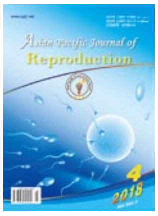

Asian Pacific Journal of Reproduction

Journal homepage: www.apjr.net

doi: 10.4103/2305-0500.237057

Treatment of cows with clinical endometritis Ⅲ as cows affected by pyometra−Non antibiotic treatment of severe clinical endometritis

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ARTICLE INFO

Article history:
Received 13 January 2018
Revision 15 February 2018
Accepted 10 March 2018
Available online 18 July 2018

Keywords:
Cow
Endometritis
Reproductive performance
Prostaglandin $F_2\alpha$

ABSTRACT

Objective: To confirm the efficacy of non-antibiotic treatment with prostaglandin $F_2\alpha$ ($PGF_2\alpha$) in dairy cows affected by severe clinical endometritis in (30±3) days in milk. **Methods:** Cows with clinical endometritis Ⅲ (*n*=399) were aligned into three groups randomly. The first group (*n*=115) received $PGF_2\alpha$, the second group (*n*=84) received intrauterine infusion (IUI) of oxytetracycline 10% + $PGF_2\alpha$, and the third group (*n*=200) received IUI. Cows were inseminated following estrus. The pregnancy status, parity, calving and artificial insemination season, ovaries with corpus luteum at the time of treatment, dystocia, body condition score and treatment groups were included in data analysis. **Results:** Total pregnancy rate was 40.1% after the first insemination and 94.2% after the third insemination. Overall pregnancy rate of treated cows with IUI+$PGF_2\alpha$ (84.5%) was significantly lower than the treated cows with $PGF_2\alpha$ (98.3%) or IUI (96%) (P<0.05). The first service pregnancy rate of inseminated cows in summer (14.3%) was lower in comparison with cows inseminated in spring (40.4%), fall (41.4%) and winter (51.7%) (P<0.05). **Conclusions**: $PGF_2\alpha$ could treat severe clinical endometritis in dairy cows with corpus luteum in comparison with other treatments.

1. Introduction

Postpartum uterine infections like metritis and clinical endometritis are common diseases of dairy cows that influence reproductive efficiency negatively[1] and decrease advantages of dairy farms[2]. The most prevalent uterine infection in dairy cows is endometritis which declines fertility and leads to high economic wastes[3]. There are risk factors related to clinical endometritis in dairy cows such as hygiene of the perineum at the time of calving[4], peripartum metabolic status[5,6], parity[7], retained fetal membranes[1], delivery of twins and dystocia[5].

Different therapies have been suggested for endometritis such as systemic antibiotic administration[8] or local antibiotics[9] as well as prostaglandin $F_2\alpha$ ($PGF_2\alpha$) or estradiol administration[8,10]. The results of cytology and antibiotic residues in post treatment milk samples have indicated that the infusion of oxytetracycline (OTC) in the uterus seems debatable for the treatment of clinical endometritis[11]. But, OTC is used in treatment of clinical endometritis because it is active in anaerobic condition of the uterus during postpartum[12]. Establishment of efficient further therapies is essential instead of antibiotics such as $PGF_2\alpha$ for the treatment of endometritis during postpartum[11].

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Foundation project: This study was supported by the Research Council of Shiraz University and School of Veterinary Medicine, Shiraz University for financial (Grant No. 95INT4M154630).

How to cite this article: Mohammad Rahim Ahmadi, Asghar Mogheiseh, Abdolah Mirzaei, Saeed Nazifi, Eisa Fallah. Treatment of cows with clinical endometritis Ⅲ as cows affected by pyometra—Non antibiotic treatment of severe clinical endometritis. *Asian Pac J Reprod* 2018; 7(4): 185-190.

Administration of $PGF_2\alpha$ is often recommended for treatment of clinical endometritis[9,13]. Recently, researchers suggest that administration of $PGF_2\alpha$ is effective in treatment of endometritis because of induction of myometrial contractions and estrus[14], and also regulation of inflammatory processes in the endometrium[8]. In postpartum period, a wide variety of factors such as time of $PGF_2\alpha$ injection in related to parturition, presence of corpus luteum (CL), uterine infection, the analog of $PGF_2\alpha$, and other unknown factors would affect the efficacy of $PGF_2\alpha$ therapy in dairy cows[15].

