Uterine Involution and Fertility of Holstein Cows Subsequent to Early Postpartum PGF$_{2\alpha}$ Treatment for Acute Puerperal Metritis*

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ABSTRACT

The objective was to evaluate the effect of 2 doses of PGF$_{2\alpha}$, injected early postpartum on uterine involution, serum concentration of acute phase proteins at 12 d postpartum, and fertility in Holstein cows with acute puerperal metritis. Only cows diagnosed with retained fetal membranes and metritis and treated with ceftiofur hydrochloride for 5 d were used in the study. Two hundred cows were assigned randomly to be treated (n = 100) or to serve as controls (n = 100). Treatment consisted of 2 i.m. injections of PGF$_{2\alpha}$ 8 h apart on d 8 postpartum. A subsample of 90 cows was selected randomly (45 treated cows; 45 controls) to evaluate uterine diameter using ultrasonography, uterine score, and serum concentrations of acute phase proteins at 12 d postpartum. The outcome variable for all cows was conception rate at first service. Postpartum, primiparous, treated cows had smaller uterine diameters and lower uterine scores than controls. Cows with a uterine diameter <5.1 cm at 12 d postpartum were 5.5 times more likely to conceive at first service than cows with larger uterine horn diameter. Treatment significantly reduced the concentrations of serum $\alpha$1-acid glycoprotein. Within primiparous cows, treatment also increased conception at first service by 17%. It was concluded that 2 doses of PGF$_{2\alpha}$ 8 h apart at d 8 postpartum in primiparous cows with acute puerperal metritis decreased the diameter of uterine horns and serum concentration of $\alpha$1-acid glycoprotein at 12 d postpartum and increased the conception rate at first service.

(Key words: acute puerperal metritis, PGF$_{2\alpha}$, fertility, uterine involution)

INTRODUCTION

Acute puerperal metritis (APM), defined as an enlarged and flaccid uterus with a foul-smelling discharge without systemic compromise, is one of the most common disorders affecting dairy cattle (Lewis, 1997). Incidence of APM varies from 2.2 to 37.3% (Kelton et al., 1998). Economic losses include decreased milk yield, reduced fertility, increased culling, and treatment costs (Kelton et al., 1998). Some studies have estimated a cost of $236 per case (Barlett et al., 1986). When prevention of APM fails, treatment that will improve reproductive performance is needed to mitigate the economic loss associated with the condition.

Use of PGF$_{2\alpha}$ is common during the early postpartum period to improve uterine involution (Lindell and Kindhal, 1983; Nakao et al., 1997) and fertility in dairy cattle (Archbald et al., 1993, 1994). Results, however, have been controversial because concentrations of PGF$_{2\alpha}$ are elevated in the first 7 d postpartum. These concentrations are even greater in cows experiencing retained fetal membranes (RFM), metritis, or both than in normal cows (Lindell et al., 1982; Risco et al., 1994). In contrast, by d 8 to 10 postpartum, concentrations of PGF$_{2\alpha}$ are basal for both normal cows and those that have experienced RFM, metritis, or both (Kindahl et al., 1992; Risco et al., 1994; Kindahl et al., 1999).

Dose, frequency, and postpartum timing of treatment are factors to be considered when evaluating and comparing clinical trials (Archbald et al., 1994). Our clinical experience indicated that PGF$_{2\alpha}$, at d 8 postpartum might mitigate the effects of APM. Indeed, PGF$_{2\alpha}$, given twice daily for 10 d starting on d 3 postpartum decreased the time of uterine involution by about 1 wk (Lindell and Kindhal, 1983). This result might be

Abbreviation key: APM = acute puerperal metritis, CRFS = conception rate at first service, OR = odds ratio, RFM = retained fetal membranes.
explained because early postpartum application of PGF$_{2\alpha}$ increased myoelectrical activity and contraction of the uterus (Patil et al., 1980; Gajewski et al., 1999).

