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The Efficacy of Different Treatment Protocols in Pyometra with Respect to Reproductive Hormones and Indices in Dairy Cows

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Abstract

Early detection of the reproductive problems is fundamental to improve reproductive efficiency of dairy farms. Therefore, the study was performed to compare between two treatment protocols of pyometra to optimize reproductive performance of dairy cows. Based on rectal and ultrasonographic examinations, 30 cows suffered from pyometra were divided into; group1 (n=10) control group, group2 (n=10): treated with two injections of prostaglandin (PGF2α) plus systemic ceftiofur and group3 (n=10): treated with systemic ceftiofur. Ultrasonographic examination was performed before and 11 days after treatment. Blood samples were collected for analysis of progesterone (P4) and estradiol 17-ß just before and 11 days after treatment. Reproductive data was obtained regarding the 1st and 2nd service conception rate (the 1st SCR and the 2nd SCR), number of services/conception (s/c) and days open. Ultrasonographic examination of the uterine horns appeared to be filled with hyperechoic granules in the lumen. However, the uterine horns at 11 days after treatment decreased in size and hyperechoic granules disappeared. No significant differences in P4 and estradiol 17- ß before and 11days after treatment. In cows received PGF2α+ ceftiofur, estradiol 17- ß was lower before treatment than 11 days after treatment. Significant improvement in the reproductive performance was recorded in treated cows with PGF2α+ceftiofur that manifested by marked increase in SCR and S/C as well as decrease in days open as compared with treated cows with ceftiofur only. It was concluded that double PGF2α injection+systemic ceftiofur is the best protocol to control pyometra that was pronounced by enhancement of reproductive performance in dairy cows.

KEYWORDS
Ceftiofur, Dairy cows, PGF2α, Pyometra

INTRODUCTION

Infection of high-producing cows during the postpartum period is a hazardous contributing factor of different deleterious infectious diseases, such as endometritis, metritis, and pyometra. That diseases adversely affect the health and productivity of dairy cows. There are many factors makes the cows more susceptible to metritis. These factors include immune response, genetic factors, management factors, infections factors, as well as nutritional and metabolic factors (Molina-Coto and Lucy, 2018). Pyometra is considered a branch of endometritis (Galvão *et al*., 2011) that results from exposure of the uterus to infection followed by cumulating of pus inside its lumen while the ovary exhibits presence of a persistent corpus luteum (CL) (Knudsen *et al*., 2016). Most cows suffer from pyometra have closed cervix. However, few cases have not fully completed cervix. Therefore, , purulent discharge can be seen come out from the vagina when the cow lies down, urinates, or defecates (Raj *et al*., 2015).

Pyometra proceeds to failure of reproductive performance which manifested by delayed uterine involution, increase calving interval, open days, number of services per conception (Noakes *et al*., 2009; Toni *et al*., 2015). Hence, breeders sustain great economical losses especially in multiparous dairy cattle farms.

Previous literatures demonstrated various protocols for treatment of postpartum metritis (Adnane *et al*., 2017; Giuliodori *et al*., 2013). Postpartum metritis is commonly treated with hormones or antibiotics or antiseptics alone or in combination (Deori and Phookan, 2015; Szenci, 2016). The hormonal treatments include prostaglandin F2 α (PGF2α), oxytocin and estrogens (Deori and Phookan, 2015; Paisley *et al*., 1986). The antiseptics includes lugol's Iodine solution, bovidine and lotagen (Deori and Phookan, 2015; Paisley *et al*., 1986). The antibiotic therapy includes oxytetracycline, gentamycin, chloramphenicol, and penicillin- streptomycin (Paisley *et al*., 1986; Noakes *et al*., 2009; Deori and Phookan, 2015).

The most commonly used antibiotic is ceftiofur hydrochloride, which is a member of the family of third-generation broad spectrum cephalosporins (Risco and Hernandez, 2003).