Pyometra occurred when purulent materials accumulated within the uterine lumen in the presence of a persistent corpus luteum and in the most cows cervix is closed or in some times, it is opened[16]. Because dominant follicle ovulate in some cows with contaminated uterus, pyometra can be considered a sub-set of endometritis[17]. Despite some differences in time and incidence rate, cervix patency and presence of CL, fortunately $PGF_2\alpha$ is effective in both of them[16]. This similarity may be much more considerable when clinical endometritis grade Ⅲ (uterus filled with pus) are accompanied with presence of CL.

In this study, the reproductive efficiency of dairy cows affected by severe clinical endometritis is evaluated after treatment with single dose of $PGF_2\alpha$ (similar to pyometra) in (30±3) days in milk.

2. Materials and methods

2.1. Animal ethics

The study was carried out under the ratification of the State Committee on Animal Ethics, Shiraz University, Shiraz, Iran (Institutional Animal Care and Use Committee No: 4687/63). Also, the instructions of European Council Directive (2010/63/EU) of September 22, 2010 were considered about the safekeeping of animals used for experimental studies.

2.2. Animals and herd

The study was conducted on 399 lactating Holstein cows from one commercial dairy farm in central Iran (29° 58′ 34″ N, 52° 40′ 45″ E) that were enrolled from October 2012 until April 2015. The machinery milking was performed three times daily (8-hour intervals) and milk production of herd was in average 52 kg/day. The voluntary waiting period was considered 50 days. Cows were calved in the clean calving open sheet. Additionally, a standard ratio was formulated for cows fed three times daily according to nutritional requirements for lactating dairy cows. There was not any treatment for cows at least 14 days before experiment. Cows were examined for uterine involution and ovarian activity at day 30 postpartum. Estrous synchronization protocols with heat detection and fix timed insemination were aligned for all normal post calving cows. Body condition score (BCS) of cows were recorded based on five scale systems and included in the statistical analysis.

Transrectal palpation and ultrasonography performed for examination of ovaries (with or without CL) and uterus with linear rectal probe (5 MHz, Easyscan®, BCF, UK). Vaginal examination performed if there were not any visible discharges around the perinea. Lactating Holstein cows affected by severe clinical endometritis were characterized with purulent or mucopurulent discharges, cervical diameter >7.5 cm, palpable uterine lumen, and lumen in ultrasound filled with pus[1].

Cows with severe clinical endometritis were randomly allocated into 3 treatment groups: Group 1 (n=115), cows with CL: $PGF_2\alpha$ injection (Estron®, Cloprostenol 0.25 mg/mL; Bioveta, Czech Republic; im.); Group 2 (n=84), cows with CL: Intrauterine infusion (IUI) of OTC 10%, (50 mL; Oxyvet®, Razak, Iran) performed with disposable trans-cervical pipette and $PGF_2\alpha$ injection; Group 3 (n=200), cows without CL: IUI of OTC 10% (50 mL; Oxyvet®, Razak, Iran) performed with disposable trans-cervical pipette (Continental Plastic, SUPA, Iran).

After treatment protocols, cows were inseminated following estrus. Pregnancy was diagnosed by transrectal ultrasonography at least 35 days post-insemination. Reproductive performance data of all animals were collected until 7 months after the last cow was enrolled in the study. Information related to interval to pregnancy for cows that were culled during the trial before pregnancy were censored on the date of culling. The following outcomes were measured to assess reproductive performance: days to the first service, the first service pregnancy rate (%), days open, cumulative pregnancy rate (%), service per conception in pregnant cows, and culling rate for reproductive failure (%).