The hypothesis tested in this study was that cows with APM treated with 2 doses of PGF$_{2\alpha}$, at 8 d postpartum would have a smaller uterine size, which may reflect an improvement of uterine involution. Accordingly, the objectives of this study were to evaluate the effect of 2 doses of PGF$_{2\alpha}$, injected 8 h apart at d 8 postpartum on uterine diameters and uterine scores, serum concentration of acute phase proteins at 12 d postpartum, and fertility in Holstein cows with RFM that subsequently produced APM and were treated with ceftiofur hydrochloride.

**MATERIALS AND METHODS**

**Dairy Farm and Management**

This study was conducted in a Holstein dairy farm located in north central Florida (Bell, FL). The herd consisted of 3000 milking cows milked 3 times daily with a 305-d mature equivalent milk yield of 10,725 kg. Transition dairy cows (between 3 to 7 d postpartum at a dose of 2.2 mg/kg BW for 5 d). Therefore, at assignment to the study, cows had APM and were under the influence of antimicrobial treatment for 1 to 5 d. Cows developing toxic puerperal metritis were excluded from the study.

Treated and control cows were exposed to the same environment and management conditions. After the voluntary waiting period (70 d), all cows were subjected to a synchronization of ovulation and timed insemination protocol (Ovsynch) for the first service. This synchronization program consisted of one i.m. dose of GnRH (100 μg Cystorelin; Merial, Iselin, NJ) administered on d 0, one 25-mg dose of PGF$_{2\alpha}$ (Lutalyse; Pharmacia Animal Health) at 8 d postpartum, 8 h apart. The first injection was applied during the first milking in the morning (0700 h), and the next was applied during the second milking (1500 h).

To find a difference in the diameter of the previously gravid uterine horn of 4 ± 4 mm between cows in the treated and control group, a random subsample (n = 45 per group) from the 200 cows was subjected to a reproductive tract evaluation (95% confidence, 80% power; Winepiscope, 2001). Outcomes for all cows (n = 200) included CRFS, and for the subset (n = 90), ultrasonographic uterine measurements, reproductive tract evaluation by palpation per rectum, and serum acute phase proteins were indicators of uterine inflammation. Evaluations of reproductive characteristics were conducted at 12 d postpartum by a faculty veterinarian of the University of Florida. The evaluator was blind to treatment.
Figure 1. Cross-sectional ultrasonographic image of a postpartum uterine horn in a primiparous cow with acute puerperal metritis at 12 d postpartum 4 d after treatment with 2 doses of PGF$_2\alpha$. a) Serosa to serosa diameter; b) submucosa to submucosa diameter.

Ultrasonography was conducted using a 5-MHz transrectal linear transducer (Aloka, 500, Wallingford, CT) to assess uterine characteristics of the previous gravid horn according to validated methodology (Okano and Tomizuka, 1987; Kamimura et al., 1993; Sheldon et al., 2003). Two diameters of the previously gravid uterine horn were evaluated approximately 10 cm from the bifurcation of the uterus. The first measurement was from serosa to serosa to obtain the gross diameter of the uterine horn (Sheldon and Dobson, 2000). The second measurement was from submucosa to submucosa to obtain lumen diameter (Figure 1). The difference between the first and the second measurements estimated the thickness of the myometrium. Because of the enlarged size of the uterus at 8 d postpartum, it was not feasible to determine accurately the uterine diameter and use it as a covariate in the statistical analysis.

Per rectum palpation was conducted to establish a uterine score (1 to 3). Uterine score considered the size and tonicity of the uterus at the greater curvature of the uterine horn (3 = flaccid uterus larger than one hand, 2 = uterus with moderate tonicity and smaller than one hand, and 1 = high tonicity and less than 3 fingers width; Zemjanis, 1970). Conception rate at first service was defined as the proportion of cows diagnosed pregnant 42 to 49 d after the timed AI.