Prostaglandin F2 α had been shown to be effective in the treatment of uterine infections (Sheldon and Noakes, 1998).The administration of exogenous PGF2α induces the secretion of endogenous PGFα from the uterus and enables the development of the immune functions (Lewis, 2003). It has been reported that the use of PGF2α and its analogues during diestrus resulted in approximately 90% of the cows showing estrus (Zobel *et al*., 2013). Each estrus enables the self-cleansing of the uterus by means of physiological leukocytosis and increased uterine motility (Folman *et al*., 1990). Moreover, the secreted estrogen increases uterine

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contractions, mucus production and leukocyte infiltration to the uterus (Noakes *et al*., 2001; Squires, 2010).

MATERIALS AND METHODS

Ethical approval

The experiment was performed according to the guidelines of the ethical committee of the Faculty of Veterinary Medicine, Suez Canal University, Egypt (approval no. 2016104).

Animals

The study was carried out in a special dairy farm; ElBarka dairy farm, Port Said governorate, North of Egypt. The period of the study ranged from September 2020 to October 2021. A total number of 30 Holstein dairy cows aged 2 – 3.5 years old (1 to 2 lactations) were used. The average milk production per cow was about 9 tons /milking season. They were milked three times daily. The animals were free from brucellosis, leucosis and TB according to the certificate of origin and the regular veterinary health checks performed to them. Cows were kept in a free yard with a sufficient shadow. All cows were fed total mixed ration according to the NRC (2001). The water was added ad libidum. Experimented cows were selected with body condition score (BCS) 3.25 to 3.75 by visual observation and palpation. The BCS was determined on a scale from 1 to 5 with a 0.25-unit precision where 1 is extremely thin and 5 is extremely fat (Edmonson *et al*., 1989).

Ultrasonographic examination

Starting from day 30 to 35 after parturition, animals were examined rectally and ultrasonography (B-mode, linear transrectal transducer, 5-8 MHz, Sonoscape M12, China).

Treatment groups

Cows diagnosed suffering from pyometra were classified into 3 groups:
Group 1: Control group (n=10) did not be treated at all.
Group 2: Systemic ceftiofur group (n=10) was injected by ceftiofur only (EXCEDE®, each ml contains 200 mg ceftiofur crystalline free acid, Zeotis company, USA. Subcutaneous under base of ear) with a dose 6.6 mg/kg body weight as recorded by Risco and Hernandez (2003) .
Group 3: two injections of PGF2α+ systemic ceftiofur group (n=10) were administered as follow; at day 0 of treatment, cows were injected by PGF2-α 500 µg (Estrumate®, 1ml contains 250 µg cloprostenol, MSD company, Germany) (Sheldon and Noakes, 1998) and 6.6mg/kg body weight ceftiofur (Risco and Hernandez, 2003). Afterwards, 500 µg PGF2-α was repeated after 11 days. The ultrasonography was performed to the pyometra group at the 11th days of treatment.

Sampling

Blood was obtained from tail vein of the studied cows. Blood was collected on plain tube for hormonal analysis. A total of 60 blood samples were collected from control at the same time of their herd mates as well as treated cows before and after the 11th day of treatment. The samples were chilled on ice packs immediately after collection then transferred immediately to the lab to be centrifugated at 3500 round per minute for 10 minutes. Harvested sera were frozen at – 20ºC until analysis.

Artificial insemination

Estrus was detected by well-trained persons continuously throughout the day and night. Artificial insemination (AI) of those cows was performed by visual heat detection without any treatment by the am-pm rule i.e., cows came in heat in the morning were inseminated at the evening and others came in the evening were inseminated in the next morning (Graves *et al*., 1997).

Moreover, animals returned to heat were inseminated by the same veterinarian again depending on heat detection (Michael and Thomas, 2005). A frozen-thawed semen from approved sires was used for insemination of all the groups.

Other non-returned cows were checked for pregnancy by ultrasonography at 32nd days after insemination, then confirmed rectally at 55th days post insemination.

Hormonal analysis

Bovine ELISA kits were used for assessment of serum progesterone (P4) and estradiol 17-ß (NEOGEN Co., USA). Analysis was performed according to manufacture instructions.