2.3. Statistical analysis

The statistical analysis performed by the SPSS statistical software (Version 15.0, SPSS Inc, Chicago, Illinois). Frequency of pregnancy rate was compared among different treatment groups with the *Chi*-squared test. The first service pregnancy rate of treated cows among different seasons of parturition and artificial insemination was analyzed by *Chi*-squared test. One-way analysis of variance (LSD, Post Hoc Multiple Comparisons) test was used to compare mean ± standard deviation (Mean ± SD) of reproductive performance indices such as days open, calving to the first service interval and service per conception and BCS among three treatment groups. Possible effects of risk factors on the first service pregnancy rate of studied cows were explored using logistic regression analysis.

The data from the treated cows were compared by binary logistic regression analysis using a pregnant status as the dependent variable (0 denotes not-pregnant and 1 denotes pregnant) and parity, calving and artificial insemination season, ovaries with or without CL, dystocia, BCS and treated group as independent variables. Univariate general liner model (GLM) procedures were used to make the best fitting model for factors influencing calving to the first service interval. The significant factors (P<0.05) during the analysis were considered in the main fitting model. Also, possible two-way interactions among the variables during model development were investigated. Descriptive statistics are presented as Mean±SD and percentages (numbers) for reproductive parameters, BCS and pregnancy rate. The results of comparisons were considered significant when P<0.05.

3. Results

Total pregnancy rate of all studied cows (n=399) was 40.1% (160/399) after the first insemination and 94.2% (376/399) after the third insemination. Overall pregnancy rate of treated cows with IUI + $PGF_2\alpha$ (Group 2; 84.5%) was significantly less than the other treated cows with $PGF_2\alpha$ (Group 1; 98.3%) and IUI (Group 3; 96%). Percentages (numbers) of the first, second and third service pregnancy rate of studied cows in various treatment groups were shown in Table 1. The second service pregnancy rate of treated cows in Group 2 was significantly lower in comparison with those of treated cows in Group 1 and Group 3 (P<0.05; Table 1)

Table 1

Percentage of the first, second and third service pregnancy rate of studied cows in different treatment groups.

Groups	First	Second	Third
Group 1	43.9% (50/114)	40.6% (26/64)^{a}	34.2% (13/38)
Group 2	39.3% (33/84)	19.6% (10/51)^{b}	46.3% (19/41)
Group 3	39.1% (77/197)	37.5% (45/120)^{a}	36.0% (27/75)

^{a,b} Different superscripts in rows indicate significant differences (P<0.05).

The cumulative percentage of pregnancy rates after two inseminations was significantly lower in Group 2 in comparison with that of cows in Group 1 (P<0.05; Table 2).

Table 2

Percentage of pregnancy rate of studied cows in different treatment groups after two and three insemination attempts.

Groups	After two	After three
Group 1	66.7% (76/114)^{a}	78.1% (89/114)
Group 2	51.2% (43/84)^{b}	73.8% (62/84)
Group 3	61.9% (122/197)^{ab}	75.6% (149/197)

^{a,b} Different superscripts in rows indicate significant differences (P<0.05).

Table 3 showed the comparison (Mean ± SD) of the reproductive parameters and BCS at clean test exam among different treatment groups. The significant differences were not observed in the mean of days open and service per conception of cows in different treatment groups (P>0.05). Significant differences in calving to the first insemination interval were found. Cows in Group 1 were inseminated significantly earlier than that of cows in other groups (P<0.05). BCS of cows in Group 3 was significantly lower than those cows in the Group 1 and Group 2 (P<0.05).

A comparison of the percentage (number) of pregnancy rate in studied cows until 100 and 200 days after calving was shown in Table 4. Pregnancy rate was not significantly different among groups until 100 and 200 postpartum days; however, this parameter tended to be higher (P=0.06) in the treatment Group 1 (85.8%) compared with the Group 3 (77.1%) until 200 days after calving. Percentage of dystocia was not significantly different among treatment groups.

Table 4

Percentage of pregnancy rate of studied cows in different treatment groups at different postpartum days.

Groups	Until 100 d	Until 200 d
Group 1	49.6% (56/113)	85.8% (97/113)
Group 2	45.1% (32/71)	83.1% (59/71)
Group 3	43.2% (83/192)	77.1% (148/192)

The effects of treatment methods and parity were located in the main model of the univariate GLM analysis and stayed significant all over model development (P>F for type Ⅲ sums of square was 0.002 and 0.050 for treated groups and parity, respectively). The calving to the first service interval of cows in the third parity was significantly lower than that calculated for the cows in the first parity and second parity. This parameter tended to be higher (P=0.06) in the cows of the second parity in compared with the first parity.

