (2 hours)	2/3	2/2	2/2
Time from PGF <sub>2α</sub> to P <sub>4</sub> (6 hours)	1/2	--	--
Time from PGF <sub>2α</sub> to P <sub>4</sub> (12 hours)	0/2	--	--
<b>30 to 40 days (heifers)</b>	<b>7/7 (100%)</b>	<b>6/7 (86%)</b>	<b>5/6 (83%)</b>
Time from PGF <sub>2α</sub> to P <sub>4</sub> (2 hours)	2/2	2/2	2/2
Time from PGF <sub>2α</sub> to P <sub>4</sub> (6 hours)	2/2	1/2	1/1
Time from PGF <sub>2α</sub> to P <sub>4</sub> (12 hours)	3/3	3/3	2/3
Total	18/25 (72%)	10/12 (83%)	8/10 (80%)

1 Only females that responded to PGF<sub>2α</sub> (<2 ng/ml P<sub>4</sub> within 30 hours post-PGF<sub>2α</sub>) were included in this column.

2 Pregnancies were maintained for 7 days in the absence of a corpus luteum (CL).

3 Not all females in which pregnancy was maintained for 7 days were used for induction of luteal tissue.

4 Females included in this column that did not have induced luteal tissue aborted during the process of luteal tissue induction.

5 Females in this group not calving aborted while pregnancy was maintained by induced luteal tissue.

post-hCG at day 10 post-PGF<sub>2α</sub>.

Two of the three cows (from the 80 to 90 days group) maintaining pregnancy were attempted to developed induced luteal tissue after receiving hCG 7 days post-PGF<sub>2α</sub>. One receiving a second hCG administration 7 days later. In these two cows, plasma P<sub>4</sub> levels were 0.24 and 1.19 ng/ml at 24 hours post-PGF<sub>2α</sub> and were 2.51 ng/ml and 7.32 ng/ml 7 days post-hCG.

In the heifer 30 to 40 days group, induction of luteal tissue was successful in 6/7 (86%) and 5/6 (83%) of those who calved. The mean±SE hCG administrations to induce luteal tissue was 2.0±0.4 per heifer (range of 1 to 4). The mean±SE time to induce luteal tissue was 38±5.5 days (post-PGF<sub>2α</sub>) (range 7 to 49 days). The mean±SE P<sub>4</sub> concentration (72 hours post-PGF<sub>2α</sub>) for heifers maintaining pregnancy on induced luteal tissue was 0.75±0.29 ng/ml. The mean±SE P<sub>4</sub> concentration at 49 days post-PGF<sub>2α</sub> with induced luteal tissue was 6.39±1.60 ng/ml. Of the five heifers maintaining pregnancy on induced luteal tissue, gestation was ~285 days, and 4/5 (80%) were normal with the exception of one heifer that died of dystocia. The number of successful luteal tissue inductions and calving is summarized in (Table 1).

## Discussion

In this experiment, a total of 24 of 26 (92%) cows and heifers

(between 30 and 90 days of gestation) responded to the PGF<sub>2α</sub> administration with a decline in plasma P<sub>4</sub> concentrations below 2 ng/ml occurring by 30 hours of PGF<sub>2α</sub> which is consistent with other reports [3, 4, 20]. The decline in plasma P<sub>4</sub> concentrations below 2 ng/ml occurred between 12 to 24 hours post-PGF<sub>2α</sub>. The decline pattern may contribute to the 86% success in maintaining a pregnancy if P<sub>4</sub> is administered prior to 12 hours compared to a 60% success rate when P<sub>4</sub> is administered 12 hours or later post-PGF<sub>2α</sub>. This outcome indicates that the sooner P<sub>4</sub> supplementation occurs following PGF<sub>2α</sub> the more likely the pregnancy can be maintained. Of the six pregnancies successfully maintained with P<sub>4</sub> supplemented at 12 hours or later, five were among heifers from 30 to 40 days of gestation. This may be the result of heifers experiencing significantly higher P<sub>4</sub> concentrations following P<sub>4</sub> supplementation compared with cows [21].

The second objective of this experiment was to prevent dystocia and loss of calves at parturition. This problem has been well documented in cattle (beef and dairy) calving without a CL [10,11,13,14], and although it has been reported that induced luteal tissue was capable of supporting pregnancy in luteotomized cattle in the absence of maintenance progestin [12,17,18] the success rate was low when the induced luteal tissue was located on the contralateral ovary to the gravid uterine horn [12]. Only one study reports induced luteal tissue

continuing a bovine pregnancy to term [19].

The two pregnancies lost during the process of induction of luteal tissue may have been the result of loss due to rectal manipulation during ultrasonography two to three times per week [22,23]. There seemed to be no effect of follicle size and subsequent luteal tissue formation as the majority of the follicles were ~11 mm at the time of hCG administration (range 10 mm–15 mm) and several calves were born from cows receiving only one administration of hCG. All pregnancies maintained to term were the result of induced luteal tissue. This was evident as all females were also removed from maintenance P<sub>4</sub> or progestin prior to 120 days of gestation which is the minimum stage of gestation for a cow to continue pregnancy in the absence of luteal tissue [10].

The length of gestation in cows with induced luteal tissue ranges from 271 and 287 days with the majority calving ~285. Among the eight females calving only one developed dystocia with the other seven demonstrating normal parturition, lactation and maternal behavior. Calves were normal with one calf having a low birth weight.

In conclusion, these data illustrate that valuable pregnancies can be maintained following an accidental administration of PGF<sub>2α</sub> without the need for extended exogenous P<sub>4</sub> or progestin supplementation. In addition, pregnancies maintained on induced luteal tissue can result in normal parturition, maternal behavior and lactation.

### Competing interests

The authors declare that they have no competing interests.

### Authors' contributions

Authors' contributions	CEF	DJK	RAG
Research concept and design	✓	✓	✓
Collection and/or assembly of data	✓	--	--
Data analysis and interpretation	✓	--	--
Writing the article	✓	--	--
Critical revision of the article	✓	✓	--
Final approval of article	✓	✓	✓
Statistical analysis	✓	--	--

### Acknowledgement

The authors wish to acknowledge Gary Sides of Intervet, Inc. (Millsboro, DE) for supplying Regumate used in this research. This research was funded, in part, by Federal Regional Project W-171.

### Publication history

Editor: Scott Whisnant, North Carolina State University, USA.  
 EIC: Olivier A. E. Sparagano, Northumbria University, UK.  
 Received: 12-Sep-2013 Revised: 12-Nov-2013  
 Accepted: 17-Dec-2013 Published: 09-Jan-2014

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### Citation:

Edward Ferguson C, Kesler DJ and Godke RA.  
**Maintenance of Pregnancy in Beef Cattle after a Luteolytic Dose of ProstaglandinF2α.** *Vet Med Anim Sci.* 2014; **2**:1.  
<http://dx.doi.org/10.7243/2054-3425-2-1>