Reproductive indices

The fertility data of the studied cows were collected regarding:
-First service conception rate (Falkenberg *et al*., 2008): number of pregnant cows after first AI / number of inseminated cows X100.
-Second service per conception (Falkenberg *et al*., 2008): number of pregnant cows after second AI / number of inseminated cows X100 (was calculated only for cow with pyometra).
-Number of services per conception (Upham, 1991): sum of all AI used for all cows / Number of cows confirmed pregnant.
-Days open (Harman *et al*., 1996): the period between parturition and the following conception of a dairy cow.

Statistical analysis

All data was analyzed statistically using GraphPad Prism version 5.0 (GraphPad Software, San Diego, California USA). Statistical comparisons were made by one way ANOVA to compare between different groups. Furthermore, Student's t-test was applied to assess the statistical variations within each group before and after the 11th days of treatment. The obtained results expressed as mean ± SE. The results were considered significant when $P \leq 0.05$.

RESULTS

Ultrasonographic examination

By ultrasonographic examination, the uterine horns appeared filled with hyperechoic granules in the lumen (pus granules). After treatment by 11 days, the uterine horns of treated groups decreased in size and the hyperechoic granules disappeared (Fig. 1).

Hormonal analysis

Before and after treatment of pyometra by 11 days, control and treated cows by Ceftiofur + PGF2α and systemic Ceftiofur only did not exhibit any significant ($p > 0.05$) variations regarding

P4 levels (Table 1). Besides, within each group non-significant ($p > 0.05$) difference was declared regarding P4 levels before and after treatment (Table 1).

Concerning serum estradiol 17- ß, all groups had no significant ($p > 0.05$) differences before and 11 days after treatment of pyometra. However, cows treated with Ceftiofur + PGF2α revealed a significant ($p < 0.001$) decrease in estradiol 17- ß levels before and 11 days after treatment (43.8 ± 10.60 and 25.33 ± 3.8), respectively (Table 1).

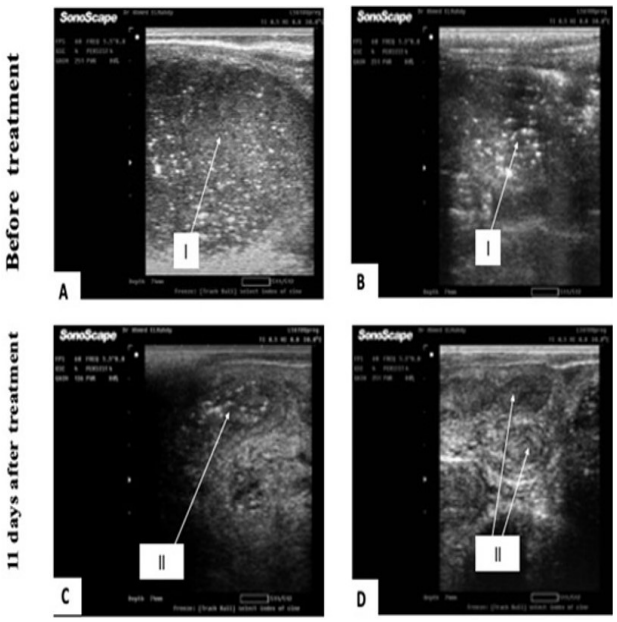

Fig. 1. Ultrasonographic images of pyometra before and 11 days after treatment Before treatment (A) & (B), (I) refers to uterine horns filled with hyperechoic granules in pyometra. In (C) & (D), (II) refers to the uterine horns 11 days after treatment which appear with no hyperechoic dots in the uterine lumen.

Reproductive data

No conception occurred in the non-treated group till the end of investigation. So reproductive data of the untreated group were excluded as none of the untreated group were inseminated because they did not come in heat or came with mucopurulent discharge.

As shown in Table 2, the 1st and 2nd service conception rate increased significantly ($p < 0.01$) in Ceftiofur + PGF2α treated cows as compared to the other treated group.

At the same time, number of services per conception inclined significantly ($p < 0.01$) in Ceftiofur + PGF2α treated cows when compared to the systemic ceftiofur treated group (Table 2).

Concerning days open, Ceftiofur + PGF2α treated cows showed significant ($p \leq 0.05$) decrease as compared to the systemic ceftiofur group (Table 2).