The first service pregnancy rate of inseminated cows in summer (14.3%) was lower in comparison with those of inseminated cows in spring (40.4%), fall (41.4%) and winter (51.7%) (P<0.05; Table 5). A tendency toward significant difference was found in first service pregnancy rate of inseminated cows in winter in comparison with those of inseminated in spring (P=0.07). The first service pregnancy rate of cows was not significantly different in various seasons

Table 3

Reproductive parameters and BCS at clean test exam among different treatment groups (Mean ± SD).

Groups	Calving to the first service interval (day)	Days open (day)	Service per conception (number of AI)	BCS (scale score 1-5)
Group 1	69.2 ± 20.8^{a}	127.4 ± 82.7	2.38 ±1.84	2.6 ± 0.2^{a}
Group 2	82.4 ± 24.8^{b}	133.7 ± 113.2	2.40 ± 1.91	2.6 ± 0.3^{a}
Group 3	75.4 ± 25.2^{c}	144.5 ± 89.3	2.53 ± 1.87	2.4 ± 0.4^{b}

^{a,b} Different superscripts in rows indicate significant differences (P<0.05).

(P>0.05; Table 5). The results of the logistic regression showed that no significant effect of BCS, parity, ovarian condition, calving season, dystocia and treated group was observed on the first service pregnancy rate of studied cows.

Table 5

Percentage of first pregnancy rate of studied cows in the different seasons of calving and artificial insemination.

Season	Calving	Insemination
Spring	43.5 (10/23)	40.4 (57/141)^{a}
Summer	31.3 (26/83)	14.3 (7/49)^{b}
Fall	43.0 (64/149)	41.4 (36/87)^{a}
Winter	42.9 (60/140)	51.7 (60/116)^{a}

^{a,b} Different superscripts in rows indicate significant differences (P<0.05).

4. Discussion

In this study, administration of IUI or $PGF_2\alpha$ injection was more effective than IUI + $PGF_2\alpha$ treatment of severe clinical endometritis to correct the reproductive performance of cows during postpartum period. Also, the present study showed that overall pregnancy rate of the treated cows in group 2 was significantly lower than cows in groups 1 and 3, and in group 3 was lower than group 1. It can be assumed that non-pregnant cows were more probably to have persistent lesions in the endometrial surface and that differences in therapeutic performance were even more promenaded[18]. Some studies did not find significant differences between $PGF_2\alpha$ and IUI treatments[19]which was confirmed by the present study results and pregnancy rate was significantly different between treatment groups at the first or third insemination. Also, this finding is similar to the report that cows are affected by endometritis and the presence of CL, and there was no significant difference in interval from calving to pregnancy between cows treated by IUI and $PGF_2\alpha$[10]. But the present study showed significant difference at the second service pregnancy rate between group 2 and others. It seems that the combination of $PGF_2\alpha$ and IUI in the presence of CL for treatment should not be used, because reproductive hormones interact with uterine immune function[3]. Calving to the first insemination intervals was significantly different between groups; as a result, the cows in group 1 were inseminated earlier than other groups (P<0.05). It has been generally accepted that production of cervical mucus, secretion and activity of uterine glands, the phagocytic function of uterine neutrophils and myometrial contractility were suppressed in a high progesterone environment[3]. Actually, there was a relationship between uterine infection and prolonged luteal phases and failure to ovulate[16]. $PGF_2\alpha$, a luteolytic agent, appears to have pro-inflammatory functions that may increase neutrophil action. But, interaction between $PGF_2\alpha$ and progesterone in immunity of uterus are not entirely realized in dairy cows[20]. In contrast, Subandrio *et al*[21] did not found any persistent association between activity of uterine neutrophils and phase of the estrous cycle. However, LeBlanc *et al* indicated that $PGF_2\alpha$ is more effective in the presence of high progesterone levels or a palpable CL[10].