Blood was collected from the coccygeal vessels at treatment assignment (8 d postpartum) and 4 d later (12 d postpartum) for the analysis of haptoglobin, a major acute phase protein in ruminants, and $\alpha_1$-acid glycoprotein, a less specific acute phase protein in cattle (Tizard, 2000). Acute phase proteins were analyzed by a radial immunodiffusion test (Cardiotech, Inc., Louisville, KY).

### Statistical Analyses

Ultrasonographic findings and acute phase protein concentrations were analyzed by ANOVA mixed models (Littell et al., 1996). Uterine score was analyzed using the Median-Rank Test because distribution of uterine score was not normal (Wilk-Shapiro Statistic = 0.78; Kolmogorov-Smirnov Statistic = 0.25). Models considered parity as a covariate. Correlation coefficients between acute phase proteins and uterine diameter were calculated. Statistical analysis was conducted using SAS for Windows 8.0 (SAS Inst., Inc, Cary, NC).

The ANOVA mixed models were defined as

$$y_{ijk} = \mu + T_i + \text{Cow} (T_i)_j + \text{Par}_k + (\text{Par}\ast T)_{ik} + e_{ijk}$$

where $y_{ijk}$ = uterine diameter, $\mu$ = population mean, $T_i$ = fixed effect of treatment, $\text{Cow} (T_i)_j$ = random effect of cow nested in treatment, $\text{Par}_k$ = fixed effect of parity, $(\text{Par}\ast T)_{ik}$ = interaction parity and treatment, and $e_{ijk}$ = random error term.

For acute phase proteins, the pretreatment concentrations were considered as covariates. Data for CRFS were analyzed by logistic regression, adjusting for parity, milk yield, and previous pathological conditions before first service. Previous pathological conditions were defined as any combination of clinical mastitis, lameness, and digestive disorder. Adjusted odds ratios (OR) and confidence intervals are reported. For cows with ultrasonographic evaluations, uterine diameter was used as a predictor of CRFS by using the median value of the distribution as a cut-off value, correcting for parity and pathological conditions prior to first service.

The logistic regression model was defined as

$$\logit \left( \frac{\pi}{1 - \pi} \right) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3$$

where $(\pi/1 - \pi)$ = log of the odds of the probability of the event (pregnant: yes, no), $\alpha$ = intercept, $X_1$ = treatment effect, $X_2$ = parity effect, and $X_3$ = previous pathological condition effect.

### RESULTS

During the study period, 1536 cows calved. From this total, 15.3% (235 cows) developed RFM, APM.
without systemic disease, and were treated with cefti-
fur hydrochloride. Two hundred cases selected at ran-
dom were assigned to the study. Only 8.5% of the total
calvings (130 cows) developed into toxic puerperal me-
tritis. None of these cows was assigned to the study.

An interaction of treatment × parity influenced di-
ameter of the previously gravid uterine horn. Treated
primiparous cows had smaller (P ≤ 0.05) serosa to se-
rosa and submucosa to submucosa diameters than con-
trol primiparous cows (49.2 vs. 56.5 mm and 24.7 vs.
25.2 mm, respectively; Table 1). Among multiparous
cows, no treatment effect was detected (Table 1).
Thickness of the myometrium did not differ between
treatments or between parities.

With regard to uterine scores in primiparous cows,
athough the median value was similar between treat-
ments, the sum of the ranks for treated cows was less
than that for control cows (P ≤ 0.05; Table 1). Fewer
rank scores meant that a greater proportion of treated
cows had a score of 1 (high tonicity) and a higher pro-
portion of control cows had a score of 3 (right skewed
distribution; Figures 2 and 3).

For acute phase proteins, pretreatment concentra-
tions were used as covariates in the analysis. Treat-
mant with PGF2α reduced (P ≤ 0.05) concentrations of
α1-acid glycoprotein concentration by d 12 postpartum
(Table 2). For haptoglobin, no significant differences
between treatments were detected. There was no asso-
ciation between parity and acute phase protein concen-
trations. The diameter of the previously gravid uterine
horns was moderately correlated with concentrations
of α1-acid glycoprotein (r = 0.25; P < 0.05) and hapto-
globin (r = 0.24; P < 0.05).