DISCUSSION

Uterine infection is one of the most serious problems in dairy cows. This uterine disease is a factor affecting fertility of dairy cattle. Studies showed that there were a decrease in the reproductive performance as a consequences of prolonged inflammation (Eckel and Ametaj 2016; LeBlanc, 2014).

In this study diagnosis of pyometra was carried out by transrectal ultrasonography as it based on the appearance of increased volume of accumulated echogenic uterine content without fetus and cotyledons, closed cervix and corpus luteum on the ovary (Bondurant, 1999; Sheldon *et al*., 2006).

Pyometra is characterized by the presence of corpus luteum on ovary and accumulation of fluid of mixed echo-density with hyperechoic dots in the uterine lumen and distention of the uterus on ultrasonographic examination (Manns *et al*., 1985).

In this study there was no significance serum glucose levels between all groups that may be attributed to the homogeneity of the studied apparently healthy cow in their physiological status postpartum that was achieved by the approximated BCS. On the contrary, Elitok *et al*. (2006) reported that glucose level reduced during the partum and postpartum periods of Holstein cows, which might be due to inadequate dry matter intake and increasing demands due to mammary gland development and milk production (Esposito *et al*., 2014). Cows with infected uterus showed disturbances in the energy metabolism till the 4th weeks postpartum (Nazifi *et al*., 2003). Furthermore, the physiological adaptations that were needed to meet energy needs were delayed.

Table 1. Mean serum progesterone and estradiol 17- ß levels before and 11 days after treatment in pyometra in dairy cows.

		Control (n=10)	Systemic Ceftiofur (n=10)	Ceftiofur + two injections of PG (n=10)	P value
Progesterone (ng/ml)	Before treatment	3.8 ± 0.2	3.9 ± 0.9	3.2 ± 0.8	0.76 (NS)
	11 days after treatment	3.4 ± 0.2	3.5 ± 0.7	3.07 ± 0.7	0.81 (NS)
	p. value	0.08 (NS)	0.09 (NS)	0.8 (NS)	
Estradiol 17-β ß (pg/ml)	Before treatment	58.5 ± 14.1	39.33 ± 4.6	43.8 ± 10.60^{A}	0.19 (NS)
	11 days after treatment	53.4 ± 11.6	33.9 ± 5.6	25.33 ± 3.8 ^{B}	0.58 (NS)
	p. value	0.1 (NS)	0.06 (NS)	0.00	

Different capital letters in the same column of the same parameter are significant at $p \leq 0.05$

Table 2. Reproductive data of different treatment methods of pyometra in dairy cows.

	Control (n=10)	Systemic Ceftiofur (n=10)	Ceftiofur+PGF2α (n=10)	P value
First service conception rate	——	(n=1) 10%^{b}	(n=3) 30 % ^{a}	0.01
Second service conception rate	——	(n=3) 33.3 % ^{b}	(n=4) 57.14 % ^{a}	0.01
Service per conception	——	3.2 ± 0.58 ^{a}	2.00 ± 0.00 ^{b}	0.01
Days open (day)	——	180.5 ± 4.3 ^{a}	93.33 ± 2.60 ^{b}	0.01

Different letters in the same raw are significant at $p \leq 0.05$

There was no significant difference between progesterone and estradiol 17 ß serum level between the treated and untreated studied groups before and after treatment of pyometra, this may be due to that the cows were selected in the same physiological reproductive stage (28-35 DIM). However, there was a significant decrease in estradiol 17-ß after 11 days of PGF2α in serum of Ceftiofur + PGF2α treated cows as this analysis was done at the luteal phase at which estrogen reached its minimum levels (Wettemann *et al*., 1972).

Marked progress in the reproductive parameters in Ceftiofur + PGF2α treated cows as compared with systemic Ceftiofur group regarding the 1st and 2nd service conception rate, number of services per conception and days open. It is known that prostaglandins enhance uterine defense mechanisms, help to promote uterine contractility, contribute to uterine involution and help to shorten periods of bacterial infection (Schofield *et al*., 1999; Melendez *et al*., 2004). Furthermore, PGF2α helps in evacuating pus from uterus via increasing contractile potential of uterine muscles and regression of persistent CL. However, early diagnosis should be done to prevent the chances of infection to ascend and infertility. PGF2α was at least as effective as or even preferable to the intrauterine infusion of antimicrobials for the treatment of endometritis (Sheldon and Noakes, 1998).