The presented data provides evidence that weak body condition is associated with clinical endometritis during postpartum and delay to return of ovarian activity in different treatment groups. It was found that there were significant differences on the interval between calving and the first service among the different treatment groups. Cows in group 1 were inseminated earlier than cows in other treatment groups. The lower body condition score was observed in group 3 (P<0.05) relative to the other groups. So, the first postpartum ovulation occurred much later after parturition in cows with lower BCS in compared with cows in normal BCS. Similar to the present study results, researchers suggested that endometritis occurred frequently in thin cows between parturition and day 20 after calving[22] and decreased dry matter intake and increased non-esterified fatty acid (NEFA) concentrations are related with periparturient suppression of the immune function, leading to a greater susceptibility of cows to disease[23]. The polymorphonuclear functions can affect by high levels of NEFA in cows[23]. Hoedemaker *et al* showed that the extent of decreasing body condition score and the speed of recovery after calving can be associated with the reproductive efficiency and the incidence of postpartum infection in dairy cattle[22] and drastic negative energy balance may prohibit cows from establishing an efficient immune response to the bacterial infections during postpartum[24]. Buckley *et al*[25] and Gillund *et al*[26] indicated significant effects of BCS. In a study, postpartum endometritis was associated with weak body condition during puerperal period. It is possible due to the increased NEFA in thin cows at the postpartum period[24]. The modified metabolic profile acts via the hypothalamo-pituitary system and decreases gonadotropin-releasing hormone and luteinizing hormone and estradiol secretions. It probably mediates the prohibitory effects of negative energy balance on postpartum fertility[27]. Researchers concluded that cows were still enduring an active uterine inflammatory response in severe negative energy balance conditions, but in mild negative energy balance conditions, the endometrium of cows reached to a more progressive phase of recovery at two weeks postpartum[28]. It has been suggested that there is a positive effect of BCS at nadir and body weight change following the first insemination and a deleterious effect of BCS loss postpartum with the majority of reproductive success indices[29].

In this study, the calving to the first service interval of cows in the third parity was significantly lower than the cows in the first parity and second parity. The highest days open needed for the cows in the first and second parity could be because of the nutritional requirements for growth and their inability to quickly begin postpartum ovarian rebound due to low level of body reserves[30]. Also, it is suggested that cows with the first and second parity may profit from greater BCS at parturition[29]. They also reported that the second-parity cows had significantly the lowest BCS at calving and nadir than other parities. In the second-parity cows, the extent and rate of BCS loss to nadir were not different from other parities with the exception of the primiparous cows. However, it was less than any of the other parity[29].

Pregnancy rate of treated cows did not significantly different between groups until 100 days postpartum. This confirms that endometrial improvement was achieved up to 100 days postpartum among all groups. The differences in the percentage of dystocia were not significant among different treatment groups. Others reported no improvement in reproductive performance between cows with retained fetal membrane, dystocia or twin pregnancy following three injections of $PGF_2\alpha$, weekly, starting early postpartum in compare to a single injection later in postpartum[6]. These results provide further indirect documents against the advantage of $PGF_2\alpha$ treatment when there was not CL on ovaries of affected cows[6].

The presented data showed no significant effect of BCS, parity, ovarian condition, calving season, dystocia and different treatments on the first service pregnancy rate of sever clinical endometritis cows. These results are similar to the findings of Knutti *et al*[31]. Lower first service pregnancy rate during summer in comparison with other seasons is due to the effect of heat stress on the reproductive system[32].

Finally, the single IUI (cows without CL) or $PGF_2\alpha$ (in the presence of CL) treatment has better efficiency than IUI+$PGF_2\alpha$ for clinical sever endometritis between 26 and 38 days in milk. So, $PGF_2\alpha$ could improve reproductive performance more effectively in cows with clinical endometritis Ⅲ.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

The authors would like to thank the Research Council of Shiraz University and School of Veterinary Medicine, Shiraz University for financial (Grant No. 95INT4M154630) and technical and Pegah Dairy Farm for their logistical cooperation support of this study.

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