For different reasons, 15 control (3 dead, 8 culled,
and 4 not synchronized) and 8 treated cows (1 dead,
4 culled, and 3 not synchronized) did not complete
the timed insemination protocol; therefore, they were
excluded from the statistical analysis of fertility data.
Days to first service did not differ between treatments
(109.3 vs. 108.2 d for treated and control groups, re-
spectively). The overall CRFS was not different be-
tween treatments. However, there was a tendency (P =
0.07) for a treatment × parity interaction. When ana-
lyzing the data within parity, treatment increased
CRFS by 17 percentage points in primiparous cows (P

**Table 1.** Ultrasonographic uterine findings and uterine scores of the previous gravid horn of cows with
acute puerperal metritis subsequently treated with 2 doses of PGF2α at 8 d postpartum (LSM ± SEM).

<table>
<thead>
<tr>
<th>Item</th>
<th>Primiparous</th>
<th>Multiparous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cows (no.)</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Uterine diameter (mm)</td>
<td>49.2 ± 2.6a</td>
<td>52.3 ± 2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>47.5 ± 2.3</td>
</tr>
<tr>
<td>Uterine wall (mm)</td>
<td>24.7 ± 2.2</td>
<td>21.7 ± 1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.0 ± 1.9</td>
</tr>
<tr>
<td>Rank sum uterine scores</td>
<td>297 ± 32.5a</td>
<td>576 ± 42.4</td>
</tr>
<tr>
<td>median = 2</td>
<td></td>
<td>median = 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>median = 2</td>
</tr>
</tbody>
</table>

a,bMeans with different superscript letters within parity differ (P ≤ 0.05).

**Figure 2.** Frequency distribution of uterine scores in primiparous treated and control cows at 12 d postpartum. Score 1 (open bars) = high tonicity and <3 fingers width, Score 2 (stippled bars) = uterus with moderate tonicity and smaller than one hand, and Score 3 (filled bars) = flaccid uterus and larger than one hand (Zemjanis, 1970).

**Figure 3.** Frequency distribution of uterine scores in multiparous treated and control cows at 12 d postpartum. Score 1 (open bars) = high tonicity and <3 fingers width, Score 2 (stippled bars) = uterus with moderate tonicity and smaller than one hand, and Score 3 (filled bars) = flaccid uterus and larger than one hand (Zemjanis, 1970).
Table 2. Plasma acute phase protein concentrations (LSM ± SEM) before (8 d postpartum) and 4 d after treating cows with acute puerperal metritis with 2 doses of PGF$_{2\alpha}$.

<table>
<thead>
<tr>
<th>Item</th>
<th>Haptoglobin (µg/mL)</th>
<th>α1-acid glycoprotein (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PGF$_{2\alpha}$</td>
<td>Control</td>
</tr>
<tr>
<td>Cows (no.)</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Before treatment</td>
<td>450.2 ± 30.1$^a$</td>
<td>470.1 ± 30.3$^a$</td>
</tr>
<tr>
<td>After treatment</td>
<td>210.4 ± 30.3$^b$</td>
<td>240.4 ± 30.2$^b$</td>
</tr>
</tbody>
</table>

$^a,b,c$ Means with different superscript letters within row differ ($P \leq 0.05$).

≤ 0.05; Table 3), which indicated that when correcting for days to first service and pathological conditions prior to first breeding, treated primiparous cows were 4.2 times more likely to conceive at first service than control primiparous cows (95% CI OR = 1.05 to 16.5). Within multiparous cows, CRFS did not differ between treatments (Table 4).

Median value for uterine diameter was 5.1 cm. Cows with a uterine diameter < 5.1 cm had a CRFS of 30.8%, whereas cows with uterine diameters ≥ 5.1 cm had a CRFS of 7.9% ($P \leq 0.05$). Adjusting for parity and pathological condition before first service, cows with uterine diameters < 5.1 cm were 5.5 times more likely (95% CI OR = 1.37 to 22.1) to conceive at first service than were cows with uterine diameters ≥ 5.1 cm (Table 5).