The obtained results were in consistence with those of Bonnett *et al*. (1990) who reported that treating cows with PGF2α reduced the incidence of vaginal discharge, decreased the diameter of the uterine horns, reduced inflammation and fibrosis in the endometrium and minimized the possibility of isolation of Actinomyces pyogenes from endometrial biopsy samples taken on the 40th day postpartum. Also, Sheldon and Noakes (1998) and LeBlanc (2008) confirmed that PGF2α has been shown to be effective in the treatment of uterine infections and so enhancement of reproductive performance. Furthermore, Melendez *et al*. (2004) stated that conception rate at first service was greater in treated cows with PGF2α than in control cows.

The efficient effect of PGF2α in treatment of uterine infection and subsequent improving of reproductive pattern could be explained by the ability of exogenous PGF2α to induce the secretion of endogenous PGF2α from the uterus and prompt the development of the immune functions (Lewis, 2003). In addition to that common treatment followed is administration of PGF2α. Treatment of endometritis with PGF2α or a synthetic analogue is done to stimulate uterine defense mechanisms by destroying the corpus luteum and removing the progesterone source (Hendricks *et al*., 2006). Moreover, PGF2α or its analogs at normal luteolytic doses helps in evacuation of the exudate and bacteriologic clearance of the uterus. That was assured by the disappearance of the hyperechoic pus granules from the ultrasonographic image of uterine horns after 11 days of treatment by PGF2α. Also, the luteolytic effect of, which induces estrus and causes estrus mucus to flush the endometrium (El-Tahawy and Fahmy, 2011). Hence, the reproductive performance of PGF2α- treated cows suffered from pyometra will be improved.

Contrasted results were recorded in several studies, Jeremejeva *et al*. (2012) recorded no variation in the first service per conception in all groups. Therefore, the probability of becoming pregnant after the first insemination was the same in the group treated by PGF2α, as well as in healthy and untreated animals. Additionally, Jeremejeva *et al*. (2012) found that the vaginal discharge, intensity of bacterial growth and the start of ovarian activity in animals treated by PGF2α were not better than in the other groups. Also, Hendricks *et al*. (2006) also showed that treatment using PGF2α did not alter the probability of pregnancy at first insemination.

The most commonly used antibiotic is ceftiofur hydrochloride, which is a member of the family of third-generation broad cephalosporines (Risco and Hernandez, 2003) . When used systemically, ceftiofur hydrochloride reached high concentrations in uterine tissues (Okker *et al*., 2002) sufficient to inhibit growth of pathogenic bacteria known to cause uterine disease in cows (Sheldon and Dobson, 2004). A significant increase was found in the duration to first estrus, the days open, in cows treated by systemic ceftiofur only and control group. This means that pyometra negatively affects the fertility parameters, which suggests a greater need for a better understanding of pyometra associated parameters to minimize the economic losses due to low fertility (Amin *et al*., 2021).

In addition, a combined treatment with PGF2α and ceftiofur showed an even stronger treatment effect than PGF2α alone. The findings of Kasimanickam *et al*. (2005) came in harmony with our results. The previous authors found that treatment of pyometra with cephapirin and cloprostenol significantly improved the reproductive performance of affected cows cephapirin and cloprostenol treatments via increase in the pregnancy rate by 62% and 63%, respectively, relative to control cows.

In the current study, the improvement in uterine health and fertility of cows was likely consequent to the systematic use of PGF2α and systemic ceftiofur which is known to reduce uterine bacterial contamination and improve fertility (Sheldon and Dobson, 2004, Kasimanickam *et al*., 2005).

CONCLUSION

The use of double doses of PGF2α beside systemic ceftiofur is beneficial in the remedy of pyometra and so improvement of reproductive performance and increase profitability in dairy cows.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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