**DISCUSSION**

Uterine involution and diameter of uterine horns can be monitored directly using transrectal ultrasonography (Okano and Tomizuka, 1987; Kamimura et al., 1993; Sheldon et al., 2003), palpation per rectum (Kindahl et al., 1999), or indirectly by estimating the concentration of PGF$_{2\alpha}$ metabolite or acute phase proteins in serum (Hirvonen et al., 1999; Sheldon et al., 2001). Transrectal ultrasonography for uterine cross-sectional images had high coefficients of determination (Okano and Tomizuka, 1987). Unfortunately, it was not technically feasible to measure uterine diameter at 8 d postpartum to conduct a covariance analysis when comparing size of the uterus at 12 d postpartum. This technicality may be a source of potential bias on the results and conclusions of our study. However, randomization, a consistent case definition, and blindness of the study play an important role in the reduction of this bias. Therefore, the results of the present study demonstrated that 2 doses of PGF$_{2\alpha}$ 8 h apart at 8 d postpartum in cows that developed APM and were treated with ceftiofur hydrochloride reduced the size of the previously gravid uterine horn, increased the tonicity of uterus, decreased concentrations of the α1-acid glycoprotein, and increased CRFS in primiparous lactating dairy cows. These findings indicated that PGF$_{2\alpha}$ had an effect on uterine involution in primiparous cows. Uterine involution was defined as the process associated with the return of the postpartum uterus to the state of initiating and supporting another pregnancy (Zemjanis, 1970).

Uterine involution is concluded around 45 d postpartum and consists of the reduction in size, loss of tissue, and tissue regeneration of the uterus (Kiracofe, 1980). Reduction in size is, in general, a response of myometrial contractility that plays a major role in clearing

**Table 3.** Logistic regression model for conception rate at first service (CRFS) in primiparous cows with acute puerperal metritis treated with 2 doses of PGF$_{2\alpha}$ at 8 d postpartum.

<table>
<thead>
<tr>
<th>Item</th>
<th>CRFS, %</th>
<th>OR$^1$</th>
<th>95% CI$^2$ OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primiparous treated (n = 39)</td>
<td>28.2$^a$</td>
<td>4.15</td>
<td>1.05–16.5</td>
<td>≤0.05</td>
</tr>
<tr>
<td>Primiparous control (n = 35)</td>
<td>11.4$^b$</td>
<td>Referent</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Days to first breeding &lt; 108 d</td>
<td>19.2</td>
<td>3.32</td>
<td>0.79–13.9</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Days to first breeding ≥ 108 d</td>
<td>24.4</td>
<td>Referent</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No pathological condition prior to first service</td>
<td>23.1</td>
<td>2.84</td>
<td>0.32–24.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pathological condition detected before first service</td>
<td>17.3</td>
<td>Referent</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

$^{a,b}$ Means with different superscript letters within item differ ($P \leq 0.05$).

$^1$ OR = Odds ratio.

$^2$ CI = Confidence interval.
lochial debris from the uterus after calving (Slama et al., 1991; Hirshbrunner et al., 2002). Therefore, our results are consistent with studies that have investigated myometrial physiology in dairy cows. Normal myoelectrical activity of the uterus is greater at calving and decreases drastically around 7 to 9 d postpartum (Gajewski and Faundez, 1992; Gajewski et al., 1999). However, when exogenous uterotonic products are administered (oxytocin, depotocin, or prostaglandins), the myometrium responded with strong contractions (Patil et al., 1980; Gajewski et al., 1999). In the case of PGF2α, uterine myoelectrical activity was increased during the early postpartum period (14 d postpartum; Gajewski et al., 1999). Interestingly, although an inflammed uterus (metritis) produces additional prostaglandins, the uterine musculature does not respond to these endogenous prostaglandins, and the involution process is delayed (Kindahl et al., 1999). Conversely, other mechanisms such as leukocyte function, cytokines, endotoxin response, and antibody production might play additional roles in uterine involution (Mateus et al., 2002, 2003) that we were not able to determine in the present study. In contrast, other studies (Eiler et al., 1984; Burton et al., 1987) did not find a positive effect of PGF2α on myometrial activity in dairy cows during the first 4 d postpartum.

Multiparous cows with metritis were not affected by treatment. We can speculate that older cows with metritis were not affected by treatment because of physiological differences between primiparous and multiparous cows. Although many important mechanisms might explain differences between parities, we focus our discussion on one of these processes, which is related to uterine size in the short term, a key indicator of uterine involution (Zemjanis, 1970). Multiparous cows are consistently more likely to develop hypocalcemia (plasma Ca < 7.5 mg/dL) than primiparous cows within the first 10 d postpartum (Goff and Horst, 1997; Horst et al., 1997; Goff, 1999). Concentrations of plasma Ca are less in cows with retained fetal membranes within 24 h after parturition and during the first week postpartum compared with control cows without RFM (6.3 ± 0.2 vs. 7.4 ± 0.2 mg/100 mL; Risco et al., 1994). By d 8 postpartum, concentrations of Ca are >7.5 mg/dL (Risco et al., 1994). Unfortunately, in the present study, the dynamics of Ca concentration were not evaluated. Concentration of Ca at 8 d postpartum in cows with metritis has not been reported.

Calcium is a key mediator for muscle contraction (Nelson and Cox, 2000). Indeed, Coruzzi et al. (1989) demonstrated that Ca channel blockers inhibited spontaneous and electrically induced contractions in the uterus of the mare. Those researchers concluded that Ca channel blockers are potent inhibitors of mare uterine motility in vitro and emphasized the importance of Ca-related mechanisms in the control of uterine smooth muscle contractility. Consequently, uterotonic compounds, such as PGF2α, might be less effective in triggering uterine motility and toxicity in hypocalcemic cows. Indeed, mean diameter of the uterine horns in cows with milk fever was greater than that of the controls between d 15 and 32 postpartum (Risco et al., 1994). In addition, cows that developed hypocalcemia within the first 10 d postpartum had more prolonged intervals to complete uterine and cervical involution than normocalcemic cows (Kamgarpour et al., 1999). Calcium is also important for the activation of many enzymatic processes at the cellular level through phosphorylation of key enzymes. Therefore, other mechanisms involved in uterine involution, such as tissue degeneration and regeneration, might be Ca-dependent mechanisms as well (Nelson and Cox, 2000).

Uterine score was a combination of size and toxicity of the uterus assessed by palpation per rectum. Dynamics of the size of the uterus obtained by palpation per rectum during the first 14 d postpartum was conducted based on Zemjanis (1970). To our knowledge, uterine tone has been barely evaluated as an outcome variable in clinical trials conducted on dairy cattle. Reasons for this are the subjectivity of the method. However, using a well-defined scoring system, which is conducted consistently, usefulness of uterine toxicity might have practical implications (Loeffler et al., 1999). Indeed, in studies evaluating ovarian anovulatory conditions (ovarian cysts), uterine toxicity has been a key factor for diagnostic purposes (Bartolome et al., 2000). The difference in uterine toxicity and size might be a reflection of uterine contractility, reduction of uterine diameter, and shorter time until anatomical involution after PGF2α treatment. Uterine tone and diameter of the uterine horns have been related in the early postpartum period. Cows with smaller uterine diameters had greater toxicity (Slama et al., 1991).

Acute phase proteins are typical pathological responses to tissue damage or inflammation produced by infections, trauma, neoplasia, or other causes. Haptoglobin is one of the most reactive proteins in cattle, and α1-acid glycoprotein is less specific in the bovine (Gruys et al., 1994; Tizard, 2000). In the present study, concentrations of haptoglobin and α1-acid glycoprotein were similar to those reported in other studies in cows with APM (Smith et al., 1998; Hirvonen et al., 1999; Sheldon et al., 2001). Furthermore, concentrations of both proteins, as in previously cited studies, decreased over time. Interestingly, α1-acid glycoprotein was significantly less in treated than control cows, which was probably related to the reduction of uterine
horn diameter caused by the effect of PGF$_{2_{α}}$. Haptoglobin was not different between treatments, and perhaps this resulted from its greater variability among animals (Hirvonen et al., 1999). A moderately strong positive correlation was detected for haptoglobin and $α_{1}$-acid glycoprotein concentrations with the diameter of the previously gravid horn. This weak association indicated that acute phase protein concentrations are related slightly to size of uterus. Similar findings were reported by Sheldon et al. (2003), who found a positive correlation between uterine diameter and acute phase protein concentrations ($r = 0.37$ and 0.46 for $α_{1}$-acid glycoprotein and haptoglobin, respectively). If PGF$_{2_{α}}$ reduced the diameter of uterine horns in cows that developed metritis, it is reasonable to suggest that the size of the uterus decreased, but does not necessarily indicate that the inflammation and infection were resolved.

Cows with smaller uterine diameters ($< 5.1 \text{ cm}$) had greater CRFS (30.8% vs. 7.9%, respectively) than cows with a uterine diameter $≥ 5.1 \text{ cm}$. This finding is consistent with other studies that reported uterine diameter during the postpartum period was associated with reduced fertility (LeBlanc et al., 2002).

Table 4. Logistic regression model for conception rate at first service (CRFS) in multiparous cows with acute puerperal metritis treated with 2 doses of PGF$_{2_{α}}$, at 8 d postpartum.

<table>
<thead>
<tr>
<th>Item</th>
<th>CRFS, %</th>
<th>OR$^1$</th>
<th>95% CI$^2$ OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiparous treated (n = 50)</td>
<td>20.8</td>
<td>1.03</td>
<td>0.39–2.72</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Multiparous control (n = 53)</td>
<td>26.0</td>
<td>Referent</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Days to first breeding $&lt; 108$ d</td>
<td>21.6</td>
<td>1.05</td>
<td>0.38–2.89</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Days to first breeding $≥ 108$ d</td>
<td>25.7</td>
<td>Referent</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No pathological condition prior to first service</td>
<td>29.1$^a$</td>
<td>4.18</td>
<td>1.27–13.74</td>
<td>≤0.05</td>
</tr>
<tr>
<td>Pathological condition detected before first service</td>
<td>13.8$^b$</td>
<td>Referent</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

$^a,b$Means with different superscript letters within item differ ($P ≤ 0.05$).

$^1$OR = Odds ratio.

$^2$CI = Confidence interval.

Conception rate at first service was greater in treated primiparous cows than in control primiparous cows. At the same time, treatment reduced the size of the uterus at 12 d postpartum in primiparous cows. In addition, cows with smaller uterine size had a greater CRFS than cows with larger uterine size. Although, in the present study, improved fertility also might be related to other confounding variables that we were not able to identify, it is suggestive that 2 doses of PGF$_{2_{α}}$, as early as 8 d postpartum hastened uterine involution in primiparous cows that developed APM within the first week postpartum. Hastened uterine involution might have enhanced the uterine environment for establishment of a successful conception at first service. Indeed, PGF$_{2_{α}}$, given twice daily during the early postpartum period decreased the time of uterine involution in about 1 wk in healthy cows (Lindell and Kindahl, 1983) and improved CRFS and decreased the incidence of endometritis in cows with dystocia and RFM (Nakao et al., 1997).

CONCLUSIONS

It was concluded that 2 doses of PGF$_{2_{α}}$, 8 h apart at 8 d postpartum in primiparous cows with APM de-
increased the diameter of uterine horns and serum concentration of α₁-acid glycoprotein at 12 d postpartum and increased the CRFS. This response might be attributed to a positive effect of PGF₂α, on the process of uterine involution.

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